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Pilot assessment using the HTA Core Model[®] for Rapid Relative Effectiveness Assessment

CANAGLIFLOZIN FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

Final version, 26 February 2014

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The model represents a consolidated view of the non-binding recommendations of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals.

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Authoring organisations:

Agency for Quality and Accreditation in Health Care and Social Welfare
Finnish Medicines Agency, Assessment of Pharmacotherapies
Regione Veneto

Dedicated reviewing organisations:

Catalan Agency for Health Information, Assessment and Quality
Direction Générale de Santé/ Haute Autorité de Santé
Hauptverband der Österreichischen Sozialversicherungsträger
Medical University of Sofia
Ministry of Health of the Czech Republic

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Consultation of the draft Pilot Rapid Assessment

The following WP5 Strand A members have provided comments during WP5 consultation (v1.2)	<ul style="list-style-type: none"> • Haute Autorité de Santé, France • Directorate for Pharmaceutical Affairs, Ministry for Health, the Elderly and Community Care, Malta • A. Gemelli University, Italy, • Scottish Medicines Consortium, Scotland • Administration du Contrôle Médical de la Sécurité Sociale, Luxembourg • Nasjonalt kunnskapssenter for helsetjenesten, Norway • Rijksinstituut voor Ziekte- en Invaliditeitsverzekering, Belgium
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SUMMARY OF RELATIVE EFFECTIVENESS OF CANAGLIFLOZIN

The assessment element ID codes in brackets (e.g. A0001) refer to the result cards in Appendix 2, which give details of the relevant results.

Scope

Description	Project scope
Population	<p>Adults (≥18 years) with type 2 diabetes mellitus (type 2 DM) with inadequate glycaemic control on oral antidiabetic therapies and/or insulin</p> <ul style="list-style-type: none"> • Dual therapy: adults with type 2 DM with inadequate glycaemic control on monotherapy with either metformin or a sulphonylurea. • Triple therapy: adults with type 2 DM with inadequate glycaemic control on dual therapy with either of the following <ul style="list-style-type: none"> · metformin in combination with a sulphonylurea · metformin or a sulphonylurea in combination with a thiazolidinedione, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a glucagon-like peptide 1 (GLP-1) analogue. • Add-on therapy to insulin: adults with type 2 DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.
Intervention	<p>Canagliflozin is an inhibitor of subtype 2 sodium-glucose transport protein (SGLT2);</p> <ul style="list-style-type: none"> • 1-(glucopyranosyl)-4-methyl-3-(5-(4-fluorophenyl)-2-thienylmethyl) benzene. <p>Doses of 100 mg or 300 mg per day; administered orally.</p>
Comparison	<p>Dual therapy</p> <p>For the combination of canagliflozin and metformin, the comparators are:</p> <ul style="list-style-type: none"> • sulphonylureas (with metformin) • pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin) • dapagliflozin (with metformin). <p>For the combination of canagliflozin and sulphonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with sulphonylurea) • DPP-4 inhibitors (with sulphonylurea) • GLP-1 analogues (with sulphonylurea) • dapagliflozin (with sulphonylurea). <p>Triple therapy</p> <p>For the combination of canagliflozin, metformin and a sulphonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with metformin + sulphonylurea) • dapagliflozin (with metformin + sulphonylurea) • DPP-4 inhibitors (with metformin + sulphonylurea)

Description	Project scope
	<ul style="list-style-type: none"> • GLP-1 analogues (with metformin + sulphonylurea). <p>For the combination of canagliflozin, metformin and pioglitazone, the comparators are:</p> <ul style="list-style-type: none"> • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • insulin (with metformin and pioglitazone). <p>For the use of canagliflozin in any other triple therapy regimen, the comparator is:</p> <ul style="list-style-type: none"> • insulin (alone or in combination with one or more oral antidiabetic agents). <p>Add-on therapy to insulin</p> <p>For the use of canagliflozin as add-on therapy to insulin, the comparator is:</p> <ul style="list-style-type: none"> • one or more oral antidiabetic agents (in combination with insulin). <p>Comparators are chosen according to those listed in the evidence-based clinical guidelines, HTA-reports and textbooks [American Diabetes Association. 2013; Fauci 2013; Gale 2012; Inzucchi 2012; Royal College of Physicians 2008; Scottish Intercollegiate Guidelines Network, 2010; World Health Organization 2006 and 2011; EUnetHTA method guide on choice of the most appropriate comparators, 2013].</p>
<p>Outcomes</p>	<p>Efficacy</p> <ul style="list-style-type: none"> • Glycated haemoglobin (HbA1c) change (%) • Proportion achieving <7% HbA1c target (%) • Change in fasting plasma glucose (FPG; mmol/L) • Body mass index change • Change in cardiovascular risk factors (including blood pressure and/or serum lipids) • Weight change • Complications of diabetes (e.g., cardiovascular, renal, and eye) • Mortality • Change in insulin requirements (in patients using insulin) • Proportion achieving <7% HbA1c target (%) without hypoglycaemia <p>Safety*</p> <ul style="list-style-type: none"> • Most frequent adverse events • Serious adverse events <p>Health-related quality of life</p> <p><i>Outcomes were chosen as commonly used outcomes in diabetes studies (often surrogate outcomes) and clinical outcomes important for REA, based on recommendations from the EUnetHTA methods guideline on clinical and surrogate endpoints and safety [European Network for Health Technology Assessment (EUnetHTA) 2013]</i></p>
<p>Setting</p> <p>Study design</p>	<p>Any</p> <p>RCTs</p>

* In the safety assessment, placebo controlled studies were also considered.

Introduction

Health problem

The population of interest addressed by this assessment is: Adults (≥ 18 years) with type 2 DM with inadequate glycaemic control on oral antidiabetic therapies and/or insulin (A0007).

Type 2 DM has developed into a worldwide health problem. Prevalence data from European countries show that up to 8% of people suffer from DM, of which the majority is Type 2 DM (A0006). Type 2 DM results from a progressive insulin secretory defect with a variable degree of insulin resistance resulting in higher levels of glucose in the blood (A0002). The main risk factor for type 2 DM is obesity (A0003). Apart from acute metabolic disturbance and hyperglycaemia, type 2 DM is associated with considerable long-term morbidity due to micro- and macrovascular complications (e.g. ischaemic heart disease, retinopathy, nephropathy) and premature mortality (A0004). People suffer from several symptoms such as fatigue, weakness, poor wound healing or blurred vision and overall diminished health-related quality of life (A0005).

Diabetes is diagnosed by measuring fasting plasma glucose (FPG; ≥ 7.0 mmol/L), by the oral glucose tolerance test (OGTT; plasma glucose ≥ 11.1 mmol/l at 2 hours after 75 g oral glucose load), by measuring random blood glucose concentration (≥ 11.1 mmol/l) or by measuring HbA1c ($> 6.5\%$) (A0024).

Type 2 DM is managed in a stepwise approach that starts with education and lifestyle changes. If the target level of HbA1c is not achieved by non-pharmacological management, pharmacological glucose control therapies are required (biguanides, sulphonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists or insulins) (A0025). Metformin (biguanides) is the optimal first-line drug. If metformin is contraindicated or not tolerated, other drugs can be used in monotherapy. Combination therapy with additional one (dual therapy) or two oral or injectable agents (triple therapy) is reasonable, aiming to minimise side effect of such drug combination where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centred approach should be used to guide the choice of therapy, bearing in mind efficacy, side effects, cost, comorbidities and patient preferences (A0025).

A new class of drug is available on the EU market, the sodium glucose co-transporter 2 (SGLT2) inhibitors, and dapagliflozin is the first drug to be approved in the class. Canagliflozin belongs to this class, as the first drug of the class approved in the US market.

Description of technology

Canagliflozin is an orally active inhibitor of SGLT2, the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. SGLT2 is expressed in the proximal renal tubules, and not in other tissues, and is responsible for the majority of the reabsorption into the blood of glucose filtered through the glomerulus. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (B0001).

Canagliflozin is available in 100 mg and 300 mg film-coated tablets. Canagliflozin 100 mg once-daily orally, should be administered before the first meal of the day. Increasing the dose to 300 mg once daily may be considered if patients are currently tolerating canagliflozin 100 mg once daily, have an estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m² or a creatinine clearance [CrCl] > 60 mL/min, and require additional glycaemic control.

Canagliflozin should not be initiated in patients with an estimated GFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min. In patients tolerating canagliflozin whose estimated GFR falls persistently below 60 mL/min/1.73 m² or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when estimated GFR is persistently below 45 mL/min/1.73 m² or CrCl persistently below 45 mL/min.

Canagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in such populations (B0001).

Indications

Canagliflozin is indicated in adults aged 18 years and older with type 2 DM to improve glycaemic control as:

- monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- add-on therapy, with other antihyperglycaemic medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (B0002).

Canagliflozin is contraindicated in patients who are hypersensitive to canagliflozin or to any of the excipients.

Results

Available evidence

The clinical effectiveness assessment is based on three phase III trials including active comparators. Canagliflozin 100 mg and 300 mg was compared with glimepiride 6 mg or 8 mg or sitagliptin 100 mg in dual therapy as add-on to metformin. In triple therapy, canagliflozin 300 mg was compared with sitagliptin 100 mg as add-on to metformin and sulphonylurea. In addition, indirect evidence and simulations using the diabetes CORE model are presented.

The general safety assessment is mainly based on direct evidence from nine phase III randomised controlled trials in more than 10000 subjects with T2DM. In all phase III trials two different doses of canagliflozin were tested, 100 mg and 300 mg per day. Special safety aspects were investigated in smaller trials. The phase III studies were in patients with different background therapies; they were either placebo-controlled (including one monotherapy trial) or used an active comparator (glimepiride 6 mg or 8 mg or sitagliptin 100 mg). A large trial (CANVAS) in 4330 patients at increased cardiovascular risk (DIA3008), with the aim to evaluate the effects of canagliflozin on the risk of cardiovascular disease and to assess safety and tolerability in patients with inadequately controlled T2DM and increased cardiovascular risk is still ongoing, but interim safety data on cardiovascular events are presented in this assessment. Data from two 18-week substudies in CANVAS trial, sulphonylurea substudy and insulin substudy are also included in the assessment. Smaller phase III (sub-) trials investigated the effects of canagliflozin in patients with moderate renal impairment (DIA3004, estimated GFR between 30 and 50 mL/min/1.73 m² at baseline) and in patients with poor glycaemic control (part of DIA3005).

Upcoming evidence

According the ClinicalTrials.gov Register, three RCTs are currently ongoing.

CANVAS trial is a randomised, multicentre, double-blind, parallel-group, placebo-controlled study of the effects of canagliflozin 100 mg or 300 mg on cardiovascular outcomes in adults with type 2 DM. The first phase comprises 4,330 individuals randomized on a 1:1:1 basis to placebo, canagliflozin 100 mg, or canagliflozin 300 mg who were scheduled to be followed initially for an average of about 2 years. If the potential for cardiovascular protection was confirmed and initial safety criteria were met, the trial was planned to then enter a second 5-year phase that would recruit and follow an additional 14,000 individuals with the goal of demonstrating cardiovascular protection. Participants were either 30 years or older with a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular, or peripheral) or they were 50 years or older with 2 or more of the following risk factors for vascular disease—duration of diabetes 10 years or more, systolic blood pressure above 140 mmHg while on 1 more or antihypertensive agents, current smoking, micro- or macroalbuminuria, or high-density lipoprotein cholesterol [HDL-C] b1 mmol/L). The primary outcome is the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke (MACE). Safety will be evaluated on the basis of the incidence of all AEs, all serious AEs, and all deaths. AEs pre-specified as of specific interest included vulvovaginal infections in women, genital mycotic infections in men, UTIs, hypoglycaemia, fractures, cardiovascular events, skin AEs and cancer events (due to a reported imbalance in breast and bladder cancer incidence in association with dapagliflozin). According the recently published data out of 4330 randomized patients 34% are female and 57% had a history of atherosclerotic

vascular disease. The planned second phase will not be undertaken, but a separate large outcome trial may be done.

A randomised, double-blind, 5-arm, parallel-group, 26-week, multicentre study to evaluate the efficacy, safety, and tolerability of canagliflozin in combination with metformin as initial combination therapy in the treatment of people with type 2 DM with inadequate glycaemic control with diet and exercise (NCT01809327) estimates to include 1180 participants (randomisation 1:1:1:1:1 canagliflozin 100 mg: canagliflozin 300 mg:metformin XR: canagliflozin 100 mg + metformin XR: canagliflozin 300 mg+ metformin XR) with the primary endpoint as change in glycated haemoglobin (HbA1c) from baseline to week 26, and overall safety and tolerability as well. Estimated primary completion date (final data collection date for primary outcome measure) is May 2014.

A randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the blood pressure reduction with ambulatory blood pressure monitoring (ABPM), safety, and tolerability of canagliflozin in the treatment of participants with hypertension and type 2 DM (NCT01939496). This 6-week, phase IV study, estimates to include 189 patients (randomised 1:1:1; canagliflozin 100 mg: canagliflozin 300 mg: placebo on a background of a stable dose of anti-hyperglycaemic and anti-hypertensive agents). The primary endpoint is change in mean 24-hour systolic blood pressure (SBP) measured by ambulatory blood pressure monitoring (ABPM) and overall safety and tolerability as secondary outcomes. Estimated primary completion date is August 2014.

Clinical effectiveness

In this section, an overview of the results concerning mortality and long-term outcomes, HbA1c, weight, systolic blood pressure, fasting plasma glucose and quality of life is presented. Unless indicated differently, the evidence below is derived from direct comparisons.

Durations of studies including active comparators were 52 (DIA3006 and DIA3015) or 104 weeks (DIA3009). Results at 52 weeks, which were available for all active controlled studies, are presented here unless stated otherwise. More detailed and statistically oriented representation of the results, including also additional outcomes, can be found in the domain report. Additionally, the appendices also include more detailed description of the results derived from direct and indirect comparisons at various time points.

Mortality and long-term outcomes

To date, there seems to be no conclusive evidence about the effects of canagliflozin on overall mortality, disease-specific mortality or long-term outcomes (for example retinopathy and nephropathy) compared with other treatment options (D0001, D0002 and D0006). The simulations suggested a minor positive impact of canagliflozin on the long-term outcomes compared with other treatments. Severe limitations and uncertainty apply to these results (D0001, D0006).

Surrogate endpoints

HbA1c (D0005A)

Canagliflozin 100 mg as an add-on therapy (with metformin) was comparable with glimepiride (mean change in HbA1c: -0.8% vs. -0.8%, respectively) or sitagliptin 100 mg (mean change: -0.7% vs. -0.7%, respectively) in reducing HbA1c values. Additionally, results at 104 weeks indicate that canagliflozin 100 mg is non-inferior to glimepiride (between group difference in change in HbA1c: -0.09%).

Canagliflozin 300 mg induced slightly greater (statistically significant) reductions in HbA1c than did the comparators in direct comparisons (mean change: -0.9 % vs. -0.8% compared with glimepiride, and -0.9% vs -0.7% compared with sitagliptin 100 mg) in dual therapy. Additionally, results at 104 weeks indicate that canagliflozin 300 mg is superior to glimepiride (between group difference in change in HbA1c: -0.18%).

In triple therapy, canagliflozin 300 mg induced statistically significantly greater reduction in HbA1c compared with sitagliptin 100 mg (mean change: -1% vs. -0.7%, respectively). The between-treatment differences in HbA1c in comparisons between canagliflozin 300 mg and glimepiride or sitagliptin were 0.12% or 0.15–0.37%, respectively.

Indirect comparisons at 52 weeks suggest that in dual therapy (with metformin), liraglutide 1.2 mg and 1.8 mg might be more effective than canagliflozin 100 or 300 mg in reducing HbA1c. In addition, canagliflozin 300 mg might be more effective than canagliflozin 100 mg, sitagliptin 100 mg and saxagliptin 5 mg. Additionally, indirect comparisons at 104 weeks suggested that canagliflozin 300 mg might be more effective than gliptins and sulphonylurea. In triple therapy, in combination with metformin and sulphonylurea (at 26 weeks), the results suggest that canagliflozin 300 mg might be more effective than canagliflozin 100 mg and linagliptin 5 mg.

Fasting plasma glucose (D0005C)

Canagliflozin 100 mg and 300 mg, added on metformin, seemed to induce statistically significantly greater changes in fasting plasma glucose (FPG) than glimepiride (-1.4 vs. -1.5 vs. -1.0 mmol/L, respectively) or sitagliptin 100 mg (-1.5 vs. -2.0 vs. -1.0 mmol/L, respectively) at 1 year. A similar statistically significant finding was obtained in a trial comparing canagliflozin 300 mg with sitagliptin 100 mg in a combination treatment with metformin and sulphonylurea (-1.7 vs. -0.3 mmol/L, respectively).

Proportion of patients achieving HbA1c target < 7% (D0005B)

Canagliflozin 100 mg treatment, as added on metformin treatment, was associated with similar proportions of participants achieving the HbA1c target during the trial compared with glimepiride (54% vs 56%, respectively) but not with sitagliptin 100 mg (41% vs 51%, respectively).

Canagliflozin 300 mg treatment (added on metformin) was associated with a similar proportion of participants achieving the HbA1c target compared with glimepiride (60% vs 56%, respectively). Added on metformin, canagliflozin 300 mg was associated with a greater proportion of subjects achieving the HbA1c target when compared with sitagliptin 100 mg (55% vs 51%, respectively).

Added on metformin-sulphonylurea combination, canagliflozin 300 mg seemed to be associated with a greater proportion of participants achieving the HbA1c target compared with sitagliptin (48% vs 35%, respectively).

Weight (D0005F)

Added to metformin treatment, canagliflozin at either dosage seems to result in statistically significant weight reduction of approximately 4–5 %, compared with a 1% increase with glimepiride or a 1% decrease with sitagliptin 100 mg. Additionally, the observed body weight changes were sustained in dual therapy over the 104-week treatment period compared with glimepiride.

Added to metformin and sulphonylurea treatment, canagliflozin 300 mg seemed to result in weight loss (mean 2.5% or 2.3 kg) whereas with sitagliptin 100 mg no clear weight change could be observed (increase of 0.3 kg). The difference between treatments was statistically significant.

Indirect comparisons at 52 weeks suggest that in dual therapy (in combination with metformin), canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, vildagliptin 50 mg, glimepiride, glipizide and pioglitazone 30 mg in reducing weight. In addition, canagliflozin 300 mg might be more effective than canagliflozin 100 mg. Additionally, indirect comparisons at 104 weeks suggested that canagliflozin 100 and 300 mg might be more effective than gliptins and sulphonylurea. In triple therapy, in combination with metformin and sulphonylurea (at 26 weeks), there is no clear evidence on differences in weight change between the treatments.

Systolic blood pressure (D0005E)

Added to metformin, and compared with glimepiride or sitagliptin 100 mg, canagliflozin seems to induce a statistically significantly greater decrease in systolic blood pressure (SBP) (-3 mmHg, -5

mmHg, no change, and -1 mmHg at 52 weeks for canagliflozin 100 mg, canagliflozin 300 mg, glimepiride, and sitagliptin, respectively). At 104 weeks, systolic blood pressure increased slightly from week 52 in all the treatment groups in dual therapy but the differences between canagliflozin 100 and 300 mg compared with glimepiride remained quite similar.

In combination treatment with metformin and sulphonylurea, canagliflozin 300 mg treatment resulted in statistically significantly greater decreases in SBP compared with sitagliptin 100 mg (reduction of approximately 5 mmHg compared with increase of 1 mmHg, respectively).

Indirect comparisons at 52 weeks suggest that in dual therapy (in combination with metformin), canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, liraglutide 1.2 mg and glimepiride in reducing SBP. Additionally, indirect comparisons at 104 weeks suggested that canagliflozin 100 and 300 mg might be more effective than sulphonylurea. In triple therapy, in combination with metformin and sulphonylurea, results after 26 weeks suggest that canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg in reducing SBP.

Patient reported outcomes and quality of life

Quality of life (D0011A, D0011B, D0012, D0013, D0016, D0017)

Canagliflozin or its comparators did not have any relevant effect on functional ability or general health-related quality of life during the follow-up of up to 1 year.

General health-related quality of life, as described by the physical component summary score of SF-36, was unchanged at 52 weeks of treatment: on dual therapy (on metformin), mean changes in score for canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg were 1.0 and 0.8 and 0.4, respectively, and for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride were 1.2, 1.7 and 0.9, respectively. In triple therapy (on metformin and sulphonylurea), mean changes for canagliflozin 300 mg and sitagliptin 100 mg were 0.9 and -0.1, respectively.

Likewise, the mental component summary scores of SF-36 were unchanged at 52 weeks of treatment: on dual therapy (on metformin), mean changes for canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg were 0.6 and -0.1 and 1.0, respectively, and for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride 0.7, 1.1 and 0.2, respectively. In triple therapy (on metformin and sulphonylurea), mean changes for canagliflozin 300 mg and sitagliptin 100 mg were 1.1 and -0.4, respectively.

No evidence was available about patient satisfaction with the use of canagliflozin.

Subgroup analyses

The add-on use of canagliflozin has been studied in people with moderate renal impairment, in older adults and in people at high cardiovascular risk. However, these trials are or were placebo controlled and therefore out of scope of the comparative efficacy assessment. At this point, there is no evidence concerning the efficacy of canagliflozin compared with glimepiride or sitagliptin in these clinically important subgroups (see discussion in [D0005A](#)). Additional data can be found in the safety domain.

Safety

Except for one safety outcome (any documented hypoglycaemia in DIA3009 trial), p values and confidence intervals were not available.

Most frequent adverse events (AEs) and serious AEs

In the pooled, placebo-controlled trials (*DIA3002, DIA3005, DIA3006, DIA3012*) the proportion of participants who experienced any AEs or serious AEs was similar across treatment groups. Percentages of any AEs were 60.1, 59.2 and 59.4% for canagliflozin 100 mg, canagliflozin 300 mg and placebo, respectively; percentages of serious AEs were 3.4, 2.6 and 3.4% for canagliflozin 100 mg, canagliflozin 300 mg and placebo respectively. The incidence of AEs leading to study discontinuation was low across groups but slightly higher with canagliflozin

versus placebo, with no dose relationship: 4.3, 3.6 and 3.1% for canagliflozin 100 mg, canagliflozin 300 mg and placebo respectively (C0001).

In these placebo-controlled trials, the most commonly reported adverse reactions during treatment with canagliflozin in combination with insulin or a sulphonylurea, were hypoglycaemia, vulvovaginal candidiasis, urinary tract infection (UTI), and polyuria or pollakiuria (i.e., urinary frequency). Adverse reactions leading to discontinuation of $\geq 0.5\%$ of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of women) and balanitis or balanoposthitis (0.5% of men) (C0001).

The overall incidence of AEs with canagliflozin in the active comparator studies (DIA3009 and DIA3015) was 64.4%, 68.5%, and 68.5% for canagliflozin 100 mg and 300 mg and glimepiride 6 mg or 8 mg, respectively, for DIA3009; and 76.7% and 77.5% for canagliflozin 300 mg and sitagliptin 100 mg, respectively, for DIA3015 (C0001, C0008).

Overall incidences of AEs in participants on background metformin (DIA3006) were slightly higher with canagliflozin 100 mg compared with canagliflozin 300 mg and sitagliptin 100 mg, over 52 weeks (72.3%, 62.7% and 64.5% respectively) and over 104 weeks in the DIA3009 study, the overall incidence of AEs was slightly lower with canagliflozin 100 mg and similar with canagliflozin 300 mg compared with glimepiride 6 mg or 8 mg (73.3%, 77.9%, and 78.4%, respectively) (C0001, C0008).

Special populations (DIA 3004, DIA3008, DIA3010)

Concerning special populations [patients with stage 3 chronic kidney disease (estimated GFR ≥ 30 and < 50 ml/min/1.73 m²), older people (aged 55–80 years) and patients at cardiovascular risk (ongoing trial)], in an interim safety analysis of CANVAS (DIA3008), the overall AE rate was slightly higher with canagliflozin 300 mg (73.4%) compared with canagliflozin 100 mg (71.0%) and placebo (69.6%) (C0002).

In subjects with moderate renal impairment (DIA3004), the overall incidence of AEs was generally similar for canagliflozin 100 and 300 mg and placebo (78.9%, 74.2%, and 74.4%, respectively) (C0002).

In older subjects (DIA3010), the overall AE rate was similar: canagliflozin 100 mg (72.2%) and slightly higher with canagliflozin 300 mg (78%) compared with placebo (73.4%) (C0002).

Most of the imbalances in AEs reflect the known physiological actions of canagliflozin as an SGLT2 inhibitor, or known side effects resulting from SGLT2 inhibitors. These comprise of e.g. thirst, polyuria, hypotension (due to increased diuresis) and all signs of urogenital infection. Also increased serum creatinine can most likely be explained by elevated diuresis (for detailed discussion, see section on changes in renal function below). The reduced incidence of increased blood pressure and hyperglycaemia in the canagliflozin groups can also be explained by SGLT2 inhibition (C0002).

AEs of special interest

Hypoglycaemia

In the pooled placebo-controlled trials (DIA3005, DIA3006, DIA3012) there was a small and dose-dependent increase in hypoglycaemic events in the canagliflozin groups as compared with placebo. Severe hypoglycaemias were rare. In the presence of hypoglycaemic background therapy (i.e. insulin or sulphonylurea) the incidence was increased by canagliflozin (C0001).

In the active comparator trial DIA3009 hypoglycaemic events were significantly lower in both groups treated with canagliflozin (100 mg and 300 mg) compared with the group treated with glimepiride 6 mg or 8 mg ($p < 0.0001$). DIA3015 reported similar results in the two groups both for any documented hypoglycaemia and severe hypoglycaemia (canagliflozin 300 mg and sitagliptin 100 mg) (C0001 and C0008).

Urinary tract infection

In the pooled placebo-controlled trials (DIA3002, DIA3005, DIA3006, DIA3012), the incidence of UTIs differed little between canagliflozin and placebo. For unknown reasons the incidence was higher in the low-dose canagliflozin group compared with the other two groups (5.5%, 4.1% and 4.0% for canagliflozin 100 mg, 300 mg and placebo respectively). Serious AEs, including ascending UTIs were rare (C0001).

In the active-controlled studies (DIA 3006, DIA3009, DIA3015), canagliflozin was associated with a slightly higher incidence of UTIs compared with glimepiride 6 mg or 8 mg (DIA3009): 6.0%, 6.0% and 5.0% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride 6 mg or 8 mg, respectively and with a slightly lower incidence of UTIs compared with sitagliptin 100 mg (DIA3015): 4.0% and 5.6% for canagliflozin 300 mg and sitagliptin 100 mg respectively. In participants on background metformin (DIA3006), the incidence of UTIs was higher with canagliflozin 100 mg compared with sitagliptin 100 mg and lower with canagliflozin 300 mg: 7.9%, 4.9% and 6.3% for canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg respectively (C0008).

Genital infection

In the pooled placebo-controlled trials (DIA3002, DIA3005, DIA3006, DIA3012), there was a clear greatly increased incidence of genital infection in women in both canagliflozin groups compared with placebo, and the increase was slightly dose-dependent. No serious AEs were observed that lead to discontinuation of study drug. Many of the infections were caused by fungi. The incidence of any vulvovaginitis was 10.4, 11.4 and 3.2% for canagliflozin 100 mg, 300 mg and placebo respectively. The incidence of genital infections in men was lower than that in women (C0001).

In the active-controlled trials (DIA 3006, DIA3009, DIA3015), compared with glimepiride 6 mg or 8 mg, canagliflozin treatment was associated with an increased incidence of genital mycotic infections in women in the DIA3009 study at week 52: 11.0%, 14.0%, and 2.0% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively. Such an increase was also seen compared with sitagliptin 100 mg in the two further studies at week 52: DIA3015; 15.3% and 4.3% for canagliflozin 300 mg and sitagliptin 100 mg, respectively, and DIA3006: 11.3%, 9.9% and 2.6% for canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg, respectively (C0008).

Canagliflozin treatment was associated with higher incidences of genital mycotic infections in men relative to active comparators (glimepiride 6 mg or 8 mg) in DIA3009 at week 52: 7%, 8.0% and 1% for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively. Compared with sitagliptin 100 mg in two further studies at week 52: DIA3015; 9.2% and 0.5% for canagliflozin 300 mg and sitagliptin 100 mg, respectively, and DIA3006 : 5.2%, 2.4%, 1.2% for canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg, respectively. Overall, male genital mycotic infections were generally manageable with the usual treatments; these AEs occasionally led to study discontinuation and rarely resulted in more serious complications (C0008).

Market authorisation and reimbursement status

Canagliflozin has recently been approved by the US Food and Drug Administration (FDA) and was given marketing authorisation in Australia on 6 September 2013. The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the product Invokana (100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 diabetes on 19 September 2013. This recommendation was forwarded to the European Commission, which approved the product on 22 November 2013.

The reimbursement status of canagliflozin in different EU countries is decided at national level. For more information please see following results cards (A0021, B0003).

Summary table of relative effectiveness of canagliflozin

Type II Diabetes Mellitus						
<i>The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.</i>						
	Health benefit			Harm		
	Overall survival	QoL, mean (SD) change from baseline at 52 weeks (SF-36)	Mean HbA1c change (%) at 52 weeks (95% CI*)	Any AEs (%)**	Serious AEs (%)**	Frequent AEs of any severity grade between treatment arms (%)**
DIA 3006 (AEs at 52 weeks)	(D0001)	(D0012A)	(D0005A)	(C0008)	(C0008)	(C0008)
Canagliflozin 100 mg + metformin	No relevant evidence available	PCS: 1.0 (6.7) MCS: 0.6 (8.2)	-0.73 (-0.83 to -0.63)	266(72.3)	15(4.1)	Any documented hypoglycaemia: 16 (4.3):17 (4.6): 5 (1.4); Genital mycotic infections†: f 22 (11.3)/m 9 (5.2):f 20 (9.9)/m 4 (2.4):f 5 (2.6)/m 2 (1.2) UTI 29 (7.9): 18 (4.9): 23 (6.3)
Canagliflozin 300 mg + metformin		PCS: 0.8 (6.8) MCS: -0.1(8.5)	-0.88 (-0.98 to -0.78)	230(62.7)	12(3.3)	
Sitagliptin 100 mg + metformin		PCS: 0.4 (6.2) MCS: 1.0(9.8)	-0.73 (-0.83 to -0.63)	236(64.5)	18(4.9)	
Quality of body of evidence***	Not applicable	Low	Moderate	Low	Low	Low
DIA 3009 (AEs at 52 weeks)	(D0001)	(D0012A)	(D0005A)	(C0008)	(C0008)	(C0008)
Canagliflozin 100 mg + metformin	No relevant evidence available	PCS: 1.2 (6.3) MCS: 0.7(9.7)	-0.82 (-0.90 to -0.74)	311(64.0)	24(5.0)	Any documented hypoglycaemia 27 (5.6): 24 (4.9): 165 (34.2), p<0.0001 (significantly lower in both canagliflozin arms); Genital mycotic infections† f 26 (11.0)/m 17 (7):f 34 (14.0)/m 20 (8.0):f 5 (2.0)/ 3 (1%); UTI 31 (6.0):31 (6.0):22 (5.0)
Canagliflozin 300 mg + metformin		PCS: 1.7 (6.4) MCS: 1.1(9.1)	-0.93 (-1.01 to -0.85)	332(69.0)	26(5.0)	
Glimepiride + metformin		PCS: 0.9 (6.5) MCS: 0.2(8.7)	-0.81 (-0.89 to -0.73)	330(69.0)	39(8.0)	
Quality of body of evidence***	Not applicable	Low	Moderate	Low	Low	Moderate (for any documented hypoglycaemia) to Low

Type II Diabetes Mellitus						
<i>The assessment element ID codes (e.g. D0001) refer to the result cards in Appendix 1, which give details of the relevant results.</i>						
	Health benefit			Harm		
	Overall survival	QoL, mean (SD) change from baseline at 52 weeks (SF-36)	Mean HbA1c change (%) at 52 weeks (95% CI*)	Any AEs (%)**	Serious AEs (%)**	Frequent AEs of any severity grade between treatment arms (%)**
DIA 3015 (AEs at 52 weeks)	<i>(D0001)</i>	<i>(D0012A)</i>	<i>(D0005A)</i>	<i>(C0008)</i>	<i>(C0008)</i>	<i>(C0008)</i>
Canagliflozin 300 mg + metformin + Sulphonylurea	No relevant evidence available	PCS: 0.9 (6.1) MCS: 1.1(9.0)	-1.03 (-1.13 to -0.93)	289(76.7)	24(6.4)	Any documented hypoglycaemia 163 (43.2):154 (40.7); Genital mycotic infections† f 26 (15.3)/m 19 (9.2):f 7 (4.3)/m 1(0.5); UTI 15 (4.0):21 (5.6)
Sitagliptin 100 mg + metformin+ Sulphonylurea		PCS: -0.1 (7.1) MCS: -0.4(7.7)	-0.66 (-0.76 to -0.56)	293 (77.5)	21(5.6)	
Quality of body of evidence***	<i>Not applicable</i>	<i>Low</i>	<i>Moderate</i>	<i>Low</i>	<i>Low</i>	<i>Low</i>
Pooled placebo[§]: DIA 3002 /excluded for hypoglycaemia/, DIA 3005, DIA 3006, DIA 3012 (AE at 26 weeks)				<i>(C0001)</i>	<i>(C0001)</i>	<i>(C0001)</i>
Canagliflozin 100 mg				501 (60.1)	28 (3.4)	Any documented hypoglycaemia 26 (3.8): 29 (4.3): 11 (2.2); Any vulvovaginitis 44 (10.4): 49 (11.4): 10 (3.2); UTI 46 (5.5): 34 (4.1): 26 (4.0)
Canagliflozin 300 mg				494 (59.2)	22 (2.6)	
Pooled placebo				384 (59.4)	22 (3.4)	
Quality of body of evidence***				Not assessed	Not assessed	Not assessed

Abbreviations: AE = adverse event; CI = confidence interval; HbA1c = glycated haemoglobin; MCS = mental component summary score of SF-36 = short form (36) health survey; PCS = physical component summary score of SF-36 = short form (36) health survey; QoL = quality of life; SD = standard deviation; SF-36 = short form (36) health survey; UTI = urinary tract infection.

†Presented separately for women and men; higher rates are observed in women

* CIs were calculated based on normal approximation using standard errors

** p-value and confidence interval not applicable (exception is p value on one outcome: any documented hypoglycaemia in DIA3009 trial).

*** Quality of body of evidence was evaluated using GRADE approach, only for active comparator trials DIA3006, DIA 3009, DIA3015, at 52 weeks

§ Only for harm assessment

Discussion

Evidence of effects on mortality and long-term outcomes is highly important for REA. However, to date, there seems to be no conclusive evidence about the effect of canagliflozin on overall or disease-specific mortality or long-term outcomes (such as nephropathy, neuropathy, micro- and macrovascular complications, retinopathy) compared with other treatment options. Overall, the duration of studies conducted during phase II and III in the canagliflozin program is too short to provide reliable evidence about the effects on mortality and long-term outcomes. However, the lack of reliable evidence on long-term outcomes is typical at this stage in a drug development program due to limited duration of the studies. Further studies (or results) with longer follow-up times are needed in order to assess the effects of canagliflozin on overall mortality, mortality due to diabetes-related diseases, and long-term outcomes. The MAH undertook several simulations to demonstrate effects of canagliflozin on long-term outcomes. These attempts to predict long-term effects are appreciated but the results should be interpreted with great caution since considerable limitations and uncertainty apply to these results.

Canagliflozin seemed to be able to induce comparable (100 mg) and even greater (300 mg) reductions in HbA1c compared with glimepiride or sitagliptin 100 mg in dual or triple therapy. The mean differences in reductions in HbA1c were less than 0.5% in general across trials. Recent meta-analyses have questioned the role of intensive glucose control in preventing the complications of diabetes, thereby calling into question the clinical importance of the observed differences. Many other factors are also important for the development of diabetic complications, such as blood pressure and possibly lipids. Therefore, for any given antidiabetic drug, long-term trials are needed addressing directly the effects of the drug on these clinical outcomes.

Quality of life, functional ability and effects on activities of daily living are important aspects of the medication of chronic diseases. More evidence is needed to reach further conclusions on the effects of canagliflozin on quality of life.

Except for one safety outcome (any documented hypoglycaemia in DIA3009 trial), safety parameters were not defined as primary or secondary endpoints and statistical analyses were not performed. The overall quality of evidence (assessed only in three active comparator trials DIA3006, DIA 3009, DIA3015, at 52 weeks), was moderate to low. Long-term data on canagliflozin side effects are needed, both for rare AEs and for long-term effects of significant glucosuria on the urinary tract. Increased genital infections (especially in women) and increased UTIs should be considered in long-term therapy; these AEs may affect patient compliance and quality of life.

In the manufacturer's meta-analysis of cardiovascular events across trials (including patients enrolled in the CANVAS clinical study and patients included in other clinical trials) there was no increased risk with canagliflozin vs. comparator (active or placebo) for the combined cardiovascular endpoint MACE or MACE-plus (the latter including MACE and hospitalisation for cardiovascular events). The hazard ratio (HR) for MACE was 0.98 (95% CI: 0.70, 1.37). In the same analysis HR updated to November 2012 (CANVAS study start date December 2009) showed an increased risk in the population at risk for fatal/nonfatal stroke (1.29; 95% CI: 0.8, 2.09), lower than was observed in the previous analysis (HR: 1.47; January 2012). However data from the ongoing clinical trial (CANVAS, estimated primary completion date, March 2017) will help to clarify this potential risk. The incidence of all AEs, all serious AEs, all deaths, AEs pre-specified as of specific interest included vulvovaginal infections in women, genital mycotic infections in men, UTIs, hypoglycaemia, fractures, cardiovascular events, skin AEs and cancer events (due to a reported imbalance in breast and bladder cancer incidence in association with dapagliflozin) will be presented after follow-up of 7 years as well. The other two ongoing studies are of short duration, one is assessing only a surrogate primary outcome; safety parameters were again not defined as primary or secondary endpoints.

In the recent systematic review and meta-analysis [Vasilakou et al. 2013], of 49 RCTs and 9 extension trials, 45 trials (11,232 participants) compared SGLT2 inhibitors with placebo and 13 trials (5175 participants) compared SGLT2 inhibitors with active comparators. The authors concluded that SGLT2 inhibitors (including dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, luseogliflozin, tofogliflozin, ertugliflozin and remogliflozin) may improve some short-term outcomes

in adults with type 2 DM, but the effects on long-term outcomes and safety were unclear. The quality of evidence was rated as low for the primary outcome, and low or moderate for the remaining outcomes. Compared with active comparators, SGLT2 inhibitors were significantly associated with a higher rate of UTIs (OR 1.42, 95% CI 1.06 to 1.90; $I^2=25\%$, eight trials) and genital tract infections (OR 5.06, 95% CI 3.44 to 7.45; $I^2 0\%$; eight trials). The results for cardiovascular outcomes and death were inconclusive. An imbalance in the incidence of bladder and breast cancer was found in trials that compared dapagliflozin with controls. Results did not show any differences in incidence of bladder cancer between canagliflozin and control; the same was true on incidence of breast cancer.

An increase in genital and urinary tract infections is a class effect of SGLT2 inhibitors. Although inhibition of SGLT2 is anticipated to be safe since chronic glucosuria appears to be safe, based on observation of patients with familial renal glucosuria (with mutations of SGLT2) who do not develop significant clinical problems over a long period of time, systematic review mentioned above produced contradictory evidence. Clinical data from real-world experience are needed (long-term pragmatic clinical trials and prospective observational studies, in a large number of patients, including those at higher risk with a prior history of UTIs). Possible consequences of recurrent UTIs and AEs as a result of antimicrobial therapy should be kept in mind.

Validity and applicability of the evidence

The overall validity of the evidence is challenged by some issues. The proportion of missing data is considerable as the percentage of discontinuation was high across all trials. The use of pivotal off-study medications has not been reported in detail, which leads to uncertainties about the individual effects of canagliflozin treatment on several important outcomes. Increasing the glucose concentration of urine and the subsequent increase in urine volume due to osmotic diuresis was associated with an increased incidence of genital infections in women and of pollakiuria. These symptoms and events may have made it possible to detect treatment assignment. This may have affected the treatment of the participants as a whole, in spite of initially successful blinding during the trials.

In general, the applicability of the evidence is limited. This is due to extensive exclusion criteria and the limited duration of the studies conducted. The participants suffering from the most advanced comorbidities and the most labile disease were excluded and therefore the results cannot be directly applied to a considerable proportion of the patients treated in daily clinical practice.

Evidence about the effects of canagliflozin treatment compared with an active comparator in people with renal impairment is limited. According to placebo-controlled studies, the ability of canagliflozin to decrease HbA1c levels is much diminished in people with an estimated GFR of $< 45 \text{ mL/min/1.73 m}^2$. This is consistent with the mechanism of action of canagliflozin.

The effects of canagliflozin treatment compared with an active comparator in elderly people remain unclear, as the mean age in the three pivotal trials was 55–57 years. There is no evidence of the effects of canagliflozin treatment in people over 80 years of age, as they were excluded from the trials. The effectiveness and safety evidence of canagliflozin cannot be generalised to people over 80 years of age as such, because of, for example the high prevalence of comorbidities, susceptibility to orthostatic hypotension and dehydration, and increased prevalence of impaired renal function among elderly people.

Conclusion

Regarding the surrogate endpoints (such as HbA1c, weight or SBP) used in the relevant trials with active comparators, canagliflozin treatment at either dose (100 mg or 300 mg) seems to induce effects that are at least as favorable as those of its comparators, and canagliflozin 300 mg may be even more effective. In particular, the capacity of canagliflozin to reduce weight and SBP by more than its comparators may be beneficial overall in a typical type 2 DM population but the benefits on an individual level may depend on patient characteristics (such as BMI or SBP at baseline). On the other hand, increases in both LDL and HDL cholesterol were seen. The clinical relevance of these findings related to lipids remains unclear.

There is insufficient evidence to determine whether canagliflozin has any relevant effect on long-term outcomes and mortality compared with glimepiride or sitagliptin. The net benefit of canagliflozin treatment compared with its comparators remains unclear and requires trials in which long-term outcomes are assessed.

Canagliflozin was generally well tolerated in the short term; overall rates of AEs were similar to those in patients on placebo. Higher rates of genital mycotic infections, UTIs, pollakiuria/polyuria and osmotic diuresis-related AEs were observed with canagliflozin compared with placebo and active comparator. Severe ascending UTIs were rare. Documented hypoglycaemia was infrequent and occurred significantly less often with canagliflozin compared with glimepiride. Long-term data on canagliflozin side effects are needed to assess, both for rare AEs and the long-term effects of significant glucosuria on the urinary tract. Increased genital (especially in women) and urinary tract infections should be considered in long-term therapy; these AEs may affect patient compliance and quality of life. Important potential risks have already been identified; these include renal impairment/renal failure, clinical consequences of increased haematocrit, bone fractures, photosensitivity, and hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues as well as off-label use for weight loss.

Further important information on the following topics is not yet available: long-term cardiovascular safety, use in patients with congestive heart failure defined as NYHA class IV, use in paediatric patients between 10 and 18 years of age, use in pregnancy, use in nursing mothers, use in very elderly patients (≥ 85 years), use in patients with severe hepatic impairment, and use in patients with severe renal impairment (estimated GFR <30 mL/min/1.73 m²). Therefore, long-term data on canagliflozin safety are needed.

LIST OF ABBREVIATIONS

AE	adverse event
AHA	antihyperglycaemic agent
AUC	area under the concentration-time curve
Ca	calcium
CANVAS	Study DIA3008
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cl	chloride
CrCl	creatinine clearance
C _{max}	maximum plasma concentration
DPP-4	dipeptidyl peptidase-4
GFR	glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GFR	glomerular filtration rate
GLP-1	glucagon-like peptide-1
HbA1c	haemoglobin A1c (glycated haemoglobin)
HDL	high-density lipoprotein
HR	hazard ratio
I ²	I ² heterogeneity index
K	potassium
LDL	low-density lipoprotein
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MACE plus	MACE and hospitalised for cardiovascular events
MAH	marketing authorisation holder
MCS	mental component summary score of SF-36
NA	not applicable
OGTT	oral glucose tolerance test
OR	Odds Ratio
OS	overall survival
PCS	physical component summary score of SF-36
QoL	quality of life
SBP	systolic blood pressure
SD	standard deviation
SF-36	short form (36) health survey
SGLT1	sodium-glucose co-transporter-1
SGLT2	sodium-glucose co-transporter -2
SU	sulphonylurea

type 2 DM	type 2 diabetes mellitus
UGT	uridine diphosphate glucuronyltransferase
UTI	urinary tract infection

1 SCOPE

Description	Project scope
<p>Population</p>	<p>Health condition: type 2 diabetes mellitus (type 2 DM). E11: Type 2 diabetes mellitus includes:</p> <ul style="list-style-type: none"> • diabetes (mellitus) due to insulin secretory defect • diabetes (not otherwise specified) • insulin-resistant diabetes (mellitus) <p>MeSH-terms diseases: Diabetes Mellitus, Type 2: C18.452.394.750.149</p> <p>Population: Adults (≥18 years) with type 2 DM with inadequate glycaemic control on oral antidiabetic therapies and/or insulin</p> <p>Dual therapy: Adults with type 2 DM with inadequate glycaemic control on monotherapy with either metformin or a sulfonylurea.</p> <p>Triple therapy: Adults with type 2 DM with inadequate glycaemic control on dual therapy with either of the following:</p> <ul style="list-style-type: none"> • metformin in combination with a sulfonylurea • metformin or a sulfonylurea in combination with a thiazolidinedione, a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a glucagon-like peptide 1 (GLP-1) agonist. <p>Add-on therapy to insulin: Adults with type 2 DM that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.</p> <p>The present EUnetHTA assessment is focussed on: Adults with type 2 DM with inadequate glycaemic control on oral antidiabetic therapies and/or insulin.</p> <p>Therapeutic indications according to EMA: canagliflozin is indicated for treatment of diabetes mellitus type 2 in adult populations (for individuals of ≥18 years of age), as monotherapy, dual and triple therapy and as an add-on to insulin.</p>
<p>Intervention</p>	<p>Canagliflozin is an inhibitor of subtype 2 sodium-glucose transport protein (SGLT2), doses of 100 mg or 300 mg per day; administered orally.</p> <p>ATC: A10BX11 MeSH-term intervention: canagliflozin [Supplementary Concept] Structure in first source Date introduced: September 28, 2010 Registry number: 0SAC974Z85 Heading mapped to:</p> <ul style="list-style-type: none"> • Glucosides • Thiophenes <p>Entry Terms: 1-(glucopyranosyl)-4-methyl-3-(5-(4-fluorophenyl)-2-thienylmethyl)benzene</p>
<p>Comparison</p>	<p>Dual therapy: For the combination of canagliflozin and metformin, the comparators are:</p> <ul style="list-style-type: none"> • sulphonylureas (with metformin) • pioglitazone (with metformin) • DPP-4 inhibitors (with metformin) • GLP-1 analogues (with metformin) • dapagliflozin (with metformin) <p>For the combination of canagliflozin and sulfonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with sulphonylurea) • DPP-4 inhibitors (with sulphonylurea)

Description	Project scope
	<ul style="list-style-type: none"> • GLP-1 analogues (with sulphonylurea) • dapagliflozin (with sulphonylurea) <p>Triple therapy: For the combination of canagliflozin, metformin and a sulphonylurea, the comparators are:</p> <ul style="list-style-type: none"> • pioglitazone (with metformin + sulphonylurea) • dapagliflozin (with metformin + sulphonylurea) • DPP-4 inhibitors (with metformin + sulphonylurea) • GLP-1 analogues (with metformin + sulphonylurea) <p>For the combination of canagliflozin, metformin and pioglitazone, the comparators are:</p> <ul style="list-style-type: none"> • DPP-4 inhibitors (with metformin and pioglitazone) • GLP-1 analogues (with metformin and pioglitazone) • insulin (with metformin and pioglitazone). <p>For the use of canagliflozin in any other triple therapy regimen, the comparator is</p> <ul style="list-style-type: none"> • insulin (alone or in combination with one or more oral antidiabetic agents). <p>Add-on therapy to insulin</p> <ul style="list-style-type: none"> • One or more oral antidiabetic agents (in combination with insulin). <p>Comparators are chosen according those listed in the evidence-based clinical guidelines, HTA-reports and text-books [American Diabetes Association. 2013; Fauci 2013; Gale 2012; Inzucchi 2012; Scottish Intercollegiate Guidelines Network, 2010; Royal College of Physicians 2008; World Health Organization 2006 and 2011; EUnetHTA method guide on choice of the most appropriate comparators, 2013].</p>
Outcomes	<p>Efficacy</p> <ul style="list-style-type: none"> • HbA1c change (%) • Proportion achieving <7% HbA1c target (%) • Change in fasting plasma glucose (FPG; mmol/L) • Body mass index change • Change in cardiovascular risk factors (including blood pressure and/or serum lipids) • Weight change • Complications of diabetes (e.g., cardiovascular, renal, and eye) • Mortality • Change in insulin requirements (in patients using insulin) • Proportion achieving <7% HbA1c target (%) without hypoglycaemia <p>Safety</p> <ul style="list-style-type: none"> • Most frequent adverse events • Serious adverse events <p>Health-related quality of life</p> <p><i>Outcomes were chosen as commonly used outcomes in diabetes studies (surrogate) and clinical outcomes important for REA, based on recommendations from the EUnetHTA methods guideline on clinical and surrogate endpoints and safety [European Network for Health Technology Assessment (EUnetHTA) 2013]</i></p>
Setting	Any
Study design	RCTs

2 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY

2.1 Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan. Assessment element A0002 has been split into 2 separate questions.

Research questions

The following research questions have been selected and formulated for this domain.

Element ID	Research question
A0002	What is the precise definition of type 2 diabetes mellitus (type 2 DM) and which diagnosis is given to type 2 DM according to ICD-10? What are the main features of type 2 DM?
A0003	What are the known risk factors for type 2 diabetes mellitus (type 2 DM)?
A0004	What is the natural course of type 2 diabetes mellitus (type 2 DM)?
A0005	What is the burden (main symptoms and consequences) of type 2 diabetes mellitus (type 2 DM) for the patient?
A0006	What is the burden of type 2 diabetes mellitus (type 2 DM) for society (prevalence, incidence, costs)?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population? (as A0006)
A0001	For which indication or for what purposes is the canagliflozin used and are there any contraindications?
A0011	How much canagliflozin is used (What is the expected annual use of canagliflozin)?
A0024	How is type 2 DM currently diagnosed according to published guidelines and in practice?
A0025	How is type 2 DM currently managed according to published guidelines and in practice?
A0020	What is the marketing authorisation status of canagliflozin?
A0021	What is the reimbursement status of canagliflozin?

Sources

- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without type 2 diabetes mellitus, Version 1.4, 29 July 2013 (available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>): parts of the text from this recently published rapid REA were re-used for answering some assessment elements.
- Manufacturer's submission file (Johnson & Johnson)
- CHMP report on canagliflozin, redacted version and full version
- SmPC for canagliflozin
- Literature from basic search: the authors searched the relevant literature and trials databases in order to ensure that all relevant evidence for the direct comparisons was included in the marketing authorisation holder (MAH) submission (see Appendix 1: Direct evidence methodologies; Literature review).
- MICROMEDEX Drugdex database 2.0; assessed 1 November 2013

Analysis

The sources were sufficient to answer the questions. We did not perform additional data analysis. No quality assessment of the sources was conducted.

Synthesis

The results are presented in text format, supplemented by overview tables.

2.2 Main results

Definition

Diabetes mellitus is defined as a metabolic disorder of multiple aetiologies characterised by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, World Health Organization 2006]. Several types of diabetes mellitus exist that can be classified into type 1 and type 2 DM, gestational diabetes and other less common forms of diabetes that are caused by genetic defects, endocrine pancreas disorders, endocrinopathies or infections, or that are medication-induced [Rieder 2004] (A0002).

Criteria for the diagnosis of diabetes include one of the following:

- Fasting Plasma Glucose (FPG) ≥ 7.0 mmol/l
- Plasma glucose ≥ 11.1 mmol/l 2 hours after a 75 g oral glucose load (oral glucose tolerance test (OGTT))
- Random blood glucose concentration ≥ 11.1 mmol/l in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis
- HbA1c $> 6.5\%$.

The results should be confirmed by repeated testing unless unequivocal hyperglycaemia is present [American Diabetes Association 2013, Fauci 2013, Gale 2012, World Health Organization 2011] (A00024).

Type 2 DM results from a progressive insulin secretory defect with a variable degree of insulin resistance in the background, resulting in higher levels of glucose in the blood [American Diabetes Association 2013, Fauci 2013, Gale 2012]. People are normally thought to have type 2 DM if they do not have type 1 DM (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. However, there can be uncertainty in the diagnosis, particularly in overweight people of younger age, children or adolescents. The true diagnosis may become more obvious over time [American Diabetes Association 2013, Royal College of Physicians 2008]. According to the ICD-10 classification, the code for type 2 DM is 'E11' [International Statistical Classification of Diseases and Related Health Problems 2013b] (A0002).

Risk factors of type 2 DM

Increasing age, obesity, ethnicity and family history are the four major determinants of type 2 DM, of which being overweight or obese is the main contributing factor, increasing the risk 80-100 fold [Gale 2012]. In addition, having a large waist circumference increases the risk of developing type 2 DM. Men are at high risk if they have a waist circumference of 94–102 cm (37–40 inches). They are at very high risk if it is > 102 cm (> 40.0 inches). Women are at high risk if they have a waist circumference of 80–88 cm (31.5–35.0 inches). They are at very high risk if it is > 88 cm (> 35.0 inches). Some population groups, for example South Asian adults or older people, may be at risk of developing type 2 DM even if they have a BMI lower than the overweight classification [National Institute for Health and Clinical Excellence 2011]. Also, high rates affect people of Middle-Eastern and Hispanic American origin living western lifestyles [Gale 2012] (A0003).

Natural course of type 2 DM

Type 2 DM is preceded by an asymptomatic stage, called prediabetes that is characterised by mild hyperglycaemia, insulin resistance, and early decrements in insulin secretory capacity [Inzucchi 2012]. Under certain circumstances, type 2 DM can lead to acute situations of metabolic disturbance (A0004).

Diabetes is usually irreversible and its late complications result in increased morbidity and reduced life expectancy [Gale 2012, Inzucchi 2012]. In the long term, type 2 DM increases the risk of microvascular damage (retinopathy, nephropathy and neuropathy). Furthermore, it is associated with macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease) [Fauci 2013, Gale 2012, World Health Organization 2006]. Many people with type 2 DM have the same risk of a cardiovascular event as someone without diabetes who has already had their first heart attack; people with diabetes and a previous cardiovascular event are at very high risk – around 10 times that of the average (background) population [Royal College of Physicians 2008] (A0004).

Additionally, type 2 DM is associated with increased risk of further diseases such as cancer, psychiatric diseases, cognitive decline or chronic liver disease [Inzucchi 2012]. The clinical presentation of diabetes can be acute, subacute or asymptomatic. Common symptoms are polyuria, polydipsia, weight loss, thirst, fatigue, weakness, blurred vision, superficial infection, poor wound healing and paraesthesias [American Diabetes Association 2013, Fauci 2013, Gale 2012]. Additionally, type 2 DM is associated with diminished quality of life [World Health Organization 2006] (A0005).

The burden of type 2 diabetes mellitus

Type 2 DM is considered a global health problem. The prevalence of type 2 DM is increasing worldwide as well as in Europe due to the increasing prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis thanks to better cardiovascular risk protection [Royal College of Physicians 2008, World Health Organization 2006]. DM is considered the fifth leading cause of death worldwide [Fauci 2013]. According to the International Diabetes Federation [International Diabetes Federation (IDF) 2013] 366 million people worldwide had diabetes in 2011 and the number is expected to rise to 552 million by 2030. However, 80% of people with diabetes live in low- and middle-income countries. Type 2 DM accounts for 85–95% of all diabetes cases [International Diabetes Federation (IDF) 2013] (A0006).

The WHO stated in 2002 that in Europe 22.5 million people suffer from diabetes, of whom 80–95% have type 2 DM [World Health Organization 2002]. Data for 2011 from the International Diabetes Federation give the considerably higher figure of 52.8 million people (20–79 years) or 8.1% for the European region [International Diabetes Federation (IDF) 2013].

The disease has changed from an ‘old people’s disease’ to a disease afflicting people in the first half of their life [World Health Organization 2002]. The greatest number of people with diabetes is in the 40–59 years age group and, globally (not yet in individual countries), the prevalence in men and women is almost equivalent [International Diabetes Federation (IDF) 2013] (A0006).

The publication of the Global Burden of Disease Study 2010 estimated that 1.3 million deaths were attributable to diabetes in 2010, approximately double the number from 20 years ago. T2DM was ranked 13th, 14th, and 33rd in leading causes of years of life lost in Western, Central, and Eastern Europe, respectively, compared with the global rank of 19 [Lozano 2012].

The costs of diabetes internationally range from 5% to 10% of the total healthcare spending [Rieder 2004, World Health Organization 2002]. A cost-of-illness study that covered 8 European countries estimated annual direct medical costs per patient of € 2834 and total costs of € 29 billion [Jönsson 2002]. Estimates indicate that at least USD 131 billion was spent on healthcare due to diabetes in Europe in 2011, accounting for almost one-third of global healthcare expenditures due to diabetes [International Diabetes Federation (IDF) 2013] (A0006).

Current management

Type 2 DM is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life [Royal College of Physicians 2008]. Type 2 DM is addressed by a combination of several strategies including structured education about lifestyle interventions, psychological interventions, pharmacological management and management of diabetes-related diseases such as cardiovascular diseases, kidney diseases, visual impairment and nerve damage [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines

Network 2010b, Royal College of Physicians 2008]. Updated standards of medical care in diabetes have recently been published by the American Diabetes Association [American Diabetes Association 2013].

Type 2 DM is usually managed in a stepwise approach. With current recommendations, management usually starts with structured education that meets the cultural, linguistic, cognitive and literacy needs of the patient and lifestyle management with non-pharmacological management (e.g. dietary advice, smoking cessation, management of psychosocial distress). This needs to be accompanied by clinical monitoring of blood glucose levels by means of HbA1c [Scottish Intercollegiate Guidelines Network 2010b, Royal College of Physicians 2008] (A0025).

The primary HbA1c goal is <6.5%. A reasonable HbA1c goal for many non-pregnant adults is <7%. HbA1c <8% may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and in those in whom the general goal is difficult to achieve despite all appropriate care [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012]. If the target level of HbA1c is not achieved by non-pharmacological management, pharmacological glucose control therapies are required (biguanides, sulphonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists or insulins). Blood glucose control deteriorates inexorably in most people with type 2 diabetes over a period of years, due to a waning of insulin production. In these circumstances, oral glucose-lowering therapies can no longer maintain blood glucose control and insulin replacement therapy becomes inevitable [Royal College of Physicians 2008].

Metformin (biguanides) is the optimal first-line drug (Box1). If metformin therapy is contraindicated or not tolerated, other drugs can be used in monotherapy. Combination therapy with additional one (dual therapy) or two (triple therapy) oral or injectable agents is reasonable, aiming to minimise side effects of such drug combination where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centred approach should be used to guide the choice of therapy, bearing in mind efficacy, side effects, cost, comorbidities, and patient preferences [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012] (A0025).

Box 1. Pharmacological therapy for type 2 DM

Monotherapy

- Metformin as a first choice (if not contraindicated and if tolerated)
- If it is contraindicated and not tolerated, further drugs could be used:
 - Sulphonylurea
 - Pioglitazone
 - DPP-4 inhibitor.

Dual therapy

- If non-insulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target level over 3–6 months, the second oral agent, GLP-1 receptor agonist or insulin could be added:
- Sulphonylurea
 - Pioglitazone
 - DPP-4 inhibitor
 - GLP-1 agonist
 - Basal insulin.

Triple therapy

- Metformin + sulphonylurea* + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)
- Metformin + thiazolidinedione + sulphonylurea* or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)
- Metformin + DPP-4 inhibitor + sulphonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)
- Metformin + GLP-1 receptor agonist + sulphonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)
- Metformin + insulin (basal: NPH, glargine or detemir) + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist.

Insulin (multiple daily doses)

- NPH: Neutral protamine Hagedorn;

*Meglitinides therapy in case of late postprandial hypoglycaemia during sulphonylurea therapy;
Source: [Inzucchi 2012]

In managing diabetes-related cardiovascular diseases, blood pressure therapy and managing blood-lipid levels play a most important role, starting with lifestyle management followed by antihypertensive medication and lipid-lowering drugs [Scottish Intercollegiate Guidelines Network 2010b, Royal College of Physicians 2008]. Additionally, antithrombotic therapy may be indicated [Royal College of Physicians 2008]. Furthermore, measurement of several laboratory parameters is recommended to detect and monitor diabetes-related kidney disease. Regular structured eye surveillance is recommended to detect eye damage as is enquiry for neuropathic symptoms to detect nerve damage as well as annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations [Scottish Intercollegiate Guidelines Network 2010b, Royal College of Physicians 2008, American Diabetes Association 2013].

Marketing authorisation status

Canagliflozin has recently been approved by the US Food and Drug Administration (FDA) and was given marketing authorisation in Australia on 6 September 2013.

The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the product Invokana (canagliflozin 100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 DM on 19 September 2013. This recommendation was forwarded to the European Commission, which approved the product on 22 November 2013. The applicant for this medicinal product is Janssen-Cilag International N.V. ([A0020](#)).

The indication and contraindications ([A0001](#))

The indication recommended by the CHMP is as follows:

Canagliflozin (Invokana) is indicated in adults aged 18 years and older with type-2 DM to improve glycaemic control as:

- Monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Canagliflozin is contraindicated in patients who are hypersensitive to canagliflozin or to any of the excipients. A pharmacovigilance plan for canagliflozin (Invokana) will be implemented as part of the marketing authorisation. The medicine is to be available only on prescription. Detailed recommendations for the use of this product are described in the summary of product characteristics (SmPC), which is published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

2.3 Discussion

Most patients with type 2 DM require multiple medications; a new mechanism of action with acceptable safety profiles may help patients to achieve and maintain glycaemic control. Canagliflozin presents a new option and could be useful in type 2 DM patients who are obese or have weight gain associated with antidiabetic therapy. Due the different current type 2 DM therapies a patient-centred approach should be used to guide the choice of therapy, bearing in mind efficacy, side effects, cost, comorbidities, and patient preferences.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

3.1 Methods

Domain framing

No deviation was required from the general scope of the project, according to the final project plan.

Research questions

The following research questions have been selected and formulated for this domain.

Element ID	Research question
B0001	What is canagliflozin and the comparator(s) (taking into account different dosages)? And what is the mechanism of action?
B0002	What is the approved indication and claimed benefit of canagliflozin and the evidence-based comparators?
B0003	What is the phase of development and implementation of canagliflozin and the comparator(s)?
B0004	Who performs or administers canagliflozin and the comparators?
B0005	In what context and level of care are canagliflozin and the comparators used?
B0008	There is no need of special premises for canagliflozin
B0009	No specific supplies are needed for canagliflozin
B0010	What kind of data and records are needed to monitor the use of the canagliflozin and the comparators?
B0011	Is the use of registries worthwhile?

Sources

- Manufacturer's submission file (Johnson & Johnson)
- CHMP report on canagliflozin, redacted version and full version
- SmPC for canagliflozin
- Literature from basic search: the authors searched the relevant literature and trials databases in order to ensure that all relevant evidence for the direct comparisons was included in the MAH submission (see Appendix 1: Direct evidence methodologies; Literature review).
- MICROMEDEX Drugdex database 2.0; assessed 1 November 2013
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without type 2 diabetes mellitus, Version 1.4, 29 July 2013, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>

Analysis

The sources were sufficient to answer the questions. We did not perform additional data analysis. No quality assessment of the sources was made.

Synthesis

The results are presented in text format, supplemented by overview tables.

3.2 Main results

Characteristics of canagliflozin

Canagliflozin is an orally active inhibitor of the sodium glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney. The SGLT2 is expressed in the proximal renal tubules, and not in other tissues, and is responsible for the majority of reabsorption into the blood of glucose filtered through the glomerulus. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion (B0001).

Canagliflozin is available in 100 mg and 300 mg film-coated tablets. Canagliflozin 100 mg once-daily orally, should be administered before the first meal of the day. Increasing the dose to 300 mg once daily may be considered if patients are currently tolerating canagliflozin 100 mg once daily, have an estimated glomerular filtration rate (GFR) ≥ 60 mL/min/1.73 m² or a creatinine clearance [CrCl] > 60 mL/min, and require additional glycaemic control.

Canagliflozin should not be initiated in patients with an estimated GFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min. In patients tolerating canagliflozin whose estimated GFR falls persistently below 60 mL/min/1.73 m² or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when estimated GFR is persistently below 45 mL/min/1.73 m² or CrCl persistently below 45 mL/min.

Canagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in such populations (B0001).

Indications

Canagliflozin is indicated in adults aged 18 years and older with type 2 DM to improve glycaemic control as:

- monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- add-on therapy with other antihyperglycaemic medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control (B0002).

Claimed benefit

As indicated by MAH, by inhibiting SGLT2, canagliflozin reduces reabsorption of the glucose filtered by the kidney and thus increases urinary glucose excretion. By promoting glucosuria, canagliflozin treatment reduces hyperglycaemia through an insulin-independent mechanism. Canagliflozin is expected to be effective across the spectrum of beta cells function, providing clinically meaningful glycaemic improvements for patients with new-onset type 2 DM who have only moderate impairment of β -cell function and for patients with greater β -cell functional loss, such as those with long-standing type 2 DM who require insulin.

Increased urinary glucose excretion also translates to osmotic diuresis, with the diuretic effect leading to a reduction in SBP, and to a net loss of calories (4 kcal/g of glucose) and therefore a reduction in body weight (B0002).

Personnel, equipment and precautions

Since canagliflozin is a new oral drug for type 2 DM, treatment should be initiated by physicians experienced in managing patients with diabetes. Although no specific training is required for healthcare professionals, because canagliflozin has a novel mechanism of action that may not be familiar to all healthcare and pharmacy professionals, education may be required for nursing and pharmacy staff (B0004).

All the relevant/important precautions reported by the FDA label and the EMA SmPC on canagliflozin are listed below:

General

Canagliflozin has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients. Canagliflozin should not be used for the treatment of diabetic ketoacidosis as it is not effective in this setting.

Use in patients with renal impairment

The efficacy of canagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. The canagliflozin dose should be limited to 100 mg once daily in patients with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min and canagliflozin should not be used in patients with an eGFR < 45 mL/min/1.73 m² or CrCl < 45 mL/min. Canagliflozin has not been studied in severe renal impairment (estimated GFR < 30 mL/min/1.73 m² or CrCl < 30 mL/min) or end-stage renal disease. If renal function falls persistently below estimated GFR 45 mL/min/1.73 m² or CrCl < 45 mL/min, canagliflozin treatment should be discontinued.

Use in patients at risk for adverse reactions related to volume depletion

Due to its mechanism of action, canagliflozin, by increasing urinary glucose excretion (UGE) induces an osmotic diuresis, which may reduce intravascular volume and decrease blood pressure. Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an estimated GFR < 60 mL/min/1.73 m², patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥ 65 years of age). Canagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g., due to acute illness (such as gastrointestinal illness).

Elevated haematocrit

Haematocrit increase was observed with canagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted.

Elderly (≥ 65 years old)

Elderly patients may be at a greater risk for volume depletion, are more likely to be treated with diuretics, and to have impaired renal function. In patients ≥ 75 years of age, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension) was reported.

Cardiac failure

Experience in New York Heart Association (NYHA) class III is limited, and there is no experience in clinical studies with canagliflozin in NYHA class IV.

Lactose intolerance

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Drug interactions

Coadministration of canagliflozin (a substrate of UGT) with several drugs, such as rifampin, ritonavir, phenobarbital, phenytoin, fosphenytoin (a nonselective inducer of UGT enzymes [including UGT1A9 and UGT2B4]), potentially reduce canagliflozin efficacy. Coadministration of canagliflozin with digoxin increased digoxin AUC and C_{max} by 20% and 36%, respectively (B0004, B0010).

People diagnosed with type 2 DM require access to immediate and ongoing care. Who provides this care, and where and when, will depend on local circumstances, but it needs to be organised in a systematic way. A multidisciplinary approach has been recommended including nurses trained in teaching skills and adult education, and formally trained dietitians and podiatrists within the specifically relevant areas of diabetes care [American Diabetes Association 2013, IDF Clinical Guidelines Task Force 2005] (B0004 and B0005).

Although canagliflozin was still in clinical development when the 2012 position statement from the ADA and EASD on the management of type 2 DM was prepared, many components of this guidance can be used to incorporate canagliflozin into a patient-centred type 2 DM treatment

algorithm: as monotherapy, as part of dual therapy (add-on to metformin or sulphonylurea), as part of triple therapy (add-on to metformin + sulphonylurea or metformin + pioglitazone), and as add-on therapy to insulin with or without other antihyperglycaemic medicinal products.

Canagliflozin is a once-daily, continuous oral therapy, and therefore may be self-administered by the patient at home. Administration of canagliflozin should incur no additional hospital or physician's office visits compared with the administration of comparator agents. Because canagliflozin is administered orally it does not require the use of any special equipment for administration (e.g., needles, syringes, or other injection devices). Treatment with canagliflozin does not require the patient to use any special blood-monitoring equipment, test strips, or other devices (B0004 and B0005).

Drug therapy and lifestyle advice are primarily provided in primary care (B0005). No specific data were retrieved for the use of registries for canagliflozin throughout different countries (B0011).

Comparators

Different pharmacological glucose control therapies are on the market and are included in clinical practice guidelines as monotherapy, dual or triple therapy (biguanides, sulphonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, DPP-4 inhibitors, GLP-1 analogues or insulins). A new class of drugs is available on the EU market, SGLT2 inhibitors, with dapagliflozin as the first drug approved in the class. Canagliflozin, as SGLT2 inhibitors, was approved in USA. Metformin (biguanides) is the optimal first-line drug. If metformin is contraindicated or not tolerated, other drugs could be used: combination therapy with an additional one or two oral or injectable agent is reasonable, aiming to minimise side effects where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.

In this rapid REA further comparators were used in direct and indirect comparisons:

In dual therapy: For the combination of canagliflozin and metformin, the comparators were: sulphonylureas (with metformin); pioglitazone (with metformin); DPP-4 inhibitors (with metformin); GLP-1 analogues (with metformin); dapagliflozin (with metformin).

For the combination of canagliflozin and sulphonylurea, the comparators were: pioglitazone (with sulphonylurea); DPP-4 inhibitors (with sulphonylurea); GLP-1 analogues (with sulphonylurea); dapagliflozin (with sulphonylurea).

In triple therapy: For the combination of canagliflozin, metformin and a sulphonylurea, the comparators were: pioglitazone (with metformin + sulphonylurea); dapagliflozin (with metformin + sulphonylurea); DPP-4 inhibitors (with metformin + sulphonylurea); GLP-1 analogues (with metformin + sulphonylurea);

For the combination of canagliflozin, metformin and pioglitazone, the comparators were: DPP-4 inhibitors (with metformin + pioglitazone); GLP-1 analogues (with metformin + pioglitazone); insulin (with metformin + pioglitazone).

For the use of canagliflozin in any other triple therapy regimen, the comparator was insulin (alone or in combination with one or more oral antidiabetic agents).

In add-on therapy to insulin: One or more oral antidiabetic agents (in combination with insulin).

Canagliflozin has recently been approved by the US Food and drug Administration (FDA) and was given marketing authorisation in Australia on 6 September 2013. The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the product Invokana (canagliflozin 100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 DM on 19 September 2013. This recommendation was forwarded to the European Commission, which approved the product on 22 November 2013. No further information is available concerning the marketing authorisation status of canagliflozin in other countries.

The SGLT2 inhibitors are the newest class of drugs approved for type 2 DM patients. Dapagliflozin is approved for use in the EU for type 2 DM in adults aged ≥ 18 . Empagliflozin has been submitted for marketing approval to FDA and EMA for the treatment of adults with type 2 DM. Ipragliflozin has been submitted for marketing approval in Japan. Several new potential therapies are being evaluated, such as G protein-coupled receptor 119 agonists, free fatty acid receptor 1 activators, inhibitors of 11 β -hydroxysteroid dehydrogenase type 1 and glucokinase activators (B0003).

A patient-centred approach should be used to guide the choice of therapy, bearing in mind efficacy, side effects, cost, comorbidities, and patient preferences [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012] (B0001).

3.3 Discussion

The SGLT2 inhibitors are the newest class of drugs approved for type 2 DM patients, with dapagliflozin as first in the class approved for use in EU. Canagliflozin, as SGLT2 inhibitor, was first approved by FDA in USA.

By promoting glucosuria, canagliflozin treatment reduces hyperglycaemia through an insulin-independent mechanism. Therefore, canagliflozin is expected to be effective across the spectrum of β -cell function, providing clinically meaningful glycaemic improvements both for patients with new-onset type 2 DM who have only moderate impairment of β -cell function and for patients with greater β -cell functional loss, such as those with long-standing type 2 DM who require insulin. These expected benefits are also described both by Micromedex drug details and by FDA Advisory Committee on Canagliflozin.

In this rapid REA different comparators were used in direct and indirect comparisons for canagliflozin use as dual therapy, as triple therapy and as an add-on to insulin therapy, according to recommendations in evidence-based clinical guidelines. Although canagliflozin was still in clinical development when the 2012 position statement from the ADA and EASD on the management of type 2 DM was prepared, many components of this guidance can be used to incorporate canagliflozin into a patient-centred type 2 DM treatment algorithm: as monotherapy, as part of dual therapy (add-on to metformin or sulphonylurea), as part of triple therapy (add-on to metformin + sulphonylurea or metformin + pioglitazone), and as add-on therapy to insulin with or without other oral antidiabetic agents.

Different precautions and clinically important possible drug–drug interactions should be kept in mind when prescribing canagliflozin therapy.

Although no specific data were retrieved for the use of registries with canagliflozin throughout different countries, this could be a valid instrument for collecting additional evidence when needed.

4 SAFETY

4.1 Methods

Domain framing

For safety domain evaluation, only direct data was analysed, including data from the canagliflozin monotherapy study (DIA3005); therefore a slight deviation from the Project Scope was made in this Domain.

Research questions

The following research questions have been selected and formulated for this domain.

Element ID	Research question
C0001	What are the most frequent and serious adverse events in patients on canagliflozin therapy?
C0002	Is there a relationship between the dose of canagliflozin and the most frequent and serious adverse events in special populations?
C0004	How does the frequency or severity of harms change over time in different settings?
C0005	What are the susceptible patient groups that are most likely to be harmed?
C0008	How safe is canagliflozin in relation to the comparator?

Sources

- Manufacturer's submission file (Johnson & Johnson)
- CHMP report on canagliflozin, redacted version and full version
- SmPC for canagliflozin
- Literature from basic search: the authors searched the relevant literature and trials databases in order to ensure that all relevant evidence for the direct comparisons was included in the MAH submission (see Appendix 1: Direct evidence methodologies; Literature review).
- MICROMEDEX Drugdex database 2.0; assessed 1 November 2013
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal–jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>

Analysis

The sources were sufficient to answer the questions, but in case of discrepancies on same data in different sources mentioned above, published articles of RCTs were used as primary source for extraction. We did not perform additional data analysis.

The quality of included trials was assessed using the Cochrane Collaboration risk of bias tool. The criteria included randomisation sequence generation, allocation concealment, blinding, selective outcome reporting, incomplete outcome reporting and other bias (sponsor bias). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the strength of evidence only for three active comparator studies DIA3006, DIA3009, DIA3015 at 52 weeks.

Synthesis

The results are presented in plain text format, supplemented by overview tables.

4.2 Main results

The interpretation of the results and quality of evidence assessments (done only for three active comparator studies DIA3006, DIA3009, DIA3015 at 52 weeks) represent the authors' view which, may differ from the view expressed by the manufacturer.

Canagliflozin leads to dose- and blood glucose-dependent osmotic diuresis with increased urine volume and glucosuria. Resulting adverse events (AEs) observed in the clinical trials are genital infection, urinary tract infections (UTIs), haemoconcentration/dehydration, electrolyte disturbances and arterial hypotension. These are established AEs for SGLT2 inhibitors.

For all but one of safety outcomes (any documented hypoglycaemia in DIA3009 trial), p-values and confidence intervals were not available,

Placebo-controlled trials (C0001)

In the pooled, placebo-controlled trials the proportion of participants who experienced any AEs or serious AEs was similar across treatment groups. The incidence of AEs leading to study discontinuation was low across groups but slightly higher with canagliflozin versus placebo, with no dose relationship. The most commonly reported AEs during treatment with canagliflozin were hypoglycaemia in combination with insulin or a sulphonylurea, vulvovaginal candidiasis, urinary tract infection (UTI), and polyuria or pollakiuria (i.e., urinary frequency). AEs leading to discontinuation of $\geq 0.5\%$ of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of women) and balanitis or balanoposthitis (0.5% of men) [Johnson & Johnson Submission file, 2013, CHMP Assessment report Canagliflozin 2013]. Similar to other glucose-lowering agents that have low hypoglycaemic potential themselves, canagliflozin increases the frequency of hypoglycaemic events when given in combination with insulin or an insulin secretagogue. Even then, however, severe hypoglycaemic events were rare and were observed at a frequency similar to that observed with placebo.

Active comparator trials (C0001, C0008)

The overall incidence of AEs with canagliflozin was generally comparable to that observed with the active comparators over 52 weeks: 64.4%, 68.5%, and 68.5% for canagliflozin 100 mg and 300 mg and glimepiride 6 mg or 8 mg, respectively; and 76.7% and 77.5% for canagliflozin 300 mg and sitagliptin 100 mg, respectively [Cefalu 2013, Schernthaner 2013].

Overall incidences of AEs in participants on background metformin (DIA3006) were slightly higher with canagliflozin 100 mg compared with canagliflozin 300 mg and sitagliptin 100 mg, over 52 weeks (72.3%, 62.7% and 64.5% respectively) [Lavalle-González 2013].

Over 104 weeks in the DIA3009 study, the overall incidence of AEs was slightly lower with canagliflozin 100 mg and similar with canagliflozin 300 mg compared with glimepiride (73.3%, 77.9%, and 78.4%, respectively).

Canagliflozin itself has a low propensity to cause hypoglycaemia. This was especially evident in comparison with glimepiride (incidence of any documented hypoglycaemia was 5.6% vs. 4.9% vs. 34.2.7% in the canagliflozin 100 mg, canagliflozin 300 mg and glimepiride groups, respectively). The incidences of hypoglycaemic events were similar with the two doses of canagliflozin to those with sitagliptin 100 mg [Cefalu 2013, Schernthaner 2013, Lavalle-González 2013].

Genital infections, mainly fungal infections, are clearly increased with canagliflozin use, in comparisons with glimepiride and sitagliptin, especially in women [Cefalu 2013, Schernthaner 2013, Lavalle-González 2013].

There was only a slight increase in UTIs with canagliflozin and no imbalance in serious/severe urogenital infections [Cefalu 2013, Schernthaner 2013, Lavalle-González 2013].

In line with the observed haemoconcentration, increases in serum creatinine and, consequently, decreases in calculated eGFR are observed upon treatment initiation, which are generally

attenuated with continued treatment, are reversible after cessation of treatment and do not indicate renal damage.

Table 1. Summary of adverse events (AE) and adverse events of special interest in placebo-controlled and active comparator trials

	Canagliflozin 100 mg number (%)	Canagliflozin 300 mg number (%)	Comparator number (%)
PLACEBO CONTROLLED			
Pooled placebo-controlled trials (DIA3002, DIA3005, DIA3006, DIA3012) 26 weeks	N = 833	N = 834	Placebo N =646
Any AE	501 (60.1)	494 (59.2)	384 (59.4)
AEs leading to discontinuation	36 (4.3)	30 (3.6)	20 (3.1)
Serious AEs	28 (3.4)	22 (2.6)	22 (3.4)
Death	1 (0.1)	1 (0.1)	2 (0.3)
Any vulvovaginitis	44 (10.4)	49 (11.4)	10 (3.2)
UTIs*	46 (5.5)	34 (4.1)	26 (4.0)
Pooled placebo-controlled trials excluding DIA 3002 (DIA3005, DIA3006, DIA3012) 26 weeks	N = 676	N = 678	Placebo N = 490
Any documented hypoglycaemia	26 (3.8)	29 (4.3)	11 (2.2)
Severe hypoglycaemia, number (%)	1 (0.1)	1 (0.1)	0
ACTIVE COMPARATOR			
Placebo and active comparator (DIA3006) 52 weeks	N = 368 first 26 weeks	N = 367 first 26 weeks	Sitagliptin 100 mg, N = 366; Placebo, N = 183 first 26 weeks
	N = 316 second 26 weeks	N = 321 second 26 weeks	Sitagliptin 100 mg, N = 313; Placebo-Sitagliptin 100 mg, N = 153 second 26 weeks
Any AE	266 (72.3)	230 (62.7)	236 (64.5) 122 (66.7)
AEs leading to discontinuation	19 (5.2)	12 (3.3)	16 (4.4) 8 (4.4)
Serious AEs	15 (4.1)	12 (3.3)	18 (4.9) 7 (3.8)
Death	0	1 (0.3)	1 (0.3) 1 (0.5)
Any documented hypoglycaemia	16 (4.3)	17 (4.6)	5 (1.4)
Severe hypoglycaemia	1 (0.3)	1 (0.3)	0
Genital mycotic infections	f 22 (11.3) / m 9 (5.2)	f 20 (9.9) / m 4 (2.4)	f 5 (2.6) / m 2 (1.2)
UTIs	29 (7.9)	18 (4.9)	23 (6.3)
Active comparator (DIA3009) 52 week	N = 483	N = 485	Glimepiride 6 or 8 mg, N = 482
Any AE	311 (64.0)	332 (69.0)	330 (69.0)
AEs leading to discontinuation	25 (5.0)	32 (7.0)	28 (6.0)
Serious AEs	24 (5.0)	26 (5.0)	39 (8.0)

	Canagliflozin 100 mg number (%)	Canagliflozin 300 mg number (%)	Comparator number (%)
Death	0	2, <1%	2, <1%
Any documented hypoglycaemia	27 (5.6)**	24 (4.9)**	165 (34.2)
Severe hypoglycaemia	2 (0.4)	3 (0.6)	15 (3.1)
Genital mycotic infections	f 26 (11.0) / m 17 (7)	f 34 (14.0) / m 20 (8.0)	f 5 (2.0) / m 3 (1%)
UTIs	31 (6.0)	31 (6.0)	22 (5.0)
Active comparator, background metformin + sulphonylurea (DIA3015) 52 week	NA	N = 378	Sitagliptin 100 mg, N =378
Any AE number (%)	NA	289 (76.7)	293 (77.5)
AEs leading to discontinuation number (%)	NA	20 (5.3)	1 (2.9)
Serious AEs number (%)	NA	24 (6.4)	21 (5.6)
Death number (%)	NA	2 (0.5)	0
Subjects with any documented hypoglycaemia	NA	163 (43.2)	154 (40.7)
Severe hypoglycaemia	NA	15 (4.0)	13 (3.4)
Genital mycotic infections	NA	f 26 (15.3) / m 19 (9.2)	f 7 (4.3) / m 1 (0.5)
UTIs	NA	15 (4.0)	21 (5.6)

Abbreviations: AEs=Adverse events

*UTIs Urinary tract infections

**p<0.0001 compared with the glimepiride group

Safety in special populations (C0002, C0005)

Three phase III clinical trials analysed the efficacy and safety of canagliflozin in special populations with type 2 DM: patients with type 2 DM with stage 3 chronic kidney disease (estimated GFR ≥ 30 and < 50 ml/min/1.73 m²), older people (aged 55–80 years) and patients at cardiovascular risk (ongoing trial).

Patients with type 2 DM with stage 3 chronic kidney disease.

The overall incidence of AEs was generally similar for canagliflozin 100 and 300 mg and placebo (78.9%, 74.2%, and 74.4%, respectively). Changes in measures of renal function were observed in patients with renal impairment (stage 3 chronic kidney disease): decrease in estimated GFR and urinary albumin:creatinine ratio, increase of blood urea nitrogen and progression of albuminuria in the treatment group compared with placebo. However, these changes occurred at the start of canagliflozin use and gradually stabilised over time during follow-up.

The frequencies of certain AEs suggested a dose-related trend in patients with renal impairment: nasopharyngitis, hypotension, back pain, pollakiuria, postural dizziness, orthostatic hypotension, progression of albuminuria, and cardiac and vascular disorders. However these possible trends should be considered with caution because of the limited number of patients involved: 90, 90 and 89 patients treated with placebo, canagliflozin 100 mg and 300 mg respectively [Yale 2013].

Older people (aged 55–80 years)

The incidence of type 2 DM increases with age. The choice of blood glucose lowering agents is limited by the specific safety concerns in this population with greater risks of comorbidities such as cardiovascular complications, renal failure, retinopathy and neuropathy. The overall AE rate was similar: canagliflozin 100 mg (72.2%) and slightly higher with canagliflozin 300 mg (78%) compared with placebo (73.4%). Also AEs leading to discontinuation and AEs related to study drug were higher in the patients treated with canagliflozin 300 mg compared with placebo but

lower in those treated with canagliflozin 100 mg compared with placebo. Serious AEs were not frequent and were lower in both treatment groups compared with placebo. However specific AEs were more frequent in both treatment groups compared with placebo: UTIs, genital mycotic infections, pollakiuria (frequency \approx 5%) and polyuria, postural dizziness and orthostatic hypotension (frequency $<$ 5%).

In these patients total AEs (excluding serious AEs) were slightly more frequent in the canagliflozin 300 mg group compared with canagliflozin 100 mg (41.5% versus 38.2% respectively). Treatment discontinuation due to AE, back pain, UTI and genital mycotic infections occurred more frequently with canagliflozin 300 mg compared with canagliflozin 100 mg. When the frequencies of AEs in older people were compared with those in patients with renal impairment, there were higher rates of discontinuation due to AEs and genital mycotic infections with canagliflozin in older patients compared with patients with renal impairment. Lower incidences of serious AEs occurred in older patients compared with patients with renal impairment both in treatment and placebo groups [Bode 2013].

Patients at cardiovascular risk

Assessment of patients at cardiovascular risk is still ongoing in a clinical trial (CANVAS trial, study start date December 2009, estimated primary completion date March 2017). No definitive conclusions can be drawn. Preliminary data suggest a need for caution in the use of canagliflozin therapy in these patients, although cardiovascular risk does not seem to be dose related. In a cardiovascular meta-analysis performed by the manufacturer across trials (including patients enrolled in the CANVAS trial and patients included in other clinical trials) there was no increased risk with canagliflozin vs. comparator (active or placebo) for the combined cardiovascular endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke known as MACE (major adverse cardiovascular events) or MACE-plus (the latter including MACE and hospitalisation for cardiovascular events). The hazard ratio (HR) for MACE was 0.98 (95% CI: 0.70, 1.37). The same analysis updated to November 2012 showed an increased risk in particular for fatal/nonfatal stroke (HR 1.29; 95% CI: 0.8, 2.09), but the increase was less than that observed in the previous analysis updated to January 2012 (HR: 1.47; 95% CI, 0.83-2.59). Definitive conclusions will be possible only at the end of the ongoing clinical trial. The overall AE rate was slightly higher with canagliflozin 300 mg (73.4%) compared with canagliflozin 100 mg (71.0%) and placebo (69.6%) [Johnson & Johnson Submission file, 2013].

4.3 Discussion

Canagliflozin was generally well tolerated in the short term; overall rates of AEs with canagliflozin were similar to those in placebo groups. Higher rates of genital mycotic infections, UTIs, pollakiuria/polyuria and osmotic diuresis-related AEs such as postural dizziness and hypotension were observed, compared with placebo and active comparator.

Documented hypoglycaemia was infrequent, occurring statistically significantly less often with canagliflozin compared with glimepiride 6 mg or 8 mg. Similar to other glucose-lowering agents that have low hypoglycaemic potential themselves, canagliflozin increased the frequency of hypoglycaemic events when given in combination with insulin or an insulin secretagogue. Even then, however, severe hypoglycaemic events were rare and occurred at a frequency similar to that observed with placebo.

The majority of AEs that occur during canagliflozin treatment are not serious and seem to be manageable. However caution should be taken with special populations: patients with renal impairment, older people and patients at cardiovascular risk. Certain AEs may occur more frequently in these populations, with canagliflozin compared with placebo, and in some cases the increase in frequency may be dose related.

Hyperkalaemia and AEs related to dehydration and hypotension were more frequent in patients with moderate renal impairment. Long-term data on canagliflozin side effects are needed to assess both rare AEs and the long-term effect of significant glucosuria on the urinary tract. Increased genital (especially in women) and UTIs should be considered in long-term therapy; these AEs may affect patient compliance. Little definitive evidence is so far available about AEs in patients at cardiovascular risk. Preliminary data, provided by the manufacturer (a meta-analysis

including patients enrolled in the CANVAS clinical study and patients included in other clinical trials, updated to November 2012) indicated an increased risk in the population at risk in particular for fatal/nonfatal stroke (HR 1.29; 95% CI: 0.8, 2.09). Data from the ongoing clinical trial should help to clarify the evidence.

In the recent systematic review and meta-analysis [Vasilakou 2013], 49 RCTs and 9 extension trials (45 trials (11,232 participants) compared SGLT2 inhibitors with placebo and 13 trials (5175 participants) compared SGLT2 inhibitors with active comparators with the aim of assessing the efficacy and safety of SGLT2 inhibitors in adults with type 2 diabetes. The authors concluded that SGLT2 inhibitors may improve some short-term outcomes in adults with type 2 diabetes, but the effects on long-term outcomes and safety were unclear.

The included trials evaluated different SGLT2 inhibitors, including dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, luseogliflozin, tofogliflozin, ertugliflozin and remogliflozin. Most trials used placebo as the control; the rest used an active comparator (metformin, sitagliptin or sulphonylurea) as monotherapy or add-on treatment; the duration of the intervention ranged from 12 days to 104 weeks; mean HbA1c level at baseline ranged from 6.9% to 9.2%; all but one of the trials excluded patients with severe renal impairment; the sample size ranged from 18 to 1237 participants. Due to the high discontinuation rate or inadequate methods for dealing with missing data most trials had high overall risks of bias and nine trials had unclear overall risks of bias. All but three of the trials had a double-blind design. Fourteen studies had attrition rates that were high (>20%) or unbalanced between treatment groups (where reported). Almost all trials were sponsored by pharmaceutical companies. The quality of evidence was rated as low for the primary outcome, and low or moderate for the remaining outcomes. Compared with active comparators, SGLT2 inhibitors were significantly associated with a higher rate of UTIs (odds ratio (OR) 1.42, 95% CI 1.06 to 1.90; $I^2=25%$, eight trials) and genital tract infections (OR 5.06, 95% CI 3.44 to 7.45; $I^2=0%$; eight trials). The results for cardiovascular outcomes and death were inconclusive. An increase incidence of bladder and breast cancer was found in trials that compared dapagliflozin with controls. Results did not show any differences in incidence of bladder cancer between canagliflozin and control; the same was true on incidence of breast cancer.

Increased genital and urinary tract infections are a class effect of SGLT2 inhibitors. Based on observation of patients with familial renal glucosuria (with mutations of SGLT2) who do not develop significant clinical problems over a long period of time inhibition of SGLT2 is anticipated to be safe. However, results from a recent systematic review mentioned above indicated that there were significant UTIs and genital tract infection problems with these drugs. Also pharmacological inhibition of SGLT2 is not completely specific for SGLT2 and may affect other SGLTs. Clinical data from real-world experience are needed (long-term pragmatic clinical trials and prospective observational studies, in large numbers of patients, including those at higher risk with a prior history of UTIs) [Calado 2011, Clar 2012, Freeman 2013, Neumiller 2010, Nicolle 2012, Santer 2003, Santer 2010, Scholl-Burg 2004].

Further head-to-head comparator trials are needed to determine the role (effectiveness and safety) of SGLT2 inhibitors in relation to other therapeutic options in type 2 DM.

Authors noted some discrepancies on same data in different sources used for this assessment. In such a case published articles of RCTs are used as primary source for data extraction. Recent publications again stressed insufficient information on clinical trials in journal publications and reports posted in clinical trials results registries, but they could supplement each other to overcome the publication and outcome reporting bias. Full clinical study reports provide the most complete information on the large majority of methods and results data items; HTA doers should rely on systematic review of full clinical study reports when they become publicly available to solve the problem of overestimating benefits and underestimating harms [Doshi 2012, Doshi 2013, Eichler 2012, Wiesler 2012].

5 CLINICAL EFFECTIVENESS

5.1 Methods

Domain framing

D0005 has been split up into 9 separate result cards. D0011 has been split up in 2 separate questions and result cards.

Research questions

The following research questions have been selected and formulated for this domain.

Element ID	Research question
D0001	What is the expected beneficial effect of canagliflozin on overall mortality?
D0002	What is the expected beneficial effect of canagliflozin on mortality due to diabetes-related diseases and conditions?
D0005A-I	How does canagliflozin affect the following outcomes? A) HbA1c change (%) (D0005A) B) proportion achieving <7% HbA1c target (%) (D0005B) C) FPG change (mmol/L) (D0005C) D) body mass index change (D0005D) E) blood pressure (D0005E) F) weight change (D0005F) G) insulin requirements change (in patients using insulin) (D0005G) H) proportion achieving <7% HbA1c target (%) without hypoglycaemia (D0005H) I) serum lipids (D0005I)
D0006	How does canagliflozin affect long-term complications of diabetes (e.g. cardiovascular, renal and eye complications)? (D0006)
D0011A-B	A) What is the effect of canagliflozin on patients' global functions: SF-36 Physical functioning, mental health and vitality? (D0011A) B) What is the effect of canagliflozin on patient's global functions: EQ-5D Mobility, anxiety/depression and pain/discomfort? (D0011B)
D0012	What is the effect of canagliflozin on generic health-related quality of life? (D0012)
D0013	What is the effect of canagliflozin on disease-specific quality of life? (D0013)
D0016	How does use of canagliflozin affect activities of daily living? (D0016)
D0017	Was the use of canagliflozin worthwhile? (D0017)

Sources

- Manufacturer's submission file (Johnson & Johnson)
- CHMP report on canagliflozin, redacted version
- CHMP assessment report on canagliflozin
- Comments for indirect comparisons including code and partial data extraction check performed by subcontractor
- Literature from basic search: the authors searched the relevant literature and trials databases in order to ensure that all relevant evidence for the direct comparisons was included in the MAH submission (see Appendix 1: Direct evidence methodologies; Literature review).

Analysis

Analyses include evidence from direct comparisons, indirect comparisons and simulations. The indirect comparisons included canagliflozin, sulphonylureas, GLP-1 agonists, DPP-4 inhibitors, thiazolidinediones, SGLT2 inhibitors, insulin and placebo. Indirect comparisons were performed for the following surrogate endpoints: HbA1c change, proportion of patients achieving HbA1c target, weight, BMI, FPG, SBP. The results for HbA1c change, weight and SBP are presented here. Simulations were represented for long-term outcomes and mortality. Risk of bias, quality of evidence (GRADE) and applicability were evaluated for the phase III canagliflozin trials with active comparators.

Synthesis

Evidence tables and plain text were used to answer the research questions.

5.2 Main results

In this section, an overview of the results concerning mortality and long-term outcomes, surrogate endpoints and quality of life is presented. Unless indicated differently, the evidence below is derived from direct comparisons. All the results are derived from the manufacturer's submission file [Johnson & Johnson, 2013] unless otherwise stated and in such case the additional reference will be provided. In addition, the references included in the indirect comparison are provided in Appendix 1, Table 9. The interpretation of the results and quality of evidence assessments represent the authors' view which may differ from the view expressed by manufacturer.

Durations of studies including active comparators were 52 (DIA3006 and DIA3015) or 104 weeks (DIA3009). Results at 52 weeks, which were available for all active controlled studies, are presented here unless stated otherwise. The appendices include more detailed description of the results derived from direct and indirect comparisons at various time points.

Mortality and long-term outcomes

To date, there seems to be no conclusive evidence about the effects of canagliflozin on overall mortality, disease-specific mortality or long-term outcomes compared with other treatment options (D0001, D0002 and D0006).

According to the simulations based on the CORE diabetes model, life expectancy in the simulation cohort was approximately 23 years. A small gain in life expectancy of approximately 0.5–2 months was achieved with canagliflozin treatment compared with other treatments. The simulations also suggested a minor positive impact of canagliflozin on long-term outcomes compared with other treatments. Severe limitations and uncertainty apply to these results (D0001, D0006).

Surrogate endpoints

The main results of surrogate endpoints at 52 weeks (direct evidence) are summarised in the table below (Table 2). Further results, quality of evidence and the most important results of indirect comparisons are presented as text.

Table 2. Summary of relevant results for surrogate endpoints

	Canagliflozin 100 mg	Canagliflozin 300 mg	Comparator
DIA 3009, 104 weeks, add-on with metformin. Results at 52 weeks (LOCF, mITT)	N = 474	N = 478	Glimepiride 6–8 mg, N = 474
HbA1c change, % - <i>difference vs. glimepiride</i>	-0.82 (0.04) -0.01 (-0.11, 0.09)	-0.93 (0.04) -0.12 (-0.22, -0.02)	-0.81 (0.04)
FPG change, mmol/L - <i>difference vs. glimepiride</i>	-1.4 (0.1) -0.3 (-0.6, -0.1)	-1.5 (0.1) -0.5 (-0.7, -0.3)	-1.0 (0.1)
Proportion achieving HbA1c target of <7.0%	53.6%	60.1%	55.7%
Proportion achieving HbA1c target of <7.0% without hypoglycaemias	50%	57%	33%
Body mass index change	-1.32 (0.07)	-1.46 (0.07)	0.26 (0.07)
Body weight, % change - <i>difference vs. glimepiride</i>	-4.2 (0.2) -5.2 (-5.7, -4.7)	-4.7 (0.2) -5.7 (-6.2, -5.1)	1.0 (0.2)
Systolic BP change, mmHg - <i>difference vs. glimepiride</i>	-3.3 (0.6) -3.5 (-4.9, -2.1)	-4.6 (0.6) -4.8 (-6.2, -3.4)	0.2 (0.6)
LDL cholesterol, % change - <i>Difference vs. glimepiride</i>	9.6 (1.9) 4.5 (0.0, 9.1)	14.1 (1.9) 9.0 (4.4, 13.7)	5.0 (1.9)
Insulin requirements	no data	no data	no data
DIA 3006, 52 weeks, add-on with metformin. Results at 52 weeks (LOCF, mITT).	N = 368	N = 367	Sitagliptin 100 mg N = 366
HbA1c change, % - <i>Difference vs. sitagliptin</i>	-0.73 (0.05) 0.0 (-0.12, 0.12)	-0.88 (0.05) -0.15 (-0.27, -0.03)	-0.73 (0.05)
FPG change, mmol/L - <i>Difference vs. sitagliptin</i>	-1.5 (0.1) -0.5 (-0.7, -0.2)	-2.0 (0.1) -1.0 (-1.2, -0.7)	-1.0 (0.1)
Proportion achieving HbA1c target of <7.0%	41.4%	54.7%	50.6%
Proportion achieving HbA1c target of <7.0% without hypoglycaemias	36%	50%	48%
Body mass index change	-1.21 (0.06)	-1.32 (0.06)	-0.41 (0.06)
Body weight % change - <i>Difference vs. sitagliptin</i>	-3.8 (0.2) -2.4 (-3.0, -1.8)	-4.2 (0.2) -2.9 (-3.4, -2.3)	-1.3 (0.2)
Systolic BP change, mmHg - <i>Difference vs. sitagliptin</i>	-3.5 (0.6) -2.9 (-4.5, -1.3)	-4.7 (0.6) -4.0 (-5.6, -2.4)	-0.7 (0.6)
LDL cholesterol, % change - <i>Difference vs. sitagliptin</i>	7.7 (1.7) 1.7 (-2.8, 6.2)	8.7 (1.8) 2.8 (-1.8, 7.4)	6.0 (1.8)
Insulin requirements	No data	No data	No data
DIA 3015, add-on with metformin + sulphonylurea. Results at 52 weeks (LOCF, mITT).	NA	N = 377	Sitagliptin 100 mg N = 378
HbA1c change, % - <i>Difference vs. sitagliptin</i>	NA	-1.03 (0.05) -0.37 (-0.50, -0.25)	-0.66 (0.05)
FPG change, mmol/L - <i>Difference vs. sitagliptin</i>	NA	-1.7 (0.1) -1.3 (-1.7, -1.0)	-0.3 (0.1)
Proportion achieving HbA1c target of <7.0%	NA	47.6%	35.3%
Proportion achieving HbA1c target of <7.0% without hypoglycaemias	NA	22%	13%
Body mass index change	NA	-0.82 (0.07)	0.06 (0.07)
Body weight % change - <i>Difference vs. sitagliptin</i>	NA	-2.5 (0.2) -2.8 (-3.3, -2.2)	0.3 (0.2)
Systolic BP change, mmHg - <i>Difference vs. sitagliptin</i>	NA	-5.1 (0.7) -5.9 (-7.6, -4.2)	0.9 (0.7)
LDL cholesterol, % change - <i>Difference vs. sitagliptin</i>	NA	11.7 (1.8) 6.4 (1.7, 11.2)	5.2 (1.8)
Insulin requirements	NA	No data	No data

Abbreviations: LOCF= last observation carried forward; NA= not applicable; DIA 3006, 3009 and 3015 refer to certain trial identification numbers.

Continuous data are presented as means and standard errors or 95% confidence intervals as appropriate. Categorical outcomes are presented as proportions in percentages.

HbA1c (D0005A)

Canagliflozin 100 mg in dual therapy (with metformin) was comparable with glimepiride (mean reductions of -0.8% vs. -0.8%, respectively) or sitagliptin 100 mg (-0.7% vs. -0.7%, respectively) in reducing HbA1c values. Additionally, results at 104 weeks indicate that canagliflozin 100 mg is non-inferior to glimepiride (between group difference in change in HbA1c: -0.09%).

Canagliflozin 300 mg induced slightly greater (statistically significant) reductions than did the comparators (mean change: -0.9 % vs. -0.8% compared with glimepiride, and -0.9% vs. -0.7% compared with sitagliptin 100 mg) in dual therapy (with metformin). Additionally, results at 104 weeks indicate that canagliflozin 300 mg is superior to glimepiride (between group difference in change in HbA1c: -0.18%).

In triple therapy (with metformin and sulphonylurea), canagliflozin 300 mg induced statistically significantly greater reduction in HbA1c compared with sitagliptin 100 mg (mean change: -1% vs. -0.7%, respectively). The between-treatment differences in HbA1c in comparisons between canagliflozin 300 mg and glimepiride or sitagliptin were 0.12% and 0.15-0.37%, respectively.

For the direct evidence on HbA1c change, the risk of bias was evaluated as high and the quality (level) of evidence as moderate referring to that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Indirect comparisons at 52 weeks suggest that in dual therapy (with metformin) liraglutide 1.2 mg and 1.8 mg might be more effective than canagliflozin 100 or 300 mg in reducing HbA1c. In addition, canagliflozin 300 mg might be more effective than canagliflozin 100 mg, sitagliptin 100 mg and saxagliptin 5 mg. Additionally, indirect comparisons at 104 weeks suggested that canagliflozin 300 mg might be more effective than gliptins and sulphonylurea. In triple therapy (with metformin and sulphonylurea) at 26 weeks, the results suggest that canagliflozin 300 mg might be more effective than canagliflozin 100 mg and linagliptin 5 mg. Indirect comparisons have well known limitations (see e.g. EUnetHTA guideline: Comparator and comparisons), and consequently the quality of such evidence is very low referring to that we are very uncertain about the estimate.

Fasting plasma glucose (D0005C)

As with HbA1c, in dual therapy (with metformin) canagliflozin 100 mg and 300 mg, seemed to induce statistically significantly greater reductions in fasting plasma glucose (FPG) than did glimepiride (-1.4 vs. -1.5 vs. -1.0 mmol/L, respectively) or sitagliptin 100 mg (-1.5 vs. -2.0 vs. -1.0 mmol/L, respectively) at 1 year.

A similar statistically significant finding was obtained in a trial comparing canagliflozin 300 mg with sitagliptin 100 mg in triple therapy with metformin and sulphonylurea (reductions -1.7 vs. -0.3 mmol/L, respectively).

In the case of FPG change the risk of bias was evaluated as high and the quality (level) of evidence as moderate referring to that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. The results of the indirect comparisons can be found in the result card.

Proportion of patients achieving HbA1c target < 7% (D0005B)

Canagliflozin 100 mg in dual therapy (with metformin), was associated with similar proportions of participants achieving the HbA1c target during the trial compared with glimepiride (54% vs. 56%, respectively) but not compared with sitagliptin 100 mg (41% vs. 51%, respectively).

Canagliflozin 300 mg in dual therapy (with metformin) was associated with a similar proportion of participants achieving the HbA1c target compared with glimepiride (60% vs. 56%, respectively). Added to metformin, canagliflozin 300 mg was associated with a slightly greater proportion of

patients achieving the HbA1c target when compared with sitagliptin 100 mg (55% vs. 51%, respectively).

In triple therapy (with the metformin-sulphonylurea combination) canagliflozin 300 mg seemed to be associated with a greater proportion of participants achieving the HbA1c target compared with sitagliptin 100 mg (48% vs. 35%, respectively).

For this outcome, the risk of bias was evaluated as high and the quality (level) of evidence as low referring to that we are very uncertain about the estimate. The results of the indirect comparisons can be found in the result card.

Proportion of patients achieving HbA1c target < 7% without hypoglycaemias (D0005H)

The composite endpoint of HbA1c < 7.0% without hypoglycaemias seems to be reached more often with canagliflozin 100 mg or 300 mg treatment than with glimepiride treatment, when these are added to metformin (50% vs. 57% vs. 33%, respectively).

In dual therapy (with metformin), canagliflozin 100 mg seems to be less effective than sitagliptin 100 mg, whereas canagliflozin 300 mg seems to be at least as effective as sitagliptin 100 mg (36% vs. 48% vs. 50% with canagliflozin 100 mg, sitagliptin 100 mg, and canagliflozin 300 mg treatments, respectively).

In triple therapy (with metformin and sulphonylurea), canagliflozin 300 mg resulted in this outcome (HbA1c < 7.0% without hypoglycaemia) more often compared with sitagliptin 100 mg (22% vs. 13%, respectively).

For this composite outcome, the risk of bias was evaluated as high and the quality (level) of evidence as low referring to that we are very uncertain about the estimate.

Body mass index (D0005D)

In dual therapy (with metformin) canagliflozin seemed to induce a decrease of slightly over 1 kg/m² in body mass index (BMI) whereas glimepiride was associated with a slight increase in BMI (-1.3, -1.5 kg/m² and 0.3 kg/m² for canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride, respectively).

In dual therapy (with metformin) canagliflozin was somewhat more effective in reducing BMI compared with sitagliptin 100 mg (-1.2 vs. -1.3 vs. -0.4 kg/m² for canagliflozin 100 mg, canagliflozin 300 mg, and sitagliptin, respectively).

In triple therapy (with metformin and sulphonylurea), canagliflozin 300 mg resulted in a small reduction in BMI whereas sitagliptin 100 mg seemed neutral in this regard (-0.8 vs. 0.1 kg/m², respectively). The use of sulphonylurea seemed to modify (decrease) the effect of canagliflozin (300 mg) on BMI.

For the direct evidence on BMI change, the risk of bias was evaluated as high and the quality (level) of evidence as low referring to that we are very uncertain about the estimate. The results of the indirect comparisons can be found in the result card.

Weight (D0005F)

In dual therapy (with metformin), canagliflozin at either dosage seems to result in statistically significant weight reduction of approximately 4-5 %, which was greater than that induced by glimepiride (1% increase) or sitagliptin (1% decrease). Additionally, the observed body weight changes were sustained in dual therapy over the 104-week treatment period compared with glimepiride.

In triple therapy (with metformin and sulphonylurea) canagliflozin 300 mg seemed to result in weight loss (mean of 2.5%, 2.3 kg) whereas with sitagliptin 100 mg (added to metformin and sulphonylurea) no clear weight change was observed (increase of 0.3 kg). The difference

between treatments was statistically significant. Use of sulphonylurea may modify the effect of canagliflozin on weight.

For the direct evidence on weight change, the risk of bias was evaluated as high and the quality (level) of evidence as moderate referring to that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Indirect comparisons at 52 weeks suggest that in dual therapy (with metformin), canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, vildagliptin 50 mg, glimepiride, glipizide and pioglitazone 30 mg in reducing weight. In addition, canagliflozin 300 mg might be more effective than canagliflozin 100 mg. Additionally, indirect comparisons at 104 weeks suggested that canagliflozin 100 and 300 mg might be more effective than gliptins and sulphonylurea. In triple therapy (with metformin and sulphonylurea) at 26 weeks there is no clear evidence on differences in weight change between the treatments (the estimates are imprecise). The limitations of indirect comparisons are well known (see e.g. EUnetHTA guideline: Comparator and comparisons), and consequently, the quality of such evidence is very low referring to that we are very uncertain about the estimate.

Systolic blood pressure (D0005E)

In dual therapy (with metformin), canagliflozin seems to induce a statistically significantly greater decrease in systolic blood pressure (SBP) compared with glimepiride or sitagliptin 100 mg (-3 mmHg, -5 mmHg, no change, and -1 mmHg at 52 weeks for canagliflozin 100 mg, canagliflozin 300 mg, glimepiride, and sitagliptin, respectively). At 104 weeks, systolic blood pressure increased slightly from week 52 in all the treatment groups in dual therapy but the differences between canagliflozin 100 and 300 mg compared with glimepiride remained quite similar.

In triple therapy (with metformin and sulphonylurea) canagliflozin 300 mg treatment resulted in a statistically significantly greater decrease in SBP compared with sitagliptin 100 mg (-5 mmHg compared with increase of 1 mmHg, respectively).

The risk of bias was evaluated as high and the quality (level) of evidence as low referring to that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Indirect comparisons at 52 weeks suggest that in dual therapy (with metformin), canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, liraglutide 1.2 mg and glimepiride in reducing SBP. Additionally, indirect comparisons at 104 weeks suggested that canagliflozin 100 and 300 mg might be more effective than sulphonylurea. In triple therapy (with metformin and sulphonylurea) the results at 26 weeks suggest that canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg in reducing SBP. The limitations of indirect comparisons are well known (see e.g. EUnetHTA guideline: Comparator and comparisons), and consequently, the quality of such evidence is very low referring to that we are very uncertain about the estimate.

Lipids (D0005I)

Both HDL and LDL cholesterol seem to show a tendency to increase with canagliflozin treatment. In dual therapy (with metformin), canagliflozin 100 mg and 300 mg increased LDL cholesterol more than glimepiride (approximate increases of 10% vs. 14% vs. 5%, respectively). The absolute increases were 0.14, 0.24 and 0.06 mmol/L, respectively.

In dual therapy (with metformin), when compared with sitagliptin, the corresponding increases in LDL were approximately 8%, 9%, and 6% for canagliflozin 100 mg, canagliflozin 300 mg, and sitagliptin 100 mg, respectively.

In triple therapy (with metformin and sulphonylurea), canagliflozin 300 mg induced an increase of approximately 12% in LDL cholesterol compared with a 5% increase for sitagliptin 100 mg treatment.

For the direct evidence on changes in lipids, the risk of bias was evaluated as high and the quality (level) of evidence as low referring to that we are very uncertain about the estimate.

Insulin requirements (D0005G)

An outcome of interest was the change of insulin requirements during canagliflozin treatment, but no data for this outcome were available in the MAH submission file.

Patient reported outcomes and quality of life

Canagliflozin or its comparators did not have any relevant effect on functional ability or general health-related quality of life during the follow-up of, at most, 1 year.

Canagliflozin or its comparators had no effect on functional ability and global functions such as physical functioning, mental health and vitality in SF-36 (D0011A) and mobility, anxiety/depression and pain/discomfort in EQ-5D (D0011B) (See Results cards for more details).

General health-related quality of life, as described by the physical component summary score of SF-36, did not change during 52 weeks of treatment: on dual therapy (with metformin), mean changes in the scores for the comparison of canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg were 1.0 and 0.8 and 0.4, respectively, and for the comparison of canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, were 1.2, 1.7 and 0.9, respectively. In triple therapy (with metformin and sulphonylurea), mean changes for canagliflozin 300 mg and sitagliptin 100 mg were 0.9 and -0.1, respectively. The baseline scores were approximately 47 to 49. (D0012)

Likewise, the mental component summary scores of SF-36 were unchanged during 52 weeks of treatment: on dual therapy (with metformin), mean changes for canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg were 0.6 and -0.1 and 1.0, respectively, and for canagliflozin 100 mg, canagliflozin 300 mg and glimepiride 0.7, 1.1 and 0.2, respectively. In triple therapy (on metformin and sulphonylurea), mean changes for canagliflozin 300 mg and sitagliptin were 1.1 and -0.4, respectively (D0012).

No evidence was available about disease-related quality of life, activities of daily living and patient satisfaction with the use of canagliflozin (D0013, D0016, D0017).

Subgroup analyses

The add-on use of canagliflozin has been studied in people with moderate renal impairment (glomerular filtration rate of 30–49 ml/min/1.73 m²), in older adults (55 to 80 years) and in people at high cardiovascular risk. However, these trials are or were placebo controlled and therefore outside the scope of the comparative efficacy assessment. At present, there is no evidence concerning the efficacy of canagliflozin compared with glimepiride or sitagliptin in these clinically important subgroups (see discussion in D0005A). Additional data can be found in the safety domain.

5.3 Discussion

Mortality and long-term outcomes

Evidence of effects on mortality and long-term outcomes is highly important for REA. However, to date, there seems to be no conclusive evidence about the effects of canagliflozin on overall or disease-specific mortality or long-term outcomes compared with other treatment options. Overall, the duration of studies conducted in the canagliflozin program is too short to provide reliable evidence about effects on mortality and long-term outcomes. Further studies (or results) with longer follow-up times are needed in order to assess the effects of canagliflozin on overall mortality, mortality due to diabetes-related diseases and long-term outcomes.

Attempts to model the effects on mortality and long-term outcomes were made by the MAH. In principle the approach taken is supported by the EUnetHTA guidelines in this case, even though there are limitations in transparency. Since the results are based on simulation and demonstrate only minor differences in life expectancy or long-term outcomes between treatments, strong conclusions based on these results should be avoided.

Surrogate endpoints

The ability of an antidiabetic drug to improve patients' prognoses or to reduce the rate of diabetic complications is pivotal. Recent meta-analyses have raised the question of the actual role of intensive glucose control in preventing these complications [Boussageon et al 2011, Coca et al 2012, Hemmingsen et al 2011]. Many other factors are also important for the development of diabetic complications, such as blood pressure and possibly lipids. Therefore, for any given antidiabetic drug, long-term trials are needed addressing directly the effects of the drug on clinical outcomes.

However, surrogate endpoints are accepted to be used in clinical trials as they are expected to predict clinical benefit. HbA1c is the most widely accepted measure of long-term diabetes control [EMA 2012]. Fasting plasma glucose has also been accepted as secondary efficacy endpoint [EMA 2012]. A new antidiabetic drug is also preferred to display a neutral or beneficial effect on parameters related to cardiovascular risk.

Regarding the surrogate endpoints used in the relevant trials, canagliflozin treatment (at either dose) seems to induce effects that are at least as favourable as those of its comparators, and canagliflozin 300 mg may be even more effective. Its ability to reduce weight/BMI and SBP may also be beneficial. On the other hand, increases in both LDL and HDL cholesterol were seen. The clinical relevance of these findings related to lipids remains unclear. On an individual level, canagliflozin's ability to reduce SBP may have different implications depending on the baseline SBP of the patient. The net benefit of canagliflozin treatment compared with its comparators remains unclear and requires trials in which long-term outcomes are assessed.

Patient reported outcomes and quality of life

Effects on quality of life, functional ability and activities of daily living are important aspects of the medication of chronic diseases. Canagliflozin seems to have no or at most a marginal effect on these outcomes. Furthermore, there seems to be no difference between the effects of canagliflozin, sitagliptin and glimepiride in dual or triple therapy. However, findings from studies with a follow-up of a year or less and with remarkable losses to follow-up are not predictive enough when long-term medication is under consideration.

General notes

The overall validity of the evidence is challenged by some issues. The proportion of missing data is considerable as the percentage of discontinuations was high across all trials. The use of pivotal off-study medications has not been reported in sufficient detail, which leads to uncertainties in the individual effects of canagliflozin treatment on several important outcomes. Glucose measures, including hypoglycaemias, weight/BMI, lipids and blood pressure, are all influenced by many other factors, such as concomitant therapies and life-style factors. These were not restricted in the relevant trials. Increasing the glucose concentration of urine and the subsequent increase in urine volume due to osmotic diuresis was associated with an increased incidence of genital infections in women and in pollakiuria. These symptoms and events may have made it possible to deduce the treatment assignment. This may have affected the treatment of the participants as a whole, in spite of initially successful blinding during the trials.

The trial populations represent middle-aged patients except in the trials on postmenopausal women and patients with renal impairment. The majority of the patients were closer to the lower boundary of HbA1c for inclusion (7%) than the upper one (9.5–10.5% depending on the trial).

Patients with a history of severe hypoglycaemia, major cardiovascular event, unstable blood pressure, renal or liver impairment were excluded. Concomitant medications are reported for 3 trials (DIA3006, DIA3009, DIA3015): about 50–65% of the participants were using agents that act on the renin–angiotensin system, about 30–40% antithrombotic drugs, and about 40–55% lipid-modifying agents, implying that the participants were also at increased risk for cardiovascular disease due to hypertension and hypercholesterolemia. Of the patients, 19–33% had microvascular complications, and the duration of diabetes was on average less than 10 years.

Thus, the trial participants seem to represent a relatively healthy group of patients with diabetes so caution is needed when generalising the findings to the usual range of diabetic patients.

The evidence concerning effects of canagliflozin treatment compared with an active comparator in people with renal impairment is limited. According to placebo-controlled studies, the ability of canagliflozin to decrease HbA1c levels is much diminished in people with an estimated GFR < 45 mL/min/1.73 m². This is consistent with the mechanism of action of canagliflozin.

The effects of canagliflozin treatment compared with an active comparator in elderly people remain unclear, as the mean age in the three pivotal trials was 55.4–56.7 years (with SDs of slightly over 9). There is no evidence on the effects of canagliflozin treatment in people over 80 years of age, as they were excluded from the trials. The effectiveness and safety evidence of canagliflozin cannot be generalised to people over 80 years of age as such, because of, for example, the high prevalence of comorbidities, susceptibility to orthostatic hypotension and dehydration, and increased prevalence of impaired renal function among elderly people. In the recent systematic review and meta-analysis [Vasilakou et al. 2013], which aimed to assess the efficacy and safety of SGLT2 inhibitors in adults with type 2 diabetes, the authors concluded that SGLT2 inhibitors may improve some short-term outcomes in adults with type 2 diabetes, but the effects on long-term outcomes and safety were unclear. In principle the conclusions drawn in this review (Vasilakou et al. 2013) support the conclusions of the present assessment in terms of effectiveness. However, the present results cannot be directly compared with those of the review because of the choice of comparator, and the pooling of substances and doses in some cases.

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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Pilot assessment using the HTA Core Model[®] for Rapid Relative Effectiveness Assessment

CANAGLIFLOZIN FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

Version 1.3, February 2014

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE THAT WAS USED

Methods

Project approach and method in the Project plan

Project approach and method

Project was primarily based on the MAH's (Janssen-Cilag International N.V., pharmaceutical companies of Johnson & Johnson) submission file. Direct evidence included in the MAH's submission file was checked for completeness against published literature. The systematic literature search concerning indirect evidence was partly reviewed. Risk of bias was evaluated using the Cochrane risk of bias checklist and the EUnetHTA methods guidelines for studies and this forms the basis for the direct evidence assessment. Direct evidence related to efficacy and safety was assessed by using the GRADE-methodology as this methodology allows for a transparent summary of the evidence in a qualitative manner. Indirect comparison methodology and mixed treatment comparisons (MTC) used for relative effectiveness as well as the methodology used for extrapolation from intermediate to final endpoints with the CORE diabetes model was reviewed according EUnetHTA methods guidelines. Statistical methodology for indirect comparisons was checked by the subcontractor.

Direct evidence methodologies

Literature review

Authors' notes:

In order to check whether all relevant evidence for the direct comparisons was included in the MAH submission and up-to-date, authors performed a new search in the following databases: PubMed (33 hits), Cochrane Library (3 hits), clinicaltrials.gov (58 hits), the metaRegister of Controlled Trials (28 hits), the Australian and New Zealand Clinical Trials Registry (5 hits), The World Health Organization International Clinical Trials Registry platform (117 records for 52 trials) and The EU Clinical Trials Register (10 hits). The search word used was canagliflozin in all these databases with no restrictions. The search was performed on 3rd July 2013. Update was performed on the 1st November 2013.

In the original search performed by MAH, phase I trials were excluded. We identified one trial (DIA2001, NCT00642278, Nyirjesy et al 2012, Nicolle et al 2012, Rosenstock et al 2012) comparing canagliflozin (several doses) with placebo and sitagliptin. This phase II trial lasted 12 weeks and as a monotherapy trial it is not relevant in the current assessment. Several trials comparing canagliflozin treatment with placebo were identified as well as one trial comparing canagliflozin with metformin as monotherapy (DIA3011, NCT01809327). New published articles was found (with update literature search) and used, in addition to already published, for Evidence Tables in Safety Domain.

The European Public Assessment Report (EPAR) and the Summary of Product Characteristics (SmPC) were used also as a source of data for this assessment.

Mainly for the first domain in this assessment, parts of the text appropriate for answering assessment elements questions were re-used from recently published rapid REA: EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without type 2 diabetes mellitus, Version 1.4, 29 July 2013 (available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>).

Analysis methods

[Johnson & Johnson submission file 2013]:

Direct comparisons of the long-term (52- or 104-week) **efficacy results** (non-inferiority and superiority) of the use of canagliflozin as add-on to metformin monotherapy (DIA3009 and DIA3006) and as add-on to dual therapy with metformin plus sulphonylurea (DIA3015) were performed versus glimepiride (DIA3009) and sitagliptin (DIA3006 and DIA3015), respectively. All reported efficacy analyses are based on the modified intent-to-treat (mITT) populations, which (marginally) differ from ITT, as patients randomised but not initiated on the study medication are excluded (only 2 patients in the glimepiride arm in study DIA3009, and 1 patient in the canagliflozin arm in DIA3015). For the analysis of change from baseline values for all endpoints, only patients with ≥ 1 post-baseline value could be included.

Additionally, results account for potential confounding effect of baseline and the study stratification factors via modelling. Analysis of continuous efficacy variables was based on an analysis of covariance (ANCOVA) model with treatment and stratification factors (whether or not a subject underwent the metformin dose stabilization/AHA washout period prior to run-in, and country) as fixed effects, and the corresponding baseline value as a covariate.

Primary efficacy results were generated using the last observation carried forward (LOCF) method for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred. Regulatory agencies have traditionally viewed LOCF as the preferred method of analysis, considering it likely (but not certain) to be conservative. An alternative approach for the analysis of longitudinal data is the mixed model repeated measures (MMRM) method, which takes into account all observed data without having to impute any imputation. As there is increasing consensus in the statistical community on the superiority of MMRM over LOCF, all efficacy parameters have additionally been analysed using MMRM, a restricted maximum likelihood (REML) repeated measures approach using the mITT analysis set. The MMRM model included the fixed, categorical effects of treatment, stratification factors, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline value and baseline-by-visit interaction (with unstructured covariance to model the within-subject errors).

For **Safety** Domain evaluation, only direct data was analysed, including data from canagliflozin monotherapy study (DIA3005); therefore slight deviation from Project Scope was done in this Domain. In total, two safety data sets were created by compiling different patient populations, see Table 1 below. In Longer term Exposure Broad data set results from DIA 3015 study were analysed also. Data from RCTs conducted in special population (with moderate renal impairment, in older patients and in patient with CV risk) were analysed separately.

Phase II trials were not included in these data pools because the largest phase II trials were dose finding studies so most patients received different canagliflozin doses than in the phase III trials.

Independent data extraction was done from scientific publications and publicly available register ClinicalTrials.gov with both, study protocol registration and results registration data (Evidence Tables in C0001). Data from canagliflozin CHMP Report (EPAR) was based on four safety data sets, see Table 2. Data from Manufacturer JJ submission file was presented also. In case of discrepancies on same data in different sources mentioned above, published articles of RCTs are used as primary source for extraction. The overall quality of evidence using GRADE methodology was assessed only for three active comparator trials, DIA3006, DIA 3009, DIA3015, at 52 weeks.

Table 1. Data sets and individual RCTs conducted in special population

Data sets and individual RCTs conducted in special population		
Placebo-Controlled Studies Dataset Includes the 26-week placebo controlled Phase III studies	DIA3002, DIA3005,a DIA3006,b DIA3012	Evaluate the safety and tolerability of canagliflozin based upon a large subject sample by pooling placebo-controlled Phase III studies of generally similar design
Longer-term Exposure Broad Dataset	DIA 3009, DIA 3015, DIA 3002, DIA 3005,	Longer-term exposure dataset to provide information on safety with longer exposure; to evaluate selected adverse

Data sets and individual RCTs conducted in special population		
52-weeks, all, Active- and Placebo-controlled studies	DIA 3006, DIA 3012, DIA 3004, DIA 3008, DIA 3010	events occurring with low incidence (e.g., skin photosensitivity, specific malignancies)
RCTs in special population		
Moderate renal impairment	DIA 3004	Evaluate safety and tolerability within a special population of subjects with renal insufficiency with eGFR ≥ 30 to < 60 mL/min/1.73m ²
Older patients	DIA 3010	Evaluate safety and tolerability within a special population of older patients
In patients with CV risk	DIA 3008	Evaluate safety and tolerability within a special population with CV risk

a: excluding the high glycaemic substudy

b: excluding sitagliptin treatment group

Table 2. Committee for Medicinal Products for Human Use (CHMP) Report Safety Datasets

Dataset Name	Dataset Description	Studies Pooled	Objectives
Placebo-Controlled Studies Dataset (ISS Dataset 1 [DS1])	Includes the 26-week placebo controlled Phase III studies	DIA3002, DIA3005,a DIA3006,b DIA3012	Evaluate the safety and tolerability of canagliflozin based upon a large subject sample by pooling placebo-controlled Phase III studies of generally similar design
Moderate Renal Impairment Dataset (ISS Dataset 2 [DS2])	Subjects with baseline eGFR ≥ 30 to < 60 mL/min/1.73m ²	DIA3004 and subgroups from DIA3005, DIA3008, DIA3010	Evaluate safety and tolerability within a special population of subjects with renal insufficiency with eGFR ≥ 30 to < 60 mL/min/1.73m ²
Broad Dataset (ISS Dataset 3 [DS3])	All Active- and Placebo-controlled studies	DIA3002, DIA3004, DIA3005,a DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	Large pooled dataset from controlled clinical studies (active and placebo-controlled) to identify less common safety signals, and to support safety assessments in the Placebo-Controlled Studies Dataset (DS1).
Longer-term Exposure Broad Dataset (ISS Dataset 4 [DS4])	All Active- and Placebo-controlled studies	DIA3002, DIA3004, DIA3005,a DIA3006, DIA3008, DIA3009	Longer-term exposure dataset to provide information on safety with longer exposure, and to support safety assessments in the Placebo-Controlled Studies Dataset (DS1); to evaluate selected adverse events occurring with low incidence (e.g., skin photosensitivity, specific

Dataset Name	Dataset Description	Studies Pooled	Objectives
		DIA3010, DIA3012	malignancies) and events undergoing adjudication (including CV events).

a DIA3005: Excluding the high glycaemic substudy

b DIA3006: Excluding sitagliptin treatment group

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013.

Discussion

The literature search for direct comparison evidence can be considered adequate and up-to-date. We did not identify any new published or registered trials to be included in the clinical effectiveness assessment (only new published articles based on RCTs presented in Manufacturer submission folder and canagliflozin CHMP report was found with update search).

For Safety Domain, with update search, we found new published articles based on RCTs presented in Manufacturer submission folder and canagliflozin CHMP report. These data were used also for Evidence tables in Safety Domain (C0001).

Indirect comparison methodologies

Literature review

Authors' note:

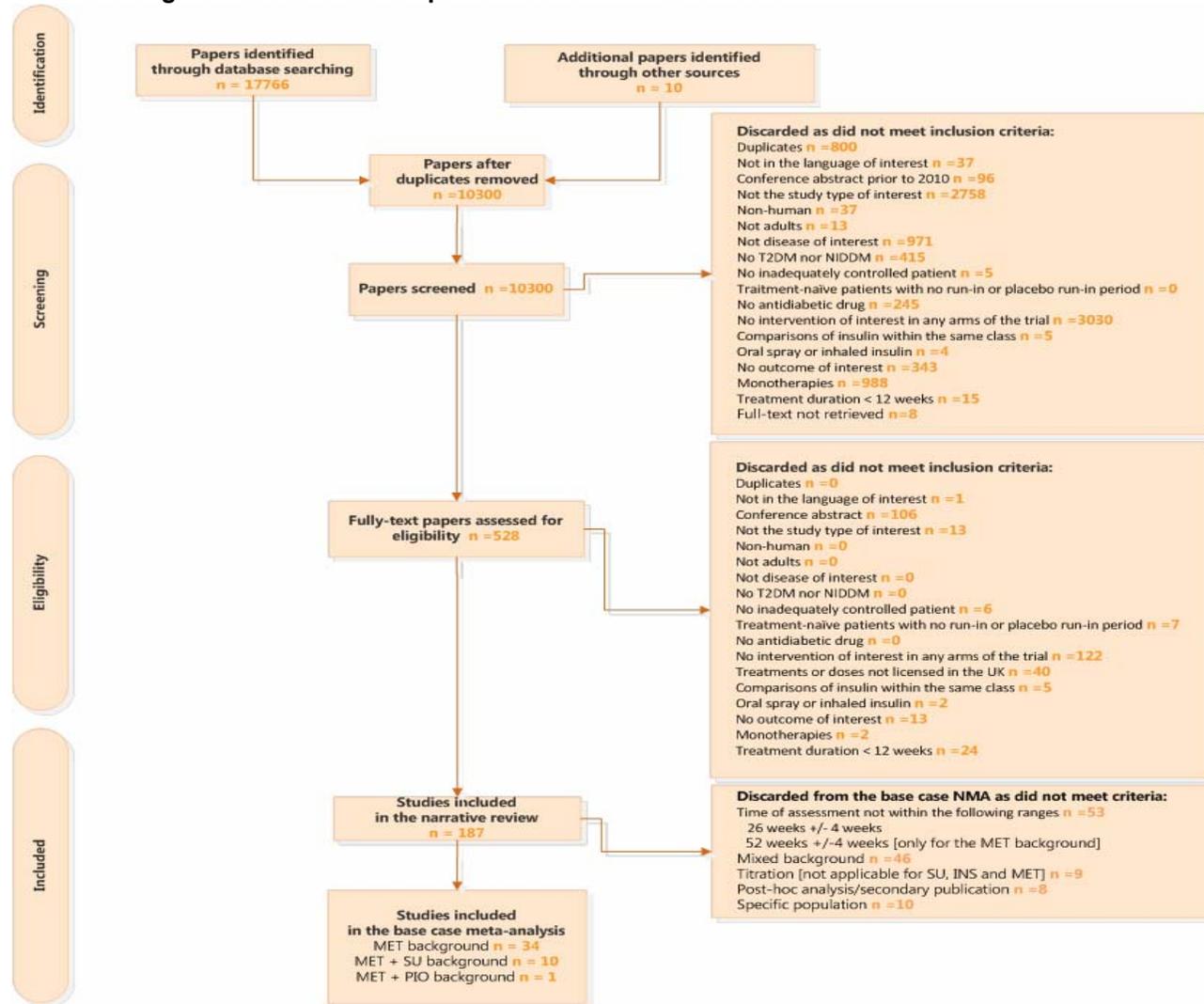
MAH presented an extensive and tractable literature search according to the PICO of the assessment (Figure 1). The search was originally intended for NICE submission. Only articles in English were included. Details of the search are not described here. The PRISMA diagram for the original literature search performed for MAH submission [Johnson & Johnson 2013] is presented below.

Networks of evidence

Authors' note:

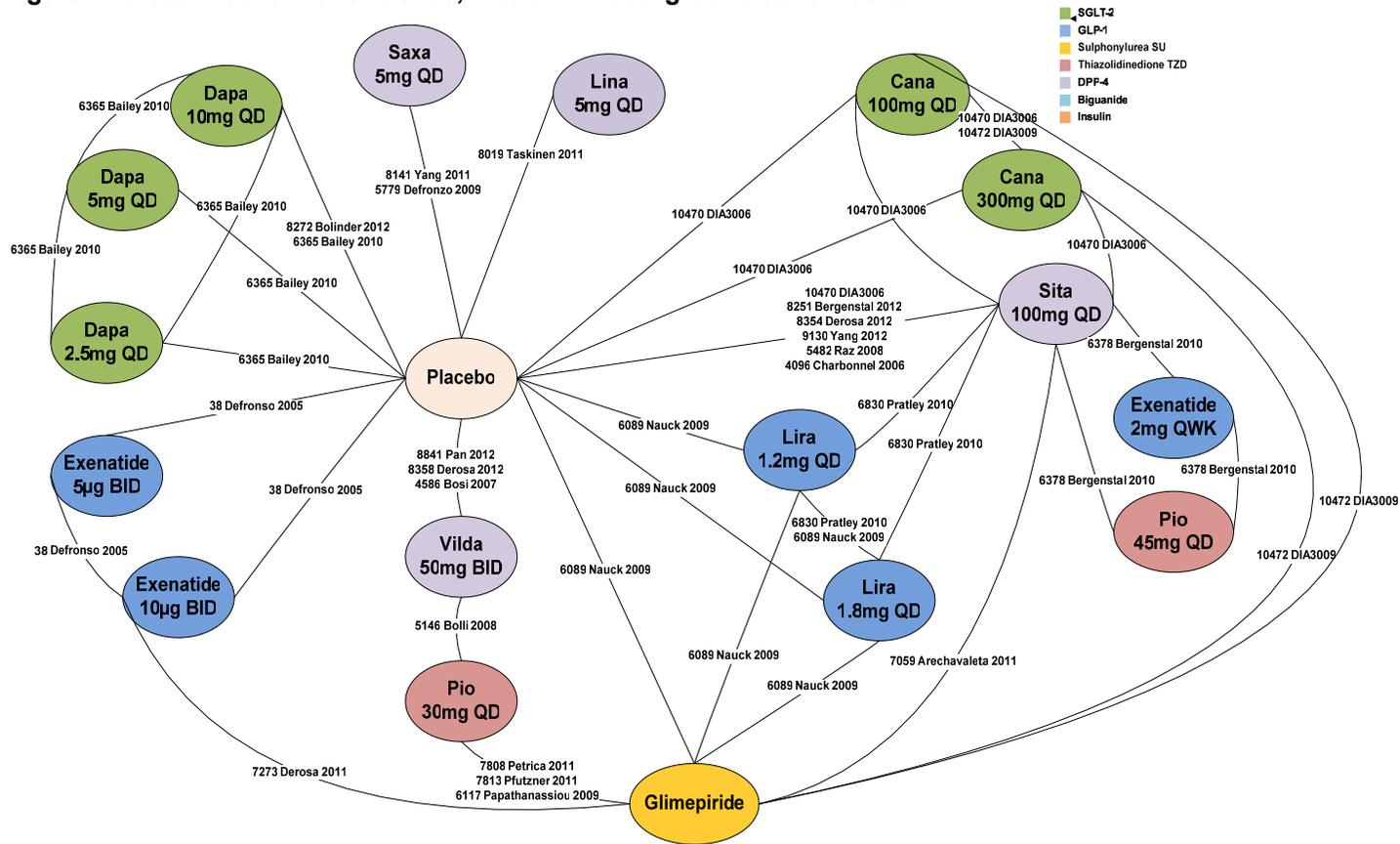
Based on the literature review, the following networks of evidence were used as basis for the indirect comparisons (Figure 2,3,4 and 5). Some outcomes were not always reported in the publications (e.g. BMI, SBP) leading to missing data in the NMA. Missing data resulted in reduced networks of evidence for these outcomes. These networks were reported in the submission file, but are not separately shown here.

Figure 1. The PRISMA diagram for the original literature search performed for MAH submission



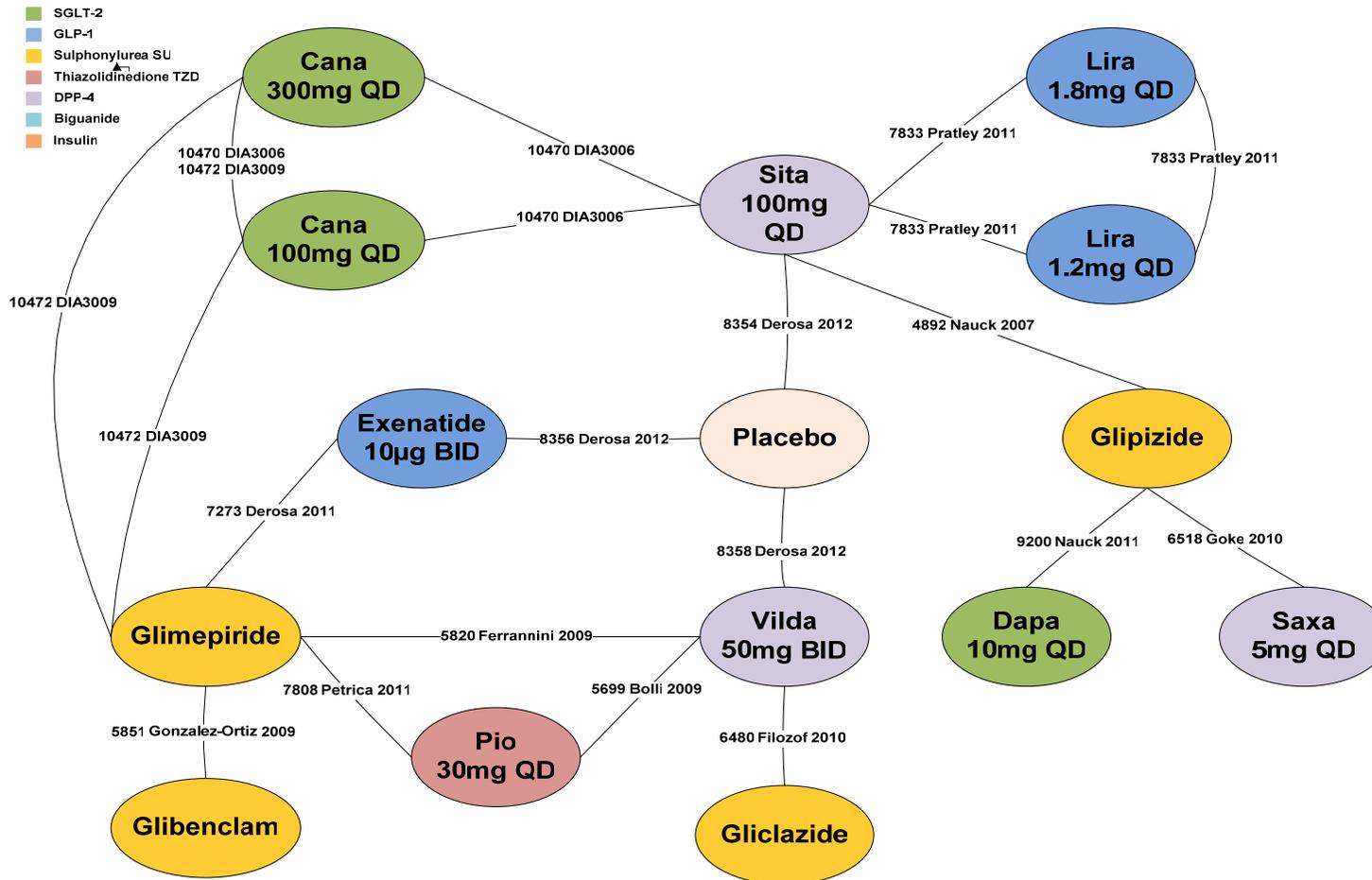
Source: Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Figure 2. Global network of evidence, metformin background at 26 weeks



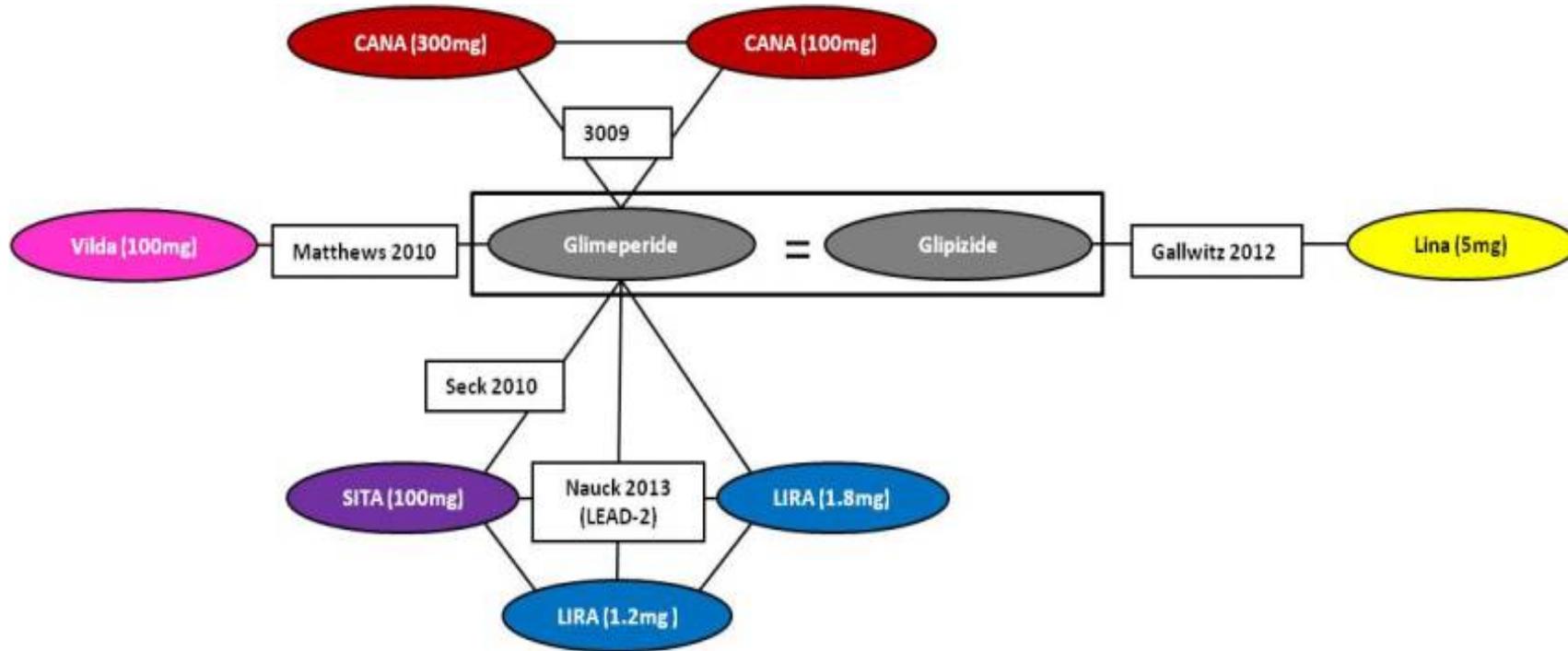
Source: [Johnson & Johnson submission file 2013]

Figure 3. Global network of evidence, metformin background at 52 weeks



Source: [Johnson & Johnson submission file 2013]

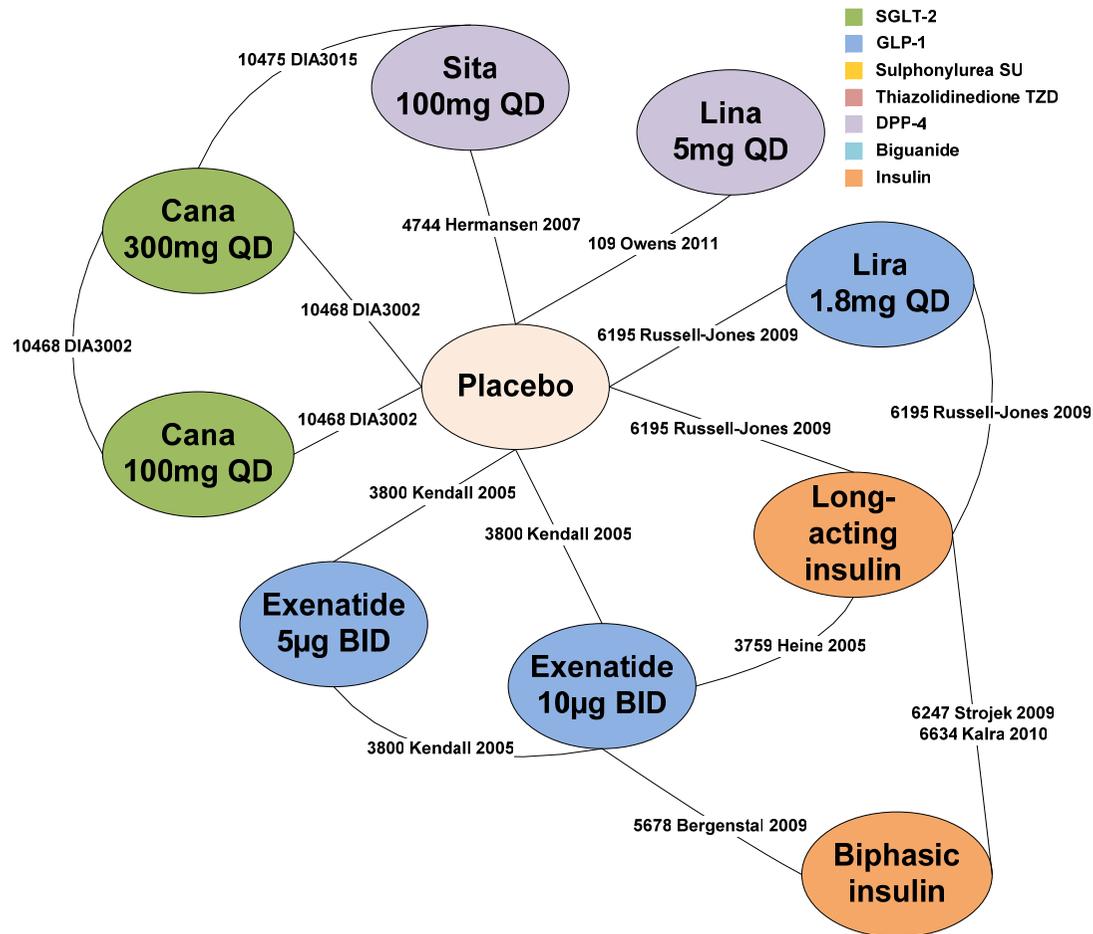
Figure 4. Network of evidence for the analysis at 104 weeks, metformin background (LOCF)



Source: [Johnson & Johnson submission file 2013]

Triple therapy, 26 weeks

Figure 5. Base case analysis – Global network of evidence, metformin + sulphonylurea background



Source: [Johnson & Johnson submission file 2013]

Subcontractor's notes on statistical methodologies for indirect comparisons (shortened by authors)

Indirect comparisons of canagliflozin versus all other available treatments studied as dual therapy (add-on to MET) or as triple therapy (add-on to metformin + SU), were generated using Bayesian network meta-analysis.

Network meta-analysis fits into the Generalized Linear Model (GLM) framework, where a (link) function of the treatment effect (in a certain treatment arm of a specific trial) is modelled as a linear combination of baseline effects and relative effects (compared to control).

A Bayesian analysis results in a posterior probability distribution for the parameter of interest (e.g. treatment effects), which combines our previous beliefs about this parameter (prior distribution) and the information provided by the data about the parameter (likelihood function).

Therefore, depending on the nature of the data, the link and likelihood functions are chosen, which determines the type of GLM used in the meta-analysis. Thus, for binary data the standard approach is to use the logit link and to model the number of events in each treatment arm according to a Binomial likelihood (where the parameters of interest are the probability of experiencing events and the number of patients in each treatment arm). For continuous data the standard approach is to use the identity link and a Normal likelihood.

Moreover, for all Bayesian analyses, non-informative prior distributions are typically used. This choice of prior distributions illustrates the idea of completely lack of knowledge about the value of the parameter at hand. In that way, it is expected that the posterior distribution is not influenced by the choice of the prior distribution (thus, only driven by the data).

The GLM was applied under the assumption of both fixed-effects (FE) and random-effects (RE). Model fit was assessed based on the Deviance Information Criterion (DIC), i.e. the choice between FE and RE was based on the lowest DIC value (since a lower DIC value indicates a better fit).

All models were run in WinBugs version 1.4, employing Markov chain Monte Carlo (MCMC) simulation, based on 20,000 iterations after 10,000 burn-in iterations for FE models, and 200,000 iterations after 100,000 burn-in iterations for RE models. Posterior means and medians, 95% credible intervals (CrI) and probabilities for being the most effective treatment, were estimated from the MCMC simulations.

As with the direct comparisons, the standard approach for handling drop-outs/missing values is based on LOCF imputation.

Code check

We checked the syntax used to do the MTCs and we found no issues. Also, we were able to reproduce all results as presented in Appendix 14 of the submission.

Data extraction

We were unable to check all data extraction in the time available, but we did check about 30% of the tables. This showed that various errors were made in data extraction. In most cases the errors were very minor with no impact on the results, but slightly larger errors were found for the data extraction for the proportion of patients reaching HbA1c<7% (metformin background at 26 weeks and metformin+sulphonylurea background at 26 weeks). These errors were all caused by relating the reported proportion to the original sample size of the study. However, in many papers the actual number of patients available for this evaluation was reported, and in most instances this was smaller than the original sample size. As this leads to larger standard errors, these data extraction errors mostly influenced the uncertainty around the point estimates.

Bayesian versus frequentist direct comparison

In the study report, the direct comparisons are done within a frequentist frame work whilst the MTC is done within the Bayesian frame work. We find this discrepancy remarkable.

In the submission it is mentioned that "*Meta-analyses based on direct comparisons were carried out between each pair of treatments when possible, i.e. when the two treatments have been compared in two or more clinical trials. A frequentist model was used as it is the standard approach for direct comparisons. (Whitehead 2002)*" (page 21, Appendix 14).

However, when the use of frequentist versus Bayesian MTC is discussed it is mentioned that “A conventional frequentist approach dichotomises results to be either ‘significant’ or ‘non-significant’, based on the chosen *P* value. This is not well suited for decision-making, as it does not indicate to what extent (probability) a hypothesis will be true or false.” (page 145, submission).

We think that this reasoning is inconsistent. To check whether this approach had any impact on the result, we reran some of the direct comparisons, and we found only small changes.

Fixed versus random effect models

The choice between the FE or RE model was assessed using the DIC (Deviance Information Criterion) so that the one with the lowest DIC was deemed as more appropriate. This approach is supported for example by the DSU in their guidelines, although they also propose the use of leverage plots as a way of assessing goodness-of-fit.

Some problems may arise when for example a FE model was chosen for the base case and a RE model was chosen for the sensitivity analyses or otherwise.

Modelling methodologies

Description of the methodology

Authors' note:

MAH presented simulations for prediction of life expectancy and long-term outcomes using the IMS Core Diabetes Model. The model has been described shortly in the literature (Palmer et al. 2004a, 2004b, Cummins 2009). In the following, we summarize the description of the model and approach used in Johnson & Johnson submission file (2013) for simulations based on comparisons for which direct evidence was available.

Simulations in which the clinical inputs (estimates for the treatment effects used in the model) were based partly on network meta-analysis and partly on direct evidence were also presented in the Johnson & Johnson submission file (2013). The rationale of this approach was not justified. In addition, the background (sources and methodology of analysis) of the clinical inputs based on network meta-analysis could not be verified. Due to these limitations along with the lack of transparency and tractability, the simulations based partly on network meta-analysis were not included.

Short description of the model

The CORE model is an internet based model which simulates the main complications of diabetes [Cummins et al. 2009; Palmer et al. 2004a]. Disease progression is based on a series of interdependent Markov submodels that simulate progression of disease-related complications (angina, MI, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, nephropathy and ESRD, neuropathy, foot ulcer, amputation) and other-cause mortality [Johnson & Johnson submission file 2013]. Each sub-model employs Monte Carlo simulation which incorporates the time, the state, the time in state and transition probabilities which are typically diabetes type dependent as derived from published sources [Cummins et al. 2009]

The baseline population characteristics and baseline complication rates can be specified within the CORE model. Treatments can be specified as modifying glycaemic control, hypoglycaemic event rates, severe hypoglycaemic event rates, blood pressure, the body mass index and lipid levels [Cummins et al. 2009].

Model has been validated using published data for the incidence of the complications by Palmer et al. (2004b). This exercise appears to show reasonably good validation for the incidence of the complications examined [Cummins et al. 2009]

Approach, key assumptions (Table 4) and sensitivity analyses applied in Johnson & Johnson submission file 2013

According to Johnson & Johnson submission file (2013) clinical inputs (treatment effects) and population characteristics at baseline (demographic characteristics, history of disease and health condition) in the simulation using IMS Core Diabetes Model correspond to those observed in clinical trials (DIA3006, DIA3009 and DIA3015). Mortality from other causes is based on adjusted European mortality numbers (mortality which reflects the average non-diabetes related mortality in average European population).

Base case analyses for simulations based on comparisons for which direct evidence was available are shown below:

Table 3. Base Cases Supported by Direct Head-to-Head Evidence

	Intervention (canagliflozin)	Comparator
Dual therapy: add-on to MET	100 mg and 300 mg	SU (glimepiride)
	100 mg and 300 mg	DPP-4 inhibitor (sitagliptin 100 mg)
Triple therapy: add-on to SU + MET	300 mg	DPP-4 inhibitor (sitagliptin 100 mg)

Abbreviations: MET, metformin; SU, sulphonylurea; DPP-4, dipeptidyl peptidase 4.
Source: [Johnson & Johnson submission file 2013]

Sensitivity analyses [Johnson & Johnson submission file 2013]:

Sensitivity analyses include the following:

- HbA1c effect in intervention arm as comparator
- BMI effect in intervention arm as comparator
- Cholesterol effect in intervention arm as comparator (measured by total cholesterol: HDL-C ratio)
- SBP effect in intervention arm as comparator
- Hypoglycaemic event rates in intervention arm as comparator
- Time horizon 10 years (base case is 40 years)
- HbA1c threshold 7% (base case is 7.5%)

In addition, sensitivity to the population characteristics was tested by comparing outcomes of 2 scenarios, where 1 scenario represents a well-controlled diabetes population and the other scenario represents a less well-controlled diabetes population.

Table 4. Key assumptions

Assumption	Argument
Life long time horizon approximated by 40 years.	Assessment of outcomes of treating chronic diseases requires a lifelong time horizon.
Threshold of treatment failure is 7.5% HbA1c.	Common threshold in EU region.
BMI in intervention arm catch up with control arm after switch to rescue therapy.	Conservative assumption.
Cholesterol in intervention arm catch up with control arm after switch to rescue therapy.	Conservative assumption.
Rescue therapy is insulin therapy.	In line with guidelines in many European guidelines.
Outcomes are not discounted.	Assumption.
Baseline characteristics of patients as in trial populations.	Supports internal validity, we perform sensitivity analysis of real life populations.
All-cause mortality adjusted for non-diabetes related mortality in average of European population.	Mortality should reflect European population.
Results are presented undiscounted and discounted at a rate of 3.5%.	Recommended discount rates for life-year and QALY gain in Europe varies with 3%-4% being typical values.

Source: [Johnson & Johnson submission file 2013]

Model parameters [Johnson & Johnson submission file 2013]

Clinical inputs

Clinical inputs of efficacy in CDM are changes of HbA1c, systolic blood pressure (SBP), total cholesterol, HDL cholesterol, BMI and major and minor hypoglycaemic event rates matched those in the corresponding trial population (DIA3006, DIA3009 and DIA3015).

Patient characteristics

Population characteristics at baseline (demographics, physiological conditions and disease history) are assumed to match relevant trial populations. In dual therapy as add-on to metformin the population characteristics match CSR 3006, in dual therapy as add-on to SU the population characteristics match the population in CSR 3009, in triple therapy as add-on to metformin + SU the population characteristics match the population in CSR 3015.

Mortality due to other causes

Adjusted European mortality numbers were based on data from EUROSTAT (2013) and WHO (2013).

Discussion

The predictions of life years have been performed with simulations using the CORE diabetes model [Palmer et al. 2004a]. The Core Diabetes Model has been validated in terms of operational and predictive validity against epidemiological and clinical studies [Palmer et al. 2004b]. Further revalidation studies have been performed recently but the results have not yet been published in scientific literature. Simulated/predicted results concerning life expectancies in different treatment arms were presented. All the results shown were from simulations of comparisons for which direct evidence from clinical trials was available.

In principle the approach taken is supported by the EUnetHTA guidelines in this case, even though there are limitations in transparency. The general limitations of extrapolating intermediate to final endpoints are also described in EUnetHTA guidelines. The specific limitations related to results presented in the MAH submission are discussed below.

Limitations

There are well-known limitations in terms of transparency related to Diabetes Core model (see e.g. Cummins et al. 2009). This lack of transparency limits the possibility to thoroughly assess the model quality and the accuracy of the results.

Secondly, several sensitivity analyses were performed in Johnson & Johnson submission file (2013) mostly according to what was requested. However, the approach used for the sensitivity analysis does not fully address the question of parameter uncertainty. Setting a parameter value equal with the comparator in a univariate sensitivity analysis leads to a small change in the outcome (e.g. life-expectancy) if the difference between treatments with respect to the particular parameter is small. This approach does not reflect the possible impact of the parameter in general. Results using a shorter time horizon (2 or 5 years; closer to the duration of the actual clinical trials) could have also been useful.

Results of simulations in which the clinical inputs (estimates for the treatment effects used in the model) were based partly on network meta-analysis and partly on direct evidence were also presented in the Johnson & Johnson submission file (2013). The rationale of this approach was not justified. In addition, the background (sources and methodology of analysis) of the clinical inputs based on network meta-analysis could not be verified. Also the sensitivity analyses were not presented for these simulations. Due to these limitations along with the lack of transparency and tractability, the results of simulations based partly on network meta-analysis were not included into the results section.

Table 5. Preliminary evidence table in the project plan

Author, year, reference number
Study Registration number (Registry identifier)
Country
Sponsor
Comparator
Study design
Number of patients
Patient characteristics
Study duration
Primary efficacy endpoint
Secondary endpoints
Inclusion and exclusion criteria
Outcomes
<i>Efficacy</i>
<ul style="list-style-type: none"> • HbA1c change (%) • Proportion achieving <7% HbA1c target (%) • FPG change (mmol/L) • Body mass index change • Change in cardiovascular risk factors (including blood pressure and/or serum lipids) • Weight change • Complications of diabetes (e.g., cardiovascular, renal, and eye)

<ul style="list-style-type: none"> • Mortality • Insulin requirements change (in patients with insulin) • Proportion achieving <7% HbA1c target (%) without hypoglycaemia
<i>Safety</i>
<ul style="list-style-type: none"> • Most frequent adverse events • Serious adverse events
<ul style="list-style-type: none"> • Adverse events (AE) in n (%) of patients
<ul style="list-style-type: none"> • Description of AE in n (%) of patients
<ul style="list-style-type: none"> • Serious adverse events (SAE) in n (%) of patients
<ul style="list-style-type: none"> • Description of SEA in n (%) of patients
<i>Health-related quality of life</i>

Table 6. Selection of assessment elements

ID	Domain	Topic	Issue	Relevance in this assessment Yes/No	Preliminary research question(s) or Reason for non-relevance/
Health problem and current use of technology					
A0002	Health Problem and Current Use of the Technology	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	What is the precise definition of Type 2 Diabetes Mellitus (T2DM) and which diagnosis is given to Type 2 DM according to ICD-10? What are the main features of Type 2 DM?
A0003	Health Problem and Current Use of the Technology	Target Condition	What are the known risk factors for the condition?	Yes	What are the known risk factors for the Type 2 Diabetes Mellitus (T2DM)?
A0004	Health Problem and Current Use of the Technology	Target Condition	What is the natural course of the condition?	Yes	What is the natural course of the Type 2 Diabetes Mellitus (T2DM)?
A0005	Health Problem and Current Use of the Technology	Target Condition	What is the burden of disease for the patient?	Yes	What is the burden (main symptoms and consequences) of the Type 2 Diabetes Mellitus (T2DM) for the patient?
A0006	Health Problem and Current Use of the Technology	Target Condition	What is the burden of the disease for society?	Yes	What is the burden of the Type 2 Diabetes Mellitus (T2DM) for society (prevalence, incidence, costs)?
A0007	Health Problem and Current Use of the	Target Population	What is the target population in this assessment?	Yes	What is the target population in this assessment?

ID	Domain	Topic	Issue	Relevance in this assessment Yes/No	Preliminary research question(s) or Reason for non-relevance/
	Technology				
A0023	Health Problem and Current Use of the Technology	Target Population	How many people belong to the target population?	Yes	How many people belong to the target population? (as A0006)
A0001	Health Problem and Current Use of the Technology	Utilisation	For which health conditions and populations, and for what purposes is the technology used?	Yes	For which indication/ for what purposes is the canagliflozin used and are there any contra-indications?
A0011	Health Problem and Current Use of the Technology	Utilisation	How much are the technologies utilised?	Yes	How much is the canagliflozin utilised (What is the expected annual utilisation of canagliflozin)?
A0024	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the health condition currently diagnosed according to published guidelines and in practice?	Yes	How is the T2DM currently diagnosed according to published guidelines and in practice?
A0025	Health Problem and Current Use of the Technology	Current Management of the Condition	How is the health condition currently managed according to published guidelines and in practice?	Yes	How is the T2DM currently managed according to published guidelines and in practice?
A0020	Health Problem and Current Use of the Technology	Regulatory Status	What is the marketing authorisation status of the technology?	Yes	What is the marketing authorisation status of the canagliflozin?

ID	Domain	Topic	Issue	Relevance in this assessment Yes/No	Preliminary research question(s) or Reason for non-relevance/
A0021	Health Problem and Current Use of the Technology	Regulatory Status	What is the reimbursement status of the technology?	Yes	What is the reimbursement status of the canagliflozin?
Description and technical characteristics of technology					
B0001	Description and technical characteristics of technology	Features of the technology	What is the technology and the comparator(s)?	Yes	What is canagliflozin and the comparator(s)? (taking into account different dosages) and what is the mechanism of action?
B0002	Description and technical characteristics of technology	Features of the technology	What is the approved indication and claimed benefit of the technology and the comparator(s)?	Yes	What is the approved indication and claimed benefit of the canagliflozin and the evidence-based comparators?
B0003	Description and technical characteristics of technology	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	What is the phase of development and implementation of the canagliflozin and the comparator(s)?
B0004	Description and technical characteristics of technology	Features of the technology	Who performs or administers the technology and the comparator(s)?	Yes	Who performs or administers the canagliflozin and the comparators?
B0005	Description and technical characteristics of technology	Features of the technology	In what context and level of care are the technology and the comparator used?	Yes	In what context and level of care are the canagliflozin and the comparators used?
B0008	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	No	There is no need of special premises for canagliflozin

ID	Domain	Topic	Issue	Relevance in this assessment Yes/No	Preliminary research question(s) or Reason for non-relevance/
B0009	Description and technical characteristics of technology	Investments and tools required to use the technology	What supplies are needed to use the technology and the comparator?	No	No specific supplies are needed for canagliflozin
B0010	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use of the technology and the comparator?	Yes	What kind of data and records are needed to monitor the use of the canagliflozin and the comparators?
B0011	Description and technical characteristics of technology	Investments and tools required to use the technology	What kind of registry is needed to monitor the use of the technology and comparator?	Yes	Is the use of registries worthwhile?
Safety					
C0001	Safety	Patient safety	What kind of harms can use of the technology cause to the patient?	Yes	What are the adverse events and serious adverse events in patients with canagliflozin therapy?
C0002	Safety	Patient safety	What is the dose relationship of the harms?	Yes	Is there a relationship between the dose of canagliflozin and adverse events and serious adverse events?
C0004	Safety	Patient safety	How does the frequency or severity of harms change over time or in different settings?	Yes	How does the frequency or severity of harms change over time or in different settings?
C0005	Safety	Patient safety	What are the susceptible patient groups that are more likely to be harmed?	Yes	What are the susceptible patient groups that are more likely to be harmed?
C0007	Safety	Patient safety	What are the user-dependent harms?	Yes	Can adverse events be caused by the behaviour of patients, professionals or manufacturers?
C0008	Safety	Patient safety	How safe is the technology in relation to the comparator?	Yes	How safe is canagliflozin in relation to the comparator?
C0040	Safety	Environmental	What kind of harms are there	No	Not relevant for canagliflozin

ID	Domain	Topic	Issue	Relevance in this assessment Yes/No	Preliminary research question(s) or Reason for non-relevance/
		safety	for public and environment?		
Clinical effectiveness					
D0001	Clinical effectiveness	Mortality	What is the expected beneficial effect of the intervention on overall mortality?	Yes	What is the expected beneficial effect of canagliflozin on overall mortality?
D0002	Clinical effectiveness	Mortality	What is the expected beneficial effect on the disease-specific mortality?	Yes	What is the expected beneficial effect of canagliflozin on mortality due to diabetes-related diseases and conditions?
D0005	Clinical effectiveness	Morbidity	How does the technology affect symptoms and findings?	Yes	How does canagliflozin affect the following outcomes? <ul style="list-style-type: none"> • HbA1c change (%) • Proportion achieving <7% HbA1c target (%) • FPG change (mmol/L) • Body mass index change • Change in cardiovascular risk factors (including blood pressure and/or serum lipids) • Weight change • Insulin requirements change (in patients with insulin) • Proportion achieving <7% HbA1c target (%) without hypoglycaemia
D0006	Clinical effectiveness	Morbidity	How does the technology affect progression of disease?	Yes	How does canagliflozin affect long-term complications of diabetes (e.g. cardiovascular, renal and eye complications)?

ID	Domain	Topic	Issue	Relevance in this assessment Yes/No	Preliminary research question(s) or Reason for non-relevance/
D0011	Clinical effectiveness	Function	What is the effect of the technology on patients' body functions?	Yes	What is the effect of canagliflozin on patient's global functions?
D0016	Clinical effectiveness	Function	How does the use of technology affect activities of daily living?	Yes	How does the use of canagliflozin affect activities of daily living?
D0012	Clinical effectiveness	Health-related quality of life	What is the effect of the technology on generic health-related quality of life?	Yes	What is the effect of canagliflozin on generic health-related quality of life?
D0013	Clinical effectiveness	Health-related quality of life	What is the effect of the technology on disease-specific quality of life?	Yes	What is the effect of canagliflozin on disease-specific quality of life?
D0017	Clinical effectiveness	Patient satisfaction	Was the use of the technology worthwhile?	Yes	Do the patients consider the use of canagliflozin worthwhile?

Description of the evidence that was used

Please note that studies provided from the manufacturer's dossier are marked with an asterisk * to distinguish from studies recovered from other sources by the authors.

Table 7. Characteristics of the phase 3 randomized controlled studies of canagliflozin

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
DIA3009: A randomised, double-Blind, 3-arm parallel-group, 2-year (104-week), multicentre study to evaluate the efficacy, safety, and tolerability canagliflozin 100 mg and canagliflozin 300 mg compared with glimepiride in the treatment of subjects with type 2 diabetes mellitus not optimally controlled on metformin monotherapy.								
Protocol number: 28431754DIA3009 EudraCT Number: 2009-009320-36 ClinicalTrials.gov Identifier: NCT00968812 Clinical Registry No.: CR016480 The CANTATA-SU Trial In- and exclusion criteria: see [table 12]	Start: 28 August 2009 End: 30 January 2013 Duration of Main phase: 52 weeks Duration of Extension phase: 52 weeks	Phase 3, randomised, double-blind, 3-arm, parallel-group, multicentre, 104-week study consisting of a 52-week active-controlled (vs glimepiride) core treatment period followed by a 52-week, active-controlled (vs glimepiride) extension period	1452	Canagliflozin 100 mg (483) Canagliflozin 300 mg (485)	Glimepiride (484)	Subjects aged 18-80 with type 2 diabetes mellitus and currently treated with metformin; HbA1c between 7% and 9.5% Baseline characteristics: <u>Canagliflozin 100 mg</u> Age = 56.4 y HbA1c = 7.8% (62 mmol/mol) FPG = 9.2 mmol/L (165.8 mg/dL) BW = 86.9 kg <u>Canagliflozin 300 mg</u> Age = 55.8 y HbA1c = 7.8% (62 mmol/mol) FPG = 9.1 mmol/L (164.0 mg/dL) BW = 86.6 kg <u>Glimepiride</u> Age = 56.3 y HbA1c = 7.8% (62 mmol/mol) FPG = 9.2 mmol/L (165.8 mg/dL) BW = 86.5 kg	Change from baseline to Week 52 in HbA1c % change from baseline to Week 52 in body weight Proportion of subjects with documented hypoglycaemia episodes at Week 52	Cefalu WT et al. Lancet. 2013; 382:941-50.
DIA3006: A randomised, double-blind, placebo- and active-controlled, 4-arm, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of canagliflozin compared with sitagliptin and placebo in the treatment of subjects with type 2 diabetes mellitus with inadequate glycaemic control on metformin monotherapy								

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
Protocol number: 28431754DIA3006 EudraCT Number: 2009-016525-34 ClinicalTrials.gov Identifier: NCT01106677 Clinical Registry No.: CR017023 The CANTATA-D Trial In- and exclusion criteria: see [table 12]	Start date: 07 April 2010 End date: 17 August 2012 Duration of Main phase: 26 weeks Duration of Extension phase: 26 weeks	Phase 3, randomised, double-blind, placebo- and active-controlled, 4-arm, parallel-group, multicentre, 52-week study consisting of a 26-week placebo-and active-controlled (vs sitagliptin) period followed by a 26-week, active-controlled (vs sitagliptin) period	1284	Canagliflozin 100 mg (368) Canagliflozin 300 mg (367)	Sitagliptin (366) Placebo (183)	Subjects aged 18-80 with type 2 diabetes mellitus and currently treated with metformin; HbA1c between 7% and 10.5% Baseline characteristics: <u>Placebo/sitagliptin</u> (n = 183) Age = 55.3 y HbA1c = 8.0% (64 mmol/ mol) FPG = 9.1 mmol/L (164.0 mg/dL) BW = 86.6 kg <u>Sitagliptin 100 mg</u> (n = 366) Age = 55.5 y HbA1c = 7.9% (63 mmol/ mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 87.7 kg <u>Canagliflozin 100 mg</u> (n = 368) Age = 55.5 y HbA1c = 7.9% (63 mmol/ mol) FPG = 9.3 mmol/L (167.6 mg/dL) BW = 88.8 kg <u>Canagliflozin 300 mg</u> (n = 367) Age = 55.3 y HbA1c = 7.9% (63 mmol/ mol) FPG = 9.6 mmol/L (173.0 mg/dL) BW = 85.4 kg	Change from baseline to Week 26 and Week 52 in HbA1c Proportion of subjects achieving HbA1c <7% (goal) at Week 26 Change from baseline to Week 26 and Week 52 in fasting plasma glucose Change from baseline to Week 26 in 2-hour postprandial glucose % change from baseline to Week 26 and Week 52 in body weight Change from baseline to Week 26 and Week 52 in systolic BP % change from baseline to Week 26 and Week 52 in HDL-cholesterol % change from baseline to Week 26	Lavalle-González FJ et al. Diabetologia. 2013; 56:2582-92.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
							and Week 52 in triglycerides	
DIA3015: A randomised, double-blind, active-controlled, multicentre study to evaluate the efficacy, safety, and tolerability of canagliflozin versus sitagliptin in the treatment of subjects with type 2 diabetes mellitus with inadequate glycaemic control on metformin and sulphonylurea therapy								
Protocol number: 28431754DIA3015 EudraCT Number: 2010-020053-14 ClinicalTrials.gov Identifier: NCT01137812 Clinical Registry No.: CR017185 The CANTATA-D2 Trial In- and exclusion criteria: see [table 12]	Start date: 30 June 2010 End date: 9 March 2012 Duration: 52 weeks	Phase 3, randomised, double-blind, active-controlled (vs sitagliptin), 2 arm, parallel-group, multicentre, 52-week study	756	Canagliflozin 300 mg (378)	Sitagliptin 100 mg (378)	Subjects aged 18-80 with type 2 diabetes mellitus and currently treated with metformin and a sulphonylurea (SU); HbA1c between 7% and 10.5% Baseline characteristics: <u>Canagliflozin 300 mg</u> (n = 377) Age = 56.6 y HbA1c = 8.1% (65 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 87.4 kg <u>Sitagliptin 100 mg</u> (n = 378) Age = 56.7 y HbA1c = 8.1% (65 mmol/mol) FPG = 9.2 mmol/L (165.8 mg/dL) BW = 89.1 kg	Change from baseline to Week 52 in HbA1c Change from baseline to Week 52 in fasting plasma glucose % change from baseline to Week 52 in body weight Change from baseline to Week 52 in systolic BP % change from baseline to Week 52 in HDL-cholesterol % change from baseline to Week 52 in triglycerides	Scherthaner G et al. Diabetes Care. 2013; 36:2508-15.
DIA3005: A randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of canagliflozin as monotherapy in the treatment of subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise								
Protocol number: 28431754DIA3005 EudraCT Number: 2009-015883-32 ClinicalTrials.gov Identifier: NCT01081834 Clinical Registry No.:	Start date: 8 February 2010 End date: 20 March 2012 Duration of Main	Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multicentre, 52-week study	587	Canagliflozin 100 mg (196) Canagliflozin 300 mg (197)	Placebo (194)	Subjects aged 18-80 with type 2 diabetes mellitus; HbA1c between 7% and 10% Baseline characteristics: <u>Placebo</u> (n = 192)	Change from baseline to Week 26 in HbA1c Proportion of subjects achieving HbA1c <7%	Stenlöf K et al. Diabetes Obes Metab. 2013; 15:372-82.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
CR017011 The CANTATA-M Trial In- and exclusion criteria: see [table 12]	phase: 26 weeks Duration of Extension phase: 26 weeks	consisting of a 26-week placebo-controlled period followed by a 26-week, active-controlled (vs sitagliptin) period				Age = 55.7 y HbA1c = 8.0% (64 mmol/mol) FPG = 9.3 mmol/L (167.6 mg/dL) BW = 87.6 kg <u>Canagliflozin 100 mg</u> (n = 195) Age = 55.1 y HbA1c = 8.1% (65 mmol/mol) FPG = 9.6 mmol/L (173.0 mg/dL) BW = 85.8 kg <u>Canagliflozin 300 mg</u> (n = 197) Age = 55.3 y HbA1c = 8.0% (64 mmol/mol) FPG = 9.6 mmol/L (173.0 mg/dL) BW = 86.9 kg	(goal) at Week 26 Change from baseline to Week 26 in fasting plasma glucose Change from baseline to Week 26 in 2-hour postprandial glucose % change from baseline to Week 26 in body weight Change from baseline to Week 26 in systolic BP % change from baseline to Week 26 in HDL-cholesterol % change from baseline to Week 26 in triglycerides	
DIA3002: A randomised, double-blind, placebo-controlled, 3-arm, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of canagliflozin in the treatment of subjects with type 2 diabetes mellitus with inadequate glycaemic control on metformin and sulphonylurea therapy								
Protocol number: 28431754DIA3002 EudraCT Number: 2009-016366-88 ClinicalTrials.gov Identifier: NCT01106625 Clinical Registry No.: CR017005 The CANTATA-MSU	Start date: 7 April 2010 End date: 17 April 2012 Duration of Main phase: 26 weeks	Phase 3, randomised, double-blind, 3-arm, parallel-group, placebo-controlled, multicentre, 52-week study consisting of a 26-week core	469	Canagliflozin 100 mg (157) Canagliflozin 300 mg (156)	Placebo (156)	Subjects aged 18-80 with type 2 diabetes mellitus and currently treated with metformin and an SU; HbA1c between 7% and 10.5% Baseline characteristics: <u>Placebo</u> (n = 156)	Change from baseline to Week 26 in HbA1c Proportion of subjects achieving HbA1c <7% (goal) at Week 26	Wilding JP et al. Int J Clin Pract. 2013.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
Trial In- and exclusion criteria: see [table 12]	Duration of Extension phase: 26 weeks	double-blind treatment period followed by a 26-week extension double-blind treatment period				<p>Age = 56.7 y HbA1c = 8.1% (65 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 91.2 kg <u>Canagliflozin 100 mg</u> (n = 157)</p> <p>Age = 57.3 y HbA1c = 8.1% (65 mmol/mol) FPG = 9.6 mmol/L (173.0 mg/dL) BW = 93.8 kg <u>Canagliflozin 300 mg</u> (n = 156)</p> <p>Age = 56.0 y HbA1c = 8.1% (65 mmol/mol) FPG = 9.3 mmol/L (167.6 mg/dL) BW = 93.5 kg</p>	Change from baseline to Week 26 in fasting plasma glucose % change from baseline to Week 26 in body weight Change from baseline to Week 26 in systolic BP % change from baseline to Week 26 in HDL-cholesterol % change from baseline to Week 26 in triglycerides	
DIA3012: A randomised, double-blind, placebo-controlled, 3-arm, parallel-group, 26-week multicentre study with a 26-week extension to evaluate the efficacy, safety, and tolerability of canagliflozin compared with placebo in the treatment of subjects with type 2 diabetes mellitus with inadequate glycaemic control on metformin and pioglitazone therapy								
<p>Protocol number: 28431754DIA3012 EudraCT Number: 2009-018070-64 ClinicalTrials.gov Identifier: NCT01106690 Clinical Registry No.: CR017032 The CANTATA-MP Trial In- and exclusion criteria: see [table 12]</p>	<p>Start date: 13 April 2010 End date: 10 July 2012 Duration of Main phase: 26 weeks Duration of Extension phase: 26 weeks</p>	Phase 3, randomised, double-blind, placebo-controlled, 3-arm, parallel-group, multicentre, 52-week study consisting of a 26-week placebo-controlled period followed by a 26-week, active-controlled (vs sitagliptin) period	344	Canagliflozin 100 mg (115) Canagliflozin 300 mg (114)	Placebo (115)	<p>Subjects aged 18-80 with type 2 diabetes mellitus and currently treated with metformin and pioglitazone; HbA1c between 7% and 10.5%</p> <p>Baseline characteristics:</p> <p><u>Placebo</u> (n = 115) Age = 58.3 y HbA1c = 8.0% (64 mmol/mol) FPG = 9.1 mmol/L (164.0 mg/dL) BW = 93.8 kg <u>Canagliflozin 100 mg</u> (n = 113) Age = 56.7 y</p>	Change from baseline to Week 26 in HbA1c Proportion of subjects achieving HbA1c <7% (goal) at Week 26 % change from baseline to Week 26 in body weight Change from baseline to Week 26 in fasting plasma	

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
						HbA1c = 8.0% (64 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 94.2 kg <u>Canagliflozin 300 mg</u> (n = 114) Age = 57.0 y HbA1c = 7.9% (63 mmol/mol) FPG = 9.1 mmol/L (164.0 mg/dL) BW = 94.4 kg	glucose Change from baseline to Week 26 in systolic BP % change from baseline to Week 26 in HDL-cholesterol % change from baseline to Week 26 in triglycerides Change in homeostasis model assessment (HOMA2-%B)	
DIA3004: A Randomised, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicentre Study With a 26-Week Extension, to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus Who Have Moderate Renal Impairment								
Protocol number: 28431754DIA3004, Amendment INT-2 EudraCT Number: 2009-017136-40 ClinicalTrials.gov Identifier: NCT01064414 Clinical Registry No.: CR017008 In- and exclusion criteria: see [table 12]	Start: 02 March 2010 End: 02 August 2012 26 weeks	Phase 3, randomised, double-blind, placebo-controlled, 3-arm, parallel-group, multicentre, 52-week study consisting of a 26-week placebo-controlled period followed by a 26-week, placebo-controlled period.	272	Canagliflozin 100 mg (90) Canagliflozin 300 mg (91)	Placebo (91)	Subjects aged over 25 with type 2 diabetes mellitus and having moderate renal impairment.; HbA1c between 7% and 10.5% Baseline characteristics: <u>Canagliflozin 100mg</u> (n = 90) Age = 69.5 y HbA1c = 7.9% (63 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 90.5 kg <u>Canagliflozin 300mg</u> (n = 89) Age = 67.9 y HbA1c = 8.0% (64 mmol/mol) FPG = 8.8 mmol/L (158.6 mg/dL)	Change from baseline to Week 26 in HbA1c Proportion of subjects achieving HbA1c <7% (goal) at Week 26 Change from baseline to Week 26 in fasting plasma glucose	Yale JF et al. Diabetes Obes Metab. 2013; 15:463-73.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
						BW = 90.2 kg <u>Placebo</u> (n = 90) Age = 68.2 y HbA1c = 8.0% (64 mmol/mol) FPG = 8.9 mmol/L (160.4 mg/dL) BW = 92.8 kg		
DIA3010: A randomised, double-blind, placebo-controlled, parallel-group, multicentre study to evaluate the efficacy, safety, and tolerability of canagliflozin compared with placebo in the treatment of older subjects with type 2 diabetes mellitus inadequately controlled on glucose lowering therapy								
Protocol number: 28431754DIA3010, Amendment INT-1 EudraCT Number: 2010-018411-15 ClinicalTrials.gov Identifier: NCT01106651 Clinical Registry No.: CR017014 In- and exclusion criteria: see [table 12]	Start date: 12 April 2010 End date: 18 November 2011 Duration of Main phase: 26 weeks Duration of Extension phase: 26 weeks	Phase 3, randomised, double-blind, placebo-controlled, parallel-group, 3-arm, multicentre study consisting of a 26-week placebo-controlled core period followed by a 78-week, placebo-controlled period	716	Canagliflozin 100 mg (241) Canagliflozin 300 mg (236)	Placebo (239)	Subjects aged 55-80 with type 2 diabetes mellitus women must be at least 3 years postmenopausal; HbA1c between 7% and 10.0% Baseline characteristics: <u>Placebo</u> (n = 237) Age = 63.2 y HbA1c = 7.8% (62 mmol/mol) FPG = 8.7 mmol/L (156.8 mg/dL) BW = 91.1 kg <u>Canagliflozin 100 mg</u> (n = 241) Age = 64.3 y HbA1c = 7.8% (62 mmol/mol) FPG = 8.9 mmol/L (160.4 mg/dL) BW = 88.4 kg <u>Canagliflozin 300 mg</u> (n = 236) Age = 63.4 y HbA1c = 7.7% (61 mmol/mol) FPG = 8.5 mmol/L (153.2 mg/dL) BW = 88.8 kg	Change from baseline to Week 26 in HbA1c Proportion of subjects achieving HbA1c <7% (goal) at Week 26 Change from baseline to Week 26 in fasting plasma glucose % change % change from baseline to Week 26 in body weight Change from baseline to Week 26 in systolic BP % change % change from baseline to Week 26 in HDL-cholesterol % change % change from baseline to Week 26 in	Bode B et al. Hosp Pract. 2013; 41:72-84.

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
							triglycerides	
DIA3008: A randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus, The CANVAS Trial (Canagliflozin cardioVascular Assessment Study) Sulphonylurea Substudy								
Protocol number: 28431754DIA3008 EudraCT Number: 2009-012140-16 ClinicalTrials.gov Identifier: NCT01032629 Clinical Registry No.: CR016627 The CANVAS Trial (CANagliflozin cardioVascular Assessment Study) (SU Substudy) In- and exclusion criteria: see [table 12]	Start date: 16 November 2009 End date: 08 July 2011 Duration: 18 weeks Estimated primary completion date (Clinical Trials.gov): June 2018	Phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre, 18-week substudy	127	Canagliflozin 100 mg (42) Canagliflozin 300 mg (40)	Placebo (45)	Subjects with a diagnosis of T2DM with history of cardiovascular diseases (aged over 30) or high risk of cardiovascular (CV) disease (aged over 50); HbA1c level $\geq 7.0\%$ to $\leq 10.5\%$ Baseline characteristics: <u>Canagliflozin 100 mg</u> (n = 42) Age = 64.1 y HbA1c = 8.3% (67 mmol/mol) FPG = 10.1 mmol/L (182.0 mg/dL) BW = 83.7 kg <u>Canagliflozin 300 mg</u> (n = 40) Age = 65.5 y HbA1c = 8.2% (66 mmol/mol) FPG = 9.7 mmol/L (174.8 mg/dL) BW = 79.9 kg <u>Placebo</u> (n = 45) Age = 64.8 y HbA1c = 8.5% (69 mmol/mol) FPG = 10.3 mmol/L (185.6 mg/dL) BW = 85.2 kg		
DIA3008: A randomised, multicentre, double-blind, parallel, placebo-controlled study of the effects of canagliflozin on cardiovascular outcomes in adult subjects with type 2 diabetes mellitus. The CANVAS Trial (CANagliflozin cardioVascular Assessment Study) Insulin Substudy								

Study	Time	Study type	N	Intervention (N)	Comparator (N)	Patient population	Endpoints	Main publication or duplicate publications from the same study
Protocol number: 28431754DIA3008 EudraCT Number: 2009-012140-16 ClinicalTrials.gov Identifier: NCT01032629 Clinical Registry No.: CR016627 The CANVAS Trial (CANagliflozin cardioVascular Assessment Study) (Insulin Substudy) In- and exclusion criteria: see [table 12]	Start date: 16 November 2009 End date: 08 July 2011 Duration: 18 weeks Estimated primary completion date (Clinical Trials.gov): June 2018	Phase 3, randomised, double-blind, placebo-controlled, 3 parallel-group, multicentre, 18-week substudy	1718	Canagliflozin 100 mg (566) Canagliflozin 300 mg (587)	Placebo (587)	Subjects with a diagnosis of T2DM with history of cardiovascular diseases (aged over 30) or high risk of cardiovascular (CV) disease (aged over 50); HbA1c level $\geq 7.0\%$ to $\leq 10.5\%$ Baseline characteristics: <u>Placebo</u> (n = 565) Age = 62.4 y HbA1c = 8.3% (67 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 97.5 kg <u>Canagliflozin 100 mg</u> (n = 566) Age = 62.5 y HbA1c = 8.3% (67 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 96.8 kg <u>Canagliflozin 300 mg</u> (n = 587) Age = 63.4 y HbA1c = 8.3% (67 mmol/mol) FPG = 9.4 mmol/L (169.4 mg/dL) BW = 96.7 kg	Change from baseline to Week 18 in HbA1c Proportion of subjects achieving HbA1c <7% (goal) at Week 18 Change from baseline to Week 18 in fasting plasma glucose % change from baseline to Week 18 in body weight Change from baseline to Week 18 in systolic BP % change from baseline to Week 18 in HDL-cholesterol % change from baseline to Week 18 in triglycerides	

Table 8. Relevant non-RCTs identified

Trial no. / Primary reference source	Study design	Objective	Intervention(s)	N	Patient population	Endpoints	Justification for inclusion
none identified							

Table 9. List of references that were cited in the part of MAH submission file related to meta-analyses and indirect comparisons

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Table 10. List of ONGOING studies with canagliflozin in ClinicalTrials.gov register**Patients with *history or high risk of cardiovascular disease* DIA3008 – CANVAS trial (NCT01032629)**

Study Identifier/Status	Estimated Completion Date/ Primary Completion Date/ Duration	Study type	N	Intervention	Comparator	Patient population	Primary Endpoints	Safety	Sponsor
<p><u>DIA 3008 - CANVAS trial</u></p> <p>NCT01032629, http://prsinfo.clinicaltrials.gov/ct2/show/record/NCT01032629?id=01032629&rank=1</p> <p>Neal B et al. Am Heart J. 2013 Aug; 166(2):217-223.e11.</p> <p>ONGOING</p>	<p>June 2018/March 2017</p> <p>1st phase: 2-year safety analysis;</p> <p>2nd phase: 5 year safety and efficacy analyses</p> <p>(In Register: 9 years)</p>	<p>RCT, phase 3, double-blind, placebo-controlled, parallel group, multicentre</p>	<p>1st phase: 4330 (randomized 1:1:1; canagliflozin 100 mg: canagliflozin 300 mg:placebo)</p> <p>2nd phase: 14000</p>	<p>canagliflozin 100 mg or 300 mg</p>	<p>Placebo on background standard of care for diabetes</p>	<p>Patients with diagnosis of type 2 diabetes mellitus and a history of, or a high risk for, cardiovascular disease;</p> <p>Patients with inadequate diabetes control (as defined by glycosylated haemoglobin greater than or equal to 7.0% to less than or equal to 10.5% at screening) and be either (1) not currently on diabetes drug therapy or (2) on therapy with any approved class of diabetes drugs</p>	<p>Major adverse cardiovascular events, including CV death, nonfatal MI, and nonfatal stroke</p> <p>(composite of CV death, nonfatal MI, and nonfatal stroke, hospitalization for unstable angina)</p>	<p>Incidence of all AEs, all serious AEs, all deaths;</p> <p>Effects on laboratory parameters, clinical signs, ECG findings; tolerability; pre-specified of specific interest: vulvovaginal and genital mycotic infection, urinary tract infections; hypoglycaemia, fractures, cardiovascular events, skin adverse events, cancer events</p>	<p>Janssen Research & Development, LLC</p>

Table 11. List of **ONGOING** studies with canagliflozin: Other Ongoing Studies in ClinicalTrials.gov (NCT01939496, NCT01809327)

Study Identifier/Status	Estimated Completion Date/ Primary Completion Date/ Duration	Study type	N	Intervention	Comparator	Patient population	Primary Endpoints	Safety	Sponsor
<p>NCT01939496</p> <p>http://prsinfo.clinicaltrials.gov/ct2/show/NCT01939496?term=canagliflozin&type=Intr&cond=diabetes+mellitus+type+2&intr=canagliflozin&phase=123&rank=4</p> <p>A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicentre Study to Evaluate the Blood Pressure Reduction With Ambulatory Blood Pressure Monitoring (ABPM), Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Hypertension and Type 2 DM</p>	<p>December 2014/August 2014</p> <p>6 week</p>	RCT, phase 4, double-blind, placebo-controlled, parallel group, multicentre	189 (randomized 1:1:1; canagliflozin 100 mg: canagliflozin 300 mg: placebo	canagliflozin 100 mg or 300 mg	Placebo on background on stable dose of anti-hyperglycaemic and anti-hypertensive agents	<p>patients with a diagnosis of type 2 diabetes mellitus;</p> <p>patients with hypertension (seated office SBP of ≥ 130 mmHg and < 160 mmHg and seated office DBP of ≥ 70 mmHg at screening and at Week -2;</p> <p>patients on stable doses of 1 to 3 anti-hypertensive agents for at least 5 weeks before screening</p> <p>patients on stable doses of 1 to 3 oral anti-hyperglycaemic agents which must include metformin, for at least 8 weeks before screening</p>	Change in mean 24-hour systolic blood pressure (SBP) by Ambulatory Blood Pressure Monitoring (ABPM)	Overall safety and tolerability	Janssen Scientific Affairs, LLC
<p>NCT01809327</p> <p>http://prsinfo.clinicaltrials.gov/ct2/show/NCT01809327?term=canagliflozin&type=Intr&cond=diabetes+mellitus+type+2&intr=canagliflozin&phase=123&rank=4</p>	<p>December 2014/May 2014</p> <p>26 weeks</p>	RCT, phase 3, 5-Arm, Parallel-Group, 26-Week, Multicentre Study	1180 (randomization 1:1:1:1:1; canagliflozin 100 mg: canagliflozin 300 mg: Metformin	canagliflozin 100 mg: canagliflozin 300 mg: Metformin XR:	Diet and exercise	<p>Must have type 2 diabetes mellitus with inadequate glycaemic control on diet and exercise;</p> <p>Not on antihyperglycaemic agent therapy (at least 12 weeks before screening) and have a screening visit</p>	Change in glycated haemoglobin (HbA1c) from baseline to Week 26	Overall safety and tolerability	Janssen Research & Development, LLC

Study Identifier/Status	Estimated Completion Date/ Primary Completion Date/ Duration	Study type	N	Intervention	Comparator	Patient population	Primary Endpoints	Safety	Sponsor
<p>=7</p> <p>A Randomized, Double-Blind, 5-Arm, Parallel-Group, 26-Week, Multicentre Study to Evaluate the Efficacy, Safety, and Tolerability of canagliflozin in Combination With Metformin as Initial Combination Therapy in the Treatment of Subjects With Type 2 DM With Inadequate Glycaemic Control With Diet and Exercise</p>			<p>n XR: canagliflozin 100 mg+ Metformin XR : canagliflozin 300 mg Metformin XR</p>	<p>canagliflozin 100+ Metformin XR: canagliflozin 300 mg+ Metformin XR</p>		<p>fingerstick glycated haemoglobin (HbA1c) of more than or equal to 7 percent and less than or equal to 12.5 percent;</p> <p>Have a screening visit HbA1c of more than or equal to 7.5 percent and less than or equal to 12 percent as determined by the central laboratory;</p> <p>Must have a fasting plasma glucose of less than or equal to 300 mg/dL (16.7 mmol/L) prior to randomization;</p> <p>Must have a fasting fingerstick glucose of greater than 120 mg/dL (6.7 mmol/L) performed at home or at the study centre prior to randomization</p>			

Table 12. Inclusion and exclusion criteria of the phase 3 randomized controlled studies of canagliflozin.

Inclusion and exclusion criteria of the phase 3 randomized controlled studies of canagliflozin
<p>DIA3009 (Add-on to Metformin vs Glimepiride)</p> <p><i>Inclusion Criteria</i></p> <p>The following key inclusion criteria must have been met before a subject was enrolled into the study:</p> <ul style="list-style-type: none"> • Man or woman ≥ 18 and ≤ 80 years of age with type 2 diabetes mellitus (T2DM) and currently treated with metformin, meeting the following HbA1c eligibility criteria: <ul style="list-style-type: none"> ○ On metformin monotherapy at a stable protocol-specified dose for at least 12 weeks before screening and has an HbA1c of $\geq 7.0\%$ and $\leq 9.5\%$ at screening <li style="padding-left: 20px;">or ○ On metformin monotherapy at a dose $< 2,000$ mg/day with an HbA1c of $\geq 7.5\%$ and $\leq 10.0\%$ at screening and has a Week -2 visit HbA1c of $\geq 7.0\%$ and $\leq 9.5\%$, after at least 10 weeks on a stable protocol-specified dose of metformin <li style="padding-left: 20px;">or ○ On metformin at a stable protocol-specified dose in combination with one other oral non-thiazolidinedione (TZD) antihyperglycaemic agent (AHA) with an HbA1c of $\geq 6.5\%$ and $\leq 9.0\%$ at screening and has a Week -2 visit HbA1c of $\geq 7.0\%$ and $\leq 9.5\%$, after discontinuing the AHA and on a stable protocol-specified dose of metformin at least 10 weeks <li style="padding-left: 20px;">or ○ On metformin at a dose $< 2,000$ mg/day in combination with one other oral non-TZD AHA with an HbA1c of $\geq 6.5\%$ and $\leq 9.0\%$ at screening and had a Week -2 visit HbA1c of $\geq 7.0\%$ and $\leq 9.5\%$, after discontinuing the AHA and on a stable protocol-specified dose of metformin at least 10 weeks <p style="padding-left: 40px;">Protocol-specified dose of metformin: $\geq 2,000$ mg/day (or $\geq 1,500$ mg/day, if unable to tolerate a higher dose)</p> <p><i>Exclusion Criteria</i></p> <p>Potential subjects who met any of the key exclusion criteria were to be excluded from participating in the study:</p> <ul style="list-style-type: none"> • Repeated (i.e., 2 or more over a 1 week period) fasting plasma glucose (FPG) and/or fasting self-monitored blood glucose (SMBG) measurements ≥ 15 mmol/L during the Metformin Dose Stabilization/AHA Washout Period, despite reinforcement of diet and exercise counselling • History of diabetic ketoacidosis, type 1 diabetes mellitus (T1DM), pancreas or β-cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy • History of > 1 severe hypoglycaemic episode, defined as an episode that requires the help of another person, or resulting in seizure, or loss of consciousness, within 6 months before screening. • History of an ongoing eating disorder or significant weight loss or weight gain, defined as an increase or decrease of 5% in body weight (based on subject report) within 3 months before screening • History of myocardial infarction, unstable angina, or cerebrovascular accident within 3 months before screening, or history of New York Heart Association (NYHA) Class III-IV cardiac disease • History of prior bariatric surgical procedures

- Serum creatinine ≥ 124 $\mu\text{mol/L}$ for men and ≥ 115 $\mu\text{mol/L}$ for women; or estimated glomerular filtration rate (eGFR) < 55 mL/min/1.73 m^2 (or < 60 mL/min/1.73 m^2 if based upon restriction of metformin use in the metformin local label)
- Note:** A 1-time repeat measurement was allowed, at the discretion of the investigator, if the values for serum creatinine/eGFR were not consistent with prior values
- Alanine aminotransferase (ALT) > 2.0 times the upper limit of normal (ULN) or total bilirubin > 1.5 times the ULN, at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings were consistent with Gilbert's disease. A 1-time repeat was allowed, at the discretion of the investigator.
 - Have taken TZD therapy in the past 16 weeks before screening

DIA3006 (Add-on to Metformin vs Placebo and Sitagliptin)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into the study:

- Man or woman ≥ 18 and ≤ 80 years of age with T2DM who met 1 of the following 4 criteria:
 - On metformin immediate release (IR) monotherapy at a stable protocol-specified dose* for at least 8 weeks before screening and had an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at screening (or at Week -2, if screening measurement was more than 3 weeks before Week -2)
 - or
 - On metformin extended release (XR) monotherapy at a protocol-specified dose* with an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at screening and had a Week -2 visit HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$, after at least 8 weeks on a stable protocol-specified dose* of metformin IR
 - or
 - On metformin monotherapy (IR or XR) at a dose $< 2,000$ mg/day with an HbA1c of $\geq 7.5\%$ and $\leq 11.0\%$ at screening and had a Week -2 visit HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$, after at least 8 weeks on a stable protocol-specified dose* of metformin IR
 - or
 - On metformin (IR or XR) in combination with an SU with an HbA1c of $\geq 6.5\%$ and $\leq 9.5\%$ at screening and had a Week -2 visit HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$, after at least 8 weeks on a stable protocol-specified dose* of metformin IR

*Protocol-specified dose of metformin: $\geq 2,000$ mg/day (or $\geq 1,500$ mg/day , if unable to tolerate a higher dose)

- FPG < 15 mmol/L at Week -2.

Note: At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Week -2 FPG criterion were allowed to return to the investigational centre within 7 days for a 1-time repeat FPG and could have continued in the study if the subject's repeat FPG met the criterion

- centre fasting fingerstick glucose of ≥ 6.1 mmol/L and < 15 mmol/L on Day 1

Note: At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Day 1 criterion were allowed to return to the investigational centre within 7 days for a 1-time repeat fingerstick glucose and could have continued in the study if the subject's repeat fingerstick glucose met the criterion

Exclusion Criteria

Potential subjects who met any of the following key exclusion criteria were excluded from participating in the study:

- Repeated (i.e., 2 or more over a 1-week period) FPG and/or fasting SMBG glucose measurements ≥ 15 mmol/L during the pre-treatment phase, despite reinforcement of diet and exercise

counselling

- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On either a PPAR γ agonist (e.g., a TZD [pioglitazone or rosiglitazone]), ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine that have indications in some regions for treatment of T2DM) except as specified in the study inclusion criteria within 12 weeks before the screening visit
- Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 3 months before screening, or revascularization is planned, or subject has a history of NYHA Class III-IV cardiac disease
- Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance)
- Uncontrolled hypertension (i.e., using an average of 3 seated BP readings with a diastolic BP \geq 100 mmHg or systolic BP \geq 160 mmHg) at Week -2
Note: Subjects may have their BP-lowering medication regimen adjusted and be re-evaluated to assess this criterion
- eGFR $<$ 55 mL/min/1.73 m² (or $<$ 60 mL/min/1.73 m² if based upon restriction of metformin use in the metformin local label) or serum creatinine \geq 124 μ mol/L for men and \geq 115 μ mol/L for women
Note: A 1-time repeat measurement is allowed, at the discretion of the investigator, if the values for serum creatinine/eGFR are not consistent with prior values

DIA3005 (Monotherapy)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into the study:

- Man or woman \geq 18 and \leq 80 years of age with T2DM who met 1 of the 2 following criteria:
 - Not on an AHA at screening (off for at least 12 weeks) with HbA1c \geq 7.0% and \leq 10.0% at the screening (or pre-screening) visit (Note: if HbA1c measurement was not within 3 weeks of the Week -2 visit, HbA1c testing must have been repeated at the Week -2 visit to assess this inclusion criterion)
 - or
 - On an oral AHA in monotherapy (except a PPAR γ agonist, e.g., TZD) or on low-dose combination therapy with metformin (\leq 1,000 mg) and SU (at \leq 50% of maximally or near-maximally effective doses) with HbA1c \geq 6.5% and \leq 9.5% at the screening (or pre-screening) visit and had a Week -2 (after the 8-week diet and exercise and AHA washout period) HbA1c \geq 7.0% and \leq 10.0% and FPG $<$ 15 mmol/L
- For the High Glycaemic Substudy subjects were required to have HbA1c $>$ 10% and \leq 12% at screening or at Week -1 visit after the 8-week washout period and a FPG value \leq 19.4 mmol/L at the Week -1 visit

Exclusion Criteria

Potential subjects who met any of the following key exclusion criteria were excluded from participating in the study:

- Repeated (i.e., 2 or more over a 1-week period) FPG and/or fasting SMBG glucose measurements $>$ 15 mmol/L during the pre-treatment phase, despite reinforcement of diet and exercise counselling
Note: During the single-blind placebo run-in period, subjects eligible for the High Glycaemic Substudy based upon screening visit or Week -1 HbA1c measurement, may have continued in the study if their FPG and/or SMBG values were $>$ 19.4 mmol/L
- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy

- Fasting C-peptide <0.7 ng/mL in subjects for whom the investigator could not reasonably exclude T1DM based upon clinical evaluation (e.g., young age at onset [e.g., <40 years], new onset diabetes and/or negative family history of T2DM and/or lower range body mass index [BMI])
- Note:** C-peptide determination was measured at screening only in subjects for whom the investigator could not reasonably exclude T1DM based upon clinical evaluation
- On either a PPAR γ agonist (e.g., pioglitazone or rosiglitazone), required ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine that have indications in some regions for treatment of T2DM) except as specified in the study inclusion criteria within 12 weeks before the screening visit
 - Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 3 months before screening, or revascularization procedure is planned, or subject has a history of NYHA Class III-IV cardiac disease
 - Uncontrolled hypertension (i.e., using an average of 3 seated BP readings with a diastolic BP \geq 100 mmHg or systolic BP \geq 160 mmHg) at Week -2
 - Findings on 12-lead ECG that would require urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance)
 - ALT level >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening (for elevations in bilirubin: if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's disease, the subject may participate)
 - eGFR <50 mL/min/1.73 m² at screening (provided by the central laboratory)

DIA3002 (Add-on to Metformin plus Sulphonylurea)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into the study:

- Man or woman \geq 18 and \leq 80 years of age with T2DM and currently treated with metformin and an SU, meeting the following HbA1c eligibility criteria:
 - On metformin and an SU at protocol-specified doses* for at least 8 weeks prior to screening and has an HbA1c of \geq 7.0% and \leq 10.5% at screening[†]
 - or
 - On metformin and an SU, either or both at doses below protocol-specified* with an HbA1c of \geq 7.5% at screening and has a Week -2 visit HbA1c of \geq 7.0% and \leq 10.5%

*Metformin \geq 2,000 mg/day (or \geq 1,500 mg/day if intolerant of higher dose)

[†]If measured at screening more than 3 weeks prior to the Week -2 visit, obtain HbA1c at the Week -2 visit to assess inclusion criterion

Exclusion Criteria

Potential subjects who met any of the key exclusion criteria were to be excluded from participating in the study:

- Repeated (i.e., 2 or more over a 1-week period) FPG and/or fasting SMBG measurements \geq 15 mmol/L during the pre-treatment phase, despite reinforcement of diet and exercise counselling
- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On either a PPAR γ agonist (e.g., a TZD [pioglitazone or rosiglitazone]), ongoing insulin therapy, another SGLT2 inhibitor, or any other AHA (including agents such as colesevelam and bromocriptine that have indications in some regions for treatment of T2DM) except as specified in the study inclusion criteria within 12 weeks before the screening visit

Note: Subjects who were treated with only a single dose of insulin were allowed to participate

- Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 3 months before screening, or revascularization procedure is planned, or a history of NYHA Class III-IV cardiac disease
- Findings on 12-lead ECG that required urgent diagnostic evaluation or intervention (e.g., new clinically important arrhythmia or conduction disturbance)
- Uncontrolled hypertension (i.e., using an average of 3 seated BP readings with a diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg at Week -2)
- ALT level >2.0 times the ULN or total bilirubin >1.5 times the ULN at screening
- eGFR <55 mL/min/1.73 m² (or <60 mL/min/1.73 m² if based upon restriction of metformin use in the metformin local label) or serum creatinine ≥ 124 μ mol/L for men and ≥ 115 μ mol/L for women

DIA3012 (Add-on to Metformin plus Pioglitazone)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into the study:

- Man or woman ≥ 18 and ≤ 80 years of age with T2DM who met 1 of the following 5 criteria:
 - On dual combination metformin and pioglitazone, both agents at protocol-specified doses* (stable doses for at least 16 weeks prior to screening), with an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at screening (or at Week -2, if screening measurement is more than 3 weeks prior to Week -2)
 - or
 - On dual combination metformin and pioglitazone (stable doses for at least 8 weeks prior to screening), with either agent at a dose below protocol-specified*, with an HbA1c of $\geq 7.5\%$ and $\leq 11.0\%$ at screening, and has an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone
 - or
 - On dual combination metformin and rosiglitazone, with an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at screening (stable doses for at least 8 weeks prior to screening), and has an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone
 - or
 - On a PPAR γ agent (pioglitazone or rosiglitazone) in dual combination with another oral AHA, with an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at screening (stable doses for at least 8 weeks prior to screening), and has an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone
 - or
 - On metformin, a PPAR γ agent (pioglitazone or rosiglitazone), and an SU (or meglitinide) or a dipeptidyl peptidase-4 (DPP-4) inhibitor in triple combination therapy with an HbA1c of $\geq 6.5\%$ and $\leq 9.5\%$ at screening (stable doses for at least 8 weeks prior to screening), and has an HbA1c of $\geq 7.0\%$ and $\leq 10.5\%$ at Week -2, after at least 8 weeks on stable protocol-specified* doses of metformin and pioglitazone

*Protocol-specified doses = metformin $\geq 2,000$ mg per day (or $\geq 1,500$ mg per day, if unable to tolerate a higher dose) and pioglitazone 30 or 45 mg per day

- FPG <15 mmol/L at Week -2

Note: At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Week -2 FPG criterion were allowed to return to the investigational centre within 7 days for a 1-time repeat FPG and could have continued in the study if the subject's repeat FPG met the criterion

- Site fasting fingerstick glucose of ≥ 6.1 mmol/L and < 15 mmol/L on Day 1

Note: At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Day 1 criterion were allowed to return to the investigational centre within 7 days for a 1-time repeat fingerstick glucose and could have continued in the study if the subject's repeat fingerstick glucose met the criterion

Exclusion Criteria

Potential subjects who met any of the following key exclusion criteria were excluded from participating in the study:

- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- Repeated (i.e., 2 or more over a 1-week period) FPG and/or fasting SMBG glucose measurements ≥ 15 mmol/L during the pre-treatment phase, despite reinforcement of diet and exercise counselling
- Ongoing eating disorder or significant weight loss or weight gain within 12 weeks, defined as an increase or decrease of 5% in body weight based upon clinic-based measurement or, if not available, subject report
- Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 3 months before screening, or revascularization procedure is planned, or subject has a history of NYHA Class III-IV cardiac disease
- Uncontrolled hypertension (i.e., using an average of 3 seated BP readings with a diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg) at Week -2
- eGFR < 55 mL/min/1.73 m² (or < 60 mL/min/1.73 m² if based upon restriction of metformin use in the metformin local label) or serum creatinine ≥ 124 μ mol/L for men and ≥ 115 μ mol/L for women
- ALT level > 2.0 times the ULN or total bilirubin > 1.5 times the ULN at Screening
- Contraindication to the use of metformin or pioglitazone or sitagliptin (per local prescribing information [i.e., local label])

DIA3004 (Moderate Renal Impairment)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into the study:

- Man or woman with T2DM, ≥ 25 years of age
- Have a HbA1c $\geq 7.0\%$ to $\leq 10.5\%$ at pre-screening or screening and at Week -2 visits
- Have moderate renal impairment, as defined by eGFR values (estimated by the 4-variable Modification of Diet in Renal Disease [MDRD] equation) ≥ 28 and ≤ 55 mL/min/1.73 m² at the pre-screening or screening visit, and ≥ 30 and < 50 mL/min/1.73 m² at the Week -2 visit, with generally stable renal function, as demonstrated by $\leq 25\%$ decline in eGFR at Week -2 relative to the (pre)screening visit value

Exclusion Criteria

Potential subjects who met any of the following key exclusion criteria were excluded from participating in the study:

- Repeated (i.e., 2 or more over a 1-week period) FPG and/or fasting SMBG glucose measurements > 15 mmol/L during the pre-treatment phase, despite reinforcement of diet and exercise counselling

- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- Ongoing eating disorder or significant weight loss or weight gain within 12 weeks before the screening visit, defined as an increase or decrease of 5% in body weight based upon clinic-recorded measurement or, if not available, subject report
- Renal disease that required treatment with immunosuppressive therapy or a history of dialysis or renal transplant
- Presence of nephrotic syndrome (e.g., severe proteinuria with hypoalbuminemia and/or oedema), or inflammatory renal disease (e.g., acute interstitial nephritis, acute or rapidly progressive glomerulonephritis)
- Subject is likely to require dialysis or transplantation during participation in the study
- Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 3 months before screening, or revascularization procedure is planned, or subject has a history of NYHA Class III-IV cardiac disease
- ALT level >2.0 times the ULN or total bilirubin >1.5 times the ULN at (pre)screening
- Haemoglobin concentration <100 g/L at the screening visit

DIA3010 (Older Subjects)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into the study:

- Man or woman ≥ 55 to ≤ 80 years of age with T2DM; women must be at least 3 years postmenopausal
 - Had a HbA1c $\geq 7.0\%$ to $\leq 10.0\%$ at screening (or at Week -2, if HbA1c obtained more than 3 weeks prior to Week -2 visit), and
 - Not currently on AHA therapy (off for at least 12 weeks)
- or
- On a stable regimen of AHA(s) in monotherapy or on combination therapy, with any approved agent (including metformin, SU, DPP-4 inhibitor, alpha-glucosidase inhibitor [AGI], glucagon-like peptide-1 [GLP-1] analogue, or insulin for at least 12 weeks; or pioglitazone for at least 6 months before screening visit) used in accordance with local prescribing information

Note: A stable dose of insulin is defined as no change in the insulin regimen (i.e., type[s] of insulin) and $\leq 15\%$ change in the average total daily dose of insulin (i.e., average over 1 week to account for day to day variability, changes $\leq 15\%$ over the preceding 12 weeks)

- FPG <15 mmol/L at Week -2

Note: At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Week -2 FPG criteria could return to the investigational site within 7 days for a 1-time repeat FPG and continue in the study if the subject's repeat FPG met the criterion

- Fasting fingerstick glucose of ≥ 6.1 mmol/L and <15 mmol/L on Day 1 of the site visit

Note: At the investigator's discretion, based upon review of recent SMBG values, subjects not meeting the Day 1 criteria could return to the investigational site within 7 days for a 1-time repeat fingerstick glucose and continue in the study if the subject's repeat fingerstick glucose met the criterion

- BMI ≥ 20 to ≤ 40 kg/m²

Exclusion Criteria

Potential subjects who met any of the following key exclusion criteria were excluded from participating in the study:

- Repeated (i.e., 2 or more over a 1-week period) FPG and/or fasting SMBG glucose measurements ≥ 15 mmol/L during the pre-treatment phase, despite reinforcement of diet and exercise counselling
- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- Use of a bisphosphonate within 12 months prior to screening or expected to receive treatment with bisphosphonate during the study period
- If on medication treatment for osteoporosis (e.g., oestrogen replacement, selective oestrogen receptor modulator [SERM] therapy, or calcitonin), not on a stable regimen (for at least 6 months prior to screening)
- T-score < -2.5 ("at any site") in a subject not currently on treatment (i.e., not on treatment with oestrogen replacement, SERM, calcitonin, or other non-bisphosphonate therapy indicated to treat osteoporosis)

Note: Bone sites referenced by the phrase "at any site" include:

- Composite T-score of evaluable lumbar vertebrae
- T- score of the total hip
- T-score of femoral neck
- T-score of 1/3 radius of distal forearm
- Parathyroid hormone (e.g., teriparatide) or denosumab treatment within 12 months before screening
- Severe vitamin D deficiency with serum 25-hydroxy-vitamin D level ≤ 10 ng/mL at screening or within 12 months prior to screening
- Hypercalcaemia (defined by elevated serum calcium level greater than the ULN at screening)
- Conditions that interfere with accurate measurement of bone mineral density (e.g., severe scoliosis, spine degenerative disease, spinal fusion or metal implants, bilateral hip replacement or other surgery resulting in metal implants in both hips)
- Non-healed fracture, or any fracture with 12 months of screening
- Acquired or inherited bone disorders that may confound assessment of bone density or bone turnover (e.g., Paget's disease, osteomalacia, osteopetrosis, osteogenesis imperfect) or elevation of alkaline phosphatase > 1.5 times the ULN
- Myocardial infarction, unstable angina, revascularization procedure (e.g., stent or bypass graft surgery), or cerebrovascular accident within 3 months before screening, or revascularization procedure is planned, or subject has a history of NYHA Class III-IV cardiac disease
- Uncontrolled hypertension (i.e., using an average of 3 seated BP readings with a diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg) at Week -2
- eGFR < 50 mL/min/1.73 m² at screening (provided by the central laboratory)
- For subjects taking metformin: serum creatinine ≥ 124 μ mol/L for men and ≥ 115 μ mol/L for women; no contraindication to the use of metformin (including eGFR) based upon the label of the country of the investigational site
- ALT level > 2.0 times the ULN or total bilirubin > 1.5 times the ULN at screening (for elevations in bilirubin: if, in the opinion of the investigator and agreed upon by the sponsor's medical officer,

the elevation in bilirubin was consistent with Gilbert's disease, the subject may participate)

DIA3008 (CANagliflozin CardioVascular Assessment Study [CANVAS] Insulin and SU Substudies)

Inclusion Criteria

The following key inclusion criteria must have been met before a subject was enrolled into CANVAS:

- Man or woman with a diagnosis of T2DM with HbA1c level $\geq 7.0\%$ to $\leq 10.5\%$ at screening and be either (1) not currently on AHA therapy or (2) on AHA monotherapy or combination therapy with any approved agent: e.g., SU, metformin, pioglitazone, AGI, GLP-1 analogue, DPP-4 inhibitor, or insulin
- History or high risk of cardiovascular (CV) disease defined on the basis of either:
 - Age ≥ 30 years with documented symptomatic atherosclerotic CV disease: including stroke; myocardial infarction; hospital admission for unstable angina; coronary artery bypass graft; percutaneous coronary intervention (with or without stenting); peripheral revascularization (angioplasty or surgery); symptomatic with documented haemodynamically-significant carotid or peripheral vascular disease; or amputation secondary to vascular disease
 - Age ≥ 50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, systolic BP > 140 mmHg (average of 3 readings) recorded at the screening visit, while the subject is on at least 1 BP-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria, or documented high-density lipoprotein cholesterol (HDL-C) of < 1 mmol/L

Exclusion Criteria

Potential subjects who met any of the following key exclusion criteria were excluded from participating in the study:

- Fasting fingerstick glucose at home or at investigational site > 15 mmol/L at Baseline/Day 1
- For subjects on an SU agent or on insulin: fasting fingerstick glucose at home or at investigational site < 6 mmol/L at baseline/Day 1
- History of diabetic ketoacidosis, T1DM, pancreas or β -cell transplantation, or diabetes secondary to pancreatitis or pancreatectomy
- On an AHA and not on a stable regimen (i.e., agents and doses) for at least 8 weeks before the screening visit and through the screening/run-in period

Note: A stable dose of insulin is defined as no change in the insulin regimen (i.e., type[s] of insulin) and $\leq 15\%$ change in the total daily dose of insulin (averaged over 1 week to account for day to day variability)
- eGFR < 30 mL/min/1.73 m² at screening (provided by the central laboratory)
- For subjects taking metformin: at screening, serum creatinine ≥ 124 μ mol/L for men or ≥ 115 μ mol/L for women; no contraindication to the use of metformin (including eGFR) based on the label of the country of investigational site
- ALT levels > 2.0 times the ULN or total bilirubin > 1.5 times the ULN at screening, unless in the opinion of the investigator and as agreed upon by the sponsor's medical officer, the findings were consistent with Gilbert's disease

Source: [Johnson and Johnson submission file]

Risk of bias tables

For guidance see guideline '[Internal validity of randomized controlled trials](#)'.

Table 13. Risk of bias table – study level, active comparator trials DIA3009, DIA3006, DIA3015

Trial	Adequate generation of randomization sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
DIA3009	Yes	Yes	Yes	Yes	Yes	Unclear	High ¹
DIA3006	Yes	Yes	Yes	Yes	Yes	Unclear	High ²
DIA3015	Yes	Yes	Yes	Yes	Yes	Unclear	High ³

Comments:

The options for Risk of bias at study level are “low” and “high”. In case unclear or high risk of bias was identified, the risk of bias at study level was classified as high categorically.

¹ The drop-out rate in the trial was approximately 20% in each arm at 52 weeks, and it was 29% in canagliflozin 100 mg arm, 33.4% in canagliflozin 300 mg arm, and 34.9% in glimepiride arm at 104 weeks. . The last observation carried forward approach is used in the primary efficacy results. The average time in between the end of the study and the last observation collecting point was 44 days in canagliflozin 100 mg arm, 52 days in canagliflozin 300 mg arm and 53 days in glimepiride arm at 52 weeks, and the corresponding numbers of days at 2 years were 186 days, 189 days and 214 days. . Mixed model for repeated measures approach were also conducted for the main outcomes. The characteristics of the dropped-out participants compared with the completed participants have not been reported. The medications used have not been reported in sufficient detail (e.g. doses used in non-study antidiabetic drugs). The rating “unclear” refers to results at 1 year.

² After completion of the 26-week core treatment period, the database was locked and the study was unblinded although subjects, study centre and local personnel remained blinded during the extension period. Outcome assessment was not blinded after the core period (26 weeks). The drop-out rate was 12–13% in canagliflozin 100 mg and 300 mg groups as well as sitagliptin 100 mg group at 26 weeks, and at end of the extension period (52 weeks) the drop-out rate was 18–19% in canagliflozin groups (both) and 22.1% in sitagliptin 100 mg group. The last observation carried forward approach is used in the primary efficacy results. The average time in between the end of the study and the last observation collecting point was 64 days in canagliflozin 100 mg arm, 54 days in canagliflozin 300 mg group and 73 days in sitagliptin 100 mg group, at 52 weeks. Mixed model for repeated measures approach were also conducted for the main outcomes. The characteristics of

the dropped-out participants compared with the completed participants have not been reported. The medications used have not been reported in sufficient detail (e.g. doses used in non-study antidiabetic drugs).

³ The drop-out rate in the trial was high: 32.5% in the canagliflozin arm and 44.4% in the sitagliptin arm. The last observation carried forward approach is used in the primary efficacy results. The average time in between the end of the study and the last observation collecting point was 67 days in canagliflozin 300 mg arm and 78 days in sitagliptin 100 mg arm, at 52 weeks. Mixed model for repeated measures approach were also conducted for the main outcomes. The characteristics of the dropped-out participants compared with the completed participants have not been reported. The medications used have not been reported in sufficient detail (e.g. doses used in non-study antidiabetic drugs).

Table 14. Trial-specific risk of bias assessment, active comparator trials DIA3009, DIA3006, DIA3015

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
TRIAL: DIA3009			
Random sequence generation adequate (selection bias)	Yes	Yes	Quote submission file Appendix 8: "subjects were then randomised... via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). The computer-generated randomisation schedule was prepared before the study. Randomisation was balanced using permuted blocks of 3 subjects per block and stratified according to..." Quote Cefalu et al. Lancet 2013:"Participants were then randomly assigned, in 1:1:1 ratio, by an interactive voice or web response system to be given canagliflozin 100 mg or 300 mg or glimepiride. The sponsor prepared the computer-generated randomisation schedule before the study. Randomisation was balanced with the use of permuted blocks of three patients per block and stratified by whether the patient was taking a stable, protocol-specified dose of metformin before screening versus whether they had either undergone metformin dose adjustment or discontinued use of second antihyperglycemic drug, or both, and by country".
Allocation concealment adequate (selection bias)	Yes	Yes	See above.
Blinding of patients (performance bias)	Yes	Yes	Quote submission file Appendix 8: "Subjects, investigators, and local personnel remained masked to treatment assignment until the final database lock. To maintain masked treatment, study drug was supplied in levels... Subjects assigned to the canagliflozin groups were mock up-titrated." Quote Cefalu et al. Lancet 2013: "After randomization HbA1c and fasting plasma glucose values were masked to staff at the study centres unless values met glycaemic rescue criteria (and were subsequently provided unmasked)."

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
Blinding of treating personnel (performance bias)	Yes	Yes	See above.
Blinding of outcome assessment (detection bias)	Yes	Yes	See above.
Incomplete outcome assessment unlikely (attrition bias)	Yes	Unclear	<p>The drop-out rate in the trial was considerable (submission file appendix 9): at week 52 18.2% in canagliflozin 100 mg arm, 21.6% in canagliflozin 300 mg arm and 19.8% in glimepiride arm. At 104 weeks the drop-out rate was 29% in canagliflozin 100 mg arm, 33.4% in canagliflozin 300 mg arm, and 34.9% in glimepiride arm at 104 weeks. Even though the drop-out rate is similar in each study arm, as a whole it results in a substantial loss of real data.</p> <p>The MAH attempted to replace missing data. Quote submission file main document page 141: "Primary efficacy results were generated using the last observation carried forward (LOCF) method for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred." The average time in between the end of the study and the last observation collecting point was 44 days in canagliflozin 100 mg arm, 52 days in canagliflozin 300 mg arm and 53 days in glimepiride arm at 52 weeks, and the corresponding numbers at 2 years were 186 days, 189 days and 214 days. The drop-out rate at 104 weeks was 29% in canagliflozin 100 mg arm, 33.4% in canagliflozin 300 mg arm, and 34.9% in glimepiride arm. Mixed model for repeated measures approach were also conducted for the main outcomes.</p> <p>The combination of LOCF imputation with exclusion of post rescue data can lead to overstated or understated results.</p> <p>The characteristics of the dropped-out participants compared with the completed participants have not been reported.</p>
ITT principle appropriately implemented (attrition bias)	Yes	Yes	Quote submission file main document page 141: "All reported efficacy analyses are based on the modified intent-to-treat (mITT) populations, which (marginally) differ from ITT, as patients randomised but not initiated on the study medication are excluded (only 2 patients in the glimepiride arm in study DIA3009, ...). For the analysis of change from baseline values for all endpoints, only patients with ≥ 1 post-baseline value could be included... Primary efficacy results were generated using the last observation carried forward (LOCF) method for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred." .The number of patients excluded from the mITT analysis was small (2 patients in DIA3009), and therefore using mITT is not considered to result in risk of attrition bias. .
Selective outcome reporting unlikely (reporting bias)	Yes (question in Appendix 13: "Was the reporting of all relevant outcomes independent of the	Unclear	The results for the prespecified (according to the trial report in clinicaltrials.gov and Appendix 8 in submission file) primary outcomes and most of the secondary outcomes have been reported. Lacking is the proportion of subjects reaching HbA1c less than 6.5% and diastolic blood pressure. Results of unprespecified outcomes reported include percentages of subjects achieving HbA1c target less than 7.0% and without hypoglycaemias, and without hypoglycaemias and weight gain, and without weight gain. MAH has been asked to include subjects achieving HbA1c target without hypoglycaemias as an outcome by the assessor group.

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
	results?")		<p>Quote Cefalu et al. Lancet 2013: "Adverse events indicative of osmotic diuresis, polyuriawere assessed by investigators as mild or moderate in severity, and led to few discontinuations (data not shown). We recorded no notable differences in serum electrolytes, sodium and potassium) with canagliflozin compared with glimepiride (data not shown)."</p> <p>Confidence intervals are not shown for the proportions of patient with documented hypoglycaemia episodes.</p>
Other bias unlikely	Yes (question in Appendix 13: Is the trial free from other aspects that affect the risk of bias?)	Unclear	<p>The medications at end of study (e.g. doses used) in different study groups are not reported in sufficient detail. Use of non-study antidiabetic medicines was allowed during the trial.</p> <p>The trial is sponsored by pharmaceutical industry. There is an agreement between Principal Investigators and the Sponsor that restricts the investigators rights to discuss or publish trial results after the trial is completed: A copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. If requested in writing, such publication will be withheld for up to an additional 60 days Quote Cefalu et al Lancet 2013: "The sponsor of the study had a role in study design and conducts; data collection, analysis, and interpretation; and writing the article. The authors prepared the report with editorial assistance funded by the sponsor. All authors had full access to all study data, were responsible for the integrity of the data and the accuracy of the data analysis, and reviewed, edited and approved the report for publication (four authors are full-time employees of Janssen Research Development, other authors' consultancy or funding research studies or advisory boards or speaker fee)."</p> <p>The incidences of female genital infections and osmotic diuresis-related adverse events were higher in canagliflozin groups compared with glimepiride group. This may have made it possible to predict which treatment arm the patients were assigned to. If this happened, the off-study treatment of the patients may have been affected as well as patient-reported outcomes.</p> <p>Prespecified secondary efficacy endpoints: proportion of patients with documented hypoglycaemic episodes, including biochemically documented episode and severe episodes. Proportions and p values are given, without confidence intervals. AEs were not prespecified primary or secondary endpoints.</p>
TRIAL: DIA3006			
Random sequence generation adequate (selection bias)	Yes	Yes	<p>Quote submission file Appendix 8: "Subjects were randomised via an Interactive Voice Response System/Interactive Web Response System ...once daily for 26 weeks. The computer-generated randomisation schedule was prepared before the study. Randomisation was balanced using permuted blocks of 7 and stratified..."</p> <p>Quote Lavalle-Gonzales et al. 2013: "Participants were randomised to receive canagliflozin 100 mg or 300 mg, sitagliptin 100 mg or placebo (2:2:2:1) once daily for 26 weeks. The computer-generated randomisation schedule</p>

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
			was prepared by the sponsor before the study. Randomisation was balanced using permuted blocks of seven and stratified by whether a participant was on metformin monotherapy or metformin plus sulfonylurea at screening."
Allocation concealment adequate (selection bias)	Yes	Yes	See above.
Blinding of patients (performance bias)	Yes	Yes	Quote submission file Appendix 8: "After completion of the 26-week core treatment period, the database was locked and the study was unblinded for regulatory filing; subjects and study centre and local personnel remained blinded throughout 26-week extension period." Quote Lavalle-Gonzales et al 2013: "After randomisation, HbA1c and FPG values were masked to the study centres unless they met glycaemic rescue criteria. After completion of period I, the database was locked and the study was unblinded by the sponsor for regulatory filing; the participants and the study centre and local sponsor personnel remained blinded throughout period II."
Blinding of treating personnel (performance bias)	Yes	Yes	See above.
Blinding of outcome assessment (detection bias)	Yes	No	See above. According to the quote the outcome assessors were not blinded after the core period.
Incomplete outcome assessment unlikely (attrition bias)	Yes	Unclear	The drop-out rate in the trial was (submission file Appendix 9) at week 26 12.5% in canagliflozin 100 mg arm, 12.0% in canagliflozin 300 mg arm and 12.8% in sitagliptin arm. There was an additional placebo arm in the trial, and the discontinuation rate in this arm at 26 weeks was 15.3%. At end of the extension period (52 weeks) the drop-out rate was 18–19% in canagliflozin groups (both) and 22.1% in sitagliptin 100 mg group. The MAH attempted to replace missing data. Quote submission file main document, page 141: "Primary efficacy results were generated using the last observation carried forward (LOCF) method for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred. "The average time in between the end of the study and the last observation collecting point was 64 days in canagliflozin 100 mg arm, 54 days in canagliflozin 300 mg group and 73 days in sitagliptin 100 mg group, at 52 weeks. Mixed model for repeated measures approach were also conducted for the main outcomes. The combination of LOCF imputation with exclusion of post rescue data can lead to overstated or understated results. The characteristics of the dropped-out participants compared with the completed participants have not been reported.

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
ITT principle appropriately implemented (attrition bias)	Yes	Yes	Quote submission file main document, page 141: "All reported efficacy analyses are based on the modified intent-to-treat (mITT) populations, which (marginally) differ from ITT, as patients randomised but not initiated on the study medication are excluded (only 2 patients in the glimepiride arm in study DIA3009, and 1 patient in the canagliflozin arm in DIA3015). For the analysis of change from baseline values for all endpoints, only patients with ≥ 1 post-baseline value could be included." The number of patients excluded from the mITT analysis was small (no patients in DIA3006), and therefore using mITT is not considered to result in risk of attrition bias.
Selective outcome reporting unlikely (reporting bias)	Yes (question in Appendix 13: "Was the reporting of all relevant outcomes independent of the results?")	Yes	The results for the prespecified (according to the trial report in clinicaltrials.gov and Appendix 8 in submission file) primary outcomes and most of the secondary outcomes have been reported. Lacking is the change in apolipoprotein B that has been assessed in a subset of subjects. Quote Lavalle-Gonzales et al 2013: "The primary hypothesis was that canagliflozin 300 mg is statistically superior to placebo in reducing HbA1c from baseline to week 26. Key secondary hypotheses were statistical superiority of canagliflozin 100 mg to placebo in HbA1c lowering effect at week 26 and non-inferiority of canagliflozin 300 mg or both canagliflozin doses to sitagliptin 100 mg in reducing HbA1c from baseline to week 52. It was designed with pre-specified comparisons between canagliflozin and sitagliptin only at week 52, consistent with the assessment time point commonly used in other active-controlled studies; therefore, statistical comparisons of canagliflozin with sitagliptin at week 26 are not reported." AEs were not prespecified as primary or secondary endpoints. No statistical analysis with p value or CI were done for any AEs outcome.
Other bias unlikely	Yes (question in Appendix 13: Is the trial free from other aspects that affect the risk of bias?)	Unclear	The medications at end of study (e.g. doses used) in different study groups are not reported in sufficient detail. Use of non-study antidiabetic medicines was allowed during the trial. The trial is sponsored by pharmaceutical industry. Quote Lavalle-Gonzales et al 2013: "The sponsor of the study had assistance and contribution to the clinical management, data review and preparation of study report. The authors prepared the report with editorial assistance funded by the sponsor. (four authors are full-time employees of Janssen Research Development, other authors declare funding research studies or advisory boards or speaker fee)." The incidences of female genital infections and osmotic diuresis-related adverse events were higher in canagliflozin groups compared with sitagliptin group. This may have made it possible to predict which treatment arm the patients were assigned to. If this happened, it may have affected the off-study treatment of the patients and patient-reported outcomes.
TRIAL: DIA3015			

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
Random sequence generation adequate (selection bias)	Yes	Yes	<p>Quote submission file Appendix 8: "using an Interactive Voice Response System/Interactive Web Response System. The computer-generated randomisation schedule was prepared before the study, and randomisation was balanced using permuted blocks with 2 stratification criteria..."</p> <p>Quote Schernthaner et al. 2013: "After the placebo run-in period, subjects were randomly assigned to receive oral doses of canagliflozin 300 mg or sitagliptin 100 mg once daily (1:1) using an Interactive Voice Response System/Interactive Web Response System. The computer-generated randomization schedule was prepared by the sponsor before the study, and randomization was balanced using permuted blocks with the following two stratification criteria: whether the prerandomization A1C was >9.0% (75 mmol/mol) and whether a subject underwent the frequently sampled mixed-meal tolerance test (FS-MMTT)."</p>
Allocation concealment adequate (selection bias)	Yes	Yes	See above.
Blinding of patients (performance bias)	Yes	Yes	<p>Quote submission file Appendix 8: "Subjects, investigators, and local personnel remained blinded to treatment assignment and urine samples for glucosuria until all subjects completed the study (Week 52 visit) and the final database was locked."</p> <p>Quote Schernthaner et al 2013: "After randomization, A1C and FPG values and all glucose levels from the FSMMTT were masked to the study centres, unless FPG/A1C values met specific study criteria for discontinuation; similarly, urine glucose results were not reported for urine dipsticks. Subjects, investigators, and local sponsor personnel remained blinded to treatment assignment and urine samples for glucosuria until all subjects completed the study (week 52 visit) and the final database was locked."</p>
Blinding of treating personnel (performance bias)	Yes	Yes	See above.
Blinding of outcome assessment (detection bias)	Yes	Yes	See above.

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
Incomplete outcome assessment unlikely (attrition bias)	Yes	No	<p>The drop-out rate in the trial was (submission file Appendix 9) at week 52 was 32.5% in the canagliflozin 300 mg arm and 44.4% in the sitagliptin arm.</p> <p>Quote Schernthaner et al 2013: "Of 756 randomized subjects, 755 received one or more doses of study drug and were included in the modified intent-to-treat analysis set; 464 (61%) completed the 52-week treatment period. A higher rate of discontinuation was observed with sitagliptin 100 mg (44.4%) than with canagliflozin 300 mg (32.6%); the largest contribution was the discontinuation of subjects who met glycaemic withdrawal criteria (22.5% [sitagliptin] and 10.6% [canagliflozin]), because glycaemic rescue therapy was not provided in this study, with the majority (88%) of these subjects discontinued after week 26. After meeting glycaemic withdrawal criteria, the most common reasons for withdrawal were meeting creatinine or eGFR withdrawal criteria or AEs."</p> <p>Quote submission file main document, page 141: "Primary efficacy results were generated using the last observation carried forward (LOCF) method for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred. The average time in between the end of the study and the last observation collecting point was 67 days in canagliflozin 300 mg arm and 78 days in sitagliptin 100 mg arm, at 52 weeks. Mixed model for repeated measures approach were also conducted for the main outcomes.</p> <p>The combination of LOCF imputation with exclusion of post rescue data can lead to overstated or understated results.</p>
ITT principle appropriately implemented (attrition bias)	Yes	Yes	<p>Quote submission file main document, page 141: "All reported efficacy analyses are based on the modified intent-to-treat (mITT) populations, which (marginally) differ from ITT, as patients randomised but not initiated on the study medication are excluded (...1 patient in the canagliflozin arm in DIA3015). For the analysis of change from baseline values for all endpoints, only patients with ≥ 1 post-baseline value could be included." The number of patients excluded from the mITT analysis was small (1 patient in DIA3015), and therefore using mITT is not considered to result in risk of attrition bias.</p>
Selective outcome reporting unlikely (reporting bias)	Yes (question in Appendix 13: "Was the reporting of all relevant outcomes independent of the results?")	Yes	<p>The results for the prespecified (according to the trial report in clinicaltrials.gov and Appendix 8 in submission file) primary outcomes and most of the secondary outcomes have been reported. Change in diastolic BP and proportion of subjects reaching HbA1c less than 6.5%, proinsulin/insulin ratio are not reported yet they were predefined study endpoints. In a subset of subjects who underwent a frequently-sampled mixed-meal tolerance test, the ratio of C-peptide area under the concentration-time curve to glucose AUC was assessed. The results of this assessment have not been reported.</p> <p>P values are reported for prespecified comparisons only, not for any AEs outcome.</p>
Other bias unlikely	Yes (question in Appendix 13: Is the trial free from other aspects that affect the risk of bias?)	Unclear	<p>The medications at end of study (e.g. doses used) in different study groups are not reported in sufficient detail. Use of non-study antidiabetic medicines was allowed during the trial.</p> <p>The trial is sponsored by pharmaceutical industry. There is an agreement between principal investigators and the sponsor that restricts the principal investigator's rights to discuss or publish trial results after the trial is completed: A copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. If requested in writing, such publication will be withheld for up to an additional 60 days Quote</p>

Bias	MAH submission file judgement (submission file, Appendix 13)	Authors' judgement	Support for authors' judgement (criteria from EUnetHTA guideline: Internal validity of randomized controlled trials and Cochrane Risk of bias tool)
			<p>Schernthaner et al 2013: "The authors prepared the report with editorial assistance funded by the sponsor. (four authors are full-time employees of Janssen Research Development, other authors declare funding research studies or advisory boards or speaker or consulting fee)."</p> <p>The incidence of genital infections (especially in females) was higher in canagliflozin groups compared with glimepiride group. This may have made it possible to predict which treatment arm the patients were assigned to. This possibility may have affected the off-study treatment of the patients, and patient reported outcomes.</p>

Table 15. Risk of bias – outcome level: summarised assessment, active comparator trials DIA3009, DIA3006, DIA3015

Outcome	Clinical effectiveness								
	Study level	Overall survival	[Disease specific mortality]	[HbA1c change]	Proportion achieving HbA1c target]	Proportion achieving HbA1c target without hypoglycaemias	Fasting blood glucose change	Weight change	BMI change
DIA3009	High	-1	-1	High	High	High	High	High	High

Outcome	Clinical effectiveness								
	Study level	Overall survival	[Disease specific mortality]	[HbA1c change]	Proportion achieving HbA1c target	Proportion achieving HbA1c target without hypoglycaemias	Fasting blood glucose change	Weight change	BMI change
DIA3006	High	¹	¹	High	High	High	High	High	High
DIA3015	High	¹	¹	High	High	High	High	High	High

Comments:

The options for risk of bias at outcome level are “low” or “high”. In case high or unclear risk of bias was identified at study level, the risk of bias at outcome level was classified as high categorically.

¹ Not feasible, as the available evidence does not enable to draw any definitive conclusions regarding overall mortality or cause-specific mortality

Table 16. Risk of bias – outcome level: summarised assessment, continued

Outcome ►	Study level	Insulin requirements change	Clinical effectiveness			Adverse events		
			Long-term outcomes	Health-related quality of life	Cardiovascular risk factors	[AE]	[SAE]	[Treatment discount. due to AEs]
Trial ▼								
DIA3009	High	²	³	High	High	High	High	High
DIA3006	High	²	³	High	High	High	High	High
DIA3015	High	²	³	High	High	High	High	High

² Not feasible, as the available evidence does not enable to draw any definitive conclusions regarding changes in insulin requirements induced by canagliflozin compared to its comparators, as this outcome was not assessed in the relevant trials.

³ Not feasible, as the available evidence does not enable to draw any definitive conclusions regarding long-term outcomes as they were not assessed in the relevant trials.

Table 17. Risk of bias – outcome level, active comparator trials DIA3009, DIA3006, DIA3015

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Overall survival¹						
DIA3009	High	-	-	-	-	-
DIA3006	High	-	-	-	-	-
DIA3015	High	-	-	-	-	-
Disease-specific mortality¹						
DIA3009	High	-	-	-	-	-
DIA3006	High	-	-	-	-	-
DIA3015	High	-	-	-	-	-
HbA1C change						
DIA3009	High	Low	Low	Low	Unclear ²	High
DIA3006	High	Low	Low	Low	Unclear ²	High
DIA3015	High	Low	Low	Low	Unclear ²	High
Proportion achieving HbA1c target						
DIA3009	High	Low	Low	Low	Unclear ²	High
DIA3006	High	Low	Low	Low	Unclear ²	High
DIA3015	High	Low	Low	Low	Unclear ²	High

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
Proportion achieving HbA1c target without hypoglycaemias						
DIA3009	High	Low	Low	Low	Unclear ²	High
DIA3006	High	Low	Low	Low	Unclear ²	High
DIA3015	High	Low	Low	Low	Unclear ²	High
Fasting blood glucose change						
DIA3009	High	Low	Low	Low	Unclear ²	High
DIA3006	High	Low	Low	Low	Unclear ²	High
DIA3015	High	Low	Low	Low	Unclear ²	High
Weight change						
DIA3009	High	Low	Low	Low	Low	High
DIA3006	High	Low	Low	Low	Low	High
DIA3015	High	Low	Low	Low	Low	High
BMI change						
DIA3009	High	Low	Low	Low	Low	High
DIA3006	High	Low	Low	Low	Low	High
DIA3015	High	Low	Low	Low	Low	High
Insulin requirements change in patients with insulin¹						

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
DIA3009	High	-	-	-	-	-
DIA3006	High	-	-	-	-	-
DIA3015	High	-	-	-	-	-
Long-term outcomes¹						
DIA3009	High	-	-	-	-	-
DIA3006	High	-	-	-	-	-
DIA3015	High	-	-	-	-	-
Health-related quality of life						
DIA3009	High	Low	Low	Low	Low	High
DIA3006	High	Low	Low	Low	Low	High
DIA3015	High	Low	Low	Low	Low	High
Cardiovascular risk factors (systolic blood pressure, lipids)						
DIA3009	High	Low	Low	Low	Low	High
DIA3006	High	Low	Low	Low	Low	High
DIA3015	High	Low	Low	Low	Low	High
Frequency of hypoglycaemia						
DIA3009	High	Low	Low	Unclear	High	High

Outcome Trial	Risk of bias – study level	Blinding – outcome assessors	ITT principle adequately realized	Selective outcome reporting unlikely	No other aspects according to risk of bias	Risk of bias – outcome level
DIA3006	High	Low	Low	Low	High	High
DIA3015	High	Low	Low	Low	High	High
Frequency of severe hypoglycaemia						
DIA3009	High	Low	Low	Low	High	High
DIA3006	High	Low	Low	Low	High	High
DIA3015	High	Low	Low	Low	High	High
Frequency of adverse events						
DIA3009	High	Low	Low	Low	Low	High
DIA3006	High	High ³	Low	Low	Low	High
DIA3015	High	Low	Low	Low	Low	High
Frequency of serious adverse events						
DIA3009	High	Low	Low	Low	Low	High
DIA3006	High	High ³	Low	Low	Low	High
DIA3015	High	Low	Low	Low	Low	High
<p>comments:</p> <p>The options for risk of bias at outcome level are “low” or “high”. In case high or unclear risk of bias was identified at study level, the risk of bias at outcome level was classified as high categorically.</p> <p>¹ – indicates endpoint was not assessed/reported</p> <p>² Use of non-study antidiabetic drugs was allowed in the relevant trials. This non-study drug use has not been reported in sufficient detail, for example the dosages used are not reported.</p>						

<p>Outcome Trial</p>	<p>Risk of bias – study level</p>	<p>Blinding – outcome assessors</p>	<p>ITT principle adequately realized</p>	<p>Selective outcome reporting unlikely</p>	<p>No other aspects according to risk of bias</p>	<p>Risk of bias – outcome level</p>
<p>³Outcome assessors were not blinded after the core period (possible implications in outcomes that are not measured with laboratory methods, for example).</p>						

GRADE the quality (level) of the evidence

The Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE Working Group) has developed a system for grading the quality of evidence (Higgins and Green 2011). For purposes of systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. Quality of a body of evidence involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The GRADE system entails an assessment of the quality of a body of evidence for each individual outcome.

The GRADE approach specifies four levels of quality. The highest quality rating is for randomized trial evidence. Review authors can, however, downgrade randomized trial evidence to moderate, low, or even very low quality evidence, depending on the presence factors such as limitations in the design and implementation of available studies suggesting high likelihood of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results and high probability of publication bias.

Table 18. Summary of findings table assessed with the GRADE approach.

Outcome	Quality of evidence	Risk of bias (internal validity)	Directness of evidences	Heterogeneity	Precision of effect estimates	Risk of publication bias
Clinical effectiveness						
Overall survival	Very low	High ¹	Indirect	Not applicable	No limitations	Unlikely
Disease-specific mortality	Not assessable	High ¹	Not applicable	Not applicable	Not applicable	Unlikely
HbA1c change						
• direct evidence	Moderate	High ²	Direct	No limitations	No limitations	Unlikely
• indirect evidence	Very low	High ²	Indirect	Not assessed ³	Not assessed ³	Unclear
Proportion achieving HbA1c target						
• direct evidence	Low	High ²	Direct	No limitations	Limitations	Unlikely
• indirect evidence	Very low	High ²	Indirect	Not assessed ³	Not assessed ³	Unclear
Proportion achieving HbA1c target without hypoglycaemias	Low	High ²	Direct	No limitations	Limitations	Unlikely
Fasting blood glucose change						
• direct evidence	Moderate	High ²	Direct	No limitations	No limitations	Unlikely
• indirect evidence	Very low	High ²	Indirect	Not assessed ³	Not assessed ³	Unclear
Weight change						
• direct evidence	Moderate	High ²	Direct	No limitations	No limitations	Unlikely
• indirect evidence	Very low	High ²	Indirect	Not assessed ³	Not assessed ³	Unclear
BMI change						
• direct evidence	Low	High ²	Direct	Limitations	Not assessed	Unlikely
• indirect evidence	Very low	High ²	Indirect	Not assessed ³	Not assessed ³	Unlikely
Insulin requirements change in patients with insulin	Not assessable	High ¹	Not applicable	Not applicable	Not applicable	Unlikely
Long-term outcomes	Very low	High ¹	Only simulations	Not applicable	Not applicable	Unlikely
Health-related quality of life	Low	High ²	Direct	No limitations	Limitations	Unlikely
Systolic blood pressure						
• direct evidence	Moderate	High ²	Direct	No limitations	No limitations	Unlikely
• indirect evidence	Very low	High ²	Indirect	Not assessed ³	Not assessed ³	Unlikely

Outcome	Quality of evidence	Risk of bias (internal validity)	Directness of evidences	Heterogeneity	Precision of effect estimates	Risk of publication bias
Lipids	Low	High ²	Direct	No limitations	Limitations	Unlikely
Adverse events						
Frequency of hypoglycaemia	Moderate (DIA3009) to Low	High	Direct	No limitations	Limitations	High ⁴
Frequency of severe hypoglycaemia	Low	High	Direct	No limitations	Limitations	High ⁴
Frequency of adverse events	Low	High	Direct	No limitations	Limitations	High ⁴
Frequency of serious adverse events	Low	High	Direct	No limitations	Limitations	High ⁴

¹ Mortality cannot be assessed reliably due to the limitations in the trials, such as duration.

² Risk of bias at outcome level high across all efficacy outcomes mainly deriving from high risk of bias at study level across all studies.

³ Not assessed, since the quality of evidence is very low because of indirectness and high risk of bias.

⁴ Funded by industry and authors affiliated with industry (based on published articles).

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Applicability tables

This table pertains to the trials DIA3005, DIA3006, DIA3009, DIA3002, DIA3012, DIA3015, DIA3004, and DIA3010 by Johnson & Johnson (1).

Table 19. Summary table characterising the applicability of a body of studies.

Domain	Description of applicability of evidence
Population	<p>Monotherapy (DIA3005) Age 55.1 - 55.7 years HbA1c 8.0 - 8.1% (64 - 65 mmol/mol) FPG 9.3 - 9.6 mmol/L (167.6 - 173.0 mg/dL) BW 85.8 - 87.6 kg Duration of diabetes: 6.5–6.7 years</p> <p>Dual therapy (DIA3006, DIA3009: on metformin) Age 55.3 - 56.3 years HbA1c 7.8 - 8.0% (62 - 64 mmol/mol) FPG 9.1 - 9.6 mmol/L (164.0 - 173.0 mg/dL) BW 85.4 - 86.9 kg Duration of diabetes: 6.7–7.1 years</p> <p>Triple therapy (DIA3002, DIA3015: on metformin & sulphonylurea; 3012: on metformin & pioglitazone) Age 55.1 - 58.3 years HbA1c 7.9% - 8.1% (63 - 65 mmol/mol) FPG 9.1 - 9.6 mmol/L (164.0 - 173.0 mg/dL) BW 85.8 - 94.4 kg</p> <p>Special populations Postmenopausal women (DIA3010) Age 63.2 - 63.4 y HbA1c 7.7% - 7.8% (61 - 62 mmol/mol) FPG 8.5 - 8.9 mmol/L (153.2 - 160.4 mg/dL) BW 88.4 - 91.1 kg Duration of diabetes: 9.4–9.7 years</p> <p>Moderate renal impairment (DIA3004) Age 67.9 - 69.5 y HbA1c 7.9% - 8.0% (63 - 64 mmol/mol) FPG 8.8 - 9.4 mmol/L (158.6 - 169.4 mg/dL) BW 90.2 - 92.8 kg</p> <p>Values are ranges of means among the intervention groups. (The manufacturer does not report standard deviations.) FPG = Fasting blood glucose; BW = body weight.</p> <p>The trial populations represent middle-aged patients except in the trials on postmenopausal women and patients with renal impairment. The manufacturer does not report the distribution for gender or ethnicity. All trials were multicentre, patients coming from countries all-over the world, and based on the participating countries, the ethnic distribution varies from trial to trial.</p> <p>The majority of the patients were closer to the lower boundary of HbA1c for inclusion (7%) than the upper one (9.5 – 10.5% depending on the trial).</p> <p>Patients with history of severe hypoglycaemia, major cardiovascular event, unstable blood pressure, renal or liver impairment were excluded.</p> <p>Comorbidities were reported for active-controlled trials. In DIA3006, cardiac disorders were prevalent in 20.2% of patients in the sitagliptin arm, in 14.7% of patients in canagliflozin 100 mg arm and in 17.7% of patients in canagliflozin 300 mg arm. Nervous system disorders were reported in 21.9% of patients in the sitagliptin 100 mg arm, in 17.9% of patients in canagliflozin 100 mg arm and in 15.5% of patients in canagliflozin 300 mg arm. In DIA3009, cardiac disorders were prevalent in 19.7% of patients in glimepiride arm, in 14.9% of patients in canagliflozin 100 mg arm and in 17.3% of patients in canagliflozin 300 mg arm. In DIA3015, cardiac disorders were prevalent in 18.5% of patients in sitagliptin 100 mg arm and in 22.8% of patients in canagliflozin 300 mg arm. Endocrine disorders were reported in 5.6% of patients in sitagliptin 100 mg arm and in 11.7% of patients in canagliflozin 300 mg arm.</p> <p>Concomitant medications are reported for 3 trials (DIA3006, DIA3009, DIA3015): about 50 – 65% of the participants were using agents acting on renin-angiotensin system, about 30 – 40%</p>

	<p>antithrombotic drugs, and about 40 – 55% lipid modifying agents implying that the participants' had an increased risk for cardiovascular disease also due to hypertension and hypercholesterolemia.</p> <p>The trial participants seem to represent the healthiest ones among the diabetes patients so caution is needed when generalizing the findings to usual range of diabetic patients Whether ethnicity modifies the treatment effect is unknown.</p>
Intervention	<p>Canagliflozin 100 mg (all trials except DIA3015) Canagliflozin 300 mg (all trials) Canagliflozin is a new drug and has been in experimental use only.</p>
Comparators	<p>Placebo (all trials except DIA3009, DIA3015) Glimepiride 1-8 mg (DIA3009) Sitagliptin 100 mg (DIA3006, DIA3015) The doses of glimepiride and sitagliptin are similar to those commonly used in clinical practice.</p>
Outcomes	<p>Follow-up times 26 weeks (all trials except DIA3009, DIA3015) 52 weeks (DIA3006, DIA3009, DIA3015)</p> <p>Main efficacy outcome (all trials) Change in HbA1c (26 wk)</p> <p>Other efficacy outcomes (vary from trial to trial) HbA1c <7% (goal) at (26 wk) Change in fasting plasma glucose (26 wk) Change SBP (26 wk) % Change in HDL-cholesterol (26 wk) % Change in triglycerides (26 wk) % Change in body weight (26 wk)</p> <p>Safety outcomes Frequency of adverse events 26 weeks and 52 weeks Frequency of severe adverse events 26 weeks and 52 weeks Hypoglycaemia Frequency of hypoglycaemia 26 weeks and 52 weeks Frequency of severe hypoglycaemia 26 weeks and 52 weeks</p> <p>Other safety outcomes Genital mycotic infection, Urinary tract infection, Osmotic diuresis 26 weeks and 52 weeks</p> <p>The efficacy outcomes are surrogate endpoints. The purpose of the treatment of diabetes is to prevent clinical complications, but the evidence on clinical events is scanty. The follow-up times are too short for reliable evaluation of either clinical effectiveness or long-term safety.</p>
Setting	<p>All trials were multicentre with centres in countries all-over the world. The manufacturer does not report the nature of the clinical centres (e.g., hospital outpatient clinics, general practices) participating in the trials.</p>

APPENDIX 2: RESULT CARDS

HEALTH PROBLEM AND CURRENT USE OF TECHNOLOGY

[A0001] For which indication/ for what purposes is the canagliflozin used and are there any contra-indications?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- SmPC of canagliflozin

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Canagliflozin is indicated for the treatment of adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications;

Add-on therapy

Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

According the SmPC of canagliflozin, canagliflozin is contraindicated in patients who are hypersensitive to canagliflozin or to any of the excipients. According the Micromedex Drugdex evaluation canagliflozin is **contraindicated** in patients on/with:

a) dialysis:

b) hypersensitivity to canagliflozin:

c) renal impairment, severe (estimated GFR less than 30 mL/min/1.73 m²) or ESRD.

Safety and effectiveness not established in paediatric patients younger than 18 years.

Precautions:

- A)** elderly; symptomatic hypotension may occur; monitoring recommended; correct hypovolemia prior to initiating therapy
- B)** genital mycotic infections have been reported; uncircumcised men or patients with prior genital mycotic infections are at increased risk; monitoring recommended
- C)** hepatic impairment, severe; not recommended
- D)** hyperkalaemia may occur; increased risk in patients with moderate renal impairment receiving medications that interfere with potassium excretion (e.g., potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system); monitoring recommended
- E)** hypersensitivity reactions (e.g., generalized urticaria), some serious, have been reported; discontinue use if occurs
- F)** hypoglycaemia has been reported; concomitant use with insulin or insulin secretagogues (e.g., sulfonylureas) may increase risk; dose reduction of insulin or sulfonylurea may be required
- G)** hypotension, symptomatic, has been reported, especially in those with low systolic blood pressure, elderly, renally impaired (estimated GFR less than 60 mL/min/1.73 m²), and those receiving diuretics or drugs that interfere with the renin-angiotensin-aldosterone system; monitoring recommended; correct hypovolemia prior to initiating therapy
- H)** LDL-C increases have been reported; monitoring recommended
- I)** renal function abnormalities (e.g., increased serum creatinine and decreased estimated GFR) and renal impairment have been reported; increased risk in patients who are hypovolemic; correct hypovolemia prior to initiating therapy; monitoring recommended; discontinuation may be necessary
- J)** renal impairment; dosage adjustment required for estimated GFR of 45 to less than 60 mL/min/1.73 m²; use not recommended for estimated GFR of less than 45 mL/min/1.73 m²

Serious Adverse Effects:

- a) Angioedema
- b) Hyperkalaemia, Severe
- c) Hypersensitivity reaction
- d) Hypoglycaemia, Severe
- e) Hypovolemia
- f) Mycosis, Male genital
- g) Pancreatitis
- h) Renal impairment

Teratogenicity/Effects in Pregnancy

- U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

Drugs interactions

Table 20. Canagliflozin Drug-Drug Combinations interactions

	Interaction
Digoxin	Coadministration of canagliflozin with digoxin increased digoxin AUC and C _{max} by 20% and 36%, respectively.
Fosphenytoin	Coadministration of canagliflozin (a substrate of UDP-glucuronosyltransferase [UGT]) with rifampin (a nonselective inducer of UGT enzymes [including UGT1A9 and UGT2B4]) decreased canagliflozin AUC by 51% and C _{max} by 28%,

	Interaction
	potentially reducing canagliflozin efficacy.
Phenobarbital	Coadministration of canagliflozin (a substrate of UDP-glucuronosyltransferase [UGT]) with rifampin (a nonselective inducer of UGT enzymes [including UGT1A9 and UGT2B4]) decreased canagliflozin AUC by 51% and Cmax by 28%, potentially reducing canagliflozin efficacy.
Phenytoin	Coadministration of canagliflozin (a substrate of UDP-glucuronosyltransferase [UGT]) with rifampin (a nonselective inducer of UGT enzymes [including UGT1A9 and UGT2B4]) decreased canagliflozin AUC by 51% and Cmax by 28%, potentially reducing canagliflozin efficacy.
Rifampin	Coadministration of canagliflozin (a substrate of UDP-glucuronosyltransferase [UGT]) with rifampin (a nonselective inducer of UGT enzymes [including UGT1A9 and UGT2B4]) decreased canagliflozin AUC by 51% and Cmax by 28%, potentially reducing canagliflozin efficacy.
Ritonavir	Coadministration of canagliflozin (a substrate of UDP-glucuronosyltransferase [UGT]) with rifampin (a nonselective inducer of UGT enzymes [including UGT1A9 and UGT2B4]) decreased canagliflozin AUC by 51% and Cmax by 28%, potentially reducing canagliflozin efficacy.

Source: MICROMEDEX Drugdex database 2.0, 2014.

Discussion

Two different sources of data listed different contraindications for canagliflozin. According to the SmPC, canagliflozin is contraindicated in patients who are hypersensitive to canagliflozin or to any of the excipients. According to the Micromedex Drugdex evaluation, canagliflozin is contraindicated in patients on/with dialysis; hypersensitivity to canagliflozin and renal impairment, severe (estimated GFR less than 30 mL/min/1.73 m²) or ESRD.

References

canagliflozin CHMP Report
 Johnson & Johnson submission file
 MICROMEDEX Drugdex database 2.0
 SmPC of canagliflozin

Importance and transferability

How important is this piece of information for decision making?

- Critical
 Important
 Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

- Completely
 Partly
 Not

HEALTH PROBLEM AND CURRENT USE OF TECHNOLOGY

[A0002] What is the precise definition of Type 2 Diabetes Mellitus (T2DM) and which diagnosis is given to Type 2 DM according to ICD-10?

What are the main features of Type 2 DM?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at: <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0002a and A0002b Results cards of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Diabetes Mellitus (DM) is defined as a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, World Health Organization 2006]. Several types of DM exist that can be classified into Type 1 and Type 2 DM, gestational diabetes and other less common forms of diabetes that are caused by genetic defects, endocrine pancreas disorders, endocrinopathies or infections or that are medication-induced [Rieder 2004].

Criteria for the diagnosis of DM include one of the following:

- Fasting Plasma Glucose (FPG) ≥ 7.0 mmol/l; or
- Plasma glucose ≥ 11.1 mmol/l at 2 h after a 75 g oral glucose load (oral glucose tolerance test (OGTT)); or
- Random blood glucose concentration ≥ 11.1 mmol/l in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis; or
- Haemoglobin A1c (HbA1c) $> 6.5\%$.

The results should be confirmed by repeat testing unless unequivocal hyperglycaemia is present [American Diabetes Association 2013, Fauci 2013, Gale 2012, World Health Organization 2011].

Type 2 DM results from a progressive insulin secretory defect with a variable degree of insulin resistance in the background [American Diabetes Association 2013, Fauci 2013, Gale 2012].

People are normally thought to have Type 2 DM if they do not have Type 1 diabetes (rapid onset, often in childhood, insulin dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. However, there can be uncertainty in the diagnosis, particularly in overweight people of younger age, children or adolescents. The true diagnosis may become more obvious over time [American Diabetes Association 2013, The Royal College of Physicians 2008]. According to the ICD-10 classification, the code for Type 2 DM is 'E11' [International Statistical Classification of Diseases and Related Health Problems 2013b].

The underlying disorder for Type 2 DM is usually insulin insensitivity combined with a failure of pancreatic insulin secretion to compensate for increased glucose levels. The insulin insensitivity is usually evidenced by excess body weight or obesity, and exacerbated by overeating and inactivity. It is commonly associated with raised blood pressure and a disturbance of blood lipid levels. The insulin deficiency is progressive over time, leading to a need for lifestyle change often combined with blood glucose lowering therapy [National Institute for Health and Clinical Excellence 2011].

Discussion

No comment.

References

- American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2013; 36:S11-S66.
- Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. *Clinical Medicine*. 8th ed. Edinburgh: Elsevier 2012:1001-45.
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- NICE. Preventing type 2 diabetes. Population and community level interventions. 2011. [cited 12 Febr 2014]. Available from; <http://guidance.nice.org.uk/PH35>
- Obesity and Diabetes Mellitus. In: Longo D, Fauci A, Braunwald E , et al, eds.. *Harrison's manual of medicine*. 18th edition: New York: McGraw-Hill; 2013:1137-44.
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- The Royal College of Physicians. *Type 2 diabetes. National clinical guideline for primary and secondary care (update)*. London: The Royal College of Physicians; 2008.
- World Health Organization. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia*. 2006.
- World Health Organization. *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus*. Geneva: World Health Organisation; 2011.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0003] What are the known risk factors for the Type 2 Diabetes Mellitus (T2DM)?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0003 Results card of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Increasing age, obesity, ethnicity and family history are the four major determinants of Type 2 DM [Gale 2012]. Being overweight or obese is the main contributing factor for Type 2 diabetes, increasing the risk 80-100 fold [Gale 2012]. In addition, having a large waist circumference increases the risk of developing Type 2 diabetes. Men are at high risk if they have a waist circumference of 94–102 cm (37.0–40.0 inches). They are at very high risk if it is more than 102 cm. Women are at high risk if they have a waist circumference of 80–88 cm (31.5–35.0 inches). They are at very high risk if it is more than 88 cm. Some population groups, for example South Asian adults or older people may be at risk of developing Type 2 DM even if they have a BMI lower than the overweight classification [National Institute for Health and Clinical Excellence

2011]. Also, high rates affect people of Middle-eastern and Hispanic American origin living western lifestyles [Gale 2012].

Discussion

No comment.

References

Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine. 8th ed. Edinburgh: Elsevier 2012:1001-45.

NICE. Preventing type 2 diabetes. Population and community level interventions. 2011. [cited 12 Febr 2014]. Available from; <http://guidance.nice.org.uk/PH35>

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0004] What is the natural course of the Type 2 Diabetes Mellitus (T2DM)?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0004a Results card of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Type 2 DM is preceded by an asymptomatic stage, called prediabetes that is characterised by mild hyperglycaemia, insulin resistance, and early decrements in insulin secretory capacity [Inzucchi 2012]. Under certain circumstances, Type 2 DM can lead to acute situations of metabolic disturbance.

Diabetes is usually irreversible and its late complications result in reduced life expectancy [Gale 2012, Inzucchi 2012]. In the long term, Type 2 DM increases the risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life [Fauci 2013, Gale 2012, World Health Organization 2006]. Additionally, Type 2 DM is associated with increased risk of further diseases such as cancer, psychiatric diseases, cognitive decline or chronic liver disease [Inzucchi 2012].

Many people with Type 2 DM have the same risk of a cardiovascular event as someone without diabetes who has already had their first heart attack; people with diabetes and a previous cardiovascular event are at very high risk – around 10 times the background population [The Royal College of Physicians 2008].

Discussion

No comment.

References

Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine. 8th ed. Edinburgh: Elsevier 2012:1001-45.

Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes. A patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012:1364-79.

Obesity and Diabetes Mellitus. In: Longo D, Fauci A, Kasper D, , et al, eds. Harrison's manual of medicine. 18th ed. New York: McGraw-Hill; 2013:1134-44

The Royal College of Physicians. Type 2 diabetes. National clinical guideline for primary and secondary care (update). London: The Royal College of Physicians; 2008.

World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0005] What is the burden (main symptoms and consequences) of the Type 2 Diabetes Mellitus (T2DM) for the patient?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0005 Results card of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Clinical presentation of diabetes can be acute, subacute or asymptomatic. Common symptoms are polyuria, polydipsia, weight loss, thirst, fatigue, weakness, blurred vision, superficial infection, poor wound healing and paraesthesias [American Diabetes Association 2013, Fauci 2013, Gale 2012].

Apart from adverse health consequences, Type 2 DM is associated with diminished quality of life [World Health Organization 2006]. Many studies have shown a relationship between diabetes and an individual's health-related quality of life (HRQoL), which demonstrate that individuals with diabetes have a lower quality of life than those without diabetes in the general population.

In addition to improved HbA1c levels, effective management of T2DM may result in improvement in individuals' quality of life. Bergenstal and colleagues, 2011, evaluated the clinical effectiveness of exenatide BID in 452 people living with T2DM and measured changes in Impact of Weight on Quality of Life-Lite (IWQOL-Lite) scores over 12 months as part of the study. Compared with baseline values, there was a mean improvement of 2.88 points in the total IWQOL-Lite score at 6 months ($P = 0.012$) and 4.56 points at 12 months ($P = 0.001$). Significant improvements were seen in all IWQOL-Lite domains at 12 months, with the exception of physical function, thus demonstrating the quality-of-life benefits of T2DM treatment.

Discussion

No comment.

References

American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2013; 36:S11-S66.

Bergenstal RM, Garrison LP, Jr., Miller LA, et al. Exenatide BID Observational Study (ExOS): results for primary and secondary endpoints of a prospective research study to evaluate the clinical effectiveness of exenatide BID use in patients with type 2 diabetes in a real-world setting. Curr Med Res Opin. 2011;27:2335-42.

Gale E, Anderson J. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, eds. Clinical Medicine. 8th ed. Edinburgh: Elsevier 2012:1001-45.

Obesity and Diabetes Mellitus. In: Longo D, Fauci A, Kasper D, , et al, eds. Harrison's manual of medicine. 18th ed.: New York: McGraw-Hill; 2013:1134-44.

World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0006] What is the burden of the Type 2 Diabetes Mellitus (T2DM) for society (prevalence, incidence, costs)?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at

<http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>; ☒

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0006 Results card of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Type 2 DM is considered a global health problem. The prevalence of Type 2 DM is increasing worldwide as well as in Europe due to the increasing prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis thanks to better cardiovascular risk protection [The Royal College of Physicians 2008, World Health Organization 2006]. DM is connected with serious morbidity and significant mortality, as fifth leading cause of death worldwide [Fauci 2013].

According to the International Diabetes Federation [International Diabetes Federation (IDF) 2013] 366 million people *worldwide* had diabetes in 2011 and the number is expected to rise to 552 million by 2030. However, 80% of people with diabetes live in low- and middle-income countries. Type 2 DM accounts for 85% to 95% of all diabetes cases [International Diabetes Federation (IDF) 2013].

The WHO stated in 2002 that in *Europe* 22.5 million people suffer from diabetes, of whom 80%-95% have Type 2 DM [World Health Organization 2002]. Data from the International Diabetes Federation show considerably higher figures of 52.8 million people (20-79 years) in 2011 (8.1%) for the European region [International Diabetes Federation (IDF) 2013].

The disease has changed from an 'old people's disease' to a disease afflicting people in the first half of their life [World Health Organization 2002]. The greatest number of people with diabetes is in the 40-59-years age group and, globally, there is little gender distribution [International Diabetes Federation (IDF) 2013].

In a WHO-estimation prevalence of DM overall in adults >20 years was 2.1% or 130,000 in 2000. 55% of those were female. In a health survey in 1999 prevalence of self-reported DM was also 2.1% [Rieder 2004]. Other data show a prevalence of Type 2 DM of 6% [Rathmanner 2006, Statistik Austria 2010]. The standardised discharge rates with the diagnosis DM were 546.44 per 100,000 inhabitants of the same age, sex and federal state (544.75 for men, 548.04 for women) [Rieder 2004]. The prevalence of Type 2 diabetes increases with age and body weight.

Country-Specific Estimates of Type 2 Diabetes Mellitus Incidence and Prevalence are presented below in Table 21.

Table 21. Country-Specific Estimates of Type 2 Diabetes Mellitus Incidence and Prevalence

Country	Source, year	Link	Incidence of T2DM	Prevalence of T2DM
Austria	2013	http://www.aktiv-e-diabetiker.at/index.php?article_id=451	n.a.	Only estimates available: 400-600k; 300k treated
Belgium	IDF 2012 Integoproject 2011. Chronische aandoeningen: incidentie en prevalentie. Beschikbaar	International Diabetes Federation. IDF Diabetes Atlas, 5th edn., Brussels, Belgium: International	433/100 000 person years, corresponds with 45 000 new type 2 diabetes patients a year (Intego)	547 340 with diabetes of which 80-90% with type 2. Approximately 227 530 don't know they have diabetes (1/3). Prevalence according to IDF is 7.03% for diabetes and 9.64% for prediabetes (20-79 years old). According to another source (farmanet) prevalence is 8.1% in adults above 40

Country	Source, year	Link	Incidence of T2DM	Prevalence of T2DM
	op http://www.intego.be Van der Heyden J., Mimildis H., Bartholomeeusen S., Vanthomme K., Van Casteren V. Tafforeau J. Diabetesprevalentie in België: vergelijking van beschikbare data. Vlaams tijdschrift voor Diabetologie	Diabetes Federation, 2011 (with update 2012)		years or a prevalence of 4.3% for total Belgian population (all ages)
Bulgaria	2008, National Guidelines	http://www.endo = bg.com/node/13 1	n.a	520 000, 8.3% of the population
Cyprus	2009, Cyprus Diabetic Association, Epidemiological Study,		7-8%	10%
Czech Republic	2011, Zvolsky M: Activity in the field of diabetology, care for diabetics in 2011, Volume: 39/12, ÚZIS ČR, 2012.	http://www.uzis. cz/rychle- informace/cinno st-oboru- diabetologie- pece-diabetiky- roce-2011	2.4%	8%
Croatia	HRVATSKI ZDRAVSTVENO- STATISTIČKI LJETOPIS ZA 2012. GODINU- Croatian Health Service Yearbook, 2012	http://www.hzjz. hr/publikacije/00 _2012_WEB.pdf	NA	8.5% In Croatia, the prevalence of DM is 6.1%. The majority (90%) have Type 2 DM [Metelko 2008]. According to the Croatian Registry [Croatian Diabetes Registry 2013, Croatian National Institute of Public Health 2013], the overall number of patients registered is 115,149, while in 2012 registrations were collected for 32,572 patients.
Denmark	Institute for Rational Pharmacotherapy (IRF), 2013	http://www.sst.d k/Webudgivelser /Tal%20paa%20 diabetes%20i%2 0kommunerne.a spx	0.6%	4.4%
Estonia	2011 data		42 000	77 529
Finland	Kaypahoito, 2013	http://www.diabe tes.fi/en/finnish _diabetes_associ ation/diabetes_i n_finland	0.7%	4.3%
France	IGAS, 2012	IGAS report	2.7 million	4.4% (2009)
Germany	Wilke T et al., 2013	Incidence and prevalence of type 2 diabetes mellitus in Germany	0.26% (statistical projection 2009)	5.75% (statistical projection 2009)
Greece	Hellenic diabetes association, 2013	http://www.ede.g r/		8%
Hungary	Vokó Z., Nagyjánosi L., Kaló Z.: Direct health care cost of diabetes	http://egk.tatk.el te.hu/index.php? option=com_doc	n.a.	Around 500 000

Country	Source, year	Link	Incidence of T2DM	Prevalence of T2DM
	mellitus in Hungary. LAM 2009;19(12):775–780;2009	man&task=doc_download&gid=548.		
Ireland	Institute of Public Health, Diabetes Briefing, 2012	LINK		<p><i>(All figures refer to Type 1&2)</i></p> <p>In 2010 it is estimated that more than 135 000 (8.9%) adults aged 45+ years have diabetes.</p> <p>This estimate consists of more than 94 000 (6.2%) adults aged 45+ years who had clinically diagnosed diabetes in the previous 12 months and more than 41 000 (2.7%) adults aged 45+ years with undiagnosed diabetes.</p> <p>More than 12 000 (0.7%) adults aged 18-44 years have clinically diagnosed diabetes. There are no data on undiagnosed diabetes among adults aged 18-44 years.</p> <p>The rate of clinically diagnosed diabetes for all adults aged 18+ years is 3.2% (106 000 people).</p>
	Institute of Public Health, Making Chronic Conditions Count, 2010	LINK		2007: 143 618 adults aged 20+ have diabetes (Type 1 and 2), with a prevalence estimate of 4.5%.
	IDF, The Policy Puzzle, 3 rd Edition, 2011	LINK		(All Diabetes, of those aged 20-70) 2011: 6.1% (191 380)
	Irish College of General Practitioners, 2008	http://www.icgp.ie/speck/properties/asset/asset.cfm?type=Document&id=DE8B3956-19B9-E185-839C541F594AB5F2&property=document&filename=A_Practical_Guide_to_Integrated_Type_II_Diabetes_Care.pdf&revision=tip&mimetype=application%2Fpdf&app=icgp&disposition=attachment		It affects nearly 5% of Irish adults; however, the true prevalence is underestimated. ¹
	National Medicines Information Centre, 2012	LINK		It affects approximately 5% of Irish adults; however, the true prevalence is probably underestimated. ^{2,3}
Italy	ISTAT 2012	http://www3.istat.it/dati/catalogo/20121218_00/contenuti.html "sanità e salute" page 48	6/100 000/year	5.5% of Italian population (3 268 000 people with diabetes – 3 104 600 people with T2DM)
Latvia	Local Health Insurance report 2010	http://www.google.lt/url?sa=t&rct=j&q=&esrc=s&frm=1&source=w	54 000	121 786

Country	Source, year	Link	Incidence of T2DM	Prevalence of T2DM
		eb&cd=1&cad=rja&ved=0CCwQFjAA&url=http%3A%2F%2Fwww.vmnvd.gov.lv%2Fuploads%2Ffiles%2F4e0f4110cf5e2.doc&ei=Y0mnUfz7Jl6BPbn8gfAl&usq=AFQjCNGECNlrQAZuDgUbc4Jw3CrfWYGHgA&sig2=7u98-YrtGHim2xPbX7zBDQ		
Lithuania	2012, Lithuanian health centre	http://www.hi.lt/images/leid2012.pdf	86 826	175 764
Luxembourg	2005	http://www.sante.public.lu/fr/maladies-traitements/027-diabete/recherche-scientifique/index.html	4.42%	
Malta	2012 2005	http://www.oecd-ilibrary.org/docserver/download/8112121ec017.pdf?expires=1369122034&id=id&accname=guest&checksum=9F814B34C9457FF2672F248FD387867B http://www.um.edu.mt/umms/mmj/PDF/80.pdf	10	6.9
Netherlands	National Kompas Volksgezondheid	http://www.naalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/endoecriene-voedings-en-stofwisselingsziekten-en-immuniteitsstoornissen/diabetes-mellitus/omvang/	78 300 T2DM	720 900 T2DM + Approximately 25% don't know they have diabetes
Poland	2008, Prevalence of diabetes and cardiovascular risk factors of industrial area in southern Poland. Witteck A et al. Exp. Clin. Endocrinal Diabetes. 2009 Jul; 117(7):350-3.	link	8.06% (2.52%) – for both types	No data

Country	Source, year	Link	Incidence of T2DM	Prevalence of T2DM
Portugal	Relatório do Observatório Nacional da Diabetes, 2012	Annual Report of the National Diabetes Observatory - Portugal	Incidence (2011): 652 new cases of Diabetes per 100 000 inhabitants (all types).	Prevalence (2011): 12.7% (all types; population 20-79 yrs).
Romania	IDF, 2012	IDF Diabetes Atlas	No official data available, but according to different publications, more than 50 000 new cases per year	According to the latest update (2012) of IDF's Diabetes Atlas, diabetes prevalence in Romania is 9.29% in adults (20-79).
Slovakia	2008, Mokaň M et al.: Prevalence of diabetes mellitus and metabolic syndrome in Slovakia, Diabetes research and clinical practice, Volume 81, Issue 2, August 2008, Pages 238–242.	http://www.sciencedirect.com/science/article/pii/S0168822708001800	1.7%	7%
Slovenia	National Diabetes Prevention and Care Development Programme 2010-2020, April 2010	http://www.mz.gov.si/fileadmin/mz.gov.si/pageupload/mz_dokument/delovna_podrocja/javno_zdravje/diabetes/National_Diabetes_Prevention_and_Care_Development_Programme_e.pdf	5000 patients/year	125 000 patients, 6.25 % of total population (95% type 2)
Spain	Di@bet.es Study, 2012 Spanish Ministry of Health, 2006	CIBERDEM website Spanish Ministry of Health website	Prevalence between 8.1 and 10.8 cases per 1000 habitants.	From the Di@bet.es Study, the most comprehensive study conducted in Spain, the total prevalence = 13.8% <ul style="list-style-type: none"> • Known = 7.8% • Unknown = 6.0%
Sweden	The National Board of Health and Welfare - Socialstyrelsen, 2011	https://www.ndr.nu/pdf/Arsrapport_NDR_2011.pdf	0.5%	7.4
United Kingdom	2011, 'Diabetes in the UK 2012'	http://www.diabetes.org.uk/Documents/Reports/Diabetes-in-the-UK-2012.pdf		2 621 000 (4.1%)
	2011, National Diabetes Audit Executive Summary 2010-2011	http://www.hscic.gov.uk/catalogue/PUB06325		Prevalence of 4.07%

Abbreviations: T2DM: Type 2 Diabetes Mellitus

Source: Balanda et al. making Diabetes Count. A systematic approach to estimating population prevalence on the island of Ireland in 2005. The Institute of Public Health.

Harkins V, A Practical Guide to Integrated type 2 diabetes care, Department of Health and Children, Irish College of General Practitioners and the Irish Endocrine Society published June 2008, downloaded from www.icgp.ie on the 23rd December 2011.

Johnson & Johnson submission file, Appendix 3.

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD), guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary, European Heart Journal 2007; 28:88-136.

The publication of the Global Burden of Disease Study 2010⁴⁴ estimated that 1.3 million deaths were attributable to diabetes in 2010, approximately double the number from 20 years ago. T2DM was ranked 13th, 14th, and 33rd in leading causes of years of life lost in Western, Central, and Eastern Europe, respectively, compared with the global rank of 19 [Lozano 2012].

The costs of diabetes internationally range from 5% to 10% of the total health care spending [Rieder 2004, World Health Organization 2002]. A cost-of-illness study that covered eight European countries estimated annual direct medical costs/patient of € 2,834 and € 29 billion in total [Jönsson 2002].

Estimates indicate that at least USD 131 billion was spent on healthcare due to diabetes in the Europe Region in 2011, accounting for almost one-third of global healthcare expenditures due to diabetes [International Diabetes Federation (IDF) 2013].

Discussion

No comment.

References

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- World Health Organization. The European Health Report 2002. Copenhagen: World Health Organization; 2002.
- World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0007] What is the target population in this assessment?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

In this assessment the target population are:

Adults (≥ 18 years) with type 2 diabetes mellitus (T2DM) with inadequate glycaemic control on oral anti-diabetic therapies and/or insulin

Dual therapy: Adults with type 2 diabetes with inadequate glycaemic control on monotherapy with either metformin or a sulfonylurea.

Triple therapy: Adults with type 2 diabetes with inadequate glycaemic control on dual therapy with either of the following:

- metformin in combination with a sulfonylurea
- metformin **or** a sulfonylurea in combination with a thiazolidinedione, a DPP-4 inhibitor, or a GLP-1 analogue.

Add-on therapy to insulin:

Adults with type 2 diabetes that is inadequately controlled on monotherapy with insulin or on therapy with insulin and up to two other oral agents.

Discussion

No comment.

References

canagliflozin CHMP Report

Johnson & Johnson submission file

MICROMEDEX Drugdex database 2.0

Rapid Relative Effectiveness Assessment of canagliflozin (Invokana) for the treatment of Type 2 Diabetes Mellitus, Project ID: WP5-SA-2, Project description and planning.

SmPC of canagliflozin

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0011] How much is the canagliflozin utilised (What is the expected annual utilisation of canagliflozin)?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

The expected annual utilisation of canagliflozin is reported for France (Table 22) and Germany (Table 23).

Patient Share

For simplification of the analysis, 3 patient share scenarios are presented representing 2.5%, 5.0%, and 7.5%. The daily dose of canagliflozin is either 100 mg or 300 mg according to the level of glycaemic control needed. For the purpose of this analysis Manufacturer used a 50% distribution of eligible patients between the 100-mg and 300-mg canagliflozin tablets. Furthermore, they applied an equal distribution between package sizes of 30, 90, and 100 tablets per pack. The time frame of this analysis is 1 year.

Table 22. Canagliflozin 100 mg and 300 mg Patient Share Estimations in France

Canagliflozin 100 mg patient share	2.5%	5.0%	7.5%
Yearly consumption in mg per 100 000 inhabitants	733 650	1 470 950	2 204 600
Packs (100 mg*30) per 100 000 inhabitants per year (1/3)	82	163	245
Packs (100 mg*90) per 100 000 inhabitants per year (1/3)	27	54	82
Packs (100 mg*100) per 100 000 inhabitants per year (1/3)	24	49	73
Canagliflozin 300 mg patient share	2.5%	5.0%	7.5%
Consumption in mg per 100 000 inhabitants per year	2 200 950	4 412 850	6 613 800
Packs (300 mg*30) per 100 000 inhabitants per year (1/3)	82	163	245
Packs (300 mg*90) per 100 000 inhabitants per year (1/3)	27	54	82
Packs (300 mg*100) per 100 000 inhabitants per year (1/3)	24	49	73

Source: Johnson & Johnson submission file

Table 23. Canagliflozin 100 mg and 300 mg Patient Share Estimations in Germany

Canagliflozin 100 mg patient share	2.5%	5.0%	7.5%
Yearly consumption in mg per 100 000 inhabitants	525 600	1 047 550	1 573 150
Packs (100 mg*30) per 100 000 inhabitants per year (1/3)	58	116	175
Packs (100 mg*90) per 100 000 inhabitants per year (1/3)	19	39	58
Packs (100 mg*100) per 100 000 inhabitants per year (1/3)	18	35	52
Canagliflozin 300 mg patient share	2.5%	5.0%	7.5%
Consumption in mg per 100 000 inhabitants per year	1 576 800	3 142 650	4 719 450
Packs (300 mg*30) per 100 000 inhabitants per year (1/3)	58	116	175
Packs (300 mg*90) per 100 000 inhabitants per year (1/3)	19	39	58
Packs (300 mg*100) per 100,000 inhabitants per year (1/3)	18	35	52

Source: Johnson & Johnson submission file

Discussion

No comment.

References

Johnson & Johnson submission file

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0020] What is the marketing authorisation status of the canagliflozin?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Canagliflozin has recently been approved by the US Food and Drug Administration (FDA) and was given marketing authorisation in Australia on 6 September 2013. The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the product Invokana (100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 diabetes on 19 September 2013. This recommendation was forwarded to the European Commission, which approved the product on 22 November 2013. The reimbursement status of canagliflozin in different EU countries is decided at national level.

The indication recommended by the CHMP is as follows:

Invokana is indicated in adults aged 18 years and older with type-2 diabetes mellitus to improve glycaemic control as:

Monotherapy

When diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.

Add-on therapy

Add-on therapy with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control. The active substance of Invokana, canagliflozin, is a blood glucose-lowering medicine. It works by blocking a protein in the kidney called the human sodium-glucose co-transporter 2 (SGLT2). This reduces glucose re-absorption in the kidney leading to glucose excretion in the urine, thereby lowering levels of glucose in the blood of patients with type-2 diabetes.

The most common side effects with canagliflozin are hypoglycaemia (when used in combination with insulin or a sulphonylurea), vulvovaginal candidiasis, urinary-tract infection, and polyuria or pollakiuria (i.e. urinary frequency).

A pharmacovigilance plan for Invokana will be implemented as part of the marketing authorisation.

The medicine is to be available only on prescription.

Detailed recommendations for the use of this product were described in the summary of product characteristics (SmPC), published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

Discussion

No comment.

References

canagliflozin CHMP Report

EMA. Invokana European public assessment report. 2013. [cited 17 Febr. 2014] Available from <http://www.ema.europa.eu>

Johnson & Johnson submission file

MICROMEDEX Drugdex database 2.0

SmPC of canagliflozin

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0021] What is the reimbursement status of the canagliflozin?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Canagliflozin has recently been approved by the US Food and Drug Administration (FDA) and was given marketing authorisation in Australia on 6 September 2013. The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the product Invokana (100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 diabetes on 19 September 2013. This recommendation was forwarded to the European Commission, which approved the product on 22 November 2013. The reimbursement status of canagliflozin in different EU countries is decided at national level.

Discussion

No comment.

References

canagliflozin CHMP Report

EMA. Invokana European public assessment report. 2013. [cited 17 Febr. 2014] Available from <http://www.ema.europa.eu> 2.

Johnson & Johnson submission file

MICROMEDEX Drugdex database 2.0

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0023] How many people belong to the target population? (as A0006)**Methods**

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0006, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;
- MICROMEDEX Drugdex database 2.0.

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Please see also Result card A0006.

The treatment guidelines for T2DM differ across the European countries and only limited data are available on the distributions of products across treatment lines. Data from France and Germany were used to estimate the number of eligible patients for canagliflozin according to the proposed label to the EMA/CHMP.

France

Dual or Second-line/Monotherapy Treatment

The total population inadequately controlled by diet and exercise and metformin/SU monotherapy treatment in dual or second line/monotherapy treatment is 947 299.

Triple or Third-line Treatment

The population eligible for canagliflozin in France in triple or third-line treatment is 335 158.

Germany

Dual or Second-line/Monotherapy Treatment

The total population inadequately controlled by diet and exercise and metformin/SU monotherapy treatment in dual or second line/monotherapy treatment is 690 100.

Triple or Third-line Treatment

The population eligible for canagliflozin in Germany in triple or third-line treatment is 206 000.

Discussion

No comment.

References

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Importance and transferability

How important is this piece of information for decision making?

- Critical
- Important
- Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

- Completely
- Partly
- Not

[A0024] How the T2DM is currently diagnosed according to published guidelines and in practice?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0024 Results card of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Criteria for the diagnosis of DM include one of the following:

- Fasting plasma glucose (FPG) ≥ 7.0 mmol/l
- Plasma glucose ≥ 11.1 mmol/l at two hours after a 75 g oral glucose load (oral glucose tolerance test (OGTT))
- Random blood glucose concentration ≥ 11.1 mmol/l in patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis
- Haemoglobin A1c $> 6.5\%$

The results should be confirmed by repeat testing unless unequivocal hyperglycaemia is present [Fauci 2013, Gale 2012, World Health Organization 2011].

HbA1c is a key measure for assessing glycaemic control in people with established diabetes [Scottish Intercollegiate Guidelines Network 2010b, World Health Organization 2006].

Discussion

No comment.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[A0025] How is the T2DM currently managed according to published guidelines and in practice?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Critical appraisal criteria: Not applicable

Method of synthesis: Narrative

Result

Part of A0025 Results card of EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, was used for answering these questions.

Type 2 DM is a progressive long-term medical condition that is predominantly managed by the person with the diabetes and/or their carer as part of their daily life [The Royal College of Physicians 2008]. Type 2 DM is addressed by a combination of several strategies including education and lifestyle interventions, psychological interventions, pharmacological management and management of diabetes-related diseases such as cardio-vascular diseases, kidney diseases, visual impairment and nerve damage [Fauci 2013, Gale 2012, Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. Standards of medical care in diabetes have recently been published by the American Diabetes Association [American Diabetes Association 2013].

Type 2 DM is usually managed in a stepwise approach. In existing recommendations management usually start with structured education that meets the cultural, linguistic, cognitive and literacy needs of the patient and lifestyle management with non-pharmacological management (e.g. dietary advice, smoking cessation, management of depression). This needs to be accompanied by clinical monitoring of the blood glucose level by means of glycated haemoglobin

(HbA1c) [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008].

The primary HbA1c goal is <6.5%. A reasonable HbA1c goal for many nonpregnant adults is <7%. HbA1c <8% may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and in those in whom the general goal is difficult to achieve despite all appropriate care [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

If the target level of HbA1c is not achieved by non-pharmacological management, pharmacological glucose control therapies are required (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonist or insulins). Blood glucose control deteriorates inexorably in most people with Type 2 diabetes over a period of years, due to a waning of insulin production. In these circumstances, oral glucose-lowering therapies can no longer maintain blood glucose control and insulin replacement therapy becomes inevitable [The Royal College of Physicians 2008].

Metformin (biguanides) is the optimal first-line drug (Box 1). If metformin is contraindicated or not tolerated, other drugs could be used in monotherapy. Combination therapy with an additional one (dual therapy) or two oral or injectable agents (triple therapy) is reasonable, aiming to minimise side effect of such drug combination where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centred approach

should be used to guide choice of therapy, bearing in mind their efficacy, side effects, cost, comorbidities, and patient preferences [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

Box 1. Pharmacological therapy for Type 2 Diabetes Mellitus

Monotherapy
<p>Metformin as a first choice (if not contraindicated and if tolerated) If it is contraindicated and not tolerated, further drugs could be used:</p> <ul style="list-style-type: none"> - Sulfonylurea - Pioglitazone - DPP-4 inhibitor.
Dual therapy
<p>If non-insulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target level over 3–6 months, the second oral agent, GLP-1 receptor agonist or insulin could be added:</p> <ul style="list-style-type: none"> - Sulfonylurea - Pioglitazone - DPP-4 inhibitor - GLP-1 agonist - Basal insulin.
Triple therapy
<ul style="list-style-type: none"> - Metformin + sulfonylurea* + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir) - Metformin + thiazolidinedione + sulfonylurea* or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir) - Metformin + DPP-4 inhibitor + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir) - Metformin + GLP-1 receptor agonist + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir) - Metformin + insulin (basal: NPH, glargine or detemir) + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist.
Insulin (multiple daily doses)

Abbreviations: DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1NPH: Neutral protamine Hagedorn; *meglitinides therapy in case of late postprandial hypoglycaemia during sulfonylurea therapy;

Source: Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes. A patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;1364-79.

In managing diabetes-related cardiovascular diseases, blood pressure therapy and managing blood-lipid levels play a most important role (starting with lifestyle management followed by anti-hypertensive medication and lipid-lowering drugs) [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008]. Additionally, antithrombotic therapy may be indicated [The Royal College of Physicians 2008].

Furthermore, measurement of several laboratory parameters is recommended to detect and monitor diabetes-related kidney disease. Regular structured eye surveillance is recommended to detect eye damage as is enquiry for neuropathic symptoms to detect nerve damage [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008].

In Table 24 summary of European Clinical Guidelines on Type Diabetes Mellitus treatment are presented.

Table 24. Summary of European Clinical Guidelines on Type 2 Diabetes Mellitus treatment

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
ADA/EASD (regional)	ADA/EASD, 2012	Guidelines ADA/EASD	<p>Glycaemic targets:</p> <p>HbA1c < 7.0% (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])</p> <p>Pre-prandial PG <130 mg/dl (7.2 mmol/l)</p> <p>Post-prandial PG <180 mg/dl (10.0 mmol/l)</p> <p>Individualisation is key:</p> <ul style="list-style-type: none"> - Tighter targets (6.0 - 6.5%) - younger, healthier - Looser targets (7.5 - 8.0 %+)- older, comorbidities, hypoglycaemia prone, etc. <p>Avoidance of hypoglycaemia</p>	MET + diet and exercise	<p>Add on to first line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 - Insulin <p>With additional guidance including in the document based on criteria:</p> <ul style="list-style-type: none"> • Efficacy • Hypoglycaemia • Weight • Side effects • Cost 	<p>Add on to second line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 - Insulin <p>With additional guidance including in the document based on criteria:</p> <ul style="list-style-type: none"> • Efficacy • Hypoglycaemia • Weight • Side effects • Cost 	Complex dose of insulin
Austria	ÖDG guidelines, 2012	http://www.oedg.org/pdf/1302_OEDG_Leitlinien.pdf	HbA1c individual target between 6.5% and 8.0%	MET	MET + SU, TZD, DPP-4, GLP-1, Insulin	Add on to 2 nd line: SU, TZD, DPP-4, GLP-1, Insulin	More complex insulin strategies
Belgium	1. Diabetes Mellitus type 2. Aanbevelingen voor goede medische praktijkvoering. Gent, 2005	<p>http://www.zorgtraject.be/nl/Bibliotheek/pdf/N_RB_P_Diabetes2_NL.pdf</p> <p>http://www.riziv.fgov.be/drug/nl/st</p>	<p>Until recently there was the guideline of 2005.</p> <p>In the meantime, a consensus meeting was organised by the INAMI. A recent publication (number 3) refers to the EASD/ADA consensus forum</p>	Step 1: Always MET. There is also the note that in case of contraindications, DPP-4 in monotherapy is reimbursed under certain	Step 2: MET + SU/ MET + DPP-4. Or MET +PIO	Step 3: Triple therapy: MET + SU + DPP-4 or MET + SU + GLP-1	<p>Step 4: Insulin Basal + MET (ONLY).</p> <p>Insulin + DPP-4</p> <p>In case the threshold of HbA1c >7.5% is not reached. If</p>

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
	<p>2. Consensusvergadering, 29 November 2012.</p> <p>3. Tijdschrift voor geneeskunde, 69, nr 6, 2013</p>	<p>atistics-scientific-information/consensus/2012-11-29/pdf/literatuurstudie_samenvatting.pdf</p> <p>http://www.tvg.be/index.php?issue_year=2013&issue_nr=6</p>		conditions			severe hypoglycaemia, switch to Insulin glargine
Bulgaria	Bulgarian Endocrinology Association, Algorithms for Treatment of Diabetes, 2012	http://www.endo-bg.com/kak2012/1-DiabetesMellitus.pdf	<ul style="list-style-type: none"> ●HbA1c <7.0% in most patients ●More stringent HbA1c targets (6.0– 6.5%) - patients with short disease duration, long life expectancy, no significant CVD if this can be achieved without significant hypoglycaemia or other adverse effects of treatment ●Less stringent HbA1c goals (7.5–8.0%) for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of multiple glucose-lowering agents, including insulin. ●Blood glucose <7.2 mmol/l before eating (on empty stomach) and blood glucose after eating <10.0 mmol/l. ●BMI <25.0 kg/m² ●Lipid profile – total cholesterol <4.5 mmol/l; HDL>1.0 mmol/l (men) and >1.3 mmol/l (women); LDL <2.6 mmol/l and <1.8 mmol/l in cardiovascular compromised patients; triglycerides <1.7 mmol/l ●Blood pressure <130/80 mmHg and <125/75 mmHg in case of albuminuria > 1 gr/24 h 	<p>Start with MET + diet and exercise; In case of adverse events or contraindications to MET, start with</p> <ul style="list-style-type: none"> - SU <p>or</p> <ul style="list-style-type: none"> - Meglitinides <p>or</p> <ul style="list-style-type: none"> - TZD <p>or</p> <ul style="list-style-type: none"> - Alpha-glucosidase inhibitors <p>or</p> <ul style="list-style-type: none"> - DPP-4 	When HbA1c > 9.0% - oral combination of 2 drugs is recommended as a start therapy	Insulin is recommended in case of blood glucose > 17 mmol/l or HbA1c > 10.0-12%	
Cyprus	ADA/EASD, 2012	Guidelines	HbA1c <6.5% in most patients	MET + diet and	Add on to first	Add on to	Insulin

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
		ADA/EASD	<p>More stringent HbA1c targets (6.0– 6.5%) - patients with short disease duration, long life expectancy, no significant CVD if this can be achieved without significant hypoglycaemia or other adverse effects of treatment.</p> <p>Less stringent HbA1c goals (7.5–8.0%) for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of multiple glucose-lowering agents, including insulin</p>	exercise	<p>line:</p> <ul style="list-style-type: none"> - DPP-4 - SU - GLP-1 - Insulin <p>With additional guidance including in the document</p>	<p>second line:</p> <ul style="list-style-type: none"> - SU - DPP-4 - GLP-1 - Insulin <p>With additional guidance including in the document</p>	
Czech Republic	Doporučený postup péče o diabetes mellitus 2. Typu (Treatment recommendation for T2DM), 2012.	http://www.diab.cz/dokumenty/dm2_2011.pdf	<p>HbA1c <6.0 - 8.0% in most patients</p> <p>More stringent HbA1c targets (6.0– 6.5%) - in patients with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycaemia or other adverse effects of treatment (weight gain).</p>	MET + diet and exercise	<p>Add on to first line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 - Insulin 	<p>Add on to second line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 - Insulin 	Complex dose of insulin
Croatia	ADA/EASD, 2012 (Croatian guidelines lean on ADA/EASD)	Guidelines ADA/EASD	<p>HbA1c <7.0% in most patients, significant hypoglycaemia or other adverse effects of treatment. Less stringent HbA1c goals (7.5–8.0%) for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of multiple glucose-lowering agents, including insulin</p>	MET + diet and exercise	<p>Add on to first line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 - Insulin 	<p>Add on to second line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 - Insulin 	Complex dose of insulin
Denmark	Institute for Rational Pharmacotherapy (IRF), 2011	http://www.irf.dk/download/Publikationer/vejledninger/diabetesfolder.pdf	<p>HbA1c < 48 mmol/mol (6.5%)</p> <p>First years after diagnosis if low risk of hypoglycaemia.</p> <ul style="list-style-type: none"> • HbA1c < 53 mmol/mol (7.0%) <p>In later years tight control can be difficult and individual goal must be agreed upon.</p>	MET	<p>DPP-4 inhibitors</p> <p>SU</p> <p>GLP-1 analogs</p> <p>or insulin</p>	Triple combination with or without insulin	

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
			<ul style="list-style-type: none"> HbA1c < 58 mmol/mol (7.5%) <p>For patients with fluctuation of glucose levels and tendency to have hypoglycaemia.</p> <ul style="list-style-type: none"> HbA1c 58-75 mmol/mol (7.5-9.0%) <p>If the goal is only to be free of symptoms.</p>				
Estonia	Health Care information portal	http://www.ravijuhend.ee/ravijuhendikasutajale/ravijuhendite-andmebaas/87/Eesti+2.+t%C3%BC%C3%BCbi+diabeedi+ravijuhend	T2D target HbA1c 7%	MET + diet and exercise	Add on: SU, DPP4, TZD	Triple therapy	
Finland	Kaypahoito, 2011	http://www.kaypahoito.fi/web/kh/suosituksset/naytaartikkeli/tunnus/hoi50056	HbA1c < 7.0% when taking medication (53 mmol/mol)	MET	Glinides, DPP-4 inhibitors , glitazones, SU, Insulin, GLP-1 analogs	Triple combination with or without insulin	
France	HAS, 2013	Guidelines HAS	<p>These guidelines define the glycaemic goal for different categories of patients (standard patients, patients age >75 y, patients with cardiovascular complication history, and renal failure patients.</p> <p>The target is 7% for the standard patients, elderly patients in good health, patients with a cardiovascular complication history than is not developed, and patients with a moderate renal failure.</p> <p>Between 7% and 8% for patients who have a serious co-morbidity and/or a life expectancy of less than five years, in those with long standing macrovascular complications, severe or terminal renal insufficiency.</p> <p>Target 8% for patients diagnosed more than ten years ago and for which the 7% target is difficult to</p>	<p>MET + diet and exercise</p> <p>If MET intolerance or contraindication → SU</p>	<p>Add on to first line: SU</p> <p>IF intolerance or contraindication to SU:</p> <p>-Repaglinide or alpha glucosidase inhibitors or DPP4 if the gap to the therapeutic objective is less than 1%</p> <p>-Insulin or GLP1 (BMI ≥ 30) if the gap is ≥1%</p>	<p>Add on to second line:</p> <p>-Alpha glucosidase inhibitors or DPP4 if the gap to the therapeutic objective is less than 1%</p> <p>-Insulin or GLP1 (BMI ≥ 30) if the gap is ≥1%</p>	Complex dose of insulin

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
			<p>achieve because intensifying the medications provokes cases of severe hypoglycaemia as well as people over the age of 75 considered to be fragile.</p> <p>Target 9% for elderly ill patients, for whom the priority is to avoid "acute diabetic complications and hypoglycaemia"</p> <p>The target is 6.5% for newly-diagnosed patients with diabetes, with a life expectancy greater than 15 years, who do not have a history of heart disease</p>		<p>IF monotherapy with SU:</p> <p>-Alpha glucosidase inhibitors or DPP4 if the gap to the therapeutic objective is less than 1%</p> <p>-Insulin or GLP1 (BMI ≥ 30) if the gap is ≥1%</p>		
Germany	<p>Nationale VersorgungsLeitlinie "Therapie Typ-2-Diabetes", 2013</p> <p>Note: A valid version of National treatment guidelines for T2DM is not available → a version of March 2013 has been temporarily withdrawn on April 30, and a modified version will be republished in the very near future; here we present the recommendations (still to be confirmed) from version March 2013 (recommendations may differ between DEGAM/AkdÄ and DDG/DGIM)</p>	<p>Nationale VersorgungsLeitlinie</p> <p>Document withdrawn on April 30</p>	<p><i>Still to be confirmed:</i></p> <p>HbA1c 6.5-7.5% in most patients</p> <p>More stringent HbA1c targets (<6.0%) – if HbA1c reduction can be achieved only by means of lifestyle modification or if using the supplied drugs does not involve an increased risk for severe hypoglycaemia, substantial weight gain, heart failure, pancreatitis, and if the supplied drugs have an established benefit for clinical outcome.</p>	<p><i>Still to be confirmed:</i></p> <p>Diet + exercise + smoking cessation</p>	<p><i>Still to be confirmed:</i></p> <p>Add on to first line:</p> <p>MET</p> <p>If MET is not tolerated –</p> <p>DEGAM/AkdÄ:</p> <ul style="list-style-type: none"> - human insulin - glibenclamide (SU) <p>DDG/DGIM:</p> <ul style="list-style-type: none"> - DPP-4 - Insulin - SGLT2 - Glinide - glucosidase inhibitor - pioglitazone 	<p><i>Still to be confirmed:</i></p> <p>Add on to second line:</p> <p>DEGAM/AkdÄ:</p> <ul style="list-style-type: none"> - Insulin (monotherapy where appropriate) - glibenclamide - DPP-4 <p>DDG/DGIM:</p> <ul style="list-style-type: none"> - DPP-4 - GLP-1 - Glucosidase inhibitor - Insulin - SGLT2 - SU/glinide 	<p><i>Still to be confirmed:</i></p> <p>DEGAM/AkdÄ:</p> <p>Complex dose of insulin / obesity: insulin combination (MET)</p> <p>DDG/DGIM:</p> <p>Complex dose of insulin +</p> <ul style="list-style-type: none"> - MET - DPP-4 - SGLT2

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
					(TZD)	- pioglitazone (TZD) With additional guidance including in the document	
Greece	Hellenic diabetes association, 2013	http://www.ede.gr/	HbA1c <7.0% in most patients More stringent HbA1c targets < 6.5% - patients with short disease duration, long life expectancy, no significant CVD if this can be achieved without significant hypoglycaemia or other adverse effects of treatment. Less stringent HbA1c goals (7.0–7.5%) for patients with a history of severe hypoglycaemia, limited life expectancy, advanced complications, extensive comorbid conditions and those in whom the target is difficult to attain despite intensive self-management education, repeated counselling, and effective doses of multiple glucose-lowering agents, including insulin.	MET + diet and exercise	Add on to first line: - SU - TZD - DPP-4 - GLP-1 - Insulin With additional guidance including in the document	Add on to second line: - Or SU - Or TZD - Or DPP-4 - Or GLP-1 - Or Insulin With additional guidance including in the document	Complex dose of insulin
Hungary	Diabetes treatment guideline, Financing algorithm of National Health Insurance Fund, 2010, 2011	n.a.	The main therapeutic aim is to keep the HbA1c level of the patient below 7.0%. If this goal is not met in a 3-month period, MET monotherapy is followed by other treatment options (Alpha-glucosidase inhibitors, SU, TZD, DPP-4, GLP-1, Insulin). As of 2012 a new legislation is effective: Patients, who received human insulin therapy for 3 months, and have higher HbA1c level than 8.0% can be treated with analogue insulin therapy with 100% reimbursement. [In certain cases patients do not have to be treated for 3 months with human insulin therapy to be eligible for analogue therapy (documented severe hypoglycaemia)].	MET + diet and lifestyle changes	- Alpha-glucosidase inhibitors - SU - TZD - DPP-4 - GLP-1 - Insulin	- Insulin (human)	- Insulin (analogue) - Insulin (human)
Ireland	Irish College of General	<i>Awaiting</i>	Targets should be individualised				

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
	Practitioners (ICGP), 2013	<i>Publication</i>	<p>HbA1c \leq 53mmol/mol (\leq7.0%) is appropriate for the majority of patients with T2DM and has been shown to reduce diabetes-related complications</p> <p>HbA1c \leq 58mmol/mol (\leq7.5%) or less stringent HbA1c goals may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive co-morbid conditions or where social circumstance may prevent tight glucose control</p>				
	Irish College of General Practitioners (ICGP), 2008	http://www.icgp.ie/speck/properties/asset/asset.cfm?type=Document&id=DE8B3956-19B9-E185-839C541F594AB5F2&property=document&filename=A_Practical_Guide_to_Integrated_Type_II_Diabetes_Care.pdf&revision=tip&mimetype=application%2Fpdf&pp=icgp&disposition=attachment	<p>Tight control of blood glucose with diet and/or medication reduces long-term complications rates and is central to the overall management of diabetes.</p> <p>Composite criteria by the major organisations (IDF, EASD, ADA, Diabetes UK) recommend:</p> <ul style="list-style-type: none"> • Target HbA1c should be set under 6.5%, which equates to fasting glucometer levels at home mainly in the 5's and 6's. • A target pre-prandial capillary glucose of less than 6.0 mmol/l • Peak post-prandial capillary glucose should if possible be less than 8.0 mmol/l <p>Patients should be advised to maintain a healthy weight to maintain a BMI of between 20 and 24.99 kg/m²</p>	<p>Diet & exercise</p> <p>MET</p> <p><i>(citing, ADA, IDF and NICE)</i></p> <p>Insulin secretagogues (including SUs and rapid-acting insulin secretagogues) may be considered first line therapy when MET is not tolerated or contraindicated, patients are not overweight</p> <p><i>(citing NICE)</i></p>	<p>Insulin secretagogues should be used in combination with MET in overweight or obese patients when glucose control becomes unsatisfactory</p> <p>Glitazones, incretins and DPP-4 inhibitors are also legitimate second-line therapy</p> <p>People should be offered a TZD as oral combination therapy if they are unable to take MET and Insulin</p>		

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
					secretagogues as combination therapy, or the HbA1c remains unsatisfactory despite an adequate trial of MET with Insulin secretagogues <i>(citing NICE)</i>		
	National Medicines Information Centre, 2012	LINK	<p>The aims of treatment are to reduce blood glucose and to manage the CV risk factors and long-term complications of T2DM. ^{1,2,3}</p> <p>Most consensus groups recommend that the HbA1c target level should be in the region of 53 mmol/mol (or 7%), however it needs to be individualised to the patient. ^{1,2,4,5,6}</p> <p>For selected individuals, more stringent HbA1c targets could be suggested, provided that the level can be achieved without substantial hypoglycaemia or other adverse effects of treatment; these patients may include those with a short duration of diabetes, a long life expectancy and no significant cardiovascular disease. ^{5,7}</p> <p>Conversely, higher HbA1c goals should be considered for patients with a history of severe hypoglycaemia, a limited life expectancy, advanced microvascular or macrovascular complications or extensive co-morbid conditions. ^{5,7}</p>	<p>(in addition to lifestyle intervention)</p> <p>Commence MET if no contraindications or commence alternative oral hypoglycaemic agent authorised for monotherapy use and suitable for individual patient ^{1,2}</p>	<p>(in addition to lifestyle intervention, dose optimisation and advice on adherence to medication)</p> <p>Add SU or thiazolidinedione (if hypoglycaemia a concern and no congestive heart failure) or DPP-4 inhibitor</p> <p>(if hypoglycaemia and weight gain a concern) or GLP-1 agonists (if hypoglycaemia a concern, weight loss desired and BMI >30 kg/m² ^{1,2}</p>	<p>(in addition to lifestyle measures, dose optimisation and advice on adherence to medication)</p> <p>Add or substitute with one of: thiazolidinedione, (if no congestive heart failure), DPP-4 inhibitor (if hypoglycaemia and weight gain a concern)</p> <p>or GLP-1 agonists (if hypoglycaemia a concern, weight loss desired and BMI >30 kg/m²) or insulin (a structured programme is recommended for initiation of insulin) ^{1,2}</p>	

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
	Trinity Health Ireland (Departments of Endocrinology and Diabetes at Tallaght, St. James's and Naas Hospitals), 2009 (This is a group of hospitals in South West Dublin and nearby counties, including the country's largest hospital St. James's)	LINK	HbA1c <6.5% Plasma glucose (mmol/l) Fasting <6.0 Post-prandial (peak) <7.5	Lifestyle advice and MET	SU	Refer for consideration of insulin or other agents	
Italy	SID/AMD, 2011	http://www.aemmedi.it	HbA1c <7.0% in most patients More stringent HbA1c targets (6.5%) in patients with short disease duration FPG 70-130 mg/dl	MET when diet and exercise alone are not enough	Add on to first line: - SU - TZD - Glinides - DPP-4 - GLP-1 - Insulin With additional guidance including in the document	Add on to second line: - SU - TZD - Glinides - DPP-4 - GLP-1 - Insulin With additional guidance including in the document	Insulin
Latvia		http://www.diabets-asoc.lv/Anglu_valoda/what_does_lda_do/saturs_what_does_lda_do.htm	T2D target HbA1c = 7	MET + diet and exercise	SU/MET + DPP-4 or TZD or alpha glucosidase	Insulin, DPP-4, TZD, GLP-1	

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
Lithuania	2012, Signed by the Health Care minister	http://www.vlk.lt/resources/files/2012/kv/SAMv159_RedakcijaNr1.pdf	T2D target HbA1c = 7	MET + diet and exercise or if Met is not tolerated SU/BRD (Monotherapy)	Dual therapy: MET+SU, if no tolerance and HbA1c = 7 SU+DPP-4 or SU+TZD if HbA1c more than 7.5% SU+GLP-1	MET+SU+DPP-4, MET+SU+TZD, MET+SU+GLP-1	Insulin
Luxembourg	There are no national guidelines. Specialists are free to prescribe as they wish						
Malta	NICE, 2013	http://www.nice.org.uk/nicemedi a/pdf/CG87NICE Guideline.pdf MET and SUs – glibenclamide/gliclazide are available FOC in MOH formulary. Other oral anti-hyperglycaemic agents have to be bought out of pocket by the patient	HbA1c 6.5-7.0%	MET + diet/exercise	MET + SU	MET + SU + DPP-4i	Insulin
Netherlands	NHG standard diabetes, 2006	www.nhg.org/standaarden/volledig/nhg-standaard-diabetes-mellitus-type-2	Go to the next step if dose increase is no longer possible (side effects, maximum daily dose) and HbA1c >7%. DPP-4 and GLP-1 are reimbursed, but not included in the guidelines from 2006. We expect new guidelines in Q3 2013. DPP-4 is reimbursed for step 1 in case of contraindications with MET, for step 2 MET+DPP-4 and step 3 MET+SU+DPP-4 GLP-1 is only reimbursed in triple therapy with BMI>35	MET + diet and exercise. Start with low dose, increase the dose every 2-4 weeks	MET+ SU - if no risk of HF MET + pioglitazone - if already CVD but no risk of HF	Add insulin (Once daily)	Twice daily NPH insulin or insulin-mix
Poland	Diabetes Poland	PTD link	General:	MET (SU, gliptins-	MET + SU	MET + 2 drugs of different	MET + basal insulin and

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
	Guidelines, 2013		<p>HbA1c (%) \leq 7% (\leq 53 mmol/mol)</p> <p>Detailed:</p> <p>HbA1c (%) \leq 6.5%</p> <p>patients with short disease duration HbA1c \leq 8.0% (64 mmol/mol):</p> <p>Patient 70 years old + with long disease duration (> 20 years), with significant macroangiopathy complication (myocardial infarction and/or stroke)</p> <p>65 year old + patient with life expectancy above 10 years, should be treated according to general treatment guidelines (HbA1c (%) \leq 7%).</p> <ul style="list-style-type: none"> • TCHOL: <175 mg/dl (<4.5 mmol/l) • LDL: < 100mg/dl (<2.6 mmol/l); • LDL for patient suffering on diabetes and coronary heart disease: <70 mg/dl (<1.9 mmol/l) • HDL: >40 mg/dl (>1.0 mmol/l)[for women higher by 10 mg/dl (0.275 mmol/l) • Non HDL cholesterol: <130 mg/dl (<3.4 mmol/l) • Triglycerides: <150 mg/dl (<1.7 mmol/l) <p>Blood pressure:</p> <ul style="list-style-type: none"> • SBP: <140 mm Hg • DBP: <90 mm Hg 	conditional)	MET + incretins	mechanism of action (SU or incretins or acarbose)	further insulin intensification
Portugal	DGS, 2011	Norma n.º 052/2011	<p>Target HbA1c level should be defined on individual basis (life expectancy, diabetes years, hypoglycaemia risk, cardiovascular disease, and/or other co-morbidities).</p> <p>HbA1c <6.5% in most patients.</p>	<p>MET + diet and exercise</p> <p>Consider SU in patients with intolerance or contra-indication</p>	<p>Double Therapy.</p> <p>Add on to first line:</p> <p>- SU or Glinide</p>	<p>Triple Therapy.</p> <p>Add on to second line:</p> <p>- SU or Glinide</p>	<p>Complex dose of insulin and/or Other Agents.</p> <p>With additional guidance included in the document.</p>

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
				<p>to MET:</p> <p>(1) if patient requires fast control of hyperglycaemia' symptoms;</p> <p>(2) is not overweighting;</p> <p>(3) preferentially presents HbA1c > 7.5%, in order to prevent hypoglycaemia.</p> <p>Consider DPP-4 Inhibitor in patients with intolerance or contra-indication to MET and HbA1c < 7.5%.</p> <p>With additional guidance included in the document.</p>	<ul style="list-style-type: none"> - TZD - DPP-4 Inhibitor - Alpha-glucosidase inhibitors <p>With additional guidance included in the document.</p>	<ul style="list-style-type: none"> - TZD - DPP-4 Inhibitor - Insulin - Alpha-glucosidase inhibitors <p>With additional guidance included in the document.</p>	
	Sociedade Portuguesa de Diabetologia, 2013	National Guidelines	Target HbA1c level should be defined on individual basis (life expectancy, diabetes years, hypoglycaemia risk, cardiovascular disease, and/or other co-morbidities). Target HbA1c levels between 6.5 and 7.0% should not be pursued to all patients considering the therapeutic risk.	MET + diet and exercise	<p>Add on to first line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 Inhibitor - GLP-1 - Insulin <p>With additional guidance</p>	<p>Add on to second line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 Inhibitor - GLP-1 - Insulin <p>With additional guidance</p>	Complex dose of insulin

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
					included in the document	included in the document	
Romania	Ministry of Health, Ordinance 1059, 2009 with its further modifications and amendments	Clinical Guideline for Diabetes Patients	HbA1c < 7% Fasting glycaemia between 90 – 130 mg/dl Postprandial glycaemia < 180 mg/dl BP systolic below 130 mmHG BP diastolic below 80 mmHG BMI < 25 kg/m ²	Biguanides (MET or Buformin) + lifestyle changes (diet and physical exercise) For patients who present intolerance to biguanides: first line treatment with SUs and glinides, alpha glucose inhibitors, TZDs or even insulin	included in the document Add on to first line: - SUs and glinides - alpha glucosidase inhibitors - GLP-1 - TZDs - DPP-4 - Insulin	Initiate or intensify insulin regimen If HbA1c < 8%, triple oral therapy may be considered as a therapeutic option, but its cost-effectiveness is inferior to the insulin regimen.	-
Slovakia	Uličiansky V.1, Schroner Z.2, Galajda P.3, Mokáč M.3, Némethyová Z.4: Algoritmus liečby diabetes mellitus 2. typu 2011 v klinickej praxi, DIABETES A OBEZITA, 11. 2011, Č. 2 2, s. 9-32. (Treatment Algorithm of T2DM in Clinical Practice).	http://www.diaslovakia.sk/contentData/0205/Algoritmus%20liecby%20DM%202%20typu%202011.pdf	HbA1c <6.0% in most patients More stringent HbA1c targets (HbA1c <4.5%) - in patients with short disease duration, long life expectancy, no significant CVD) if this can be achieved without significant hypoglycaemia or other adverse effects of treatment (weight gain).	MET + diet and exercise	Add on to first line: - SU - TZD - DPP-4 - GLP-1 - insulin	Add on to second line: - SU - TZD - DPP-4 - GLP-1 - insulin	Complex dose of insulin
Slovenia	Slovene guidelines for type 2 diabetes, 2011 (Slovenske smernice za klinično)	http://www.endodiab.si/priporocila/sb/index.dot	HbA1c <7.0%	MET + non-pharmacological measures	Add on to first line: • SU	Add on to 2nd line: • SU	Insulin

Country	Source, year	Link	T2DM Treatment goal	First line	Second line	Third Line	Fourth Line
	Spanish Ministry of Health, 2012	Spanish Ministry of Health website	<p>complications</p> <ul style="list-style-type: none"> pathologies that recommend avoiding hypoglycaemia over 10 years of diabetes evolution <p>These criteria have also been validated in the latest national strategy on diabetes issued by the Ministry of Health in late 2012.</p>	<p>MET, the following could be considered as first line treatment:</p> <ul style="list-style-type: none"> -SU -DPP-4 -TZD -Repaglinide -Disaccharidase inhibitors 	<ul style="list-style-type: none"> - DPP-4 - TZD - Basal insulin - GLP-1 <p>With additional guidance including in the document</p>	<p>following to have an oral triple therapy:</p> <ul style="list-style-type: none"> - SU or meglitinide - DPP-4 - TZD <p>With additional guidance included in the document</p>	
Sweden	The National Board of Health and Welfare - Socialstyrelsen, 2012	http://www.socialstyrelsen.se/nationellariktlinjerfor-diabetesvarden	HbA1c < 6.0 % (52 mmol/mol) (MonoS)	MET	SU or insulin	Triple combination with or without insulin	
United Kingdom	NICE, 2013	http://www.nice.org.uk/nicemedia/pdf/CG87NICEGuideline.pdf	<p>HbA1c target should be above 6.5% for people with type 2 diabetes in general (NICE CG66 and CG87).</p> <p>HbA1c <7.5% in most patients although patient-specific targets can also be set.</p> <p>The NHS also consider threshold of HbA1c <8% and <9% in T2DM patients with a history of severe hypoglycaemia.</p> <p>If HbA1c levels remain above target levels, but pre-meal self-monitoring levels remain well controlled (< 7.0 mmol/l), consider self-monitoring to detect postprandial hyperglycaemia (> 8.5 mmol/l) and manage to below this level if detected (NICE CG66 & CG87)</p>	MET + diet and exercise	<p>Add on to first line:</p> <ul style="list-style-type: none"> - SU - TZD - DPP-4 - GLP-1 (sub-group only) - Insulin (if HbA1c ≥ 9%) <p>With additional guidance including in the document</p>	<p>Add on to second line:</p> <p>Met + SU +</p> <ul style="list-style-type: none"> - TZD - DPP-4 - GLP-1 - Insulin <p>With additional guidance including in the document</p>	Insulin based regimen with potential insulin intensification

Abbreviations: MET: metformin; SUL: sulfonylurea; TZD: thiazolidinedione; DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; PIO: pioglitazone; HbA1c; haemoglobin A1c (glycated haemoglobin); BMI: body mass index

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Discussion

Data on clinical guidelines in different MSs could be important data at the national level to inform national HTA adaptations and national reports. These data are provided by canagliflozin Manufacturer; survey for MSs partners was not performed to check these data.

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Importance and transferability

How important is this piece of information for decision making?

- Critical
- Important
- Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

- Completely
- Partly
- Not

DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY

[B0001] What is canagliflozin and the comparator(s)? (taking into account different dosages) And what is the mechanism of action?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- EMA: Summary of opinion (initial authorisation)
- Approved label; FDA: 2013.,
- SmPC of canagliflozin

Critical appraisal criteria None

Method of synthesis Narrative

Result

Canagliflozin is an orally active inhibitor of the sodium glucose co-transporter 2 (SGLT2), the transporter responsible for reabsorbing the majority of glucose filtered by the kidney (3). The SGLT2 is a glucose transporter expressed in the proximal renal tubules, and not in other tissues, that is responsible for the majority of the reabsorption into the blood stream of glucose filtered through the glomerulus.

By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion (2).

Canagliflozin is available in 100 mg and 300 mg film-coated tablets.

Administration: 100 mg once-daily orally administration before the first meal of the day. Increasing the dose to 300 mg once daily may be considered if patients are currently tolerating canagliflozin 100 mg once daily, have an eGFR ≥ 60 mL/min/1.73 m² or CrCl > 60 mL/min, and require additional glycaemic control.

Canagliflozin should not be initiated in patients with an eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min. In patients tolerating canagliflozin whose eGFR falls persistently below 60 mL/min/1.73 m² or CrCl 60 mL/min, the dose of canagliflozin should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 mL/min/1.73 m² or CrCl persistently below 45 mL/min.

Canagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis as it is not expected to be effective in such populations.

Type 2 DM is usually managed in a stepwise approach. In existing recommendations management usually start with structured education that meets the cultural, linguistic, cognitive and literacy needs of the patient and lifestyle management with non-pharmacological management (e.g. dietary advice, smoking cessation, management of depression) [Scottish Intercollegiate Guidelines Network 2010b, The Royal College of Physicians 2008].

If the target level of HbA1c is not achieved by non-pharmacological management, pharmacological glucose control therapies are required (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonist or insulins). New class of drug is available on the EU market, SGLT2 inhibitors, with dapagliflozin as a 1st drug approved in the class.

Metformin (biguanides) is the optimal first-line drug (Box 2). If metformin is contraindicated or not tolerated, other drugs could be used in monotherapy. Combination therapy with an additional one (dual therapy) or two oral or injectable agents (triple therapy) is reasonable, aiming to minimise side effect of such drug combination where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centred approach should be used to guide choice of therapy, bearing in mind their efficacy, side effects, cost, comorbidities, and patient preferences, Box 3 [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

Box 2. Pharmacological therapy for Type 2 Diabetes Mellitus

Monotherapy

Metformin as a first choice

(if not contraindicated and if tolerated)

If it is contraindicated and not tolerated, further drugs could be used:

- Sulfonylurea
- Pioglitazone
- DPP-4 inhibitor.

Dual therapy

If non-insulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA1c target level over 3–6 months, the second oral agent, GLP-1 receptor agonist or insulin could be added:

- Sulfonylurea
- Pioglitazone
- DPP-4 inhibitor
- GLP-1 agonist
- Basal insulin.

Triple therapy

- Metformin + sulfonylurea* + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)
- Metformin + thiazolidinedione + sulfonylurea* or DPP-4 inhibitor or GLP-1 receptor agonist or insulin (basal: NPH, glargine or detemir)
- Metformin + DPP-4 inhibitor + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)
- Metformin + GLP-1 receptor agonist + sulfonylurea* or thiazolidinedione or insulin (basal: NPH, glargine or detemir)
- Metformin + insulin (basal: NPH, glargine or detemir) + thiazolidinedione or DPP-4 inhibitor or GLP-1 receptor agonist.

Insulin (multiple daily doses)

Abbreviations: DPP-4: dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; NPH: Neutral protamine Hagedorn; *meglitinides therapy in case of late postprandial hypoglycaemia during sulfonylurea therapy;

Source: Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes. A patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;1364-79.

Box 3. American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) 2012 Consensus Overview of the Clinical Advantages and Disadvantages of Current Type 2 Diabetes Mellitus (T2DM) Therapies

Class	Drug(s)	Main advantages	Main disadvantages
Biguanides	Metformin	<ul style="list-style-type: none"> Extensive experience No weight gain No hypoglycaemia Likely decrease CVD events (UKPDS) 	<ul style="list-style-type: none"> Gastrointestinal side effects (diarrhoea, abdominal cramping) Lactic acidosis risk (rare) Vitamin B12 deficiency Multiple contraindications: CKD, acidosis, hypoxia, dehydration, etc.
Sulphonylureas	<ul style="list-style-type: none"> 2nd generation Glyburide/ glibenclamide Glipizide Gliclazide Glimepiride 	<ul style="list-style-type: none"> Extensive experience Decrease microvascular risk (UKPDS) 	<ul style="list-style-type: none"> Hypoglycaemia Weight gain ? Blunts myocardial ischemic preconditioning Low durability
Meglitinides (glinides)	<ul style="list-style-type: none"> Repaglinide Nateglinide 	<ul style="list-style-type: none"> Decrease postprandial glucose excursions Dosing flexibility 	<ul style="list-style-type: none"> Hypoglycaemia Weight gain ? Blunts myocardial ischemic preconditioning Frequent dosing schedule
Thiazolidinediones	Pioglitazone	<ul style="list-style-type: none"> No hypoglycaemia Durability Increase HDL-C Decrease triglycerides (pioglitazone) ? decrease CVD events (ProACTIVE, pioglitazone) 	<ul style="list-style-type: none"> Weight gain Oedema/heart failure Bone fractures ? Increase bladder cancer (pioglitazone)

Class	Drug(s)	Main advantages	Main disadvantages
α -Glucosidase inhibitors	Acarbose Miglitol	No hypoglycaemia Decrease postprandial glucose excursions ? decrease CVD events (STOP-NIDDM) Nonsystemic	Generally modest HbA1c efficacy Gastrointestinal side effects (flatulence, diarrhoea) Frequent dosing schedule
DPP-4 inhibitors	Sitagliptin Vildagliptin Saxagliptin Linagliptin	No hypoglycaemia Well tolerated	Generally modest HbA1c efficacy Urticaria/angioedema ? Pancreatitis
Bile acid sequestrants b	Colesevelam	No hypoglycaemia Decrease LDL-C	Generally modest HbA1c efficacy Constipation Increase triglycerides May decrease absorption of other medications
GLP-1 receptor agonists	Exenatide Exenatide extended release Liraglutide	No hypoglycaemia Weight reduction ? Potential for improved β -cell mass/function ? Cardiovascular protective actions	Gastrointestinal side effects (nausea/vomiting) ? Acute pancreatitis C-cell hyperplasia/medullary thyroid tumours in animals Injectable Training requirements
Insulins	Human NPH Human Regular	Universally effective Theoretically unlimited efficacy	Hypoglycaemia Weight gain

Class	Drug(s)	Main advantages	Main disadvantages
	Lispro Aspart Glulisine Glargine Detemir Premixed (several types)	Decrease microvascular risk (UKPDS)	? Mitogenic effects Injectable Training requirements “Stigma” (for patients)

Abbreviations: ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; UKPDS: UK Prospective Diabetes Study; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; ProACTIVE: Prospective Pioglitazone Clinical Trial in Macrovascular Events; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; SGLT2, sodium glucose co-transporter 2.

a It should be noted that SGLT2 inhibitors are not included in the 2012 ADA/EASD guidelines because they were not licensed at the time these guidelines were developed.

b Limited use in Europe.

Source: Johnson & Johnson submission file

According to the NICE technology appraisal guidance 288, Dapagliflozin in combination therapy for treating type 2 diabetes, June 2013, dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87). Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes. Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial. People currently receiving dapagliflozin in a dual or triple therapy regimen that is not recommended for them in guide above should be able to continue treatment until they and their clinician consider it appropriate to stop.

Discussion

References

American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2013;36:S11-S66.

Approved label; FDA: 2013.

EMA: Summary of opinion (initial authorisation). Invokana. 19 September 2013.

EMA/CHMP/564958/2013 Committee for Medicinal Products for Human Use (CHMP) Micromedex-Drug details. April 2013

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NICE. Dapagliflozin in combination therapy for treating type 2 diabetes. 2013. [cited 17 Febr. 2014]. Available from <http://guidance.nice.org.uk/TA288>.

Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes. A patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;1364-79.

Obesity and Diabetes Mellitus. In: Longo D, Fauci A, Kasper D, et al. *Harrison's manual of medicine*. 18th ed. New York: McGraw-Hill; 2013:1134-44.

Scottish Intercollegiate Guidelines Network. *Management of Diabetes*. Edinburgh: Scottish Intercollegiate Guidelines Network; 2010.

SmPC of canagliflozin

The Royal College of Physicians. *Type 2 diabetes. National clinical guideline for primary and secondary care (update)*. London: The Royal College of Physicians; 2008.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[B0002] What is the approved indication and claimed benefit of canagliflozin and the evidence-based comparators?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- Approved label; FDA: 2013,
- Advisory Committee FDA: January 10; 2013.
- SmPC of canagliflozin

Critical appraisal criteria None

Method of synthesis Narrative

Result

Indications

Canagliflozin is indicated in adults aged 18 years and older with T2DM to improve glycaemic control as:

- Monotherapy: when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
- Add-on Therapy: add-on therapy with other antihyperglycaemic medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Claimed benefit

Canagliflozin, by the inhibition of the sodium glucose co-transporter 2 (SGLT2), determines reduced reabsorption of the glucose filtered by the kidney thus increases urinary glucose excretion (UGE). By promoting glucosuria, canagliflozin treatment reduces hyperglycaemia through an insulin-independent mechanism. Therefore, canagliflozin is expected to be effective across the spectrum of β -cell function, providing clinically meaningful glycaemic improvements for patients with new-onset T2DM who have only moderate impairment of β -cell function to patients with greater β -cell functional loss, such as those with long-standing T2DM who require insulin.

Increased UGE also translates to osmotic diuresis, with the diuretic effect leading to a reduction in SBP, and in a net loss of calories (4 kcal/g of glucose) and therefore a reduction in body weight.

Different pharmacological glucose control therapies are on the market and are included in clinical practice guidelines as monotherapy dual or triple therapy (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonist or insulins). New class of drug is available on the EU market, SGLT2 inhibitors, with dapagliflozin as a 1st drug approved in the class. Metformin is the optimal first-line drug. If metformin is contraindicated or not tolerated, other drugs could be used: combination therapy with an additional one or two oral or injectable agents is reasonable, aiming to minimise side effect where possible. Many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. A patient-centred approach should be used to guide choice of therapy, bearing in mind their efficacy, side effects, cost, comorbidities, and patient preferences [American Diabetes Association 2013, Fauci 2013, Inzucchi 2012].

For more details on claimed benefits please see Result card B0001.

Discussion

This report will focus on add-on therapy rather than treatment with canagliflozin on monotherapy.

The FDA labelling specifies that canagliflozin not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis contraindication not underlined in the REA manufacturer document.

Due the different current T2DM therapies a patient-centred approach should be used to guide choice of therapy, bearing in mind their efficacy, side effects, cost, comorbidities, and patient preferences.

References

Advisory Committee FDA, January 10, 2013

American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2013;36:S11-S66.

Approved label; FDA: 2013

Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes. A patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012:1364-79.

Micromedex-Drug details. April 2013

Obesity and Diabetes Mellitus. In: Longo D, Fauci A, Kasper D, et al. Harrison's manual of medicine. 18th ed. New York: McGraw-Hill; 2013:1134-44.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[B0003] What is the phase of development and implementation of the canagliflozin and the comparator(s)?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- Approved label; FDA: 2013.,
- SmPC of canagliflozin

Critical appraisal criteria None

Method of synthesis Narrative

Result

Canagliflozin has recently been approved by the US Food and drug Administration (FDA) (1).

Canagliflozin has been given a Marketing Authorisation on Australia on 6 September 2013.

The EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the product Invokana (100 mg and 300 mg film-coated tablet) intended for the treatment of type-2 diabetes on 19 September 2013. This recommendation was forwarded to the European Commission, which approved the product on 22 November 2013. The reimbursement status of canagliflozin in different EU countries is decided at national level.

The SGLT2 inhibitors are the newest class of drugs approved for T2DM patients. Dapagliflozin is approved for use in EU for Type2DM in adults aged ≥ 18 . Empagliflozin has been submitted for marketing approval to FDA and EMA for the treatment adult with Type2DM. Ipragliflozin has been submitted for marketing approval in Japan.

Several new potential therapies are being evaluated, as G protein-coupled receptor 119 agonist, free fatty acid receptor 1 activators, inhibitors of 11beta-hydroxysteroid dehydrogenase type 1 and glucokinase activators (2).

Marketing Application Status of Antihyperglycaemic Agents in Europe is presented in Table 25.

Table 25. Marketing Application Status of Antihyperglycaemic Agents in Europe

	Actos (pioglitazone)	Avandia (rosiglitazone)	Januvia (sitagliptin)	Galvus (vildagliptin)	Onglyza (saxagliptin)	Trajenta (linagliptin)
Austria	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Belgium	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Bulgaria	NOT STARTED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED

	Actos (pioglitazone)	Avandia (rosiglitazone)	Januvia (sitagliptin)	Galvus (vildagliptin)	Onglyza (saxagliptin)	Trajenta (linagliptin)
Cyprus	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	NOT STARTED
Czech Republic	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Croatia	DATA NOT AVAILABLE	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Denmark	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Estonia	APPROVED	WITHDRAWN	APPROVED	NOT STARTED	APPROVED	APPROVED
Finland	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
France	DENIED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Germany	DENIED	WITHDRAWN	APPROVED	APPROVED	APPROVED	DENIED
Greece	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Hungary	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Ireland	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Italy	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	IN PROGRESS
Latvia	APPROVED	WITHDRAWN	APPROVED	NOT STARTED	APPROVED	APPROVED
Lithuania	APPROVED	WITHDRAWN	APPROVED	NOT STARTED	APPROVED	IN PROGRESS
Luxembourg	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Malta	DATA NOT AVAILABLE	WITHDRAWN	APPROVED	APPROVED	DATA NOT AVAILABLE	APPROVED

	Actos (pioglitazone)	Avandia (rosiglitazone)	Januvia (sitagliptin)	Galvus (vildagliptin)	Onglyza (saxagliptin)	Trajenta (linagliptin)
Netherlands	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Norway	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Poland	DENIED	WITHDRAWN	DENIED	DENIED	DENIED	DENIED
Portugal	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Romania	APPROVED	WITHDRAWN	APPROVED	IN PROGRESS	IN PROGRESS	IN PROGRESS
Slovakia	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Slovenia	DATA NOT AVAILABLE	WITHDRAWN	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE
Spain	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
Sweden	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	NOT STARTED
United Kingdom - SMC	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED
United Kingdom - NICE	APPROVED	WITHDRAWN	APPROVED	APPROVED	APPROVED	APPROVED

	Byetta (exenatide)	Victoza (liraglutide)	Bydureon (exenatide)	Lyxumia (lixisenatide)	Forxiga (dapagliflozin)	Invokana (canagliflozin)
Austria	DENIED	DENIED	DENIED	IN PROGRESS	IN PROGRESS	NOT STARTED
Belgium	APPROVED	APPROVED	NOT STARTED	PROBABLY IN PROGRESS	IN PROGRESS	NOT STARTED
Bulgaria	APPROVED	APPROVED	APPROVED	NOT STARTED	NOT STARTED	NOT STARTED
Cyprus	APPROVED	APPROVED	NOT STARTED	NOT STARTED	NOT STARTED	NOT STARTED
Czech Republic	APPROVED	APPROVED	NOT STARTED	IN PROGRESS	IN PROGRESS	NOT STARTED
Croatia	APPROVED	APPROVED	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	NOT STARTED
Denmark	APPROVED	APPROVED	APPROVED	APPROVED	APPROVED	NOT STARTED
Estonia	APPROVED	APPROVED	IN PROGRESS	NOT STARTED	IN PROGRESS	NOT STARTED
Finland	APPROVED	WITHDRAWN	APPROVED	PROBABLY IN PROGRESS	PROBABLY IN PROGRESS	NOT STARTED
France	APPROVED	APPROVED	APPROVED	APPROVED	APPROVED	IN PROGRESS
Germany	APPROVED	APPROVED	APPROVED	APPROVED	APPROVED	IN PROGRESS
Greece	APPROVED	APPROVED	APPROVED	APPROVED	APPROVED	NOT STARTED
Hungary	APPROVED	APPROVED	IN PROGRESS	NOT STARTED	IN PROGRESS	NOT STARTED
Ireland	APPROVED	APPROVED	APPROVED	IN PROGRESS	IN PROGRESS	NOT STARTED
Italy	APPROVED	APPROVED	IN PROGRESS	IN PROGRESS	IN PROGRESS	NOT STARTED

	Byetta (exenatide)	Victoza (liraglutide)	Bydureon (exenatide)	Lyxumia (lixisenatide)	Forxiga (dapagliflozin)	Invokana (canagliflozin)
Latvia	APPROVED	APPROVED	NOT STARTED	NOT STARTED	NOT STARTED	NOT STARTED
Lithuania	APPROVED	IN PROGRESS	NOT STARTED	NOT STARTED	NOT STARTED	NOT STARTED
Luxembourg	APPROVED	APPROVED	DENIED	IN PROGRESS	IN PROGRESS	NOT STARTED
Malta	APPROVED	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	NOT STARTED
Netherlands	APPROVED	APPROVED	APPROVED	NOT STARTED	IN PROGRESS	NOT STARTED
Norway	APPROVED	APPROVED	APPROVED	PROBABLY IN PROGRESS	PROBABLY IN PROGRESS	NOT STARTED
Poland	DENIED	DENIED	NOT STARTED	NOT STARTED	NOT STARTED	NOT STARTED
Portugal	DENIED	IN PROGRESS	IN PROGRESS	IN PROGRESS	IN PROGRESS	IN PROGRESS
Romania	APPROVED	IN PROGRESS	APPROVED	NOT STARTED	IN PROGRESS	NOT STARTED
Slovakia	APPROVED	APPROVED	APPROVED	NOT STARTED	NOT STARTED	NOT STARTED
Slovenia	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	DATA NOT AVAILABLE	NOT STARTED
Spain	APPROVED	APPROVED	APPROVED	IN PROGRESS	IN PROGRESS	NOT STARTED
Sweden	APPROVED	APPROVED	APPROVED	PROBABLY IN PROGRESS	PROBABLY IN PROGRESS	NOT STARTED
United Kingdom - SMC	APPROVED	APPROVED	APPROVED	IN PROGRESS	APPROVED	NOT STARTED
United Kingdom - NICE	APPROVED	APPROVED	APPROVED	NOT STARTED	IN PROGRESS	NOT STARTED

Source: Johnson & Johnson submission file, Appendix 5.

Reimbursement Status of Antihyperglycaemic Agents in Europe is presented in Table 26.

Table 26. Reimbursement Status of Antihyperglycaemic Agents in Europe

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
AUSTRIA	PIOGLITAZONE	ACTOS	15MG	YES	100%	YELLOW BOX: PRE APPROVAL BY CHIEF PHYSICIANS OF SICK FUNDS IS NECESSARY. LIMITATIONS: SECOND LINE, HBA1C > 7 RI, FIXED PRESCRIPTION FEE OF € 5,15 PER PRESCRIPTION
			30MG	YES	100%	
			45MG	YES	100%	
AUSTRIA	SITAGLIPTIN	JANUVIA	100 MG	YES	100%	YELLOW BOX: PRE APPROVAL BY CHIEF PHYSICIANS OF SICK FUNDS IS NECESSARY. LIMITATIONS: SECOND LINE, HBA1C > 7 RI, FIXED PRESCRIPTION FEE OF € 5,15 PER PRESCRIPTION
AUSTRIA	VILDAGLIPTIN	GALVUS	50MG	YES	100%	YELLOW BOX: PRE APPROVAL BY CHIEF PHYSICIANS OF SICK FUNDS IS NECESSARY. LIMITATIONS: SECOND LINE, HBA1C > 7 RI, FIXED PRESCRIPTION FEE OF € 5,15 PER PRESCRIPTION
AUSTRIA	SAXAGLIPTIN	ONGLYZA	2.5MG	YES	100%	YELLOW BOX: PRE APPROVAL BY CHIEF PHYSICIANS OF SICK FUNDS IS NECESSARY. LIMITATIONS: SECOND LINE, HBA1C > 7 RI, FIXED PRESCRIPTION FEE OF € 5,15 PER PRESCRIPTION
			5MG	YES	100%	
AUSTRIA	LINAGLIPTIN	TRAJENTA	5MG	YES	100%	YELLOW BOX: PRE APPROVAL BY CHIEF PHYSICIANS OF SICK FUNDS IS NECESSARY. LIMITATIONS: SECOND LINE, HBA1C > 7 RI, FIXED PRESCRIPTION FEE OF € 5,15 PER PRESCRIPTION. NO COMBINATION WITH INSULIN
AUSTRIA	EXENATIDE	BYETTA	N/A	NO		
AUSTRIA	LIRAGLUTIDE	VICTOZA	N/A	NO		
AUSTRIA	EXENATIDE	BYDUREON	N/A	NO		
AUSTRIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
AUSTRIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
BELGIUM	PIOGLITAZONE	ACTOS	15MG	YES	100%	CATEGORY A, NO COPAYMENT
			30MG	YES	100%	
BELGIUM	SITAGLIPTIN	JANUVIA	25MG	YES	100%	CATEGORY A, NO COPAYMENT
			50MG	YES	100%	
			100MG	YES	100%	
BELGIUM	VILDAGLIPTIN	GALVUS	50MG	YES	100%	CATEGORY A, NO COPAYMENT
BELGIUM	SAXAGLIPTIN	ONGLYZA	5MG	YES	100%	CATEGORY A, NO COPAYMENT
BELGIUM	LINAGLIPTIN	TRAJENTA	5MG	YES	100%	CATEGORY A, NO COPAYMENT
BELGIUM	EXENATIDE	BYETTA	300 MCG	YES	100%	CATEGORY A, NO COPAYMENT
			600 MCG	YES	100%	
BELGIUM	LIRAGLUTIDE	VICTOZA	6MG/ML	YES	100%	CATEGORY A, NO COPAYMENT
BELGIUM	EXENATIDE	BYDUREON	N/A	N/A		
BELGIUM	LIXISENATIDE	LYXUMIA	N/A	N/A		
BELGIUM	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
BULGARIA	PIOGLITAZONE	ACTOS	N/A	N/A		
BULGARIA	SITAGLIPTIN	JANUVIA	100MG	YES	100%	REIMBURSED AT WHOLESALE PRICE
BULGARIA	VILDAGLIPTIN	GALVUS	50MG	YES	100%	REIMBURSED AT WHOLESALE PRICE
BULGARIA	SAXAGLIPTIN	ONGLYZA	5MG	YES	100%	REIMBURSED AT WHOLESALE PRICE
BULGARIA	LINAGLIPTIN	TRAJENTA	5MG	YES	100%	REIMBURSED AT WHOLESALE PRICE
BULGARIA	EXENATIDE	BYETTA	300MCG	YES	100%	REIMBURSED AT WHOLESALE PRICE
			600MCG	YES	100%	
BULGARIA	LIRAGLUTIDE	VICTOZA	18MG	YES	100%	REIMBURSED AT WHOLESALE PRICE
BULGARIA	EXENATIDE	BYDUREON	2MG	YES	100%	REIMBURSED AT WHOLESALE PRICE
BULGARIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
BULGARIA	DAPAGLIFLOZIN	FORXIGA	5MG	NO		
CROATIA	PIOGLITAZONE	ACTOS	N/A	N/A		
CROATIA	SITAGLIPTIN	JANUVIA	100MG	YES	75%	28 X 100MG PACK
CROATIA	VILDAGLIPTIN	GALVUS	50MG	YES	75%	60 X 50MG PACK
CROATIA	SAXAGLIPTIN	ONGLYZA	5MG	YES	75%	28 X 5MG PACK
CROATIA	LINAGLIPTIN	TRAJENTA	5MG	YES	75%	30 X 5MG PACK
CROATIA	EXENATIDE	BYETTA	300 MCG	YES	100%	GENERAL REIMBURSEMENT
			600 MCG	YES	100%	
CROATIA	LIRAGLUTIDE	VICTOZA	18 MG	NO		
CROATIA	EXENATIDE	BYDUREON	N/A	N/A		
CROATIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
CROATIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
CYPRUS	PIOGLITAZONE	ACTOS	N/A	N/A		
CYPRUS	SITAGLIPTIN	JANUVIA	100MG	YES	N/A	
CYPRUS	VILDAGLIPTIN	GALVUS	50MG	NO		
CYPRUS	SAXAGLIPTIN	ONGLYZA	5MG	NO		
CYPRUS	LINAGLIPTIN	TRAJENTA	N/A	N/A		
CYPRUS	EXENATIDE	BYETTA	300 MCG 600 MCG	NO		
CYPRUS	LIRAGLUTIDE	VICTOZA	1.8 MG	NO		
CYPRUS	EXENATIDE	BYDUREON	N/A	N/A		
CYPRUS	LIXISENATIDE	LYXUMIA	N/A	N/A		
CYPRUS	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
CZECH REPUBLIC	PIOGLITAZONE	ACTOS	15 MG 30 MG	YES YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	SITAGLIPTIN	JANUVIA	100MG	YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	VILDAGLIPTIN	GALVUS	50MG	YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	SAXAGLIPTIN	ONGLYZA	5MG	YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	LINAGLIPTIN	TRAJENTA	5MG	YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	LIRAGLUTIDE	VICTOZA	18 MG	YES	N/A	PARTIALLY FUNDED
CZECH REPUBLIC	EXENATIDE	BYDUREON	N/A	N/A		
CZECH REPUBLIC	LIXISENATIDE	LYXUMIA	N/A	N/A		
CZECH REPUBLIC	DAPAGLIFLOZIN	FORXIGA	10 MG	NO		
DENMARK	PIOGLITAZONE	ACTOS	15 MG 30MG	YES YES	85%~~ 85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	SITAGLIPTIN	JANUVIA	25 MG 50 MG 100 MG**	NO NO YES**	85%~~ 85%~~ 85%~~	**GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	VILDAGLIPTIN	GALVUS	50 MG	YES	85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	SAXAGLIPTIN	ONGLYZA	2.5 MG	YES	85%~~	GENERAL

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
			5 MG	YES	85%~~	REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	LINAGLIPTIN	TRAJENTA	5 MG	YES	85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	85%~~ 85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	LIRAGLUTIDE	VICTOZA	18 MG	YES	85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	EXENATIDE	BYDUREON	2 MG	YES	85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
DENMARK	LIXISENATIDE	LYXUMIA	N/A	N/A		
DENMARK	DAPAGLIFLOZIN	FORXIGA	5 MG 10 MG	YES YES	85%~~ 85%~~	GENERAL REIMBURSEMENT ~~ MAXIMUM SUPPORT, COULD RISE TO 100% IN SPECIAL CIRCUMSTANCES
ESTONIA	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES YES YES	75% OR 90% 75% OR 90% 75% OR 90%	90% FOR PENSIONERS
ESTONIA	SITAGLIPTIN	JANUVIA	25 MG 50 MG 100 MG	YES YES YES	75% OR 90% 75% OR 90% 75% OR 90%	90% FOR PENSIONERS
ESTONIA	VILDAGLIPTIN	GALVUS	N/A	N/A		
ESTONIA	SAXAGLIPTIN	ONGLYZA	2.5 MG 5MG	YES YES	75% OR 90% 75% OR 90%	90% FOR PENSIONERS
ESTONIA	LINAGLIPTIN	TRAJENTA	5 MG	YES	75% OR 90%	90% FOR PENSIONERS
ESTONIA	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	75% OR 90% 75% OR 90%	90% FOR PENSIONERS
ESTONIA	LIRAGLUTIDE	VICTOZA	18 MG	NO		
ESTONIA	EXENATIDE	BYDUREON	N/A	N/A		
ESTONIA	LIXISENATIDE	LYXUMIA	N/A	N/A		

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
ESTONIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
FINLAND	PIOGLITAZONE	ACTOS	15 MG	YES	100%	
			30 MG	YES	100%	
FINLAND	SITAGLIPTIN	JANUVIA	25 MG	YES	100%	
			50 MG	YES	100%	
			100 MG	YES	100%	
FINLAND	VILDAGLIPTIN	GALVUS	50 MG	YES	100%	
FINLAND	SAXAGLIPTIN	ONGLYZA	2.5 MG	YES	100%	
			5 MG	YES	100%	
FINLAND	LINAGLIPTIN	TRAJENTA	5 MG	YES	35%	
FINLAND	EXENATIDE	BYETTA	300 MCG	YES	100%	RESTRICTED TO BE PRESCRIBED BY SPECIALISTS AND FOR PATIENTS THAT ARE DIFFICULT TO CONTROL ON OTHER ORAL ANTIDIABETES TREATMENT OR HAVE A BMI \geq 35
600 MCG			YES	100%		
FINLAND	LIRAGLUTIDE	VICTOZA	18 MG	YES	35 %	REIMBURSEMENT WAS WITHDRAWN IN JANUARY 2013. NEW APPROVAL OF BASIC REIMBURSEMENT (35%) APPROVED AS PER AUG 1, 2013 FOR A MAX DAILY DOSAGE OF 1,2 MG AND SAME RESTRICTIONS AS BYETTA. BYDUREON.
FINLAND	EXENATIDE	BYDUREON	2 MG	YES	100%	RESTRICTED TO BE PRESCRIBED BY SPECIALISTS AND FOR PATIENTS THAT ARE DIFFICULT TO CONTROL ON OTHER ORAL ANTIDIABETES TREATMENT OR HAVE A BMI \geq 35
FINLAND	LIXISENATIDE	LYXUMIA	N/A	N/A		
FINLAND	DAPAGLIFLOZIN	FORXIGA	5MG	NO		
			10 MG	NO		
FRANCE	PIOGLITAZONE	ACTOS	15 MG	NO		
			30 MG	NO		
FRANCE	SITAGLIPTIN	JANUVIA	100 MG	YES	65%	
FRANCE	VILDAGLIPTIN	GALVUS	50 MG	YES	65%	
FRANCE	SAXAGLIPTIN	ONGLYZA	5 MG	YES	65%	
FRANCE	LINAGLIPTIN	TRAJENTA	N/A	N/A		
FRANCE	EXENATIDE	BYETTA	300 MCG	YES	65%	
			600 MCG	YES	65%	
FRANCE	LIRAGLUTIDE	VICTOZA	18 MG	YES	65%	
FRANCE	EXENATIDE	BYDUREON	N/A	N/A		

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
FRANCE	LIXISENATIDE	LYXUMIA	N/A	N/A		
FRANCE	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
GERMANY	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES YES YES	90% 90% 90%	MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10 no reimbursement in general, only in exceptional cases
GERMANY	SITAGLIPTIN	JANUVIA	100 MG	YES	90%	MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	VILDAGLIPTIN	GALVUS	50 MG	YES	90%	MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	SAXAGLIPTIN	ONGLYZA	2.5 MG 5 MG	YES YES	90% 90%	MINIMUM CO MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	LINAGLIPTIN	TRAJENTA	5 MG	YES	90%	MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10 WITHDRAWN FROM MARKET AFTER BENEFIT EVALUATION
GERMANY	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	90% 90%	MINIMUM CO MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	LIRAGLUTIDE	VICTOZA	18 MG	YES	90%	MINIMUM CO MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	EXENATIDE	BYDUREON	2 MG	YES	90%	MINIMUM CO MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	LIXISENATIDE	LYXUMIA	10 MCG 20 MCG	YES YES	90% 90%	MINIMUM CO MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GERMANY	DAPAGLIFLOZIN	FORXIGA	5 MG 10 MG	YES YES	90% 90%	MINIMUM CO-PAYMENT: EUR5, MAXIMUM CO- PAYMENT: EUR10
GREECE	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES YES YES	90% 90% 90%	
GREECE	SITAGLIPTIN	JANUVIA	100 MG	YES	90%	
GREECE	VILDAGLIPTIN	GALVUS	50 MG	YES	90%	
GREECE	SAXAGLIPTIN	ONGLYZA	5MG	YES	90%	
GREECE	LINAGLIPTIN	TRAJENTA	N/A	N/A		
GREECE	EXENATIDE	BYETTA	5 MCG/20 MCL 10 MCG/40	YES YES	90% 75%	

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
			MCL			
GREECE	LIRAGLUTIDE	VICTOZA	18 MG	YES	90%	
GREECE	EXENATIDE	BYDUREON	N/A	N/A		
GREECE	LIXISENATIDE	LYXUMIA	N/A	N/A		
GREECE	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
HUNGARY	PIOGLITAZONE	ACTOS	30 MG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	SITAGLIPTIN	JANUVIA	100 MG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	VILDAGLIPTIN	GALVUS	50 MG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	SAXAGLIPTIN	ONGLYZA	5 MG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	LINAGLIPTIN	TRAJENTA	5 MG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	EXENATIDE	BYETTA	300 MCG	YES	70%	INDICATION-LINKED REIMBURSEMENT
			600 MCG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	LIRAGLUTIDE	VICTOZA	6 MG	YES	70%	INDICATION-LINKED REIMBURSEMENT
HUNGARY	EXENATIDE	BYDUREON	N/A	N/A		
HUNGARY	LIXISENATIDE	LYXUMIA	N/A	N/A		
HUNGARY	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
IRELAND	PIOGLITAZONE	ACTOS	15 MG	YES	100%	
			30 MG	YES	100%	
			45 MG	YES	100%	
IRELAND	SITAGLIPTIN	JANUVIA	25 MG	YES	100%	
			50 MG	YES	100%	
			100 MG	YES	100%	
IRELAND	VILDAGLIPTIN	GALVUS	50 MG	YES	100%	
IRELAND	SAXAGLIPTIN	ONGLYZA	5 MG	YES	100%	
IRELAND	LINAGLIPTIN	TRAJENTA	5 MG	YES	100%	
IRELAND	EXENATIDE	BYETTA	300 MCG	YES	100%	
			600 MCG	YES	100%	
IRELAND	LIRAGLUTIDE	VICTOZA	18 MG	YES	100%	
IRELAND	EXENATIDE	BYDUREON	2 MG	YES	100%	
IRELAND	LIXISENATIDE	LYXUMIA	N/A	N/A		
IRELAND	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
ITALY	PIOGLITAZONE	ACTOS	15 MG	YES	100%	
			30 MG	YES	100%	
			45 MG	YES	100%	
ITALY	SITAGLIPTIN	JANUVIA	25 MG	YES	100%	

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
			50 MG 100 MG	YES YES	100% 100%	
ITALY	VILDAGLIPTIN	GALVUS	50 MG	YES	100%	
ITALY	SAXAGLIPTIN	ONGLYZA	5 MG	YES	100%	
ITALY	LINAGLIPTIN	TRAJENTA	5MG	NO		
ITALY	EXENATIDE	BYETTA	300 MCG 600 MCG	YES	100%	
ITALY	LIRAGLUTIDE	VICTOZA	18 MG	YES	100%	
ITALY	EXENATIDE	BYDUREON	N/A	NO		
ITALY	LIXISENATIDE	LYXUMIA	N/A	NO		
ITALY	DAPAGLIFLOZIN	FORXIGA	5MG 10 MG	NO NO		
LATVIA	PIOGLITAZONE	ACTOS	15 MG 30 MG	YES YES	100% 100%	
LATVIA	SITAGLIPTIN	JANUVIA	100 MG	YES	100%	
LATVIA	VILDAGLIPTIN	GALVUS	N/A	N/A		
LATVIA	SAXAGLIPTIN	ONGLYZA	5 MG	YES	100%	
LATVIA	LINAGLIPTIN	TRAJENTA	5 MG	YES	100%	
LATVIA	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	100% 100%	PRESCRIBED BY ENDOCRINOLOGIST IN PATIENTS WITH BMI>35KG/M2 IN COMBINATION WITH METFORMIN OR SU, IF THEY IN MAX DOSES CANT REACH HBA1C,7%
LATVIA	LIRAGLUTIDE	VICTOZA	18 MG	YES	100%	PRESCRIBED BY ENDOCRINOLOGIST IN PATIENTS WITH BMI>35KG/M2 IN COMBINATION WITH METFORMIN OR SU, IF THEY IN MAX DOSES CANT REACH HBA1C,7%
LATVIA	EXENATIDE	BYDUREON	N/A	N/A		
LATVIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
LATVIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
LITHUANIA	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES YES YES	100% 100% 100%	
LITHUANIA	SITAGLIPTIN	JANUVIA	100 MG	YES	100%	
LITHUANIA	VILDAGLIPTIN	GALVUS	N/A	N/A		
LITHUANIA	SAXAGLIPTIN	ONGLYZA	5 MG	YES	100%	
LITHUANIA	LINAGLIPTIN	TRAJENTA	N/A	N/A		
LITHUANIA	EXENATIDE	BYETTA	300 MCG 600MCG	YES YES	100% 100%	PRESCRIBED BY ENDOCRINOLOGIST IN PATIENTS WITH BMI>32KG/M2 IN COMBINATION WITH METFORMIN OR SU, IF

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
						THEY IN MAX DOSES CANT REACH HBA1C,7.5%
LITHUANIA	LIRAGLUTIDE	VICTOZA	N/A	N/A		
LITHUANIA	EXENATIDE	BYDUREON	N/A	N/A		
LITHUANIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
LITHUANIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
LUXEMBURG	PIOGLITAZONE	ACTOS	15 MG 30 MG	YES YES	100% 100%	
LUXEMBURG	SITAGLIPTIN	JANUVIA	100 MG	YES	100 %	
LUXEMBURG	VILDAGLIPTIN	GALVUS	50 MG	YES	100%	
LUXEMBURG	SAXAGLIPTIN	ONGLYZA	2.5 MG 5MG	YES	100%	
LUXEMBURG	LINAGLIPTIN	TRAJENTA	5 MG	YES	100%	
LUXEMBURG	EXENATIDE	BYETTA	300 MCG 600 MCG	YES	100%	
LUXEMBURG	LIRAGLUTIDE	VICTOZA	12 MG 18 MG	YES	100%	
LUXEMBURG	EXENATIDE	BYDUREON	N/A	N/A		
LUXEMBURG	LIXISENATIDE	LYXUMIA	N/A	N/A		
LUXEMBURG	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
NETHERLANDS	PIOGLITAZONE	ACTOS	15 MG 30 MG	YES YES	100% 100%	
NETHERLANDS	SITAGLIPTIN	JANUVIA	25 MG 50 MG 100 MG	YES YES YES	100% 100% 100%	
NETHERLANDS	VILDAGLIPTIN	GALVUS	50 MG	YES	100 %	
NETHERLANDS	SAXAGLIPTIN	ONGLYZA	2.5 MG 5 MG	YES YES	100% 100%	
NETHERLANDS	LINAGLIPTIN	TRAJENTA	5MG	YES	100%	
NETHERLANDS	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	100% 100%	
NETHERLANDS	LIRAGLUTIDE	VICTOZA	6MG/ML	YES	100%	
NETHERLANDS	EXENATIDE	BYDUREON	2MG	YES	100%	
NETHERLANDS	LIXISENATIDE	LYXUMIA	N/A	N/A		
NETHERLANDS	DAPAGLIFLOZIN	FORXIGA	5MG 10MG	NO NO		
NORWAY	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG**	YES YES YES	62% 62% 62%	100% WHEN THE CEILING OF EXPENSES IS REACHED **RESTRICTED TO USE AFTER HIGHEST TOLERATED DOSE OF COMBINATION OF METFORMIN AND SU. INSULIN SHOULD HAVE BEEN EVALUATED AS AN

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
						ALTERNATIVE.
NORWAY	SITAGLIPTIN	JANUVIA	25 MG	NO	0%	~100% WHEN THE CEILING OF EXPENSES IS REACHED
			50 MG	NO	0%	
			100 MG~~	YES	62%~~	
NORWAY	VILDAGLIPTIN	GALVUS	50 MG	YES	62%	100% WHEN THE CEILING OF EXPENSES IS REACHED
NORWAY	SAXAGLIPTIN	ONGLYZA	5 MG	YES	62%	100% WHEN THE CEILING OF EXPENSES IS REACHED
NORWAY	LINAGLIPTIN	TRAJENTA	5 MG	YES	62 %	100% WHEN THE CEILING OF EXPENSES IS REACHED
NORWAY	EXENATIDE	BYETTA	300 MCG	YES	62%	100% WHEN THE CEILING OF EXPENSES IS REACHED
			600 MCG	YES	62%	
NORWAY	LIRAGLUTIDE	VICTOZA	18 MG	YES	62%	100% WHEN THE CEILING OF EXPENSES IS REACHED
NORWAY	EXENATIDE	BYDUREON	2 MG	YES	62%	100% WHEN THE CEILING OF EXPENSES IS REACHED
NORWAY	LIXISENATIDE	LYXUMIA	10 MCG	NO		
			20 MCG	NO		
NORWAY	DAPAGLIFLOZIN	FORXIGA	5 MG	NO		
			10 MG	NO		
POLAND	PIOGLITAZONE	ACTOS	N/A	NO		
POLAND	SITAGLIPTIN	JANUVIA	N/A	NO		
POLAND	VILDAGLIPTIN	GALVUS	N/A	NO		
POLAND	SAXAGLIPTIN	ONGLYZA	N/A	NO		
POLAND	LINAGLIPTIN	TRAJENTA	N/A	NO		
POLAND	EXENATIDE	BYETTA	N/A	NO		
POLAND	LIRAGLUTIDE	VICTOZA	N/A	NO		
POLAND	EXENATIDE	BYDUREON	N/A	NO		
POLAND	LIXISENATIDE	LYXUMIA	N/A	NO		
POLAND	DAPAGLIFLOZIN	FORXIGA	N/A	NO		
PORTUGAL	PIOGLITAZONE	ACTOS	15 MG	YES	90%	REIMBURSEMENT LEVEL A
			30 MG	YES	90%	
			45 MG	YES	90%	
PORTUGAL	SITAGLIPTIN	JANUVIA	25 MG	YES	90%	REIMBURSEMENT LEVEL A
			50 MG	YES	90%	
			100 MG	YES	90%	
PORTUGAL	VILDAGLIPTIN	GALVUS	50 MG	YES	90%	REIMBURSEMENT LEVEL A
PORTUGAL	SAXAGLIPTIN	ONGLYZA	5 MG	YES	90%	REIMBURSEMENT LEVEL A
PORTUGAL	LINAGLIPTIN	TRAJENTA	5 MG	YES	90%	REIMBURSEMENT LEVEL A

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
PORTUGAL	EXENATIDE	BYETTA	5 MCG/20 MCL	NO		
			10 MCG/40 MCL	NO		
PORTUGAL	LIRAGLUTIDE	VICTOZA	6MG/ML	NO		
PORTUGAL	EXENATIDE	BYDUREON	2MG	NO		
PORTUGAL	LIXISENATIDE	LYXUMIA	10 MCG/0.2ML	NO		
			20 MCG/0.2 ML	NO		
PORTUGAL	DAPAGLIFLOZIN	FORXIGA	5MG	NO		
			10MG	NO		
ROMANIA	PIOGLITAZONE	ACTOS	15 MG	YES	100%	
			30 MG			
			45 MG			
ROMANIA	SITAGLIPTIN	JANUVIA	100 MG	YES	100%	
ROMANIA	VILDAGLIPTIN	GALVUS	50 MG	NO		IT WILL BE 100% REIMBURSED WITH THE NEW REIMBURSEMENT LIST UPDATE EXPECTED TO BE IN PLACE SINCE AUGUST 1-ST 2013.
ROMANIA	SAXAGLIPTIN	ONGLYZA	2.5MG 5MG	NO NO		IT WILL BE 100% REIMBURSED WITH THE NEW REIMBURSEMENT LIST UPDATE EXPECTED TO BE IN PLACE SINCE AUGUST 1-ST 2013.
ROMANIA	LINAGLIPTIN	TRAJENTA	5MG	NO		IT WILL BE 100% REIMBURSED WITH THE NEW REIMBURSEMENT LIST UPDATE EXPECTED TO BE IN PLACE SINCE AUGUST 1-ST 2013.
ROMANIA	EXENATIDE	BYETTA	300 MCG	YES	100%	
			600 MCG	YES	100%	
ROMANIA	LIRAGLUTIDE	VICTOZA	18 MG	NO		IT WILL BE 100% REIMBURSED WITH THE NEW REIMBURSEMENT LIST UPDATE EXPECTED TO BE IN PLACE SINCE AUGUST 1-ST 2013.
ROMANIA	EXENATIDE	BYDUREON	2 MG	YES	100%	
ROMANIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
ROMANIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
SLOVAKIA	PIOGLITAZONE	ACTOS	15 MG	YES	81.2%	
			30 MG	YES	94.4%	
			45 MG	YES	98.4%	
SLOVAKIA	SITAGLIPTIN	JANUVIA	100 MG**	YES	95.9%	**28X100MG PACK

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
			100 MG ~ 100 MG ^^	YES YES	96.6% 97.0%	~84X100MG PACK ^^98X100
SLOVAKIA	VILDAGLIPTIN	GALVUS	50MG** 50MG~	YES YES	93.0% 97.7%	**60X50MG PACK ~180X50MG PACK
SLOVAKIA	SAXAGLIPTIN	ONGLYZA	5MG	YES	94.3%	
SLOVAKIA	LINAGLIPTIN	TRAJENTA	5 MG	YES	98.3%	
SLOVAKIA	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	93.9% 87.9%	
SLOVAKIA	LIRAGLUTIDE	VICTOZA	18MG	YES	83.7%	
SLOVAKIA	EXENATIDE	BYDUREON	2 MG	YES	77.6%	
SLOVAKIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
SLOVAKIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
SLOVENIA	PIOGLITAZONE	ACTOS	N/A	N/A		
SLOVENIA	SITAGLIPTIN	JANUVIA	25MG 50MG 100MG	YES	100%	
SLOVENIA	VILDAGLIPTIN	GALVUS	50MG	YES	100%	30 TAB PACK REIMBURSED; 60 TAB PACK NOT REIMBURSED
SLOVENIA	SAXAGLIPTIN	ONGLYZA	5 MG	YES	100%	
SLOVENIA	LINAGLIPTIN	TRAJENTA	5 MG	YES	100%	
SLOVENIA	EXENATIDE	BYETTA	300 MCG 600 MCG	YES	25%	
SLOVENIA	LIRAGLUTIDE	VICTOZA	18 MG	YES	25%	
SLOVENIA	EXENATIDE	BYDUREON	2 MG	NO		
SLOVENIA	LIXISENATIDE	LYXUMIA	N/A	N/A		
SLOVENIA	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
SPAIN	PIOGLITAZONE	ACTOS	15 MG 30 MG	YES YES	90% 90%	MAXIMUM COPAYMENT €4.20
SPAIN	SITAGLIPTIN	JANUVIA	25MG 50 MG 100 MG	YES YES YES	90% 90% 90%	MAXIMUM COPAYMENT €4.20
SPAIN	VILDAGLIPTIN	GALVUS	50 MG	YES	90%	MAXIMUM COPAYMENT €4.20
SPAIN	SAXAGLIPTIN	ONGLYZA	2.5MG 5MG**	NO YES**	0% 90%**	**MAXIMUM COPAYMENT €4.20; ONLY 28X5MG PACK IS REIMBURSED.
SPAIN	LINAGLIPTIN	TRAJENTA	5 MG	YES	90%	MAXIMUM COPAYMENT €4.20
SPAIN	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	90% 90%	MAXIMUM COPAYMENT €4.20
SPAIN	LIRAGLUTIDE	VICTOZA	18 MG	YES	90%	MAXIMUM COPAYMENT €4.20
SPAIN	EXENATIDE	BYDUREON	2 MG	YES	90%	MAXIMUM COPAYMENT

Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
						€4.20
SPAIN	LIXISENATIDE	LYXUMIA	N/A	N/A		
SPAIN	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
SWEDEN	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES	N/A	
SWEDEN	SITAGLIPTIN	JANUVIA	25 MG 50 MG 100 MG	YES	N/A	
SWEDEN	VILDAGLIPTIN	GALVUS	50 MG	YES	N/A	
SWEDEN	SAXAGLIPTIN	ONGLYZA	5 MG	YES	N/A	
SWEDEN	LINAGLIPTIN	TRAJENTA	N/A	N/A	N/A	
SWEDEN	EXENATIDE	BYETTA	300 MCG 600 MCG	YES	N/A	
SWEDEN	LIRAGLUTIDE	VICTOZA	18 MG	YES	N/A	
SWEDEN	EXENATIDE	BYDUREON	2mg	YES	N/A	
SWEDEN	LIXISENATIDE	LYXUMIA	N/A	N/A		
SWEDEN	DAPAGLIFLOZIN	FORXIGA	5 MG 10 MG	NO		
SWITZERLAND	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES YES YES	90% 90% 90%	
SWITZERLAND	SITAGLIPTIN	JANUVIA	25 MG 50 MG 100 MG	YES YES YES	90% 90% 90%	
SWITZERLAND	VILDAGLIPTIN	GALVUS	50 MG	YES	90%	
SWITZERLAND	SAXAGLIPTIN	ONGLYZA	2.5 MG 5 MG	YES YES	90% 90%	
SWITZERLAND	LINAGLIPTIN	TRAJENTA	5 MG	YES	90%	
SWITZERLAND	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	90% 90%	
SWITZERLAND	LIRAGLUTIDE	VICTOZA	18 MG	YES	90%	
SWITZERLAND	EXENATIDE	BYDUREON	2 MG	YES	90%	
SWITZERLAND	LIXISENATIDE	LYXUMIA	N/A	N/A		
SWITZERLAND	DAPAGLIFLOZIN	FORXIGA	N/A	N/A		
UNITED KINGDOM	PIOGLITAZONE	ACTOS	15 MG 30 MG 45 MG	YES YES YES	100% 100% 100%	
UNITED KINGDOM	SITAGLIPTIN	JANUVIA	25 MG 50 MG 100 MG	YES YES YES	100% 100% 100%	
UNITED	VILDAGLIPTIN	GALVUS	50 MG	YES	100%	

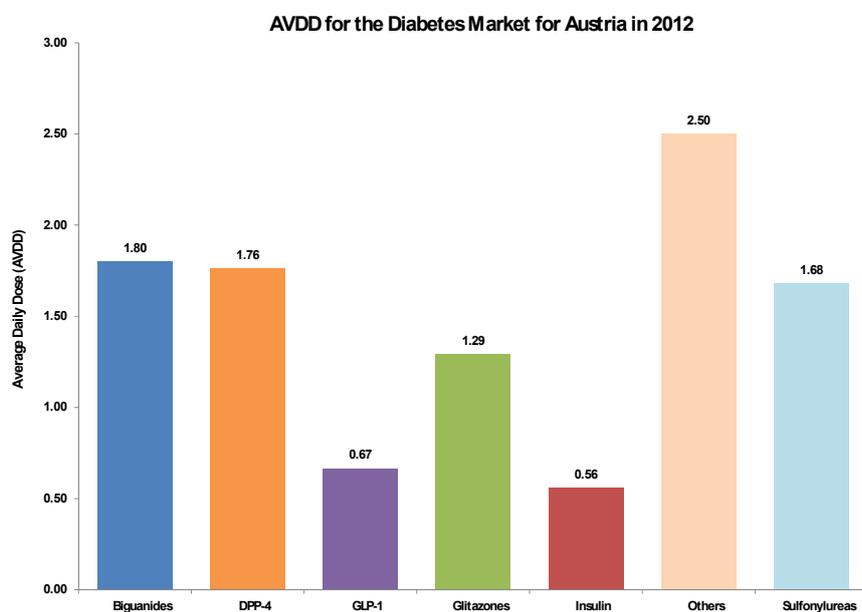
Country	Active Ingredient	Brand Name	Strength	Reimbursement Status	Reimbursement Level	Additional Comments
KINGDOM						
UNITED KINGDOM	SAXAGLIPTIN	ONGLYZA	2.5 MG 5 MG	YES YES	100%	
UNITED KINGDOM	LINAGLIPTIN	TRAJENTA	5 MG	YES	100%	
UNITED KINGDOM	EXENATIDE	BYETTA	300 MCG 600 MCG	YES YES	100%	
UNITED KINGDOM	LIRAGLUTIDE	VICTOZA	18 MG	YES	100%	ONLY 1.2MG DAILY DOSE IS REIMBURSED
UNITED KINGDOM	EXENATIDE	BYDUREON	2 MG	YES	100%	
UNITED KINGDOM	LIXISENATIDE	LYXUMIA	150 MCG 300 MCG	YES YES	100%	
UNITED KINGDOM	DAPAGLIFLOZIN	FORXIGA	N/A	YES	100%	

Source: Johnson & Johnson submission file, Appendix 6.

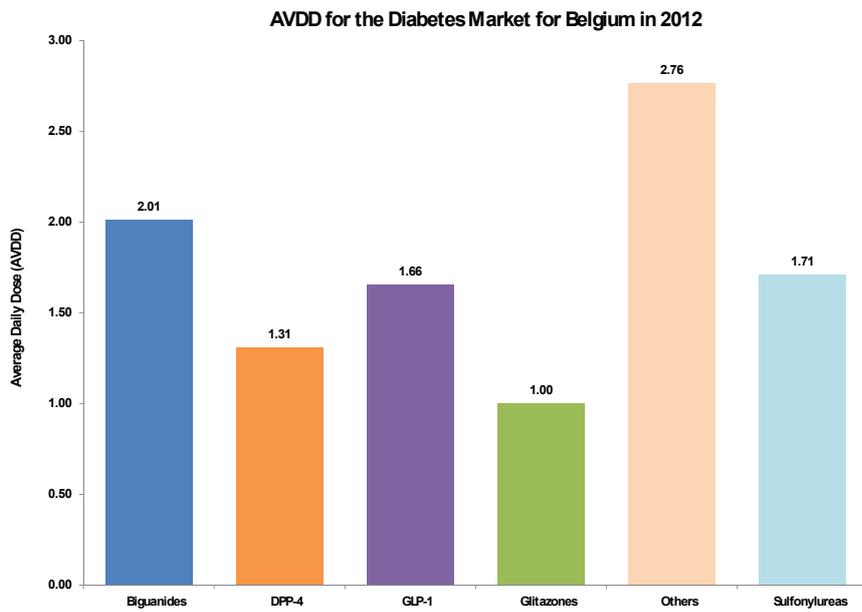
In the following figures below; drug utilisation of different antidiabetics in 2012 by European countries is presented (Source: Johnson & Johnson submission file, Appendix 4).

Figure 6. Drug utilisation of different antidiabetics by European countries, 2012

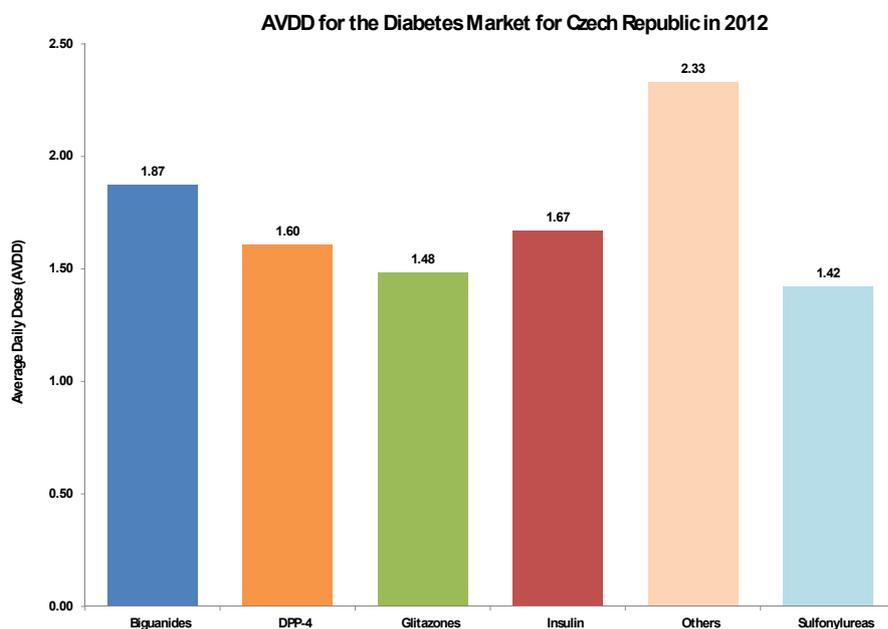
Austria



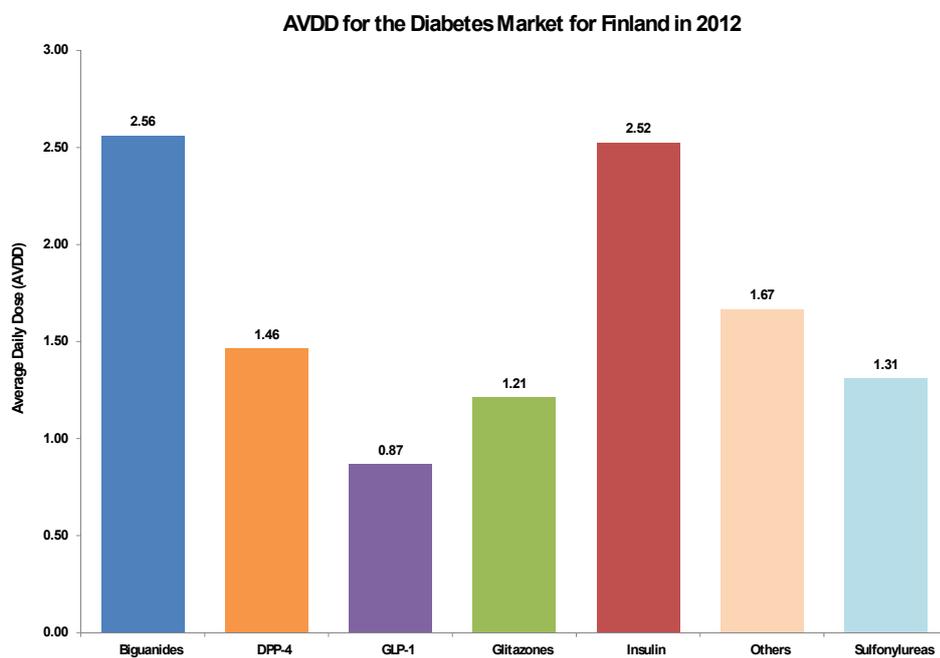
Belgium



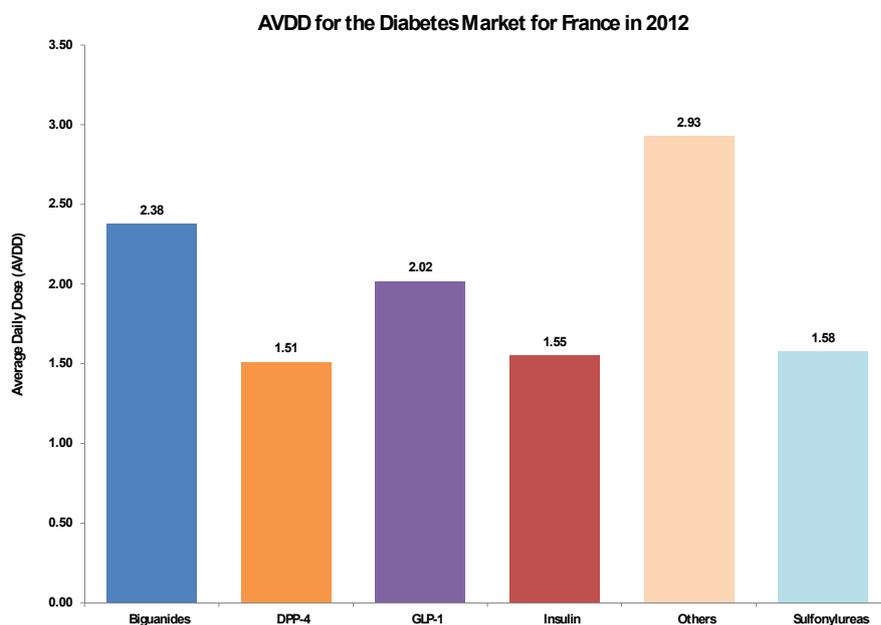
Czech Republic



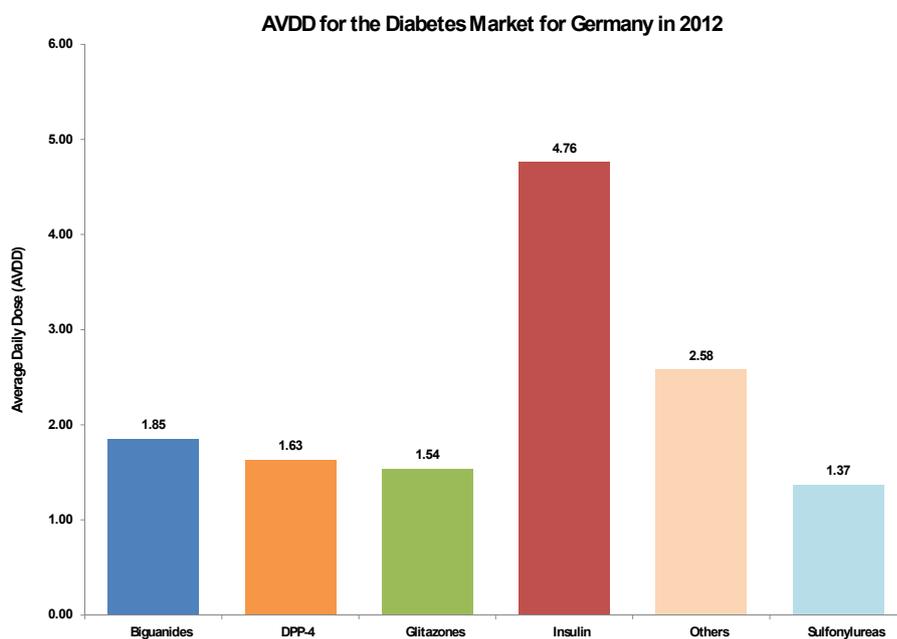
Finland



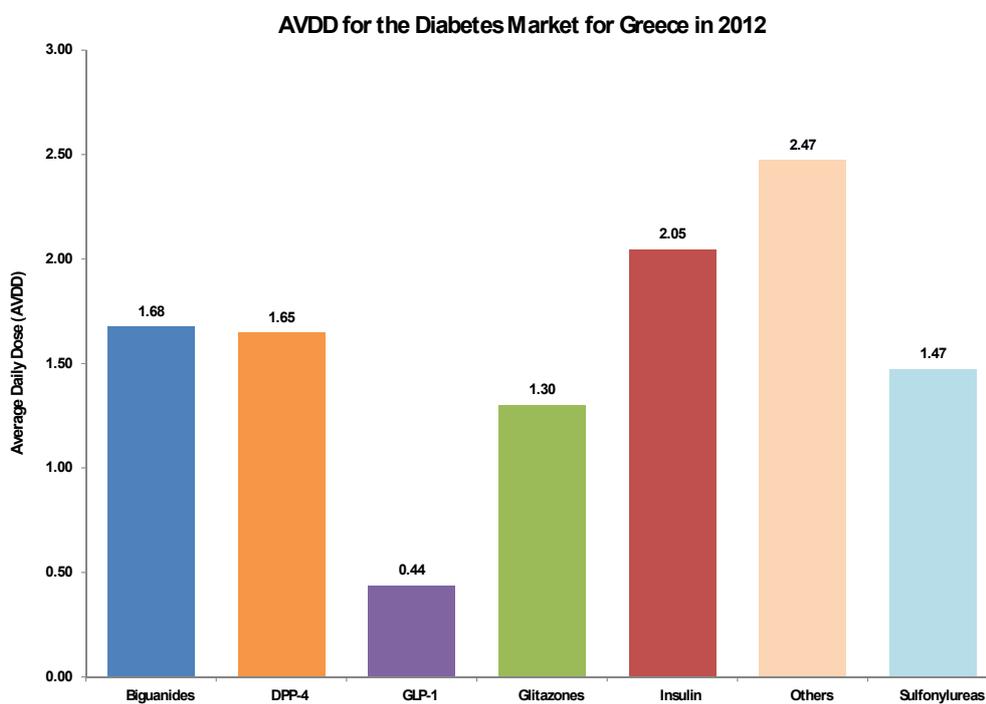
France



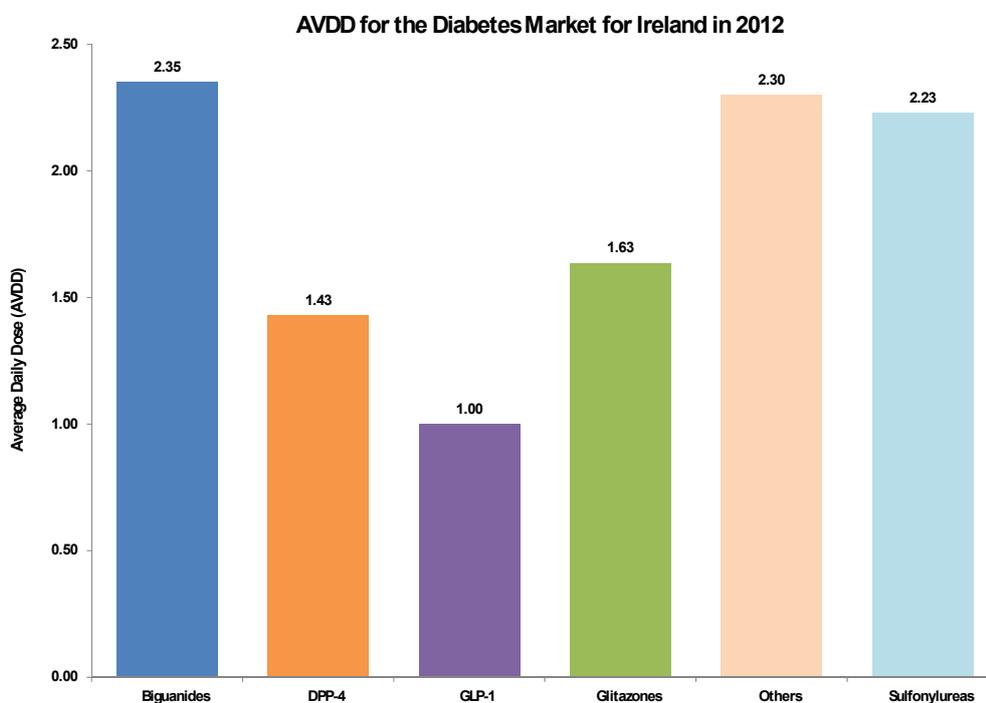
Germany



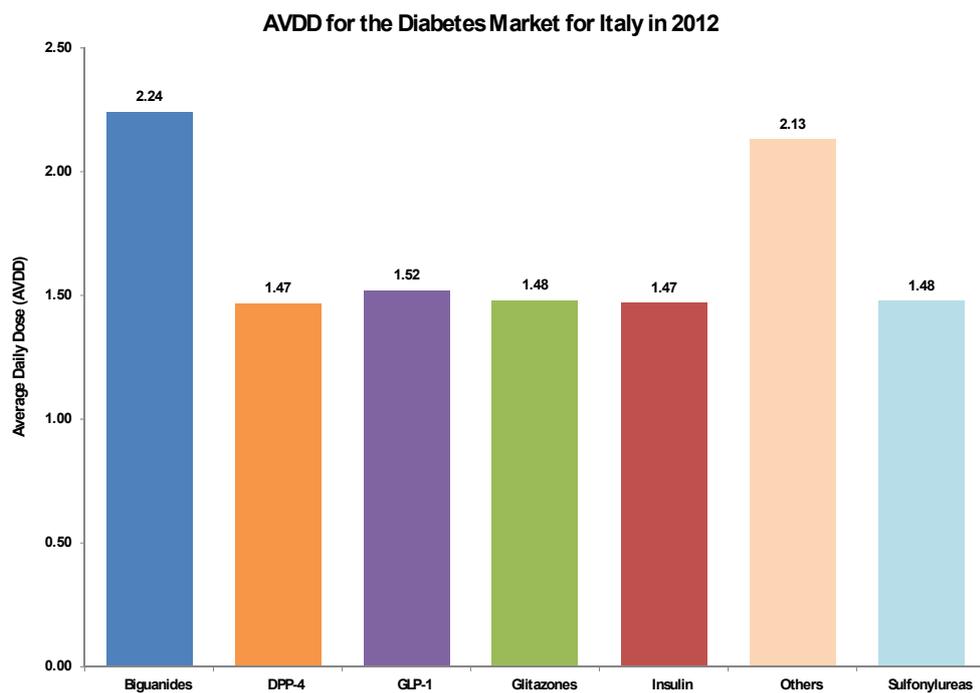
Greece



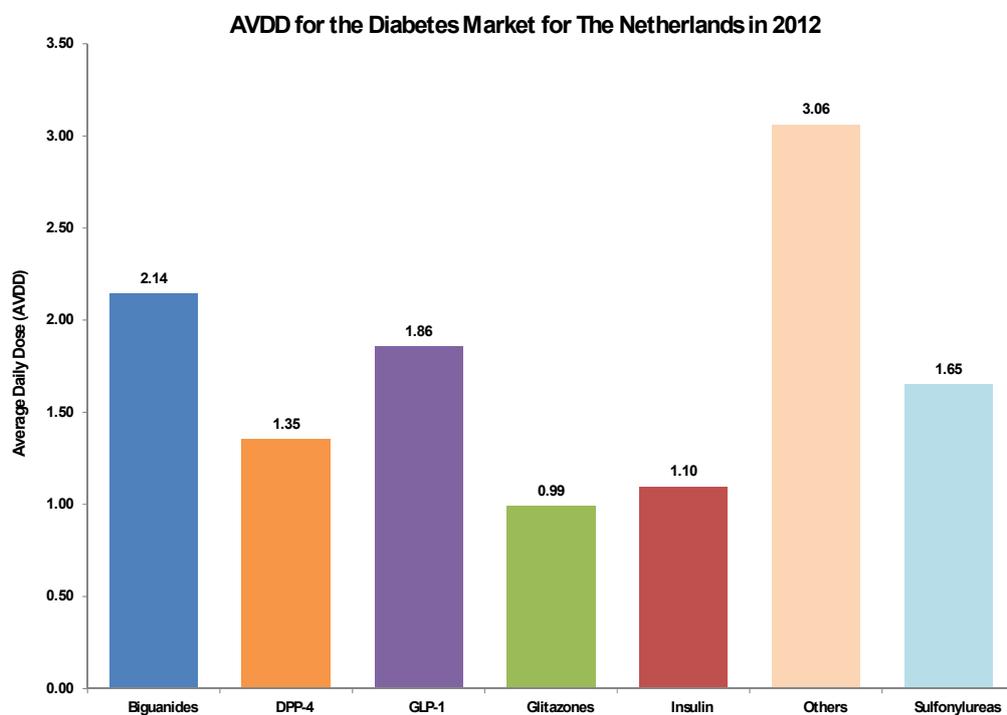
Ireland



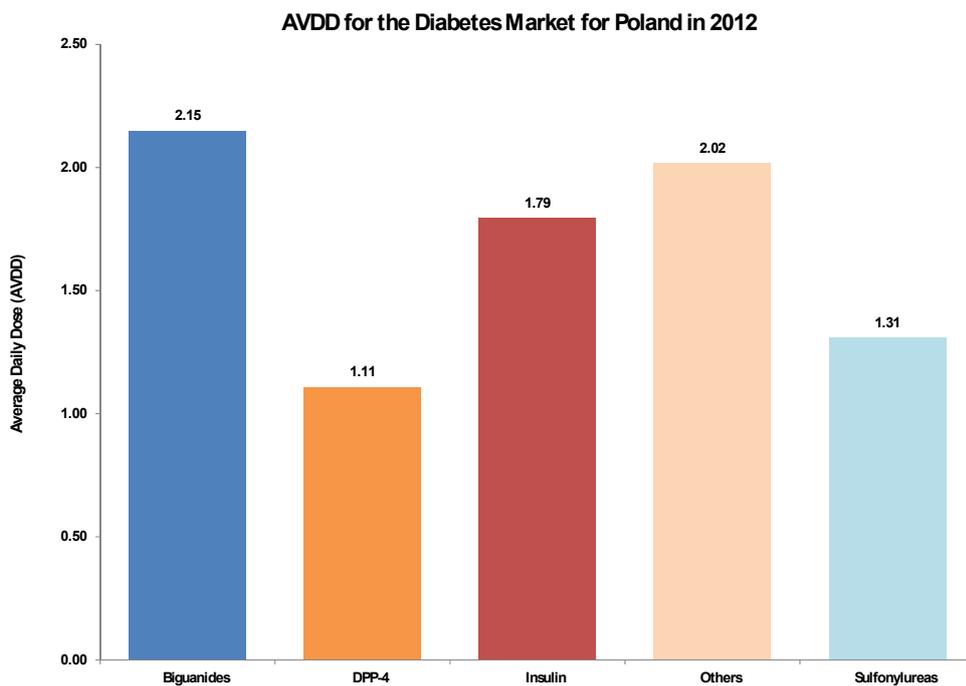
Italy



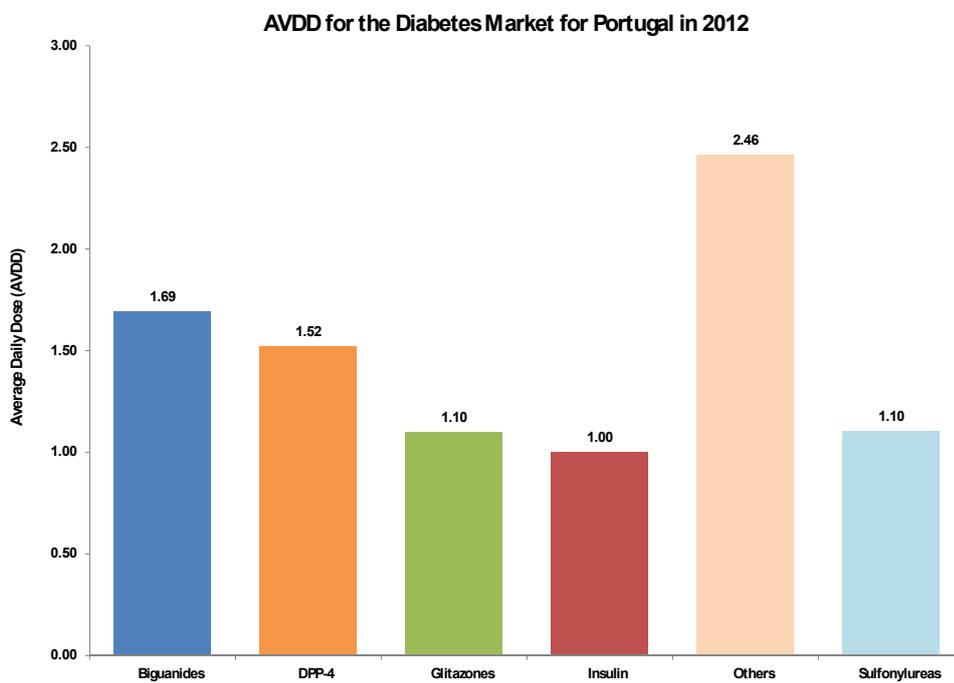
The Netherlands



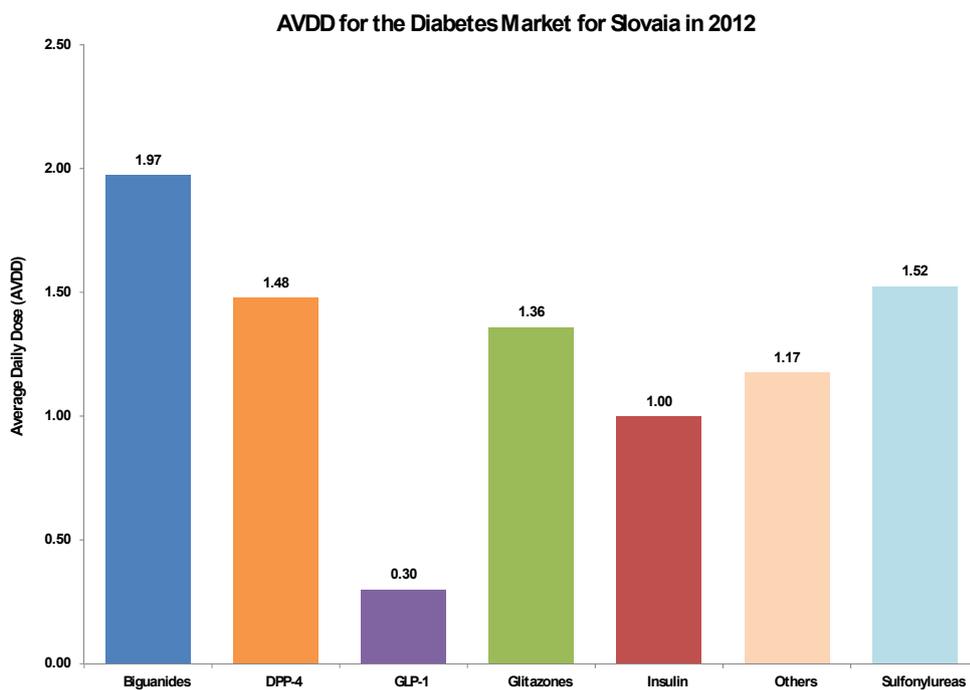
Poland



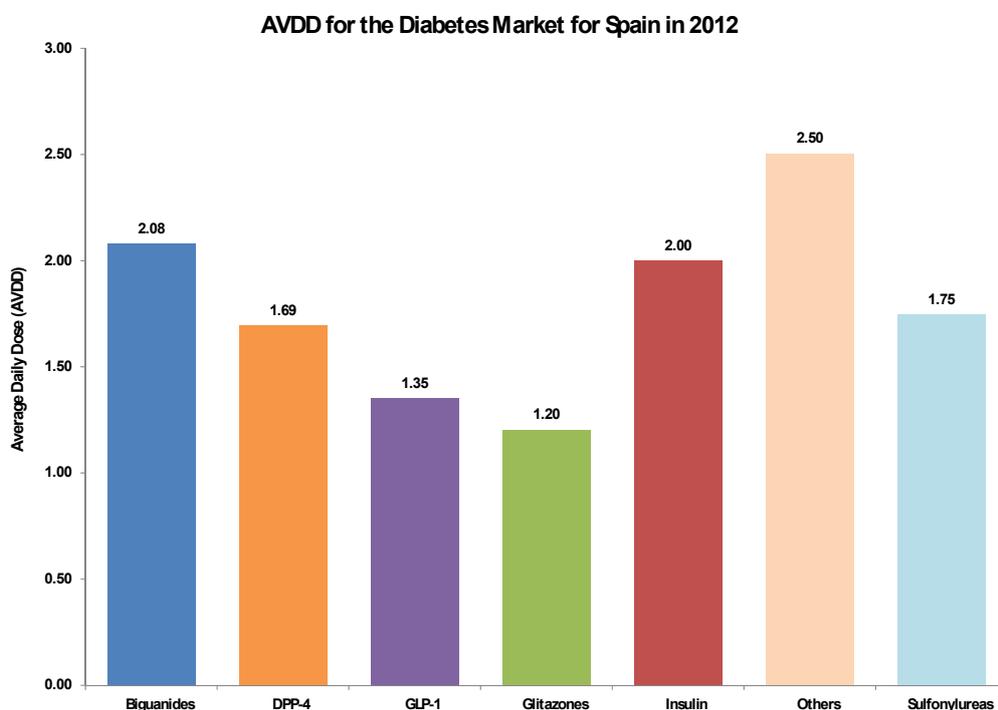
Portugal



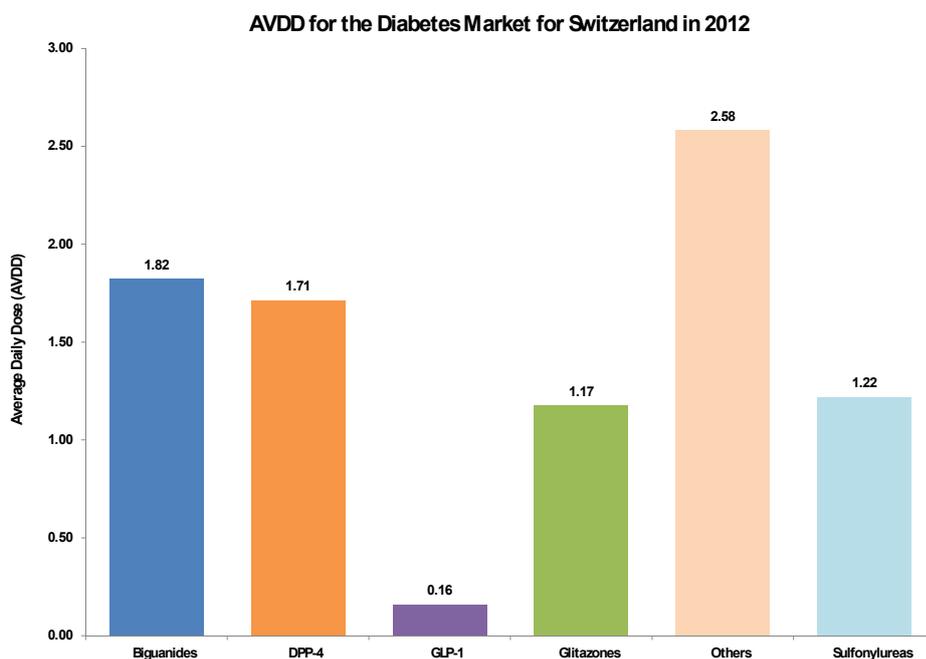
Slovakia



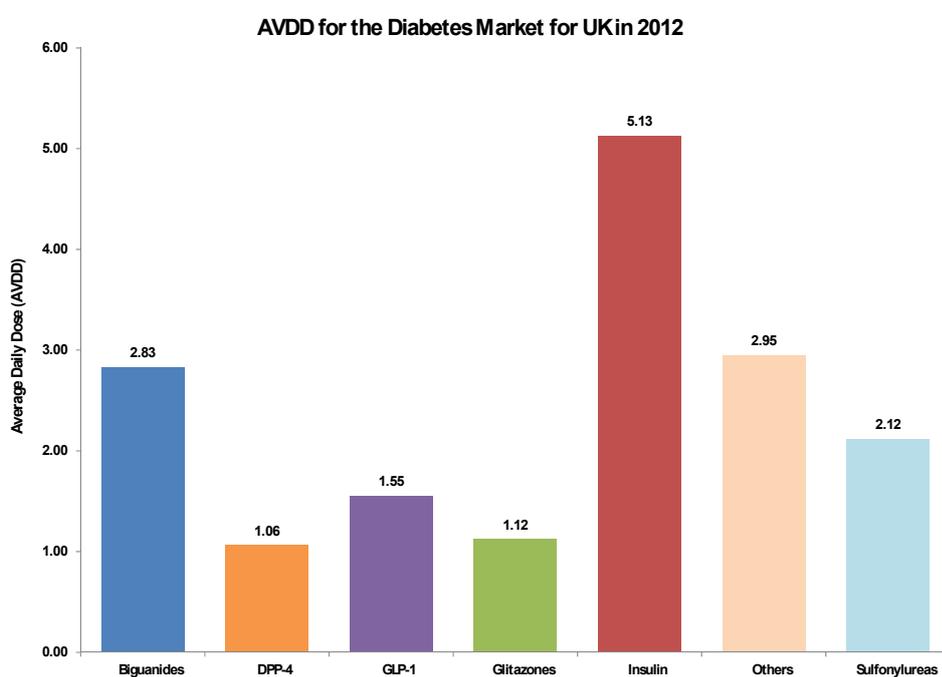
Spain



Switzerland



United Kingdom



Abbreviation: AVDD, average daily dose; DPP-4, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1 analogues.

Source: [Johnson & Johnson submission file, Appendix 4].

Discussion

Data on marketing authorisation status, reimbursement status, drug utilisation are data important at national level to inform reimbursement and coverage decision. These data are provided by canagliflozin Manufacturer; survey for MSs partners was not performed to check these data.

References

Approved label; FDA: 2013.

Freeman JS. Review of insulin-dependent and insulin-independent agents for treating patients with type 2 diabetes mellitus and potential role for sodium-glucose co-transporter 2 inhibitors. Postgrad Med 2013;125:214-26.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[B0004] Who performs or administers the canagliflozin and the comparators?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0002a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;
- Approved label; FDA: 2013
- SmPC of canagliflozin

Critical appraisal criteria None

Method of synthesis Narrative

Result

Since canagliflozin is a new oral drug for T2DM, treatment should be initiated by physicians experienced in patients with diabetes. Although no specific training is required for healthcare professionals, as canagliflozin has a novel mechanism of action that may not be familiar to all healthcare and pharmacy professionals, education may be required for nursing and pharmacy staff.

Below some precautions reported by the **FDA label** on canagliflozin:

Limitation of Use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis

DOSAGE AND ADMINISTRATION

- The recommended starting dose is 100 mg once daily, taken before the first meal of the day
- Dose can be increased to 300 mg once daily in patients tolerating canagliflozin 100 mg once daily who have an estimated GFR of 60 mL/min/1.73 m² or greater and require additional glycaemic control
- Canagliflozin is limited to 100 mg once daily in patients who have an estimated GFR of 45 to less than 60 mL/min/1.73 m²
- Assess renal function before initiating canagliflozin. Do not initiate canagliflozin if estimated GFR is below 45 mL/min/1.73 m²
- Discontinue canagliflozin if estimated GFR falls below 45 mL/min/1.73 m²

SmPC of canagliflozin

Special warnings and precautions for use

General

Canagliflozin has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients.

Canagliflozin should not be used for the treatment of diabetic ketoacidosis as it is not effective in this setting.

Use in patients with renal impairment

The efficacy of canagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. In patients with an eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported, particularly with the 300 mg dose. In addition, in such patients more events of elevated potassium and greater increases in serum creatinine and blood urea nitrogen (BUN) were reported. Therefore, the canagliflozin dose should be limited to 100 mg once daily in patients with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min and canagliflozin should not be used in patients with an eGFR < 45 mL/min/1.73 m² or CrCl < 45 mL/min. Canagliflozin has not been studied in severe renal impairment (eGFR < 30 mL/min/1.73 m² or CrCl < 30 mL/min) or ESRD.

Monitoring of renal function is recommended as follows:

- Prior to initiation of canagliflozin and at least annually, thereafter
- Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter
- For renal function approaching moderate renal impairment, at least 2 times to 4 times per year.

If renal function falls persistently below eGFR 45 mL/min/1.73 m² or CrCl < 45 mL/min, canagliflozin treatment should be discontinued.

Use in patients at risk for adverse reactions related to volume depletion

Due to its mechanism of action, canagliflozin, by increasing urinary glucose excretion (UGE) induces an osmotic diuresis, which may reduce intravascular volume and decrease blood pressure. In controlled clinical studies of canagliflozin, increases in adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, or hypotension) were seen more commonly with the 300 mg dose and occurred most frequently in the first three months.

Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an eGFR < 60 mL/min/1.73 m², patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥ 65 years of age).

Due to volume depletion, generally small mean decreases in eGFR were seen within the first 6 weeks of treatment initiation with canagliflozin. In patients susceptible to greater reductions in intravascular volume as described above, larger decreases in eGFR (> 30%) were sometimes seen, which subsequently improved, and infrequently required interruption of treatment with canagliflozin.

Patients should be advised to report symptoms of volume depletion. Canagliflozin is not recommended for use in patients receiving loop diuretics or who are volume depleted, e.g., due to acute illness (such as gastrointestinal illness).

For patients receiving canagliflozin, in case of intercurrent conditions that may lead to volume depletion (such as a gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including renal function tests), and serum electrolytes is recommended. Temporary interruption of treatment with canagliflozin may be considered for patients who develop volume depletion while on canagliflozin therapy until the condition is corrected. If interrupted, consideration should be given to more frequent glucose monitoring.

Elevated haematocrit

Haematocrit increase was observed with canagliflozin treatment; therefore, caution in patients with already elevated haematocrit is warranted.

Elderly (≥ 65 years old)

Elderly patients may be at a greater risk for volume depletion, are more likely to be treated with diuretics, and to have impaired renal function. In patients ≥ 75 years of age, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension,

hypotension) was reported. In addition, in such patients greater decreases in eGFR were.

Genital mycotic infections

Consistent with the mechanism of sodium glucose co-transporter 2 (SGLT2) inhibition with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical trials. Male and female patients with a history of genital mycotic infections were more likely to develop an infection. Balanitis or balanoposthitis occurred primarily in uncircumcised male patients. In rare instances, phimosis was reported and sometimes circumcision

was performed. The majority of genital mycotic infections were treated with topical antifungal treatments, either prescribed by a healthcare professional or self-treated while continuing therapy with Invokana.

Cardiac failure

Experience in New York Heart Association (NYHA) class III is limited, and there is no experience in clinical studies with canagliflozin in NYHA class IV.

Urine laboratory assessments

Due to its mechanism of action, patients taking canagliflozin will test positive for glucose in their urine.

Lactose intolerance

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

People diagnosed with Type 2 DM require access to immediate and ongoing care. Who provides this care, and where and when, will depend on local circumstances, but it needs to be organised in a systematic way. A multidisciplinary approach has been recommended including nurses trained in teaching skills and adult education and formally trained dieticians and podiatrists within the specifically relevant areas of diabetes care [American Diabetes Association 2013, IDF Clinical Guidelines Task Force 2005].

Discussion

No discussion is required.

References

American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2013;36:S11-S66.

Approved label; FDA: 2013

EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0004a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>

IDF Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. Brussels: International Diabetes Federation; 2005.

SmPC of canagliflozin

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[B0005] In what context and level of care are the canagliflozin and the comparators used?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search

Critical appraisal criteria: None

Method of synthesis: Narrative

Result

Although canagliflozin was still in clinical development when the 2012 position statement from the ADA and EASD on the management of T2DM was prepared, many components of this guidance can be used to incorporate canagliflozin into a patient-centred T2DM treatment algorithm: as monotherapy, as part of dual therapy (add-on to metformin or sulfonylurea), as part of triple therapy (add-on to metformin + sulfonylurea or metformin + pioglitazone), and as add-on therapy to insulin with or without other AHAs.

Canagliflozin is a once-daily, continuous oral therapy, and therefore may be self-administered by the patient at home. Administration of canagliflozin should incur no additional hospital or physician's office visits compared with the administration of comparator agents.

Because canagliflozin is administered orally does not require the use of any special equipment for administration (e.g., needles, syringes, or other injection devices). Treatment with canagliflozin does not require the patient to use any special blood-monitoring equipment, test strips, or other devices.

Drug therapy and lifestyle advice are primarily provided in primary care.

Discussion

No comment

References

EUnetHTA WP5 Strand B, Using the HTA Core Model for Rapid REA for other health technologies, Duodenal-jejunal bypass sleeve for the treatment of obesity with or without Type 2 diabetes mellitus, Version 1.4, 29 July 2013, A0004a, available at <http://www.eunetha.eu/outputs/1st-pilot-rapid-assessment-wp5-ja2-strand-b-duodenal-jejunal-bypass-sleeve-treatment-obesity>;

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely Partly Not

[B0010] What kind of data and records are needed to monitor the use of the canagliflozin and the comparators?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- Micromedex-Drug details. April 2013

Critical appraisal criteria None

Method of synthesis Narrative

Result

Treatment with canagliflozin does not require the use of any special blood-monitoring equipment, test strips, or other devices but glycaemic levels may be monitored as for other anti-diabetic drugs.

Lower doses of insulin or insulin secretagogue should be considered to reduce the risk of hypoglycaemia when used in combination with canagliflozin.

We report below the indications provided by the manufacturer concerning precautions that should be taken for patients in treatment with canagliflozin. Precautions refer to specific populations, drug and pharmacokinetic interactions.

Finally we report also the US-based assessment and analysis that will be conducted by the manufacturer to monitor specific adverse events and the FDA post-marketing requirements.

The following precautions should be taken when initiating canagliflozin treatment:

- Patients at risk for volume depletion: due to its mechanism of action, canagliflozin, by increasing UGE induces an osmotic diuresis, which may reduce intravascular volume and decrease BP. In controlled clinical studies of canagliflozin, increases in adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, or hypotension) were seen more commonly with the 300-mg dose and occurred most frequently in the first 3 months. Caution should be exercised in patients for whom a canagliflozin-induced drop in BP could pose a risk, such as patients with known CVD, patients with an eGFR <60 mL/min/1.73 m², patients on antihypertensive therapy with a history of hypotension, patients on diuretics, or older patients.

- Impairment in renal function: monitoring of renal function is recommended prior to initiation of canagliflozin and at least annually during therapy. For renal function approaching moderate renal impairment, monitor patients at least 2 to 4 times per year. If renal function falls persistently below an eGFR of 45 ml/min/1.73 m² or CrCl <45 ml/min, canagliflozin treatment should be discontinued.
- Hypersensitivity reactions: Discontinue canagliflozin and monitor until signs and symptoms resolve.
- Severe hepatic impairment: treatment with canagliflozin is not recommended.

Drug interactions:

- If a combined inducer of these UGT enzymes and transport proteins must be co-administered with canagliflozin, monitoring of glycaemic control to assess response to canagliflozin is appropriate. If an inducer of these UGT enzymes must be co-administered with canagliflozin, increasing the dose to 300 mg once daily may be considered if patients are currently tolerating canagliflozin 100 mg once daily, have an eGFR \geq 60 mL/min/1.73 m² or CrCl >60 mL/min, and require additional glycaemic control. In patients with an eGFR of 45 mL/min/1.73 m² to <60 mL/min/1.73 m² or CrCl of 45 mL/min to <60 mL/min taking canagliflozin 100 mg who are receiving concurrent therapy with a UGT enzyme inducer and who require additional glycaemic control, other antihyperglycaemic therapies should be considered.
- Cholestyramine may potentially reduce canagliflozin exposure. Dosing of canagliflozin should occur at least 1 hour before or 4 to 6 hours after administration of a bile acid sequestrant to minimise possible interference with their absorption.

Pharmacokinetic Effects of Canagliflozin on Other Medicinal Products:

- Digoxin: the combination of canagliflozin 300 mg once daily for 7 days with a single dose of digoxin 0.5 mg followed by 0.25 mg daily for 6 days resulted in a 20% increase in AUC and a 36% increase in C_{max} of digoxin, possibly due to inhibition of P-gp. Canagliflozin has been observed to inhibit P-gp in vitro. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately.
- Dabigatran: the effect of concomitant administration of canagliflozin (a weak P-gp inhibitor) on dabigatran etexilate (a P-gp substrate) has not been studied. As dabigatran concentrations may be increased in the presence of canagliflozin, patients should be monitored (i.e., look for signs of bleeding or anaemia) when dabigatran is combined with canagliflozin.
- Simvastatin: The combination of canagliflozin 300 mg once daily for 6 days with a single dose of simvastatin (CYP3A4 substrate) 40 mg resulted in a 12% increase in AUC and a 9% increase in C_{max} of simvastatin and an 18% increase in AUC and a 26% increase in C_{max} of simvastatin acid. The increases in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Micromedex also focuses on the necessity of the following precautions not clearly outlined in the REA submission file of the manufacturer:

-genital mycotic infections have been reported: uncircumcised men or patients with prior genital mycotic infections are at increased risk. Monitoring recommended for patients in treatment with canagliflozin;

- hyperkalaemia may occur: increased risk in patients with moderate renal impairment receiving medications that interfere with potassium excretion (e.g., potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system). Monitoring recommended for patients in treatment with canagliflozin;

- LDL-C increases have been reported. Monitoring recommended for patients in treatment with canagliflozin.

Post-Approval Pharmacovigilance Commitment reported by the manufacturer in the submission file:

A US-based assessment and analysis of all foreign and domestic spontaneous reports originating from the Janssen product marketed within the Janssen territories will be conducted for events of malignancy (pheochromocytoma, Leydig cell tumour, and renal cell carcinoma), fatal pancreatitis, haemorrhagic/necrotising pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy in patients treated with canagliflozin. The enhanced pharmacovigilance should continue for 10 years from the date of approval for malignancies and 5 years for all other events.

FDA Post-marketing Requirements:

FDA determined that an analysis of spontaneous post marketing adverse events will not be sufficient to assess signals of serious risks of malignancy (pheochromocytoma, Leydig cell tumour, renal cell carcinoma), pancreatitis, hypersensitivity reactions, photosensitivity reactions, hepatotoxicity, bone fractures, nephrotoxicity, and adverse pregnancy outcomes in patients treated with Invokana (canagliflozin).

Therefore, based on appropriate scientific data, FDA required to the manufacturer to conduct the following study:

- An assessment and analysis of all foreign and domestic spontaneous reports of malignancy (pheochromocytoma, Leydig cell tumour, and renal cell carcinoma), fatal pancreatitis, haemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy in patients treated with canagliflozin. The enhanced pharmacovigilance should continue for 10 years from the date of approval for malignancies and 5 years for all other events.

The timetable submitted by the manufacturer on March 27, 2013, states that the manufacturer will conduct this study according to the following schedule:

Final Protocol Submission: December 2013. Interim Report Submissions: May 2014, May 2015, May 2016, May 2017, May 2018, May 2019, May 2020, May 2021, May 2022. Study Completion: March 2023. Final Report Submission: November 2023.

In addition FDA determined also that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of an increased risk of bone fractures in patients treated with Invokana (canagliflozin). Furthermore, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Invokana (canagliflozin).

FDA has also determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Invokana (canagliflozin). Therefore, based on appropriate scientific data, FDA has determined that the manufacturer is required to conduct the following studies:

- Completion and submission of the final report for the 78-week double-blind extension phase of DIA3010, a clinical trial to assess the long-term safety of canagliflozin, including, but not limited to,

the effect of the addition of canagliflozin to the addition of placebo on bone mineral density and markers of bone turnover.

The timetable the manufacturer submitted on March 27, 2013, states that the manufacturer will complete this trial according to the following schedule:

Final Report Submission: December 2013.

- A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

The timetable you submitted on March 27, 2013, states that you will conduct this trial according to the following schedule: Final Protocol Submission: September 2013. Trial Completion: June 2017 Final Report Submission: September 2017.

Discussion

In addition to what reported by the manufacturer, besides the monitoring of glycaemic levels, of the renal function and caution in patients with CVD for the risk of volume depletion, the details on canagliflozin reported by Micromedex suggest to monitor also uncircumcised men or patients with prior genital mycotic infections and levels of potassium and LDL-C in patients treated with canagliflozin.

Concerning post-marketing studies required by FDA, besides the study reported in the manufacturer submission file, two more studies were recommended by FDA to assess the risk on bone depletion and MACE.

References

Micromedex-Drug details. April 2013

NDA 204042, FDA NDA Approval letter 29 March 2013

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[B0011] Is the use of registries worthwhile?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search

Critical appraisal criteria None

Method of synthesis Narrative

Result

No data concerning the institution of registries for canagliflozin were retrieved.

Discussion

Although no data concerning the institution of registries for canagliflozin were retrieved, FDA required to the manufacturer the conduction of post-approval studies (see Result Card B0010).

The same is true for EMA requirements.

Risk Management Plan

PRAC Advice

The RMP needs revision with the next RMP update to include consistent wording about toxicology results of the juvenile rat study on pregnancy and lactation. However, the preliminary view is that the RMP is approvable as the requested revision concerns minor issues that do not require immediate action or would preclude RMP approval. Important identified risk, important potential risk and missing information are listed below.

Important identified risks

Vulvovaginal candidiasis

Balanitis or balanoposthitis

Urinary tract infections

Hypoglycaemia in combination with insulin or glucose-independent insulin secretagogues

Volume depletion

Important potential risks

Renal impairment/Renal failure

Clinical consequences of increased haematocrit

Bone fractures

Photosensitivity

Hypoglycaemia in the absence of insulin or glucose-independent insulin secretagogues

Off-label use for weight loss

Missing information

Long-term cardiovascular safety in patients

Use in patients with congestive heart failure defined as NYHA class IV

Use in paediatric patients between 10 and 18 years of age

Use in pregnancy

Use in nursing mothers

Use in very elderly patients (≥ 85 years)

Use in patients with severe hepatic impairment

Use in patients with severe renal impairment ($eGFR < 30 \text{ mL/min/1.73m}^2$)

Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP. In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

References

EPAR

FDA

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly Not **SAFETY****[C0001]** What are the most frequent and serious adverse events in patients with canagliflozin therapy?**Methods** See general description of methods (Appendix 1) Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0
- ClinicalTrials.gov Register (Study protocols, Study results)
- SmPC of canagliflozin

Critical appraisal criteria: Risk of bias was evaluated by using the Cochrane risk of bias checklist, EUnetHTA methods and the GRADE-methodology, only for three active comparator studies DIA3006, DIA3009, DIA3015 at 52 weeks

Method of synthesis: Narrative.

For Safety evaluation, only direct data was analysed, including data from canagliflozin monotherapy study (DIA3005), so slight deviation from Scope was done in Safety Domain.

In total, two safety data sets were created by compiling different patient populations, see Table 27 below.

Independent data extraction was done from scientific publications and register ClinicalTrials.gov with both, study protocol registration and results registration data (Evidence tables below).

Data from CHMP Report was based on 4 safety data sets, see Table 28. Data from Manufacturer JJ submission file was presented also.

Data from RCTs conducted in special population (with moderate renal impairment, in older patients and in patient with CV risk) were analysed separately.

Phase II trials were not included in these data pools because the largest phase II trials were dose finding studies so that most patients received different canagliflozin doses than in the phase III trials. In the case of discrepancies on the same data from different sources, published articles of RCTs were used as the primary source for extraction. The interpretation of the results and quality of evidence assessments (done only for three active comparator studies DIA3006, DIA3009, DIA3015 at 52 weeks) represent the authors' view which may differ from the view expressed by manufacturer.

Table 27. Two Safety Data-sets performed by authors of this assessment and studies in special population

Dataset Name	Studies	Objective
Placebo-Controlled Studies Dataset Includes the 26-week placebo controlled Phase III studies	DIA3002, DIA3005,a DIA3006,b DIA3012	Evaluate the safety and tolerability of canagliflozin based upon a large subject sample by pooling placebo-controlled Phase III studies of generally similar design
Longer-term Exposure Broad Dataset 52-weeks, all, Active- and Placebo-controlled studies	DIA 3009, DIA 3015, DIA 3002, DIA 3005, DIA 3006, DIA 3012, DIA 3004, DIA 3008, DIA 3010	Longer-term exposure dataset to provide information on safety with longer exposure; to evaluate selected adverse events occurring with low incidence (e.g., skin photosensitivity, specific malignancies)
RCTs in special population		
Moderate renal impairment	DIA 3004	Evaluate safety and tolerability within a special population of subjects with renal insufficiency with eGFR ≥ 30 to < 60 mL/min/1.73m ²
Older patients	DIA 3010	Evaluate safety and tolerability within a special population of older patients
In patients with CV risk	DIA 3008	Evaluate safety and tolerability within a special population with CV risk

a: excluding the high glycaemic substudy

b: excluding sitagliptin treatment group

Table 28. Committee for Medicinal Products for Human Use (CHMP) Report on canagliflozin Safety Datasets

Dataset Name	Dataset Description	Studies Pooled	Objectives
Placebo-Controlled Studies Dataset (ISS Dataset 1 [DS1])	Includes the 26-week placebo controlled Phase III studies	DIA3002, DIA3005,a DIA3006,b DIA3012	Evaluate the safety and tolerability of canagliflozin based upon a large subject sample by pooling placebo-controlled Phase III studies of generally similar design
Moderate Renal Impairment Dataset (ISS Dataset 2 [DS2])	Subjects with baseline eGFR ≥ 30 to < 60 mL/min/1.73m ²	DIA3004 and subgroups from DIA3005, DIA3008, DIA3010	Evaluate safety and tolerability within a special population of subjects with renal insufficiency with eGFR ≥ 30 to < 60 mL/min/1.73m ²
Broad Dataset	All Active- and	DIA3002,	Large pooled dataset from controlled clinical studies (active and placebo-

Dataset Name	Dataset Description	Studies Pooled	Objectives
(ISS Dataset 3 [DS3])	Placebo-controlled studies	DIA3004, DIA3005,a DIA3006, DIA3008, DIA3009, DIA3010, DIA3012	controlled) to identify less common safety signals, and to support safety assessments in the Placebo-Controlled Studies Dataset (DS1).
Longer-term Exposure Broad Dataset (ISS Dataset 4 [DS4])	All Active- and Placebo-controlled studies	DIA3002, DIA3004, DIA3005,a DIA3006, DIA3008, DIA3009 DIA3010, DIA3012	Longer-term exposure dataset to provide information on safety with longer exposure, and to support safety assessments in the Placebo-Controlled Studies Dataset (DS1); to evaluate selected adverse events occurring with low incidence (e.g., skin photosensitivity, specific malignancies) and events undergoing adjudication (including CV events).

a DIA3005: Excluding the high glycaemic substudy

b DIA3006: Excluding sitagliptin treatment group

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013.

Result

The general safety assessment is mainly based on direct evidence from nine phase III randomised controlled trials in more than 10000 subjects with T2DM. In all phase III trials two different doses of canagliflozin were tested, 100 mg and 300 mg per day. Special safety aspects were investigated in smaller trials. The phase III studies were in patients with different background therapies; they were either placebo-controlled (including one monotherapy trial) or used an active comparator (glimepiride 6 mg or 8 mg or sitagliptin 100 mg). A large trial (CANVAS) in 4330 patients at increased cardiovascular risk (DIA3008), with the aim to evaluate the effects of canagliflozin on the risk of cardiovascular disease and to assess safety and tolerability in patients with inadequately controlled T2DM and increased cardiovascular risk is still ongoing, but interim safety data on cardiovascular events are presented in this assessment. Data from two 18-week substudies in CANVAS trial, sulphonylurea substudy and insulin substudy are also included in the assessment. Smaller phase III (sub-) trials investigated the effects of canagliflozin in patients with moderate renal impairment (DIA3004, estimated GFR between 30 and 50 mL/min/1.73 m² at baseline) and in patients with poor glycaemic control (part of DIA3005).

The larger phase II trial was for dose finding (DIA2001).

For all of the phase III studies, safety evaluations included the collection of adverse events, safety laboratory tests (including haematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs (blood pressure and pulse rate), body weight, physical examinations, self-monitored blood glucose (SMBG), and collection of potential hypoglycaemic episodes (e.g., from the subject diary provided to subjects).

Most frequent adverse events (AEs) and serious AEs

Placebo-controlled trial

In the pooled, placebo-controlled trials the proportion of subjects who experienced any AE or serious AEs was similar across treatment groups. The incidence of AEs leading to study discontinuation was low across groups but slightly higher with canagliflozin versus placebo, with no dose relationship (Table 29).

Table 29. Adverse events in pooled placebo controlled trials (DIA3002, DIA3005, DIA3006, DIA3012)

	Canagliflozin 100 mg (n=833)	Canagliflozin 300 mg (n=834)	Placebo (n=646)
Any AE n (%)	501 (60.1)	494 (59.2)	384 (59.4)
AEs leading to discontinuation n (%)	36 (4.3)	30 (3.6)	20 (3.1)
Serious AEs n (%)	28 (3.4)	22 (2.6)	22 (3.4)
Death n (%)	1 (0.1)	1 (0.1)	2 (0.3)

Abbreviations: AE: adverse event

Source: Johnson & Johnson submission file

The most commonly reported adverse reactions during treatment with canagliflozin were hypoglycaemia in combination with insulin or an sulfonylurea, vulvovaginal candidiasis, urinary tract infection (UTI), and polyuria or pollakiuria (i.e., urinary frequency). Adverse reactions leading to discontinuation of $\geq 0.5\%$ of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of female patients) and balanitis or balanoposthitis (0.5% of male patients).

These adverse reactions are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data). (Table 30)

Table 30. Frequency of Adverse Reactions (MedDRA) in Placebo-controlled Studies

System Organ Class	Adverse reactions
Frequency	
<i>Metabolism and nutrition disorders</i>	
Very common	Hypoglycaemia in combination with insulin or SU
Uncommon	Dehydration b
<i>Nervous system disorders</i>	
Uncommon	Postural dizziness,b syncope b
<i>Vascular disorders</i>	
Uncommon	Hypotension,b orthostatic hypotension b
<i>Gastrointestinal disorders</i>	
Common	Constipation, thirst,c nausea
<i>Skin and subcutaneous tissue disorders</i>	
Uncommon	Rash,d urticaria
<i>Renal and urinary disorders</i>	

System Organ Class	Adverse reactions
Frequency	
Common	Polyuria or pollakiuria,e UTIf
Reproductive system and breast disorders	
Very common	Vulvovaginal candidiasis g
Common	Balanitis or balanoposthitis h
Investigations	
Common	Dyslipidaemia,i haematocrit increased j
Uncommon	Blood creatinine increased,k blood urea increased,l blood potassium increased m

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SU, sulphonylurea; UTI, urinary tract infection; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

a Safety data profiles from individual pivotal studies (including studies in moderately renally impaired patients, older patients, and patients with increased CV risk) were generally consistent with the adverse reactions identified in this table;

b Related to volume depletion;

c Includes the terms thirst, dry mouth, and polydipsia;

d Includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular;

e Includes the terms polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia;

f Includes the terms urinary tract infection, cystitis, kidney infection, and urosepsis. There was no imbalance among canagliflozin 100 mg, canagliflozin 300 mg, and placebo for kidney infection or urosepsis;

g Includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal;

h Includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection funga; .

i Mean percent increases from baseline for canagliflozin 100 mg and 300 mg versus placebo, respectively, were total cholesterol, 3.4% and 5.2% versus 0.9%; HDL-C, 9.4% and 10.3% versus 4.0%; LDL-C, 5.7% and 9.3% versus 1.3%; non-HDL-C, 2.2% and 4.4% versus 0.7%; triglycerides, 2.4% and 0.0% versus 7.6%;

j Mean changes from baseline in haematocrit were 2.4% and 2.5% for canagliflozin 100 mg and 300 mg, respectively, compared with 0.0% for placebo;

k Mean percent changes from baseline in creatinine were 2.8% and 4.0% for canagliflozin 100 mg and 300 mg, respectively, compared with 1.5 % for placebo;

l Mean percent changes from baseline in blood urea nitrogen were 17.1% and 18.0% for canagliflozin 100 mg and 300 mg, respectively, compared with 0.0% for placebo;

m Mean percent changes from baseline in blood potassium were 0.5% and 1.0% for canagliflozin 100 mg and 300mg, respectively, compared with 0.6% for placebo.

Source: Johnson & Johnson submission file

Active-Comparator Studies

The overall incidence of AEs with canagliflozin in the DIA3009 and DIA3015 studies was generally comparable to those observed with the active comparators over 52 weeks: 64.4%, 68.5%, and 68.5% for canagliflozin 100 and 300 mg and glimepiride, respectively, for DIA3009; and 76.7% and 77.5% for canagliflozin 300 mg and sitagliptin 100 mg, respectively, for DIA3015.

In subjects on background metformin (DIA3006), overall incidences of AEs were slightly higher with canagliflozin 100 mg compared with canagliflozin 300 mg, sitagliptin 100 mg, and placebo/sitagliptin (subjects who switched from placebo to sitagliptin after the 26-week core treatment period) over 52 weeks (72.3%, 62.7%, 64.5%, and 66.7%, respectively). Over 104 weeks in the DIA3009 study, the overall incidence of AEs was slightly higher with canagliflozin 300 mg and glimepiride compared with canagliflozin 100 mg (77.9%, 78.4%, and 73.3%, respectively).

Special Populations

In an interim safety analysis of CANVAS (DIA3008), the overall AE rate was slightly higher with canagliflozin 300 mg (73.4%) compared with canagliflozin 100 mg (71.0%) and placebo (69.6%).

In subjects with moderate renal impairment (DIA3004), the overall incidence of AEs was generally similar for canagliflozin 100 mg and 300 mg and placebo (78.9%, 74.2%, and 74.4%, respectively).

In older subjects (DIA3010), the overall AE rate was slightly higher with canagliflozin 300 mg (78.0%) compared with canagliflozin 100 mg (72.2%) and placebo (73.4%).

In CHMP report, in longer-term exposure broad dataset (including DIA3015 study), the overall rate of AEs is fairly balanced between the treatment groups. This is also true for serious AEs and AEs leading to discontinuation. The AEs considered related were often genital or urinary tract infections, a known side effect of SGLT2 inhibitors (Table 31).

Table 31. Adverse events in Committee for Medicinal Products for Human Use (CHMP) Longer-term exposure broad dataset, including DIA3015 study

	Canagliflozin 100 mg (n=3092)	Canagliflozin 300 mg (n=3463)	All non-Canagliflozin (n=3640)
Any AE n (%)	2274 (73.5)	2563 (74.0)	2648 (72.74)
AEs leading to discontinuation n (%)	147 (4.8)	221 (6.38)	143 (3.9)
Serious AEs n (%)	329 (10.64)	354 (10.2)	398 (10.9)
Death n (%)	18 (0.6)	19 (0.5)	26 (0.7)

Abbreviations: AE: adverse event

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013, modified by authors with DIA3015 study

The overall incidence in AEs was balanced between the treatment groups, but some individual AEs or AEs in certain organ systems had markedly different incidences in Data-set DS4 (Table 32). Most salient and important findings are marked with incidences in **bold**.

Table 32. Adverse events by body system or organ class in Data-set 4 (DS4)

Body System or Organ Class	CANAGLIFLOZIN 100mg	CANAGLIFLOZIN 300mg	Non-CANAGLIFLOZIN
General disorders and administration site conditions	346 (11.2)	387 (12.5)	355 (10.9)
Thirst	42 (1.4)	68 (2.2)	2 (0.1)
Infections and infestations	1234 (39.9)	1216 (39.4)	1229 (37.7)
Genital infection fungal	20 (0.6)	27 (0.9)	4 (0.1)
Vulvovaginal mycotic infection	70 (2.3)	72 (2.3)	21 (0.6)
Investigations	247 (8.0)	266 (8.6)	278 (8.5)
Blood potassium increased	12 (0.4)	13 (0.4)	2 (0.1)
Blood pressure increased	10 (0.3)	11 (0.4)	32 (1.0)
Urine output increased	1 (<0.1)	19 (0.6)	15 (0.5)
Metabolism and nutrition disorders	402 (13.0)	406 (13.2)	496 (15.2)
Hypercalcaemia	3 (0.1)	14 (0.5)	4 (0.1)
Hyperglycaemia	44 (1.4)	38 (1.2)	103 (3.2)
Renal and urinary disorders	317 (10.3)	332 (10.8)	192 (5.9)
Polyuria	10 (0.3)	30 (1.0)	33 (1.1)
Reproductive system and breast disorders	237 (7.7)	291 (9.4)	110 (3.4)
Balanitis	70 (2.3)	67 (2.2)	13 (0.4)
Balanoposthitis	25 (0.8)	51 (1.7)	5 (0.2)
Vulvovaginal pruritus	42 (1.4)	58 (1.9)	5 (0.2)
Vascular disorders	181 (5.9)	191 (6.2)	228 (7.0)
Hypertension	64 (2.1)	48 (1.6)	125 (3.8)
Hypertensive crisis	1 (<0.1)	3 (0.1)	10 (0.3)

Body System or Organ Class	CANAGLIFLOZIN 100mg	CANAGLIFLOZIN 300mg	Non- CANAGLIFLOZIN
Hypotension	40 (1.3)	54 (1.8)	17 (0.5)
Orthostatic hypotension	8 (0.3)	21 (0.7)	4 (0.1)

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

Most of the imbalances displayed in the table above reflect the known physiological actions of canagliflozin as an SGLT2 inhibitor or known side effects resulting from them. These comprise e.g. thirst, polyuria, hypotension (due to increased diuresis), weight decrease and all signs of urogenital infection. Also increased serum creatinine can be most likely explained by elevated diuresis (for detailed discussion, see section on changes on renal function below). Reduced incidence of increased blood pressure and hyperglycaemia in the canagliflozin groups can also be explained by SGLT2 inhibition.

There is a small increase in AEs related to skin and subcutaneous tissue, most pronounced for erythema and skin ulcer. The reason for this finding (if true and not due to chance) is not obvious. Phototoxicity of canagliflozin was observed in non-clinical studies but clear phototoxicity was not observed in dedicated studies of the Manufacturer.

All other imbalances are not considered meaningful, either because of being too small or because the absolute number of patients affected is very low.

AEs of special interest

Hypoglycaemia

Data report any documented hypoglycaemia or severe hypoglycaemia. The previous is defined when the renal threshold for glucose is ≤ 3.9 mmol/L (70 mg/dL), the latter is defined when the events require the assistance of another person, loss of consciousness or a seizure.

There is a small and dose-dependent increase in hypoglycaemic events in the canagliflozin groups as compared to placebo. Reassuringly, severe hypoglycaemias were rare (Table 33).

Table 33. Documented hypoglycaemia in Pooled placebo controlled trials (DIA3005, DIA3006, DIA3012; DIA3002 excluded): Incidences of hypoglycaemia in patients without hypoglycaemic background therapy

	Canagliflozin 100 mg (n=676)	Canagliflozin 300 mg (n=678)	Placebo (n=490)
Subjects with any documented hypoglycaemia	26(3.8)	29(4.3)	11(2.2)
Severe hypoglycaemia	1(0.1)	1(0.1)	0

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

In the presence of hypoglycaemic background therapy (i.e. insulin or SU) the incidence was increased by canagliflozin.(Table 34)

Table 34. Incidences of hypoglycaemia in patients with hypoglycaemic background therapy

	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Comparator sitagliptin
DIA3002 (background: met+SU)	N=157	N=156	N=156	N.A
Subjects with any documented hypoglycaemia	43(27.4)	47(30.1)	24(15.4)	N.A
Severe hypoglycaemia	01(0.6)	0	1(0.6)	N.A

	Canagliflozin 100 mg	Canagliflozin 300 mg	Placebo	Comparator sitagliptin
DIA3008 Insulin Substudy	N=566	N=587	N=565	N.A
Subjects with any documented hypoglycaemia	279(49.3)	285(48.6)	208(36.8)	N.A
Severe hypoglycaemia	10(1.8)	16(2.7)	14(2.5)	N.A
DIA3008 Sulphonylurea Substudy	N=74	N=72	N=69	N.A
Subjects with any documented hypoglycaemia	3(4.1)	9(12.5)	4(5.8)	N.A
DIA3015 (comparator sitagliptin, background metformin+sulphonylurea)	N.A	N=377	N.A	N=378
Subjects with any documented hypoglycaemia	N.A	163(43.2)	N.A	154(40.7)
Severe hypoglycaemia	N.A	15(4.0)	N.A	13(3.4)

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

Sulphonylurea and insulin have high hypoglycaemic propensity themselves and canagliflozin further increases thy hypoglycaemia incidence of a hypoglycaemic background therapy including insulin or an insulin secretagogue. Hypoglycaemic events were not so different for canagliflozin+metformin+Sulphonylurea compared to sitagliptin+metformin+Sulphonylurea. No relevant differences were observed for severe hypoglycaemias (canagliflozin vs. placebo).

Events of hypoglycaemia in DIA3009 were significantly lower in both patients groups treated with canagliflozin (100 and 300 mg) respect to the group treated with glimepiride 6mg or 8mg ($p < 0.001$). Although severe hypoglycaemia was still lower in patients treated with canagliflozin rather than those in glimepiride treatment, the difference was not reported as significant.

DIA3015 report similar both for any documented hypoglycaemia and severe hypoglycaemia between the two groups (canagliflozin 300 mg and sitagliptin 100 mg).

Active comparator studies concerns patients not on background insulin or insulin secretagogues (Table 35).

Table 35. Incidences of hypoglycaemia in active comparator studies with patients not on background insulin or insulin secretagogues

	CANAGLIFLOZIN 100 mg N (%)	CANAGLIFLOZI N 300 mg N (%)	All CANAGLIFLOZIN N (%)	Comparator N (%)
DIA3006, n	368	367	735	SITAGLIPTIN 100 mg 366
Any documented hypoglycaemia	16 (4.3)	17 (4.6)	33 (4.5)	5 (1.4)
Severe hypoglycaemia	1 (0.3)	1 (0.3)	2 (0.3)	0
DIA3009, n	483	485	968	GLIMEPIRID E 6 or 8 mg 482
Any documented hypoglycaemia	27 (5.6)	24 (4.9)	51 (5.3)	165 (34.2)
Severe hypoglycaemia	2 (0.4)	3 (0.6)	5 (0.5)	15 (3.1)

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

Urinary tract infections (UTI)

The incidence of urinary tract infections (UTI) hardly differed between canagliflozin and placebo. For unknown reasons the incidence is higher in low-dose canagliflozin group. Serious AE were rare (Table 36).

Table 36. Incidences of urinary tract infection, Pooled placebo controlled trials (DIA3002, DIA3005, DIA3006, DIA3012)

	Canagliflozin 100 mg (n=833)	Canagliflozin 300 mg (n=834)	Placebo (n=646)
Total no.subject with any UTI	49(5.9)	36 (4.3)	26(4.0)
Cystitis n (%)	2(0.2)	2(0.2)	0
Kidney infection n (%)	0	1(0.1)	0
Urinary tract infection n (%)	46(5.5)	34(4.1)	26(4.0)
Urosepsis	1(0.1)	0	26(4.0)
Serious AEs of UTI	2(0.2)	1(0.1)	0

Abbreviations: UTI: urinary tract infection; AE: adverse event

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

Genital infection

There was clear and highly increased incidence of female genital infection in both canagliflozin groups, slightly dose-dependent, as compared to placebo. No serious AEs were observed, part lead to discontinuation of study drug. Many of them were caused by fungi (Table 37).

The incidence of genital infections in males were lower than in females.

Table 37. Vulvovaginitis, Pooled placebo controlled trials (DIA3002, DIA3005, DIA3006, DIA3012)

	Canagliflozin 100 mg (n=425)	Canagliflozin 300 mg (n=430)	Placebo (n=312)
Any vulvovaginitis n (%)	44 (10.4)	49 (11.4)	10 (3.2)
Vulvovaginitis leading to discontinuation	4 (0.9)	2 (0.5)	0
Serious AEs of vulvovaginitis	0	0	0

Abbreviations: AE: adverse event

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

In published article of Nyirjesy P et al. based on NCT00642278 RCT (of which overall efficacy and safety data have been published in Rosenstock J et al. Diabetes Care. 2012;35:1232-8.) of those with negative cultures at baseline, 31% of canagliflozin and 14% of placebo/sitagliptin subjects converted to positive at week 12 (OR, 2.8; 95% CI, 1.0-7.3 for canagliflozin vs. placebo/sitagliptin). Two placebo/sitagliptin (3%) and 16 canagliflozin subjects (10%) experienced VVAE. Positive vaginal culture for *Candida* species at baseline was a risk factor for VVAE (OR, 9.1; 95% CI, 2.4-34.0). All 9/9 subjects in the canagliflozin group with a vaginal culture taken at the time of the VVAE were positive for *Candida* species. Most VVAE were treated with antifungal therapy and resolved without study drug interruption; none led to discontinuation. Study limitations include small population, short duration, and not obtaining cultures in all women with VVAE. Authors concluded that canagliflozin treatment was associated with an increase in vaginal colonization with *Candida* species and in VVAE in women with T2DM.

In published article of Nicolle LE et al. based on NCT00642278 RCT (of which overall efficacy and safety data have been published in Rosenstock J et al. Diabetes Care. 2012;35:1232-8.) asymptomatic bacteriuria (ASB) were present in 6.4% of canagliflozin and 6.5% of placebo/sitagliptin (control) subjects at randomization and, at 12 weeks, in 7.7% and 6.3% of subjects, respectively (odds ratio [OR] 1.23; 95% confidence interval [CI], 0.45-3.89). There were 21 adverse event (AE) reports of UTI; 16 (5.0%) in canagliflozin subjects and 5 (3.8%) in control subjects (OR 1.31; 95% CI, 0.45-4.68). Authors concluded that in comparison with control subjects, canagliflozin increased UGE but was not associated with increased bacteriuria or AE reports of UTI; further studies enrolling larger numbers of subjects with longer term exposure to canagliflozin are necessary to more fully understand the impact of this agent on the risk of developing UTI.

Regarding markers of renal function, there was a consistent decrease in eGFR associated with canagliflozin use, caused by an increase in serum creatinine. eGFR returns to baseline after cessation of canagliflozin therapy which argues for dehydration as the cause. Signs of volume depletion and AEs related to volume depletion may be expected with canagliflozin therapy in dose dependent manner. The absolute number of events was low. A serious complication of dehydration and haemoconcentration is venous thrombosis; percentage was low (0.2-0.3%).

Serious AEs/deaths

There was no increase in overall death rate or deaths considered related to study drug as compared to control group: one death in the placebo and one cardiac death in canagliflozin 300 mg were considered possibly related to study drug by the investigator in DS4. Serious AEs were overall balanced between canagliflozin and non-canagliflozin groups. 2.5%, 2.5% and 2.9% of the patients in the comparator, canagliflozin 100 mg and canagliflozin 300 mg had a finding of neoplasm. Till now there is no hint from clinical data that canagliflozin is generally associated with an increased tumour risk.

Immunological events

Hypersensitivity AE was reported in 9(0.3%) in canagliflozin 100 mg, 6 (0.2%) on canagliflozin 300 mg and 1 subject in the non-canagliflozin groups.

Drug-drug interactions

The most relevant interactions of canagliflozin are expected with diuretics and blood lowering agents.

Teratogenicity/Effects in Pregnancy

U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.

EVIDENCE TABLES: Data from scientific publications, register ClinicalTrials.gov with both study registration and results registration data

Table 38. Scientific publications and ClinicalTrials.gov register data on canagliflozin - MONOTHERAPY

Authors, Year, Ref number	Stenlof K et al. Diabetes Obes Metab. 2013 Apr;15(4):372-82. DIA3005	Stenlof K et al. Curr Med Res Opin. 2013 Oct 28 DIA3005	Inagaki N et al. Diabetes Obes Metab. 2013 Jun 19
Registry number	NCT01081834	NCT01081834	NCT01022112
RCT phase	3	3	2, from Register
Placebo control/Active control	Placebo (Canagliflozin 100 mg, n=195/Canagliflozin 300 mg, n=197/Placebo, n=192; randomization 1:1:1;	Placebo and Active (Canagliflozin 100 mg, n=195/Canagliflozin 300 mg, n=197/Placebo, n=192; randomization 1:1:1; during 1st 26 week; Canagliflozin 100 mg, n=195/Canagliflozin 300 mg, n=197/Placebo-Sitagliptin 100 mg, n=192; randomization 1:1:1; during 2nd 26 week	Placebo (Canagliflozin 50mg, n=82/Canagliflozin 100mg, n=74/Canagliflozin 200 mg, n=77/Canagliflozin 300 mg, n=75/Placebo, n=75; randomization 1:1:1:1:1
Duration (weeks)	26	52	12
Any AE n (%)	119 (61.0):118 (59.9):101 (52.6)	131(67.2):130(66.0):123(64.1)	37(45.1):34(45.9):38(49.4):34(45.3):26(34.7)
Serious AE n (%)	8 (4.1):2 (1.0):4 (2.1)	11 (5.6):5(2.5):11(5.7)	1(1.2):0:0:0:0
Deaths n (%)	1 (0.5):0:1 (0.5)	1 (0.5):0:2 (1.0)	0
Description of Serious AE n (%)	No more than 1 or 2 per group (MEDDRA 14.0) MI 0:0:0; nausea, vomiting, hepatitis, prostatitis, diverticulitis, pneumonia, septic shock, osteoarthritis, acute renal failure, pulmonary embolism, thrombosis 1(0.51):0:0; ankle fracture, brain herniation 0:0:1(0.52); urticarial 2(1.03):0:0	No more than 1 or 2 per group (MEDDRA 14.0) MI,nausea, vomiting, hepatitis, prostatitis, diverticulitis, pneumonia, septic shock, osteoarthritis, acute renal failure, pulmonary embolism, thrombosis 1(0.51):0:0; ankle fracture, brain herniation 0:0:1(0.52); urticarial 2(1.03):0:0	N.A

Authors, Year, Ref number	Stenlof K et al. Diabetes Obes Metab. 2013 Apr;15(4):372-82. DIA3005	Stenlof K et al. Curr Med Res Opin. 2013 Oct 28 DIA3005	Inagaki N et al. Diabetes Obes Metab. 2013 Jun 19
Most frequent AEn (%)	Above 5% (MEDDRA 14.0)	Above 5% (MEDDRA 14.0)	In ≥3% of patients in any group
	Nasopharyngitis 10(5.13):16(8.12):10(5.21)	Nasopharyngitis 14(7.18):20(10.15):15(7.8)	Nasopharyngitis 8(9.8):10(13.5):8(10.4):9(12.0):10(13.3)
	Upper respiratory tract inflammation 7(3.59):9(4.57):11(5.73)	Upper respiratory tract inflammation 8(4.10):14(7.11):18(9.38)	Increased blood ketone bodies 4(4.9):5(6.8):9(11.7):6(8.0):2(2.7)
	Influenza 0:0:0	Influenza 12(6.15):8(4.06):7(3.65)	Hypoglycaemia unawareness 1(1.2):1(1.4):3(3.9):2(2.7):0
	Back pain 5(2.56):12(6.09):6(3.13)	Back pain 5(2.56):15(7.61):9(4.69)	Hypoglycaemia 3(3.7):2(2.7):2(2.6):1(1.3):0
	Arthralgia 0:0:0	Arthralgia 10(5.13):3(1.52):13(6.77)	Gastritis 0:1(1.4):0:1(1.3):3(4.0)
	Headache 14(7.18):12(6.09):7(3.65)	Headache 19(9.74):17(8.63):12(6.25)	Periodontitis 3(3.7):0:1(1.3):0:0
			Upper respiratory tract inflammation 0:5(6.8):3(3.9):1(1.3):1(1.3)
			Malaise 3(3.7):0:0:0:0
Treatment discontinued due AEn (%)	6(3.1):4(2.0):2(1.0)	6(3.1):4(2.0):2(1.0)	2(2.4):2(2.7):0:1(1.3):0
Genital mycotic infections n (%)			0:1:0:1:0
Male n (%)	2(2.5):5(5.6):0	5(6.2):8(9.0):0	
Females n (%)	10(8.8):8(7.4):4(3.8)	13(11.4):10(9.0):5(4.8)	
UTIs n (%)	14(7.2):10(5.1):8(4.2)	16(8.2):14(7.1):12(6.3)	0
Documented hypoglycaemia episodes n (%)	3.6%:3.0%:2.6%	5.1%:3.6%:3.6%	See above
Severe hypoglycaemia episodes n (%)	0	0	0
Osmotic diuresis related AEn		9(4.6):15(7.6):4(2.1)	

Authors, Year, Ref number	Stenlof K et al. Diabetes Obes Metab. 2013 Apr;15(4):372-82. DIA3005	Stenlof K et al. Curr Med Res Opin. 2013 Oct 28 DIA3005	Inagaki N et al. Diabetes Obes Metab. 2013 Jun 19
(%)			
Pollakiuria n (%)	5 (2.6):6 (30):1 (0.5)		3 in canagliflozin group:0
Polyuria n (%)	0:6 (3.0):0		
Volume-related AEs n (%)		3(1.5):4(2.0):1(0.5)	0:0:0:3:1
Postural dizziness n (%)	1 (0.5):2 (1.0):0		
Orthostatic hypotension n (%)	0:2 (1.0):0		
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)
Measures of renal function	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)
Renal safety parameters: changes from baseline±SD			
Blood Urea Nitrogen	20.4% ±33.5: 17.7% ±29.5: 3.1%±24.1	21.0±38.2: 22.5±30.0: 6.9±20.2:	
Creatinine	2.8%±12.5: 3.5%±11.2: 1.9%±10.1	1.8±10.6: 4.4±11.4: 5.2±11.4	
eGFR		-1.6±11.7: -3.6±12.2: -4.7±12.1	

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate

Sources:

Inagaki N, Kondo K, Yoshinari T, et al. Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. Diabetes Obes Metab. 2013;15:1136-45;

Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013;15:372-82.;

Stenlof K, Cefalu WT, Kim KA, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Curr Med Res Opin. 2014;30:163-75.

Table 39. Scientific publications and ClinicalTrials.gov register data on canagliflozin - DUAL THERAPY

Authors, Year, Ref number	Lavalle-González FJ et al. Diabetologia. 2013 Sep 13 DIA 3006	Cefalu WT et al. Lancet. 2013 Sep 14;382(9896):941-50 DIA 3009	Rosenstock J et al. Diabetes Care. 2012 Jun;35(6):1232-8. DIA 2001
Registry number	NCT01106677	NCT00968812	NCT00642278

Authors, Year, Ref number	Lavalle-González FJ et al. Diabetologia. 2013 Sep 13 DIA 3006	Cefalu WT et al. Lancet. 2013 Sep 14;382(9896):941-50 DIA 3009	Rosenstock J et al. Diabetes Care. 2012 Jun;35(6):1232-8. DIA 2001
RCT phase	3	3	2, from Register
Add on to	metformin	metformin	metformin
Placebo control/Active control	Placebo and active control (Canagliflozin 100 mg, n=368/Canagliflozin 300 mg, n=367/Sitagliptin 100 mg, n=366/Placebo, n=183; 2:2:2:1; during 1st 26 week; Canagliflozin 100 mg, n=316/Canagliflozin 300 mg, n=321/Sitagliptin 100 mg, n=313/Placebo-Sitagliptin 100 mg, n=153; randomization 2:2:2:1; during 2nd 26 week	Active (Canagliflozin 100 mg, n=483/Canagliflozin 300 mg, n=485/glimepiride 6 or 8 mg/day, n=482; randomization 1:1:1	Placebo and active control (Canagliflozin 50mg, n=64/Canagliflozin 100mg, n=64/Canagliflozin 200 mg, n=65/Canagliflozin 300 mg, n=64/Canagliflozin 300 bid, n=64/Sitagliptin 100 mg, n=65/Placebo, n=65; randomization 1:1:1:1:1:1
Duration (weeks)	26+26=52	52	12
Any AE n (%)	266(72.3):230(62.7):236(64.5):122(66.7)	311(64.0):332(69.0):330(69.0)	32(50.0):30(47.0):26(40.0):26(41.0):36(56.0):23(35):26(40)
Serious AE n (%)	15(4.1):12(3.3):18(4.9):7(3.8)	24(5.0):26(5.0):39(8.0)	1(2): 1(2): 1(2): 1(2): 1(2):0: 1(2):
Deaths n (%)	0:1(0.3):1(0.3):1(0.5)	0:2, <1%:2, <1%)	0
Description of Serious AE n (%)	MEDDRA 15.0 Acute coronary sy 0:0:0:1(0.55); unstable angina, AMI, cardiac arrest, asthma, respiratory failure, acute renal failure, cerebrovascular accident, septic shock, abdominal hernia 0:0.1(0.27):0; cholangitis, cholecystitis, pneumonia, sepsis, cervical cerebral fracture 1(0.27):0:0:0, cancers (bronchia, colorectal, prostate, breast, meningioma) 0:1:0:0	MEDDRA 14.1 Anaemia, acute coronary sy, cardiomyopathy, abd. Pain, duodenitis, umbilical hernia, endometritis, muscle fracture, renal cancer, incontinence 0:1(0.21):0; Angina pectoris 1(0.21):2(0.41):2(0.41); pneumonia 1(0.21):1(0.21):2(0.41); uterine leiomyoma 0:2(0.41):0; Cerebrovascular accident 2(0.41):1(0.21):0; urticarial 1(0.21):0:0	MEDDRA 11.1 Atrial fibrillation 0:0:0:1:0:0:0; Pneumonia and hypoxia 0:0:0:0:0:1
Most frequent AE n (%)	Above 5%	Above 5%	In ≥10 subjects in any group, above 5%
	Nasopharyngitis 18(4.89):16(4.36):22(6.01):13(7.10); upper respiratory tract infection 12(3.26):23(6.27):22(6.01):1	Nasopharyngitis 33(6.83):37(7.63):37(7.68); upper respiratory tract infection 17(3.52):27(5.57):41(Headache 1(2):5(8):2(3):3(5):1(2):1(2):2(3)

Authors, Year, Ref number	Lavalle-González FJ et al. Diabetologia. 2013 Sep 13 DIA 3006	Cefalu WT et al. . Lancet. 2013 Sep 14;382(9896):941-50 DIA 3009	Rosenstock J et al. Diabetes Care. 2012 Jun;35(6):1232-8. DIA 2001
	0(5.46)	8.51)	
	Back pain 13(3.53):15(4.09):10(2.73):10(5.46); Arthralgia 10(2.72):9(2.45):17(4.64):11(6.01)	Back pain 29(6.0):18(3.71):20(4.15)	Nausea 3(5):1(2):1(2):3(5):5(8):1(2):0
	Headache 19(5.16):13(3.54):19(5.19):13(8.10)	Headache 14(2.9):25(5.15):24(4.98); Diarrhoea 24(4.97):33(6.8):29(6.02); Nausea 16(3.31):25(5.15):13(2.70)	Nasopharyngitis 5(8):0:0:1(2):1(2):3(5):2(3)
Treatment discontinued due AE n (%)	19 (5.2):12(3.3):16(4.4):8(4.4)	25(5.0):32(7.0):28(6.0)	2(2.4):2(2.7):0:1(1.3):0
Genital mycotic infections n (%)			
Male n (%)	2 (2.5):5(5.6):0	17(7):20(8.0):3(1%)	
Females n (%)	10 (8.8):8 (7.4):4 (3.8)	26(11.0):34(14.0):5(2.0)	6(29):7(25):4(13):4(14):7(19):2(7):1(3)
UTIs n (%)	29(7.9):18(4.9):23(6.3):12(6.6)	31(6.0):31(6.0):22(5.0)	3(5):2(3):6(9):2(3):3(5):1(2):4(6)
Documented hypoglycaemia episodes n (%)	6.8%:6.8%:4.1%:2.7%	Sign lower in canagliflozin: glimepiride p<0.0001	0:1(2):4(6):0:2(3):3(5):1(2)
Severe hypoglycaemia episodes n (%)	1:0:1:0	Lower in canagliflozin 100 n=2, <1%: canagliflozin 300 n=3, <1%:15 (3%)	0
Osmotic diuresis related AE n (%)			
Pollakiuria n (%)	21(5.7):11(3.0):2(0.5):1(0.5)	12 (3.0):12(3.0):1 (<1%)	2(3):3(5):1(2):2(3):0:2(3):1(2)
Polyuria n (%)	2(0.5):2(0.5):0:0	4(<1%):4(<1%):2(<1%)	

Authors, Year, Ref number	Lavalle-González FJ et al. Diabetologia. 2013 Sep 13 DIA 3006	Cefalu WT et al. . Lancet. 2013 Sep 14;382(9896):941-50 DIA 3009	Rosenstock J et al. Diabetes Care. 2012 Jun;35(6):1232-8. DIA 2001
Volume-related AEs n (%)			0:4(6):3(5):1(2):1(2):1(2):1(2)
Postural dizziness n (%)	2(0.5):2(0.5):1(0.3):1(0.5)	3(<1%):2(<1%):3(<1%)	
Orthostatic hypotension n (%)	0:1(0.3):0:0	1(<1%):1(<1%):0	
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)
Renal safety parameters: changes from baseline± SD			Supplementary tables?
Blood Urea Nitrogen	14.8±26.7: 16.1±33.4: 3.5±26.6: 5.9±33.8:	15,3% ±29,1: 22,0%±30,8: 6,5% ±26,4:	
Creatinine	2.3±11.4: 2.5±12.4: 3.4±13.6: 3.3±18.0:	Urine albumin/creatinine -0,1±4,7: -0,9±6,7: 0,7±15,3:	
eGFR	-1.4±12.8: -1.5±12.9: -2.4±12.8: -1.4±18.2:		

Abbreviations : RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate

Sources: Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013;382:941-50.;Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia 2013;56:2582-92;Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care. 2012;35:1232-8.

Table 40. Scientific publications and ClinicalTrials.gov register data on canagliflozin - TRIPLE THERAPY

Authors, Year, Ref number	Wilding JP et al. Int J Clin Pract. 2013 Oct 13. DIA 3002	Scherthner G et al. Diabetes Care. 2013 Sep;36(9):2508-15 DIA 3015	Data from Register (term from vocabulary, MEDDRA 15.0): A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicentre Study to Evaluate the Efficacy, Safety, and Tolerability of canagliflozin in the Treatment of Subjects With Type2DM With Inadequate Glycaemic Control on Metformin and Pioglitazone Therapy DIA 3012
Registry number	NCT 01106625	NCT01137812	NCT01106690
RCT phase	3	3	3
Add on to	Metformin and sulphonylurea	Metformin and sulphonylurea	Metformin and pioglitazone
Placebo control/Active control	Placebo (canagliflozin 100 mg, n=157/canagliflozin 300 mg, n=156/Placebo, n=156; randomization 1:1:1; during 1st 26 week; Canagliflozin 100 mg, n=127/Canagliflozin 300 mg, n=128/Placebo, n=119) during 2nd 26 week	Active (Canagliflozin 300 mg, n=378/sitagliptin 100 mg, n=378; randomization 1:1	Placebo and active (canagliflozin (100 mg or 300 mg) for 52 weeks OR placebo for 26 weeks switched to double-blind sitagliptin 100 mg for 26 weeks 344 patients were randomly allocated to the 3 treatment arms. 342 patients received at least 1 dose of study drug and were included in the modified intent-to-treat (mITT) analysis set (used for the Week 26 efficacy analysis) and safety analysis set (used for the Week 26 and Week 52 safety analyses); n= 113:114:115
Duration (weeks)	26+26=52	52	26+26=52
Any AE n (%)	106(67.5):114(73.1):111(71.2)	289(76.7):293(77.5)	Total, other (not including serious) adverse events 48(42.4):57(50):49(42.6)
Serious AE n (%)	7(4.5):8(5.1):13(8.3)	24(6.4):21(5.6)	8(7):7(6.1):6(5.2)
Deaths n (%)	0	2(0.5):0	N.A
Description of Serious AE n (%)	MEDDRA 15.0 Angina pectoris, MI, ankle fracture, colon cancer 0:0:1 (0.65); coronary artery stenosis 1:0:1; lobar pneumonia 0:1:1; cerebrovascular accident, hydronephrosis 1:0:0; deep vein thrombosis 0.1:0	MEDDRA 14.1; No more than 1-2 per group; Angina unstable, pancreatitis, bronchopneumonia, hip fracture, carcinoma (cervix, lung, uterine	No more than 1 per group: acute coronary sy 0:0:1(0.87); breast cancer 0:1(0.88):0; cerebrovascular accident 0:1(0.88):0; hypotension 1(0.88):0:1(0.87)

Authors, Year, Ref number	Wilding JP et al. Int J Clin Pract. 2013 Oct 13. DIA 3002	Schernthaner G et al. Diabetes Care. 2013 Sep;36(9):2508-15 DIA 3015	Data from Register (term from vocabulary, MEDDRA 15.0): A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicentre Study to Evaluate the Efficacy, Safety, and Tolerability of canagliflozin in the Treatment of Subjects With Type2DM With Inadequate Glycaemic Control on Metformin and Pioglitazone Therapy DIA 3012
		leiomyoma), CVI, suicide attempt, respiratory arrest, arterial thrombosis limb 1(0.27):0; MI, pneumonia 0:2(0.53); cardiac arrest 2(0.53):0; TIA, convulsion 0:1	
Most frequent AE n (%)	AE above 5% Diarrhoea 8(5.10):11(7.05):5(3.21); influenza 4(2.55):8(5.13):8(5.13); nasopharyngitis 9(5.73):9(5.77):10(6.41); upper respiratory tract infection 21(13.38):9(5.77):13(8.33); arthralgia 8(5.10):8(5.13):8(5.13); headache 11(7.01):2(1.28):5(3.21)	AE above 5% Diarrhoea 17(4.52):26(6.88); influenza 22(5.84):15(3.9); nasophaygitis 33(8.75):38(10.05); upper respiratory tract infection 33(8.75):21(5.6); headache 29(7.69):27(7.14)	Threshold above which other AE are reported=5% Diarrhoea 7(6.19):6(5.26):7(6.09); oedema peripheral 2(1.77):6(5.26):4(3.48); nasopharyngitis 11(9.73):15(13.16):13(11.3); upper respiratory infection 14(12.39):8(7.02):9(7.83); arthralgis 3(2.65):9(7.89):3(2.61); back pain 10(8.85):7(6.14):4(3.48)
Treatment discontinued due AE n (%)	11(7.0):12(7.7):7(4.5)	20(5.3):1(2.9)	N.A
Genital mycotic infections n (%)			
Male n (%)	6(7.9):5(5.7):1(1.3)	19(9.2):1(0.5)	
Females n (%)	15(18.5):13(18.8):4(5.0)	26(15.3):7(4.3)	Vulvovaginal 3(2.65):6(5.26):1(0.87)
UTIs n (%)	13(8.3):13(8.3):12(7.7)	15(4.0):21(5.6)	5(4.42):9(7.89):9(7.83)
Documented hypoglycaemia episodes n (%)	53(33.8):57(36.5):28(17.9)	43.2%:40.7%	3(2.65):5(4.39):3(2.61)
Severe hypoglycaemia episodes n (%)	1(0.6):1(0.6):1(0.6)	4.0%:3.4%	
Osmotic diuresis related AE n	9(5.7):11(7.1):3(1.9)		

Authors, Year, Ref number	Wilding JP et al. Int J Clin Pract. 2013 Oct 13. DIA 3002	Schernthaner G et al. Diabetes Care. 2013 Sep;36(9):2508-15 DIA 3015	Data from Register (term from vocabulary, MEDDRA 15.0): A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicentre Study to Evaluate the Efficacy, Safety, and Tolerability of canagliflozin in the Treatment of Subjects With Type2DM With Inadequate Glycaemic Control on Metformin and Pioglitazone Therapy DIA 3012
(%)			
Pollakiuria n (%)		6 (1.6):5(1.3)	6(5.31):8(7.02):1(0.87)
Polyuria n (%)		3(0.8):0	
Volume-related AEs n (%)	1(0.6):6(3.8):3(1.9)		
Postural dizziness n (%)		0:2(0.5)	
Orthostatic hypotension n (%)		0:1(0.3)	
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)	Statistical comparison was not performed (not prespecified)
Renal safety parameters change from baseline±SD			Statistical comparison was not performed (not prespecified)
Blood Urea Nitrogen	14.5 ±29.0: 17.5 ±29.3: 5.5 ±24.5:		
Creatinine	2.5±11.8: 7.7 ± 20.5: 2.8 ± 12.2		
eGFR	-5.8%, -1.6%, and -1.9%,		

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate

Sources:

Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. *Diabetes Care*. 2013;36:2508-15; Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract*. 2013;67:1267-82.

Table 41. Scientific publications and ClinicalTrials.gov register data on canagliflozin - Add on Insulin

Authors, Year, Ref number	Devineni D et al. Diabetes Obes Metab. 2012 Jun;14(6):539-45	Insulin substudy DIA3008
Registry number	N.A	NCT01032629

Authors, Year, Ref number	Devineni D et al. Diabetes Obes Metab. 2012 Jun;14(6):539-45	Insulin substudy DIA3008
RCT phase	N.A	3
Add on to	Insulin and one oral AHA	Insulin as monoth or in combination with other AHA
Placebo control/Active control	Placebo (Canagliflozin 100 mg, n=10/Canagliflozin 300 mg bid, n=10/Placebo, n=9)	Placebo (Canagliflozin 100 mg, n=566/Canagliflozin 300 mg, n=587/Placebo, n=565)
Duration (weeks)	28 days	18 weeks
Any AE n (%)	9(90.0):8(80.0):8(88.9)	
Serious AE n (%)	0	
Deaths n (%)	0	
Description of Serious AE n (%)	N.A	
Most frequent AE n (%)	At least 20% subjects in any treatment group: Headache (3:6:2); nausea (2:2:2); diarrhoea (0:3:1); pain in extremity (2:1:0); dizziness (1:0:2); nasal congestion (0:3:0); feeling hot (2:0:=); peripheral oedema (2:0:0); contusion (2:0:0)	
Treatment discontinued due AE n (%)	0	
Genital mycotic infections n (%)	N.A	
Male n (%)		
Females n (%)		
UTIs n (%)	N.A	
Documented hypoglycaemia episodes n (%)		279(49.3):283(48.2):208(36.8)
Severe hypoglycaemia episodes n (%)	6 (69):3(30):3(33)	10(18):16(2.7):14(2.5)
Osmotic diuresis related AE n (%)	N.A	
Pollakiuria n (%)		
Polyuria n (%)		
Volume-related AEs n (%)		
Postural dizziness n (%)		
Orthostatic hypotension n (%)	2:1:1	
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)	

Authors, Year, Ref number	Devineni D et al. Diabetes Obes Metab. 2012 Jun;14(6):539-45	Insulin substudy DIA3008
Renal safety parameters change from baseline±SD		
Blood Urea Nitrogen	14.5 ±29.0: 17.5 ±29.3: 5.5 ±24.5:	
Creatinine	2.5±11.8: 7.7 ± 20.5: 2.8 ± 12.2	
eGFR	-5.8%, -1.6%, and -1.9%,	

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate; N.A: not applicable

Sources:

Devineni D, Morrow L, Hompesch M, et al. Canagliflozin improves glycaemic control over 28 days in subjects with type 2 diabetes not optimally controlled on insulin. Diabetes Obes Metab. 2012;14:539-45.

Table 42. Scientific publications and ClinicalTrials.gov register data on canagliflozin in special population

Authors, Year, Ref number	Yale JF et al. Diabetes Obes Metab. 2013 ;15(5):463-73. Moderate renal impairment DIA 3004	Bode B et al. Hosp Pract (1995). 2013 ;41(2):72-84 Older subjects DIA 3010
Registry number	NCT01064414	NCT01106651
RCT phase	3	3
Add on to	Either not on AHA th or on a stable AHA regiment (98% of patients; mono th or combination th with any approved agent; 97.8% in Placebo group: 96.7% in canagliflozin 100 mg: 98.9% in canagliflozin 300 mg)	Either with/without stable AHA regiment (canagliflozin100:canagliflozin300:Placebo)
Placebo control/Active control	Placebo (canagliflozin 100 mg, n=90/ canagliflozin 300 mg, n=89/Placebo, n=90)	Placebo (canagliflozin 100 mg, n=241/ canagliflozin 300 mg, n=236/Placebo, n=237)
Duration (weeks)	26-week	26-week
Any AE n (%)	71(78.9):66(74.2):67(74.4)	Total, other (not including serious) adverse events 174(72.2):184(78.0):174(73.4)
Serious AE n (%)	10(11.1):10(11.1):16(17.8)	10(4.1):8(3.4):12(5.1)
Deaths n (%)	1(1.1):0:1(1.1)	0:0:0
Description of Serious AE n (%)	MEDDRA 14.1, no more than 1 per group Cardiac arrest, splenic rupture, pulmonary embolism, deep vein thrombosis 0:1:0; Acute coronary sy, coronary artery disease, MI, VF, sepsis, renal failure 0:0:1; Pneumonia 0:0:2; Lung cancer 1:0:0;	No more than 1-2 per group Angina pectoris 1(0.41):0:0; atrial fibrillation 1(0.41):0:0; myocardial infarction 0:1(0.42):2(0.84); intestinal infarction 1(0.41):0:0; pneumonia 0:2(0.85):0; urosepsis 0:0:2(0.84); carcinoma 2(0.82):1(0.42):0; CVI 1(0.41):0:0; renal impairment 0:1(0.42):1(0.42); respiratory failure (1(0.41):0:0

Authors, Year, Ref number	Yale JF et al. Diabetes Obes Metab. 2013 ;15(5):463-73. Moderate renal impairment DIA 3004	Bode B et al. Hosp Pract (1995). 2013 ;41(2):72-84 Older subjects DIA 3010
	Acute renal failure 1:1:0	
Most frequent AE n (%)	MEDDRA 15.0, more than 5% Diarrhoea 3(3.3):4(4.49):5(5.56) Nasopharyngitis 3(3.3):7(7.87):10(11.11) Influenza 3(3.3):1(1.12):1(1.11) Upper respiratory tract infBack pain 0:2(2.25):5(5.56) Arthralgia 4(4.44):2(2.25):2(2.22) Headache 2(2.22):2(2.25):3(3.33) Hypotensia 1(1.11):6(6.74):0	Threshold above which other AE are reported=5% Diarrhoea 10(4.15):11(4.66):14(5.91); influenza 14(5.81):9(3.81):5(2.11); nasopharyngitis 23(9.54):19(8.05):19(8.02); upper respiratory tract infection 13(5.39):10(4.24):11(4.64); arthralgia 4(1.66):5(2.12):12(5.06); back pain 6(2.49):12(5.08):8(3.38)
Treatment discontinued due AE n (%)	4(4.4):2(2.2):5(5.6)	5(2.1):17(7.2):10(4.2)
Genital mycotic infections n (%)		
Male n (%)	1(1.7):1(1.2):0	4(3.2):8(6.2):0
Females n (%)	1(3.1):1(2.4):0	18(15.4):12(11.2):2(2.1)
UTIs n (%)	5(5.6):7(7.9):5(5.6)	14(5.8):19(8.1):12(5.1)
Documented hypoglycaemia episodes n (%)	52.9%:51.2%:36.4%	78(43.1):82(47.4):66(37.7) on baseline AHA 4(6.7):3(4.8):2(3.2) not on baseline AHA
Severe hypoglycaemia episodes n (%)	4(4.7):1(1.2):1(1.1)	2(1.1):1(0.6):7(4.0) on baseline AHA 1(1.7):0:0 not on baseline AHA
Osmotic diuresis related AE n (%)		
Pollakiuria n (%)	2(2.2):4(4.5):1(1.1)	6(2.49):12(5.08):5(2.1)
Polyuria n (%)	0	4(1.7):4(1.7):0
Volume-related AEs n (%)		
Postural dizziness n (%)	1(1.1):2(2.2):0	2(0.8):3(1.3):1(0.4)
Orthostatic hypotension n (%)	0:1(1.1):0	2(0.8):1(0.4):0
Safety laboratory parameters	Statistical comparison for canagliflozin100 mg and 300 mg versus Placebo was not performed (not prespecified)	Statistical comparison for canagliflozin100 mg and 300 mg versus Placebo was not performed (not prespecified)
Measures of renal function	Statistical comparison for canagliflozin100 mg and 300 mg versus Placebo was not performed (not prespecified); change in estimated glomerular filtration rate (eGFR) and albumin/creatinine ration (ACR)	Statistical comparison for canagliflozin100 mg and 300 mg versus Placebo was not performed (not prespecified)

Authors, Year, Ref number	Yale JF et al. Diabetes Obes Metab. 2013 ;15(5):463-73. Moderate renal impairment DIA 3004	Bode B et al. Hosp Pract (1995). 2013 ;41(2):72-84 Older subjects DIA 3010
Progression of albuminuria	5.1%:8.3%:11.8%; OR (95% CI)=0.33 (0.08,1.48) and 0.51 (0.14,1.91) for canagliflozin 100 and 300 mg to placebo, respectively	
Renal safety parameters change from baseline±SD		
Blood Urea Nitrogen, %	12.1: 12.5: 4.9	
albumin/creatinine ratio, %	-29.9: -20.9: -7.5	
eGFR, %	-9.1: -10.1: -4.5	

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate; OR: Odds Ratio

Sources:

Chronic kidney disease: Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013 ;15:463-73; Older patients: Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995). 2013;41:72-84 and Data from Register ClinicalTrials.gov).

Table 43. Published articles data on vulvovaginal symptoms and Candida colonization and bacteriuria and urinary tract infection (based on NCT00642278 RCT of which overall efficacy and safety data have been published in Rosenstock J et al. Diabetes Care. 2012;35:1232-8)

Nyirjesy P, Zhao Y, Ways K, Usiskin K. Evaluation of vulvovaginal symptoms and Candida colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. Curr Med Res Opin. 2012 ;28(7):1173-8. As part of NCT00642278 RCT /of which overall efficacy and safety data have been published in Rosenstock J et al. Diabetes Care. 2012 ;35(6):1232-8./	Part of NCT00642278 RCT Double-blind study; subjects with T2DM and inadequate glycaemic control on metformin were randomized to placebo; canagliflozin 50, 100, 200, 300 mg daily or 300 mg twice daily; or sitagliptin 100 mg daily for 12 weeks; Vaginal swabs for Candida culture were collected from 198 female subjects at baseline and week 12, and during the trial if symptoms consistent with vulvovaginal candidiasis occurred.	215 female subjects (154 on canagliflozin; 27 on sitagliptin; 34 on placebo); At baseline, 23/198 (12%) females had vaginal cultures positive for Candida (C. glabrata: 14; C. albicans: 5; other: 4), with age ≤55 years associated with increased risk (odds ratio [OR], 3.5; 95% confidence interval [CI], 1.1-10.7). Of those with negative cultures at baseline, 31% of canagliflozin and 14% of placebo/sitagliptin subjects converted to positive at week 12 (OR, 2.8; 95% CI, 1.0-7.3 for canagliflozin vs. placebo/sitagliptin). Two placebo/sitagliptin (3%) and 16 canagliflozin subjects (10%) experienced vulvovaginal adverse event (VVAE).. Positive vaginal culture for Candida species at baseline was a risk factor for VVAE (OR, 9.1; 95% CI, 2.4-34.0). All 9/9 subjects in the canagliflozin group with a vaginal culture taken at the time of the VVAE were positive for Candida species. Most VVAE were treated with antifungal therapy and resolved without study drug interruption; none led to discontinuation. Study limitations include small population, short duration, and not obtaining cultures in all women with VVAE. Canagliflozin treatment was associated with an increase in vaginal colonization with Candida species and in VVAE in women with T2DM.
Nicolle LE, Capuano G, Ways K, Usiskin K. Effect of canagliflozin, a sodium	Part of NCT00642278 RCT Double-blind study; subjects with T2DM and	Asymptomatic bacteriuria (ASB) were present in 6.4% of canagliflozin and 6.5% of placebo/sitagliptin (control) subjects at randomization and, at 12

<p>glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study. <i>Curr Med Res Opin.</i> 2012 ;28(7):1167-71.</p> <p>As part of NCT00642278 RCT /of which overall efficacy and safety data have been published in Rosenstock J et al. <i>Diabetes Care.</i> 2012 ;35(6):1232-8.</p>	<p>inadequate glycaemic control on metformin were randomized to placebo; canagliflozin 50, 100, 200, 300 mg daily or 300 mg twice daily; or sitagliptin 100 mg daily for 12 weeks;</p> <p>to examine the effects of canagliflozin on asymptomatic bacteriuria and urinary tract infections (UTIs)</p>	<p>weeks, in 7.7% and 6.3% of subjects, respectively (odds ratio [OR] 1.23; 95% confidence interval [CI], 0.45-3.89).</p> <p>For subjects with initially negative urine cultures at baseline, 3 out of 82 (3.7%) who received controls and 10 out of 207 (4.8%) who received canagliflozin developed bacteriuria ($p=0.76$) at week 12.</p> <p>There were 21 adverse event (AE) reports of UTI; 16 (5.0%) in canagliflozin subjects and 5 (3.8%) in control subjects (OR 1.31; 95% CI, 0.45-4.68).</p> <p>In comparison with control subjects, canagliflozin increased UGE but was not associated with increased bacteriuria or AE reports of UTI; further studies enrolling larger numbers of subjects with longer term exposure to canagliflozin are necessary to more fully understand the impact of this agent on the risk of developing UTI.</p>
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Discussion

Canagliflozin leads to dose- and blood glucose-dependent osmotic diuresis with increased urine volume and glucosuria. Resulting adverse events observed in the clinical trials are genital infection, haemoconcentration/dehydration, electrolyte disturbances and arterial hypotension. These are established AEs for SGLT2 inhibitors. In line with the observed haemoconcentration increases in serum creatinine and, consequently, decreases in calculated eGFR are observed upon treatment initiation, which are in general attenuated with continued treatment and reversible after cessation of treatment and do not indicate renal damage.

Genital infections, mainly fungal infections, are clearly increased with canagliflozin use, especially in females. There was only a slight increase in UTIs and no imbalance in serious/severe urogenital infections.

Canagliflozin itself has low propensity to cause hypoglycaemia. This was especially evident in comparison to glimepiride (hypoglycaemia incidence 3.1 vs. 1.9 vs. 12.7% in the canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively). Similar to other glucose-lowering agents that have low hypoglycaemic potential themselves, canagliflozin increases the frequency of hypoglycaemic events when given in combination with insulin or an insulin secretagogue. Even then, however, severe hypoglycaemic events were rare and of similar frequency as observed with placebo.

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Cefalu WT, Leiter LA, Yoon K-H, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial *Lancet.* 2013;382:941-50.

CHMP report

Inagaki N, Kondo K, Yoshinari T, et al Efficacy and safety of canagliflozin in Japanese patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, 12-week study. *Diabetes Obes Metab.* 2013;15: 1136-45.

Johnson & Johnson submission file

MICROMEDEX Drugdex database 2.0

Nicolle LE, Capuano G, Ways K, et al Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study. *Curr Med Res Opin.* 2012;28:1167-71.

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Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab.* 2013;15:372-82

Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. *Int J Clin Pract.* 2013;67:1267-82.

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab.* 2013;15:463-73.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[C0002] Is there a relationship between the dose of canagliflozin and most frequent and serious adverse events in special populations?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- ClinicalTrials.gov Register (Study protocols, Study results)

Critical appraisal criteria: See general description of methods (Appendix 1),

Method of synthesis: Narrative

Result

- **Special populations: renal impairment**

Patients with renal impairment with stage 3 chronic Kidney disease (estimated glomerular filtration rate (eGFR) ≥ 30 and < 50 ml/min/1.73 m²) were investigated in a specific RCT phase 3 trial (registry number NCT01064414). Patients were randomly assigned to three groups: canagliflozin 100 mg (n=90), canagliflozin 300 mg (n=89) and placebo (n=90). Data reported in the tables of evidence are related to published data (Yale et al.) with a 26-week follow up period. However data on 52-week follow-up are available in data register. Total AE, excluding serious AE, both at 26-week and 52-week follow-up and serious AE only at 52-week show a trend of dose related events: at 52-week respectively for canagliflozin 100 mg and 300 mg percentages of total AE were 51.11 and 53.93 while percentages of serious AE were 20.0 and 23.60. AE which seem to be dose related are: fatigue, urinary tract infection, nasopharyngitis, hypotension, back pain, pollakiuria, postural dizziness, orthostatic hypotension and progression of albuminuria (Table 44). However, of these, fatigue, nasopharyngitis, back pain and progression of albuminuria had higher incidence in the placebo group compared to canagliflozin.

Concerning serious AE both cardiac and vascular disorders may be dose related although these AE rates were similar or even higher in the placebo group (for details in specific serious AE see Table 45).

- **Special populations: Older Subjects**

Older subjects were investigated in a specific phase 3 clinical trial (NCT01106651) with 26-week follow-up. 716 patients between 55 and 80 years either with or without stable AHA regiment were randomized in three groups: canagliflozin 100 mg (n=241), canagliflozin 300 mg (n=236) and placebo (n=237). Published data are available in full text (Bode et al.). AE both serious and not seem to be well balanced between the different groups. Total AE (excluding serious AE) were slightly higher in the canagliflozin 300 mg group (41.5%) compared to the canagliflozin 100 mg group (38.2%), while serious AE were higher in the canagliflozin 100 mg group. Higher incidence rates with canagliflozin 300 mg compared to canagliflozin 100 mg were in treatment discontinuation due to AE, back pain, urinary tract infection (UTI) and genital mycotic infections. Fewer differences merged for myocardial

infarction and pneumonia. In table 46 together with total and serious AE we focus on specific AE which might have a relationship with canagliflozin dosage.

- **Patients at cardiovascular risk**

A specific clinical trial (DIA3008, NCT NCT01032629) which is still ongoing assess the risk of cardiovascular events in patients already at risk. Subsequently characteristics of patients included in the study:

- ✓ age >30 years with documented symptomatic atherosclerotic CVD, including stroke, MI, hospital admission for unstable angina, coronary artery bypass graft, percutaneous coronary intervention (with or without stenting), peripheral revascularization (angioplasty or surgery), symptomatic with documented haemodynamically significant carotid or peripheral vascular disease, or amputation secondary to vascular disease;
- ✓ age >50 years with 2 or more of the following risk factors determined at the screening visit: duration of T2DM of 10 years or more, SBP >140 mmHg (average of 3 readings) recorded at the screening visit, while the subject was on at least 1 BP-lowering treatment, current daily cigarette smoker, documented micro- or macroalbuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).

However a specific meta-analysis investigated incidence of MACE (major adverse cardiovascular events including cardiovascular death, nonfatal MI, and nonfatal stroke)/MACE-plus (major adverse cardiovascular events-plus including also events of hospitalised unstable angina) in patients treated with canagliflozin. This meta-analysis includes 9632 patients with the exclusion of patients from DIA3015, while DIA3008-CANVAS trial (including patients at high cardiovascular risk) contributes to 45% of the patients involved (n=4327). The non-CANVAS trials included in the meta-analysis are: DIA3009, DIA3010, DIA3004 and other five Phase 2/3 studies.

Data on cardiovascular safety were not retrieved in primary literature nor in data register, thus we report only data from the manufacturer submission file.

In table 47 the summary of Mace-plus events in patients both from the CANVAS study (DIA3008) and not.

Data report HR for the CANVAS+non-CANVAS studies and for only CANVAS and only non-CANVAS: 0.91 (0.68-1.22), 1.00 (0.72-1.39) and 0.65 (0.35-1.21) respectively. Data do not suggest a relationship between events and canagliflozin dosage.

Table 44. Adverse events (excluding serious AE) which show a trend towards a dose related frequency in patients with renal impairment

Other Adverse Events	26-week			52-week		
	canagliflozin 100mg: n/tot(%)	canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)	canagliflozin 100mg n/tot(%)	canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)
Total, other (not including serious) adverse events	21/90	33/89	27/90	46/90	48/89	46/90
Fatigue	0/90 (0.00)	4/89 (4.49)	4/90 (4.44)	1/90 (1.11)	5/89 (5.62)	5/90 (5.56)
Urinary tract infection	4/90 (4.44)	7/89 (7.87)	5/90 (5.56)	4/90 (4.44)	12/89(13.48)	6/90 (6.67)
Nasopharyngitis	3/90(3.3)	7/89(7.87)	10/90(11.11)	5/90 (5.56)	9/89 (10.11)	13/90(14.44)
Back pain	0	2/89 (2.25)	5/90 (5.56)	1/90 (1.11)	4/89 (4.49)	5/90 (5.56)
Hypotension	1/90 (1.11)	6/89 (6.74)	0/90 (0.00)	1/90 (1.11)	6/89 (6.74)	3/90 (3.33)

Other Adverse Events	26-week			52-week		
	canagliflozin 100mg: n/tot(%)	canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)	canagliflozin 100mg n/tot(%)	canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)
Osmotic diuresis related AE n (%)						
Pollakiuria n (%)	2/90 (2.2)	4/89 (4.5)	0	–	–	–
Volume-related AEs n (%)						
Postural dizziness n (%)	1/90 (1.1)	2/89 (2.2)	0	1/90 (1.11)	5/89 (5.62)	4/89 (4.49)
Orthostatic hypotension n (%)	0/90	1/89 (1.1)	0	1/90 (1.11)	6/89 (6.74)	3/90 (3.33)
Measures of renal function						
Progression of albuminuria	(5.1)	(8.3)	(11.8)	–	–	–

Abbreviations: AE: adverse event.

Source:

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease and Data from Register ClinicalTrials.gov.

Table 45. Serious Adverse Events in patients with renal impairment

Serious Adverse Event	26-week			52-week		
	canagliflozin 100mg: n/tot(%)	canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)	canagliflozin 100mg n/tot(%)	canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)
Cardiac disorders	1/90 (1.11)	2/89 (2.25)	5/90 (5.55)	5/90 (5.55)	8 (9.0)	10 (11.11)
Acute coronary syndrome	0/90 (0.00)	0/89 (0.00)	1/90 (1.11)	0/90 (0)	0/89 (0.00)	1/90 (1.11)
Cardiac arrest	0/90 (0.00)	1/89 (1.12)	0/90 (0.00)	0/90 (0)	1/89 (1.12)	0/90 (0)
Cardiac failure congestive	0/90 (0.00)	1/89 (1.12)	1/90 (1.11)	0/90 (0)	2/89 (2.25)	1/90 (1.11)
Coronary artery disease	0/90 (0.00)	0/89 (0.00)	1/90 (1.11)	0/90 (0)	1/89 (1.12)	1/90 (1.11)
Myocardial infarction	0/90 (0.00)	0/89 (0.00)	1/90 (1.11)	0/90 (0)	2/89 (2.25)	2/90 (2.22)
Myocardial ischemia	1/90 (1.11)	0/89 (0.00)	0/90 (0.00)	1/90 (1.11)	0/89 (0.00)	1/90 (1.11)
Ventricular fibrillation	0/90 (0.00)	0/89 (0.00)	1/90 (1.11)	0/90 (0)	0/89 (0.00)	1/90 (1.11)
Coronary artery insufficiency	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	0/90 (0)	0/89 (0.00)	1/90 (1.11)
Cor pulmonale	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	0/90 (0)	0/89 (0.00)	1/90 (1.11)
Cardiac failure acute	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	0/90 (0)	1/89 (1.12)	0/90 (0)
Acute myocardial infarction	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	1/90 (1.11)	0/89 (0.00)	1/90 (1.11)
Angina pectoris	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	1/90 (1.11)	0/89 (0.00)	0/90 (0)
Angina unstable	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	0/90 (0)	1/89 (1.12)	0/90 (0)
Atrial fibrillation	0/90 (0.00)	0/89 (0.00)	0/90 (0.00)	2/90 (2.22)	0/89 (0.00)	0/90 (0)
Vascular disorders n (%)	0 (0)	3/89 (3.37)	2/90 (2.22)	0 (0)	3 (3.37)	3/90 (3.33)
Arteritis	0/90 (0.00)	1/89 (1.12)	0/90 (0)	0/90 (0)	1/89 (1.12)	0/90 (0)
Deep vein thrombosis	0/90 (0.00)	1/89 (1.12)	0/90 (0)	0/90 (0)	1/89 (1.12)	1/90 (1.11)
Femoral arterial stenosis	0/90 (0.00)	1/89 (1.12)	0/90 (0)	0/90 (0)	1/89 (1.12)	0/90 (0)
Hypertension	0/90 (0.00)	0/89 (0)	1/90 (1.11)	0/90 (0)	0/90 (0)	1/90 (1.11)
Hypotension	0/90 (0.00)	0/89 (0)	1/90 (1.11)	0/90 (0)	0/90 (0)	1/90 (1.11)

Source:

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease and Data from Register ClinicalTrials.gov.

Table 46. Total, serious and specific Adverse Events which might be dose related in older subjects.

	Canagliflozin 100 mg: n/tot(%)	Canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)
Total, other (not including serious) AE	92(38.2)	98(41.5)	99(41.7)
Treatment discontinued due AE	5 (2.1)	17(7.2)	10 (4.2)
Serious AE	10(4.15)	8(3.39)	12(5.06)
Myocardial infarction	0	1(0.42)	2(0.84)
Pneumonia	0	2(0.85)	0
Back pain	6(2.49)	12(5.08)	8(3.38)
Urinary Tract Infection (UTI)	14 (5.8)	19 (8.1)	12 (5.1)
Genital mycotic infections n (%)			
Male n (%)	4 (3.2)	8 (6.2)	0
Females n (%)	18 (15.4)	12 (11.2)	2 (2.1)

Abbreviation: AE: adverse event.

Source:

Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract (1995)* 2013;41:72-84 and Data from Register ClinicalTrials.gov.

Table 47. MACE-Plus Events for All Phase 2/3 Studies:CANVAS, and Non-CANVAS Studies

Trial	Product	N. events/TOT(%)	HR (95%CI)
Meta-analysis Phase 2 and Phase 3 Trials (CANVAS+non CANVAS)	Non-canagliflozin	74/3327	0.91 (0.68 1.22)
	All canagliflozin	135/6305	
	Canagliflozin 100	69/3156	
	Canagliflozin 300	66/3149	
CANVAS	Non-canagliflozin	56/1441	1.00 (0.72 1.39)
	All canagliflozin	113/2886	
	Canagliflozin 100	59/1445	
	Canagliflozin 300	54/1441	
Meta-analysis Phase 2 and non-CANVAS Phase 3 Trials (CANVAS+non CANVAS)	Non-canagliflozin	18/1886	0.65 (0.35 1.21)
	All canagliflozin	22/3419	
	Canagliflozin 100	10/1711	
	Canagliflozin 300	12/1708	

Abbreviations: MACE-plus: major adverse cardiovascular events-plus including also events of hospitalised unstable angina.

Source: Johnson & Johnson submission file

Discussion

Two phase 3 clinical trials analysed efficacy and safety of canagliflozin in special populations: patients with T2DM with stage 3 chronic kidney disease (estimated glomerular filtration rate (eGFR) ≥ 30 and < 50 ml/min/1.73 m²) and T2DM older subjects (aged 55-80 years).

The study focusing on renal impairment includes patients either not on AHA therapy or on a stable AHA regimen (subjects with AHA therapy: 97.8% in Placebo group, 96.7% in canagliflozin 100 mg, 98.9% in canagliflozin 300 mg). A limited number of patients are included in the study: 90, 90 and 89 patients treated with placebo, canagliflozin 100 mg and 300 mg respectively. At week 52 the number of total AE and serious AE are slightly higher in the group of patients treated with a higher dose of canagliflozin (300 mg) compared to the lower dose (100 mg). In particular certain specific AE seem to show a trend dose related in the frequency of the events both at 26 and 52-week: nasopharyngitis, hypotension, back pain, pollakiuria, postural dizziness, orthostatic hypotension, progression of albuminuria, cardiac and vascular disorders.

Concerning older subjects total AE (excluding serious AE) have a slightly higher rate in the canagliflozin 300 mg group compared to canagliflozin 100 mg (41.5% versus 38.2% respectively). Higher incidence rates with canagliflozin 300 mg compared to canagliflozin 100 mg were in treatment discontinuation due to AE, back pain, urinary tract infection (UTI) and genital mycotic infections.

Assessment of patients at cardiovascular risk is still in on ongoing clinical trial. No definitive conclusions can be taken into account. Preliminary data suggest caution in the administration of canagliflozin therapy in these patients. Although cardiovascular risk does not seem to be dose related.

References

Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract* (1995) 2013;41:72-84.

canagliflozin CHMP Report

ClinicalTrials.gov Register

Johnson & Johnson submission file

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463-73

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[C0004] How does the frequency or severity of harms change over time in different settings?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- ClinicalTrials.gov Register (Study protocols, Study results)

Critical appraisal criteria **See general description of methods (Appendix 1),**

Method of synthesis Narrative

Result

- **Special populations**

A double blind randomized placebo controlled phase 3 clinical trial (NCT01064414) enrolled 269 patients with stage 3 chronic kidney disease into 3 groups: canagliflozin 100 mg (n=90), canagliflozin 300 mg (n=89) or placebo (n=90). Data at 26-week were published (Yale et al.). However data on 52-week follow-up are available in data register. In table 48 we report AEs that show changes over time (26 to 52-week). Certain AEs which were frequent also at 26-week increase frequency at 52-week follow-up: urinary tract infection, hypoglycaemia and total serious adverse events. Other AEs which were not frequent at 26-week became frequent at 52-week follow up: postural dizziness, orthostatic hypotension, oedema peripheral, nasopharyngitis and cardiac disorders (details in incidence rates are reported in table 48). We also underline how estimated glomerular filtration rate (eGFR) and albumin to creatinine ratio (ACR) vary over time. Data concerning eGFR and ACR were available on published data (Yale et al). Both measures show an early decrease after initiation of canagliflozin therapy (both 100 and 300 mg) and subsequently seem to stabilize over time. In particular figures seem to report that eGFR decreases rapidly in the first 3 weeks and then remains constant while ACR shows decrease after canagliflozin initiation in the first 12 weeks before stabilization.

Table 48. Selected Adverse Events in patients with stage 3 chronic kidney disease showing changes over time

Other Adverse Events	26-week			52-week		
	Canagliflozin 100mg: n/tot(%)	Canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)	Canagliflozin 100mg n/tot(%)	Canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)
Urinary tract infection	4/90 (4.44)	7/89 (7.87)	5/90 (5.56)	4/90 (4.44)	12/89(13.48)	6/90 (6.67)
Hypoglycaemia	13/90(14.44)	10/89(11.24)	4/90 (4.44)	18/90(20.00)	20/89(22.47)	4/90 (4.44)
Postural dizziness	1/90 (1.1)	2/89 (2.2)	0	1/90 (1.11)	5/89 (5.62)	4/89 (4.49)
Orthostatic hypotension	0/90	1/89 (1.1)	0	1/90 (1.11)	6/89 (6.74)	3/90 (3.33)

Other Adverse Events	26-week			52-week		
	Canagliflozin 100mg: n/tot(%)	Canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)	Canagliflozin 100mg n/tot(%)	Canagliflozin 300 mg: n/tot(%)	Placebo: n/tot(%)
Oedema peripheral	2/90 (2.22 %)	3/89 (3.37 %)	4/90 (4.44 %)	5/90 (5.56 %)	6/89 (6.74 %)	6/90 (6.67%)
Nasopharyngitis	3/90(3.3)	7/89(7.87)	10/90(11.11)	5/90 (5.56)	9/89 (10.11)	13/90(14.44)
Total, serious adverse events	10/90(11.11%)	10/89(11.24%)	16/90(17.78%)	18/90(20.00%)	21/89(23.60%)	24/90 (26.67%)
Cardiac disorders	1/90 (1.11)	2/89 (2.25)	5/90 (5.55)	5/90 (5.55)	8 (9.0)	10 (11.11)
Measures of renal function						
Estimated GFR LS mean % changes	-9.1	-10.1	-4.5			
ACR Median % changes	-29.9	-20.9	-7.5			

Abbreviations: GFR: glomerular filtration rate; LS: least squares; ACR: urine albumin/creatinine ratio.

Source: Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463-73 and Data from Register ClinicalTrials.gov.

No data are available related to changes over time and in different setting for older subjects (Bode et al.).

Comparing differences of adverse events between older patients and patients with stage 3 chronic kidney disease we can underline the higher incidence rate of AEs leading to discontinuation in older subject compared to patients with stage 3 chronic kidney disease in particular at the dosage of 300 mg of canagliflozin (7.2% versus 2.2%). Moreover higher incidence rates merged also in genital mycotic infections in older patients respect to patients with renal impairment at both dosages of canagliflozin. On the contrary higher incidence rates resulted for serious AEs in patients with renal impairment compared to older subjects (11.2% versus 3.4%) (see table 49).

Table 49. Selected Adverse Events which change between patients with renal impairment and older subjects

Subjects, n(%)	Treatment groups in in DIA3010 (older subjects)			Treatment groups in in DIA3004 (patients with renal impairment)		
	Canagliflozi n 100mg, n=241	Canagliflozi n 300 mg, n=236	Placebo , n=237	Canagliflozi n 100mg, n=90	Canagliflozi n 300 mg, n=89	Placebo , n=90
Treatment discontinued due to AEs	5 (2.1)	17(7.2)	10 (4.2)	4 (4.4)	2 (2.2)	5 (5.6)
Serious AE	10 (4.1)	8(3.4)	12(5.1)	10 (11.1)	10 (11.2)	16 (17.8)
Genital mycotic infections n (%)						
Male n (%)	4 (3.2)	8 (6.2)	0	1 (1.7)	1 (2.1)	0
Females n (%)	18 (15.4)	12 (11.2)	2 (2.1)	1 (3.1)	1 (2.4)	0

Abbreviation: AE: adverse event.

Source: Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract* (1995) 2013;41:72-84; Johnson & Johnson submission file; Yale JF,

Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463-73.

Patients at cardiovascular risk

Few data are available concerning patients at cardiovascular risk. A specific on-going phase 3 clinical trial (DIA3008, NCT NCT01032629) is being performed to assume clear information on the cardiovascular safety of canagliflozin. However a specific meta-analysis was performed updated to January 2012 and then November 2012. We only underline changes in HR for fatal and/non-fatal stroke: HR 1.29 (95% CI: 0.8, 2.09) at the last meta-analysis update versus HR 1.47 observed in the initial cardiovascular meta-analysis (January 2012).

Discussion

Few data are available concerning changes of frequency and severity of AEs over time in special populations (patients with renal impairment, older subjects and patients at cardiovascular risk). Above we detail variations of AEs in patients with renal impairment comparing results at 26-week and 52-week and variation over time up to week 26 in measures of renal function. Comparison of AEs between older subjects and patients with renal impairment underlined higher rates in the treatment discontinuation due to AEs and genital mycotic infections in older subject but lower incidence of serious AEs compared to AEs occurred in patients with renal impairment.

References

Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract (1995)* 2013;41:72-84.

ClinicalTrials.gov Register

canagliflozin CHMP Report

Johnson & Johnson submission file

MICROMEDEX Drugdex database 2.0;

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463-73

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[C0005] What are the susceptible patient groups that are more likely to be harmed?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- ClinicalTrials.gov Register (Study protocols, Study results)

Critical appraisal criteria: See general description of methods (Appendix 1),

Method of synthesis: Narrative

Result

• Patients with renal impairment

Progression of chronic kidney disease is a common complication in patients with T2DM which can lead to end-stage renal failure. The interest in focusing on these kind of patients is also related to the mechanism of action of the drug: canagliflozin is an inhibitor of the sodium glucose co-transporter 2 (SGLT2) lowering the renal threshold for glucose (RTg), increasing, as a consequence, urinary glucose excretion (UGE). As a result this determines the decrease of plasma glucose levels in T2DM patients. Patients with renal impairment may be less responsive to canagliflozin since their disease may interfere with the drug mechanism of action resulting in a decrease in efficacy endpoints. Thus, a specific phase 3 clinical trial analysed safety and efficacy of canagliflozin 100 mg and 300 mg towards placebo (registry number NCT01064414). The study included 269 patients with stage 3 chronic kidney disease (estimated glomerular filtration rate (eGFR) ≥ 30 and < 50 ml/min/1.73 m²) which were randomized to receive canagliflozin 100 mg (n=90), canagliflozin 300 mg (n=89) or placebo (n=90). Patients were either not on AHA therapy or on a stable AHA regimen (subjects with AHA therapy: 97.8% in Placebo group, 96.7% in canagliflozin 100 mg, 98.9% in canagliflozin 300 mg).

As measures of renal function decreases of eGFR and urine albumin/creatinine ratio (ACR), increase of blood urea nitrogen (BUN) and progression of albuminuria should be underlined as described in the table 50. Decreases in eGFR from baseline were observed both with canagliflozin 100 mg and canagliflozin 300 mg. Least squares (LS) changes from baseline were -9.1, -10.1 and -4.5 for canagliflozin 100mg, canagliflozin 300mg and placebo respectively. Increases in blood urea nitrogen were observed both with canagliflozin 100 mg and canagliflozin 300 mg. Least squares (LS) changes from baseline were 12.1, 12.5 and 4.9 for canagliflozin 100mg, canagliflozin 300mg and placebo respectively. Decreases in ACR from baseline were observed both with canagliflozin 100 mg and canagliflozin 300 mg. Median percent reduction from baseline were -29.9, -20.9 and -7.5 for canagliflozin 100mg, canagliflozin 300mg and placebo respectively. Finally lower progressions of albuminuria was observed in patients treated with canagliflozin compared to the placebo group: 5.1, 8.3 and 11.8 for canagliflozin 100mg, canagliflozin 300mg and placebo respectively; HR 0.33 (CI95%: 0.08-1.48) and HR 0.51 (CI95%: 0.14-1.91) for canagliflozin 100 mg and canagliflozin 300 mg respectively.

Table 50. Measures of renal function in patients with stage 3 chronic kidney disease

	WEEK 26		
	Canagliflozin 100 mg	Canagliflozin 300 MG	Placebo
Estimated GFR LS mean % changes	-9.1	-10.1	-4.5
BUN LS mean % changes	12.1	12.5	4.9
ACR Median % changes	-29.9	-20.9	-7.5
Progression of Albuminuria	5.1 (HR: 0.33; CI: 0.08-1.48)	8.3 (HR: 0.51; CI: 0.14-1.91)	11.8

Abbreviations: GFR: glomerular filtration rate; LS: least squares; BUN: blood urea nitrogen; ACR: urine albumin/creatinine ratio.

Sources: Johnson & Johnson submission file; Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463-73.

- **Older subjects**

The incidence of T2DM increases with age. The choice of blood glucose lowering agents is critical in these patients because it imposes attentive evaluation and concerns related to comorbidities to which this special population might be at increased risk such as cardiovascular complications, renal failure, retinopathy and neuropathy. A specific phase 3 clinical trial (DIA3010; NCT01106651) investigated at week 26 safety and efficacy outcomes in 716 patients aged 55 to 80 years who were randomly assigned to three treatment groups: canagliflozin 100 mg (n=241), canagliflozin 300 mg (n= 236) and placebo (n=237). No deaths occurred in the three groups. Data concerning any AE, AE leading to discontinuation, AE related to study drug were higher in the canagliflozin 300 mg group, compared to canagliflozin 100 mg and the placebo group. Although higher incidence rates of the above mentioned AE resulted in the placebo group compared to canagliflozin 100 mg. Higher incidence rates of specific frequent AE such as urinary tract infections (UTI), genital mycotic infections and pollakiuria resulted in both groups treated with canagliflozin compared to placebo. Higher incidence rates of not frequent AE resulted in canagliflozin treated groups compared to placebo (polyuria and volume related AE). Summary of overall safety and selected AE are reported in table 51.

Table 51. Summary of overall safety and selected Adverse Events in older subjects.

Subjects, n(%)	Canagliflozin 100mg, n=241	Canagliflozin 300 mg, n=236	Placebo, n=237
Any AE	174 (72.2)	184 (78.0)	173 (73.4)
Treatment discontinued due to AEs	5 (2.1)	17(7.2)	10 (4.2)
AEs related to study drug	64 (26.6)	79 (33.5)	66 (26.8)
Serious AE	10 (4.1)	8(3.4)	12(5.1)
Deaths	0	0	0
Urinary Tract Infection (UTI)	14 (5.8)	19 (8.1)	12 (5.1)
Genital mycotic infections n (%)			
Male n (%)	4 (3.2)	8 (6.2)	0
Females n (%)	18 (15.4)	12 (11.2)	2 (2.1)
Osmotic diuresis-related AEs			
Pollakiuria	6 (2.5)	12 (5.1)	5 (2.1)
Polyuria	4 (1.7)	4 (1.7)	0
Volume –related AEs			
Postural dizziness	2 (0.8)	3 (1.3)	1 (0.4)

Subjects, n(%)	Canagliflozin 100mg, n=241	Canagliflozin 300 mg, n=236	Placebo, n=237
Orthostatic Hypotension	2 (0.8)	1 (0.4)	0

Abbreviations: AE: adverse event.

Source: Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract* (1995) 2013;41:72-84.

- **Patients at cardiovascular risk**

Dyslipidemia, an established risk factor for cardiovascular disease (CVD), is common in patients with T2DM, affecting almost 50% of the population. Considering also the recent concerns of cardiovascular safety of rosiglitazone, the U.S. Food and Drug Administration provided new guidance regarding the conditions under which new therapies for the management of diabetes will be considered for registration and marketing. As a result a specific on-going phase 3 clinical trial (DIA3008, NCT NCT01032629) is being performed to assume clear information on the cardiovascular safety of canagliflozin. The study enrolls 4330 patients at cardiovascular risk (age >30 years with documented symptomatic atherosclerotic CVD and age >50 years with 2 or more of the risk factors for CVD) but unfortunately data by the register are not available.

However a specific meta-analysis provided by the manufacturer investigates incidence of MACE (major adverse cardiovascular events including cardiovascular death, nonfatal MI, and nonfatal stroke)/MACE-plus (major adverse cardiovascular events-plus including also events of hospitalised unstable angina) in patients treated with canagliflozin. This meta-analysis includes 9632 patients with the exclusion of patients from DIA3015, while DIA3008-CANVAS trial (including patients at high cardiovascular risk) contributes to 45% of the patients involved (n=4327). The non-CANVAS trials included in the meta-analysis are: DIA3009, DIA3010, DIA3004 and other five Phase 2/3 studies.

In table 52 the summary of Mace-plus events in patients both from the CANVAS study (DIA3008) and not updated to January 2012.

Data report hazard ratio (HR) for the CANVAS+non-CANVAS studies and for only CANVAS and only non-CANVAS: 0.91 (0.68-1.22), 1.00 (0.72-1.39) and 0.65 (0.35-1.21) respectively.

However EMA requested the update of the analysis that was updated to November 2012. The point estimate of the HR for MACE-plus is consistent with the original meta-analysis 0.91 with a 95% CI of 0.712, 1.171 (original analysis 0.91 with a 95% CI of 0.68, 1.22). A lower HR for fatal and nonfatal strokes (1.29 with a 95% CI of 0.8, 2.09) was observed relative to the HR observed in the initial cardiovascular meta-analysis (1.47) (Figure 7).

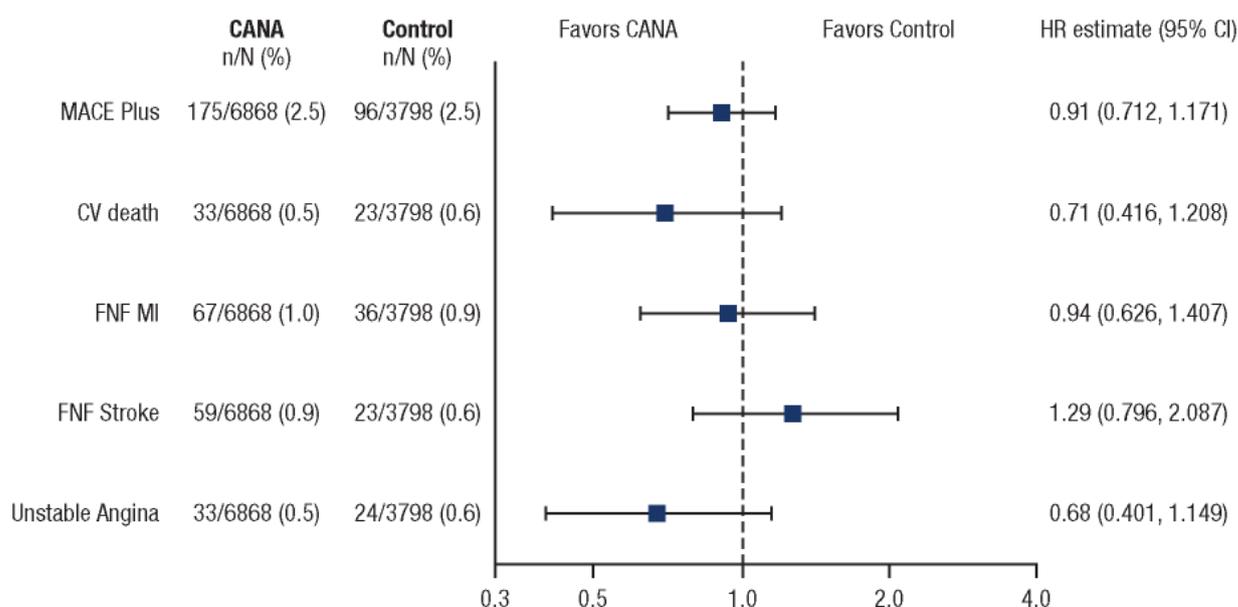
Table 52. MACE-Plus Events for All Phase 2/3 Studies, CANVAS, and Non-CANVAS Studies (update January 2012)

Trial	Product	N. events/TOT(%)	HR (95%CI)
Meta-analysis Phase 2 and Phase 3 Trials (CANVAS+non CANVAS)	Non-Canagliflozin	74/3327	0.91 (0.68 1.22)
	All Canagliflozin	135/6305	
	Canagliflozin 100	69/3156	
	Canagliflozin 300	66/3149	
CANVAS	Non- Canagliflozin	56/1441	1.00 (0.72 1.39)
	All Canagliflozin	113/2886	
	Canagliflozin 100	59/1445	
	Canagliflozin 300	54/1441	
Meta-analysis Phase 2 and non-CANVAS Phase 3 Trials (CANVAS+non CANVAS)	Non- Canagliflozin	18/1886	0.65 (0.35 1.21)
	All Canagliflozin	22/3419	
	Canagliflozin 100	10/1711	
	Canagliflozin 300	12/1708	

Abbreviations: HR: hazard ratio.

Source: Johnson & Johnson submission file.

Figure 7: Forest plot of hazard ratio (HR) for CV composite and individual event types within the Cardiovascular composite endpoint (all Phase 2/3 studies: modified intent-to-treat (mITT) analysis set – 20 November 2012 cutoff date).[submission file](#).



Abbreviations: CANA: canagliflozin; HR: hazard ratio; CI: confidence interval; MACE plus: major adverse cardiovascular events-plus including also events of hospitalised unstable angina; CV: cardiovascular; FNF: fatal/non fatal; MI: myocardial infarction.

Source: Johnson & Johnson submission file.

- **Patients with previous genital infections**

Although no specific clinical studies were conducted in patients with previous genital mycotic infections, caution must be taken into account in canagliflozin administration in these patients.

Discussion

Changes in measures of renal function were observed in patients with renal impairment (stage 3 chronic kidney disease): decrease in eGFR and ACR, increase of BUN and progression of albuminuria. Although these changes seem to occur and the beginning of the assumption of canagliflozin and go towards a stabilization over time during follow-up, clear and definitive considerations on renal protection with canagliflozin therapy will be assessed with longer-term follow-up studies.

The incidence of T2DM increases with age. The choice of blood glucose lowering agents is by the specific safety concerns of this population with greater risk of comorbidities such as cardiovascular complications, renal failure, retinopathy and neuropathy. AE such as any AE, AEs leading to discontinuation and AEs related to study drug resulted higher in the patients group in treatment with canagliflozin 300 mg compared to placebo but lower in the patients group in treatment with canagliflozin 100 mg still in comparison to placebo. Serious AE were not frequent and lower in both treatment groups respect to placebo. Although we underline that some specific AEs resulted higher in both treatment groups compared to placebo: UTI, genital mycotic infections, pollakiuria (frequency \square 5%) and polyuria, postural dizziness and orthostatic hypotension (frequency < 5%). Safety data for this population are available up to a 26-week follow-

up period, clear and definitive considerations on safety outcomes at long term with canagliflozin therapy will be assessed in future studies.

Concerning cardiovascular safety outcomes a specific phase 3 on-going clinical trial is assessing the risk of CVD in patients already at risk. Assessment in this phase can only refer to data provided by the manufacturer with a meta-analysis including patients enrolled in the clinical study mentioned above and patients included in other clinical trials. HR updated to November 2012 were provided underlying, as expected, an increased risk in the population at risk in particular for fatal/non-fatal stroke, which however results close to 1, and lower than what was observed in the previous analysis (January 2012). Definitive conclusions will be possible only at the end of the on-going clinical trial.

References

Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract (1995)* 2013;41:72-84.

canagliflozin CHMP Report

ClinicalTrials.gov Register

MICROMEDEX Drugdex database 2.0

Johnson & Johnson submission file

Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab* 2013;15:463-73

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[C0008] How safe is canagliflozin in relation to the comparator?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (Johnson & Johnson submission file and CHMP)
- Domain search
- MICROMEDEX Drugdex database 2.0;
- ClinicalTrials.gov Register (Study protocols, Study results)

Critical appraisal criteria Risk of bias was evaluated by using the Cochrane risk of bias checklist, EUnetHTA methods and the GRADE-methodology.

Method of synthesis: Narrative.

Result

For all active control phase III studies, safety evaluations included the collection of adverse events, safety laboratory tests (including haematology, chemistry, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs (blood pressure and pulse rate), body weight, physical examinations, self-monitored blood glucose (SMBG), and collection of potential hypoglycaemic episodes (e.g., from the subject diary provided to subjects).

In DIA3009 study canagliflozin was compared with glimepiride; in DIA3015 study with sitagliptin; and in DIA3006 with sitagliptin also. Main studies characteristic and results are written below (Table 53,54,and 55).

The overall incidence of AEs with canagliflozin in the DIA3009 and DIA3015 studies was generally comparable to those observed with the active comparators over 52 weeks: 64.4%, 68.5%, and 68.5% for canagliflozin 100 and 300 mg and glimepiride, respectively, for DIA3009; and 76.7% and 77.5% for canagliflozin 300 mg and sitagliptin 100 mg, respectively, for DIA3015.

Over 104 weeks in the DIA3009 study, the overall incidence of AEs was slightly higher with canagliflozin 300 mg and glimepiride compared with canagliflozin 100 mg (77.9%, 78.4%, and 73.3%, respectively).

Table 53. Scientific publication and ClinicalTrials.gov register data on canagliflozin - DIA3009 study

Authors, Year, Ref number	Cefalu WT et al. Lancet. 2013;382(9896):941-50. DIA 3009
Registry number	NCT00968812
RCT phase	3
Add on to	metformin
Placebo control/Active control	Active (Canagliflozin 100 mg, n=483/Canagliflozin 300 mg, n=485/ glimepiride 6 or 8 mg/day , n=482; randomization 1:1:1)
Duration (weeks)	52
Any AE n (%)	311(64.0):332(69.0):330(69.0)
Serious AE n (%)	24(5.0):26(5.0):39(8.0)
Deaths n (%)	0:2, <1%:2, <1%)
Description of Serious AE n (%)	MEDDRA 14.1 Anaemia, acute coronary sy, cardiomyopathy, abd. Pain, duodenitis, umbilical hernia, endometritis, muscle fracture, renal cancer, incontinence 0:1(0.21):0; Angina pectoris 1(0.21):2(0.41):2(0.41); pneumonia 1(0.21):1(0.21):2(0.41); uterine leiomyoma 0:2(0.41):0; Cerebrovascular accident 2(0.41):1(0.21):0; urticarial 1(0.21):0:0
Most frequent AE n (%)	Above 5%
	Nasopharyngitis 33(6.83):37(7.63):37(7.68); upper respiratory tract infection 17(3.52):27(5.57):41(8.51)
	Back pain 29(6.0):18(3.71):20(4.15)
	Headache 14(2.9):25(5.15):24(4.98); Diarrhoea 24(4.97):33(6.8):29(6.02); Nausea 16(3.31):25(5.15):13(2.70)
Treatment discontinued due AE n (%)	25(5.0):32(7.0):28(6.0)

Authors, Year, Ref number	Cefalu WT et al. Lancet. 2013;382(9896):941-50. DIA 3009
Genital mycotic infections n (%)	
Male n (%)	17(7):20(8.0):3(1%)
Females n (%)	26(11.0):34(14.0):5(2.0)
UTIs n (%)	31(6.0):31(6.0):22(5.0)
Documented hypoglycemia episodes n (%)	Sign lower in cana:glimepiride p<0.0001
Severe hypoglycemia episodes n (%)	Lower in canagliflozin100 n=2, <1%: canagliflozin300 n=3, <1%:15 (3%)
Osmotic diuresis related AE n (%)	
Pollakiuria n (%)	12 (3.0):12(3.0):1 (<1%)
Polyuria n (%)	4(<1%):4(<1%):2(<1%)
Volume-related AEs n (%)	
Postural dizziness n (%)	3(<1%):2(<1%):3(<1%)
Orthostatic hypotension n (%)	1(<1%):1(<1%):0
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)
Renal safety parameters: changes from baseline±SD	
Blood Urea Nitrogen	15,3% ±29,1: 22,0%±30,8: 6,5% ±26,4:
Creatinine	Urine albumin/creatinine -0,1±4,7: -0,9±6,7: 0,7±15,3:
eGFR	

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate

Table 54. Scientific publication and ClinicalTrials.gov register data on canagliflozin - DIA3015 study

Authors, Year, Ref number	Schernthaner G et al. Diabetes Care. 2013;36(9):2508-15. DIA 3015
Registry number	NCT01137812
RCT phase	3
Add on to	Metformin and sulphonylurea
Placebo control/Active control	Active (Canagliflozin 300 mg, n=378/ <i>sitagliptin 100 mg</i> , n=378; randomization 1:1)
Duration (weeks)	52
Any AE n (%)	289(76.7):293(77.5)
Serious AE n (%)	24(6.4):21(5.6)
Deaths n (%)	2(0.5):0
Description of Serious AE n (%)	MEDDRA 14.1; No more than 1-2 per group; Angina unstable, pancreatitis, bronchopneumonia, hip fracture, carcinoma (cervix, lung, uterine leiomyoma), CVI, suicide attempt, respiratory arrest, arterial thrombosis limb 1(0.27):0; MI, pneumonia 0:2(0.53); cardiac arrest 2(0.53):0; TIA, convulsion 0:1
Most frequent AE n (%)	AE above 5% Diarrhoea 17(4.52):26 (6.88); influenza 22(5.84):15(3.9); nasopharyngitis 33(8.75):38(10.05); upper respiratory tract infection 33(8.75):21(5.6); headache 29(7.69):27(7.14)
Treatment discontinued due AE n (%)	20(5.3):1(2.9)
Genital mycotic infections n (%)	
Male n (%)	19(9.2):1(0.5)

Authors, Year, Ref number	Schernthaner G et al. Diabetes Care. 2013;36(9):2508-15. DIA 3015
Females n (%)	26(15.3):7(4.3)
UTIs n (%)	15(4.0):21(5.6)
Documented hypoglycemia episodes n (%)	43.2%:40.7%
Severe hypoglycemia episodes n (%)	4.0%:3.4%
Osmotic diuresis related AE n (%)	
Pollakiuria n (%)	6 (1.6):5(1.3)
Polyuria n (%)	3(0.8):0
Volume-related AEs n (%)	
Postural dizziness n (%)	0:2(0.5)
Orthostatic hypotension n (%)	0:1(0.3)
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)
Renal safety parameters change from baseline±SD	
Blood Urea Nitrogen	
Creatinine	
eGFR	

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate

In subjects on background metformin (DIA3006), overall incidences of AEs were slightly higher with canagliflozin 100 mg compared with canagliflozin 300 mg, sitagliptin 100 mg, and placebo/sitagliptin (subjects who switched from placebo to sitagliptin after the 26-week core treatment period) over 52 weeks (72.3%, 62.7%, 64.5%, and 66.7%, respectively).

Table 55. Scientific publication and ClinicalTrials.gov register data on canagliflozin - DIA3006 study

Authors, Year, Ref number	Lavalle-González FJ et al. Diabetologia. 2013;56:2582-92 DIA 3006
Registry number	NCT01106677
RCT phase	3
Add on to	metformin
Placebo control/Active control	Placebo and active control (Canagliflozin100 mg, n=368/Canagliflozin300 mg, n=367/ Sitagliptin 100 mg , n=366/Placebo, n=183; 2:2:2:1; during 1st 26 week; Canagliflozin100 mg, n=316/Canagliflozin300 mg, n=321/Sitagliptin 100 mg, n=313/Placebo-Sitagliptin 100 mg, n=153; randomization 2:2:2:1; during 2nd 26 week
Duration (weeks)	26+26=52
Any AE n (%)	266(72.3):230(62.7):236(64.5):122(66.7)
Serious AE n (%)	15(4.1):12(3.3):18(4.9):7(3.8)
Deaths n (%)	0:1(0.3):1(0.3):1(0.5)
Description of Serious AE n (%)	MEDDRA 15.0 Acute coronary sy 0:0:0:1(0.55); unstable angina, AMI, cardiac arrest, asthma, respiratory failure, acute renal failure, cerebrovascular accident, septic shock, abdominal hernia 0:0.1(0.27):0; cholangitis, cholecystitis, pneumonia, sepsis, cervical cerebral fracture 1(0.27):0:0:0, cancers (bronchia, colorectal,prostate, breast, meningioma) 0:1:0:0
Most frequent AE n (%)	Above 5% Nasopharyngitis 18(4.89):16(4.36):22(6.01):13(7.10); upper respiratory tract infection 12(3.26):23(6.27):22(6.01):10(5.46)

Authors, Year, Ref number	Lavalle-González FJ et al. Diabetologia. 2013;56:2582-92 DIA 3006
	Back pain 13(3.53):15(4.09):10(2.73):10(5.46); Arthralgia 10(2.72):9(2.45):17(4.64):11(6.01)
	Headache 19(5.16):13(3.54):19(5.19):13 87.10)
Treatment discontinued due AE n (%)	19 (5.2):12(3.3):16(4.4):8(4.4)
Genital mycotic infections n (%)	
Male n (%)	2 (2.5):5(5.6):0
Females n (%)	10 (8.8):8 (7.4):4 (3.8)
UTIs n (%)	29(7.9):18(4.9):23(6.3):12(6.6)
Documented hypoglycemia episodes n (%)	6.8%:6.8%:4.1%:2.7%
Severe hypoglycemia episodes n (%)	1:0:1:0
Osmotic diuresis related AE n (%)	
Pollakiuria n (%)	21(5.7):11(3.0):2(0.5):1(0.5)
Polyuria n (%)	2(0.5):2(0.5):0:0
Volume-related AEs n (%)	
Postural dizziness n (%)	2(0.5):2(0.5):1(0.3):1(0.5)
Orthostatic hypotension n (%)	0:1(0.3):0:0
Safety laboratory parameters	Statistical comparison was not performed (not prespecified)
Renal safety parameters: changes from baseline±SD	
Blood Urea Nitrogen	14.8±26.7: 16.1±33.4: 3.5±26.6: 5.9±33.8:
Creatinine	2.3±11.4: 2.5±12.4: 3.4±13.6: 3.3±18.0:
eGFR	-1.4±12.8: -1.5±12.9: -2.4±12.8: -1.4±18.2:

Abbreviations: RCT: randomized controlled trial; AE: adverse event; MedDRA, Medical Dictionary for Regulatory Activities; UTI: urinary tract infection; eGFR: estimated glomerular filtration rate

AEs of special interest

Hypoglycaemia

Data report any documented hypoglycaemia or severe hypoglycaemia. The previous is defined when the renal threshold for glucose is ≤ 3.9 mmol/L (70 mg/dL), the latter is defined when the events require the assistance of another person, loss of consciousness or a seizure.

In the presence of hypoglycaemic background therapy (i.e. insulin or sulfonylurea) the incidence was increased by canagliflozin (Table 56).

Table 56. Incidences of hypoglycaemia in patients with hypoglycaemic background therapy

	Canagliflozin 300 mg	Comparator sitagliptin 100 mg
DIA3015 (comparator sitagliptin, background metformin+ sulfonylurea)	N=377	N=378
Subjects with any documented hypoglycemia	163 (43.2)	154 (40.7)
Severe hypoglycemia	15 (4.0)	13 (3.4)

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

Sulfonylurea has high hypoglycemic propensity themselves and canagliflozin further increases the hypoglycaemia incidence of a hypoglycemic background therapy including an insulin secretagogue. Hypoglycemic events were not so different for canagliflozin+metformin+sulfonylurea compared to sitagliptin+metformin+sulfonylurea. No relevant differences were observed for severe hypoglycaemias (canagliflozin vs. placebo).

Events of hypoglycaemia in DIA3009 were significantly lower in both patients groups treated with canagliflozin (100 and 300 mg) respect to the group treated with glimepiride ($p < 0.001$) (1). Although severe hypoglycaemia was still lower in patients treated with canagliflozin rather than those in glimepiride treatment, the difference was not reported as significant (Table 57). DIA3015 report similar both for any documented hypoglycaemia and severe hypoglycaemia between the two groups (canagliflozin 300 mg and sitagliptin 100 mg).

Table 57. Incidences of hypoglycaemia in active comparator studies with patients not on background insulin or insulin secretagogues

	Canagliflozin 100 mg N (%)	Canagliflozin 300 mg N (%)	All Canagliflozi n N (%)	Comparator N (%)
DIA3006, n	368	367	735	SITAGLIPTIN 100 mg 366
Any documented hypoglycaemia	16 (4.3)	17 (4.6)	33 (4.5)	5 (1.4)
Severe hypoglycaemia	1 (0.3)	1 (0.3)	2 (0.3)	0
DIA3009, n	483	485	968	GLIMEPIRIDE 6 or 8 mg 482
Any documented hypoglycaemia	27 (5.6)	24 (4.9)	51 (5.3)	165 (34.2)
Severe hypoglycaemia	2 (0.4)	3 (0.6)	5 (0.5)	15 (3.1)

Source: Committee for Medicinal Products for Human Use (CHMP). Assessment report Canagliflozin. EMA/374133/2013, 19 September 2013

Genital mycotic infections

Canagliflozin treatment was associated with an increased incidence of female genital mycotic infections compared with glimepiride in the DIA3009 study at Weeks 52 and 104 and with sitagliptin in the DIA3015 and DIA3006 studies at Week 52 (Table 58).

Table 58. Summary of female genital mycotic infection adverse events (AEs) in active-comparator studies^a

	Subjects, n (%)			
	CANA 100 mg	CANA 300 mg	All CANA	GLIM
DIA3009, n	231	244	475	219
Any AE	26 (11.3)	34 (13.9)	60 (12.6)	5 (2.3)
Specific terms ^b				
Vulvovaginal mycotic infection	6 (2.6)	14 (5.7)	20 (4.2)	4 (1.8)
Vaginal infection	11 (4.8)	7 (2.9)	18 (3.8)	1 (0.5)
Vulvovaginitis	5 (2.2)	8 (3.3)	13 (2.7)	0
	CANA 100 mg	CANA 300 mg	All CANA	SITA
DIA3006, n	194	202	396	194
Any AE	22 (11.3)	20 (9.9)	42 (10.6)	5 (2.6)
Specific terms ^b				

Subjects, n (%)				
Vulvovaginal mycotic infection	12 (6.2)	7 (3.5)	19 (4.8)	1 (0.5)
Vulvovaginal candidiasis	4 (2.1)	5 (2.5)	9 (2.3)	0
Vulvovaginitis	3 (1.5)	5 (2.5)	8 (2.0)	2 (1.0)
	CANA 100 mg	CANA 300 mg	All CANA	SITA
DIA3015, n	NA	170	NA	163
Any AE	NA	26 (15.3)	NA	7 (4.3)
Specific terms ^b				
Vulvovaginal mycotic infection	NA	12 (7.1)	NA	5 (3.1)
Vulvovaginitis	NA	7 (4.1)	NA	2 (1.2)
Vulvovaginal candidiasis	NA	5 (2.9)	NA	0

Abbreviations: AE, adverse event; CANA, canagliflozin; GLIM, glimepiride; SITA, sitagliptin.

Source: Johnson & Johnson submission file

^a Week 52 assessment time point.

^b The 3 most common terms are shown.

Canagliflozin treatment was associated with higher incidences of male genital mycotic infections relative to active comparators (DIA3009 [Weeks 52 and 104], DIA3015 [Week 52], DIA3006 [Week 52]; Overall, male genital mycotic infections were generally manageable with the usual treatments; these AEs occasionally led to study discontinuation and rarely resulted in more serious complications (e.g., phimosis). (Table 59)

Table 59. Summary of male genital mycotic infection adverse events (AEs) in active-comparator studies^a

Subjects, n (%)				
	CANA 100 mg	CANA 300 mg	All CANA	GLIM
DIA3009, n	252	241	493	263
Any AE	17 (6.7)	20 (8.3)	37 (7.5)	3 (1.1)
Specific terms ^b				
Balanoposthitis	4 (1.6)	13 (5.4)	17 (3.4)	2 (0.8)
Balanitis	5 (2.0)	5 (2.1)	10 (2.0)	1 (0.4)
Genital infection fungal	6 (2.4)	2 (0.8)	8 (1.6)	0
	CANA 100 mg	CANA 300 mg	All CANA	SITA
DIA3006, n	174	165	339	172
Any AE	9 (5.2)	4 (2.4)	13 (3.8)	2 (1.2)
Specific terms ^b				
Balanitis	3 (1.7)	3 (1.8)	6 (1.8)	1 (0.6)
Balanoposthitis	5 (2.9)	1 (0.6)	6 (1.8)	1 (0.6)
Genital infection fungal	1 (0.6)	0	1 (0.3)	0
	CANA 100 mg	CANA 300 mg	All CANA	SITA
DIA3015, n	NA	207	NA	215
Any AE	NA	19 (9.2)	NA	1 (0.5)
Specific terms				
Balanoposthitis	NA	7 (3.4)	NA	0
Balanitis	NA	5 (2.4)	NA	1 (0.5)
Balanitis candida	NA	3 (1.4)	NA	0
Genital infection fungal	NA	3 (1.4)	NA	0

Abbreviations: AE, adverse event; CANA, canagliflozin; GLIM, glimepiride; SITA, sitagliptin.

Source: Johnson & Johnson submission file

^a Week 52 assessment time point.

^b The 3 most common terms are shown.

UTIs

In the active-controlled studies, canagliflozin was associated with a slightly higher incidence of UTIs compared with glimepiride at Weeks 52 and 104 (DIA3009) and a slightly lower incidence of UTIs compared with sitagliptin at Week 52 (DIA3015). In subjects on background metformin (DIA3006), the incidence of UTI was generally similar with canagliflozin compared with sitagliptin over 52 weeks.

Table 60. Summary of urinary tract infection (UTI) adverse events (AEs) in active-comparator studies

	Subjects, n (%)			
	CANA 100 mg	CANA 300 mg	All CANA	GLIM
DIA3009, n	483	485	968	482
Any AE	31 (6.4)	31 (6.4)	62 (6.4)	22 (4.6)
Specific terms				
UTI	27 (5.6)	24 (4.9)	51 (5.3)	18 (3.7)
Cystitis	4 (0.8)	7 (1.4)	11 (1.1)	4 (0.8)
Pyelonephritis chronic	0	1 (0.2)	1 (0.1)	0
	CANA 100 mg	CANA 300 mg	All CANA	SITA 100 mg
DIA3006, n	368	367	735	366
Any AE	29 (7.9)	18 (4.9)	47 (6.4)	23 (6.3)
Specific terms				
UTI	27 (7.3)	18 (4.9)	45 (6.1)	22 (6.0)
Cystitis	1 (0.3)	0	1 (0.1)	3 (0.8)
Kidney infection	0	1 (0.3)	1 (0.1)	0
Pyelonephritis	0	0	0	1 (0.3)
Pyelonephritis chronic	1 (0.3)	0	1 (0.1)	0
	CANA 100 mg	CANA 300 mg	All CANA	SITA 100 mg
DIA3015, n	NA	377	NA	378
Any AE	NA	15 (4.0)	NA	21 (5.6)
Specific terms				
UTI	NA	15 (4.0)	NA	19 (5.0)
Cystitis	NA	0	NA	1 (0.3)
Pyelonephritis	NA	0	NA	1 (0.3)
Pyelonephritis chronic	NA	0	NA	1 (0.3)

Abbreviations: UTI: urinary tract infection; AE, adverse event; CANA, canagliflozin; GLIM, glimepiride; SITA, sitagliptin. a Week 52 assessment time point.

Source: Johnson & Johnson submission file

Osmotic diuresis

A higher incidence of specific AEs related to osmotic diuresis (i.e., pollakiuria, polyuria) was seen with canagliflozin treatment compared with glimepiride in the DIA3009 study over 52 and 104 weeks and compared with sitagliptin in the DIA3006 study over 52 weeks; incidences of these AEs were slightly higher with canagliflozin than with sitagliptin in the DIA3015 study.

Reduced intravascular volume

In the active-controlled studies (DIA3009, DIA3015, DIA3006), incidences of specific AEs related to reduced intravascular volume (i.e., orthostatic hypotension, postural dizziness) were similar with canagliflozin and glimepiride (DIA3009) or sitagliptin 100 mg (DIA3015, DIA3006).

Estimated GFR

Similar patterns in estimated GFR—initial decrease from baseline (within 3-6 weeks) followed by stabilisation or attenuation over the remaining treatment period—were observed with canagliflozin in the active-controlled studies (DIA3009, DIA3015).

Canagliflozin showed mean decreases in ACR relative to glimepiride in the DIA3009 study.

Safety laboratory parameters

Generally, only small differences were observed between canagliflozin and active comparator in safety laboratory parameters across studies.

Serious AEs/deaths

There was no increase in overall death rate or deaths considered related to study drug as compared to control group.

Discussion

The overall incidence of AEs with canagliflozin was generally comparable to those observed with the active comparators over 52 weeks: 64.4%, 68.5%, and 68.5% for canagliflozin 100 and 300 mg and glimepiride, respectively, and 76.7% and 77.5% for canagliflozin 300 mg and sitagliptin 100 mg, respectively.

Over 104 weeks in the DIA3009 study, the overall incidence of AEs was slightly higher with canagliflozin 300 mg and glimepiride compared with canagliflozin 100 mg (77.9%, 78.4%, and 73.3%, respectively).

In the presence of hypoglycaemic background therapy (i.e. insulin or sulfonylurea) the incidence was increased by canagliflozin. Canagliflozin itself has low propensity to cause hypoglycaemia. This was especially evident in comparison to glimepiride 6 mg or 8 mg (hypoglycaemia incidence 3.1 vs. 1.9 vs. 12.7% in the canagliflozin 100 mg, canagliflozin 300 mg and glimepiride, respectively, ($p < 0.001$)).

Similar to other glucose-lowering agents that have low hypoglycaemic potential themselves, canagliflozin increases the frequency of hypoglycaemic events when given in combination with insulin or an insulin secretagogue. Even then, however, severe hypoglycaemic events were rare and of similar frequency as observed with placebo.

There were no differences in hypoglycaemic events between canagliflozin and sitagliptin. Canagliflozin leads to dose- and blood glucose-dependent osmotic diuresis with increased urine volume and glucosuria. Genital infections, mainly fungal infections, are clearly increased with canagliflozin use, in comparisons with glimepiride and sitagliptin, especially in females. There was only a slight increase in UTIs and no imbalance in serious/severe urogenital infections.

References

canagliflozin CHMP Report

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Johnson & Johnson submission file

MICROMEDEX Drugdex database 2.0

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Stenlöf K, Cefalu WT, Kim KA, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. *Curr Med Res Opin.* 2014;30: 163-75.

Importance and transferability

How important is this piece of information for decision making?

- Critical
- Important
- Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

- Completely
- Partly
- Not

CLINICAL EFFECTIVENESS

[D0001]: What is the expected beneficial effect of canagliflozin on overall mortality?

Methods

- See general description of methods (Appendix 1)
- Other, please specify:

Source of information:

- Basic documentation (REA submission file of J&J)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

EVIDENCE AND FINDINGS

[Johnsson & Johnsson submission file (2013)]:

To date, there have been too few mortality events (n = 48) in the canagliflozin program to make any definitive conclusions regarding overall mortality or cause-specific mortality.

SIMULATED/PREDICTED LIFE EXPECTANCY USING CORE DIABETES MODEL

Simulation methodology

No conclusive evidence is available for mortality and survival. MAH presented results for predicted life expectancy using the IMS Core Diabetes Model. The model has been described elsewhere (Palmer et al. 2004a). **All the following results for undiscounted predicted life expectancy and sensitivity analyses were presented in Johnsson & Johnsson submission file (2013).** Only the simulations and sensitivity analyses based on head-to-head comparisons are presented here.

According to Johnsson & Johnsson submission file (2013) clinical inputs (treatment effects) and population characteristics at baseline (demographic characteristics, history of disease and health condition) in the simulation using IMS Core Diabetes Model correspond to those observed in clinical trials (DIA3006, DIA3009 and DIA3015). Mortality from other causes is based on adjusted European mortality numbers (mortality which reflects the average non-diabetes related mortality in average European population). Methodology and input parameters are discussed in more detail in appendix 1:methods.

Sensitivity analyses were reported in Johnsson & Johnsson submission file (2013) for simulations for which head-to-head comparisons were available.

Sensitivity analyses included the following:

- HbA1c effect in intervention arm as comparator;
- BMI effect in intervention arm as comparator;
- Cholesterol effect in intervention arm as comparator (measured by Tchol:Hdl ratio);
- SBP effect in intervention arm as comparator;
- Hypoglycaemic event rates in intervention arm as comparator;
- Time horizon 10 years (base case is 40 years);
- HbA1c threshold 7% (base case is 7.5%).

Sensitivity analyses are further discussed in appendix 1:methods.

Simulation results

Authors' note for interpretation:

The figures presented in the following tables characterize the predicted life expectancy of 55.4-56.7 year old patients (depending on the comparison) who have similar population characteristics on average as in the clinical trial which the comparison is based on (DIA3006, DIA3009 or DIA3015 depending on the comparison). Mortality from other causes reflects the average in European population in the prediction.

Results of the sensitivity analyses for each comparison point out some factors which may have impact on the results. The results of sensitivity analyses are represented in bar charts where the base case is on top and results of sensitivity analyses follow in descending order in each comparison. The larger the difference between base case and the result of a sensitivity analysis for the parameter of interest, the greater is the impact of the change made for the parameter (for example setting the intervention and comparator values equal).

Dual therapy (canagliflozin 100 mg vs. sitagliptin 100 mg)

The predicted life expectancies in canagliflozin 100mg and sitagliptin 100 mg treatments in dual therapy as add-on to metformin is presented in the table below.

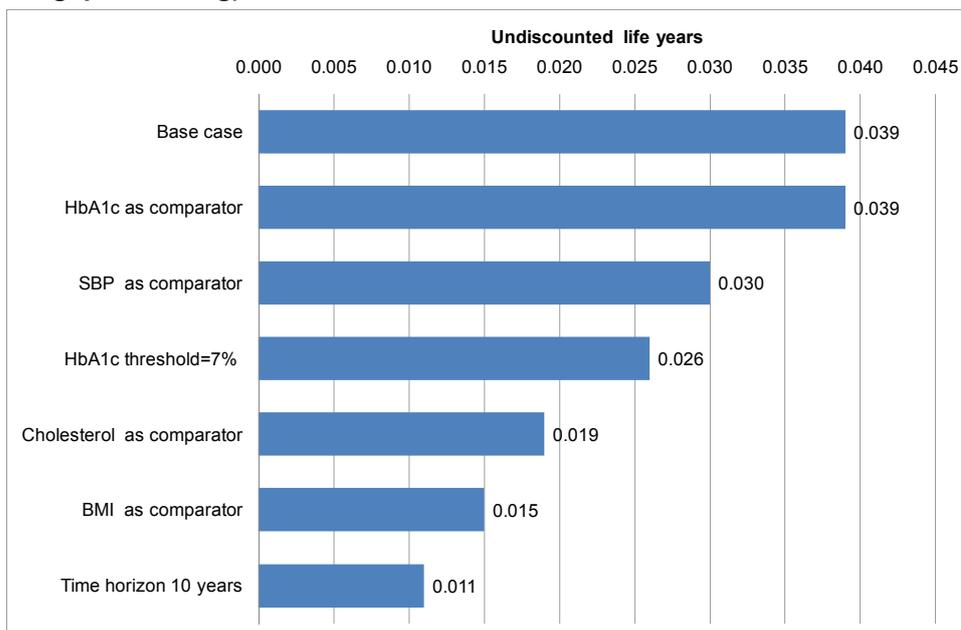
Table 61. predicted life expectancies in canagliflozin 100mg and sitagliptin 100 mg treatments in dual therapy as add-on to metformin

	Canagliflozin 100 mg		Sitagliptin 100mg		Difference, per patient	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
life expectancy (life years)	23.43	23.07-23.78	23.39	23.03-23.75	0.04	0.01-0.07

Source: [table edited from Johnsson & Johnsson submission file 2013]

Results of the sensitivity analyses are presented in the figure below.

Figure 8. Results of the sensitivity analyses of dual therapy (canagliflozin 100 mg vs. sitagliptin 100 mg)



Source: [Johnsson & Johnsson submission file 2013]

Dual therapy (canagliflozin 300 mg vs. sitagliptin 100 mg)

Predicted life expectancies in canagliflozin 300mg and sitagliptin 100 mg treatments in dual therapy as add-on to metformin is presented in the table below.

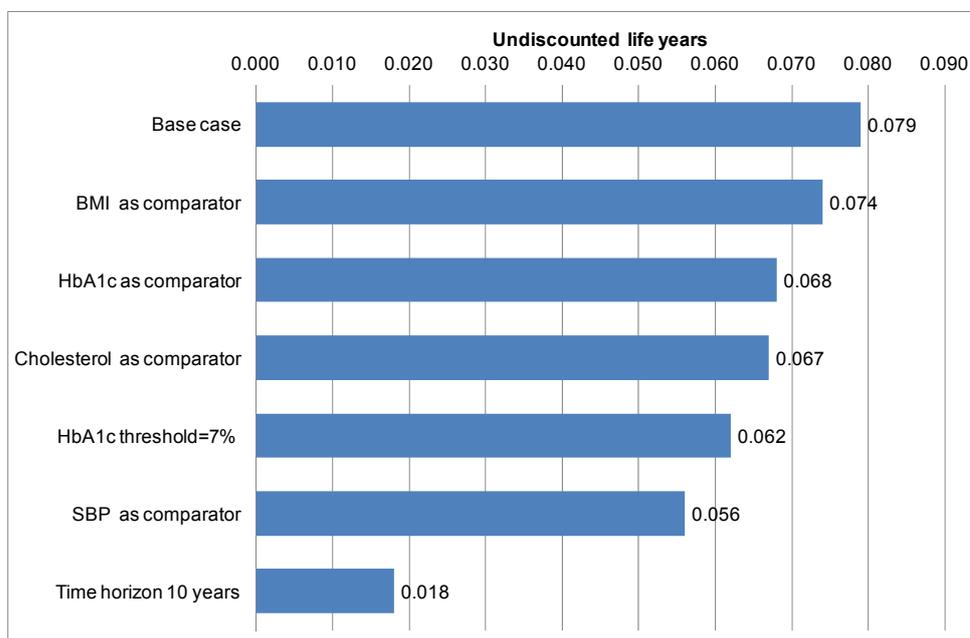
Table 62. Predicted life expectancies in canagliflozin 300mg and sitagliptin 100 mg treatments in dual therapy as add-on to metformin

	Canagliflozin 300 mg		Sitagliptin 100mg		Difference, per patient	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
life expectancy (life years)	23.47	23.11-23.82	23.39	23.03-23.75	0.08	0.05-0.10

Source: [table edited from Johnsson & Johnsson submission file 2013]

Results of the sensitivity analyses are presented below.

Figure 9. Results of the sensitivity analyses for dual therapy (canagliflozin 300 mg vs. sitagliptin 100 mg)



Source: [Johnsson & Johnsson submission file 2013]

Dual therapy (canagliflozin 100 mg vs. glimepiride)

Predicted life expectancies in canagliflozin 100mg and glimepiride treatments in dual therapy as add-on to metformin are presented in the table below.

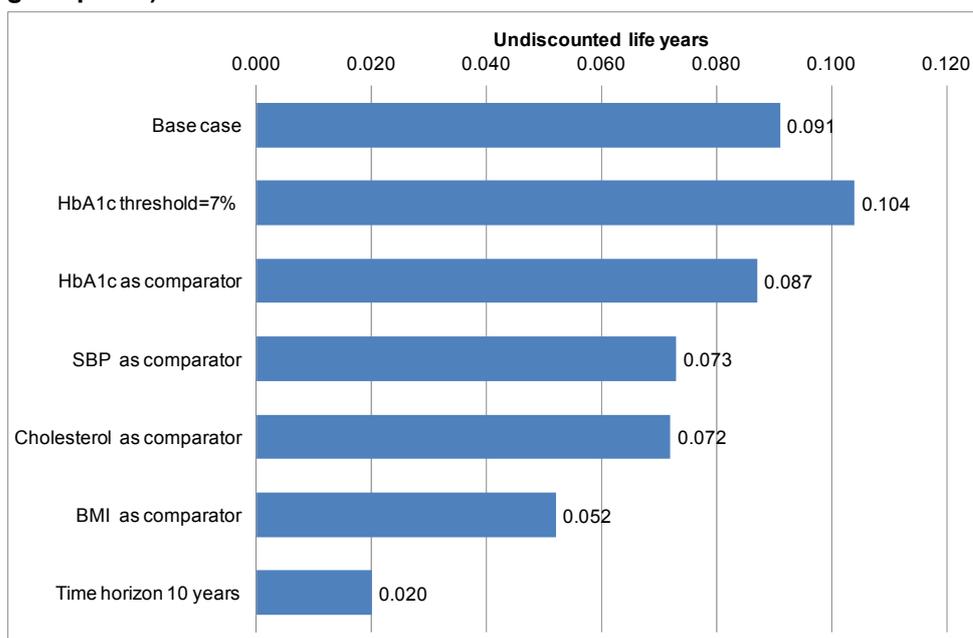
Table 63. Predicted life expectancies in canagliflozin 100mg and glimepiride treatments in dual therapy as add-on to metformin

	Canagliflozin 100 mg		Glimepiride		Difference, per patient	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
life expectancy (life years)	23.16	22.81-23.51	23.07	22.71-23.42	0.09	0.06-0.12

Source: [table edited from Johnsson & Johnsson submission file 2013]

Results of the sensitivity analyses are presented in the figure below.

Figure 10. Results of the sensitivity analyses for dual therapy (canagliflozin 100 mg vs. glimepiride)



Source: [Johnsson & Johnsson submission file 2013]

Dual therapy (canagliflozin 300 mg vs. glimepiride)

Predicted life expectancies in canagliflozin 300mg and glimepiride treatments in dual therapy as add-on to metformin are presented in the table below.

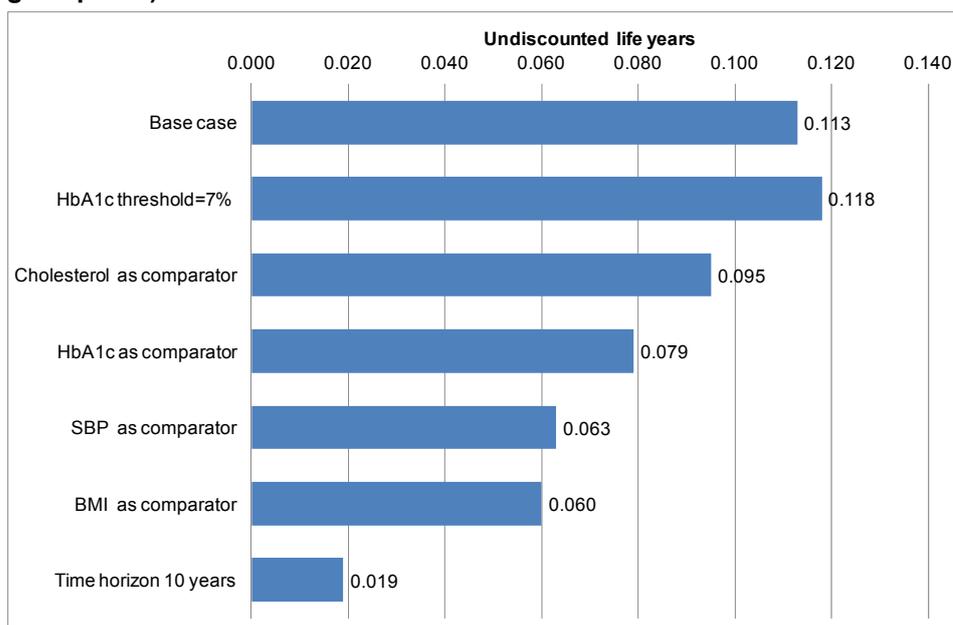
Table 64. Predicted life expectancies in canagliflozin 300mg and glimepiride treatments in dual therapy as add-on to metformin

	Canagliflozin 300 mg		Glimepiride		Difference, per patient	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
life expectancy (life years)	23.18	22.83-23.53	23.07	22.71-23.42	0.11	0.08-0.14

Source: [table edited from Johnsson & Johnsson submission file 2013]

Results of the sensitivity analyses are presented in the figure below.

Figure 11. Results of the sensitivity analyses for dual therapy (canagliflozin 300 mg vs. glimepiride)



Source: [Johnsson & Johnsson submission file 2013]

Triple therapy (canagliflozin 300 mg vs. sitagliptin 100 mg)

Predicted life expectancies in canagliflozin 300mg and sitagliptin 100 mg treatments in triple therapy as add-on to metformin and glimepiride are presented in the table below.

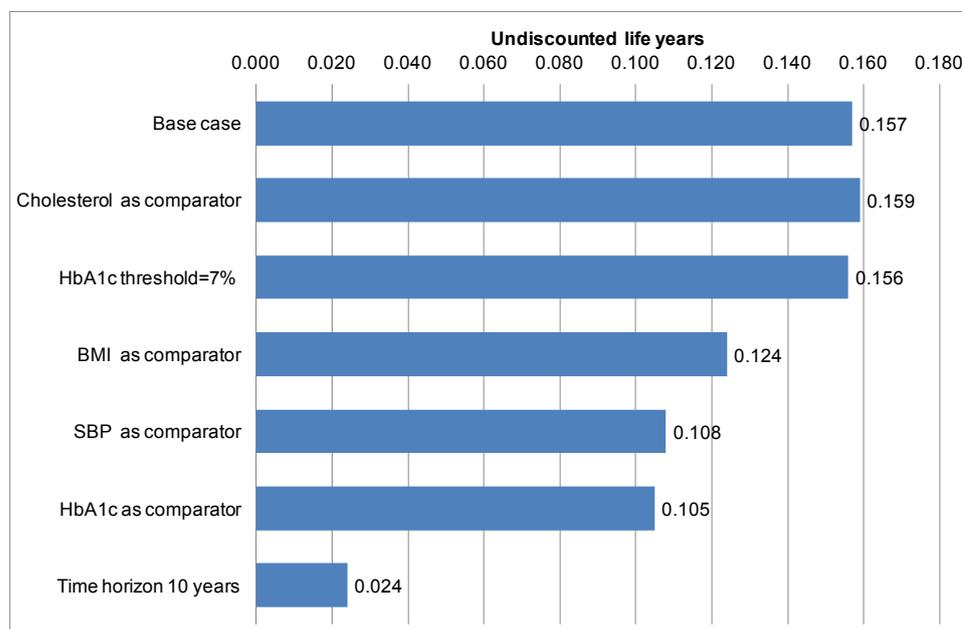
Table 65. Predicted life expectancies in canagliflozin 300mg and sitagliptin 100 mg treatments in triple therapy as add-on to metformin and glimepiride

	Canagliflozin 300 mg		Sitagliptin 100 mg		Difference, per patient	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
life expectancy (life years)	22.55	22.19-22.91	22.39	22.03-22.76	0.16	0.13-0.18

Source: [table edited from Johnsson & Johnsson submission file 2013]

Results of the sensitivity analyses (according to Johnsson & Johnsson submission file 2013):

Figure 12. Results of the sensitivity analyses for triple therapy (canagliflozin 300 mg vs. sitagliptin 100 mg)



Source: [Johnsson & Johnsson submission file 2013]

Discussion

EVIDENCE AND FINDINGS

Evidence of effects on overall mortality can be considered highly important for REA. Overall survival is also one of the most important outcomes considered in HTA. However, to date, there seems to be no conclusive evidence concerning effects of canagliflozin on overall mortality compared to other treatment options. Overall, the duration of studies conducted in the canagliflozin program is too short to provide reliable evidence on the effects on mortality. Further studies (or results) with longer follow-up time are needed to be able to assess the effects of canagliflozin on overall mortality.

SIMULATED/PREDICTED LIFE EXPECTANCY USING CORE DIABETES MODEL

The predictions of life years have been performed with simulations using the CORE diabetes model (Palmer et al. 2004a). The Core Diabetes Model has been validated in terms of operational and predictive validity against epidemiological and clinical studies (Palmer et al. 2004b). Further revalidation studies have been performed recently but the results have not yet been published in scientific literature. Simulated/predicted results concerning life expectancies in different treatment arms were presented. All the results shown were from simulations of comparisons for which direct evidence from clinical trials was available.

In principle the approach taken is supported by the EUnetHTA guidelines in this case, even though there are limitations in transparency. The general limitations of extrapolating intermediate to final endpoints are also described in EUnetHTA guidelines. The specific limitations related to results presented in the MAH submission are discussed below.

Limitations

The simulations/predictions shown in this card demonstrate a minor positive impact (approximately one month) of canagliflozin on life-expectancy. Considering the fact that the

results are based on simulation and demonstrate minor differences in life expectancy between treatments, any strong conclusions based on these results should be avoided.

Secondly, there are well-known limitations in terms of transparency related to Diabetes Core model (see e.g. Cummins et al. 2009). This lack of transparency limits the possibility to thoroughly assess the model quality and the accuracy of the results.

Thirdly, several sensitivity analyses were performed in Johnsson & Johnsson submission file (2013) mostly according to what was requested. However, the approach used for the sensitivity analysis does not fully address the question of parameter uncertainty. Setting a parameter value equal with the comparator in a univariate sensitivity analysis leads to a small change in the outcome (life-expectancy) if the difference between treatments with respect to the particular parameter is small. This approach does not reflect the possible impact of the parameter in general. Results using a shorter time horizon (2 or 5 years; closer to the duration of the actual clinical trials) could have also been useful. The sensitivity analyses with a 10 year time horizon indicate that a shorter time horizon might have a major impact on the results.

Results of simulations in which the clinical inputs (estimates for the treatment effects used in the model) were based partly on network meta-analysis and partly on direct evidence were also presented in the Johnsson & Johnsson submission file (2013). The rationale of this approach was not justified. In addition, the background (sources and methodology of analysis) of the clinical inputs based on network meta-analysis could not be verified. Also the sensitivity analyses were not presented for these simulations. Due to these limitations along with the lack of transparency and tractability, the results of simulations based partly on network meta-analysis were not included into the results section.

References

Cummins C, Royle P, Shyangdan D, et al. Liraglutide for the treatment of type 2 diabetes: a single technology appraisal. Aberdeen HTA Group, 2009. [cited 17 Febr. 2014] Available at: <http://www.nice.org.uk/nicemedia/live/11895/47393/47393.pdf>

Endpoints used in relative effectiveness assessment of pharmaceuticals: Surrogate Endpoints. 2013. [cited 17 Febr. 2014] Available from: <http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Surrogate%20Endpoints.pdf>

Endpoints used in relative effectiveness assessment of pharmaceuticals: Clinical Endpoints. 2013. [cited 17 Febr. 2014] Available from: <http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf>

Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Palmer AJ, Roze S, Valentine WJ, et al. The CORE diabetes model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin* 2004;20 (Suppl 1):S5-26.

Palmer AJ, Roze S, Valentine WJ, et al. Validation of the CORE diabetes model against epidemiological and clinical studies. *Curr Med Res Opin* 2004;20 (Suppl 1):S27-40.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely Partly Not

[D0002]: What is the expected beneficial effect of canagliflozin on mortality due to diabetes-related diseases and conditions?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file of J&J)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

[Johnsson & Johnsson submission file (2013)]:

To date, there have been too few mortality events (n = 48) in the canagliflozin program to make any definitive conclusions regarding overall mortality or cause-specific mortality.

Discussion

There seems to be no conclusive evidence concerning effects of canagliflozin on mortality due to diabetes-related diseases and conditions compared to other treatment options. Overall, the duration of studies conducted in the canagliflozin program is too short to provide reliable evidence on the effects on mortality due to diabetes-related diseases and conditions. Further studies (or results) with longer follow-up time are needed to be able to assess the effects of canagliflozin on mortality due to diabetes-related diseases and conditions.

References

Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005A]: [How does canagliflozin affect the following outcome: HbA1c change]?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

The results are represented as follows:

1. DIRECT EVIDENCE

1.1 Dual Therapy

1.2 Triple Therapy

1.3 Subgroup analyses

2. INDIRECT EVIDENCE

2.1 Dual Therapy

2.2. Triple Therapy

1. DIRECT EVIDENCE

[Johnson & Johnson submission file (2013)]:

1.1. Dual Therapy

1.1.1 Canagliflozin Versus Glimepiride as Add-on to Metformin (DIA3009, 104 weeks, N = 1450)

The mean baseline HbA1c value was 7.8 % in the trial. The results for changes in HbA1c at 52 weeks are shown below. (submission file.):

Table 66. Results for changes in HbA1c at 52 weeks: Canagliflozin Versus Glimepiride as Add-on to Metformin

Parameter ^{a,b}	CANA 100 mg	CANA 300 mg	GLIM
HbA1c change, %	-0.82 (0.04)	-0.93 (0.04)	-0.81 (0.04)
Difference vs. GLIM	-0.01 (-0.11, 0.09) ^c	-0.12 (-0.22, -0.02) ^{c,d}	

Abbreviations: CANA, canagliflozin; GLIM, glimepiride; mITT, modified intent-to-treat; LOCF, last observation carried forward.

^aLeast squares mean (SE) change from baseline using ANCOVA (except for documented hypoglycaemia rate) and GLIM-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only;

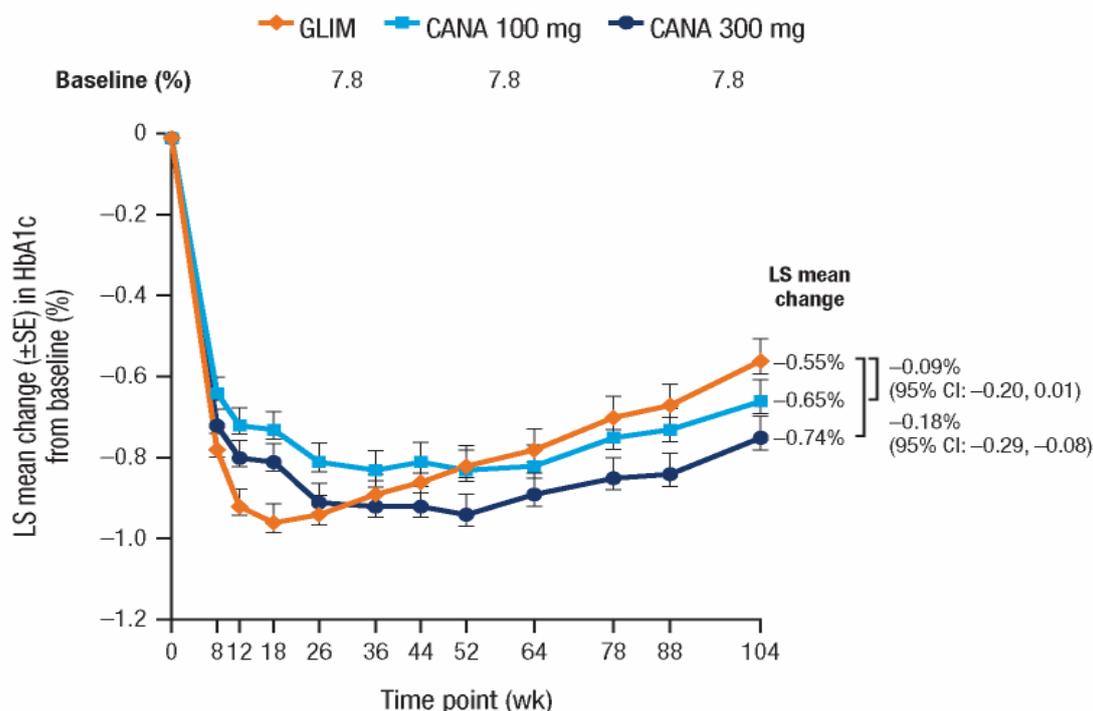
^cUpper limit of 95% CI less than pre-specified non-inferiority margin of 0.3% for the comparison to GLIM;

^dUpper limit of 95% CI <0.0% for the comparison to GLIM

Source: [Johnsson & Johnsson submission file 2013, main document, page 155, table 41, mITT, LOCF, table is modified]

Both canagliflozin doses demonstrated non-inferiority to glimepiride in reducing HbA1c (the upper limit of the 95% CI was less than the pre-specified margin of 0.3%), and canagliflozin 300 mg demonstrated superiority to glimepiride (the upper limit of the 95% CI was less than 0.0%). The LS mean changes from baseline in HbA1c at Week 104 in the mITT analysis were □0.65% and □0.74% for the canagliflozin 100- and 300-mg groups, respectively, and □0.55% for the glimepiride group, with a between-group difference of □0.09% (95% CI: □0.20% to 0.01%) for canagliflozin 100 mg relative to glimepiride and □0.18% (95% CI: □0.29% to □0.08%) for canagliflozin 300 mg relative to glimepiride (see figure 13 below).

Figure 13. Changes in HbA1c from baseline to Week 104 LOCF for DIA3009.



LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

Source: [Johnsson & Johnsson submission file 2013, main document, page 155–156, figure is modified]

1.1.2 Canagliflozin Versus Sitagliptin as Add-on to Metformin (DIA3006, N = 1284, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, 52 weeks)

The mean baseline HbA1c value in the trial was 7.9%. The results for changes in HbA1c at 52 weeks (primary assessment time point) are shown in below.

Table 67. Results for changes in HbA1c at 52 weeks: Canagliflozin Versus Sitagliptin as Add-on to Metformin

Parameter ^{a,b}	CANA 100 mg (n = 368)	CANA 300 mg (n = 367)	SITA 100 mg (n = 366)
A1C change, %	-0.73 (0.05)	-0.88 (0.05)	-0.73 (0.05)
Difference vs. SITA	0.00 (-0.12, 0.12) ^c	-0.15 (-0.27, -0.03) ^{c,d}	

Abbreviations: CANA, canagliflozin; SITA, sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; ANCOVA, analysis of covariance; CI, confidence interval; NS, not significant.

^aLS mean (SE) change from baseline using ANCOVA and SITA-subtracted LS mean (95% CI) for all parameters;

^bP values are reported for pre-specified comparisons only;

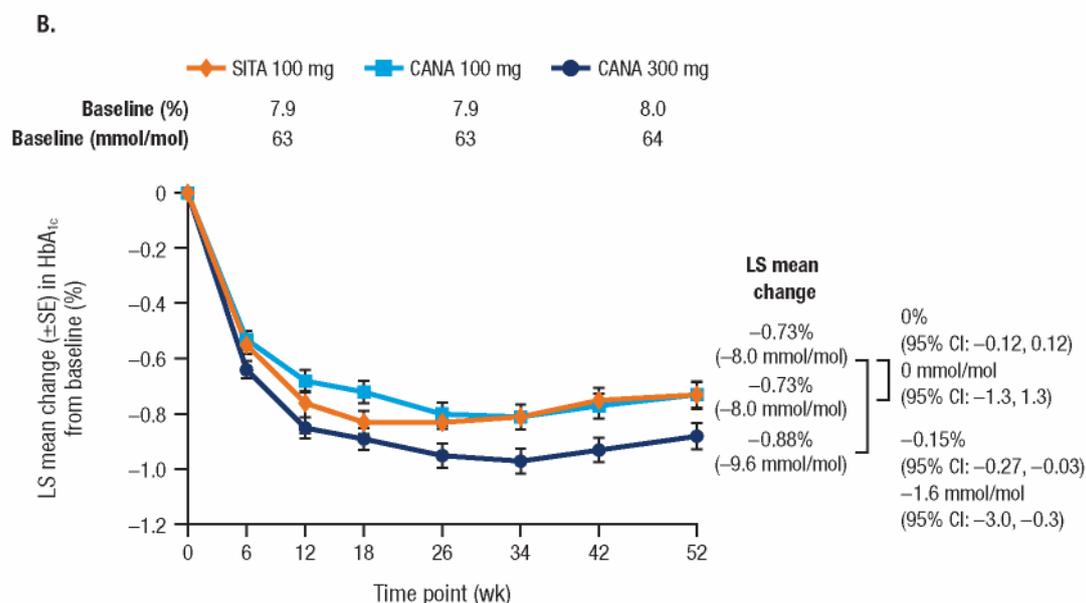
^cUpper limit of 95% CI less than pre-specified non-inferiority margin of 0.3% for the comparison to SITA;

^dUpper limit of 95% CI <0.0% for the comparison to SITA, demonstrating statistical superiority to SITA

Source: [Johnsson & Johnsson submission file 2013, main document, page 170, mITT, LOCF, table is modified]

At 52 weeks, canagliflozin 100 and 300 mg demonstrated non-inferiority to sitagliptin 100 mg in reducing HbA1c (the upper limit of the 95% CI was less than the pre-specified margin of 0.3%), and canagliflozin 300 mg demonstrated superiority to sitagliptin 100 mg (the upper limit of the 95% CI was less than 0.0%; (see Figure 14 below).

Figure 14. Changes in HbA1c (LOCF) from baseline to Week 52 for DIA3006



Abbreviations: LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

Source: [Johnsson & Johnsson submission file 2013, main document, pages 170–171]

1.2 Triple therapy

1.2.1 Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU (DIA3015, N = 755, 52 weeks)

The mean baseline HbA1c value in the trial was 8.1%. The results for change in HbA1c at 52 weeks (primary assessment time point) is shown in below.

Table 68. Results for changes in HbA1c at 52 weeks: Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU

Parameter ^{a,b}	CANA 300 mg (N = 377)	SITA 100 mg (N = 378)
HbA _{1c} change, %	-1.03 (0.05)	-0.66 (0.05)
<i>Difference vs. SITA</i>	-0.37 (-0.50, -0.25) ^{c,d}	

Abbreviations: CANA, canagliflozin; SITA, sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; SE, standard error; CI, confidence interval; ANCOVA, analysis of covariance; NS, not significant.

^aLeast squares mean (SE) change from baseline using ANCOVA and SITA-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only;

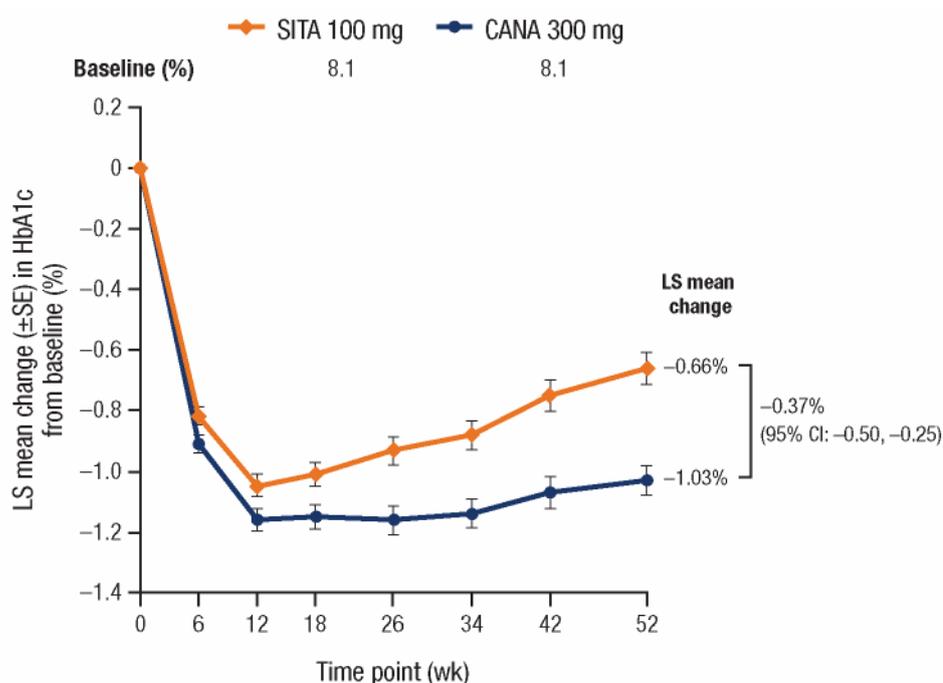
^cUpper limit of 95% CI less than pre-specified non-inferiority margin of 0.3% for the comparison to SITA;

^dUpper limit of 95% CI <0.0% for the comparison to SITA

Source: [Johnsson & Johnsson submission file 2013, main document, page 180, table 43, mITT, LOCF, table is modified]

Canagliflozincanagliflozin 300 mg demonstrated non-inferiority (the upper limit of the 95% CI was less than the pre-specified margin of 0.3%) as well as superiority (the upper limit of the 95% CI was less than 0.0%) to sitagliptin 100 mg in reducing HbA1c at 52 weeks (see table 68 above and figure 15 below).

Figure 15. Change in HbA1c from baseline to Week 52 (LOCF) for DIA3015



LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.

Source: [Johnsson & Johnsson submission file 2013 main document, page 180]

1.3. Subgroup Analyses

Authors' note: In the submission file (main document), subgroup analyses were reported. These included stratified analyses by age (<65 years/≥65 years), gender, BMI (<30/≥30 kg/m²), HbA_{1c} at baseline (<8/8%-<9/≥9%) and eGFR at baseline (<90/≥90 mL/min/1.73 m²). Originally, in depth analyses of the sub-populations a) age over 75 and b) renal impairment – eGFR 45 to 60 mL/min/1.73m² (or CrCl 45 to 60 mL/min), c) high cardiovascular risk, d) hepatic impairment, and e) paediatric less than 18 years were recommended. Results and conclusions related to these predefined subgroups are not available for relative effectiveness assessment. In MAH submission file, the following conclusions were drawn.

[Johnson & Johnson submission file (2013)]:

Univariate analyses

In the descriptive univariate analyses of HbA1c stratified by baseline characteristics, the largest differences in HbA1c reduction are observed between subgroups based on HbA1c (<8/8%-<9/≥9%), with higher reduction in the subgroups with higher baseline values, consistent across treatments and trials (DIA3009, DIA3006 and DIA3015). Differences between strata based on age and gender are much smaller, and not consistent across trials and trial arms. Patterns for eGFR-based subgroups look similar in all canagliflozin arms, suggesting better HbA1c reduction in the 90+ subgroup, while inverse in the glimepiride and sitagliptin arms. Patterns based on BMI stratification are less clear, but suggest reduced efficacy in the high BMI subgroups for sitagliptin. (main document, pages 189–192)

Multivariate analyses

In DIA3009: the relative efficacy of canagliflozin (both 100 and 300 mg) versus glimepiride is independent of baseline HbA1c and BMI, and increases with better renal functioning.

In DIA3006 and DIA3015: the results suggest that the relative efficacy of canagliflozin (100 and 300 mg) versus sitagliptin increases with baseline HbA1c and BMI in both dual (MET) as triple therapy (MET + SU), and additionally increases with eGFR in dual therapy.

2. Indirect Evidence

Authors' note for interpretation (edited from Johnson & Johnson submission file (2013)):

The indirect comparisons were based on network meta-analyses. For methodological details, see Appendix 1: Methods. Pairwise comparisons of the relative treatment effect for both canagliflozin doses versus all other comparators are presented as median estimates [95% CrI] (negative values interpreted as higher reduction for canagliflozin) and as probabilities of canagliflozin being more effective than the comparator on the endpoint of interest (columns with "Prob" heading). Tables are ranked by SUCRA values, with treatments with the highest probability of being most effective at the top.

[Johnson & Johnson submission file (2013)]:

2.1 Dual Therapy (Metformin Add-on): HbA1c Mean Reduction

Relative treatment effect versus placebo and pairwise comparison of canagliflozin 100/300 mg versus all other comparators at week 26, 52 and 104 are shown in the following tables. 52-week results are based on a reduced network, due to inconsistency in the larger network between direct and indirect evidence on comparison of canagliflozin 100/300 mg vs. sitagliptin.

Table 69. Base case analysis – Results of the RE model for the mean difference in HbA1c for canagliflozin versus active comparators, metformin background at 26 weeks

	Canagliflozin 100mg			Canagliflozin 300mg			SUCRA
	Median	CrI95%	Prob	Median	CrI95%	Prob	
Exenatide 2mg QWK	0.61	[-0.10 ; 1.32]	4%	0.49	[-0.22 ; 1.20]	8%	91%
Liraglutide 1.8mg QD	0.45	[-0.08 ; 0.97]	4%	0.33	[-0.20 ; 0.85]	10%	86%
Liraglutide 1.2mg QD	0.30	[-0.23 ; 0.82]	12%	0.17	[-0.35 ; 0.70]	24%	74%
Pioglitazone 45mg QD	0.31	[-0.41 ; 1.04]	19%	0.19	[-0.53 ; 0.91]	30%	71%
Exenatide 10µg BID	0.20	[-0.47 ; 0.87]	27%	0.08	[-0.59 ; 0.75]	41%	63%
Glimepiride	0.17	[-0.23 ; 0.57]	19%	0.05	[-0.35 ; 0.45]	40%	63%
Pioglitazone 30mg QD	0.14	[-0.35 ; 0.65]	28%	0.01	[-0.48 ; 0.53]	48%	58%

	Canagliflozin 100mg			Canagliflozin 300mg			SUCRA
	Median	CrI95%	Prob	Median	CrI95%	Prob	
Canagliflozin 300mg QD	0.12	[-0.26 ; 0.51]	25%	-			56%
Sitagliptin 100mg QD	0.01	[-0.38 ; 0.41]	48%	-0.11	[-0.50 ; 0.28]	73%	42%
Canagliflozin 100mg QD						75%	41%
Linagliptin 5mg QD	-0.03	[-0.72 ; 0.65]	53%	-0.15	[-0.84 ; 0.52]	68%	41%
Saxagliptin 5mg QD	-0.06	[-0.62 ; 0.50]	59%	-0.18	[-0.75 ; 0.38]	75%	36%
Vildagliptin 100mg QD	-0.09	[-0.56 ; 0.40]	64%	-0.21	[-0.69 ; 0.28]	82%	32%
Exenatide 5µg BID	-0.18	[-0.89 ; 0.53]	70%	-0.31	[-1.02 ; 0.41]	81%	27%
Dapagliflozin 10mg QD	-0.26	[-0.82 ; 0.30]	83%	-0.38	[-0.94 ; 0.18]	92%	19%
Placebo	-0.67	[-1.06 ; -0.28]	100%	-0.79	[-1.19 ; -0.40]	100%	1%

Source: [Johnson & Johnson submission file (2013)]

Table 70. Base case analysis – Results of the RE model for the mean difference in HbA1c for canagliflozin versus active comparators, metformin background at 52 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Liraglutide 1.8mg QD	0.65	[-0.29 ; 1.59]	5%	0.52	[-0.42 ; 1.46]	8%	93%
Liraglutide 1.2mg QD	0.43	[-0.51 ; 1.38]	10%	0.30	[-0.64 ; 1.24]	16%	83%
Canagliflozin 300mg QD	0.13	[-0.37 ; 0.63]	18%				65%
Pioglitazone 30mg QD	0.08	[-0.62 ; 1.04]	38%	-0.05	[-0.74 ; 0.91]	58%	58%
Exenatide 10µg BID	0.10	[-0.82 ; 0.82]	36%	-0.03	[-0.95 ; 0.69]	56%	58%
Glipizide	0.02	[-0.91 ; 0.96]	47%	-0.11	[-1.04 ; 0.83]	68%	49%
Dapagliflozin 10mg QD	0.02	[-1.14 ; 1.20]	47%	-0.11	[-1.28 ; 1.07]	65%	49%
Sitagliptin 100mg QD	0.02	[-0.58 ; 0.62]	45%	-0.11	[-0.72 ; 0.49]	75%	49%
Canagliflozin 100mg						82%	46%
Glimepiride	-0.03	[-0.62 ; 0.57]	58%	-0.16	[-0.75 ; 0.45]	82%	43%
Gliclazide	-0.05	[-1.03 ; 1.03]	58%	-0.18	[-1.16 ; 0.90]	74%	42%
Saxagliptin 5mg QD	-0.04	[-1.22 ; 1.13]	57%	-0.17	[-1.34 ; 1.00]	72%	42%
Glibenclamide	-0.12	[-1.14 ; 0.89]	64%	-0.25	[-1.27 ; 0.77]	75%	37%
Vildagliptin 100mg QD	-0.09	[-0.78 ; 0.69]	68%	-0.22	[-0.91 ; 0.56]	83%	34%
Placebo	-0.62	[-1.37 ; 0.07]	97%	-0.75	[-1.50 ; -0.06]	98%	4%

Source: [Johnson & Johnson submission file (2013)]

Table 71. Base case analysis – Results of the FE model for the mean difference in HbA1c for canagliflozin versus active comparators, metformin background at 104 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Canagliflozin 300	0.09	[-0.03 ; 0.21]	7%				94%
Canagliflozin 100						93%	75%
Lira 1.8	-0.02	[-0.28 ; 0.23]	56%	-0.11	[-0.36 ; 0.14]	80%	69%
Lira 1.2	-0.04	[-0.29 ; 0.21]	62%	-0.13	[-0.38 ; 0.12]	85%	64%

	Canagliflozin 100mg			Prob	Canagliflozin 300 mg			SUCRA
	Median	CrI			Median	CrI	Prob	
Vilda 100	-0.10	[-0.22 ; 0.02]		95%	-0.19	[-0.31 ; -0.07]	100%	46%
SU	-0.10	[-0.22 ; 0.02]		96%	-0.19	[-0.31 ; -0.07]	100%	46%
Sita 100	-0.12	[-0.29 ; 0.05]		91%	-0.21	[-0.38 ; -0.04]	99%	42%
Lina 5	-0.30	[-0.44 ; -0.16]		100%	-0.39	[-0.54 ; -0.24]	100%	13%

Source: [Johnson & Johnson submission file (2013)]

2.2 Triple Therapy (Metformin + SU Add-on): HbA1c Change From Baseline, 26 week results

Relative treatment effect versus placebo and pairwise comparison of canagliflozin 100/300 mg versus all other comparators are shown in the following table. For the metformin + SU add-on setting, results are limited to 26-week results, as no networks of evidence could be constructed for later time points due to the lack of published trial evidence.

Table 72. Sensitivity analysis inconsistency– Results of the FE model for the mean difference in HbA1c for canagliflozin versus active comparators, metformin+sulphonylurea background

	Canagliflozin 100mg			Prob	Canagliflozin 300 mg			SUCRA
	Median	CrI			Median	CrI	Prob	
Liraglutide 1.8mg QD	0.33	[-0.01 ; 0.67]		3%	0.08	[-0.24 ; 0.40]	31%	87%
Biphasic insulin	0.28	[-0.09 ; 0.66]		7%	0.03	[-0.32 ; 0.40]	43%	81%
Canagliflozin 300mg QD	0.25	[0.05 ; 0.45]		1%				78%
Exenatide 10µgBID	0.24	[-0.05 ; 0.52]		5%	-0.01	[-0.27 ; 0.25]	53%	76%
Long-acting insulin	0.09	[-0.25 ; 0.43]		30%	-0.16	[-0.48 ; 0.16]	84%	48%
Sitagliptin 100mg QD	0.04	[-0.17 ; 0.26]		33%	-0.21	[-0.31 ; -0.10]	100%	42%
Exenatide 5µgBID	0.02	[-0.26 ; 0.30]		44%	-0.23	[-0.48 ; 0.02]	96%	38%
Canagliflozin 100mg							99%	35%
Linagliptin 5mg QD	-0.14	[-0.37 ; 0.09]		88%	-0.39	[-0.59 ; -0.19]	100%	15%
Placebo	-0.76	[-0.96 ; -0.56]			-1.01	[-1.17 ; -0.85]		0%

Source: [Johnson & Johnson submission file (2013)]

Discussion

General notes

The change in glycosylated haemoglobin was the primary outcome in all relevant comparative trials assessing the clinical effects of canagliflozin. Glycosylated haemoglobin, HbA1c, is an established parameter in diagnosing and treating diabetes mellitus. This is a form of haemoglobin that reflects the average plasma glucose concentration over time. Normal levels of glucose result in normal levels of HbA1c (4–6%), but an increase in plasma glucose induces an increase in HbA1c. The level of HbA1c does not reveal the pattern of the glucose concentrations. A similar HbA1c level can be the result of constantly normal glucose levels or levels that are intermittently high and low. There is biological variation among individuals in the glycosylation rate of haemoglobin. Furthermore, blood loss, transfusions, anaemia, and high erythrocyte turnover in i.e. chronic renal disease, interfere with HbA1c levels. The HbA1c level is proportional to average blood glucose concentration over previous one to three months. A similar level of HbA1c can be associated with a very different treatment balance between different individuals.

As discussed above, the use of HbA1c as a primary outcome measure in diabetes trials is associated with limitations and uncertainties. However, the risk of microvascular and macrovascular complications is related to glycaemia, as measured by HbA1c (Inzucchi et al 2012, Coca et al 2012). In recent meta-analyses, however, the expectations concerning the long-term benefits of lowering HbA1c or blood glucose load have been challenged (Turnbull et al 2009, Coca et al 2012, Boussageon et al 2011, Hemmingsen et al 2011).

The study patients were allowed to use other antidiabetic medicines besides the study drugs. Initiations of non-study antidiabetic drugs or modifications of non-study or study anti-diabetic drugs were reported in 4.3–5.6% (most of these initiations, with no clear difference between study groups in incidence) of study participants in DIA3009, in 6.5–7.6% in DIA3006 (most of these were initiations, no clear difference between study groups in incidence), and in 13.0–15.9% in DIA3015 (most being modifications, no clear difference between study groups in incidence) (submission file, appendix 17). The dosages of the additional AHAs are not reported, and therefore the effect of non-study antidiabetic medication cannot be addressed reliably. Furthermore, HbA1c is influenced by multiple factors including other medications, nutrition and also physical activity. The assessment of the independent comparative effect of canagliflozin on HbA1c is challenged by these limitations.

The laboratory methods used for HbA1c measurements have not been reported. It is plausible that the same methods have been used in different trial arms, and so it is not expected that the laboratory method itself bears a crucial role in the comparative efficacy of the trial drugs.

Direct evidence

In the three relevant trials, the mean HbA1c value at baseline was approximately 8.0%.

As an add-on therapy with metformin, and compared with glimepiride, canagliflozin 100 mg produced similar changes in HbA1c levels at 52 weeks. Canagliflozin 300 mg induced a greater reduction in HbA1c levels compared with glimepiride. On average, the difference between canagliflozin and glimepiride arm was small, 0.12 %. At 2 years, the results were quite similar, with a difference of 0.18 % between canagliflozin 300 mg and glimepiride.

In DIA3006, added on metformin, and compared with sitagliptin 100 mg, the results were rather similar as in comparison with glimepiride. Canagliflozin 100 mg was comparable with sitagliptin 100 mg, whereas canagliflozin 300 mg induced a greater decrease in HbA1c, where the difference between sitagliptin and canagliflozin was 0.15% at 52 weeks. In DIA3015, where canagliflozin 300 mg and sitagliptin 100 mg were added on metformin and sulphonylurea, canagliflozin induced greater decrease in HbA1c values than sitagliptin, the difference being on average 0.37%.

The authors recommended several subgroup analyses. Data for these analyses were not available. According to the multivariate subgroup analyses presented, factors modifying the effect of canagliflozin on HbA1c values, compared with glimepiride or sitagliptin, include estimated glomerular filtration rate, where canagliflozin seemed to induce smaller decreases in subjects with eGFR less than 90 ml/min/1.73m² compared with subjects with eGFR of 90 ml/min/1.73m² or more, whereas in glimepiride and in sitagliptin treatment the reduction in HbA1c was greater in subjects with worse renal function in dual therapy trials. This finding is in line with the known pharmacokinetics of glimepiride and sitagliptin. In both dual and triple therapy, the HbA1c reduction related to canagliflozin (either dose) is independent of BMI, while increasing BMI seemed to decrease the effect of sitagliptin on HbA1c. Baseline HbA1c level seemed not to be an effect modifying factor in comparison between canagliflozin and glimepiride (in dual therapy, DIA03009). On the contrary, in comparison with sitagliptin (DIA3006, DIA3015), baseline HbA1c seemed to modify the comparative effect of canagliflozin.

In DIA3004 the add-on use of canagliflozin in subjects with moderate renal impairment (glomerular filtration rate of 30–49 mL/min/1.73 m²) was investigated. This trial was placebo-controlled, and therefore out of scope of this assessment.

In conclusion, canagliflozin as an add-on therapy was at least as effective as glimepiride or sitagliptin 100 mg in reducing HbA1c values, and canagliflozin 300 mg seemed to be able to induce even greater decreases than the comparators in direct comparisons. The between-

treatment differences were less than 0.5%, and the clinical importance of these differences remain unclear. There are also other limitations to the results of the trials, such as concomitant therapies and life-style factors. The risk of bias was evaluated as high and the quality (level) of evidence as moderate regarding HbA1c change.

Indirect evidence

The results represented in the results section indicate the following.

Dual therapy:

- At 26 weeks no obvious differences between canagliflozin 100/300 mg and other active treatments can be found. This is due to imprecise estimates (large credibility intervals) and rather small differences between the treatments.
- At 52 weeks the results suggest that
 - liraglutide 1.2 mg and 1.8 mg might be more effective than canagliflozin 100/300 mg in terms of reducing HbA1c
 - canagliflozin 300 mg might be more effective than canagliflozin 100 mg, sitagliptin 100 mg and saxagliptin 5 mg
- At 104 weeks the results suggest that
 - Canagliflozin 100 mg might be more effective than linagliptin 5 mg
 - Canagliflozin 300 mg might be more effective than vildagliptin 50 mg, SU (glimepiride), sitagliptin 100 mg and linagliptin 5 mg

Triple therapy: At 26 weeks the results suggest that canagliflozin 300 mg might be more effective than canagliflozin 100 mg and linagliptin 5 mg.

Overall, there are well known limitations related to the indirect comparisons (see e.g. EUnetHTA guideline: Comparator and comparisons). As a consequence, the quality of such evidence is very low. Further discussion on methodological issues related to indirect comparisons is found in the Appendix 1: Methods.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005B]: [How does canagliflozin affect the following outcome: proportion achieving < 7% HbA1c target?]

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

The results are represented as follows:

1. DIRECT EVIDENCE

1.1 Dual Therapy

1.2 Triple Therapy

2. INDIRECT EVIDENCE

2.1 Dual Therapy

2.2. Triple Therapy

1. Direct evidence

[Johnson & Johnson submission file (2013)]:

Dual Therapy

1.1.1 DIA3009 (Canagliflozin Versus Glimpiride as Add-on to Metformin, 104 weeks, N = 1450):

The mean HbA1c at baseline was 7.8%. A similar proportion of subjects treated with glimepiride (n = 474), canagliflozin 100 mg (n = 478), or canagliflozin 300 mg (n = 474) achieved the HbA1c goal of <7.0% (<53 mmol/mol) at 52 weeks (55.7%, 53.6%, and 60.1%, respectively) and at 104 weeks (43.9%, 42.5%, and 50.2%, respectively).

Table 73. Patients that achieved the HbA1c goal of <7.0% (Canagliflozin Versus Glimpiride as Add-on to Metformin)

Effect estimate per comparison	% to goal (HbA1c <7%)	Comparison groups	CANAGLIFLOZIN 100 mg vs GLIMIPIRIDE	CANAGLIFLOZIN 300 mg vs GLIMIPIRIDE
		Odds ratio	0.9	1.3
		95% CI	0.7; 1.2	1.0; 1.7

Source: [Johnson & Johnson submission file (2013), Appendix 9, table is modified, week 104]:

1.1.2 DIA3006 (Canagliflozin Versus Sitagliptin as Add-on to Metformin, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, N = 1284):

The mean HbA1c value at baseline was 7.9%. A greater proportion of subjects achieved HbA1c <7.0% (<53 mmol/mol) at 52 weeks with canagliflozin 300 mg (54.7%) compared with sitagliptin 100 mg (50.6%) or canagliflozin 100 mg (41.4%).

Table 74. Patients that achieved the HbA1c goal of <7.0% (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

Effect estimate per comparison	% to goal (HbA1c <7%)	Comparison groups	CANA 100 mg vs SITA 100 mg	CANA 300 mg vs SITA 100 mg
		Odds ratio	0.7	1.3
		95% CI	0.5; 0.9	0.9; 1.8

Abbreviations: CANA, canagliflozin, SITA, sitagliptin;

Source: [Johnson & Johnson submission file (2013), Appendix 9, table is modified, week 52]

1.2 Triple Therapy

1.2.1 DIA3015 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU, 52 weeks, N = 755):

The mean HbA1c value at baseline was 8.1%. A greater proportion of subjects treated with canagliflozin 300 mg versus sitagliptin 100 mg achieved HbA1c <7.0% (<53 mmol/mol) (47.6% vs. 35.3%, respectively).

2. Indirect evidence

Authors' note for interpretation (edited from Johnson & Johnson submission file (2013)):

The indirect comparisons were based on network meta-analyses. For methodological details, see Appendix 1: Methods. Pairwise comparisons of the relative treatment effect for both canagliflozin doses versus all other comparators are presented as odds ratios [95% CrI] in proportion of patients reaching HbA1c<7% for canagliflozin versus active comparators (OR values below 1 are considered as smaller probability of reaching HbA1c<7% with canagliflozin. In other words, canagliflozin is less effective than the comparator) and as probabilities of canagliflozin being more effective than the comparator on the endpoint of interest (columns with "Prob" heading). Tables

are ranked by SUCRA values, with treatments with the highest probability of being most effective at the top.

2.1 Dual therapy, 26, 52 and 104 weeks

Table 75. Base case analysis - Results of RE model for OR in proportion of patients reaching HbA1c<7% for canagliflozin versus active comparators, metformin background at 26 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300mg		Prob	SUCRA
	Median	CrI		Median	CrI		
Exenatide 2mg QWK	0.25	[0.08 ; 0.76]	1%	0.33	[0.10 ; 1.03]	3%	94%
Liraglutide 1.8mg QD	0.32	[0.14 ; 0.72]	1%	0.42	[0.18 ; 0.97]	2%	90%
Liraglutide 1.2mg QD	0.47	[0.20 ; 1.07]	3%	0.62	[0.27 ; 1.43]	11%	75%
Pioglitazone 45mg QD	0.46	[0.14 ; 1.42]	8%	0.61	[0.19 ; 1.90]	17%	74%
Exenatide 10µgBID	0.50	[0.14 ; 1.75]	13%	0.67	[0.19 ; 2.34]	26%	71%
Glimepiride	0.61	[0.31 ; 1.14]	5%	0.81	[0.42 ; 1.53]	22%	64%
Canagliflozin 300mg QD	0.75	[0.40 ; 1.39]	15%				51%
Linagliptin 5mg QD	0.81	[0.24 ; 2.66]	35%	1.08	[0.32 ; 3.57]	56%	48%
Sitagliptin 100mg QD	0.81	[0.42 ; 1.51]	22%	1.08	[0.56 ; 2.01]	61%	46%
Pioglitazone 30mg QD	0.95	[0.22 ; 4.19]	47%	1.26	[0.30 ; 5.61]	64%	41%
Exenatide 5µgBID	0.91	[0.26 ; 3.21]	47%	1.21	[0.34 ; 4.27]	65%	41%
Canagliflozin 100mg						85%	34%
Saxagliptin 5mg QD	1.10	[0.43 ; 2.76]	58%	1.46	[0.57 ; 3.69]	81%	31%
Dapagliflozin 10mg QD	1.49	[0.46 ; 4.88]	75%	1.98	[0.61 ; 6.52]	88%	20%
Vildagliptin 100mg QD	1.45	[0.46 ; 4.68]	76%	1.93	[0.61 ; 6.26]	89%	20%
Placebo	2.93	[1.52 ; 5.76]	100%	3.90	[2.02 ; 7.72]	100%	1%

Source: [Johnson & Johnson submission file (2013)]

Table 76. Base case analysis - Results of FE model for OR in percent of patients reaching HbA1c<7% for canagliflozin versus active comparators, metformin background at 52 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300mg		Prob	SUCRA
	Median	CrI		Median	CrI		
Liraglutide 1.8mg QD	0.17	[0.10 ; 0.27]	0%	0.24	[0.15 ; 0.39]	0%	100%
Liraglutide 1.2mg QD	0.29	[0.18 ; 0.46]	0%	0.41	[0.25 ; 0.66]	0%	90%
Canagliflozin 300mg QD	0.70	[0.58 ; 0.85]	0%				75%
Sitagliptin 100mg QD	0.79	[0.60 ; 1.03]	4%	1.12	[0.86 ; 1.46]	79%	62%
Gliclazide	0.83	[0.56 ; 1.24]	18%	1.19	[0.80 ; 1.77]	80%	53%
Glimepiride	0.88	[0.69 ; 1.12]	14%	1.25	[0.98 ; 1.59]	97%	47%
Glipizide	0.93	[0.65 ; 1.32]	34%	1.33	[0.93 ; 1.88]	94%	39%
Vildagliptin 100mg QD	0.93	[0.69 ; 1.26]	31%	1.32	[0.98 ; 1.78]	97%	37%
Canagliflozin 100mg QD						100%	27%
Saxagliptin 5mg QD	1.15	[0.73 ; 1.79]	73%	1.64	[1.05 ; 2.55]	98%	18%

	Canagliflozin 100mg			Canagliflozin 300mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Glibenclamide	1.95	[0.95 ; 4.11]	97%	2.79	[1.36 ; 5.81]	100%	2%

Source: [Johnson & Johnson submission file (2013)]

Table 77. Base case analysis - Results of FE model for OR of proportion of patients reaching HbA1c<7% for canagliflozin versus active comparators, metformin background at 104 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Lira 1.8	0.65	[0.40 ; 1.05]	4%	0.88	[0.55 ; 1.43]	31%	88%
Lira 1.2	0.68	[0.42 ; 1.10]	6%	0.93	[0.57 ; 1.50]	38%	84%
CANA 300	0.73	[0.57 ; 0.94]	1%			99%	80%
Sita 100	0.83	[0.58 ; 1.18]	15%	1.14	[0.81 ; 1.61]	76%	64%
SU	0.94	[0.73 ; 1.22]	33%	1.29	[1.00 ; 1.67]	97%	46%
CANA 100							36%
Vilda 100	1.00	[0.74 ; 1.35]	50%	1.37	[1.02 ; 1.84]	98%	34%
Lina 5	1.16	[0.82 ; 1.61]	80%	1.58	[1.13 ; 2.22]	100%	18%
Placebo	2.46	[1.24 ; 5.17]	100%	3.37	[1.71 ; 7.14]	100%	0%

Source: [Johnson & Johnson submission file (2013)]

2.2 Triple therapy, 26 weeks

Table 78. Base case analysis - Results of FE model for OR of the proportion of patients reaching HbA1c<7% for canagliflozin versus active comparators, metformin+sulphonylurea background

	Canagliflozin 100mg			Canagliflozin 300mg			SUCRA
	Median	CrI95%	Prob	Median	CrI95%	Prob	
Biphasic insulin	0.52	[0.23 ; 1.16]	6%	0.94	[0.43 ; 2.06]	44%	89%
Canagliflozin 300mg QD	0.55	[0.35 ; 0.86]	0%				85%
Long-acting insulin	0.62	[0.28 ; 1.36]	12%	1.13	[0.53 ; 2.41]	63%	73%
Sitagliptin 100mg QD	0.76	[0.45 ; 1.27]	15%	1.38	[1.05 ; 1.82]	99%	55%
Exenatide 10µgBID	0.79	[0.38 ; 1.62]	27%	1.44	[0.71 ; 2.88]	84%	50%
Linagliptin 5mg QD	0.89	[0.43 ; 1.79]	36%	1.61	[0.81 ; 3.18]	91%	43%
Canagliflozin 100mg						100%	32%
Exenatide 5µgBID	1.11	[0.53 ; 2.29]	61%	2.01	[0.99 ; 4.05]	97%	24%
Placebo	4.23	[2.54 ; 7.19]	100%	7.67	[4.76 ; 12.70]	100%	0%

Source: [Johnson & Johnson submission file (2013)]

Discussion

DIRECT EVIDENCE

The HbA1c treatment target (<7.0%) used in the relevant trials, DIA3009, DIA3006 and DIA3015, is in line with the current recommendations of the American Diabetes Association and the European Association for the Study of Diabetes. They recommend lowering HbA1c to < 7.0% in most patients to reduce the incidence of microvascular disease (Inzucchi et al 2012).

The mean HbA1c value at baseline was 7.8–8.1% in the relevant trials. There were no major differences between canagliflozin (either dose) and glimepiride in their ability to result in HbA1c target achievement when added on metformin at 1 or at 2 years. When canagliflozin 300 mg was compared with sitagliptin 100 mg and added on metformin, a similar proportion of trial patients achieved the treatment goal (55% and 51%, respectively). When added on both metformin and sulphonylurea, HbA1c target was reached somewhat more often in canagliflozin treatment compared with sitagliptin treatment.

The study patients were allowed to use other antidiabetic medicines besides the study drugs. Initiations of non-study antidiabetic drugs or modifications of non-study or study anti-diabetic drugs were reported in 4.3–5.6% (most of these initiations, with no clear difference between study groups in incidence) of study participants in DIA3009, in 6.5–7.6% in DIA3006 (most of these were initiations, no clear difference between study groups in incidence), and in 13.0–15.9% in DIA3015 (most being modifications, no clear difference between study groups in incidence) (submission file, appendix 17). The dosages of the additional AHAs are not reported, and therefore the effect of non-study antidiabetic medication cannot be addressed reliably. Furthermore, HbA1c is influenced by multiple factors including other medications, nutrition and also physical activity. The assessment of the independent comparative effect of canagliflozin on HbA1c is challenged by these limitations.

In conclusion, canagliflozin 100 mg or 300 mg treatment, as added on metformin treatment, was associated with similar proportions of participants achieving the HbA1c target during the trial compared with glimepiride and sitagliptin 100 mg (the latter with canagliflozin 300 mg only). Added on metformin-sulphonylurea combination, canagliflozin 300 mg seemed to be associated with a greater proportion of participants achieving the HbA1c target compared with sitagliptin. However, the available data do not enable comprehensive assessment of the comparative ability of canagliflozin to induce achieving HbA1c target. Trials with restrictions concerning other antidiabetic medicines are needed.

The laboratory method for measuring HbA1c has not been reported. It is plausible that the same laboratory method has been used in relevant treatment arms. It is not expected that the method itself bears a crucial role in the comparative efficacy of the trial drugs.

The risk of bias was evaluated as high and the quality (level) of evidence as low regarding the outcome proportion achieving HbA1c target.

INDIRECT EVIDENCE

The results represented in the results section indicate the following.

Dual therapy:

- At 26 weeks the results suggest that
 - liraglutide 1.8 mg and exenatide 2 mg might be more effective than canagliflozin 100 mg in reaching HbA1c target
 - liraglutide 1.8 mg might be more effective than canagliflozin 300 mg in reaching HbA1c target
- At 52 weeks the results suggest that
 - liraglutide 1.2 mg and 1.8 mg might be more effective than canagliflozin 100/300 mg in reaching HbA1c target

- canagliflozin 300 mg might be more effective than canagliflozin 100 mg, saxagliptin 5 mg and glibenclamide in reaching HbA1c target
- At 104 weeks the results suggest that
- Canagliflozin 300 mg might be more effective than canagliflozin 100 mg, vildagliptin 50 mg, SU (glimepiride) and linagliptin 5 mg in reaching HbA1c target

Triple therapy: At 26 weeks the results suggest that canagliflozin 300 mg might be more effective than canagliflozin 100 mg and sitagliptin 100 mg in reaching HbA1c target.

Overall, there are well known limitations related to the indirect comparisons (see e.g. EUnetHTA guideline: Comparator and comparisons). As a consequence, the quality of such evidence is very low. Further discussion on methodological issues related to indirect comparisons is found in the Appendix 1: Methods.

References

EUnetHTA guideline: Comparator and comparisons: Direct and indirect comparisons. 2013. Available at:

<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf>

Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–79.

Johnson & Johnson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005C]: [How does canagliflozin affect the following outcome: FPG change]?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)

- Domain search

- Other:

Critical appraisal criteria	None
Method of synthesis	Narrative

Result

The results are represented as follows:

1. DIRECT EVIDENCE

1.1 Dual Therapy

1.2 Triple Therapy

2. INDIRECT EVIDENCE

2.1 Dual Therapy

2.2. Triple Therapy

Authors' note:

The mean baseline fasting blood glucose levels in different treatment arms have been obtained from published articles.

1. DIRECT EVIDENCE

[Johnson & Johnson submission file (2013)]:

Dual therapy

1.1.1 DIA3009 (Canagliflozin Versus Glimepiride as Add-on to Metformin, 104 weeks, N = 1450):

The mean fasting blood glucose at baseline in the canagliflozin 100 mg group was 9.2 (S.D. 2.1), in canagliflozin 300 mg group 9.1 (S.D. 2.0), and in glimepiride group 9.2 (S.D. 2.1) mmol/L. The results for changes in fasting plasma glucose at 52 weeks (primary assessment time point) are shown below.

Table 79. Changes in fasting plasma glucose at 52 weeks (Canagliflozin Versus Glimepiride as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg	CANA 300 mg	GLIM
FPG change, mmol/L	-1.4 (0.1)	-1.5 (0.1)	-1.0 (0.1)
<i>Difference vs. GLIM</i>	-0.3 (-0.6, -0.1)	-0.5 (-0.7, -0.3)	

Abbreviations: mITT, modified intent-to-treat; LOCF, last observation carried forward; CANA, canagliflozin; GLIM, glimepiride

^aLeast squares mean (SE) change from baseline using ANCOVA (except for documented hypoglycaemia rate) and GLIM-subtracted mean (95% CI) values;

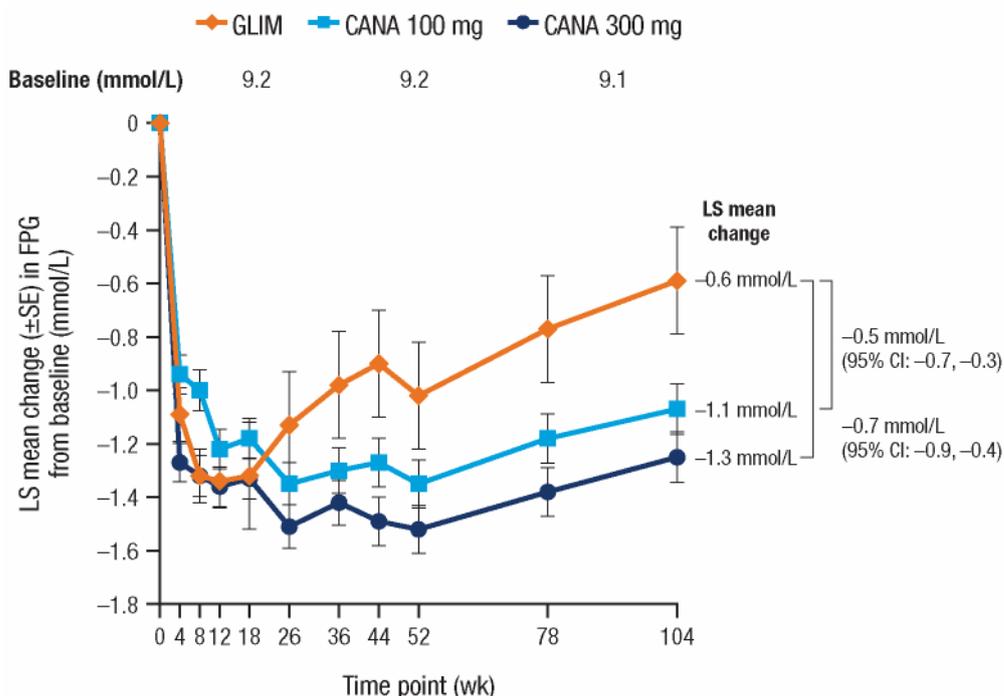
^bP values are reported for pre-specified comparisons only

Source: [Johnson & Johnson submission file (2013), main document, page 155, table 41, mITT, LOCF, table is modified]

Both canagliflozin 100 and 300 mg showed numerical improvements in FPG compared with glimepiride, which were more pronounced at 104 weeks (figure below). The nadir in FPG was reached at Week 52 for both canagliflozin groups with small increases thereafter; for the glimepiride group, the nadir in FPG was reached at Week 18 with continual increases

subsequently. The difference in FPG between each canagliflozin dose and glimepiride increased slightly more from Week 52 to Week 104.

Figure 16. Change in FPG from baseline to Week 104 (LOCF) for DIA3009



Abbreviations: FPG, fasting plasma glucose; LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin; LS, least squares; SE, standard error.

Source: [Johnson & Johnson submission file (2013), main document, pages 161–162]

1.1.2 DIA3006 (Canagliflozin Versus Sitagliptin as Add-on to Metformin, N = 1284, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, 52 weeks):

The mean fasting blood glucose at baseline was in the canagliflozin 100 mg group 9.3 (S.D. 2.3), in canagliflozin 300 mg group 9.6 (S.D. 2.5), and in sitagliptin group 9.4 (S.D. 2.3) mmol/L. The results for the changes in fasting plasma glucose are shown below.

Table 80. Changes in fasting plasma glucose at 52 weeks (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg (n = 368)	CANA 300 mg (n = 367)	SITA 100 mg (n = 366)
FPG change, mmol/L	-1.5 (0.1)	-2.0 (0.1)	-1.0 (0.1)
<i>Difference vs. SITA</i>	-0.5 (-0.7, -0.2) ^e	-1.0 (-1.2, -0.7) ^e	

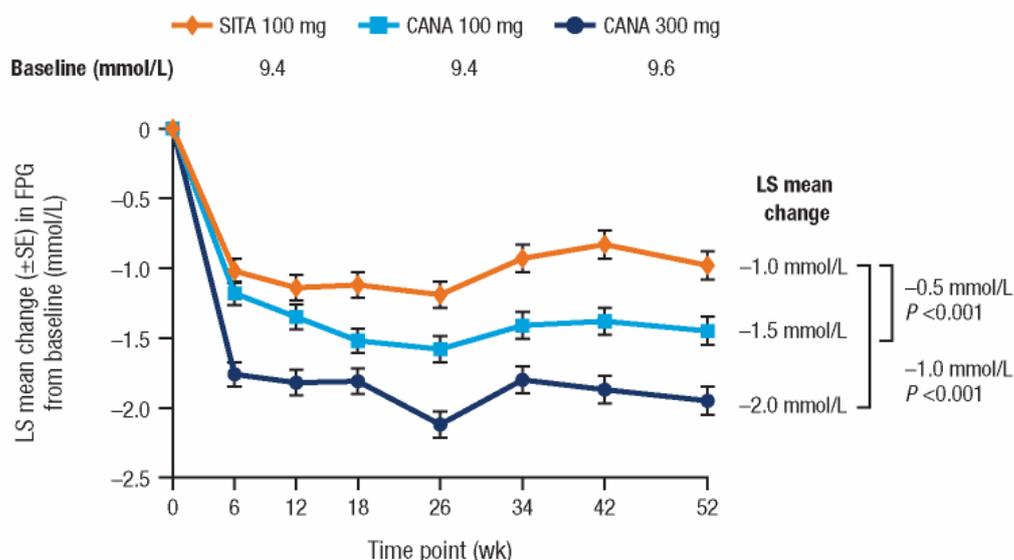
Abbreviations: CANA, canagliflozin; SITA, Sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; ANCOVA, analysis of covariance; CI, confidence interval; NS, not significant.

^aLS mean (SE) change from baseline using ANCOVA and SITA-subtracted LS mean (95% CI) for all parameters;

^bP values are reported for pre-specified comparisons only; ^eP <0.001 vs. SITA

Source: [Johnson & Johnson submission file (2013), main document, page 170, table 42, mITT, LOCF, table is modified]

Figure 17. Change in FPG from baseline to Week 52 (LOCF) for DIA3006



Abbreviations: FPG, fasting plasma glucose; LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error.

Source: [Johnson & Johnson submission file (2013)]

1.2 Triple Therapy

1.2.1 DIA3015 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU, N = 755, 52 weeks):

The mean fasting blood glucose at baseline was in the canagliflozin 300 mg group 9.4 (S.D. 2.6) and in the sitagliptin group 9.2 (S.D. 2.5) mmol/L. The results for changes in fasting blood glucose at 52 weeks (primary assessment time point) are shown in below.

Table 81. Changes in fasting plasma glucose at 52 weeks (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU)

Parameter ^{a,b}	CANA 300 mg (N = 377)	SITA 100 mg (N = 378)
FPG change, mmol/L	-1.7 (0.1)	-0.3 (0.1)
<i>Difference vs. SITA</i>	-1.3 (-1.7, -1.0) ^{d,e}	

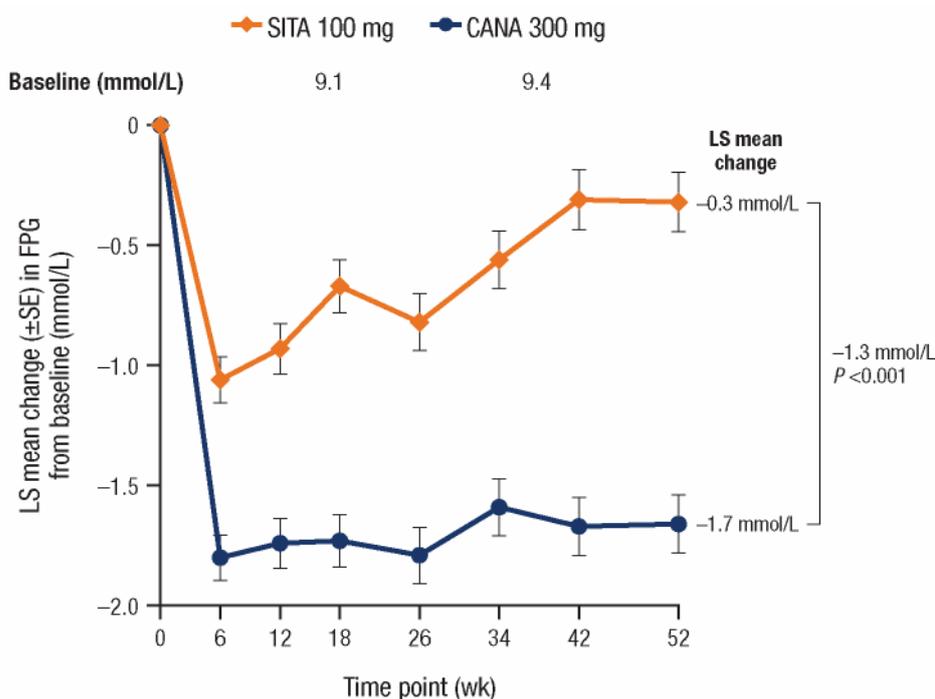
Abbreviations: SITA, sitagliptin; CANA, canagliflozin; mITT, modified intent-to-treat; LOCF, last observation carried forward; SE, standard error; CI, confidence interval; ANCOVA, analysis of covariance; NS, not significant.

^aLeast squares mean (SE) change from baseline using ANCOVA and SITA-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only; ^dUpper limit of 95% CI <0.0% for the comparison to SITA; ^eP <0.001 vs. SITA

Source: [Johnson & Johnson submission file (2013), main document, page 180, table 43, mITT, LOCF, table is modified]

Figure 18. Change in FPG from baseline to Week 52 (LOCF) for DIA3015.



Abbreviations: FPG, fasting plasma glucose; LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error.

Source: [Johnson & Johnson submission file (2013)]

2. INDIRECT EVIDENCE

Authors’ note for interpretation (edited from Johnson & Johnson submission file (2013)):

The indirect comparisons were based on network meta-analyses. For methodological details, see Appendix 1: Methods. Pairwise comparisons of the relative treatment effect for both canagliflozin doses versus all other comparators are presented as median estimates [95% CrI] (negative values interpreted as higher reduction for canagliflozin) and as probabilities of canagliflozin being more effective than the comparator on the endpoint of interest (columns with “Prob” heading). Tables are ranked by SUCRA values, with treatments with the highest probability of being most effective at the top.

[Johnson & Johnson submission file (2013)]:

2.1 Dual therapy

Table 82. Base case analysis - Results of RE model for the mean difference in FPG for canagliflozin versus active comparators, metformin background at 26 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300 mg		Prob	SUCRA
	Median	CrI		Median	CrI		
Liraglutide 1.8mg QD	0.51	[-0.50 ; 1.53]	15%	0.15	[-0.86 ; 1.17]	37%	86%
Canagliflozin 300mg QD	0.36	[-0.39 ; 1.12]	16%				80%
Liraglutide 1.2mg QD	0.33	[-0.69 ; 1.34]	25%	-0.03	[-1.05 ; 0.98]	53%	78%
Exenatide 2mg QWK	0.35	[-1.07 ; 1.77]	30%	-0.01	[-1.43 ; 1.40]	51%	76%
Pioglitazone 30mg QD	0.07	[-0.95 ; 1.15]	45%	-0.29	[-1.32 ; 0.80]	72%	66%

	Canagliflozin 100mg		Prob	Canagliflozin 300 mg		Prob	SUCRA
	Median	CrI		Median	CrI		
Pioglitazone 45mg QD	0.04	[-1.37 ; 1.46]	48%	-0.32	[-1.73 ; 1.09]	68%	62%
Canagliflozin 100mg						84%	61%
Glimepiride	-0.15	[-0.92 ; 0.63]	66%	-0.51	[-1.28 ; 0.27]	91%	53%
Exenatide 10µg BID	-0.24	[-1.45 ; 0.97]	66%	-0.60	[-1.81 ; 0.61]	85%	49%
Exenatide 5µg BID	-0.45	[-1.87 ; 0.96]	75%	-0.81	[-2.23 ; 0.60]	88%	39%
Linagliptin 5mg QD	-0.47	[-1.84 ; 0.88]	77%	-0.83	[-2.20 ; 0.51]	90%	38%
Sitagliptin 100mg QD	-0.55	[-1.32 ; 0.21]	93%	-0.91	[-1.68 ; -0.15]	99%	30%
Vildagliptin 100mg QD	-0.61	[-1.58 ; 0.44]	89%	-0.97	[-1.94 ; 0.08]	97%	29%
Dapagliflozin 10mg QD	-0.70	[-2.07 ; 0.65]	86%	-1.06	[-2.43 ; 0.28]	94%	28%
Saxagliptin 5mg QD	-0.74	[-1.83 ; 0.34]	92%	-1.10	[-2.19 ; -0.02]	98%	24%
Placebo	-1.68	[-2.45 ; -0.91]	100%	-2.03	[-2.81 ; -1.27]	100%	1%

Source: [Johnson & Johnson submission file (2013)]

Table 83. Base case analysis – Results of the FE model for the mean difference in FPG for canagliflozin versus active comparators, metformin background at 52 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300mg		Prob	SUCRA
	Median	CrI95%		Median	CrI95%		
Liraglutide 1.8mg QD	0.90	[0.38 ; 1.42]	0%	0.58	[0.07 ; 1.10]	2%	99%
Liraglutide 1.2mg QD	0.57	[0.05 ; 1.09]	2%	0.25	[-0.27 ; 0.77]	18%	90%
Canagliflozin 300mg QD	0.32	[0.13 ; 0.50]	0%				83%
Pioglitazone 30mg QD	0.19	[-0.31 ; 0.70]	23%	-0.12	[-0.62 ; 0.39]	68%	75%
Exenatide 10µg BID	0.03	[-0.29 ; 0.37]	42%	-0.28	[-0.61 ; 0.04]	95%	67%
Canagliflozin 100mg						100%	65%
Glibenclamide	-0.16	[-1.42 ; 1.09]	60%	-0.48	[-1.73 ; 0.78]	77%	52%
Gliclazide	-0.20	[-0.66 ; 0.26]	79%	-0.51	[-0.97 ; -0.06]	99%	51%
Glimepiride	-0.26	[-0.48 ; -0.05]	99%	-0.58	[-0.79 ; -0.37]	100%	47%
Vildagliptin 100mg QD	-0.41	[-0.65 ; -0.16]	100%	-0.72	[-0.96 ; -0.48]	100%	36%
Dapagliflozin 10mg QD	-0.50	[-0.97 ; -0.03]	98%	-0.81	[-1.28 ; -0.35]	100%	33%
Sitagliptin 100mg QD	-0.55	[-0.78 ; -0.33]	100%	-0.87	[-1.10 ; -0.64]	100%	26%
Glipizide	-0.69	[-1.12 ; -0.28]	100%	-1.01	[-1.44 ; -0.59]	100%	19%
Saxagliptin 5mg QD	-1.10	[-1.60 ; -0.60]	100%	-1.41	[-1.92 ; -0.91]	100%	5%
Placebo	-1.15	[-1.40 ; -0.90]	100%	-1.47	[-1.72 ; -1.22]	100%	3%

Source: [Johnson & Johnson submission file (2013)]

Table 84. Base case analysis – Results of the FE model for the mean difference in FPG for canagliflozin versus active comparators, metformin background at 104 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
CANAGLIFLOZIN 300	0.18	[-0.07 ; 0.43]	8%				90%
Lira 1.2	0.08	[-0.47 ; 0.63]	39%	-0.10	[-0.64 ; 0.44]	64%	81%
Lira 1.8	0.06	[-0.48 ; 0.59]	41%	-0.12	[-0.66 ; 0.41]	67%	79%
CANAGLIFLOZIN 100						92%	73%
SU	-0.48	[-0.73 ; -0.23]	100%	-0.66	[-0.91 ; -0.41]	100%	43%
Sita 100	-0.48	[-0.92 ; -0.04]	98%	-0.66	[-1.11 ; -0.22]	100%	42%
Vilda 100	-0.68	[-1.05 ; -0.30]	100%	-0.86	[-1.23 ; -0.49]	100%	26%
Lina 5	-0.83	[-1.17 ; -0.49]	100%	-1.01	[-1.35 ; -0.67]	100%	16%
Placebo	-1.87	[-2.49 ; -1.25]	100%	-2.05	[-2.67 ; -1.43]	100%	0%

Source: [Johnson & Johnson submission file (2013)]

2.2 Triple therapy

Table 85. Base case analysis - Results of FE model for the mean difference in FPG for canagliflozin versus active comparators, metformin+sulphonylurea background

	Canagliflozin 100mg			Canagliflozin 300mg			SUCRA
	Median	CrI95%	Prob	Median	CrI95%	Prob	
Biphasic insulin	2.44	[1.66 ; 3.19]	0%	1.73	[1.00 ; 2.41]	0%	100%
Long-acting insulin	1.06	[0.22 ; 1.89]	1%	0.35	[-0.43 ; 1.12]	19%	84%
Liraglutide 1.8mg once daily	0.81	[-0.02 ; 1.65]	3%	0.11	[-0.67 ; 0.88]	39%	74%
Canagliflozin 300mg	0.71	[0.18 ; 1.24]	0%				72%
Exenatide 10µgtwice daily	0.15	[-0.62 ; 0.89]	36%	-0.56	[-1.29 ; 0.11]	95%	47%
Exenatide 5µgBID	0.04	[-0.73 ; 0.81]	47%	-0.67	[-1.39 ; 0.02]	97%	41%
Canagliflozin 100mg						100%	40%
Sitagliptin 100mg once daily	-0.24	[-0.82 ; 0.33]	79%	-0.95	[-1.26 ; -0.65]	100%	27%
Linagliptin 5mg	-0.57	[-1.17 ; 0.03]	97%	-1.28	[-1.80 ; -0.76]	100%	13%
Placebo	-1.27	[-1.80 ; -0.73]	100%	-1.98	[-2.42 ; -1.54]	100%	0%

Source: [Johnson & Johnson submission file (2013)]

Discussion

General notes

Fasting plasma glucose (FPG) has been a pivotal parameter when diagnosing diabetes or assessing the therapeutic balance of the disease. International current care guidelines suggest maintaining or targeting FPG at below 7.2 mmol/L (Inzucchi et al 2012). However, the target may vary according to patient-related factors, i.e. tendency for severe hypoglycaemia, advanced complications).

The study patients were allowed to use other antidiabetic medicines besides the study drugs. Initiations of non-study antidiabetic drugs or modifications of non-study or study anti-diabetic drugs were reported in 4.3–5.6% (most of these initiations, with no clear difference between study groups in incidence) of study participants in DIA3009, in 6.5–7.6% in DIA3006 (most of these were initiations, no clear difference between study groups in incidence), and in 13.0–15.9% in DIA3015 (most being modifications, no clear difference between study groups in incidence) (submission file, appendix 17). The dosages of the additional AHAs are not reported, and therefore the effect of non-study antidiabetic medication cannot be addressed reliably. Furthermore, HbA1c is influenced by multiple factors including other medications, nutrition and also physical activity. The assessment of the independent comparative effect of canagliflozin on fasting blood glucose is challenged by these limitations.

The laboratory method used for measuring plasma glucose has not been reported. It is plausible that the same method has been used in all relevant treatment arms. It is not expected that the method itself plays a crucial role in the comparative efficacy of the trial drugs.

DIRECT EVIDENCE

In conclusion, canagliflozin 100 mg and 300 mg, added on metformin, seemed to induce a greater reduction (difference in mean change 0.3–1.0 mmol/L) in FPG than glimepiride or sitagliptin 100 mg at 1 year (or 2 years, glimepiride only). A similar finding was obtained in a trial comparing canagliflozin 300 mg with sitagliptin 100 mg in a combination treatment with metformin and sulphonylurea. The trial patients were allowed to use off-study antidiabetic medicines, which may constitute limitations to the conclusions that can be drawn from the results of the trials.

The risk of bias was evaluated as high and the quality (level) of evidence as moderate regarding FPG change.

Overall, only the mean changes in FPG levels have been reported in the submission file. Based on them, it can be estimated that, on average, the FPG target of current treatment recommendations was not met during the trials.

INDIRECT EVIDENCE

The results represented in the results section indicate the following.

Dual therapy:

- At 26 weeks the results suggest that
 - canagliflozin 300 mg might be more effective than sitagliptin 100 mg and saxagliptin 5 mg
- At 52 weeks the results suggest that
 - liraglutide 1.2 mg and 1.8 mg might be more effective than canagliflozin 100mg in terms of reducing FPG
 - liraglutide 1.8 mg might be more effective than canagliflozin 300mg in terms of reducing FPG
 - canagliflozin 100 mg might be more effective than glimepiride, vildagliptin 100mg, dapagliflozin 10mg, sitagliptin 100mg, glipizide and saxagliptin 5mg in reducing FPG
 - canagliflozin 300 mg might be more effective than glimepiride, vildagliptin 100mg, dapagliflozin 10mg, sitagliptin 100mg, glipizide, saxagliptin 5mg, Gliclazide and canagliflozin 100 mg in reducing FPG
 - Liraglutide 1.8 mg seems to be clearly the best treatment option in terms of reducing FPG
- At 104 weeks the results suggest that
 - Canagliflozin 100/300 mg might be more effective than SU, sitagliptin 100 mg, vildagliptin 100 mg, linagliptin 5 mg in reducing FPG

Triple therapy: At 26 weeks the results suggest that

- Biphasic and long acting insulins and canagliflozin 300 mg might be more effective than canagliflozin 100 mg in reducing FPG
- Biphasic insulin might be more effective than canagliflozin 300 mg in reducing FPG
- Canagliflozin 300 might be more effective than sitagliptin 100 mg and linagliptin 5 mg in reducing FPG
- Biphasic insulin seems to be clearly the best treatment option in terms of reducing FPG

Overall, there are well known limitations related to the indirect comparisons (see e.g. EUnetHTA guideline: Comparator and comparisons). As a consequence, the quality of such evidence is very low. Further discussion on methodological issues related to indirect comparisons is found in the Appendix 1: Methods.

References

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EUnetHTA guideline: Comparator and comparisons: Direct and indirect comparisons. 2013.

Available from:

<http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf>

Inzucchi S, Bergenstal R, Buse J, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centred approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–79.

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Schernthaner G, Gross J, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycaemic control with metformin plus sulfonylurea. *Diabetes Care* 2013;36:2508–15.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005D]: [How does canagliflozin affect the following outcome: body mass index change]?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

The results are represented as follows:

1. DIRECT EVIDENCE

1.1 Dual Therapy

1.2 Triple Therapy

2. INDIRECT EVIDENCE

2.1 Dual Therapy

2.2. Triple Therapy

Authors' note:

The baseline BMI values have been obtained from published articles.

There is no data regarding change in BMI reported in the main document of the MAH submission file. However, in Appendix 16 of the submission file, based on clinical study reports, and retrieved for CORE modelling, the following information was available (the time point for measuring the treatment effect is not reported in the submission file appendix):

1. DIRECT EVIDENCE

[Johnson & Johnson submission file (2013)]:

1.1. Dual Therapy

1.1.1 Canagliflozin Versus Glimepiride as Add-on to Metformin (DIA3009, 104 weeks, N = 1450)

The mean baseline BMI in the canagliflozin 100 mg group was 31.0 (S.D. 5.3), in canagliflozin 300 mg group 31.2 (S.D. 5.4) and in glimepiride group 30.9 (S.D. 5.5) For the canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride groups, respectively, the mean (standard error) change in BMI from baseline was -1.32 (0.07), -1.46 (0.07) and 0.26 (0.07).

1.1.2 Canagliflozin Versus Sitagliptin as Add-on to Metformin (DIA3006, N = 1284, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, 52 weeks)

The mean baseline BMI in the canagliflozin 100 mg group was 32.4 (S.D. 6.4), in canagliflozin 300 mg group 31.4 (S.D. 6.3), and in sitagliptin group 32.0 (S.D. 6.1). For the canagliflozin 100 mg, canagliflozin 300 mg, and sitagliptin 100 mg groups, respectively, the mean (standard error) change in BMI from baseline was -1.21 (0.06), -1.32 (0.06), and -0.41 (0.06).

1.2 Triple therapy

1.2.1 Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU (DIA3015, N = 755, 52 weeks)

The mean baseline BMI in the canagliflozin group was 31.5 (S.D. 6.9), and in the sitagliptin group 31.7 (S.D. 6.9). For the canagliflozin 300 mg and sitagliptin 100 mg groups, respectively, the mean (standard error) change in BMI from baseline was -0.82 (0.07) and 0.06 (0.07).

2. Indirect Evidence

Authors' note for interpretation (edited from Johnson & Johnson submission file (2013)):

The indirect comparisons were based on network meta-analyses. For methodological details, see Appendix 1: Methods. Pairwise comparisons of the relative treatment effect for both canagliflozin doses versus all other comparators are presented as median estimates [95% CrI] (negative values interpreted as higher reduction for canagliflozin) and as probabilities of canagliflozin being more effective than the comparator on the endpoint of interest (columns with "Prob" heading). Tables are ranked by SUCRA values, with treatments with the highest probability of being most effective at the top.

[Johnson & Johnson submission file (2013)]:

2.1 Dual therapy

Table 86. Base case analysis – Results of the FE model for the mean difference in BMI for canagliflozin versus active comparators, metformin background at 26 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300 mg		Prob	SUCRA
	Median	CrI		Median	CrI		
Canagliflozin 300mg	0.20	[0.09 ; 0.31]	0%				95%
Canagliflozin 100mg						100%	80%
Vildagliptin 100mg QD	-0.44	[-0.87 ; 0.00]	97%	-0.64	[-1.07 ; -0.20]	100%	63%
Exenatide 10µgBID	-0.50	[-3.77 ; 2.79]	62%	-0.70	[-3.97 ; 2.59]	67%	53%
Placebo			100%			100%	44%
Sitagliptin 100mg QD	-0.76	[-0.92 ; -0.60]	100%	-0.96	[-1.12 ; -0.80]	100%	41%
Glimepiride	-1.41	[-1.54 ; -1.27]	100%	-1.61	[-1.74 ; -1.47]	100%	12%
Pioglitazone 30mg QD	-1.48	[-2.34 ; -0.60]	100%	-1.68	[-2.53 ; -0.80]	100%	12%

Source: [Johnson & Johnson submission file (2013)]

Table 87. Base case analysis – Results of the FE model for the mean difference in BMI for canagliflozin versus active comparators, metformin background at 52 weeks

	Canagliflozin 100mg			Canagliflozin 300mg			SUCRA
	Median	CrI95%	Prob	Median	CrI95%	Prob	
Exenatide 10µgBID	0.60	[-0.04 ; 1.25]	3%	0.47	[-0.18 ; 1.11]	7%	98%
Canagliflozin 300mg QD	0.14	[0.00 ; 0.27]	3%				86%
Canagliflozin 100mg QD						97%	73%
Vildagliptin 100mg QD	-0.58	[-1.21 ; 0.05]	97%	-0.72	[-1.35 ; -0.09]	99%	55%
Sitagliptin 100mg QD	-0.77	[-0.96 ; -0.58]	100%	-0.91	[-1.10 ; -0.72]	100%	45%
Placebo	-0.88	[-1.37 ; -0.39]	100%	-1.02	[-1.51 ; -0.53]	100%	37%
Pioglitazone 30mg QD	-1.40	[-4.22 ; 1.40]	83%	-1.53	[-4.35 ; 1.27]	85%	32%
Glimepiride	-1.58	[-1.76 ; -1.41]	100%	-1.72	[-1.89 ; -1.54]	100%	17%
Glibenclamide	-1.88	[-2.42 ; -1.33]	100%	-2.01	[-2.55 ; -1.47]	100%	6%

Source: [Johnson & Johnson submission file (2013)]

2.2 Triple Therapy

Table 88. Base case analysis – Results of the FE model for the mean difference in BMI for canagliflozin versus active comparators, metformin + sulphonylurea background

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Canagliflozin 300mg	0.22	[-0.06 ; 0.50]	7%	-	-		98%
Canagliflozin 100mg						93%	69%
Placebo	-0.40	[-0.68 ; -0.12]	100%	-0.62	[-0.90 ; -0.34]	100%	32%
Sitagliptin 100mg once daily	-0.70	[-1.02 ; -0.38]	100%	-0.92	[-1.08 ; -0.76]	100%	1%

Source: [Johnson & Johnson submission file (2013)]

Discussion

Body mass index (BMI) is frequently used as an outcome in trials examining antidiabetic drugs. BMI is an established factor in assessing a subject's cardiovascular prognosis. An increase of 1 kg/m² has been shown to associate with a mean increase of 7% in the relative risk of congestive heart failure (Leal et al 2009). Recently, measures of central adiposity have been suggested as more accurate predictors of obesity-related cardiovascular risk (Lee et al 2008). However, in a quite recent meta-analysis, compared with normal weight (BMI < 25 kg/m²), obesity (BMI ≥30 kg/m²) was associated with increased mortality (hazard ratio 1.18, 95 % confidence interval. 1.12–1.25), where BMI values of ≥35 were especially a marker of increased risk (Flegal et al 2013).

DIRECT EVIDENCE

In light of the results of the relevant trials, canagliflozin seems to be able to induce a decrease of approximately 1 kg/m² in BMI when added on metformin, whereas glimepiride treatment was associated with a minor increase in BMI. Compared with sitagliptin (both added on metformin), canagliflozin was somewhat more effective in reducing BMI. Compared with sitagliptin (both

added on metformin and sulphonylurea), canagliflozin 300 mg resulted in a small reduction (-0.8 kg/m²) in BMI whereas sitagliptin seemed neutral in this regard. The use of sulphonylurea seemed to modify (decrease) the effect of canagliflozin (300 mg) on BMI.

The time points for measuring the treatment effects presented above are not reported in the submission file appendix, but as DIA3006 and DIA3015 lasted only 52 weeks, the follow-up is 1 year at most in these comparisons. The long-term effects of canagliflozin on BMI remain unclear.

The risk of bias was evaluated as high and the quality (level) of evidence as low regarding BMI change for direct evidence.

Indirect evidence was also represented in the submission file appendix 16. However, comparable estimates were not presented for canagliflozin and other relevant treatment options. Due to these reasons, the indirect evidence is not represented here.

INDIRECT EVIDENCE

The results represented in the results section indicate the following.

Dual therapy:

- At 26 weeks the results suggest that
 - Canagliflozin 100mg might be more effective than sitagliptin 100mg, glimepiride and pioglitazone 30mg in reducing BMI
 - Canagliflozin 300mg might be more effective than canagliflozin 100 mg, vildagliptin 100mg, sitagliptin 100mg, glimepiride and pioglitazone 30mg in reducing BMI
 - Canagliflozin 300mg seems to be clearly the best of the treatments in terms of reducing BMI
- At 52 weeks the results suggest that
 - Canagliflozin 100mg might be more effective than sitagliptin 100mg, glimepiride, pioglitazone 30mg and glibenclamide in reducing BMI
 - canagliflozin 300 mg might be more effective than all the other treatments except exenatide 10µg, which is the best treatment option in terms of reducing BMI

Triple therapy: At 26 weeks the results suggest that canagliflozin 100/300mg might be more effective than sitagliptin 100mg. Canagliflozin 300mg seems to be clearly the best treatment option in terms of reducing BMI.

Overall, there are well known limitations related to the indirect comparisons (see e.g. EUnetHTA guideline: Comparator and comparisons). As a consequence, the quality of such evidence is very low. Further discussion on methodological issues related to indirect comparisons is found in the Appendix 1: Methods.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005E]: [How does canagliflozin affect the following outcome: change in cardiovascular risk factors – systolic blood pressure]?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other: CHMP assessment report, redacted version

Critical appraisal criteria None

Method of synthesis Narrative

Result

Authors' note:

The effect of canagliflozin on other fasting blood glucose, HbA1c, weight and body mass index as well as fasting plasma lipids is addressed elsewhere (result cards D0005A, D0005C, D0005D, D0005F, D0005I). This result card focuses on systolic blood pressure. The results are presented in the following order:

1. DIRECT EVIDENCE

1.1 Dual Therapy (systolic blood pressure)

1.2 Triple Therapy (systolic blood pressure)

2. INDIRECT EVIDENCE

2.1 Dual Therapy (systolic blood pressure)

2.2. Triple Therapy (systolic blood pressure)

1. Direct evidence

[Johnson & Johnson submission file (2013)]:

1.1 Dual Therapy

1.1.1 DIA3009 (Canagliflozin Versus Glimepiride as Add-on to Metformin, 104 weeks, N = 1450):

A summary of efficacy endpoints at Week 52 (primary assessment time point, mITT, LOCF) is shown in table below.

Table 89. Summary of efficacy endpoints at Week 52 (Canagliflozin Versus Glimepiride as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg	CANA 300 mg	GLIM
Systolic BP change, mmHg	-3.3 (0.6)	-4.6 (0.6)	0.2 (0.6)
<i>Difference vs. GLIM</i>	-3.5 (-4.9, -2.1)	-4.8 (-6.2, -3.4)	

Abbreviations: CANA, canagliflozin, GLIM, glimepiride; mITT, modified intent-to-treat; LOCF, last observation carried forward.

^aLeast squares mean (SE) change from baseline using ANCOVA (except for documented hypoglycaemia rate) and GLIM-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only.

Source: [Johnson & Johnson submission file (2013), page 155, table is modified]

At week 104, in secondary analysis (mITT) the effects of canagliflozin are reported in table below:

Table 90. Summary of efficacy endpoints at Week 104 (Canagliflozin Versus Glimepiride as Add-on to Metformin)

Treatment group	CANA 100 mg	CANA 300 mg	GLIM
Number of subjects			
mITT	483	485	482
SBP (LSM change)	-2.0 mmHg	-3.1 mmHg	1.7 mmHg
Standard error	0.6 mmHg	0.6 mmHg	0.6 mmHg
SBP, effect estimate per comparison	-3.7 mmHg ^a	-4.8 mmHg ^a	
	-5.2; -2.3 ^b	-6.2; -3.4 ^b	
	CANA 100 mg vs GLIM	CANA 300 mg vs GLIM	

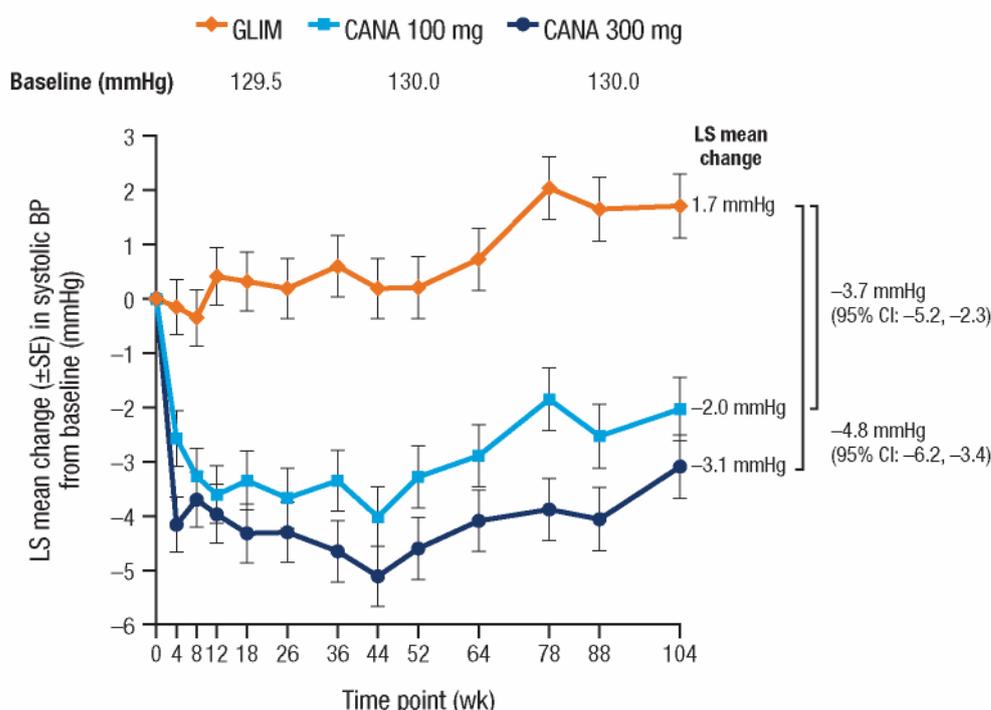
Abbreviations: CANA, canagliflozin, GLIM, glimepiride

^a LSM difference between groups; ^b 95% CI

Source: [Johnson & Johnson submission file (2013), Appendix 9, table is modified]

For both canagliflozin groups, the nadir in the change from baseline in SBP was observed at Week 44, with small increases subsequently; for the glimepiride group, no appreciable change in SBP was observed in the first 52 weeks, with a small progressive increase thereafter (Figure 19).

Figure 19. Change in SBP from baseline to Week 104 (LOCF) for DIA3009.



Abbreviations: SBP, systolic blood pressure; LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin LS, least squares; SE, standard error; CI, confidence interval.
Source: [Johnson & Johnson submission file (2013)]

1.1.2 DIA3006 (Canagliflozin Versus Sitagliptin as Add-on to Metformin, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, N = 1284):

A summary of efficacy endpoints at Week 52 is shown in table below.

Table 91. Summary of efficacy endpoints at Week 52 (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg (n = 368)	CANA 300 mg (n = 367)	SITA 100 mg (n = 366)
Systolic BP change, mmHg	-3.5 (0.6)	-4.7 (0.6)	-0.7 (0.6)
<i>Difference vs. SITA</i>	-2.9 (-4.5, -1.3) ^e	-4.0 (-5.6, -2.4) ^e	

Abbreviations: CANA, canagliflozin; SITA, sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; ANCOVA, analysis of covariance; CI, confidence interval; NS, not significant.

^aLS mean (SE) change from baseline using ANCOVA and SITA-subtracted LS mean (95% CI) for all parameters;

^bP values are reported for pre-specified comparisons only;

^eP < 0.001 vs. SITA;

^fP = NS vs. SITA;

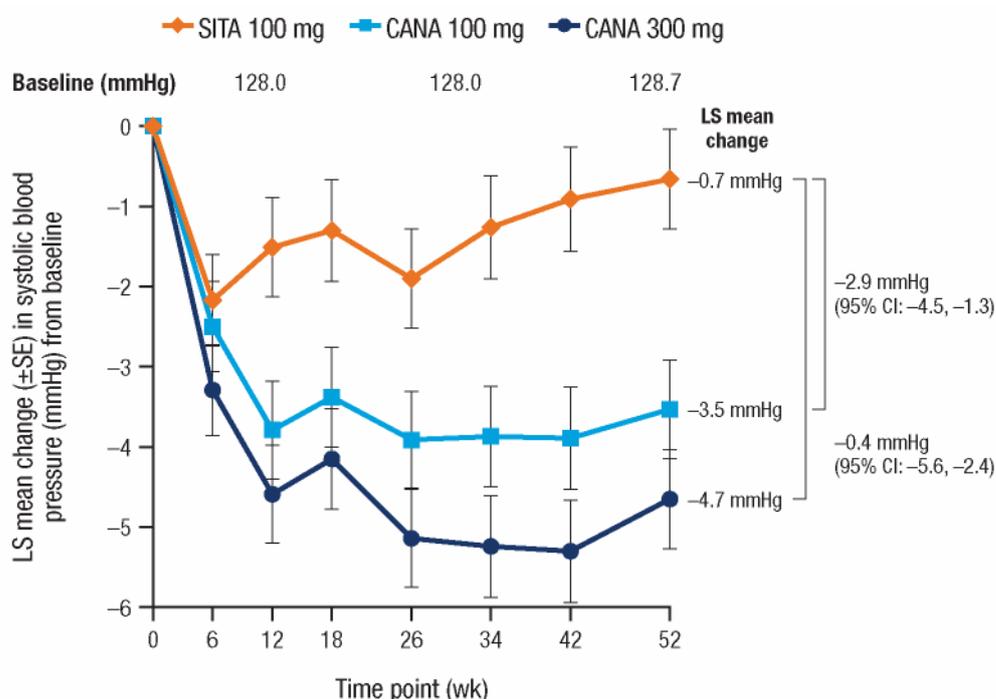
^gP = NS vs. SITA due to multiplicity control.

Source: [Johnson & Johnson submission file (2013) , page 170, modified from Table 42]

Near maximal reductions in SBP were reached by Week 12 in the canagliflozin groups; these reductions were maintained through Week 52 (Figure 20 below). Numerical reductions in diastolic BP were also seen with canagliflozin 100 and 300 mg compared with sitagliptin. No notable

differences were observed across groups in changes in pulse rate (-1.3, -1.9, and -1.4 beats per minute with canagliflozin 100 and 300 mg and sitagliptin, respectively).

Figure 20. Change in SBP from baseline to Week 52 (LOCF) for DIA3006.



Abbreviations: SBP, systolic blood pressure; LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error; CI, confidence interval.
Source: [Johnson & Johnson submission file (2013)]

1.2 Triple Therapy

1.2.1 DIA3015 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU, 52 weeks, N = 755):

A summary of efficacy endpoints at Week 52 is shown in table below.

Table 92. Summary of efficacy endpoints at Week 52 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU)

Parameter ^{a,b}	CANA 300 mg (N = 377)	SITA 100 mg (N = 378)
Systolic BP change, mmHg	-5.1 (0.7)	0.9 (0.7)
<i>Difference vs. SITA</i>	-5.9 (-7.6, -4.2) ^{d,e}	

Abbreviations: CANA, canagliflozin; SITA, sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; SE, standard error; CI, confidence interval; ANCOVA, analysis of covariance; NS, not significant.

^aLeast squares mean (SE) change from baseline using ANCOVA and SITA-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only;

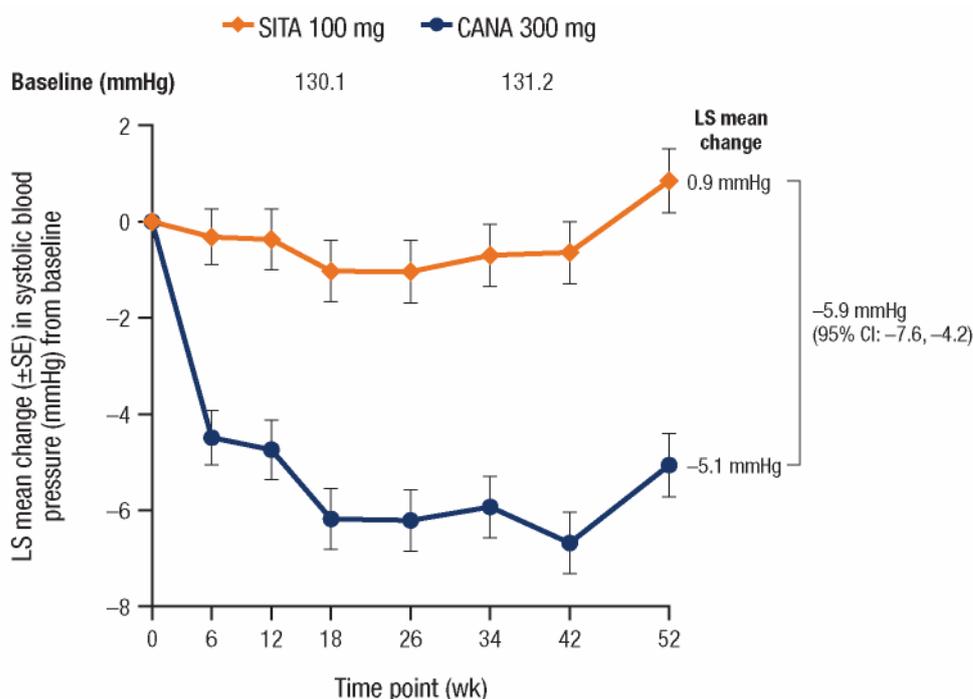
^dUpper limit of 95% CI <0.0% for the comparison to SITA;

^eP <0.001 vs. SITA;

Source: [Johnson & Johnson submission file (2013) , page 170, modified from Table 43]

The reduction in SBP with canagliflozin was sustained over the 52-week treatment period (Figure 21 below).

Figure 21. Change in SBP from baseline to Week 52 (LOCF) for DIA3015.



Abbreviations: SBP, systolic blood pressure; LOCF, last observation carried forward; SITA, sitagliptin; CANA, canagliflozin; LS, least squares; SE, standard error.
 Source: [Johnson & Johnson submission file (2013)]

2. Indirect Evidence

Authors’ note for interpretation (edited from Johnson & Johnson submission file (2013)):

The indirect comparisons were based on network meta-analyses. Pairwise comparisons of the relative treatment effect for both canagliflozin doses versus all other comparators are presented as median estimates [95% CrI] (negative values interpreted as higher reduction for canagliflozin) and as probabilities of canagliflozin being more effective than the comparator on the endpoint of interest (columns with “Prob” heading). Tables are ranked by SUCRA values, with treatments with the highest probability of being most effective at the top.

[Johnson & Johnson submission file (2013)]:

2.1 Dual Therapy (Metformin Add-on): Systolic Blood Pressure

Relative treatment effect versus placebo and pairwise comparison of canagliflozin 100/300 mg versus other comparators at week 26, 52 and 104 are shown in the following tables.

Table 93. Base case analysis – Results of the FE model for the mean difference in SBP for canagliflozin versus active comparators, metformin background at 26 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Exenatide 2mg QWK	1.79	[-1.21 ; 4.81]	12%	0.95	[-2.04 ; 3.95]	27%	92%
Canagliflozin 300mg	0.84	[-0.23 ; 1.92]	6%				86%
Canagliflozin 100mg						94%	70%
Pioglitazone 45mg QD	-0.20	[-3.20 ; 2.77]	56%	-1.05	[-4.04 ; 1.91]	75%	66%
Dapagliflozin 10mg QD	-0.74	[-3.50 ; 1.98]	70%	-1.59	[-4.32 ; 1.15]	87%	59%

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Pioglitazone 30mg QD	-0.79	[-5.65 ; 4.08]	62%	-1.61	[-6.48 ; 3.26]	74%	57%
Sitagliptin 100mg QD	-2.02	[-3.41 ; -0.62]	100%	-2.86	[-4.25 ; -1.47]	100%	38%
Liraglutide 1.2mg QD	-2.13	[-4.07 ; -0.20]	98%	-2.98	[-4.90 ; -1.06]	100%	36%
Liraglutide 1.8mg QD	-2.32	[-4.22 ; -0.41]	99%	-3.16	[-5.07 ; -1.25]	100%	33%
Glimepiride	-4.27	[-5.48 ; -3.05]	100%	-5.10	[-6.33 ; -3.90]	100%	7%
Placebo	-4.44	[-6.00 ; -2.88]	100%	-5.28	[-6.84 ; -3.71]	100%	5%

Source: [Johnson & Johnson submission file (2013)]

Table 94. Base case analysis – Results of the FE model for the mean difference in SBP for canagliflozin versus active comparators, metformin background, 52 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Canagliflozin 300mg QD	1.22	[0.06 ; 2.37]	2%				88%
Pioglitazone 30mg QD	2.07	[-3.19 ; 7.30]	22%	0.84	[-4.40 ; 6.09]	38%	86%
Canagliflozin 100mg QD						98%	67%
Liraglutide 1.8mg QD	-1.30	[-4.34 ; 1.67]	80%	-2.51	[-5.55 ; 0.46]	95%	52%
Sitagliptin 100mg QD	-2.83	[-4.41 ; -1.24]	100%	-4.04	[-5.63 ; -2.44]	100%	27%
Liraglutide 1.2mg QD	-3.49	[-6.49 ; -0.48]	99%	-4.70	[-7.73 ; -1.69]	100%	15%
Glimepiride	-3.52	[-5.00 ; -2.01]	100%	-4.73	[-6.22 ; -3.25]	100%	14%

Source: [Johnson & Johnson submission file (2013)]

Table 95. Base case analysis – Results of the FE model for the mean difference in sbp for canagliflozin versus active comparators, metformin background, 104 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Cana 300	1.05	[-0.52 ; 2.64]	10%				95%
Cana 100						91%	72%
Lira 1.2	-0.93	[-3.92 ; 2.06]	73%	-1.98	[-4.98 ; 1.02]	90%	59%
Lira 1.8	-1.44	[-4.39 ; 1.52]	83%	-2.50	[-5.41 ; 0.43]	95%	48%
Placebo	-3.31	[-6.73 ; 0.02]	97%	-4.37	[-7.76 ; -1.02]	100%	16%
SU	-3.74	[-5.32 ; -2.14]	100%	-4.79	[-6.38 ; -3.22]	100%	9%

Source: [Johnson & Johnson submission file (2013)]

2.2 Triple Therapy (Metformin + SU Add-on): Systolic Blood Pressure

Relative treatment effect versus placebo and pairwise comparison of canagliflozin 100/300 mg versus other comparators at week 26 are shown in the following table.

Table 96. Base case analysis – Results of the FE model for the mean difference in SBP for canagliflozin versus active comparators, metformin + sulphonylurea background

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Liraglutide 1.8mg once daily	0.38	[-4.40 ; 5.17]	45%	0.99	[-3.79 ; 5.80]	35%	82%
Canagliflozin 100mg						32%	80%
Canagliflozin 300mg	-0.63	[-3.31 ; 2.08]	68%	-	-		69%
Placebo	-2.26	[-4.96 ; 0.44]	95%	-1.62	[-4.32 ; 1.10]	88%	42%
Long-acting insulin	-4.18	[-8.97 ; 0.60]	96%	-3.56	[-8.32 ; 1.27]	92%	21%
Sitagliptin 100mg once daily	-5.78	[-9.02 ; -2.54]	100%	-5.16	[-6.96 ; -3.39]	100%	6%

Source: [Johnson & Johnson submission file (2013)]

Discussion

High blood pressure is reported in over two-thirds of patients with type 2 diabetes. Diabetic complications are significantly more prevalent in patients with hypertension compared with those with normotension. Furthermore, considerable part of the increased cardiovascular disease risk in diabetics may be linked to coexistent hypertension. It has been suggested that blood pressure of less than 140/85 mmHg is a reasonable therapeutic goal in patients with type 2 diabetes (Ferrannini and Cushman 2012, Mancia et al 2013), and that lowering systolic blood pressure below 130 mmHg may not increase benefits. According to the baseline characteristics of participants in the relevant trials, hypertension was well controlled in a substantial proportion of patients (baseline BP values are presented in figures above).

Antihypertensive medications were commonly used by the trial participants at baseline. The most frequently used compounds were agents acting on the renin-angiotensin system (54–65 % of patients), calcium channel blockers (17–21%), diuretics (22–32%) and beta blockers (20–21%). During the trial, changes were made in these medications, most often regarding agents acting on the renin-angiotensin system (approximately in 10 % of subjects). It has not been reported whether these changes consisted of initiations or dosing alterations. It is therefore impossible to completely exclude the effect of concomitant medication on the changes in systolic BP during the trials.

DIRECT EVIDENCE: In the three relevant trials (DIA3009, DIA3006 and DIA3015), canagliflozin seemed to induce a reduction in systolic blood pressure. In DIA3009 mean reductions of – 2.0 mmHg and -3.1 mmHg were noted with canagliflozin 100 mg and 300 mg, respectively, at 104 weeks. In DIA3006, decreases in systolic blood pressure of the same magnitude as in DIA3009 at 2 years were seen in canagliflozin treatment, whereas in DIA3015, which lasted for 52 weeks, the mean systolic BP change was -5.1 mmHg. In the comparator groups, glimepiride induced an increase of 1.7 mmHg in SBP, and sitagliptin resulted in minor changes in blood pressure. The decrease in systolic BP in canagliflozin treatment seemed to be greatest at weeks 42–44, after which the levels started to increase. The differences between canagliflozin 100 mg and canagliflozin 300 mg in their effects on systolic blood pressure were minor (slightly over 1 mmHg on average).

INDIRECT EVIDENCE: The results represented in the results section indicate the following.

Dual therapy:

- At 26 weeks the results suggest that
 - Canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, liraglutide 1.2/1.8 mg and glimepiride in reducing SBP

- At 52 weeks the results suggest that
 - Canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, liraglutide 1.2 mg and glimepiride in reducing SBP
- At 104 weeks the results suggest that
 - Canagliflozin 100 and 300 mg might be more effective than glimepiride in reducing SBP

Triple therapy: At 26 weeks the results suggest that canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg in reducing SBP.

Overall, there are well known limitations related to the indirect comparisons (see e.g. EUnetHTA guideline: Comparator and comparisons). As a consequence, the quality of such evidence is very low. Further discussion on methodological issues related to indirect comparisons is found in the Appendix 1: Methods.

Conclusions

In conclusion, added on metformin and compared with glimepiride or sitagliptin, canagliflozin seems to induce a greater decrease in systolic BP. This decrease was 2–3 mmHg at 104 weeks. Concurrent to this, in combination treatment with metformin and sulphonylurea and compared with sitagliptin, canagliflozin 300 mg treatment resulted in greater decreases in systolic BP (mean decrease 5 mmHg). In previous clinical trials examining the association between lowering systolic BP and cardiovascular disease, reductions in systolic BP of about 10–12 mmHg have been associated with relative reductions in stroke risk of 38 % in stroke risk and of 16 % in coronary heart disease risk (Neal B et al 2000). Recently, smaller reductions in systolic BP (in the range of 3–5 mmHg) have also been shown to improve the prognosis in hypertension, particularly in placebo-controlled trials (Czernichow S et al 2011, Mancini et al 2007). However, there may also be differences between antihypertensive agent classes in this respect.

The mechanism behind the decrease in systolic BP in canagliflozin treatment is largely unknown, but strong emphasis has been placed on the decreased extracellular volume caused by the treatment. In contrast to this, however, is the finding that the pulse rate was not increased during canagliflozin treatment in DIA3006.

The blood pressure lowering effect of canagliflozin may be especially relevant in elderly subjects. The exposure in them has been shown to be increased by 29% (CHMP assessment report, redacted version). Hypotension is further discussed in Safety domain.

As there is no long-term experience with canagliflozin, the clinical importance of the changes in systolic BP levels during canagliflozin treatment remains unclear at the moment. The exact mechanisms behind the BP changes should be addressed, and most importantly, long-term experience with canagliflozin treatment is called-for.

The risk of bias was evaluated as high and the quality (level) of evidence as moderate regarding changes in systolic blood pressure (direct evidence).

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005F]: [How does canagliflozin affect the following outcome: weight change]?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other: [use also Table 2 to document]

Critical appraisal criteria None

Method of synthesis Narrative

Result

The results are represented as follows:

1. DIRECT EVIDENCE

1.1 Dual Therapy

1.2 Triple Therapy

2. INDIRECT EVIDENCE

2.1 Dual Therapy

2.2. Triple Therapy

1. Direct Evidence

[Johnson & Johnson submission file (2013)]:

1.1. Dual Therapy

1.1.1 DIA3009 (Canagliflozin Versus Glimpiride as Add-on to Metformin, N = 1450, 104 weeks):

The mean body weight at baseline was 86.9 kg in canagliflozin 100 mg group, 86.6 kg in canagliflozin 300 mg group and 86.5 kg in glimepiride group. Among subjects, 95% were on metformin at ≥ 2000 mg/day, with 31% receiving ≥ 2500 mg/day. The mean metformin dose was 2180 mg/day, which was similar across all treatment groups. The results for weight changes at 52 weeks (primary assessment time point) are shown in table below.

Table 97. Weight changes at 52 weeks (Canagliflozin Versus Glimpiride as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg	CANA 300 mg	GLIM
Body weight % change	-4.2 (0.2)	-4.7 (0.2)	1.0 (0.2)
<i>Difference vs. GLIM</i>	-5.2 (-5.7, -4.7) ^{d,t}	-5.7 (-6.2, -5.1) ^{d,t}	

Abbreviations: CANA; canagliflozin, GLIM, glimepiride, mITT, modified intent-to-treat; LOCF, last observation carried forward.

^aLeast squares mean (SE) change from baseline using ANCOVA (except for documented hypoglycaemia rate) and GLIM-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only;

^dUpper limit of 95% CI $< 0.0\%$ for the comparison to GLIM;

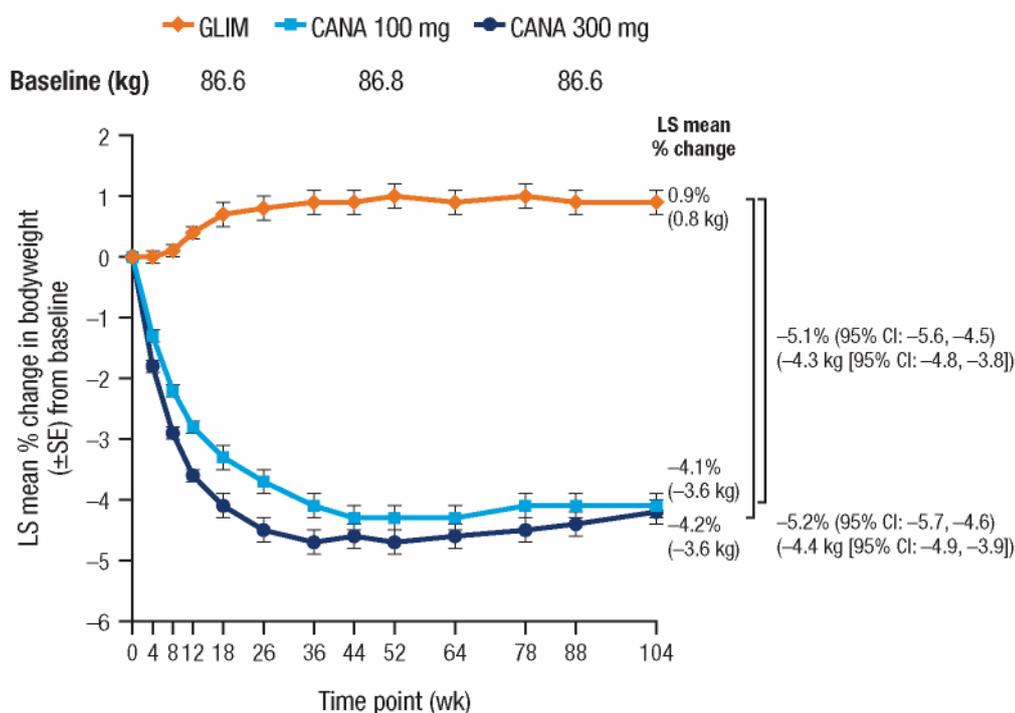
^tP < 0.001 vs. GLIM.

Source: [Johnson & Johnson submission file (2013), page 155, table 41, mITT, LOCF, table is modified]

The mean body weight loss was 3.7 kg (standard error 0.2 kg) in canagliflozin 100 mg group, 4.0 kg (SE 0.2 kg) in canagliflozin 300 mg group and the mean body weight gain was 0.7 kg (SE 0.2 kg) in glimepiride group in the primary analysis at week 52. In the secondary analysis, at week 104, the corresponding numbers were -3.6 (0.2) kg for canagliflozin 100 mg, -3.6 (0.2) kg for canagliflozin 300 mg and 0.8 (0.2) kg for glimepiride.

At Week 52, approximately 90% of all canagliflozin-treated subjects had a decrease in body weight compared with approximately 30% of subjects in the glimepiride group (submission file, main document, page 162). The observed body weight changes were sustained over the 104-week treatment period. For both canagliflozin groups, the nadir in body weight reduction was observed around Week 36, with a generally stable subsequent maintenance of the reduction; for the glimepiride group, a small progressive increase was observed through Week 26, with a subsequent stabilisation of body weight through Week 104 (Figure below).

Figure 22. Percent change in body weight from baseline to Week 104 (LOCF) for DIA3009.



Abbreviations: LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin; LS, least squares; SE, standard error.

Source: [Johnson & Johnson submission file (2013)]

1.1.2 DIA3006 (Canagliflozin Versus Sitagliptin as Add-on to Metformin, N = 1284, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, 52 weeks):

Mean body weight at baseline was 87.7 kg in sitagliptin 100 mg group, 88.8 kg in canagliflozin 100 mg group, and 85.4 kg in canagliflozin 300 mg group. The results for weight changes at 52 weeks (primary assessment time point) are shown in below.

Table 98. Weight changes at 52 weeks (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg (n = 368)	CANA 300 mg (n = 367)	SITA 100 mg (n = 366)
Body weight % change	-3.8 (0.2)	-4.2 (0.2)	-1.3 (0.2)
<i>Difference vs. SITA</i>	-2.4 (-3.0, -1.8) ^e	-2.9 (-3.4, -2.3) ^e	

Abbreviations: CANA, canagliflozin; SITA, sitagliptin; LOCF mITT, modified intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; ANCOVA, analysis of covariance; CI, confidence interval; NS, not significant.

^aLS mean (SE) change from baseline using ANCOVA and SITA-subtracted LS mean (95% CI) for all parameters;

^bP values are reported for pre-specified comparisons only;

^eP <0.001 vs. SITA

Source: [Johnson & Johnson submission file (2013), page 170, mITT, LOCF, table is modified]

In the primary analysis, at week 52, the mean body weight loss was 3.3 kg (standard error 0.2 kg) for canagliflozin 100 mg arm, 3.7 kg (SE 0.2 kg) for canagliflozin 300 mg, and 1.2 kg (0.2 kg) for sitagliptin arm (Johnsson & Johnsson submission file (2013), Appendix 9). The proportion of subjects with a ≥5% body weight reduction by the end of the 52-week treatment period was

substantially greater with canagliflozin 100 and 300 mg (31.3% and 35.7%, respectively) than with sitagliptin 100 mg (11.7%).

1.2 Triple Therapy

1.2.1 DIA3015 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU, N = 755, 52 weeks):

The mean baseline body weight 87.4 kg was in canagliflozin 300 mg arm and 89.1 kg in sitagliptin arm. The results for weight changes at 52 weeks (primary assessment time point) is shown in below.

Table 99. Weight changes at 52 weeks (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU)

Parameter ^{a,b}	CANA 300 mg (N = 377)	SITA 100 mg (N = 378)
Body weight % change	-2.5 (0.2)	0.3 (0.2)
<i>Difference vs. SITA</i>	-2.8 (-3.3, -2.2) ^{d,e}	

Abbreviations: CANA, canagliflozin, SITA, sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; SE, standard error; CI, confidence interval; ANCOVA, analysis of covariance; NS, not significant.

^aLeast squares mean (SE) change from baseline using ANCOVA and SITA-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only;

^dUpper limit of 95% CI <0.0% for the comparison to SITA;

^eP <0.001 vs. SITA

Source: [Johnson & Johnson submission file (2013), page 180, table 43, mITT, LOCF, table is modified]

In the primary analysis at 52 weeks, the mean body weight loss was 2.3 kg (standard error 0.2 kg) for canagliflozin 300 mg and the mean body weight gain was 0.1 kg (SE 0.2 kg) in sitagliptin 100 mg arm (submission file, Appendix 9, primary analysis). A moderate proportion of subjects (21%) in the canagliflozin group achieved a ≥5% weight loss, compared with approximately 6% of subjects in the sitagliptin group. Observed body weight reductions were sustained over the 52-week treatment period.

2. Indirect Evidence

Authors' note for interpretation (edited from Johnson & Johnson submission file (2013)):

The indirect comparisons were based on network meta-analyses. For methodological details, see Appendix 1: Methods. Pairwise comparisons of the relative treatment effect for both canagliflozin doses versus all other comparators are presented as median estimates [95% CrI] (negative values interpreted as higher reduction for canagliflozin) and as probabilities of canagliflozin being more effective than the comparator on the endpoint of interest (columns with "Prob" heading). Tables are ranked by SUCRA values, with treatments with the highest probability of being most effective at the top.

[Johnson & Johnson submission file (2013)]:

2.1. Dual Therapy (Metformin Add-on)

Relative treatment effect on body weight (kg) change versus placebo and pairwise comparison of canagliflozin 100/300 mg versus all other comparators at week 26, 52 and 104 are shown in the following tables.

Table 100. Base case analysis – Results of the FE model for the mean difference in weight for canagliflozin versus active comparators, metformin background at 26 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300mg		Prob	SUCRA
	Median	CrI		Median	CrI		
Canagliflozin 300mg QD	0.52	[0.22 ; 0.82]	0%				94%
Exenatide 10µgBID	0.66	[-0.55 ; 1.86]	14%	0.14	[-1.06 ; 1.34]	41%	92%
Dapagliflozin 10mg QD	0.20	[-0.43 ; 0.85]	27%	-0.31	[-0.96 ; 0.33]	83%	83%
Canagliflozin 100mg						100%	75%
Liraglutide 1.8mg QD	-0.12	[-0.63 ; 0.39]	66%	-0.63	[-1.15 ; -0.12]	99%	70%
Exenatide 5µgBID	-0.53	[-1.58 ; 0.53]	84%	-1.05	[-2.10 ; 0.01]	98%	58%
Liraglutide 1.2mg QD	-0.42	[-0.94 ; 0.09]	95%	-0.94	[-1.46 ; -0.43]	100%	57%
Exenatide 2mg QWK	-0.59	[-1.54 ; 0.36]	89%	-1.11	[-2.06 ; -0.16]	99%	56%
Placebo	-1.83	[-2.23 ; -1.43]	100%	-2.35	[-2.75 ; -1.95]	100%	38%
Sitagliptin 100mg QD	-2.09	[-2.43 ; -1.75]	100%	-2.61	[-2.95 ; -2.27]	100%	31%
Vildagliptin 100mg QD	-2.66	[-3.49 ; -1.83]	100%	-3.17	[-4.00 ; -2.35]	100%	24%
Glimepiride	-4.01	[-4.33 ; -3.69]	100%	-4.53	[-4.85 ; -4.21]	100%	13%
Pioglitazone 30mg QD	-4.25	[-5.23 ; -3.26]	100%	-4.77	[-5.75 ; -3.78]	100%	10%
Pioglitazone 45mg QD	-5.70	[-6.64 ; -4.74]	100%	-6.22	[-7.16 ; -5.26]	100%	0%

Source: [Johnson & Johnson submission file (2013)]

Table 101. Base case analysis – Results of the FE model for the mean difference in weight for canagliflozin versus active comparators, metformin background, 52 weeks

	Canagliflozin 100mg		Prob	Canagliflozin 300mg		Prob	SUCRA
	Median	CrI95%		Median	CrI95%		
Exenatide 10µgBID	1.36	[-1.76 ; 4.44]	18%	0.99	[-2.12 ; 4.07]	25%	90%
Liraglutide 1.8mg QD	0.42	[-0.46 ; 1.30]	18%	0.05	[-0.82 ; 0.93]	46%	86%
Canagliflozin 300mg QD	0.37	[-0.18 ; 0.91]	9%				85%
Dapagliflozin 10mg QD	-0.04	[-1.12 ; 1.03]	54%	-0.41	[-1.48 ; 0.66]	77%	72%
Canagliflozin 100mg QD						91%	71%
Liraglutide 1.2mg QD	-0.49	[-1.37 ; 0.39]	87%	-0.85	[-1.74 ; 0.02]	97%	59%
Sitagliptin 100mg QD	-2.11	[-2.66 ; -1.56]	100%	-2.48	[-3.03 ; -1.92]	100%	40%
Vildagliptin 100mg QD	-2.27	[-3.96 ; -0.65]	100%	-2.64	[-4.32 ; -1.01]	100%	38%
Placebo			100%			100%	32%
Glimepiride	-4.07	[-5.76 ; -2.45]	100%	-4.43	[-6.11 ; -2.82]	100%	16%
Glipizide	-4.70	[-5.65 ; -3.76]	100%	-5.07	[-6.03 ; -4.13]	100%	7%
Pioglitazone 30mg QD	-4.67	[-6.49 ; -2.90]	100%	-5.04	[-6.85 ; -3.27]	100%	5%

Source: [Johnson & Johnson submission file (2013)]

Table 102. Base case analysis – Results of the FE model for the mean difference in weight for canagliflozin versus active comparators, metformin background, 104 weeks

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
CANA 300	0.08	[-0.40 ; 0.55]	37%				94%
Cana 100mg						63%	90%
Lira 1.2	-0.61	[-1.55 ; 0.32]	90%	-0.69	[-1.62 ; 0.23]	93%	72%
Lira 1.8	-0.73	[-1.66 ; 0.18]	94%	-0.81	[-1.74 ; 0.11]	96%	68%
Lina 5	-1.65	[-2.37 ; -0.91]	100%	-1.72	[-2.46 ; -0.98]	100%	44%
Placebo	-1.84	[-2.89 ; -0.78]		-1.92	[-2.98 ; -0.85]		37%
Sita 100	-2.04	[-3.07 ; -1.02]	100%	-2.11	[-3.16 ; -1.09]	100%	32%
Vilda 100	-2.84	[-3.39 ; -2.29]	100%	-2.92	[-3.47 ; -2.38]	100%	13%
SU	-4.34	[-4.82 ; -3.88]	100%	-4.42	[-4.90 ; -3.95]	100%	0%

Source: [Johnson & Johnson submission file (2013)]

2.2 Triple Therapy (Metformin + SU Add-on)

Relative treatment effect (based on random effects model) on body weight (kg) versus placebo and pairwise comparison of canagliflozin 100/300 mg versus all other comparators at week 26 are shown in the following table.

Table 103. Base case analysis – Results of the RE model for the mean difference in weight for canagliflozin versus active comparators, metformin + sulphonylurea background

	Canagliflozin 100mg			Canagliflozin 300 mg			SUCRA
	Median	CrI	Prob	Median	CrI	Prob	
Canagliflozin 300mg QD	0.61	[-4.28 ; 5.56]	36%	-	-		77%
Exenatide 10µgBID	0.48	[-6.01 ; 7.21]	41%	-0.14	[-6.14 ; 6.10]	52%	75%
Exenatide 5µgBID	0.08	[-6.83 ; 7.11]	49%	-0.53	[-6.96 ; 6.01]	60%	67%
Canagliflozin 100mg						64%	65%
Liraglutide 1.8mg QD	-0.12	[-7.12 ; 6.95]	52%	-0.73	[-7.20 ; 5.81]	63%	64%
Placebo	-1.02	[-5.94 ; 3.92]	73%	-1.63	[-5.84 ; 2.56]	85%	48%
Linagliptin 5mg QD	-1.35	[-8.43 ; 5.71]	72%	-1.96	[-8.56 ; 4.59]	80%	45%
Sitagliptin 100mg QD	-2.03	[-7.79 ; 3.69]	83%	-2.64	[-6.82 ; 1.51]	93%	34%
Long-acting insulin	-3.97	[-10.59 ; 2.71]	92%	-4.58	[-10.69 ; 1.60]	95%	15%
Biphasic insulin	-4.52	[-11.63 ; 2.64]	92%	-5.13	[-11.73 ; 1.51]	95%	11%

Source: [Johnson & Johnson submission file (2013)]

Discussion

The methods for measuring weight have not been reported. It is plausible that the method has been similar between relevant treatment arms.

Direct evidence

Added on metformin treatment, canagliflozin with either dosage seems to be able to result in weight reduction of approximately 4 %, which was greater than that induced by glimepiride or sitagliptin treatment. Added on metformin and sulphonylurea treatment, and compared with

sitagliptin treatment, canagliflozin 300 mg seemed to be able to result in weight loss (mean of 2.5%, 2.3 kg) whereas in the sitagliptin group no clear weight change could be observed. The use of sulphonylurea may modify the effect of canagliflozin on weight.

An antidiabetic medicine with an ability to cause weight loss is a very attractive option in type 2 diabetes, as reductions in weight in general are favourable with regard to insulin resistance and therefore need of medication, and with regard to the prognosis (Aucott 2008, Kumar et al 2012). The mean absolute weight reductions induced by canagliflozin were comparable with those obtained by anti-obesity drugs such as orlistat, sibutramine and rimonabant (Zhou et al 2012). However, there are some differences between these anti-obesity drugs and canagliflozin in their effects on lipid levels, as in orlistat treatment, total and LDL cholesterol concentrations are decreased, and HDL cholesterol and triglycerides concentrations are unchanged compared with placebo treatment (Zhou et al 2012). Therefore the results obtained with anti-obesity drugs cannot be interpolated to canagliflozin treatment as such.

Although there were implications of sustained weight loss for the maximum of 52 weeks, it is important to bear in mind that there are no long-term trials on canagliflozin in Type 2 diabetes yet, and the long-term effects of the pharmaceutical are still unknown.

The risk of bias was evaluated as high and the quality (level) of evidence as moderate regarding weight change (direct evidence).

The safety and effectiveness of canagliflozin in promoting weight loss in non-diabetic overweight and obese patients has been recently addressed. The trial included 376 participants in 4 treatment arms (placebo, canagliflozin 50 mg, canagliflozin 100 mg, canagliflozin 300 mg daily), and the trial lasted 12 weeks. In this study, the per cent change in body weight from baseline to week 12 was (mean, standard deviation) -1.1 (2.4) % for placebo, -2.0 (3.0) % for canagliflozin 50 mg, -2.8 (2.9)% for canagliflozin 100 mg and -2.5 (3.0)% for canagliflozin 300 mg. The absolute changes in body weight were -1.1 (2.46) kg for placebo, -1.9 (2.90) kg for canagliflozin 50 mg, -2.8 (2.90) kg for canagliflozin 100 mg, and -2.4 (2.90) kg for canagliflozin 300 mg. However, the drop-out rates in this trial were high: 20 % in the placebo group, 27 % in canagliflozin 100 mg group, and 31 % in canagliflozin 300 mg group causing considerable risk of bias. The last-observation-carried-forward method was applied in the analyses (clinicalTrials.gov NCT00650806).

Indirect evidence

The results represented in the results section indicate the following.

Dual therapy:

- At 26 weeks the results suggest that
 - Canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, vildagliptin 50 mg, glimepiride and pioglitazone 30 and 45 mg in reducing weight
 - Canagliflozin 300 mg might be more effective than liraglutide 1.2 mg and exenatide 2 mg in reducing weight
- At 52 weeks the results suggest that
 - Canagliflozin 100 and 300 mg might be more effective than sitagliptin 100 mg, vildagliptin 50 mg, glimepiride, glipizide and pioglitazone 30 mg in reducing weight
 - Canagliflozin 300 mg might also be more effective than canagliflozin 100 mg in reducing weight
- At 104 weeks the results suggest that
 - Canagliflozin 100 and 300 mg might be more effective than linagliptin 5 mg, sitagliptin 100 mg, vildagliptin 50 mg and SU (glimepiride, glipizide) in reducing weight

Triple therapy: At 26 weeks the results suggest that there are no straightforward evidence (the estimates are imprecise) on differences in weight change between the treatments.

Overall, there are well known limitations related to the indirect comparisons (see e.g. EUnetHTA guideline: Comparator and comparisons). As a consequence, the quality of such evidence is very low. Further discussion on methodological issues related to indirect comparisons is found in the Appendix 1: Methods.

References

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005G]: [How does canagliflozin affect the following outcome: insulin requirements change]?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria: None

Method of synthesis: Narrative

Result

There is no data directly aimed at assessing this outcome in the MAH submission file.

Discussion

In the Appendix 17 included in the submission file (Concomitant medications in the active comparator studies) the medications at baseline and which were started/modified after initiation of study medication are displayed for trials DIA3006, DIA3009 and DIA3015. During the study period, in all three studies additional antidiabetic medications including insulins had been initiated or changed. There were some differences concerning the drugs that were started or changed between the study arms. There is not enough data to evaluate the rationale behind and reasons for these differences or their importance. There may have been differences in treatment patterns between the different countries, or in patient preferences. Comorbidities may also have played a role.

In conclusion, there is no data related to changes in insulin requirements in canagliflozin treatment in any combination and compared to any active comparator.

In DIA3008 the add-on use of canagliflozin to insulin in high risk subjects was investigated, either as monotherapy or in combination with other antidiabetic drugs. This is a placebo-controlled trial and therefore out of scope of this assessment.

References

Johnson & Johnson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005H]: [How does canagliflozin affect the following outcome: proportion achieving < 7% HbA1c target without hypoglycaemia?]

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None
 Method of synthesis Narrative

Result

Authors' note:

The method for measuring HbA1c has not been reported. The method for measuring plasma glucose has not been reported. The threshold for hypoglycaemia was measured blood glucose less than 3.9 mmol/L regardless of symptoms or severe events (requiring the assistance of another person, or with loss of consciousness or a seizure).

[Johnson & Johnson submission file (2013)]:

1.1. Dual Therapy

1.1.1 Canagliflozin Versus Glimepiride as Add-on to Metformin (DIA3009, 104 weeks, N = 1450)

The mean baseline HbA1c in the trial was 7.8% at baseline. For the canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride groups, respectively, 50%, 57%, and 33% of subjects had HbA1c <7.0% and no hypoglycaemia at 52 weeks.

1.1.2 Canagliflozin Versus Sitagliptin as Add-on to Metformin (DIA3006, N = 1284, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, 52 weeks)

The mean HbA1c value at baseline was 7.9%. For the canagliflozin 100 mg, canagliflozin 300 mg, and sitagliptin 100 mg groups, respectively, 36%, 50%, and 48% of subjects had HbA1c <7.0% and no hypoglycaemia at 52 weeks.

1.2 Triple therapy

1.2.1 Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU (DIA3015, N = 755, 52 weeks)

The mean HbA1c value at baseline was 8.1%. For the canagliflozin 300 mg and sitagliptin 100 mg groups, respectively, 22% and 13% of subjects had HbA1c <7.0% and no hypoglycaemia at 52 weeks.

Discussion

This outcome is pivotal for patients and especially the quality of life related to disease and treatment. Hypoglycaemia had been defined as blood glucose of ≤ 3.9 mmol/L (regardless of the presence of symptoms) or severe events (requiring the assistance of another person, or with loss of consciousness or a seizure) (submission file, main document, page 85). The threshold of 3.9 mmol/L represents all glucose values below the lower limit of the reference range and as such comprises a very conservative approach to the issue being in line with the EMA guideline (EMA 2012). In the relevant trials, hypoglycaemic events include both mild and severe hypoglycaemias. In many recent trials assessing antidiabetic drugs, the threshold for hypoglycaemia has been lower, for example 3.1 mmol/L (Nauck et al 2011, Buse et al 2009, Zinman et al 2012). Hypoglycaemias are further discussed in the **safety domain**.

The HbA1c target of 7.0% is discussed in **results card D005A**.

The proportion of trial subjects reaching the HbA1c treatment goal without hypoglycaemias was greater in canagliflozin groups (either dose) compared with glimepiride in dual therapy (combined with metformin). Approximately half of the patients in the canagliflozin arms reached this composite endpoint whereas the corresponding proportion was one third in glimepiride treatment. Added to metformin and compared with sitagliptin 100 mg, a comparable proportion of trial participants reached the HbA1c target without hypoglycaemias (approximately half of the participants) in canagliflozin 300 mg group, whereas in canagliflozin 100 mg arm, only approximately one third reached the endpoint. In triple therapy (added on metformin and sulphonylurea), only approximately one in five reached the combination endpoint with canagliflozin 300 mg and one in eight with sitagliptin 100 mg treatment.

It is not reported, if there were differences between canagliflozin and its comparators with regard to which component of the composite endpoint was not reached, i.e. whether hypoglycaemias were more common in one treatment arm, whereas not reaching the HbA1c target was more frequent in another treatment arm. However, considering the results for the outcome of proportion subjects reaching the HbA1c target, in DIA3009 at 52 weeks, a considerable proportion of participants in the glimepiride arm achieved the treatment target, but experienced hypoglycaemias (approximately 27%), whereas the corresponding number in canagliflozin 100 mg arm was 5 %. For canagliflozin 300 mg arm the submitted numbers do not match (54% reaching the target but 57 % reaching the target without hypoglycaemias) (see also **results card D0005H**). In DIA3006, the proportion of subjects reaching the target but experiencing hypoglycaemias was approximately 4 % in each study arm. In DIA3015, the corresponding figures were 26% in canagliflozin arm and 22% in sitagliptin arm possibly suggesting that hypoglycaemia may be more common in multidrug treatment.

The study patients were allowed to use other antidiabetic medicines besides the study drugs. Initiations of non-study antidiabetic drugs or modifications of non-study or study anti-diabetic drugs were reported in 4.3–5.6% (most of these initiations, with no clear difference between study groups in incidence) of study participants in DIA3009, in 6.5–7.6% in DIA3006 (most of these were initiations, no clear difference between study groups in incidence), and in 13.0–15.9% in DIA3015 (most being modifications, no clear difference between study groups in incidence) (submission file, appendix 17). The dosages of the additional AHAs are not reported, and therefore the effect of non-study antidiabetic medication cannot be addressed reliably. Furthermore, HbA1c is influenced by multiple factors including other medications, nutrition and also physical activity. The assessment of the independent comparative effect of canagliflozin on the composite outcome (HbA1c target achieved without hypoglycaemias) is challenged by these limitations.

In conclusion, the composite endpoint of HbA1c less than 7.0% without hypoglycaemias seems to be reached more often in canagliflozin 100 mg or 300 mg treatment than in glimepiride treatment, when these are added on metformin. Compared with sitagliptin 100 mg (both added on metformin or on metformin and sulphonylurea), the findings of the studies are inconsistent, but canagliflozin 300 mg seems to be at least as effective and may be more effective than sitagliptin, whereas canagliflozin 100 mg seems to be less effective. Canagliflozin seems to be at least as effective as its comparators regarding this outcome, but there are limitations to consider. In order to address this question, a study with restrictions for additional antidiabetic medication is needed.

The risk of bias was evaluated as high and the quality (level) of evidence as low regarding the composite outcome proportion achieving HbA1c with no hypoglycaemias.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0005I]: [How does canagliflozin affect the following outcome: change in cardiovascular risk factors – fasting plasma lipids?]

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

Authors' note:

The effect of canagliflozin on other fasting blood glucose, HbA1c, weight and body mass index as well as systolic blood pressure is addressed elsewhere (result cards D0005A, D0005C, D0005D, D0005F, D0005E). This result card focuses on lipids. The results are presented in the following order:

1. DIRECT EVIDENCE

1.1 Dual therapy (fasting plasma lipids)

1.2 Triple therapy (fasting plasma lipids)

Authors' note:

The baseline lipid parameters have not been reported in the submission file main document. In Appendix 16 of the submission file, based on clinical study reports, and retrieved for CORE modelling, the following information was available.

Table 104. Baseline lipid value

Baseline lipid value	DIA3009	DIA3006	DIA3015
Total cholesterol	4.78±0.62 mmol/L 184.67±23.75 mg/dL	4.90±0.51 mmol/L 189.31±19.86 mg/dL	4.62±0.77 mmol/L 178.44±29.66 mg/dL
HDL cholesterol	1.21±0.18 mmol/L 46.72±6.89 mg/dL	1.17±0.14 mmol/L 45.22±5.58 mg/dL	1.18±0.22 mmol/L 45.56±8.41 mg/dL

Source: [Johnson & Johnson submission file (2013)]

Overall, canagliflozin induced small but consistent changes in serum lipids; most pronounced were increases in LDL-C and HDL-C. The LDL-C/HDL-C ratio remained essentially unchanged. A post-hoc analysis using NMR spectroscopy was performed to assess LDL-C particle number; results showed that the increase in the total LDL-C particle number was driven primarily by a large increase in particle number of the large LDL-C subfraction, with little or no change in the small LDL-C particle number, hence leading to an increase in the less atherogenic subfraction. The increase in serum lipoproteins could also be due to haemoconcentration. This would be in line with the finding that LDL-C and HDL-C increased by around the same amount.

A greater increase was seen with canagliflozin 300 mg than with canagliflozin 100 mg.⁷⁴

1.1 Dual Therapy

1.1.1 DIA3009 (Canagliflozin Versus Glimepiride as Add-on to Metformin, 104 weeks, N = 1450):

A summary of efficacy endpoints at Week 52 (primary assessment time point, mITT, LOCF) is shown in table below.

Table 105. Summary of efficacy endpoints at Week 52 (Canagliflozin Versus Glimepiride as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg	CANA 300 mg	GLIM
Triglycerides % change	-3.7 (2.5)	2.3 (2.5)	9.5 (2.5)
<i>Difference vs. GLIM</i>	-13.2 (-19.4, -7.0)	-7.2 (-13.4, -1.0)	
HDL-C % change	7.9 (0.8)	9.0 (0.8)	0.3 (0.8)
<i>Difference vs. GLIM</i>	7.5 (5.6, 9.5)	8.6 (6.7, 10.6)	
LDL-C % change	9.6 (1.9)	14.1 (1.9)	5.0 (1.9)
<i>Difference vs. GLIM</i>	4.5 (0.0, 9.1)	9.0 (4.4, 13.7)	

Abbreviations: CANA, canagliflozin, GLIM, glimepiride; mITT, modified intent-to-treat; LOCF, last observation carried forward.

^aLeast squares mean (SE) change from baseline using ANCOVA (except for documented hypoglycaemia rate) and GLIM-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only

Source: [Johnson & Johnson submission file (2013), page 155, table was modified]

At week 104, in secondary analysis (mITT) the effects of canagliflozin are reported in table below.

Table 106. Summary of efficacy endpoints at Week 104 (Canagliflozin Versus Glimepiride as Add-on to Metformin)

Treatment group	CANA 100 mg	CANA 300 mg	GLIM
Number of subjects			
mITT	483	485	482
HDL-C (LSM % change [LSM change])	9.4% (0.10 mmol/L)	10.1% (0.11 mmol/L)	0.8% (0.00 mmol/L)
Standard error	0.9% (0.01 mmol/L)	0.9% (0.01 mmol/L)	0.9% (0.01 mmol/L)
TG (LSM % change [LSM change])	4.5% (-0.05 mmol/L)	7.9% (0.01 mmol/L)	13.9% (0.06 mmol/L)
Standard error	2.7% (0.06 mmol/L)	2.6% (0.06 mmol/L)	2.6% (0.06 mmol/L)
LDL-C (LSM % change [LSM change])	11.1% (0.14 mmol/L)	14.2% (0.24 mmol/L)	6.3% (0.06 mmol/L)
Standard error	2.1% (0.04 mmol/L)	2.1% (0.04 mmol/L)	2.1% (0.04 mmol/L)
LDL-C/HDL-C (LSM % change [LSM change])	4.3% (-0.07 mol/mol)	5.3% (-0.01 mol/mol)	7.7% (0.04 mol/mol)
Standard error	2.3% (0.03 mol/mol)	2.3% (0.03 mol/mol)	2.3% (0.03 mol/mol)
Non-HDL-C (LSM % change [LSM change])	6.3% (0.14 mmol/L)	10.3% (0.26 mmol/L)	6.1% (0.10 mmol/L)
Standard error	1.3% (0.04 mmol/L)	1.3% (0.04 mmol/L)	1.3% (0.04 mmol/L)
Effect estimate per comparison	CANA 100 mg vs GLIM	CANA 300 mg vs GLIM	
HDL-C	0.10 mmol/L ^a	0.11 mmol/L ^a	
	8.6% ^b	9.3% ^b	
	6.4; 10.7 ^c	7.1; 11.5 ^c	
TG	-0.11 mmol/L ^a	-0.06 mmol/L ^a	
	-9.4% ^b	-5.9% ^b	
	-16.0; -2.9 ^c	-12.5; 0.6 ^c	

Treatment group	CANA 100 mg	CANA 300 mg	GLIM
Number of subjects			
mITT	483	485	482
LDL-C/HDL-C	-0.11 mol/mol ^a	-0.06 mol/mol ^a	
	-3.4% ^b	-2.4% ^b	
	-9.1; 2.3 ^c	-8.1; 3.4 ^c	
LDL-C	0.08 mmol/L ^a	0.18 mmol/L ^a	
	4.9%	8.0	
	-0.4; 10.1 ^c	2.7; 13.2 ^c	
Non-HDL-C	0.04 mmol/L ^a	0.16 mmol/L ^a	
	0.3% ^b	4.2% ^b	
	-3.0; 3.6 ^c	0.9; 7.5 ^c	

Abbreviations: CANA, canagliflozin, GLIM, glimpiride

^a LSM difference between groups (change);

^b LSM difference between groups (% change);

^c 95% CI (% change)

Source: [Johnson & Johnson submission file (2013), Appendix 9, table is modified]

1.1.2 DIA3006 (Canagliflozin Versus Sitagliptin as Add-on to Metformin, for the first 26 weeks one arm used placebo followed with sitagliptin treatment for the next 26 weeks, N = 1284):

A summary of efficacy endpoints at Week 52 is shown in table below.

Table 107. Summary of efficacy endpoints at Week 52 (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

Parameter ^{a,b}	CANA 100 mg (n = 368)	CANA 300 mg (n = 367)	SITA 100 mg (n = 366)
Triglycerides % change	1.9 (2.4)	2.7 (2.4)	-0.4 (2.5)
<i>Difference vs. SITA</i>	2.3 (-3.9, 8.5) ^f	3.2 (-3.1, 9.4) ^f	
HDL-C % change	11.2 (1.0)	13.3 (1.1)	6.0 (1.1)
<i>Difference vs. SITA</i>	5.2 (2.5, 8.0) ^g	7.3 (4.5, 10.1) ^g	
LDL-C % change	7.7 (1.7)	8.7 (1.8)	6.0 (1.8)
<i>Difference vs. SITA</i>	1.7 (-2.8, 6.2)	2.8 (-1.8, 7.4)	

Abbreviations: CANA, canagliflozin, SITA, sitagliptin; mITT, modified intent-to-treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; ANCOVA, analysis of covariance; CI, confidence interval; NS, not significant

^aLS mean (SE) change from baseline using ANCOVA and SITA-subtracted LS mean (95% CI) for all parameters;

^bP values are reported for pre-specified comparisons only;

^fP = NS vs. SITA;

^gP = NS vs. SITA due to multiplicity control.

Source: [Johnson & Johnson submission file (2013), page 170, modified from Table 42]

Table 108. HDL-C and TG at Week 52 (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

HDL-C Effect estimate per comparison (Week 52)	Comparison groups	CANA 100 mg vs SITA 100 mg	CANA 300 mg vs SITA 100 mg
	LSM difference between groups (change)	0.06 mmol/L	0.08 mmol/L
	LSM difference between groups (% change)	5.2%	7.2%
	95% CI (% change)	2.5; 7.9	4.4; 10.0
	P-value (ANCOVA)	Not significant due to multiplicity control	Not significant due to multiplicity control
TG Effect estimate per comparison (Week 52)	Comparison groups	CANA 100 mg vs SITA 100 mg	CANA 300 mg vs SITA 100 mg
	LSM difference between groups (change)	0.03 mmol/L	-0.04 mmol/L

Source: [Johnson & Johnson submission file (2013), appendix 9, table is modified]

1.2 Triple Therapy

1.2.1 DIA3015 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU, 52 weeks, N = 755):

A summary of efficacy endpoints at Week 52 is shown in table below.

Table 109. Summary of efficacy endpoints at Week 52 (Canagliflozin Versus Sitagliptin as Add-on to Metformin + SU)

Parameter ^{a,b}	CANA 300 mg (N = 377)	SITA 100 mg (N = 378)
Triglycerides % change	9.6 (2.8)	11.9 (2.9)
<i>Difference vs. SITA</i>	-2.3 (-9.8, 5.3) [†]	
LDL-C % change	11.7 (1.8)	5.2 (1.8)
<i>Difference vs. SITA</i>	6.4 (1.7, 11.2)	
HDL-C % change	7.6 (0.9)	0.6 (0.9)
<i>Difference vs. SITA</i>	7.0 (4.6, 9.3) ^g	

Abbreviations: mITT, modified intent-to-treat; LOCF, last observation carried forward; SE, standard error; CI, confidence interval; ANCOVA, analysis of covariance; NS, not significant.

^aLeast squares mean (SE) change from baseline using ANCOVA and SITA-subtracted mean (95% CI) values;

^bP values are reported for pre-specified comparisons only;

^gNot significant due to multiplicity control.

Source: [Johnson & Johnson submission file (2013), page 170, modified from Table 43]

Table 110. HDL-C and TG at Week 52 (Canagliflozin Versus Sitagliptin as Add-on to Metformin)

HDL-C	Comparison groups	CANA 300 mg vs SITA 100 mg
	LSM difference between groups (change)	0.09 mmol/L
TG Effect estimate per comparison	Comparison groups	CANA 300 mg vs SITA 100 mg
	LSM difference between groups (change)	-0.04 mmol/L

Source: [Johnson & Johnson submission file (2013), appendix 9, table is modified]

Discussion

Hyperlipidaemia is common among diabetic patients, affecting almost half of the patients and remaining unsatisfactorily controlled (Vijayaraghavan 2010). Current care guidelines recommend aggressive lipid treatment goals for dyslipidaemia in type 2 diabetic population with LDL cholesterol less than 2.6 mmol/L (100 mg/dL), and less than 1.8 mmol/L in subjects with overt cardiovascular disease (ADA 2013).

In the three relevant trials (DIA3009, DIA3006 and DIA3015), canagliflozin treatment seemed to induce both favourable and unfavourable changes in lipid levels. Across the trials, canagliflozin treatment seemed to be associated with increases in HDL cholesterol concentrations. However, increases in LDL cholesterol were also observed.

In DIA3009, at 2 years, increases were seen in LDL cholesterol concentration, and these were in absolute terms 0.14 mmol/L and 0.24 mmol/L for canagliflozin 100 mg and 300 mg, respectively. Compared with glimepiride, the increases in LDL cholesterol were on average two-fold in percentages, but up to four-fold in absolute units (canagliflozin 300 mg). Generally, there seemed to be a dose-dependent effect of canagliflozin on lipid values with greater changes in canagliflozin 300 mg treatment compared with 100 mg. The increases in HDL and LDL cholesterol concentration in canagliflozin treatment were stable between 52 weeks and 104 weeks, but in contrast, the increase in triglycerides concentrations were greater at 104 weeks than at 52 weeks (related to canagliflozin 300 mg only).

In DIA3006, canagliflozin treatment was associated with greater increases in especially HDL cholesterol concentrations compared with sitagliptin, whereas the effect of both trial medications was negligible on triglycerides concentration and the effect on LDL cholesterol concentration was similar. The findings of the trial DIA3015 are partly inconsistent with the findings of the trial DIA3006. In DIA3015, canagliflozin 300 mg treatment was associated with increases in HDL cholesterol as well as in triglycerides. The inducing effect of canagliflozin on LDL cholesterol was greater than that of sitagliptin treatment. In DIA3006, the trial drug was added on metformin only, whereas in DIA3015, the trial drug was added on both metformin and a sulphonylurea. It is possible that the background medication has some effects on lipid levels, although sulphonylureas are not known to increase triglycerides concentrations (Kurukulasuriya & Sowers 2010).

It has been speculated whether the changes in lipid levels are due to hemoconcentration induced by canagliflozin treatment. The rationale behind this discussion is that both HDL cholesterol and LDL cholesterol were increased. Slight dose-dependent increases in haemoglobin, haematocrit, and serum electrolytes were observed with canagliflozin (submission file, main document, page 136). There are previous reports in which dehydration or hemoconcentration has been associated

with increases in HDL and LDL cholesterol, whereas triglycerides concentrations were not affected (Campbell et al 1994, Bachen et al 2002). These findings constitute some support to the construction of the association between hemoconcentration and lipid changes. However, in dapagliflozin trials, dapagliflozin (10 mg) versus placebo, smaller increases in LDL cholesterol and HDL cholesterol concentrations have been seen (2.7% and 5.5%, respectively, and a decrease in triglycerides (-5.4%) (Forxiga, Summary of Product Characteristics). In a trial comparing dapagliflozin with glipizide as add-on therapy to metformin, HDL cholesterol was increased by 5.9% in dapagliflozin treatment whereas LDL cholesterol was decreased by 0.5% and triglycerides by 1.1% (Nauck M et al. 2011). It is therefore plausible, that the mechanisms by which the cholesterol concentrations are increased in canagliflozin treatment are not SGLT2-inhibition-related.

However, the increase in triglycerides concentration may be due to other factors. There was also a dose- and time-dependent pattern in the association between canagliflozin and triglycerides concentration. In canagliflozin 300 mg treatment, the increase in triglycerides was 2.3% at 52 weeks and 7.9% at 104 weeks, whereas this kind of time-dependency was not seen in LDL or HDL cholesterol concentration changes. The association between canagliflozin and triglycerides seems to be mediated by other factors, like glycaemic balance for example, than the association between canagliflozin and cholesterol concentrations.

There are many factors that have an impact on the lipid levels or diabetic patients. Among these are antilipidemic drugs, other drugs with lipidemic effects, nutrition (especially energy and fat content), glycaemic balance (poor balance leads to increases in triglyceride levels), physical activity, and stress etc.

In the relevant trials a substantial number of study patients were using antilipidemic drugs at baseline. In DIA3009, lipid modifying agents were used by 46.2–52.5% of subjects at baseline, in DIA3006, lipid modifying agents were used by 41.0–42.0% of patients in the canagliflozin and sitagliptin groups, and in DIA3015, lipid modifying agents were used by 51.5–55.6% of patients at the beginning of the trial. The majority of the compounds were statins (41.2–43.6% of the whole patient population in DIA3009, 34.3–36.4% in DIA3006, and 46–52%, in DIA3015). However, 6–10% of the whole patient populations were using fibrates. During the studies, antilipidemic drugs (most often statins) were started or modified after initiation of study medication in 5–11% of subjects in the active medication arms with no clear difference between the study groups (submission file, Appendix 17). It has not been reported to which extent these were initiations or dosing or compound changes, or what percentage of patients were using antilipidemic drugs at the end of the trial or the dosages used, so it is impossible to address the effect of changes in the use of antilipidemic drugs on the lipid changes during the trial.

In conclusion, added on metformin and compared with glimepiride, canagliflozin treatment was associated with greater increases in HDL and LDL cholesterol and smaller increases in triglycerides concentration. Added on metformin and compared with sitagliptin, canagliflozin treatment was associated with greater increases in HDL cholesterol. Added on metformin and sulphonylurea, and compared with sitagliptin, canagliflozin treatment was associated with greater increases in LDL and HDL cholesterol. However, there are limitations when considering the strength of these associations, as there are many factors influencing lipid levels, including antilipidemic medication, the use and changes of which were not restricted in the relevant trials. However, as the results are rather parallel, there seems to be a trend of increasing HDL and LDL in canagliflozin treatment.

The increases in LDL cholesterol in canagliflozin treatment varied between 7.7 and 14.1%, and the absolute numerical changes were between 0.14 mmol/L and 0.24 mmol/L. In previous placebo-controlled statin trials a reduction of 1% in LDL cholesterol concentrations has been associated with a reduction of 1.7% in major cardiac event risk, or a reduction of 7% in LDL would reduce coronary heart disease incidence by 15% (Lin et al 2010). Additionally, cardiovascular risk has been found to be reduced in association with increases in HDL cholesterol concentration. In a recent meta-analysis, annual all-cause mortality and major vascular events were reduced by 10% and 22%, respectively, per 1.0 mmol/L LDL reduction, and therefore an increase of 0.2 mmol/L in LDL cholesterol would translate into an increase of 2% in all-cause mortality and of 4% in major vascular events annually (Baigent C et al 2010). The effects of canagliflozin on mortality will be discussed in **results card D0001**.

As there is no long-term experience with canagliflozin, the clinical importance of the changes in the lipid levels during canagliflozin treatment remains unclear at the moment, especially as both the HDL cholesterol and the LDL cholesterol concentrations increase possibly thus counteracting each other's impact. It is also unclear what the clinical importance of the pathophysiologic mechanisms behind increased LDL or HDL cholesterol concentrations are, if the increases are associated with prolonged hemoconcentration.

The exact mechanisms behind the lipid changes should be addressed and most importantly, long-term experience with canagliflozin treatment is called-for.

The risk of bias was evaluated as high and the quality (level) of evidence as low regarding changes in lipids.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly Not

[D0006]: How does canagliflozin affect long-term complications of diabetes (e.g. cardiovascular, renal and eye complications)?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file of J&J)
- Domain search
- Other: [use also Table 2 to document]

Critical appraisal criteria None

Method of synthesis Narrative

Result

See the methods result card for description of relevant trials.

EVIDENCE AND FINDINGS

[Johnson & Johnson submission file (2013)]:

Author note:

Diabetic complications (i.e. retinopathy, nephropathy, macroangiopathy, neuropathy) have not been prespecified outcomes in the three relevant trials (DIA3009, DIA3006 or DIA3015) comparing canagliflozin treatment with an active comparator.

SIMULATED/PREDICTED LONG TERM OUTCOMES USING CORE DIABETES MODEL

Simulation methodology

MAH presented results for predicted long-term outcomes using the IMS Core Diabetes Model. The model has been described elsewhere (Palmer et al. 2004a). **All the following results for predicted effects on long-term outcomes were presented in Johnson & Johnson submission file (2013).** Simulations were presented only for comparisons for which head-to-head evidence was available. The results of the sensitivity analyses were not reported with respect to long-term outcomes.

According to Johnson & Johnson submission file (2013) clinical inputs (treatment effects) and population characteristics at baseline (demographic characteristics, history of disease and health condition) in the simulation using IMS Core Diabetes Model correspond to those observed in clinical trials (DIA3006, DIA3009 and DIA3015). Mortality from other causes is based on adjusted European mortality numbers (mortality which reflects the average non-diabetes related mortality in average European population). Methodology and input parameters are discussed in more detail in appendix 1: methods.

Simulation results

Authors' brief note for interpretation:

The figures presented in the following tables characterize the predicted long term outcomes for 55.4-56.7 year old patients (depending on the comparison) who have similar population characteristics on average as in the clinical trial which the comparison is based on (DIA3006, DIA3009 or DIA3015 depending on the comparison). Mortality from other causes reflects the average in European population in the prediction.

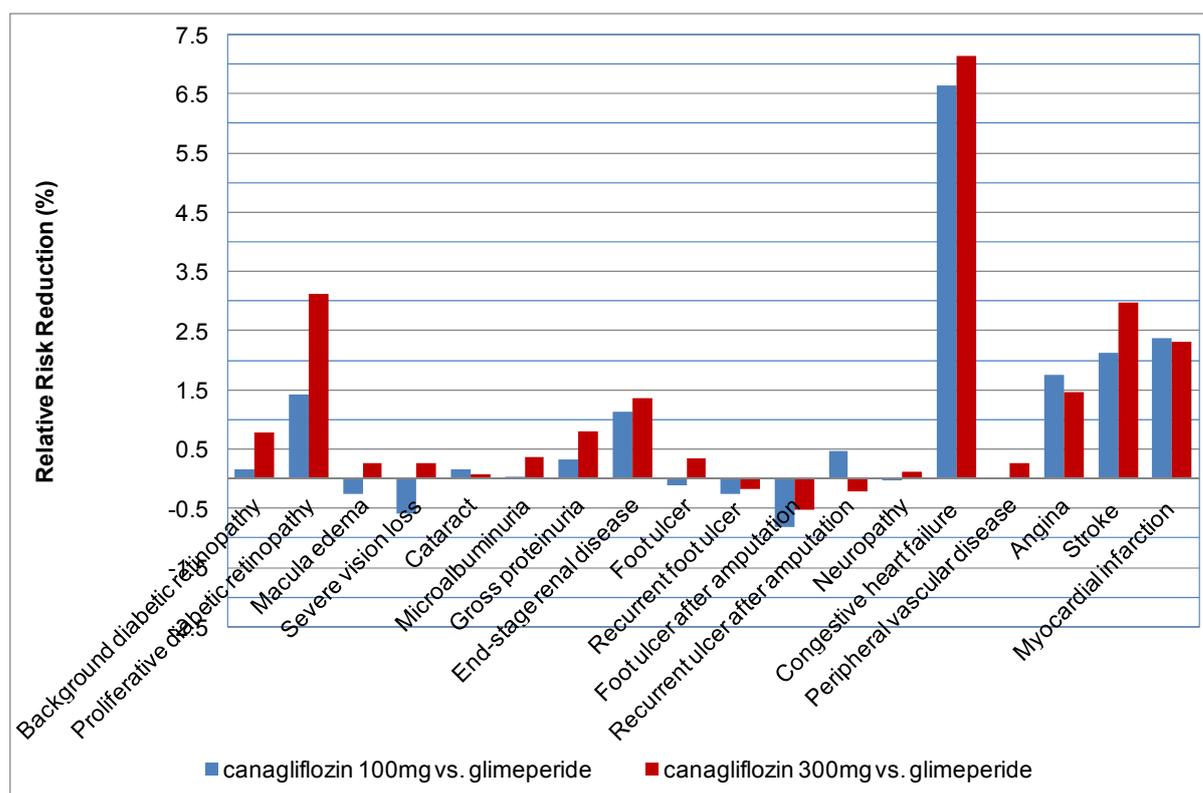
Figures describe the base case relative risk reduction (RRR) of the risk of diabetes related diseases between canagliflozin and the comparator.

[Johnsson & Johnsson submission file (2013)]:

Dual Therapy: Canagliflozin Versus Glimepiride as Add-on to Metformin

Figure 23 below describes the base case relative risk reduction (RRR) of diabetes related diseases between canagliflozin and glimepiride as add-on to metformin.

Figure 23. Base case relative risk reduction (RRR) of diabetes related diseases between canagliflozin and glimepiride as add-on to metformin

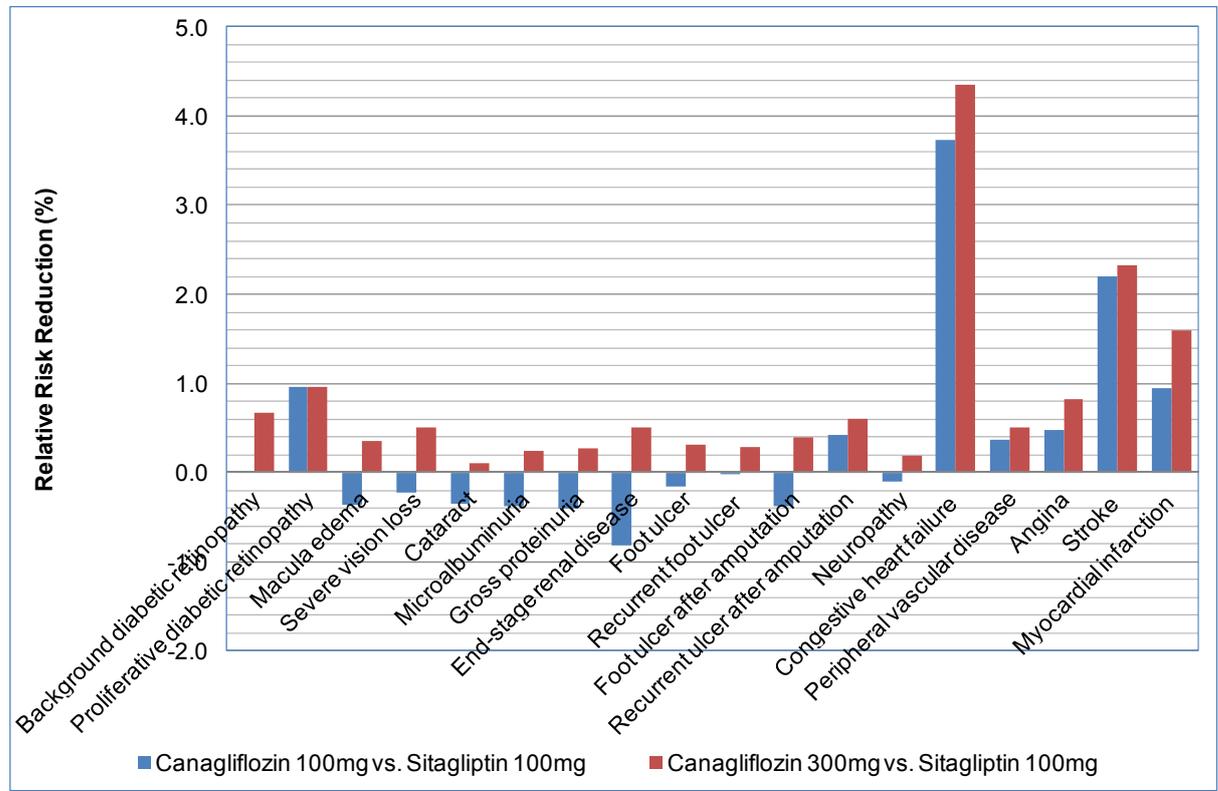


Source: [Johnson & Johnson submission file (2013)]

Dual Therapy: Canagliflozin Versus Sitagliptin as Add-on to Metformin

Figure 24 below describes the base case RRR of the risk of diabetes related diseases between canagliflozin and sitagliptin as add-on to metformin.

Figure 24. Base case relative risk reduction (RRR) of diabetes related diseases between canagliflozin and sitagliptin as add-on to metformin

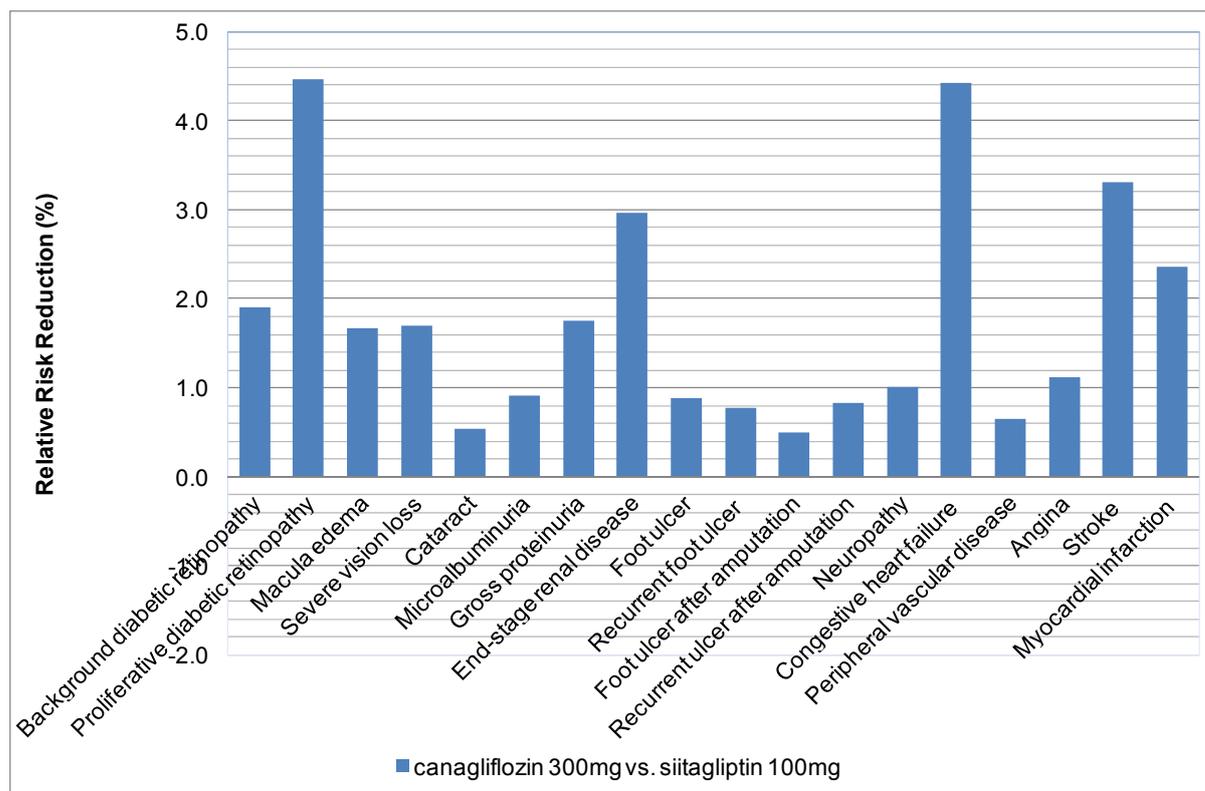


Source: [Johnson & Johnson submission file (2013)]

Triple Therapy: Canagliflozin 300 mg Versus Sitagliptin 100 mg as Add-on to Metformin + SU

Figure 25 below describes the base case RRR of the risk of diabetes related diseases between canagliflozin 300 mg and sitagliptin 100 mg as add-on to metformin plus sulphonylurea.

Figure 25. Base case relative risk reduction (RRR) of diabetes related diseases between canagliflozin 300 mg and sitagliptin 100 mg as add-on to metformin plus sulphonylurea



Source: [Johnson & Johnson submission file (2013)]

Discussion

General notes

The complications of type 2 diabetes have major impact on the patients' prognosis and quality of life. Diabetic complications can be classified as microvascular complications (retinopathy, nephropathy and neuropathy) and as macrovascular complications (i.e. peripheral artery disease or coronary heart disease).

Diabetic retinopathy has been diagnosed in approximately 60–70 % of type 2 diabetics after 20 years of disease. The major risk factors for diabetic retinopathy are hyperglycaemia, high blood pressure and duration of diabetes. Tight control of blood glucose has been shown to delay the onset and progression of diabetic retinopathy in type 2 diabetes (Chistiakov 2012).

Diabetes is the major cause of end-stage kidney failure globally. The prevalence of the microalbuminuria, the mildest form of diabetic nephropathy, has been reported to approximate 40 %, and the prevalence has increased with age, duration of diabetes, and presence of hypertension. Reduced glomerular filtration rate and albuminuria are independent risk factors for cardiovascular events and death (Atkins and Zimmet 2010). There are reports by which intensive control of blood glucose levels and blood pressure as well as lipids, have reduced the incidence and progression of diabetic kidney disease. However, according to recent meta-analyses, available evidence does not unequivocally point to a decreased risk of nephropathy with tight glucose control (Hemmingsen et al 2011, Bousageon et al 2011).

Diabetic nephropathy is also common among type 2 diabetic patients. Age and duration of diabetes increase the risk of neuropathy. In the large UK Prospective Diabetes Study, it was found that 13% of patients had neuropathy severe enough to cause increased risk of foot ulceration already at time of diagnosis (Boulton 2012). Diabetic neuropathy can manifest also as autonomic neuropathy affecting the cardiovascular system, gastrointestinal system or genitourinary system for example (Vinik et al 2003). Tight blood glucose control was not associated with less neuropathy in a recent meta-analysis (Boussageon et al 2011).

Diabetic macroangiopathy has several manifestations including peripheral artery disease, coronary or cerebrovascular disease. Chronic hyperglycaemia has been considered a risk factor for development of diabetic macrovascular disease (Milicevic et al 2008). According to a recent study, subjects with diabetes have a two-fold risk of coronary heart disease or stroke compared with those without diabetes (The Emerging Risk Factors Collaboration, 2010). In a recent meta-analysis tight blood glucose control was not unequivocally shown to decrease myocardial infarction, strokes or congestive heart failure, peripheral vascular events or amputations (Boussageon et al 2011).

The ability of an antidiabetic drug to reduce the rate of diabetic complications is pivotal for a patient's prognosis. Recent meta-analyses have raised the question of the actual role of intensive glucose control in preventing these complications. Many other factors are also important for the development of diabetic complications, such as blood pressure and possibly lipids. Therefore, for any given antidiabetic drug, long-term trials are needed addressing directly the effects of the drug on diabetic complications.

EVIDENCE AND FINDINGS

To date, there is no direct evidence concerning the effects of canagliflozin treatment on long-term outcomes in Type 2 diabetes, including diabetic complications. These have not been prespecified or reported outcomes in the three relevant trials (DIA3009, DIA3006, DIA3015). In one placebo-controlled study (DIA3004), which included only patients with reduced kidney function, and the effects of canagliflozin on renal function were assessed relative to placebo. This study lasted 52 weeks, and renal function was classified as a safety issue. Inconclusive results are available at 26 weeks.

SIMULATED/PREDICTED LONG-TERM OUTCOMES USING CORE DIABETES MODEL

The predictions of long-term outcomes have been performed with simulations using the CORE diabetes model (Palmer et al. 2004a). The Core Diabetes Model has been validated in terms of operational and predictive validity against epidemiological and clinical studies (Palmer et al. 2004b). Simulated/predicted results concerning long-term outcomes in different treatment arms were presented. All the results shown were from simulations of comparisons for which direct evidence from clinical trials was available.

In principle the approach taken is supported by the EUnetHTA guidelines in this case, even though there are limitations in transparency. The general limitations of extrapolating intermediate to final endpoints are also described in EUnetHTA guidelines. The specific limitations related to results presented in the MAH submission are discussed below.

Limitations

The simulations/predictions shown in this card demonstrate a minor positive impact on the long term outcomes. Considering the fact that the results are based on simulations and demonstrate minor differences in relative risks with no confidence intervals, no reliable conclusions based on these results can be drawn.

Secondly, there are well-known limitations in terms of transparency related to Diabetes Core model (see e.g. Cummins et al. 2009). This lack of transparency limits the possibility to thoroughly assess the model quality and the accuracy of the results.

The risk of bias was evaluated as high and the quality (level) of evidence as very low regarding outcome long-term outcomes.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0011A]: What is the effect of canagliflozin on patient’s global functions: SF-36 Physical functioning, mental health and vitality?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

DUAL THERAPY: On metformin

Table 111. Canagliflozin vs. placebo

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical functioning</i>									
Placebo	182	75.3	23.6	129	2.6	20.8	29,1		DIA3006 26 wks
CANA 100	365	76.4	22.4	317	1.8	17.1	13,2		
CANA 300	363	76.6	21.0	322	2.2	15.9	11,3		
<i>Mental health</i>									
Placebo	182	72.2	17.9	129	-0.5	18.3	29,1		DIA3006 26 wks
CANA 100	365	70.5	18.2	317	2.0	16.7	13,2		
CANA 300	363	69.3	19.2	323	-0.2	16.2	11,0		
<i>Vitality</i>									
Placebo	182	62.8	18.7	129	0.2	14.4	29,1		DIA3006 26 wks
CANA 100	365	61.3	20.3	317	2.6	17.5	13,2		
CANA 300	363	60.4	20.4	323	2.0	15.4	11,0		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily
 * Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.
 Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 23 (1).

Table 112. Canagliflozin vs. sitagliptin

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical functioning</i>									
SITA	364	76.2	22.1	302	0.9	18.4	17,0		DIA3006 26 wks
CANA 100	365	76.4	22.4	317	1.8	17.1	13,2		
CANA 300	363	76.6	21.0	322	2.2	15.9	11,3		
SITA	364	76.2	22.1	237	1.0	19.4	34,9		DIA3006 52 wks
CANA 100	365	76.4	22.4	245	1.7	17.7	32,9		
CANA 300	363	76.6	21.0	267	1.7	19.1	26,4		
<i>Mental health</i>									
SITA	364	71.1	18.4	302	0.7	17.6	17,0		DIA3006 26 wks
CANA 100	365	70.5	18.2	317	2.0	16.7	13,2		
CANA 300	363	69.3	19.2	323	-0.2	16.2	11,0		
SITA	364	71.1	18.4	237	0.7	18.2	34,9		DIA3006 52 wks
CANA 100	365	70.5	18.2	245	1.7	16.7	32,9		
CANA 300	363	69.3	19.2	267	-0.3	17.3	26,4		
<i>Vitality</i>									
SITA	364	61.2	19.5	302	2.3	17.4	17,0		DIA3006 26 wks
CANA 100	365	61.3	20.3	317	2.6	17.5	13,2		
CANA 300	363	60.4	20.4	323	2.0	15.4	11,0		
SITA	364	61.2	19.5	237	1.9	16.6	34,9		DIA3006 52 wks
CANA 100	365	61.3	20.3	245	2.2	17.6	32,9		
CANA 300	363	60.4	20.4	267	3.0	17.2	26,4		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily
 * Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.
 Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 24 (1).

Table 113. Canagliflozin vs. glimepiride

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical functioning</i>									
GLIM	481	76.3	21.3	343	0.3	19.2	28,7		DIA3009 52 wks
CANA 100	480	74.4	21.7	373	2.0	16.9	22,3		
CANA 300	483	75.3	22.0	365	2.8	14.6	24,4		
<i>Mental health</i>									

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
GLIM	481	72.6	18.7	342	0.7	16.2	28,9		DIA3009 52 wks
CANA 100	479	71.8	18.8	372	1.5	18.6	22,3		
CANA 300	481	71.5	18.6	364	1.3	17.3	24,3		
<i>Vitality</i>									
GLIM	481	62.9	19.7	342	0.5	15.9	28,9		DIA3009 52 wks
CANA 100	479	60.8	18.9	372	1.2	17.0	22,3		
CANA 300	482	61.0	20.7	365	2.6	16.2	24,3		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 21 (1).

TRIPLE THERAPY: On metformin and sulfonylurea

Table 114. Canagliflozin vs. glimepiride

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical functioning</i>									
Placebo	155	76.6	23.0	109	0.1	13.8	29,7		DIA3002 26 wks
CANA 100	154	75.3	23.2	123	1.5	16.9	20,1		
CANA 300	154	79.2	20.7	127	-0.4	15.4	17,5		
<i>Mental health</i>									
Placebo	154	72.4	19.8	109	0.3	14.7	29,2		DIA3002 26 wks
CANA 100	154	70.2	17.6	124	-0.4	16.1	19,5		
CANA 300	154	73.4	20.0	127	-0.9	16.6	17,5		
<i>Vitality</i>									
Placebo	155	61.5	23.0	110	-0.8	17.5	29,0		DIA3002 26 wks
CANA 100	154	58.4	20.4	124	2.2	15.3	19,5		
CANA 300	154	61.6	22.0	127	1.1	16.5	17,5		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 26 (1).

Table 115. Canagliflozin vs. sitagliptin

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical functioning</i>									
SITA	377	74.4	23.4	316	-1.9	20.6	16,2		DIA3015

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
CANA 300	375	75.0	22.6	306	0.83	17.9	18,4		26 wks
SITA	377	74.4	23.4	213	-1.2	20.1	43,5		DIA3015
CANA 300	375	75.0	22.6	252	0.5	16.0	32,8		52 wks
<i>Mental health</i>									
SITA	378	74.4	18.9	317	-0.4	15.6	16,1		DIA3015
CANA 300	375	73.8	18.6	306	0.8	17.7	18,4		26 wks
SITA	378	74.4	18.9	212	-1.2	15.0	43,9		DIA3015
CANA 300	375	73.8	18.6	253	1.6	16.9	32,5		52 wks
<i>Vitality</i>									
SITA	378	63.2	20.6	317	-1.1	16.7	16,1		DIA3015
CANA 300	375	62.6	20.9	306	2.4	18.1	18,4		26 wks
SITA	378	63.2	20.6	212	0.0	16.0	43,9		DIA3015
CANA 300	375	62.6	20.9	253	3.1	17.4	32,5		52 wks

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 25 (1).

Discussion

Neither canagliflozin, sitagliptin nor glimepiride affected functional ability as measured by SF-36 during a follow-up of at most 1 year.

The Short Form Health Survey (SF-36) is a widely used questionnaire on health-related quality of life (2, 3). It has 36 items and consists of eight domains: physical functioning, bodily pain, role limitations due to physical problems, mental health (or emotional well-being), limitations due to emotional problems, social functioning, vitality (or energy/fatigue), and general health perceptions. Additionally, it has a single item on perceived change in health. From the eight domains, three – physical functioning, mental health and vitality – can be considered to measure some aspect of functional ability. For these domains, a change of 10 units can be considered clinically relevant (4). Johnsson & Johnsson do not report internal consistency statistics for SF-36 in their submission file.

The trials were multi-centred, and study populations coming from all over the world were heterogeneous mix of diverse ethnicities. The baseline means for physical functioning and mental health settle between those of US norms in 1998 (1: Appendix 20) and the patient population of the Medical Outcomes Study (MOS) (5). (Note that the results reported above and US norms are for 1-week recall whereas the means for the MOS population are for 4-week recall.) This is in accordance with the fact that the trial participants were healthier than diabetes patients in general; patients with cardiovascular disease or high risk for it were excluded from the trials. The SF-36 values are for patients before glycaemic rescue therapy which partly explains the remarkable losses to follow-up especially at 1 year.

Quality of life and functional ability are important aspects when it comes to medication of chronic diseases. Considering the items of the SF-36, the instrument cannot be expected to be sensitive for change in these kinds of trials with rather healthy diabetic participants and short follow-up. Yet, it may be speculated that those lost-to-follow-up are more likely to have had a decrease in their

functional ability. Because of the ethnic heterogeneity of the trial populations and losses to follow-up, one needs to be cautious when generalizing the findings. On the other hand, findings from studies with follow-up of a year or less are not predictive enough when long-term medication is under consideration.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0011B]: What is the effect of canagliflozin on patient's global functions: EQ-5D Mobility, anxiety/depression and pain/discomfort?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result**DUAL THERAPY: On metformin****Table 116. Dual therapy: Canagliflozin vs. glimepiride**

Intervention	Baseline			Change in EQ-5D-3L from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Mobility</i>									
GLIM	481	1.3	0.45	341	0.0	0.44	29,1		DIA3009 52 wks
CANA 100	479	1.3	0.46	371	-0.1	0.44	22,5		
CANA 300	483	1.3	0.46	365	-0.1	0.44	24,4		
<i>Anxiety/depression</i>									
GLIM	481	1.3	0.50	342	0.0	0.49	28,9		DIA3009 52 wks
CANA 100	478	1.4	0.54	370	0.0	0.54	22,6		
CANA 300	480	1.4	0.52	363	-0.1	0.51	24,4		
<i>Pain/discomfort</i>									
GLIM	481	1.6	0.55	342	0.0	0.50	28,9		DIA3009 52 wks
CANA 100	479	1.6	0.55	371	-0.1	0.54	22,5		
CANA 300	483	1.6	0.54	365	-0.1	0.53	24,4		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 21 (1).

TRIPLE THERAPY: On metformin and sulfonylurea**Table 117. Triple therapy: Canagliflozin vs. sitagliptin**

Intervention	Baseline			Change in EQ-5D-5L from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Mobility</i>									
SITA	377	1.6	0.84	214	0.0	0.76	43,2		DIA3015
CANA 300	372	1.6	0.83	250	-0.1	0.76	32,8		52 wks
<i>Anxiety/depression</i>									
SITA	377	1.6	0.80	213	0.0	0.75	43,5		DIA3015
CANA 300	373	1.6	0.83	251	-0.1	0.78	32,7		52 wks
<i>Pain/discomfort</i>									
SITA	377	2.0	0.81	214	0.0	0.82	43,2		DIA3015
CANA 300	373	2.0	0.97	251	-0.1	0.94	32,7		52 wks

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 25 (1).

Discussion

Canagliflozin does not seem to affect functional ability compared with sitagliptin or glimepiride as measured by EQ-5D during a follow-up of 1 year.

The EuroQoL-5D (EQ-5D) is a widely used questionnaire on health-related quality of life (2, 3, 4). It has 5 domains, each represented by 1 item: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The instrument has two version – 3L and 5L – and item scores range from 1 to 3 or from 1 to 5, respectively. Additionally, the perceived health status is evaluated on a VAS scale. From the five domains, three – mobility, anxiety/depression and pain/discomfort – can be considered to measure functional ability.

The trials were multi-centred, and study populations coming from all over the world were heterogeneous mix of diverse ethnicities. Furthermore, patients with cardiovascular disease or high risk for it had been excluded so that the participants represented on average those with the best health among diabetes patients. The reported EQ-5D values are before glycaemic rescue therapy which partly explains the remarkable losses to follow-up. The EQ-5D-3L was used in DIA3009 and EQ-5D-5L in DIA3015.

Quality of life and functional ability are important aspects when it comes to medication of chronic diseases. Considering the items of the EQ-5D, the instrument cannot be expected to be sensitive for change in these kinds of trials with rather healthy participants and short follow-up. Yet, it may be speculated that those lost-to-follow-up are more likely to have had a decrease in their functional ability. Because of the ethnic heterogeneity of the trial populations and losses to follow-up, one needs to be cautious when generalizing the findings. On the other hand, findings from studies with follow-up of only a year are not predictive enough when long-term medication is under consideration.

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Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0012]: What is the effect of canagliflozin on generic health-related quality of life: SF-36 Physical and mental component summaries?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

DUAL THERAPY: On metformin

Table 118. Dual therapy Canagliflozin vs. placebo

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical component summary</i>									
Placebo	180	47.4	8.1	128	0.0	6.6	28,9		DIA3006 26 wks
CANA 100	364	47.3	8.1	315	1.0	5.9	13,5		
CANA 300	363	47.8	7.9	322	0.5	6.8	11,3		
<i>Mental component summary</i>									
Placebo	180	48.5	9.4	128	-0.6	8.5	28,9		DIA3006 26 wks
CANA 100	364	47.7	9.6	315	0.9	8.4	13,5		
CANA 300	363	47.1	9.9	322	0.1	7.9	11,3		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 23 (1).

Table 119. Dual therapy: Canagliflozin vs. sitagliptin

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical component summary</i>									
SITA	362	47.4	7.8	300	0.5	5.9	17,1		DIA3006 26 wks
CANA 100	364	47.3	8.1	315	1.0	5.9	13,5		
CANA 300	363	47.8	7.9	322	0.5	6.8	11,3		
SITA	362	47.4	7.8	236	0.4	6.2	34,8		DIA3006 52 wks
CANA 100	364	47.3	8.1	245	1.0	6.7	32,7		
CANA 300	363	47.8	7.9	267	0.8	6.8	26,4		
<i>Mental component summary</i>									
SITA	362	47.9	10.0	300	0.7	9.2	17,1		DIA3006 26 wks
CANA 100	364	47.7	9.6	315	0.9	8.4	13,5		
CANA 300	363	47.1	9.9	322	0.1	7.9	11,3		
SITA	362	47.9	10.0	236	1.0	9.8	34,8		DIA3006 52 wks
CANA 100	364	47.7	9.6	245	0.6	8.2	32,7		
CANA 300	363	47.1	9.9	267	-0.1	8.5	26,4		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 24 (1).

Table 120. Dual therapy: Canagliflozin vs. glimepiride

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical component summary</i>									
GLIM	478	47.3	7.6	340	0.9	6.5	28,9		DIA3009 52 wks
CANA 100	477	46.8	7.9	370	1.2	6.3	22,4		
CANA 300	480	47.4	7.9	363	1.7	6.4	24,4		
<i>Mental component summary</i>									
GLIM	478	49.3	9.9	340	0.2	8.7	28,9		DIA3009 52 wks
CANA 100	477	48.3	10.1	370	0.7	9.7	22,4		
CANA 300	480	48.2	9.9	363	1.1	9.1	24,4		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 21 (1).

TRIPLE THERAPY: On metformin and sulphonylurea

Table 121. Triple therapy: Canagliflozin vs. placebo

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical component summary</i>									
Placebo	153	47.2	8.7	108	-0.2	5.4	29,4		DIA3002 26 wks
CANA 100	152	46.8	8.7	123	0.6	6.1	19,1		
CANA 300	153	48.6	8.2	125	-0.1	6.1	18,3		
<i>Mental component summary</i>									
Placebo	153	49.0	10.8	108	0.3	6.7	29,4		DIA3002 26 wks
CANA 100	152	47.8	9.9	123	0.2	8.5	19,1		
CANA 300	153	49.2	10.4	125	0.1	8.5	18,3		

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 26 (1).

Table 122. Triple therapy: Canagliflozin vs. sitagliptin

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
<i>Physical component summary</i>									
SITA	374	46.7	8.2	313	-0.4	6.8	16,3		DIA3015 26 wks
CANA 300	374	46.8	8.6	305	0.4	7.0	18,4		
SITA	374	46.7	8.2	209	-0.1	7.1	44,1		

Intervention	Baseline			Change from baseline at follow-up			Losses to fup (%)*	Level of evidence	Trial Fup
	N	Mean	SD	N	Mean	SD			
CANA 300	374	46.8	8.6	252	0.9	6.1	32,6		52 wks
<i>Mental component summary</i>									
SITA	374	50.1	9.7	313	-0.3	8.2	16,3		DIA3015
CANA 300	374	49.4	9.9	305	0.8	9.0	18,4		26 wks
SITA	374	50.1	9.7	209	-0.4	7.7	44,1		DIA3015
CANA 300	374	49.4	9.9	252	1.1	9.0	32,6		52 wks

Abbreviations: Fup = Follow-up; Wks = Weeks; CANA 100 = Canagliflozin 100 mg once daily; CANA 300 = Canagliflozin 300 mg once daily; SITA = Sitagliptin 100 mg once daily; GLIM = Glimepiride 1-8 mg mg once daily.

* Losses to follow-up = $(1 - N \text{ at follow-up} / N \text{ at baseline}) * 100$; calculated by authors.

Source: Results from Johnsson & Johnsson REA Submission 2013: Appendix 25 (1).

Discussion

Neither canagliflozin, sitagliptin nor glimepiride affected general health-related quality of life as measured by SF-36 during a follow-up of at most 1 year.

The Short Form Health Survey (SF-36) is a widely used questionnaire on health-related quality of life (2, 3). It has 36 items and consists of eight domains: physical functioning, bodily pain, role limitations due to physical problems, mental health (or emotional well-being), limitations due to emotional problems, social functioning, vitality (or energy/fatigue), and general health perceptions. Additionally, it has a single item on perceived change in health. Physical and mental component summaries are summary scores that represent the quality of life related to physical and mental health. They are calculated based on specific algorithms that weigh each domain differently. The values represented above are based on US norms in 1998 so that mean = 50 and SD = 10 represent the distribution in a normal population (1: Appendix 20). Criteria for clinically relevant changes remain to be determined. Johnsson & Johnsson do not report internal consistency statistics for SF-36 in their submission file.

The trials were multi-centred, and study populations coming from all over the world were heterogeneous mix of diverse ethnicities. The baseline means seem to be just below the US reference population, except for trials DIA3002 and DIA3015 in which the mental component scores are similar to the reference population. This is in accordance with the fact that the trial participants were healthier than diabetes patients in general; patients with cardiovascular disease or high risk for it were excluded from the trials. The SF-36 values are for patients before glycaemic rescue therapy which partly explains the remarkable losses to follow-up especially at 1 year.

Quality of life is an important aspect in chronic diseases. Considering the items of the SF-36, the instrument is not likely to be sensitive for change in these kinds of trials with reasonably healthy diabetic participants and short follow-up. Yet, it may be speculated that those lost-to-follow-up are more likely to have had a decrease in their general health-related quality of life. Because of the ethnic heterogeneity of the trial populations and losses to follow-up, one needs to be cautious when generalizing the findings. On the other hand, findings from studies with follow-up of a year or less are not predictive enough when long-term medication is under consideration.

References

Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

SF-36. www.sf-36.org. (28.6.2013)

Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): I: Conceptual framework and item selection. *Medical Care* 1992;30:473-83.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0013]: What is the effect of canagliflozin on disease-specific quality of life?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

No direct evidence concerning patient satisfaction on the use of canagliflozin.

Discussion

Johnsson & Johnsson have used several different questionnaires in four trials on canagliflozin (DIA3006, DIA3009, DIA3015, and DIA3002) in order to measure patient-reported outcomes (1: Appendix 20): Multidimensional Diabetes Questionnaire (MDQ), Motivation for Exercise and Diet Questionnaire (DIAB-Q), Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Short Form Health Survey (SF-36), Current Health Satisfaction Questionnaire (CHES-Q), EuroQoL Dimension 5-Level (ED-5D), and Diabetes Utility Index (DUI). These questionnaires have items on health-related motivation, beliefs, well-being, and quality of life. Disease-related quality of life is not dealt with.

References

Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0016]: How does use of canagliflozin affect activities of daily living?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file and CHMP)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

No direct evidence concerning activities of daily living on the use of canagliflozin.

Discussion

Johnsson & Johnsson have used several different questionnaires in four trials on canagliflozin (DIA3006, DIA3009, DIA3015, and DIA3002) in order to measure patient-reported outcomes (1: Appendix 20): Multidimensional Diabetes Questionnaire (MDQ), Motivation for Exercise and Diet Questionnaire (DIAB-Q), Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Short Form Health Survey (SF-36), Current Health Satisfaction Questionnaire (CHES-Q), EuroQoL Dimension 5-Level (ED-5D), and Diabetes Utility Index (DUI). These questionnaires have items on health-

related motivation, beliefs, well-being, and quality of life. Activities of daily living were not specifically assessed.

References

Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

SF-36. www.sf-36.org. (28.6.2013)

McHorney CA, Ware JE Jr, Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III: Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care* 1994;32:40-66.

Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): I: Conceptual framework and item selection. *Medical Care* 1992;30:473-83.

Wyrwich KW, Tierney WM, Babu AN, et al. A comparison of clinically important differences in health-related quality of life for patients with chronic lung disease, asthma, or heart disease. *Health Serv Res* 2005;40:577-92.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

[D0017]: Was the use of canagliflozin worthwhile?

Methods

See general description of methods (Appendix 1)

Other, please specify:

Source of information:

- Basic documentation (REA submission file)
- Domain search
- Other:

Critical appraisal criteria None

Method of synthesis Narrative

Result

No direct evidence concerning patient satisfaction on the use of canagliflozin.

Discussion

Johnsson & Johnsson have used several different questionnaires in four trials on canagliflozin (DIA3006, DIA3009, DIA3015, and DIA3002) in order to measure patient-reported outcomes (1: Appendix 20): Multidimensional Diabetes Questionnaire (MDQ), Motivation for Exercise and Diet Questionnaire (DIAB-Q), Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Short Form Health Survey (SF-36), Current Health Satisfaction Questionnaire (CHES-Q), EuroQoL Dimension 5-Level (ED-5D), and Diabetes Utility Index (DUI). These questionnaires have items on health-related motivation, beliefs, well-being, and quality of life. Patient satisfaction on the use of trial treatment or specific medication are not dealt with.

References

Johnsson & Johnsson. Marketing Authorization Holder submission file for EUnetHTA Rapid-Relative Effectiveness Assessment of Canagliflozin. Submission date 15-6-2013.

Importance and transferability

How important is this piece of information for decision making?

Critical

Important

Optional

How transferable is this piece of information, i.e. can it be used in national decisions as such?

Completely

Partly

Not

Appendix 3. Checklist for potential ethical, organisational, social and legal aspects

1. Ethical	
1.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	/No
1.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be ethically relevant?	/No
<p>Example:</p> <ul style="list-style-type: none"> The marketing authorisation holder claims that its product is superior, but has decided to limit the amount of the new medicine, which means that it has to be rationed and not all patients who need it can receive it. The comparator is freely available. 	
2. Organisational	
2.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparators require organisational changes?	/No
2.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be organisationally relevant?	/No
<p>Examples:</p> <ul style="list-style-type: none"> The new medicine will replace a surgical intervention which may lead to excess capacity in relevant areas. The new intervention requires the establishment of specialised centres for administration 	
3. Social:	
3.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	/No
3.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be socially relevant?	/No
<p>Example:</p> <ul style="list-style-type: none"> A medicine which is widely used by persons with abuse problems and which colours the tongue blue, thus immediately identifying the user as such. Comparators do not have this property. 	
4. Legal:	
4.1. Does the introduction of the new medicine and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	/No
4.2. Does comparing the new medicine to the defined, existing comparators point to any differences which may be legally relevant?	/No

Examples:

- The comparator for the new medicine is a pharmaceutical which is not licensed in the indication of concern, but widely in use.
- The comparator for the new pharmaceutical is a controlled, restricted substance, the new medicine is not.
- The most appropriate comparator for the new medicine is available as a pharmacy-compounded medicine, but not as a finished product with marketing authorisation.

Note: The assessment should not address patent-related issues.

Appendix 4. Comments from WP5 members on version 1.2 of the assessment

Name of the Project: Canagliflozin for the Treatment of DIABETES MELLITUS

Project ID: [WP5-SA-2] - Comments from all WP5 members compiled

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Comments from the author
General		It is proposed to further improve the “summary of relative effectiveness” section with clear information on currently available data, type of outcomes assessed and timelines of assessment (see previous comments from HAS). A distinction has to be made between “surrogates” and clinically and patient relevant outcomes and available data clearly described (number of studies, duration). It is of particular importance to give all available information on the ongoing MACE trial. It is also important to discuss other trials that may be relevant for REA. Not many HTA bodies will go throughout the whole document to find data in result cards. Therefore, it is capital that the summary be elaborated and documented as adequately as possible.	The summary of relative effectiveness has been revised. All available data on the MACE ongoing study were included. Definitive conclusions could be drawn at the end of the study, as stated in the document. Information has been added to clarify the duration of the study.
General		General comment: well written and well thought document.	Thank you, we appreciate your input.
4		Under intervention, stating the chemical formula may be of limited value and not necessarily required.	Although of limited value for REA, for information purposes, the chemical formula could be of some interest: Therefore we have made no changes
4, 5		Scope: Please clearly indicate that monotherapy indication together with supportive trials (placebo-controlled) was excluded from the scope and justify why. Please indicate that data from placebo-controlled trials were however analysed for safety. Outcomes: all efficacy or effectiveness outcomes are listed together, there is no distinction between different types of outcomes: <ul style="list-style-type: none"> - HbA1c and related outcomes as surrogates for short-term glycaemic control - Mortality and MACE as long term outcomes for diabetes 	In a relative effectiveness assessment, the focus is on comparing active treatments. There were no studies conducted in canagliflozin monotherapy which included active comparators. To respond on your comment, we added a line indicating that placebo-controlled trials were considered for safety.

Page	Line	Comments	Comments from the author
		<p>control and control of cardiovascular complications</p> <ul style="list-style-type: none"> - BMI: mentioned but not further developed (proposal to delete it, as there is data on weight) - Patient-relevant outcomes including HRQoL - Please add hypoglycaemia as an important patient relevant outcome 	
6	3	The reference to the Element ID A0007 is missing in this section. Please, specify in brackets.	Thank you, A0007 has been added now.
6	4-32	The background on type 2 diabetes is detailed and includes information that you might expect the clinical community to be very familiar with in such a common condition. This level of detail may not necessarily be required.	It has been taken into consideration. We tried to give a fair summary from the different results cards in this Domain; level of information is important for national HTA doers and further national HTA Reports which should get recommendations for decision-makers who are not so familiar with T2DM. Some reviewers ask for even more details.
6		References used in section Health problem, but not in other sections. Consider consistency in referencing.	Thank you, we removed references from this part of the Summary text, they do not belong to Summary section.
6	16-19	Reference?	Please see above.
6	12	It refs are to be added: one is needed after "...premature mortality (A0004)"	Please see above.
6	26	Since you have presented the different types of control therapies in the sentence before, one would expect when you are introducing metformin that you state what type that is.	We added the drug class (biguanides), thank you.
6	28	Side effects: side effects due to what? What side effects are we talking about?	Text is reworded to "Metformin (biguanides) is the optimal first-line drug. If metformin is contraindicated or not tolerated, other drugs can be used in monotherapy. Combination therapy with additional one (dual therapy) or two oral or injectable agents (triple therapy) is reasonable, aiming to minimise side effect of such drug combination where possible." Thank you.
6	33-34	Since dapagliflozin is described here, maybe add just after that canagliflozin. Belong to this class too. If not you do not understand why this is stated here..	Thank you, we added the text on canagliflozin.
6	45-54	A lot of background information is included, much of which would be provided in the Summary of Product Characteristics. This duplication may be of limited value.	Since we had in mind further national adaptation we did not change this text.
6 +7	54+11	The GFR levels for not starting canagliflozin and the contraindication	We changed the text according SmPC; in the Results cards we

Page	Line	Comments	Comments from the author
		are not the same. What is the implication for practice and in this assessment?	mentioned both data and noted that one are from SmPC and one from Micromedex Drugdex database.
6 & 7	53-54 and 11-13	Is the limit less than 30 or 45ml/min/1.73?	Please see above.
6	6-8	Maybe obvious to assessors/experts, but not everybody. Between the sentence "Type 2 DM results from a progressive..." and "The main risk factor...", maybe say that this in turn results in the higher levels of glucose in the blood?"	Further text is added according your comments.
7	4	Please clarify about monotherapy and reasons not to include it	In relative effectiveness assessment, the focus is on comparing active treatments. There were no studies conducted in canagliflozin monotherapy which included active comparators. We added a line below the scoping table indicating that placebo-controlled trials were considered for safety.
7	18-	„The general safety assessment is mainly based on the phase III trials”. – It may be useful to add identifiers for these trials here. Later in the section some trials are named but it is not clear if those are the only ones included. An alternative is to state how many studies “based on XX phase..” as in line 27	Thank you, we added exact number of studies, and some further clarifications.
7	18-	Also consider adding how many patients were included	Included, thank you for your comment
7	18-31	Although in the summary table efficacy outcomes are described first, in the Results section as well as in all following sections, safety is discussed initially and in more detail than efficacy and appears to be given much more prominence than efficacy. It may be preferable to provide greater focus on efficacy and effectiveness and discuss this prior to safety. There is already one similar medicine available and much of the safety discussed is a class effect. The regulators have concluded that although there are safety issues to be followed up on there are none that prevents the licensing of this medicine.	Thank you; we changed the order of safety and effectiveness in the Summary section only. On the rest of the Document the structure has been predefined in the template and therefore the order of these two domains was not changed. HTA doers have different remit from Regulators; majority of AEs are class effects, but some maybe will not be (we need long-term safety data not yet available). Also Regulators do not analyze Risk of Bias of RCTs and RCTs quality according the GRADE.
7	32	Same comment as for page 29 line 32. “Therefore, canagliflozin provides clinically...”	We thank you for your comment, but unfortunately the reference to the comment could not be found in the text. We were unable to make changes based on this comment as a result.
7	37, 38	Please describe in detail the ongoing long-term MACE trial, as it may	We added the text to clarify this issue. CANVAS trial (DIA3008) is an

Page	Line	Comments	Comments from the author
		be capital for the REA. In the current document (pages 89, 90, 92) it is not clear if it is a CANVAS trial (duration 18 weeks?) or not. If yes, please specify.	ongoing study, but also had two sub studies with a duration of 18 weeks: Sulphonylurea Sub study and Insulin Sub study. Details on ongoing CANVAS are given also in Table 10 in Appendix (Ongoing studies).
7-11		Inconsistent specification of dose on the comparator drugs, sometimes named, sometimes not.	Doses are added, thank you.
8	8	Minor review: Please amend outcome to outcome	Corrected, thank you.
8	11	Please add summary of main data on hypoglycemia episodes (pp 184, 223)	Hypoglycaemia was an AE of special interest; data was given on page 9.
9-11		See comment on outcomes. Please specify for all data the time point of assessment (for example canagliflozin 100mg was as effective as... at 24 weeks or at one year...)	We have added a description before presenting the results. This now states clearly that 52 week results are presented unless stated otherwise.
9-	13, 18, 26	„differed little“ ; slightly higher ; clear greatly increase; these may difficult to interpret. Is it possible to tell if significant difference or not. Maybe say: was higher/lower but the difference was not stat. sign.? Is it possible to calculate RRs?	We have added more numerical data into the summary were data are available. Unfortunately, for all but one safety outcomes, p values and confidence intervals were not available. Exception was written p value on one outcome: any documented hypoglycaemia in DIA3009 trial.
10	5 & 8	Long term outcomes: you mean morbidity outcomes such as retinopathy etc?	Yes, for example retinopathy and nephropathy. We have added this to the summary text.
10		Same as above: is it possible to be more precise? Stat. sign? RR? KI?	Thank you; in response to your comment, we have added more numerical data into the summary were data are available. Unfortunately, for all but one safety outcomes, p values and confidence intervals were not available. Exception was written p value on one outcome: any documented hypoglycaemia in DIA3009 trial. Missed p values and CIs are now fully stressed (here and in discussion section, as well as in Summary table).
10	7	„To date, there seems to be no conclusive evidence about the effects of canagliflozin on overall mortality....“ CHANGE INTO “To date, there is no evidence available about the long-term effects on	We have discussed this issue. There is limited evidence but no conclusions can be made (too few cases). As a result, we have not made changes to the text.

Page	Line	Comments	Comments from the author
		canagliflozin on overall mortality....”	
10	13	Surrogate endpoint – while it is acknowledged that HbA1c is a surrogate endpoint and its limitations are widely acknowledged it is still the outcome deemed appropriate by the European Medicines Agency (EMA) for these studies. The heading of ‘surrogate endpoints’ suggests that results may not be particularly robust, this might be harsh if there is no other EMA approved alternative endpoint.	From the effectiveness point of view, HbA1c is considered as a surrogate end point and it is included under such heading. We have, however, added some additional text on this issue to section 5.3 (discussion on clinical effectiveness).
10	15	Does the proposed turn of phrase „at least as effective as“ really reflect the scientific evidence? If non-inferiority is proven, one is normally only permitted to say that the new treatment is “not considerably worse” than the comparator, which is of course not very elegant. Maybe “is not inferior to” or “is probably not less effective” might be preferable.	We have done some rewording based on this comment. Thank you.
10	15	In contrast to the section on safety, very little detail is supplied for efficacy, only the primary outcomes are reported. In the Scoping section ten efficacy outcomes are listed with at least three relating to diabetic control. None of the other supporting outcomes are noted, including responder analysis and fasting glucose which are recommended by the EMA.	We have added more outcomes and data into the summary section.
10	18	The difference in reducing HbA1c is minimal -0,1% and -0,2% respectively versus glimepiride and sitagliptin. It is suggested to mitigate the sentence: “ <i>Canagliflozin 300 mg induced statistically significantly greater reductions in HbA1c than did the comparators in direct comparisons (mean change: -0.9 % vs. -0.8% compared with glimepiride, and -0.9% vs -0.7% compared with sitagliptin 100 mg) in dual therapy.</i> ” E.g. “ <i>Canagliflozin 300 mg induced slightly greater reductions in HbA1c (statistically significantly) than did the comparators in direct comparisons (mean change: -0.9 % vs. -0.8% compared with glimepiride, and -0.9% vs -0.7% compared with sitagliptin 100 mg) in dual therapy.</i> ”	We have added this quote as suggested.
11	39	FDA approval may have little relevance to the EU.	We thank you for your comment, however we have discussed this and decided not to make changes and include the FDA information.
11	40-46	Why is this paragraph sub-headed under the title ‘Reimbursement’ – Can it be named as Authorisation or Regulatory Status	The header has been changed to Market authorisation and reimbursement status.

Page	Line	Comments	Comments from the author
11	46	We think that the last sentence referring to reimbursement decision and the decision taken at national level should be removed.	Thank you for the comments. We have not removed the sentence but we have added a sentence that refers to the assessment element for more details.
12		Summary of relative clinical effectiveness reports only reduction in HbA1c in health benefits.	This probably refers to glucose metabolism outcomes. We have added more outcomes and numerical data into the summary sections.
16		In the discussion on data on cardiovascular events, please give all available information and time/duration of assessment, as the data can radically change after 6 months as compared to 2 or 5 years. The description of the trial and summary of current findings is not found throughout the document.	Thank you for your comment. Clarity has been added on start and end date of the cardiovascular study (CANVAS).
16	3-5	In regulatory studies it is not unusual for the safety outcomes not to be primary outcomes and although they may be reported as secondary outcomes they are often descriptive. It is stated that the overall quality of the evidence is low which conflicts with the EMA conclusion that the quality of the studies was adequate.	We have used risk of bias and GRADE for assessing the quality of evidence, only in three active comparator trials DIA3006, DIA 3009, DIA3015, at 52 weeks EMA may use different criteria and therefore different conclusions can be made. Assessing marketing authorization applications are contextually also different from assessing relative effectiveness. In DIA3009 hypoglycemia is the only outcome marked as Moderate quality of evidence, so we stress this in the text and Tables. In our assessment we did not quote the recent PBAC statement either: "Overall, the PBAC did not consider that the claim that canagliflozin has a comparable safety profile to sitagliptin was adequately supported."
16	47	„to date, there seems to be no conclusive evidence....“ CHANGE INTO “to date, there is no evidence available about the long-term effects on canagliflozin on....”	We do not agree on the statement. We have discussed this issue. There is limited evidence but no conclusions can be made (too few cases).
16	53	Please delete the statement that lack of reliable evidence on long term outcomes is understandable at this stage of a drug development. Even for marketing authorisation purposes, hard outcomes are required more and more often.	Some rewording has been done but we have not removed the whole sentence.
16-17		The discussion etc seem well balanced and easy to read.	Thank you.
16-17	5-40	While taking the discussion as a whole it covers most of the limitations in the clinical evidence base there is still an overriding emphasis on safety over efficacy. The statement related to the primary outcome is: ‘canagliflozin seemed to be able to induce at least similar.... ‘ As the	At this phase of the assessment, it is virtually impossible to carry out major changes which are related to the amount of reporting.

Page	Line	Comments	Comments from the author
		studies demonstrated non inferiority this phrase might be an understatement of its effect and might be better as 'canagliflozin induced similar....'	Some rewording has been done.
17	3	idem	No changes.
18	11	idem	No changes.
24	14	The acronym FPG should be specified in "Fasting Plasma Glucose (FPG).	The information has been added.
24	35	It would be preferable to separate in two different paragraphs the "risk factors" and the "natural course of type 2 diabetes".	We separated the paragraphs.
24	51	The reference to the Element ID A0004 is missing in this section. Please, specify in brackets.	The ID has been added.
25	12-39	None estimates of disease-specific mortality and disability, life years lost, and/or disability-adjusted life years were reported in this paragraph. This information is surely important to understand the impact of the disease for society.	We add some of these data available (Lozano 2012).
27	6	The Authors recommend carrying out regular structured eye surveillance to detect eye damage as is inquiry for neuropathic symptoms to detect nerve damages. Another important recommendation, missing in the draft document but highly recommended by the American Diabetes Association Guideline is the <i>foot care</i> . " <u>For all patients with diabetes, perform an annual comprehensive foot examination to identify risk factors predictive of ulcers and amputations.</u> "	The information has been added.
28	6	The use of registries has been included among research questions but not discussed in the text. It would be worthwhile to report if the implementation of registries could be useful for this specific medicine, taking into account that some countries adopt these instruments to collect additional evidence after the marketing authorisation.	No specific data on the use of registries were found/discussed for this specific drug. Registries may be used and implemented in different countries to collect additional evidence. A brief comment has been added to the text. For additional informations we suggest to refer to results cards (B0010, B0011).
28	29	Please include the chemical structure of the molecule, i.e. glifazine, and amend as follows "Canagliflozin, a glifazine molecule, is an orally...."	Chemical formula of canagliflozin was already included. Chemical structure of glifazine may not add additional evidence for REA, not included
29	10	Please expand eGFR as "estimated glomerular filtration" and include it in the list of abbreviations.	The information has been added.
29	12	Amend Glucuronosyl transferase to Glucuronosyltransferase, with no	The suggestion is processed.

Page	Line	Comments	Comments from the author
		space	
29	32	Amend to “Therefore, canagliflozin provides clinically...”. We suggest to amend the following period: “canagliflozin is expected to be effective across the spectrum of beta cells function, providing...” in order not to draw into confusion about the pharmacological mechanism, as it is due to the inhibition of the filtration of glucose at glomerular level.	The suggestion is processed.
30	44	The sentence could be amended as follows: “A multidisciplinary approach... including trained nurses, dieticians and podiatrists within specific.....”. A rewording of the period is suggested, as teaching skills and adult education do not give adequate clarification on their professional role.	The suggestion is processed.
42	6	idem	Some rewording has been done.
43	21	idem	Some rewording has been done.
46	11-12	Please review „...robust conclusions based on these results should be avoided..“. Statistics, results or processes are robust.	Some rewording has been done.
46	17	Why is it so often mention into Summary Cards that recent meta analysis on the role of intensive glucose control?	This is to emphasize that glucose control is a surrogate end point and data on hard end points are needed.
82-91		Problem with right page margin	This has been corrected. Thank you.
129-131		Problem with right page margin	This has been corrected. Thank you.
141		A0005 is quite quickly described.	New text is added.
142	17	Please consider updating these information with data from the 6 th edition of the report 2013, available at: http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf	Thank you, we added some additional information from MAH Submission file in different Results cards.
142	34	Including prevalence data from other European countries besides Croatia could be useful.	Please see above.
143		A0006 Why country specific data is mentioned only for Croatia?	Please see above.
150	15-16	These information refer to the regulatory status of the technology instead of the reimbursement status.	Please see above. We gave data on marketing authorization with clarification that reimbursement decision will be done on national level (this is new approved drug on the market, and reimbursement decision are not made yet). We could envisage the change in new version of Rapid REA Template, to change title in “Regulatory and

Page	Line	Comments	Comments from the author
			Reimbursement status".
151	30	The result card A0006 includes different information. Therefore the data specific for the result card A0023 should be reported. Moreover it should be considered that in the result card A0006 the whole population with diabetes is reported and not the target of the medicine under evaluation.	Data are given for Result card A0023.
186		Problem with right page margin	This has been corrected. Thank you.
195	Table	Minor review: in table replace the word „hypotensia“ with „hypotension“	The suggestion is processed.
197	14	Minor review: replace the word „inzulin“ in „insulin“	The suggestion is processed.
199	Table	Minor review: in table replace the word “hypotensia“ with „hypotension“	The suggestion is processed.
217	3	Minor review: please replace begging with beginning	The suggestion is processed.
224		Problem with right page margin	This has been corrected. Thank you.
		Many cards are without discussion. Didn't emerge any critical element in the first domain?	No, the 1 st domain is the Domain in which no critical issue was raised. We added only the following text in the Discussion section of A0025: “Data on clinical guidelines in different MSs could be important data at the national level to inform national HTA adaptations and national reports. These data are provided by canagliflozin Manufacturer; survey for MSs partners was not performed to check these data.”
248	22	idem	Not relevant.
291	28	idem	Not relevant.
315	16	Specify the level version of EQ5D: EQ5D-3L or EQ5D-5L?	D0011B revised. EQ5D-3L in DIA3009, EQ5D-5L in DIA3015
338	21	In the sentence “ <i>From the five domains, three – usual activities and self-care – can be considered to measure activities of daily living.</i> ” Only two domains are listed (usual activities and self-care).	In fact, two is correct. Due to other considerations, the result cards D0016A,B were changed to D0016.

Appendix 5. Comments from marketing authorisation holder on version 1.2 of the assessment

Name of the Project: Canagliflozin for the Treatment of DIABETES MELLITUS

Project ID: [WP5-SA-2] - Comments from all WP5 members compiled

GENERAL AND SPECIFIC COMMENTS FOR THE AUTHORS

Page	Line	Comments	Comments from the author	Comment #
		<p><u>GENERAL COMMENT</u></p> <p>Please find below our comments on the Pilot REA report on canagliflozin. We recognise that there must have been difficulties in coordinating such a project between three agencies, and facilitating a review by more agencies. It continues to be a learning experience for us too. We recognise that this was a PILOT exercise, trialling a new process, and that due to constraints beyond everyone's control, timelines on both sides were tight. We do, however, hope that any shortcomings identified in either the original submission or draft report can be appropriately addressed, so that this legacy of the PILOT stands as a fair and balanced assessment of the technology, and not as an assessment of the process.</p> <p>We have separated our comments in to two sections; Major and Minor.</p> <p>Under the heading "Major", we address issues related to: 1) Proper consideration of 104-week data and network meta-analysis (NMA) results, 2) Low quality evidence and high risk of bias, 3) Inherent contradiction in reporting of existing information, particularly (but not exclusively) in the Summary, 4) Network meta-analysis, and 5) Evaluation of patient-reported outcome (PRO) data.</p> <p>Under "Minor", we address all other issues.</p>		1
Major Comments				
General comment		<u>Major point 1</u>	The following text has been added to the	2

<p>t</p>		<p>Proper consideration of 104-week data and NMA results.</p> <p>We believe that it is the intrinsic merit of a Health Technology Assessment to consider data that go beyond short-term randomised controlled trial (RCT) evidence and that all available evidence be properly considered, especially when short-term RCT data, longer-term RCT data, and other data are consistent and complementary.</p> <p>In the context of 1) the demand for longer-term data (as frequently stated in the report) and 2) the fact that differentiation between canagliflozin and comparators becomes more relevant over time, due to better durability of effect with canagliflozin (See EPAR), the omission of the 104-week data from study DIA3009, as well as omission of the 104-week NMA results, in the Executive Summary and in other critical parts of the report, is not appropriate. We realise that these data are probably omitted based on the quality / bias ratings suggested by the authors, but we will address our deep concerns related to these ratings further in this response. There is an inherent contradiction between the demand for longer-term trials and an arbitrary requirement for a clinical trial continuation rate higher than 80%.</p> <p>We also believe that the Cochrane Collaboration’s tool for assessing the risk of bias nor GRADE were designed for, or are appropriate to, evaluate the quality of the NMA. As stated in the EUnetHTA guidance: <i>“The choice between direct and indirect comparison is context specific and dependent on the question posed as well as the different evidence available. Where sufficient good quality head-to-head studies are available, direct comparisons are preferred as the level of evidence is high. Should substantial indirect evidence be available, then it can be used to validate the direct evidence. When there is limited head-to-head evidence or more than two treatments are being considered simultaneously, the use of indirect methods may be helpful.”</i> (Source: http://www.eunetha.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf)</p> <p>The merits of the NMA should be evaluated based on the internal validity and the availability of good underlying RCT evidence, which is the case for treatments of diabetes. Moreover, specifically related to canagliflozin versus comparators, for the research questions where both direct and NMA evidence is available, the results of the NMA are consistent with the results of the direct comparisons. Therefore, it is also plausible that the results of indirect comparisons for treatments which have not been directly compared (but derived from high quality, similarly designed RCTs in</p>	<p>summary to accompany the list of results: <i>“In this section, an overview of the results concerning mortality and long-term outcomes, HbA1c, weight, systolic blood pressure and quality of life is presented. Unless indicated differently, the evidence below is derived from direct comparisons. Durations of studies including active comparators were 52 (DIA3006 and DIA3015) or 104 weeks (DIA3009). Results at 52 weeks, which were available for all active controlled studies, are presented here unless stated otherwise. More detailed and statistically oriented representation of the results, including also additional outcomes, can be found in the domain report. Additionally, the appendices also include more detailed description of the results derived from direct and indirect comparisons at various time points.”</i></p>	
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comparable populations) give reliable indications of relative effectiveness. Downgrading these results by repeatedly stating that NMA have *per se* low quality and high risk of bias is not helpful for guiding decision-making. Illustration of consistency between outcomes of the head-to-head trials and NMA is presented in the Table below.

	CANA 100 mg		CANA 300 mg	
	H2H	NMA	H2H	NMA
<i>Sitagliptin-Subtracted Difference (26 weeks)</i>				
HbA _{1c} , %	0.03	0.01	-0.12	-0.11
FPG, mmol/L	-0.40	-0.55	-0.98	-0.91
Body weight, kg	-2.24	-2.09	-2.54	-2.61
Systolic BP, mmHg	-2.01	-2.02	-3.23	-2.88
<i>Sitagliptin-Subtracted Difference (52 weeks)</i>				
HbA _{1c} , %	0.00	0.02	-0.15	-0.11
FPG, mmol/L	-0.47	-0.55	-0.97	-0.87
Body weight, kg	-2.10	-2.11	-2.50	-2.48
Systolic BP, mmHg	-2.87	-2.83	-3.99	-4.04
<i>Glimepiride-Subtracted Difference (52 weeks)</i>				
HbA _{1c} , %	-0.01	-0.03	-0.12	-0.16
FPG, mmol/L	-0.33	-0.28	-0.50	-0.58
Body weight, kg	-4.52	-4.07	-4.94	-4.43
Systolic BP, mmHg	-3.47	-3.52	-4.77	-4.73
<i>Sulphonylurea-Subtracted Difference (104 weeks LOCF)</i>				
HbA _{1c} , %	-0.09	-0.10	-0.18	-0.19
FPG, mmol/L	-0.49	-0.48	-0.66	-0.66
Body weight, kg	-4.30	-4.34	-4.40	-4.42
Systolic BP, mmHg	-3.74	-3.74	-4.81	-4.79
<i>Sulphonylurea-Subtracted Difference (104 weeks MMRM)</i>				
HbA _{1c} , %	-0.20	-0.20	-0.30	-0.30
Body weight, kg	-4.60	-4.59	-4.70	-4.65
Systolic BP, mmHg	-4.10	-4.07	-5.20	-5.23

We request that the 104-week data from study DIA3009 and the 104-week NMA results be properly considered and that the generic statement that “the quality of such evidence is very low” be reconsidered or qualified in the context of the overall data assessed in the report.

In addition, results at 104 weeks are also now presented shortly in the summary for the key outcomes (HbA_{1c}, weight and SPB).

In the summary section, 52 week results for NMA are represented similarly as with direct comparisons. 104 week results have been presented shortly for the key outcomes (HbA_{1c}, weight and SPB).

Vast amounts of indirect evidence, including varying comparators and time points, were available. In order to come up with a coherent summary, the amount of reporting in the summary has to be limited. The results of the indirect comparisons are always uncertain, and their weight in the summary should be in balance with the direct evidence. The summary of indirect comparisons was limited to reporting only the most

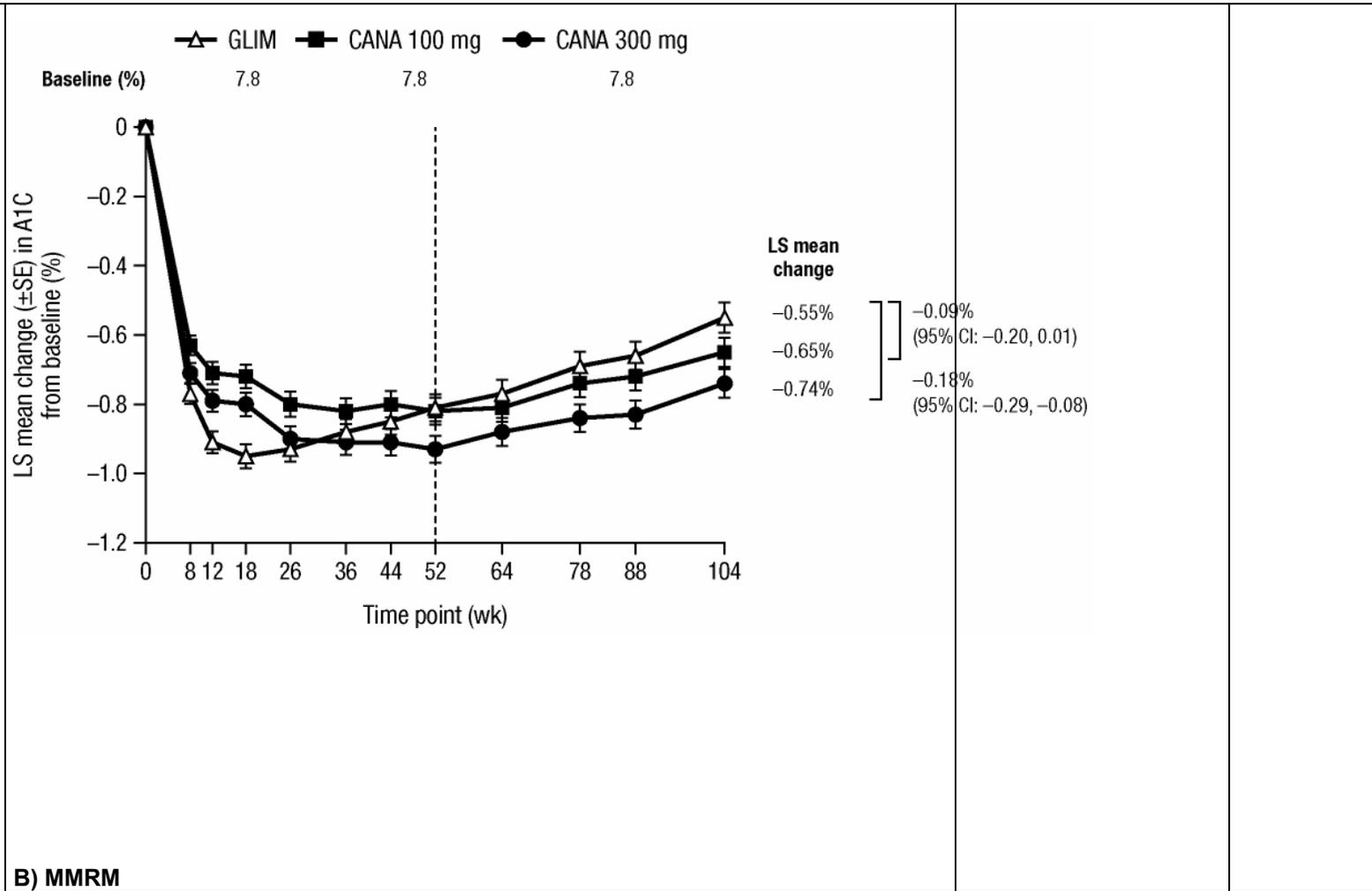
			<p>unambiguous results.</p> <p>We agree that the Cochrane risk of bias or GRADE tool may not be the most appropriate tool to evaluate the differences in quality between NMA based results. However, to relate the quality of NMA results to direct evidence, it is necessary to use the same tool for both NMA and direct evidence.</p> <p>Assessing the risk of bias and the level of evidence is critical for the assessment, and these should be stated to the reader. We have added a few lines to the domain report to facilitate correct interpretation of the GRADEing such as: the quality (level) of evidence as moderate referring to that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p>	
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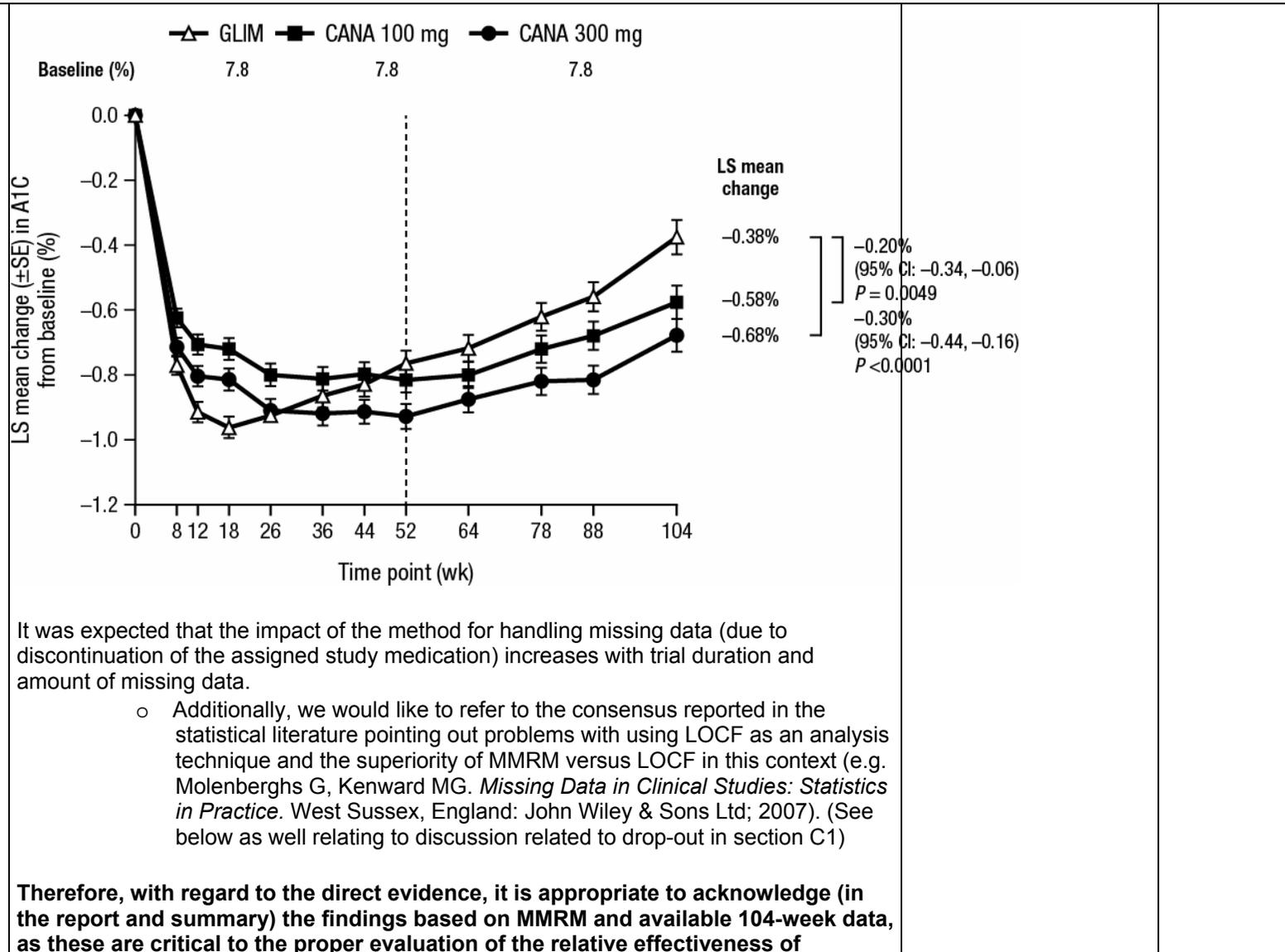
<p>P126</p> <p>Summary P16</p> <p>P38</p> <p>P111 to P128</p>	<p>4-5 & 31</p> <p>13-14</p>	<p>Major point 2</p> <p>“Risk of Bias” is high.</p> <p>The reviewers assessed key head-to-head clinical trials using the Cochrane Collaboration’s tool for assessing the risk of bias. This assessment resulted in the classification as “High Risk” of bias, reported on P111 through P128. This classification “High Risk” of bias appears to be driven by:</p> <ul style="list-style-type: none"> A. Use of modified intent-to-treat (mITT) population as the study population B. Use of Last Observation Carried Forward (LOCF) approach C. That the drop-out rate was “considerable”, and not reported at 104 weeks for trial DIA3009, or at 52 weeks for trial DIA3006. Furthermore, that the average time between end of study and LOCF collection point was not reported D. Lack of sufficient detail on patient characteristics (e.g. comorbidities) or medications at baseline or at end of study (e.g. doses used) in different study groups E. Other sources of bias: That the study was funded by Industry; relationship between company and principle investigators; incidences of some adverse events (AEs) may facilitate prediction of treatment arm <p>We address each contributing factor below.</p> <p>Note: Only a summary table for the GRADE assessment (P126-128) is provided. According to the handbook of Cochrane on GRADE, a ‘Summary of findings’ table provides key information on the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all important outcomes for a given comparison (Source: http://www.mrc-bsu.cam.ac.uk/cochrane/handbook502/).</p> <p>For example, related to Imprecision of results: “The confidence intervals included in the ‘Summary of findings’ table will provide readers with information that allows them to make, to some extent, their own rating of precision.” The EUnetHTA guidelines also state that “clear and consistent decision rules are necessary to achieve acceptable reproducibility when using these instruments” (Source: Levels of evidence - Internal validity of randomized controlled trials, February 2013. http://www.eunetha.eu/outputs/methodological-guideline-rea-pharmaceuticals-</p>	<p>We have reconsidered classification of risk of bias using the new data provided by the MAH (points A, B, C and D). These changes have resulted in changes in risk of bias and GRADE assessment as appropriate. The rating of the trial-specific risk of bias as well as the justification for the rating has been added on risk of bias tables 13, 14, 15 in appendix 1.</p> <p>As a general comment: That a risk of bias has been identified does not automatically indicate that there is bias. Moreover, risk of bias does not refer to the methodological quality either. Biases can operate in either direction: either lead to underestimation or overestimation of the true effect. High risk of bias only refers to uncertainties (to either direction) concerning the results.</p>	<p>3</p>
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		<p>internal-validity).</p> <p>The EUnetHTA assessment of GRADE as listed in the report (P126-128) does not provide the description leading to the scoring on the individual items necessary to achieve acceptable reproducibility and the appropriateness of the assessment, and can therefore not be substantiated.</p>		
P114		<p>A. ITT principle appropriately implemented (attrition bias)</p> <p>The authors report: <i>Quote submission file main document P141: “All reported efficacy analyses are based on the modified intent-to-treat (mITT) populations, which (marginally) differ from ITT, as patients randomised but not initiated on the study medication are excluded (only 2 patients in the glimepiride arm in study DIA3009, ...). For the analysis of change from baseline values for all endpoints, only patients with ≥1 post-baseline value could be included... Primary efficacy results were generated using the last observation carried forward (LOCF) method for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred.” The average transition time in the analyses using LOCF method is not reported.</i></p> <p>mITT was the pre-specified analysis population, defined in the protocol, and agreed with regulatory authorities. As reported in our submission, P141, the use of mITT resulted in the exclusion of only 3 patients across the three trials;</p> <ul style="list-style-type: none"> • 2 patients (from 1,452) in DIA3009 – glimepiride arm • 1 patient (from 756) in DIA3015 – canagliflozin arm • 0 patients (from 1,284) in DIA3006 <p>To ensure consistency in reporting (with EPAR, publications, etc.), the use of mITT was discussed at the scoping meeting in June. The pre-specified population was well documented in the original submission and appeared to be 0.1% less than the number of randomised patients, which should not affect the results and therefore does not warrant the “unclear” rating or the rating of “high risk of bias”.</p>	<p>We have amended the assessment of attrition bias according to the material provided by MAH.</p>	4
P114		<p>B. The use of LOCF (last observation carried forward) for imputing missing values and drop outs.</p> <p>The authors report that: <i>“Primary efficacy results were generated using the LOCF method</i></p>	<p>. The use of MMRM approach has been acknowledged in the assessment of risk of</p>	5

	<p><i>for imputation of missing values and dropouts. The LOCF approach uses the last value observed before dropout, regardless of when it occurred. The average transition time in the analyses using LOCF method is not reported”</i></p> <p>This was discussed at the scoping meeting, where we received feedback that the reviewers would prefer the alternative approach of MMRM to LOCF. That is why our submission included data for both LOCF (consistent with the pre-specified analysis per protocol and agreed with regulatory authorities) and the MMRM (mixed model for repeated measures) approach as requested by the reviewers at the scoping meeting. MMRM was a pre-specified sensitivity analysis to LOCF in our original trial statistical analysis plan.</p> <p>The reviewers acknowledge that MMRM data were supplied (for all three comparative trials) on P62 of the report (lines 24-27):</p> <p style="text-align: center;"><i>“As there is increasing consensus in the statistical community on the superiority of MMRM over LOCF, all efficacy parameters have additionally been analysed using MMRM, a restricted maximum likelihood (REML) repeated measures approach using the mITT analysis set”</i></p> <p>However, the results are not described in the report and no further comments are provided on these analyses. Therefore, for sake of clarity and completeness we summarize the data below:</p> <ul style="list-style-type: none"> • For the Direct Comparisons, efficacy analyses were based on the mITT populations using both LOCF and MMRM methods for missing data. In the canagliflozin dossier, primary outcomes using the MMRM method were provided (i.e. HbA_{1c}, fasting plasma glucose [FPG], body weight, systolic blood pressure [SBP]) at 52 weeks in Appendix 18 and were cross-referenced on P168, P178, and P187 in the submission. <p><u>In summary:</u></p> <ul style="list-style-type: none"> ○ At 52 weeks in all trials, the results based on LOCF imputation & MMRM are consistent. ○ At 104 weeks for DIA3009, results for the primary endpoint of HbA_{1c} 	<p>bias.</p> <p>However, the proportion of dropped-out participants was considerable and has resulted in a major loss of real data. Use of even the most sophisticated statistical approaches has limited capability to replace this lost data and therefore uncertainties remain.</p> <p>In this assessment, drop-out rate of more than 30% was classified as having high risk of bias; and drop-out rate of around or more than 20% as having unclear risk of bias. The applied rating is well in line with EUnetHTA guidelines (Internal validity of randomized controlled trials) and actually this rating is more towards liberal than conservative since the drop-out rate of more than 20% can already lead to high risk of bias when conservative approach is taken in the assessment of risk of</p>	
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		<p>reduction based on MMRM show a substantially larger relative treatment effect for <i>both</i> doses of canagliflozin (100 and 300 mg) versus glimepiride (least squares [LS] mean differences [95% CI] of -0.20% [$-0.34, -0.06$] and -0.30% [$-0.44, -0.16$]; $p < 0.005$ for both comparisons), when compared to LOCF-based results (LS mean differences [95% CI] of -0.09% [$-0.20, 0.01$] and -0.18% [$-0.29, -0.08$]). These data were also presented in the canagliflozin dossier on P157 and are provided below.</p> <p>Changes in HbA_{1c} from baseline to (A) Week 104 (LOCF) and (B) Week 104 (MMRM) for DIA3009.</p> <p>A) LOCF</p>	<p>bias.</p>	
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		<p>canagliflozin versus glimepiride.</p> <ul style="list-style-type: none"> For the Indirect Comparisons, most analyses were based on LOCF, as the systematic literature review showed that the majority of diabetes trials have been reporting such results. Recently, some long term trial results on 2 year data have been reported in the literature using MMRM. As indicated on P217 of our submission, we performed two separate analyses at 104 weeks, including trial results analysed with LOCF and MMRM separately in order to avoid bias due to statistical heterogeneity across trials. <p>The lack of any comment on the MMRM data, both for the Direct and Indirect (week 104) Comparisons, suggest they may have been overlooked in the review process, and therefore impacted the reviewers assessment of the risk of bias of the evidence.</p>		
P114 P116 P118		<p>C1. Issues related to drop-out rate: Transition time & baseline characteristics</p> <p>Transition times</p> <p>Average transition times (between end of study and LOCF collection point) in the analyses using LOCF were not reported in our submission. To rectify this omission, these data are presented below.</p> <p>There were no notable differences between treatment arms in transition times in the head-to-head studies; therefore, these data do not support the rating of high risk for bias due to drop-out.</p>	The data (transition time and baseline clinical characteristics) provided by MAH have been acknowledged in assessing the risk of bias (risk of bias tables 13, 14, 15 in appendix 1) and in the applicability table 19.	6

	Treatment arm	days FIRST - LAST	days LAST - END	N patients
3009 - 52 weeks	1. CANA 100	321.9	44.4	483
	2. CANA 300	313.3	52.2	485
	3. GLIMEPIRIDE	312.1	53.4	482
3009 - 104 weeks	1. CANA 100	544.3	186.1	483
	2. CANA 300	540.9	189.4	485
	3. GLIMEPIRIDE	516.3	214.2	482
3006 - 52 weeks	1. CANA 100	301.2	64.4	368
	2. CANA 300	312.5	53.5	367
	3. STA	293.3	72.6	365
3015 - 52 weeks	CANA 300	297.5	66.6	377
	STA 100	286.4	77.8	378

Days FIRST-LAST: Avg. time between baseline and last observed HbA_{1c} value
 Days LAST_END: Avg. time between last observed value and end of study

Impact of Baseline Characteristics

P111 states: *The characteristics of the dropped-out participants compared with the completed participants have not been reported.*

To address this question, we took the approach of a multivariate time-to-event analysis (proportional hazards regression), with event defined as last observed HbA_{1c} value during use of the study medication. Treatment, demographics (age and gender), and clinical baseline parameters (HbA_{1c}, BMI, eGFR, SBP, and total cholesterol) were included as covariates in the multivariate PHREG-model (presented in the Table below). HbA_{1c} value at baseline was included as a categorical variable.

The only baseline-variable predictive for treatment discontinuation was the baseline value for HbA_{1c}. Patients with high baseline values of HbA_{1c} discontinued earlier from the study medication. When HbA_{1c} was modelled as a continuous variable, the hazard ratios

(HRs) were:

- DIA3009: HR = 1.20 [1.12 – 1.28] (p<0.0001)
- DIA3006: HR = 1.18 [1.18 [1.10 – 1.27] (p<0.0001)
- DIA3015: HR = 1.078 [0.995 – 1.17] (p=0.065)

Table : time to last observed HbA1C-value - multivariate proportional hazards regression

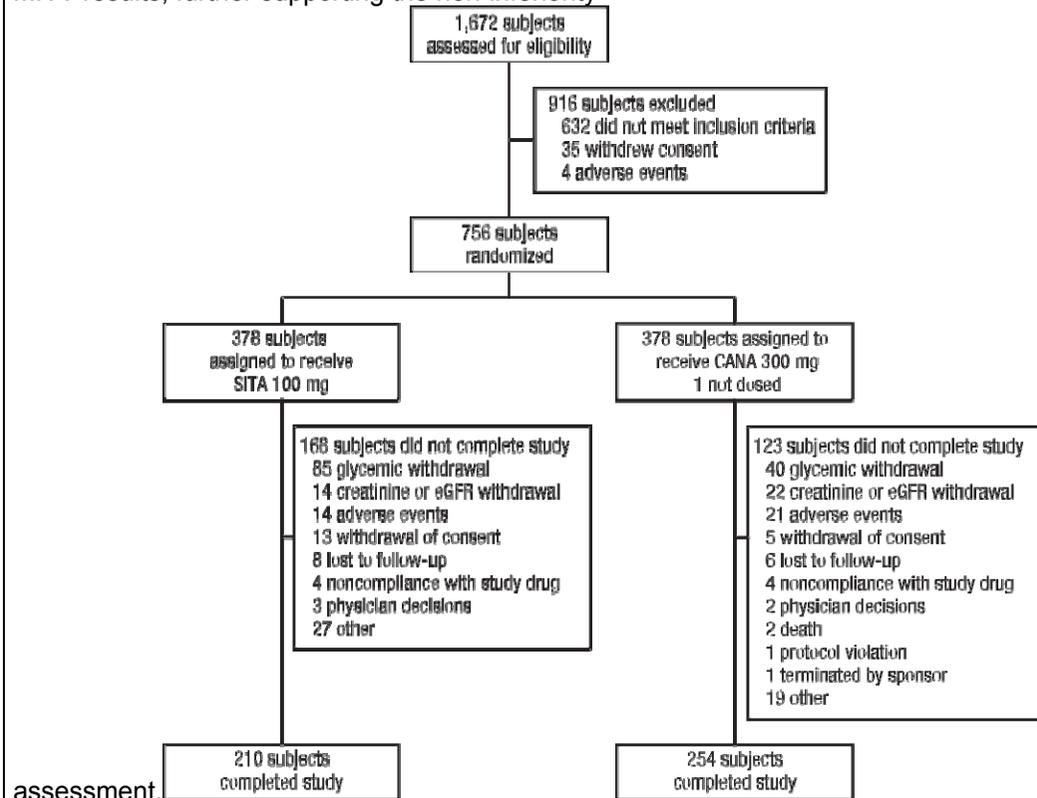
	DIA3009			DIA3006			DIA3015		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Canagliflozin 100	0,87	[0.77;0.99]	0,0319	1,03	[0.89;1.19]	0,6983			
Canagliflozin 300	0,92	[0.81;1.05]	0,1968	0,885	[0.76;1.03]	0,103	0,885	[0.77;1.02]	0,103
Glimepiride	1,00	-							
Sitagliptin 100				1,00	-	-	1,00	-	
Age	1,00	[0.99;1.01]	0,8149	0,999	[0.99;1.01]	0,8138	1,001	[0.99;1.01]	0,8138
Female	1,07	[0.96;1.19]	0,2534	1,064	[0.94;1.21]	0,33	1,081	[0.93;1.26]	0,33
HbA1c <7	0,29	[0.14;0.63]	0,0017	0,422	[0.27;0.66]	0,0002	0,775	[0.48;1.26]	0,0002
7 - <7.5	0,34	[0.16;0.72]	0,0049	0,416	[0.27;0.65]	<0.001	0,783	[0.5;1.24]	<0.001
7.5 - <8	0,32	[0.15;0.69]	0,0036	0,433	[0.28;0.67]	0,0002	0,706	[0.45;1.11]	0,0002
8 - <8.5	0,40	[0.19;0.85]	0,0174	0,477	[0.31;0.74]	0,0009	0,727	[0.46;1.15]	0,0009
8.5 - <9	0,43	[0.2;0.92]	0,0291	0,48	[0.31;0.75]	0,0014	0,926	[0.58;1.47]	0,0014
9 - <9.5	0,44	[0.2;0.96]	0,0388	0,667	[0.42;1.07]	0,0898	0,895	[0.56;1.44]	0,0898
9.5 - <10	0,79	[0.34;1.81]	0,5721	0,653	[0.4;1.08]	0,0955	0,88	[0.52;1.48]	0,0955
10+	1,00	-		1	-		1	-	
eGFR	1,00	[1;1]	0,4451	0,997	[0.99;1]	0,1732	0,997	[0.99;1]	0,1732
BMI	1,00	[0.99;1.01]	0,6864	1,004	[0.99;1.01]	0,4858	0,994	[0.98;1.01]	0,4858
Systolic blood pressure	1,00	[1;1]	0,7738	0,997	[0.99;1]	0,2091	1,002	[1;1.01]	0,2091
Total cholesterol	1,01	[0.96;1.06]	0,6805	0,979	[0.92;1.04]	0,4571	0,952	[0.89;1.02]	0,4571

Estimates of the HR related to baseline HbA_{1c} are consistent for both studies DIA3006 and DIA3009. A similar trend (not statistically significant) is observed for study DIA3015. None of the interaction terms of any of the baseline characteristics with treatment were significant.

		<p>In this context, it is relevant to refer to a recent publication in the BMJ (Bell et al. Differential dropout and bias in randomised controlled trials : When it matters and when it may not, BMJ 2013;346:e8668), co-authored by Prof Kenward (London School of Hygiene and Tropical Medicine), who is one of the experts in the field of missing data in clinical trials.</p> <p>The study nicely illustrates that (similar or dissimilar) dropout rates between study arms do not necessarily lead to biased results: even if dropout differs between treatment groups, estimates of the treatment effect will be unbiased, if an appropriate MMRM is used (under the MAR-assumption). This is because information from patients with complete data is used to implicitly impute the missing values. An appropriate MMRM should incorporate patient characteristics which drive the dropout.</p> <p>The table above shows that an appropriate MMRM-analysis of the canagliflozin -trials should include the baseline HbA_{1c}-value as part of the model specification, to generate unbiased results. The MMRM results for all comparative Canagliflozin trials did include HbA_{1c} as co-variate in the statistical models and showed, as discussed elsewhere, similar (52 weeks) or increased (104 weeks) relative treatment effect for canagliflozin, compared to LOCF results.</p> <p>Therefore, differences in baseline characteristics of the patients that dropped out cannot be the basis for the high-risk rating.</p>		
P114 P116		<p>C2. Issues related to drop-out rate: <u>Drop-out rate reporting</u></p> <p>The report states: <i>The drop-out rates at 104 weeks (3009) and at 52 weeks (3006) were not reported.</i></p> <p>This is incorrect. All completion rates for each treatment arm, by study, were reported in our submission: Table 16, P81 (DIA3006), P82 (DIA3009), and P83 (DIA3015). Completion rates are reported in the third column for all time points used in the direct comparisons.</p> <p>We ask the authors to acknowledge these data and reconsider the outcomes of the associated risk of bias assessments.</p>	This error has been corrected and acknowledged in risk of bias assessment.	7

P118		<p>C3. Issues related to drop-out rate: <u>Misunderstanding of clinical context</u></p> <p>The quote by the authors related to DIA3015, “<i>The drop-out-rate in the trial was remarkable, 32.5–44.4%</i>”, suggests they may not appreciate the clinical context within which the drug is being trialled, or there may be a misunderstanding regarding the study design.</p> <p>As referred to above, research has shown that equal dropout rates can still yield biased estimates of treatment effects, and studies with unequal dropout rates can be analysed to produce unbiased results. When data are missing completely at random or missing at random, MMRM represent one approach for valid analysis. (Source: Bell et al. Differential dropout and bias in randomised controlled trials: when it matters and when it may not. BMJ 2013;346:e8668)</p> <p>Unlike the other head-to-head studies (DIA3006 & DIA3009), the DIA3015 trial did not have a planned blinded extension period wherein patients requiring rescue therapy were retained. As expected then, the drop-out rates were comparatively higher than in the other studies.</p> <p>What the reviewers may not appreciate is what is reported in the discontinuation rate. The discontinuation rate includes both protocol driven “stops”, because the patient’s randomised treatment has failed (akin to disease progression in other therapy areas), as well as protocol violations, loss to follow-up, etc. As detailed in the figure below, subjects who met the glycaemic withdrawal criteria (“failure on randomised regimen”) was 40 (10.6%) in the canagliflozin group and 85 (22.5%) in the sitagliptin group (Source: Schernthaner G, et al. <i>Diabetes Care</i>. 2013;36(9):2508-2515).</p> <p>Adjusting for treatment failures, the drop-out rate for other reasons in DIA3015 is in line with that for the other two head-to-head studies. The discontinuation rate observed with sitagliptin is consistent with that previously reported in a 52-week study comparing sitagliptin with glipizide, which also did not provide rescue therapy (Source: Nauck MA, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, noninferiority trial. <i>Diabetes Obes Metab</i>. 2007;9:194–205). In that study, the rate of discontinuations attributable to reasons other than meeting glucose discontinuation criteria was similar to that observed in the current study.</p>	<p>High drop-out rates result in loss of data, which is challenging to replace reliably by statistical manoeuvres and approaches.</p> <p>We have defined a considerable drop-out rate as around or more than 20% and classified risk of bias associated with this kind of loss of real data as an unclear risk of attrition bias (Please also see the response in comment 5). In addition, a drop-out rate of more than 30 % was classified as high risk of attrition bias.</p>	8
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Furthermore, the power calculations for this study (DIA3015) anticipated a total discontinuation rate similar to that observed. To provide 90% power for the per-protocol analysis (including only those subjects completing the study and without protocol deviations that could impact efficacy assessment), 360 subjects per treatment group were required, which was met. Results of the per-protocol analysis were consistent with the MITT results, further supporting the non-inferiority



assessment.

Guyatt et al. (Guyatt GH, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). *J Clin Epidemiol.* 2011;64(4):407-15) suggests that the thresholds for acceptable loss to follow-up (e.g. less than 20%) may be arbitrary. Guyatt

		<p>et al. describe in an example that “loss to follow-up of 5% in both intervention and control groups would entail little threat of bias if event rates were 20% and 40% in intervention and control groups, since the significance of particular rates of loss to follow-up varies widely and is dependent on the relationship between loss to follow-up and number of events.”</p> <p>Furthermore, EUnetHTA states that thresholds for an ‘acceptable’ exclusion rate (30%) or difference in exclusion rates (15%) should be understood as an initial approximation. In certain circumstances deviations above or below these figures may be appropriate (Source: Levels of evidence - Internal validity of randomized controlled trials, February 2013. http://www.eunetha.eu/outputs/methodological-guideline-rea-pharmaceuticals-internal-validity).</p> <p>We ask the authors to acknowledge these data and reconsider the associated risk of bias assessment related to drop-out rates.</p>		
P247		<p>D. Lack of sufficient detail on patient characteristics (e.g. comorbidities) or medications at baseline or at end of study (e.g. doses used) in different study groups</p> <p>On P247, the authors refer to the possible bias associated with the fact that “<i>The study patients were allowed to use other antidiabetic medicines besides the study drugs. Initiations of non-study antidiabetic drugs or modifications of non-study or study antidiabetic drugs were reported in 4.3–5.6% (most of these initiations, with no clear difference between study groups in incidence) of study participants in DIA3009, in 6.5–7.6% in DIA3006 (most of these were initiations, no clear difference between study groups in incidence), and in 13.0–15.9% in DIA3015 (most being modifications, no clear difference between study groups in incidence) (submission file, appendix 17). The dosages of the additional AHAs are not reported, and therefore the effect of non-study antidiabetic medication cannot be addressed reliably. Also the dosages of the study add-on-to drugs (metformin or metformin and sulphonylurea) were modified during the trials, but the dosages used are not reported. Furthermore, HbA_{1c} is influenced by multiple factors including other medications, nutrition and also physical activity. The assessment of the independent comparative effect of canagliflozin on HbA_{1c} is challenged by these limitations</i>”</p> <p>Appendix 17 (as per canagliflozin dossier) presents all other concomitant medications at</p>	<p>We have inserted new data provided by MAH into applicability table 19 (comorbidities at baseline).</p> <p>Glucose metabolism is influenced by many factors, also other than antidiabetic medicines. The use of non-study antidiabetic drugs was allowed and occurred during the trials. MAH has provided data on the percentages of initiations, changes, increases, decreases and discontinuations concerning use of metformin or sulphonyl</p>	9

	<p>baseline and those started or modified after initiation of study drug; the use of these medications have been assessed to be equal across treatment arms by the authors of the report.</p> <p>As is recommended for non-inferiority designs, in all of the studies, a pre-specified analysis of the per-protocol population (including only those subjects completing the study and without protocol deviations that could impact efficacy assessment, for which a dose change or addition of a non-study drug of a sufficient length would qualify) was also performed in support of the mITT analyses. Overall, the results of the PP analyses were generally consistent with those based on the mITT analyses.</p> <p>The allowance of changes in the dosage of background medications (metformin, sulphonylurea) was a necessity to ensure patient safety. In study DIA3015 for example:</p> <p><i>A stable dose and administration regimen of metformin and a sulphonylurea, once achieved after dose up-titration during the anti-hyperglycaemic agent (AHA) adjustment period (or at screening, for subjects already on protocol-specified doses of both agents), was to be continued at stable doses throughout the run-in period and double-blind treatment phase, unless down-titration of metformin was considered clinically necessary due to intolerance, or metformin treatment must have been temporarily interrupted, per the metformin label (e.g. use of radiocontrast agent was required), or unless the dose of the sulphonylurea agent needed to be decreased to manage hypoglycaemia.</i></p> <p>Per trial medical history at baseline are summarised below and provided as separate attachments (overall summary by body system or organ class for DIA3006, DIA3009, and DIA3015 as well as complete list of preferred terms for each study). Summaries of background therapy at baseline and during the treatment period for metformin and sulphonylurea are provided below.</p> <p>As no differences were observed between the treatment groups in medical history at baseline, and as only a very low number of dosage adjustments were observed for the background therapy with metformin (DIA3006 and DIA3009) and sulphonylurea (DIA3015), in a similar way across treatment arms, we consider that the provision of these data would eliminate the risk of bias for these studies.</p> <p>DIA3006</p>	<p>urea in the three relevant trials. However, according to Appendix 17 of the submission file, other antidiabetic medicines were also initiated and used by the study participants, and these are not reported in sufficient detail to reliably rule out their possible modifying effect on the outcomes.</p> <p>In addition, it was reported that the patients were also using other medications, such as antihypertensives and other cardiovascular medicines.</p> <p>There were no differences observed between the treatment groups concerning the use of study drugs, as pointed out in the report. However, there is no detailed information available concerning the use of non-study drugs including antidiabetic non-study drugs.</p>	
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<p>Medical History At screening, 90% of subjects in the mITT analysis set (89%, 92%, 91%, and 91% in the placebo/sitagliptin, canagliflozin 100 and 300 mg, and sitagliptin 100 mg groups, respectively) had at least 1 secondary diagnosis other than T2DM. Details of secondary diagnoses by treatment arm can be found in the provided attachments. Briefly, the secondary diagnosis by system organ class (SOC) shows that the distribution of medical history incidences by SOC was similar across treatment groups. The most commonly reported secondary diagnoses (defined as reported in greater than 25% of the population) in the mITT analysis set were of the Vascular disorders SOC (64%), with the specific term of hypertension being the most commonly reported (60%), followed by the Metabolism and nutrition disorders SOC (59%), reflecting the secondary diagnoses of obesity (19%) and dyslipidemias (19%), and finally, Musculoskeletal and connective tissue disorders SOC (28%). A moderate proportion (17%) of the mITT subjects had at least 1 secondary diagnosis in the Cardiac disorders SOC at baseline.</p>						
<p>Summary of Background Therapy at Baseline and During the Treatment Period:</p>						
<p>Metformin</p>						
	--- Pbo/Sita - -- (N=183)	CANA 100 mg	CANA 300 mg-	CANA Total	- Sita 100 mg -	----- Total --- --
Metformin at Baseline	183	368	367	735	366	1284
Metformin Daily Dose at Baseline (mg/d)						
N	183	368	367	735	366	1284
Category, n (%)						
< 1500 mg/d	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)
1500 to < 2000	19 (10)	29 (8)	28 (8)	57 (8)	32 (9)	108 (8)
2000 to <2500	98 (54)	224 (61)	237 (65)	461 (63)	240 (66)	799 (62)
□2500 mg/d	66 (36)	114 (31)	101 (28)	215 (29)	93 (25)	374 (29)
Mean (SD)	2196 (389.5)	2165 (354.3)	2146 (319.9)	2156 (337.5)	2126 (356.9)	2153
Median	2000	2000	2000	2000	2000	2000
Range	(1500;4000)	(1000;4000)	(1000;3000)	(1000;4000)	(850;5100)	(850;5100)
Metformin dose after baseline						
N	183	368	367	735	366	1284

Category, n (%) Unchanged 181 (99) 361 (98) 363 (99) 724 (99) 362 (99) 1267 (99) Changed ^a - Decreased 2 (1) 7 (2) 4 (1) 11 (1) 4 (1) 17 (1) - Increased 1 (1) 7 (2) 3 (1) 10 (1) 2 (1) 13 (1) - Interrupted ^b 0 0 1 (<1) 1 (<1) 2 (1) 3 (<1) 1 (1) 0 1 (<1) 1 (<1) 1 (<1) 3 (<1)																			
CANA, canagliflozin, Pbo/Sita, placebo/sitagliptin; SD, standard deviation; Sita, sitagliptin. ^a Change is defined as a sustained (ie, at least 7 consecutive days) modification in metformin dose. ^b Interruption is defined as an interruption of at least 7 consecutive days followed by a restart of metformin at the same dose level on the day of randomisation. Note: Percentages calculated with the number of subjects in each group as denominator. Note: A subject might be counted into more than one category for dose change.																			
DIA3009 Medical History At screening, 93% of subjects in the mITT analysis set (92%, 94%, and 93% in the canagliflozin 100 and 300 mg and glimepiride groups, respectively) had at least 1 secondary diagnosis other than T2DM. Details of secondary diagnoses by treatment arm can be found in the provided attachments. Briefly, the secondary diagnosis by SOC shows only slight differences across groups in the distribution of medical history incidences by SOC. The most commonly reported secondary diagnoses were in the Vascular disorders SOC (70%), with the specific term of hypertension being the most commonly reported (68%), followed by the Metabolism and nutrition disorders SOC (59%), reflecting the specific secondary diagnoses of dyslipidemia or hyperlipidemia (36%) and obesity (15%).																			
Summary of Background Therapy at Baseline and During the Treatment Period: Metformin																			
	<table border="1"> <thead> <tr> <th></th> <th>CANA 100 mg</th> <th>CANA 300 mg</th> <th>CANA Total</th> <th>Glimepiride</th> <th>Total (N=1450)</th> </tr> </thead> <tbody> <tr> <td>Metformin at baseline</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>N</td> <td>483</td> <td>485</td> <td>968</td> <td>482</td> <td>1450</td> </tr> </tbody> </table>		CANA 100 mg	CANA 300 mg	CANA Total	Glimepiride	Total (N=1450)	Metformin at baseline						N	483	485	968	482	1450
	CANA 100 mg	CANA 300 mg	CANA Total	Glimepiride	Total (N=1450)														
Metformin at baseline																			
N	483	485	968	482	1450														

		Metformin daily dose at baseline (mg/d)					
		N	482	485	967		
		482	1449				
		Category, n (%)					
		<1500 mg/d	0	0	0		
		0	0				
		1500 to <2000 mg/d	20 (4)	30 (6)	50 (5)	25 (5)	75 (5)
		2000 to <2500 mg/d	305 (63)	308 (64)	613 (63)	321 (67)	934 (64)
		2500 mg/d	157 (33)	147 (30)	304 (31)	136 (28)	440 (30)
		Mean (SD)	2188 (344.4)	2177 (377.2)	2182 (361.1)	2167 (361.1)	2177
		Median	2000	2000	2000	2000	2000
		Range	(1500;4000)	(1500;4550)	(1500;4550)	(1500;4050)	(1500;4550)
		Metformin dose after baseline					
		N	482	485	967	482	1449
		Category, n (%)					
		Unchanged ^a	468 (97)	480 (99)	948 (98)	470 (98)	1418 ()
		Changed ^a	14 (3)	5 (1)	19 (2)	12 (2)	31 (2)
		- Decreased	8 (2)	3 (1)	11 (1)	10 (2)	21 (1)
		- Increased	4 (1)	1 (<1)	5 (1)	1 (<1)	6 (<1)
		- Interrupted ^b	2 (<1)	1 (<1)	3 (<1)	2 (<1)	5 (<1)
		CANA, canagliflozin; SD, standard deviation.					
		^a Change is defined as a sustained (ie, at least 7 consecutive days) modification in metformin dose.					
		^b Interruption is defined as an interruption of at least 7 consecutive days followed by a restart of metformin at the same dose level on the day of randomisation.					
		Note: Percentages were calculated with the number of subjects in each group as the denominator.					
		Note: A subject might have been counted for more than one category for dose change.					
		DIA3015					
		Medical History					
		At screening, 96% (96.6% and 95.8% in the canagliflozin 300 mg and sitagliptin 100 mg groups, respectively) of subjects had at least 1 secondary diagnosis other than T2DM.					
		Details of secondary diagnoses by treatment arm can be found in the provided					

attachments. The secondary diagnosis by SOC shows only modest differences between groups in the distribution of medical history incidences by SOC. The most commonly reported secondary diagnoses were in the Vascular disorders SOC (73%) with the specific term of hypertension being the most commonly reported (69%), followed by the Metabolism and nutrition disorders SOC (67%), reflecting the specific secondary diagnoses of dyslipidemia or hyperlipidemia (42%) and obesity (19%), and Musculoskeletal and connective tissue disorders SOC (44%). A moderate proportion (20.7%) of subjects had at least 1 secondary diagnosis in the Cardiac disorders SOC at baseline.

**Summary of Background Therapy at Baseline and During the Treatment Period:
Metformin**

	--- CANA 300 mg -- (N=377)	--- Sita 100 mg --- (N=378)	----- Total ----- (N=755)
Metformin at baseline			
N	377	378	755
Metformin daily dose at baseline (mg/d)			
N	377	378	755
Category, n (%)			
<1500 mg/d	0	0	0
1500 to <2000 mg/d	25 (7)	32 (8)	57 (8)
2000 to <2500 mg/d	221 (59)	229 (61)	450 (60)
≥2500 mg/d	131 (35)	117 (31)	248 (33)
Mean (SD)	2186 (338.2)	2163 (342.0)	2175
Median	2000	2000	2000
Range	(1500;3400)	(1500;3400)	(1500;3400)
Metformin dose after baseline			
N	377	378	755
Category, n (%)			
Unchanged	371 (98)	371 (98)	742 (98)
Changed ^a	6 (2)	7 (2)	13 (2)
- Decreased	3 (1)	4 (1)	7 (1)
- Increased	3 (1)	2 (1)	5 (1)
- Interrupted ^b	1 (<1)	1 (<1)	2 (<1)

CANA, canagliflozin; ER, extended release; IR, immediate release; SD, standard deviation; Sita, sitagliptin.

	<p>^aChange is defined as a sustained (ie, at least 7 consecutive days) modification of metformin dose.</p> <p>^bInterruption is defined as an interruption of at least 7 consecutive days followed by a restart of metformin at the same dose level on the day of randomisation.</p> <p>Note: Percentages were calculated with the number of subjects in each group as the denominator.</p> <p>Note: A subject might be counted in more than one category for dose change.</p> <p>Summary of Background Therapy at Baseline and During the Treatment Period:</p> <p>Sulphonylurea</p> <table border="1"> <thead> <tr> <th></th> <th>--- CANA 300 mg --- (N=377)</th> <th>--- Sita 100 mg --- (N=378)</th> <th>----- Total ----- (N=755)</th> </tr> </thead> <tbody> <tr> <td>Sulphonylurea at</td> <td></td> <td></td> <td></td> </tr> <tr> <td>N</td> <td>377</td> <td>378</td> <td>755</td> </tr> <tr> <td>Sulphonylurea daily dose at baseline (mg/d)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>N</td> <td>377</td> <td>378</td> <td>755</td> </tr> <tr> <td>Category, n (%)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>< minimum daily dose required ^b</td> <td>7 (2)</td> <td>5 (1)</td> <td>12 (2)</td> </tr> <tr> <td>≥ minimum daily dose required ^b</td> <td>370 (98)</td> <td>373 (99)</td> <td>743 (98)</td> </tr> <tr> <td>Subjects with changed sulphonylurea dose</td> <td></td> <td></td> <td></td> </tr> <tr> <td>N</td> <td>377</td> <td>378</td> <td>755</td> </tr> <tr> <td>Category, n (%)</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Changed ^a</td> <td>345 (92)</td> <td>338 (90)</td> <td>683 (91)</td> </tr> <tr> <td>- Decreased</td> <td>32 (8)</td> <td>40 (11)</td> <td>72 (10)</td> </tr> <tr> <td>- Increased</td> <td>31 (8)</td> <td>33 (9)</td> <td>64 (8)</td> </tr> <tr> <td>- Interrupted</td> <td>3 (1)</td> <td>5 (1)</td> <td>8 (1)</td> </tr> <tr> <td></td> <td>0</td> <td>4 (1)</td> <td>4 (1)</td> </tr> </tbody> </table> <p>CANA, canagliflozin; Sita, sitagliptin.</p> <p>^aOnly for subjects who had sulphonylurea dose change on at least 7 consecutive days.</p> <p>^bSulphonylurea minimum daily dose required at randomisation is defined as below: glipizide = 20 mg, glipizide ER = 10 mg, glyburide/glibenclamide = 10 mg, glimepiride = 4 mg, gliclazide = 160 mg, gliclazide MR = 60 mg,</p>		--- CANA 300 mg --- (N=377)	--- Sita 100 mg --- (N=378)	----- Total ----- (N=755)	Sulphonylurea at				N	377	378	755	Sulphonylurea daily dose at baseline (mg/d)				N	377	378	755	Category, n (%)				< minimum daily dose required ^b	7 (2)	5 (1)	12 (2)	≥ minimum daily dose required ^b	370 (98)	373 (99)	743 (98)	Subjects with changed sulphonylurea dose				N	377	378	755	Category, n (%)				Changed ^a	345 (92)	338 (90)	683 (91)	- Decreased	32 (8)	40 (11)	72 (10)	- Increased	31 (8)	33 (9)	64 (8)	- Interrupted	3 (1)	5 (1)	8 (1)		0	4 (1)	4 (1)		
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		<p>glyburide micronized = 6 mg</p> <p>Note: Percentages were calculated with the number of subjects in each group as the denominator.</p>		
P114 P116 P118		<p>E1. Other likely bias: <u>That the study was funded by Industry</u></p> <p>Chapter 10 of the Cochrane Handbook (Source: http://www.mrc-bsu.cam.ac.uk/cochrane/handbook502/) provides a detailed discussion of reporting biases, including publication bias, and how it may be tackled in a Cochrane review. A prototypical situation that may elicit suspicion of publication bias is when published evidence includes a number of small trials, all of which are industry funded (Bhandari M, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. <i>CMAJ</i>. 2004;170(4):477-80).</p> <p>Please note that that all clinical trials conducted by the manufacturer are posted on clinicaltrials.gov and full transparency is provided regarding completed and ongoing studies (including timelines, study type, etc). Therefore, the interpretation of publication bias does not seem to be appropriate.</p> <p>Based on this, we suggest that EUnetHTA update this particular point of assessment related to bias, reflecting the current environment of transparency in reporting.</p>	<p>It is a fact that at the time of marketing authorisation application for a new drug the research conducted is driven by industry. This interest is acknowledged when assessing risk of bias.</p> <p>However, it does not necessarily lead to high risk of bias as such. Regarding this assessment, relationship with the industry was brought up categorically and classified as unclear risk of bias, not reflecting that in the view of the assessors this automatically refers to high risk of bias.</p>	
P114		<p>E2. Other likely bias: <u>Relationship between company and principle investigators</u></p> <p>The report states: <i>There is an agreement between Principal Investigators and the Sponsor that restricts the investigators rights to discuss or publish trial results after the trial is completed.</i></p> <p>We are greatly concerned over this statement. It is factually incorrect, and we hope this is</p>	<p>This statement has been revised. The statement is originally derived from the ClinicalTrials.gov database where in the study reports of DIA3009 and DIA3015, it is stated under section</p>	10

	<p>the result of a simple misunderstanding. We have been unable to find the source of this reference in our submission, but suspect it may stem from a confidentiality statement on one of our appendices, such as Appendix 21; the PRO Report for study DIA3009. The report does have a confidentiality statement on the cover page which states:</p> <p><i>The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential.</i></p> <p>This is a confidentiality statement intended for individuals who come into contact with the report, to prevent its misuse. IT IS NOT a confidentiality clause related to investigators involved in the trial, or reporting thereafter.</p> <p>We feel it is important to reiterate that our studies were approved by institutional review boards or independent ethics committees at participating institutions. The studies were done in accordance with guidelines of Good Clinical Practice and the Declaration of Helsinki, and with applicable regulatory requirements. Furthermore, abstracts and manuscripts reporting the phase 3 clinical trial results have been prepared with the investigators and submitted for presentation at congresses and publication in scientific journals.</p> <p>With respect to communication and publication of the trial results, each trial protocol states:</p> <p><i>The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator.</i></p>	<p>Certain Agreements that “there is an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI’s rights to discuss or publish trial results after the trial is completed.”</p>	
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<p>P115 P116 P119</p>		<p>E3. Other likely bias: <u>Incidences of some AEs may facilitate prediction of treatment arm</u></p> <p>The report states: <i>The incidences of female genital infections and osmotic diuresis-related adverse events were higher in canagliflozin groups compared with glimepiride group. This may have made it possible to predict which treatment arm the patients were assigned to. If this happened, the off-study treatment of the patients may have been affected as well as patient-reported outcomes.</i></p> <p>The fact that differential side-effect profiles between drugs can theoretically “help” investigators to “guess” the treatment arm to which a particular patient is allocated, is a phenomenon that applies to practically all randomised double blind trials.</p> <p>The more relevant question might be whether the increase in the odds for the “guess” to be right for those patients (and only those) who experience the side-effects in question, has a material effect on the evaluation of efficacy and safety.</p>	<p>When assessing risk of bias, careful consideration of all possibilities must take place. Issues can and should be raised even though their actual ability to increase or cause risk of bias is unclear. It is also in the consideration of the reader to make his/her own judgements.</p> <p>As in the case of side-effects making it possible to predict the treatment assignment,</p>	<p>11</p>

		<p>We would postulate that this rarely is the case and we believe it is highly unlikely to be the case in this particular situation. Moreover, patients may present with multiple side-effects (some of which are not investigated drug-related, and some of which may be related to more than one drug) which would probably make the “guessing work” very difficult.</p> <p>Candidiasis is very common (irrespective of drug use) in patients with type 2 diabetes (Nyirjesy P, Sobel JD. Genital mycotic infections in patients with diabetes. <i>Postgrad Med.</i> 2013;125(3):33-46).</p> <p>Approximately 90% of female patients treated with canagliflozin did not report a genital mycotic infection (data based on an integrated analysis of pooled placebo-controlled data across phase 3 trials). The low rates of discontinuations due to these AEs suggest that these did not contribute to attrition of patients in the studies.</p> <p>These RCTs were conducted globally across many different study sites with relatively small number of patients, and it is unlikely that any single health care provider (HCP) or patient would have been able to predict the treatment allocation considering the infrequent reporting of these AEs (e.g., <10%).</p>	<p>we judged them to be able to cause risk of bias in outcomes reported by the patient (HRQoL) or outcomes concerning off-study treatment (a common example of this being hospitalizations, which was not used in this assessment).</p>	
P16	3-4	<p>Given all of the issues raised by the reviewers, and our answers presented above on Issues A-E, we request that the conclusion that “the overall quality of the evidence is low”, and that the studies are “high risk of bias” be reconsidered.</p>	<p>The risk of bias tables were revised based on the new data sent by MAH. Some changes were made based on the comments and new material. Also, further explanation was added to support each judgement. All the changes and further justification can be</p>	12

			<p>found in risk of bias tables 13, 14, 15 in appendix 1.</p> <p>Despite the fact that the rating was changed in some types of bias, the overall rating did not change. Justifications for this were provided in the appendix 1 (comments below table 13, 14, 15: study level risk of bias tables,)</p>	
		<p><u>Major point 3</u></p> <p>Inherent contradiction in reporting of existing information exists</p> <p>Our concerns here relate to the following areas:</p> <ol style="list-style-type: none"> 1) Reporting of the short-term evidence from direct (and indirect) comparisons when longer-term data (e.g. 104-week DIA3009 trial) are available, which is in contrast to the request by the authors for longer-term data (e.g. P121 Table 5 - assessment of long-term outcomes, P46 lines 27-28, P46 lines 33-35) 2) Reporting of short-term indirect results when longer-term evidence is available from the NMA 3) Reporting selective findings from the Vasilakou meta-analysis which out of context will be inappropriately interpreted 4) Discussion of AE reporting <p>Each of these issues are addressed in turn below.</p>	<p>Each of the specific concerns are addressed below:</p>	13
		<p>Reporting of the short-term evidence from direct comparisons when longer-term data are available</p> <p>The report rightly identifies that longer-term evidence is required in a condition such as diabetes.</p>	<p>We have added 104 week results into the summary for the key outcomes.</p> <p>The following text has been added to the</p>	14

		<p>We therefore request that the long-term outcomes be reported in the summary; for example, data on body weight changes are reported at 26 weeks, when evidence is also available at 52 weeks and in some instances at 104 weeks in our original submission.</p>	<p>summary to accompany the list of results: <i>“In this section, an overview of the results concerning mortality and long-term outcomes, HbA1c, weight, systolic blood pressure and quality of life is presented. Unless indicated differently, the evidence below is derived from direct comparisons. Durations of studies including active comparators were 52 (DIA3006 and DIA3015) or 104 weeks (DIA3009). Results at 52 weeks, which were available for all active controlled studies, are presented here unless stated otherwise. More detailed and statistically oriented representation of the results, including also additional outcomes, can be found in the domain report. Additionally, the appendices also include more detailed description of the results derived from direct and indirect comparisons at various time points.”</i></p>	
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P10	43	<p>Reporting of short-term indirect results when longer-term evidence is available</p> <p>A general comment on the interpretation of the results of the NMA is warranted. In the evaluation report, it seems that the Bayesian NMA results have been consistently (incorrectly) interpreted as frequentist results (e.g. Bayesian credible intervals interpreted as traditional confidence intervals) and only results of non-overlapping credible intervals were interpreted as signalling a statistically significant difference. Further, the value of the probabilistic interpretation of Bayesian results, including pairwise probabilities and ranking of treatments based on SUCRA-values, was not acknowledged.</p> <p>This is inconsistent with the discussion at the scoping meeting, where our proposal to report Bayesian NMA had been discussed, and the EUnetHTA team specifically referred to the Salanti paper as the prototype for reporting probabilistic Bayesian NMA results (i.e. reporting probabilistic ranking of treatments based on SUCRA and graphical representations of the posterior probability distributions) (Source: Salanti G, et al. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. <i>J Clin Epidemiol.</i> 2011;64(2):163-171).</p> <p>Based on the EUnetHTA submission and NMA report, we recommend the following summary for the add-on to metformin and add-on to metformin + sulphonylurea networks. Both networks have been presented (online accessible through the ISPOR Scientific Presentations Database: http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp) at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 16th Annual European Congress, Dublin, Ireland, November 2013 and were entitled:</p> <ul style="list-style-type: none"> • BAYESIAN NETWORK META-ANALYSIS TO ASSESS RELATIVE EFFICACY AND SAFETY OF CANAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM) INADEQUATELY CONTROLLED WITH METFORMIN (PRM193) <ul style="list-style-type: none"> ○ Methods: <ul style="list-style-type: none"> • Bayesian NMAs were conducted based on a systematic literature review. Methods were in line with NICE guidelines. 	<p>In the summary section, 52 week results for NMA are represented similarly as with direct comparisons. 104 week results have been presented shortly for the key outcomes (HbA1c, weight and SPB).</p> <p>Vast amount of indirect evidence, including varying comparators and time points, were available. In order to come up with any coherent summary, the amount of reporting in the summary has to be limited. The results of the indirect comparisons are always uncertain, and their weight in the summary should be in balance with the direct evidence. The summary of indirect comparisons was limited to reporting only the most unambiguous results.</p> <p>The ranking probabilities are reported in the appendices. We feel that to assess the relative effectiveness of the product nationally,</p>	15
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		<ul style="list-style-type: none"> • Outcomes of interest included HbA_{1c} change from baseline, weight change from baseline, and incidence of hypoglycaemic events at 26, 52 and 104 weeks. Separate analyses were conducted by time of assessment. • Networks were based on treatment- and dose-specific nodes where possible. Doses of sulphonylureas were pooled due to titration of these treatments in most clinical trials. • Due to missing data, canagliflozin was not compared to pioglitazone for the incidence of hypoglycaemic events. • Non-informative prior distributions were used to produce results driven by the data. The selection of using a fixed or random effects model was based on the Deviance Information Criterion (DIC), which measures the relative goodness of fit between models. Sensitivity analyses were performed to assess the impact of prior distribution on random effects models. • Studies causing heterogeneity (identified through the I2 statistic) and/or inconsistency (identified through the comparison of direct and indirect evidence in the network) were identified statistically and discussed with a clinical expert. An analysis excluding trials which were potential sources of inconsistency was conducted (i.e. analysis based on a reduced network). <ul style="list-style-type: none"> ○ Summary of outcomes: <ul style="list-style-type: none"> HbA_{1c} change from baseline <ul style="list-style-type: none"> • Canagliflozin 300 mg was associated with a higher reduction in HbA_{1c} (Δ) compared to DPP-4 inhibitors ($\Delta=-0.11$ to -0.39) and dapagliflozin 10 mg ($\Delta=-0.12$ to -0.38) across all time points; while canagliflozin 100 mg conferred at least as large reductions ($\Delta=0.01$ to -0.30 and 0.00 to -0.26 respectively). • HbA_{1c} reduction at 26 weeks and 52 weeks was greatest for exenatide 2 mg weekly and liraglutide 1.8 mg. At 104 weeks, 	<p>the actual effect size of the estimate and its credibility interval is more important than the estimated order of the comparators.</p> <p>Furthermore, the statement “estimates are imprecise” has been removed from the summary text.</p>	
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		<p>substantially larger than all other classes.</p> <ul style="list-style-type: none"> • All classes showed less risk of hypoglycaemic events compared to sulphonylureas. <ul style="list-style-type: none"> • BAYESIAN NETWORK META-ANALYSIS TO ASSESS THE RELATIVE EFFICACY AND SAFETY OF CANAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM) INADEQUATELY CONTROLLED ON METFORMIN AND SULPHONYLUREA (MET+SU) (PDB2) <ul style="list-style-type: none"> ○ Methods: <ul style="list-style-type: none"> • Bayesian NMAs were conducted based on a systematic literature review. Methods were in line with NICE guidelines. • Outcomes of interest included HbA_{1c} change from baseline, weight change from baseline, and incidence of hypoglycaemic events at 26 weeks. • Networks were based on treatment- and dose-specific nodes where possible. The following classes of insulin were used: long-acting insulin (glargine, detemir) and biphasic/pre-mixed insulin. These classes were defined in line with the NICE guidelines for the management of type 2 diabetes. • Due to missing data, canagliflozin was not compared to liraglutide 1.8 mg for the incidence of hypoglycaemic events. • Non-informative prior distributions were used to produce results driven by the data. The selection of using a fixed or random effects model was based on the DIC, which measures the relative goodness of fit between models. Sensitivity analyses were performed to assess the impact of prior distribution on random effects models. • An analysis based on a reduced network that excluded studies 		
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		<p>causing heterogeneity (identified through the I2 statistic) and/or inconsistency (identified by comparisons of direct and indirect evidence) was performed.</p> <ul style="list-style-type: none"> ○ Summary of outcomes: <ul style="list-style-type: none"> HbA_{1c} change from baseline <ul style="list-style-type: none"> • HbA_{1c} reduction (Δ) for canagliflozin 300 mg was comparable to GLP-1 agonists ($\Delta=0.08$, CrI95%: [-0.24;0.40] and $\Delta=-0.01$, CrI95%: [-0.27;0.25] versus liraglutide 1.8 mg and exenatide 10 μg) and biphasic insulin ($\Delta=0.03$, CrI95%: [-0.32;0.40]) and was higher than DPP-4 inhibitors ($\Delta=-0.21$, CrI95%: [-0.31;-0.10] and $\Delta=-0.39$ CrI95%: [-0.59;-0.19] versus sitagliptin and linagliptin, respectively). • HbA_{1c} reduction for canagliflozin 100 mg was comparable to DPP-4 inhibitors ($\Delta=0.04$, CrI95%: [-0.17;0.26] and $\Delta=-0.14$ CrI95%: [-0.37;0.09] versus sitagliptin and linagliptin, respectively). • Inconsistency was suspected within the loop placebo/long-acting insulin/biphasic insulin/exenatide 10 μg (p-value for the comparison of direct and indirect evidence of 0.0016). • The trial by Bergenstal (2009) assessing exenatide 10 μg versus biphasic insulin included patients with a higher mean HbA_{1c} at baseline (higher than 10%) compared to other trials. HbA_{1c} at baseline is an important treatment modifier and could explain the inconsistency within this loop. An analysis excluding Bergenstal (2009) was conducted, which demonstrated the study's influence on estimates of the treatment effect for canagliflozin compared to long-acting insulin and biphasic insulin. Credibility intervals were narrower compared to the full network analysis, as a fixed effects model was selected in this analysis. <p>Weight change from baseline</p> <ul style="list-style-type: none"> • With regard to the weight reduction, canagliflozin 300 mg was 		
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		<p>associated with the highest probability of ranking (26%). Weight reduction for canagliflozin 300 mg ranged from 0.14 kg (versus exenatide 10 µg) to 5.13 kg (versus biphasic insulin).</p> <ul style="list-style-type: none"> Weight reduction for canagliflozin 100 mg and 300 mg was comparable to GLP-1 agonists (probabilities associated with canagliflozin 100 mg and 300 mg of reducing weight ranged from 41% to 52% and from 52% to 63%, respectively). There was a larger weight reduction associated with the use of canagliflozin 100 mg and 300 mg compared to DPP-4 inhibitors and insulin regimens (probabilities for canagliflozin of reducing weight higher than 70% and 90%, respectively). <p>Incidence of hypoglycaemic events</p> <ul style="list-style-type: none"> Odds ratios for hypoglycaemic events of canagliflozin 100 mg and 300 mg versus long-acting insulin were 0.31 and 0.39, respectively, and ranged between 0.20 and 0.41 for other classes. Inconsistency was suspected within the loop of canagliflozin 300 mg, sitagliptin 100 mg, and placebo (p-value=0.0455). The definition of hypoglycaemic events was not reported in the publication by Hermansen (2007), therefore similarity between different definitions of hypoglycaemic events could not be assessed. <p>○ Conclusion</p> <ul style="list-style-type: none"> The NMA of add-on therapies to metformin plus sulphonylurea suggests that canagliflozin 300 mg is associated with increased HbA_{1c} reduction versus DPP-4 inhibitors while canagliflozin 100 mg provides at least similar effects. Canagliflozin 300 mg was found to be comparable to biphasic and long-acting insulin and to GLP-1 agonists. Weight reduction associated with canagliflozin 100 mg and 300 mg was comparable to GLP-1 agonists and substantially higher 		
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		<p>than all other classes.</p> <ul style="list-style-type: none"> All classes showed significantly less risk of hypoglycaemic events compared to insulin. <p>The report states: <i>The estimates are imprecise.</i></p> <p>Imprecise according to GRADE is defined as: When studies include few participants and few events and thus have wide confidence intervals, authors can lower their rating of the quality of the evidence. The confidence intervals included in the 'Summary of findings' table will provide readers with information that allows them to make, to some extent, their own rating of precision. (Source: http://www.mrc-bsu.cam.ac.uk/cochrane/handbook502/). These were, however, not provided with the necessary level of detail.</p> <p>A reason given for this data being <i>imprecise</i> is provided on P248; stated as large credibility intervals and rather small differences between the treatments. However, this statement is specifically related to the 26-week metformin + sulphonylurea NMA data for triple therapy, not the overall NMA, and appears to be reported out of context.</p> <p>As suggested by the authors (e.g. discussion P15), long-term data can provide more precise estimates. Results of the 26-week NMA data have fairly large credibility intervals and report small differences, and this is due to the fact that treatments are more likely to differentiate in the longer term.</p> <p>Therefore, the NMA data at 52 or 104 weeks are more relevant for the assessment, and are appropriate to report in the summary. Furthermore, it appears that the results quoted from the NMA evidence select those scenarios that reflect negatively for canagliflozin whilst neglecting to report the potential position with respect to other commonly used comparators.</p>		
P16	25-36	<p>Reporting selective findings from the Vasilakou meta-analysis which out of context will be inappropriately interpreted</p> <p>The Vasilakou paper and our submitted NMA seem to be given very different consideration and not to be measured against the same quality standards.</p>	Thank you for your comments. We wrote this text having in mind that this could be an advantage for canagliflozin in	16

		<p>From a methodological perspective, the Vasilakou paper is a traditional pairwise meta-analysis, generating a pooled effect of all SGLT2 inhibitors (ignoring potential differences between compounds & doses); and in a second analysis, all SGLT2 inhibitors are compared to any other therapy (pooling together all other anti-diabetic medications); therefore, there is (potentially) a great deal of heterogeneity across all these comparisons which is not mentioned.</p> <p>However, more importantly, we question the selection of evidence reported. For example, the final sentence (line 35-36) states: <i>An imbalance in the incidence of bladder and breast cancer was found in trials that compared dapagliflozin with controls.</i> Given the context of the statement in the summary report, it would be entirely understandable for a reader of the report to conclude that this was a likely flag for canagliflozin, and a potential class effect.</p> <p>The Vasilakou paper states that the dapagliflozin data are based on a database of “5501 patients with at least 5000 patient-years of exposure”. However, what the EUnetHTA comment fails to report is that in the next paragraph, Vasilakou states: <i>A pooled analysis of 9 trials with approximately 8000 person-years of exposure did not show any difference in incidence of bladder cancer between canagliflozin (5 of 6648 patients) and control (4 of 3640 patients) groups. Similarly, incidence of breast cancer did not differ between canagliflozin (12 of 2827 patients) and comparators (6 of 1501 patients).</i></p> <p>Given this is a review of canagliflozin and not dapagliflozin, we suggest to remove the reference to Vasilakou in the Executive Summary of the canagliflozin REA report, or request that this reflects the safety profile of canagliflozin.</p>	<p>comparison to dapagliflozin; to remove any doubts and different interpretations, we added new text: <i>“Results did not show any differences in incidence of bladder cancer between canagliflozin and control; the same was true on incidence of breast cancer.”</i></p>	
P16	3-4	<p>Discussion of AE reporting</p> <p>The report states: <i>In all but one (hypoglycemia only) of the studies safety parameters were not defined as primary or secondary endpoints and no statistical analyses were performed. The overall quality of the evidence was low.</i></p> <p>We do however have difficulty understanding this perspective reported in the Summary, when the body of the report comments on AE data and reporting under the heading Analysis (P33, line 23);</p>	<p>Thank you for your comments.</p> <p>Common limitations in RCTs that report harms are well known, including inconclusive findings, lack of power, short duration of</p>	17

		<p><i>“The sources were sufficient to answer the questions. We did not perform additional data analysis.”</i></p> <p>To clarify our approach to AE reporting, the trials were designed consistent with EMA guidance and support the SmPC of canagliflozin. A full analysis of the safety data collected in the trial program of over 10,000 patients (including a first-of its kind dedicated CV safety study of more than 4,000 patients; http://www.ncbi.nlm.nih.gov/pubmed/23895803) supported the registration of canagliflozin. The safety data were fully discussed in the submission.</p> <p>Of the three head-to-head studies, which were the focus of the response by the authors, two studies were versus sitagliptin (DIA3006, DIA3015) and one was versus sulphonylureas (DIA3009). The reviewers are correct in noting that documented hypoglycaemia was pre-specified as a secondary endpoint in DIA3009 only. This hypothesis was pre-specified because not only is it well-established that the mechanism of sulphonylureas is associated with an increased risk of hypoglycaemia, but also that the rate of occurrence was expected to be of sufficient magnitude to be able to discern a difference (note: the data reported in the dossier confirms the added risk of hypoglycaemia with sulphonylureas versus canagliflozin).</p> <p>A priori hypotheses were not specified for other safety parameters in each individual trial as the event rates were expected to be too infrequent. As noted per EMA guidance (ICH Topic E 9 Statistical Principles for Clinical Trials; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf), in most trials, the safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation. Using this approach, the considerable imprecision often arising from low frequencies of occurrence is clearly demonstrated. This is consistent with how safety and tolerability parameters were assessed in the canagliflozin phase 3 program (i.e. with the 95% confidence interval around the between-group difference for canagliflozin relative to control, excluding “0”).</p> <p>Furthermore, the report on P33, line 23, states: <i>“The sources were sufficient to answer the questions. We did not perform additional data analysis.”</i></p>	<p>exposure to the allocated treatment, especially for treatments of chronic diseases, multiplicity of comparisons, and post hoc analyses. The frequency and severity of adverse events may depend on the clinical setting and participants, for example we do not know how patients with recurrent UTIs or chronic UTIs will tolerate canagliflozin.</p> <p>EMA may use different criteria and therefore different conclusions can be made. Assessing marketing authorization applications are contextually also different from assessing relative effectiveness.</p> <p>We carefully re-check all data; in DIA3009 hypoglycemia is the only outcome marked as Moderate quality of evidence, so we stressed this in the text and Tables.</p> <p>The text is written now</p>	
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		<p>Given the information above we would like to suggest to reword the specific parts of the Executive Summary addressing these matters.</p>	<p>as: “In all but one (hypoglycaemia only) of the studies safety parameters were not defined as primary or secondary endpoints and statistical analyses were not performed. The overall quality of evidence (assessed only in three active comparator trials DIA3006, DIA 3009, DIA3015, at 52 weeks) was moderate to low.”</p> <p>In our assessment we did not quote the recent PBAC statement either: “Overall, the PBAC did not consider that the claim that canagliflozin has a comparable safety profile to sitagliptin was adequately supported.”</p> <p>We rewrite the following text in “The sources were sufficient to answer the questions, but in case of discrepancies of the same data in different sources as mentioned above, published articles of RCTs are</p>	
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			<p>used as a primary source for extraction.”</p> <p>In the Discussion section of the Safety Domain, new page 41, the following text is added: <i>“Authors noted some discrepancies due to the same data from different sources used for this assessment. In such a case, published articles of RCTs are used as the primary source for data extraction. Recent publications again stressed insufficient information on clinical trials in journal publications and reports posted in clinical trials results registries, but they could supplement each other to overcome the publication and outcome reporting bias. Full clinical study reports provide the most complete information on the large majority of methods and results data items; HTA doers should rely on systematic review of full clinical study reports</i></p>	
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			<i>when they become publicly available to solve the problem of overestimating benefits and underestimating harms.”</i>	
P64	22-23	<p><u>Major point 4</u></p> <p>NMA The report states: <i>Only the treatment and doses licensed in the UK were considered for this review: alpha glucosidase inhibitors, rosiglitazone, alogliptin, all inhalable insulins were excluded.</i></p> <p>This statement is factually correct. However, as with the previous comment regarding the negative statement on AE endpoints in the discussion, we are concerned over what the reviewers are trying to communicate to the intended reader, to whom the report is aimed.</p> <p>Of the drugs apparently ‘excluded’;</p> <ul style="list-style-type: none"> • alpha glucosidase inhibitors are not routinely used in the target population for canagliflozin • rosiglitazone was withdrawn by EMA in 2010 • alogliptin was only authorised by EMA in September 2013, (after our submission date) • all inhalable insulins – we are unclear by the term “all”. We are aware of Exubera, which was approved in 2006 and discontinued in 2007. We are unaware of any other approved inhaled insulin by EMA. 	We agree, these lines have been removed from the appendix.	18
P64	25-27	<p>Data Extraction: The report states: <i>The data extraction was completed by one reviewer, a second reviewer then performed the quality check on 20% of the publications.</i></p> <p>There appears to be a misunderstanding here, and the issue is therefore incorrectly reported.</p>	We agree. These lines have been removed from the appendix. No further details related to this issue are reported.	19

		<p>Two different documents were used: (1) a tabular summary for the narrative review and (2) a dataset extraction sheet for the NMA</p> <ul style="list-style-type: none"> ▪ (1) A quality check of 20% of the publications in the tabular summary was performed. Publications to be checked were selected randomly. ▪ (2) Data included in the NMA were extracted independently by 2 reviewers and 100% of data included in the NMA were quality checked by an analyst. 		
P66	3-6	<p>The report states: <i>In specific outcomes the actual network may differ depending on the evidence available in individual studies.</i></p> <p>This suggests a <i>different</i> network, whereas the issue is <i>completeness</i> of the network.</p> <p>To assist understanding, we suggest rewording to, “Some outcomes were not always reported in the publications (e.g. BMI, SBP) leading to missing data in the NMA. Missing data resulted in reduced networks of evidence for these outcomes.”</p>	We agree. We have reworded the text as suggested.	20
P70	47-48	<p>The report states: <i>“In checking the data extraction, we were unable to locate several of the values from the Cantata studies (for example in Table 129 above), since Appendix 9 only provided some of the data”.</i></p> <p>We are concerned over this comment. All data used in the NMA, including those reporting on our clinical trials, were tabulated and provided in the full report as Appendix 14 of our submission. Appendix 14 is referenced multiple times throughout the methods and results sections of our submission, starting on P142. If there was any issue in finding or validating data, we are disappointed that we were not asked. As indicated during each communication, we were willing to address any questions or clarifications as required to facilitate the pilot process. It is disappointing the reviewers did not follow up on this offer.</p>	We agree. These lines have been removed from the appendix.	21
P11	10-31	<p><u>Major point 5</u></p> <p>Evaluation of PRO</p> <p>The report states: <i>Canagliflozin or its comparators did not have any relevant effect on</i></p>	We have taken this into consideration and the text was revised as follows: <i>Canagliflozin or</i>	

	<p><i>functional ability, general health-related quality of life, disease-specific quality of life or activities of daily living during the follow-up of up to 1 year.</i></p> <ul style="list-style-type: none"> • Disease-specific quality of life and activities of daily living were not specifically measured in the phase 3 program • Overall, HRQOL improved over 1 year in all treatment arms <p>It is unclear what is meant by “relevant” effects. A 1-point lower score on selected Short-Form 36 Health Survey scales is associated with an excess risk of up to 9% for mortality and 12% for inability to work (Source: Bjorner JB, et al. Benchmarks for interpretation of score differences on the SF-36 health survey for patients with diabetes. <i>Value Health</i>. 2013;16(6):993-1000).</p> <p>The report states: <i>No evidence was available on patient satisfaction with the use of canagliflozin.</i></p> <ul style="list-style-type: none"> • Treatment satisfaction was not measured in the phase 3 program because canagliflozin is offered as one pill once per day without the need for inconveniences such as refrigeration, injection, dose adjustment, or dosing based on meals <p>Health satisfaction was measured in the phase 3 program because concepts such as weight satisfaction have been shown to be associated with positive health behaviours important for optimal management of T2DM (Source: Blake CE, et al. Adults with greater weight satisfaction report more positive health behaviours and have better health status regardless of BMI. <i>J Obes</i>. 2013;2013:291371).</p> <p>Health satisfaction results per trial were reported in the canagliflozin dossier (Appendix 23, P10; Appendix 24, P7; Appendix 25, P11; Appendix 26, P11; Appendix 27, P7):</p> <p>DIA3006 (52 weeks)</p> <ul style="list-style-type: none"> • The proportion of subjects at baseline who disagreed and strongly disagreed with the statement, “I am satisfied with my current body weight” was 47%, 53%, 52%, and 53% in the placebo, canagliflozin 100 mg, canagliflozin 300 mg, and sitagliptin 100 mg groups, respectively. At Week 52, the proportion of subjects 	<p><i>its comparators did not have any relevant effect on functional ability or general health-related quality of life during the follow-up of up to 1 year.</i></p> <p>If there was any true change in all treatment arms, no conclusions can be made that the changes were due to trial medication.</p> <p>A change of 1-point Short-Form 36 score can be considered clinically not relevant.</p> <p>Measuring health satisfaction has its merits and may be a justified measure in a trial but it does not measure patient satisfaction on trial medication, and therefore has not been used in this assessment.</p>	
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		<p>increased to 50% and 40% in the canagliflozin 300 mg and sitagliptin 100 mg groups, respectively.</p> <ul style="list-style-type: none"> The proportion of subjects at Week 52 who agreed and strongly agreed with the statement, "I am interested in taking the study medication again" was 78% and 71% in the canagliflozin 300 mg and sitagliptin 100 mg groups, respectively. <p>Canagliflozin was associated with improvements in health satisfaction (Appendix 24, P7; Appendix 25, P11).</p>		
P16 P17	8-9 50-51	<p>The report states: <i>Increased genital infections (especially in women) and increased UTIs should be considered in long-term therapy; these AEs may affect patient compliance and quality of life.</i></p> <ul style="list-style-type: none"> No dropout rate differences were observed between treatments due to these AEs We agree that genital infections and UTIs in T2DM can be a burden for some individuals (Source: Shingler SL, et al. Utilities for type 2 diabetes mellitus and associated complications. ISPOR Dublin 2013 poster PDB83. <i>Value in Health</i> 2013;16(7):A445); however, the impact is transient. The PRO evidence showed no decrement in QOL (Appendix 20, P30-59; Appendices 21-27) <p>The main body text of the submission clearly states on P34, line 34-35:</p> <p><i>"There was only a slight increase in UTIs with canagliflozin and no imbalance in serious/severe urogenital infections".</i></p> <p>These implications should therefore be assumed to be minimal which is in contradiction with the statement made by the reviewers in the Summary.</p>	<p>The long-term effects of elevated glycosuria on the urogenital tract associated with SGLT2 inhibitor treatment remain unknown.</p> <p>Recent meta-analysis reported statistically significant higher rates of UTI for SGLT2, describing it as class effects.</p> <p>Nyirjesy et al. (2012) fairly concluded that longer-term studies in larger numbers of patients, including those with a prior history of UTI are necessary to fully characterise the association of SGLT2 and UTIs.</p>	21

			<p>Authors of active comparator studies also fairly concluded that study durations beyond 52 weeks may better define the long-term efficacy and safety of canagliflozin.</p> <p>Manufacturer of dapagliflozin stated that the increased risk of urogenital infection associated with glycosuria may require temporary interruptions in treatment with dapagliflozin when treating pyelonephritis or urosepsis. Discontinuation of dapagliflozin may be considered if people develop recurrent UTIs.</p> <p>The PBAC noted a substantially higher incidence of both male and female genital mycotic infections and osmotic diuresis related adverse events in the canagliflozin arms compared to</p>	
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			<p>sitagliptin. The PBAC noted also a substantially higher proportion of patients experienced an event of mycotic vulvovaginitis at earlier time points compared with placebo. The PBAC noted that post marketing and long term safety data for canagliflozin are not yet available, and considered that the toxicity profile may differ in clinical practice from that observed in the trials. The PBAC noted the small patient numbers in the Phase III studies with long term exposure to canagliflozin and considered that the long term safety is unclear. Overall, the PBAC did not consider that the claim that canagliflozin has a comparable safety profile to sitagliptin was adequately supported.</p>	
P17	12-14	<p>The report states: <i>More evidence is needed to reach useful conclusions on the effects of canagliflozin on quality of life.</i></p> <ul style="list-style-type: none"> A battery of PRO instruments was used to capture the effects of canagliflozin on 	<p>The word “useful” was deleted from the text and changed to “further”.</p>	22

		<p>quality of life (see Appendix 20) in four phase 3 studies (Appendix 20, P9-10)</p> <ul style="list-style-type: none"> None of the PRO measures showed a decline in quality of life associated with canagliflozin and some showed improvement, e.g., IWQOL-Lite (Appendix 20, P30-59; Appendices 21-27) <p>It is unclear what is meant by “useful conclusions”.</p>	<p>The PRO instruments used and relevant for this assessment were SF-36 and EQ5D. Considering the targeted population and this treatment context, neither of these instruments can be considered sensitive enough to reliably measure true change in quality of life.</p> <p>In addition, the losses-to-follow-up were remarkable which makes any conclusions even more unsure (please see response to comment 5).</p>	
Minor points				
P7	25	Incorrect eGFR rate stated for trial 3004: inclusion criteria was 30- 50 , instead of 60	This has been corrected.	
P9	3	Typo – delete “A”, should read “Canagliflozin groups”	This has been corrected	
P9	43-44	<p>Genital mycotic infections numbers are not correctly reported for study DIA3006 (e.g., P35, Table P12 for DIA3006).</p> <p>Table P12 for DIA3006 lists the following:</p> <p>Genital mycotic infections† f 10 (8.8)/m 2 (2.5):f 8 (7.4)/m 5 (5.6):f 4 (3.8)/0 ;</p> <p>It appears that the authors summed the % females (not: Genital mycotic infections rates) from the evidence table on P190 reporting on data from trial DIA3005 (at 26 weeks).</p>	<p>Thank you for your comments; since we used different sources of data extractions, we stated now that in case of any discrepancies resulting from the same data being used in different sources, published articles of</p>	

		The Tables on P118 and 121 of the canagliflozin dossier list the appropriate values for the DIA3006 study for female and male genital mycotic infections.	RCTs were used as the primary source for extraction. So we corrected these data according data in published article.	
P 12-15	Tables	<p>Table subheadings are incorrect:</p> <p>P12 - Harm (52 weeks in active controlled and 24 weeks in placebo controlled) P13 - Harm (52 weeks in active controlled and 24 weeks in placebo controlled) P14 - Harm (52 weeks in active controlled and 24 weeks in placebo controlled) P15 - Harm (52 weeks in active controlled and 24 weeks in placebo controlled)</p> <p>Tables subheading should state:</p> <p>P12 - Harm (52 weeks in active controlled and 26 weeks in placebo controlled) P13 - Harm (104 weeks in active controlled and 52 weeks in placebo controlled) P14 - Harm (52 weeks in active controlled) P15 - Harm (52 weeks in active controlled and 26 weeks in placebo controlled)</p> <p>On P14, the last 2 rows of the table belong to the table on P15.</p>	<p>Thank you; we have made corrections and written the AEs weeks next to study DIA number (deleted from main heading Harm) to be completely precise.</p> <p>For active comparator, data for 52 weeks are presented, according the published articles.</p> <p>For pooled placebo trials specified in the table, data for 26 weeks are presented.</p>	23
P33	35-36	<p>UTIs appear to be missing from the opening list of observed AEs in the clinical trials.</p> <p>We suggest adding UTIs to the list.</p>	We added this important AE to the list.	24
P248	7	<p><i>EUnetHTA states that they recommended several subgroup analyses that were not conducted.</i></p> <p>At the scoping meeting subgroup analyses for the following subpopulations were discussed:</p> <ul style="list-style-type: none"> - Elderly above 75 y - High CV risk (DIA3008 CANVAS) - Renal impairment (DIA3004) - Hepatic impairment 	Regarding efficacy, placebo-controlled trials were not considered appropriate for the relative effectiveness assessment as discussed during the scoping meeting.	25

	<p>- Pediatric <18 y</p> <p>Data were provided where available according to the clinical trial program. Elderly analyses were conducted and presented for patients aged >65 y and ≤65 y on P254 of the EUnetHTA submission. The number of patients aged >75 y was too small to support a separate analysis.</p> <p>We did provide data on patients with high CV risk from the CANVAS DIA3008 trial (Table 15, P77), a trial dedicated to patients with high CV risk. Because it is a placebo-controlled trial, no relative effectiveness in subgroups could be provided.</p> <p>We did provide data in patients with renal impairment (DIA3004; Table 15, P75) based on a trial dedicated to patients with an eGFR ≥30 and <50 mL/min/1.73 m². DIA3004 is a placebo-controlled trial, so a relative effectiveness analysis could not be provided. Glycaemic efficacy based on pooled data from four phase 3 studies (DIA3005, DIA3008, DIA3004, and DIA3010) for patients who had a baseline eGFR between ≥30 and <60 mL/min/1.73 m² was also presented (P253). The active-controlled trials (DIA3006, DIA3009, and DIA3015) allowed inclusion of patients with an eGFR >50 mL/min/1.73 m², but there were few patients with eGFR <60 mL/min/1.73 m² due to the metformin background regimen (metformin is contraindicated in case of renal failure or renal dysfunction (creatinine clearance <60 ml/min; EMC, http://www.medicines.org.uk). Relative effectiveness data in this subgroup could not be provided due to the insufficient number of patients (40/1284 patients in DIA3006, 38/1449 patients in DIA3009, and 41/755 patients in DIA3015).</p> <p>Since PK/PD data indicated no clinically meaningful changes in patients with mild or moderate hepatic impairment, a subgroup analysis was not performed for those with non-severe hepatic impairment.</p> <p>Canagliflozin is not indicated for use in a pediatric population, patients with an eGFR <45 mL/min/1.73 m² and severe hepatic impairment (SmPC of canagliflozin); therefore, these subgroups are not relevant for a relative effectiveness assessment.</p> <p>Requested subgroup analyses were provided where data were available based on canagliflozin clinical trial program (elderly, high CV risk, renal impairment).</p>	<p>However, trial DIA3004 was briefly mentioned in the results card D0005A.</p>	
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<p>General</p>		<p>We would like to note that the report makes no mention of the evidence submitted in; Appendix 1 – country criteria for diagnosis of T2DM Appendix 2 – summary of European guidelines Appendix 3 – country estimates of T2DM incidence and prevalence Appendix 4 – drug utilisation by country Appendix 5 – marketing application status of comparators in Europe Appendix 6 – reimbursement status of comparators in Europe</p> <p>We recognise this information is required at a Country level to inform reimbursement and coverage decisions, but it needs re-working to present in the format required by the local decision-maker. We therefore question the inclusion of this evidence in the REA, as the content of the draft report does not appear to have been influenced by it.</p>	<p>These data already are (or may be) very important for MSs at national level to inform national HTA adaptations and national reports. So we added all data except data connected with country criteria for diagnosis of T2DM. Summary of European guidelines is added in result card A0025. Country estimates of T2DM incidence and prevalence added in Results card A0006. Marketing application status and reimbursement status of comparators in Europe as well as drug utilization by country are added in Results card B0003.</p> <p>We made comments also that these data are provided by canagliflozin Manufacturer; survey for MSs partners was not performed to check these data.</p>	<p>26</p>
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