EUnetHTA Joint Action 3 2016-2020

Sotagliflozin for adult patients with Type 1 Diabetes Mellitus and with a body mass index (BMI) ≥ 27 kg/m^2 who have inadequate glucose control using optimised insulin or insulin analogues

Project ID: *PTJA04*

Project description and planning

TLV, Sweden
ZIN, Netherlands
NPCE, Ireland

Version Log

Version number	Date	Modification	Reason for the modification
V1	31/08/18	1st draft	
V2	27/09/2018	2nd draft	Incorporated feedback from dedicated reviewers
V3	15/10/2018	3rd draft	Incorporated feedback from the expert, and face to face meeting with Sanofi
Final	28/02/2019	Final version	
Final	05/03/2019	Final version	Publication

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1 Project organisation

1.1 Participants

Table 1-1: Project participants

	Agency	Role in the project	Country	Distribution of work
Assessment team				
1.	The Dental and Pharmaceutical Benefits Agency, TLV (Tandvårds- och läkemedelsförmåns-verket)	Author	Sweden	• Develop first draft and final version of EUnetHTA project plan with co-author • Answer assessment elements of TEC Domains • Relative effectiveness and safety assessment. • Send “draft versions” to reviewers, compile feedback from reviewers and perform changes according to reviewer’s comments • Prepare the final assessment including a final summary of the assessment • Carry out the assessment: answer assessment elements of CUR Domain
	Dutch National Health Care Institute; ZIN (Zorginstituut Nederland)	Co-Author	Netherlands	• Develop first draft and final version of EUnetHTA project plan with 1st author • Initial literature search update if needed (including national/ European guidelines) • Responsible for supporting the authors in all project phases • Carry out the assessment: support authors in EFF and SAF Domains. Support authors in Summary, Method and Discussion sections. • Assessment related to the GRADE methodology
	National Centre for Pharmacoeconomics, NCPE, Ireland	Co-Author	Ireland	Responsible for the indirect comparison
2.	AEMPS, Spain	Dedicated Reviewer		
3.	SNHTA, Switzerland	Dedicated Reviewer		
4.	NVD, Latvia	Dedicated Reviewer		
5.	INFARMED, Portugal	Dedicated Reviewer		
6.	AOTMiT, Poland	Dedicated Reviewer		
7.	EOF, Greece	Observer		
8.	HIS(SMC), Scotland	Observer		

Contributors				
9.	Mats Eliasson, Professor i medicin, Institutionen för folkhälsa och klinisk medicin, Umeå Universitet, Luleå, Sweden	External expert		
10.	TBC	Medical Editor		
11.	Zorginstituut Nederland [ZIN]	Project Manager	Netherlands [NL]	Coordination between involved parties throughout the assessment duration

1.2 Project stakeholders

Table 1-2: Project stakeholders

Organisation	**Role in the project**
Sanofi	Manufacturer [MAH]
University, Sunderby hospital	External expert
Diabetes UK	Patient organisation
FEDE Spain	Patient organisation

1.3 Milestones and Deliverables

Table 1-3: Milestones and Deliverables

Milestones/Deliverables	Start date	End date
Project duration	**28/05/2018**	**~05/06/2019[a]**
Expression of interest of manufacturer	05/28/2018	
Team building (including identification of external experts and patients)	31/05/2018	14/06/2018
Scoping phase	**28/05/2018**	**28/01/2019**
Scoping and development of draft Project Plan incl. preliminary PICO	28/06/2018	11/09/2018
Share the preliminary PICO with MAH, external experts *(and patients)*	1/09/2018	06/09/2018
Share the preliminary PICO with WP4 partners on the intranet, to ask for input on PICO	7/09/2018	13/09/2018
Pre-scoping e-meeting with the assessment team	21/09/2018	21/09/2018
Scoping F2F meeting with manufacturer(s)	28/09/2018	28/09/2018
Amendment of draft Project Plan & final Project Plan available	1/10/2018	28/02/2019
Completion of Submission file template by manufacturer(s)	05/02/2019	
CHMP opinion	28/02/2019	
Assessment phase	**27/02/2019**	**~05/06/2019[a]**
Grace period	**TBD**	**TBD**
Writing first draft rapid assessment	27/02/2019	09/04/2019
Review by dedicated reviewer(s)	09/04/2019	19/04/2019
Writing second draft rapid assessment	23/04/2019	03/05/2019
Medical editing of second draft rapid assessment	09/05/2019	13/05/2019
Review by ≥ 2 external clinical experts and fact check by manufacturers	13/05/2019	17/05/2019
Writing third draft rapid assessment	17/05/2019	03/06/2019
Formatting	03/06/2019	05/06/2019
Final version of rapid assessment	~05/06/2019[a]	

[a] *Timelines will change slightly, due to the need of a grace period to adjust the submission file to the suggested label change by CHMP.*

2 Project Outline

2.1 Project Objectives

The rationale of this assessment is to collaboratively produce structured (rapid) core HTA information on pharmaceutical technologies. In addition, the aim is to apply those collaboratively produced assessments in the national or regional context.

Table 2-1: Project objectives

	List of project objectives	Indicator (and target)
1.	To jointly produce health technology assessments that are fit for purpose, of high quality, of timely availability.	Production of 1 (rapid) relative effectiveness assessment (REA).
2.	To apply this jointly produced assessment into local (e.g. regional or national) context.	Production of ≥2 local (e.g. national or regional) reports based on the jointly produced assessment.

This rapid assessment addresses the research questions whether Zynquista® (sotagliflozin) as add-on therapy for adult patients with Type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m^2 who have inadequate glucose control using optimised therapy with insulin or insulin analogues is more effective and/or safer than optimised insulin monotherapy alone, and to assess the relative effectiveness / safety of sotagliflozin as compared to any SGLT-2-inhibitor in this setting.

2.2 Project Method and Scope

2.2.1 Approach and Method

Table 2-2: Project approach and method

Project approach and method
<u>Planned literature search strategy</u> For Effectiveness (EFF) and Safety (SAF) domains, a systematic literature search in MEDLINE, EMBASE and Cochrane Library will be performed. Search terms include type 1 diabetes mellitus, sotagliflozin, insulin, and any SGLT-2-inhibitor (unrestricted search period). Hand searches (from reference lists of relevant studies) will also be carried out. The following clinical trials registries: ClinicalTrials.gov (http://www.clinicaltrials.gov/), WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/) will be searched in as well for registered ongoing clinical trials and observational studies (the latter might be relaxant for the safety domain). Relevant references will be screened and assessed for eligibility independently by two reviewers. References will be included or excluded according to the overall research question, Population-Intervention-Control-Outcome (PICO)-scheme (as described in Project Scope), study design, and presented according to the PRISMA Statement. Evidence included in the Manufacturer's submission file will be checked for completeness and accuracy against published literature from the literature search above and EMA and FDA pages/databases (1). If the electronic search is older than 6 months the search will be updated. If needed questions related to treatment will be sent to clinical experts at TLV or the other authorities. The submission will be evaluated by the assessment team, see table 1. The selection of assessment elements will be based on the EUnetHTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (4.2). The Checklist for potential ethical, organisational, patient and social and legal aspects of the HTA Core Model for rapid REA will be filled in as well. The selected issues (generic questions) will be translated into actual research questions (answerable questions).

For Description and technical characteristics of technology (TEC) and Health problem and current use of technology (CUR) domains no quality assessment tool will be used, but multiple sources will be used in order to validate the individual sources. Descriptive analysis will be performed on the information sources. The completed part of EUnetHTA submission file from the manufacturer will be used as starting point.

The risk of bias of included RCTs will be evaluated independently by two reviewers according to the Cochrane risk of bias assessment approach and the EUnetHTA Guideline for Internal validity. In case of divergences, this will be discussed in the presence of a third reviewer.

Study and outcomes validity and level of evidence will be assessed according to the EUnetHTA guidelines (2) (3) (4). The Cochrane Risk of bias tool will be used on study and outcome level. The quality of the body of evidence will be assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation). If deemed necessary, relevant subgroup analyses, as well as indirect comparisons (through network meta-analysis or another suitable method) will be assessed especially for the most important outcomes.
If included, indirect evidence on outcomes will be assessed by using the GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis **[5]**, and evaluation of the network meta-analysis will be based on the principles described in the EUnetHTA Guideline on Direct and indirect comparisons **[6]**.

2.2.2 Project Scope

The EUnetHTA Guidelines, available at http://www.eunethta.eu/eunethta-guidelines, need to be consulted throughout the assessment process.

Table 2-3: Project Scope: PICO (please see HTA Core Model® for rapid REA)

Description	Project Scope
Population	Add-on treatment of patients ≥ 18 years old, with Type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite using optimised therapy[1] with insulin or insulin analogues[2]. • Type 1 diabetes mellitus • ICD-10: E10.xx • MeSH terms: Diabetes Mellitus, Type 1 [1]Inadequate blood glucose control as defined in the clinical trials should be compared to definitions in European guidelines and also with possible differences from different national guidelines highlighted. According to European guidelines, inadequate blood glucose control can be defined as an individualised target not met (in general above 7%, 53 mmol/l, for HbA1c, if not prevented by symptomatic hypoglycaemia) after an insulin titration period. [2]The insulin regimen and used in the clinical trials *(e.g. number of injections, type of insulin, number of international units per kg/day, use of continuous subcutaneous delivery [CSI] versus multiple daily injections [MDI; basal/bolus versus mixed insulin])* should be compared with European and relevant national guidelines, with possible deviations highlighted. Subgroup analysis with respect to insulin regimen (add-on to MDI and add-on to CSI with type of CSI defined (which includes stand-alone or in conjunction with continuous glucose monitoring or flash glucose monitoring).
Intervention	Sotagliflozin (200 mg or 400 mg daily), administered orally, add-on to optimised insulin therapy. Sotagliflozin is a small molecule dual inhibitor of SGLT1 and SGLT2 (Sodium-glucose co-transporter) that improves glycaemic and metabolic control.

<table>
<tr><td>Comparison</td><td>Sotagliflozin (200 mg or 400 mg) versus placebo

Sotagliflozin (200 mg or 400 mg) versus any SGLT-2-inhibitor

Rationale: Comparators are chosen according to those listed in the evidence-based clinical guidelines [ESC 2013; NICE 2016; Royal College of Physicians 2008; Scottish Intercollegiate Guidelines Network, 2018; World Health Organization 2011;], the recommendations from the relevant HTAs, and the EUnetHTA guidelines [2]</td></tr>
<tr><td>Outcomes</td><td>EFF and SAF domain:

<u>Crucial endpoints:</u>

• Microvascular / macrovascular complications if available, if not (EFF):’
  ○ Surrogate endpoint HbA1c, measured over at least 26 weeks [EMA guideline 2012/2018)
  ▪ Absolute change from base line,
  ▪ Proportion of patients with HbA1c <53 mmol/mol (7%)*,
  ▪ Proportion of patients with HbA1c < 70 mmol/mol,
  ▪ Net benefit (HbA1c <53 mmol/mol (<7%) and no episode of severe hypoglycaemia or diabetic ketoacidosis),
• Mortality (EFF and SAF)
• Health-related quality of life (EFF)*
  ○ Diabetes treatment satisfaction score change from base line.
  ○ Disease-specific HRQoL measurements
  ○ EQ5D for generic health status
• Hypoglycaemia (incidence and number, by severity [level 1, 2, 3])* (SAF)
• Severe Adverse Events (incidence and number) (SAF)
• Adverse Events leading to discontinuation (incidence and number) (SAF)
• Diabetic Ketoacidosis (incidence and number; definition and validation of diabetic ketoacidosis explained) (SAF)

<u>Important endpoints:</u>

• Change from base line in body weight (EFF)
• Change in cardiovascular risk factors (e.g. serum lipids and blood pressure) (EFF)
• Change from base line in fasting plasma glucose (EFF)
• Change from base line in postprandial plasma glucose (EFF)
• Time in range (EFF)
• Insulin change from baseline (basal, bolus, total dose (IU)/day) (EFF)
• Most frequent Adverse Events

*Outcomes related to issues particularly emphasised by patient organisations.

Classification of hypoglycaemia [7]

<table>
<tr><th>Level</th><th>Glycemic criteria</th><th>Description</th></tr>
<tr><td>Hypoglycemia alert value (level 1)</td><td>≤70 mg/dL (3.9 mmol/L)</td><td>Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy</td></tr>
<tr><td>Clinically significant</td><td><54 mg/dL (3.0</td><td>Sufficiently low to indicate serious, clinically</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>hypoglycemia (level 2)</td><td>mmol/L)</td><td>important hypoglycaemia</td></tr><tr><td>Severe hypoglycemia (level 3)</td><td>No specific glucose threshold</td><td>Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery</td></tr></table> **Rationale**: Outcomes are selected based on outcome availability defined by the study design of the relevant studies, and on the recommendations from the relevant HTAs, clinical guidelines and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety. The result of the patient survey for this assessment is also to be taken into account in the selection of relevant outcomes. In addition to appropriate statistical analysis, the clinical relevance of minor changes in outcome measures should be considered (e.g. EMA has defined when a change in HbA1c is clinically relevant from a non-inferiority perspective.) Outcomes should generally be clinically relevant and applicable in suitable cost effectiveness modelling, particularly for the ones for which treatment benefits are claimed. Outcomes should also be coupled and discussed in relation to treatment goals in available guidelines and an association/correlation between a surrogate outcome and a patient-relevant outcome measure should be discussed/described
Study design	**EFF domain:** If suitable evidence syntheses (systematic reviews [SRs]/HTA reports) are available: • Evidence syntheses (SRs/HTA reports) and • Primary studies (as described in next bullet) published after the last search date of the latest SR/HTA document If suitable evidence syntheses (SRs/HTA reports) are NOT available: • Randomised controlled trials **SAF domain:** If suitable evidence syntheses (SRs/HTA reports) are available: • Evidence syntheses (SRs/HTA reports) and • Primary studies (as described in next bullets) published after the last search date of the latest SR/HTA document If suitable evidence syntheses (SRs/HTA reports) are NOT available: • Randomised controlled trials • Non-randomised controlled trials • Observational studies Only English language studies will be included.

3 Communication and collaboration

3.1 Dissemination plan

The final rapid assessment will be published on the EUnetHTA website: http://www.eunethta.eu/joint-assessments.

All stakeholders and contributors are informed about the publication of the final assessment by the project manager.

3.2 Collaboration with stakeholders

Collaboration with manufacturer

Manufacturers can indicate their willingness to participate by submitting an expression of interest. The REA submission file provided by the company applying for market authorisation is the basic documentation for a rapid assessment and is received by authors before the positive opinion of the CHMP. Therefore, the company applying for market authorisation might be asked to provide relevant parts (e.g. scientific discussion) of the CHMP report.

There will be a face-to-face scoping meeting of author(s)/co-author(s)/coordination team with the manufacturer. Within one week after face-to-face scoping meeting authors will send their data requirements for submission file to the manufacturer. The final submission file from the company is expected prior to the CHMP opinion. After the scoping F2F meeting, the authors finalise the project plan and plan the timelines.

In general, the consultation with the manufacturer includes the scoping (especially timelines) and the second draft of the pilot assessment. However, if necessary, it is possible to send queries to the manufacturer during the assessment phase

Patient involvement

EUnetHTA deems patient involvement very important for the production of Joint Assessment reports, as patients and those who support them have unique knowledge about living with a specific disease or medical condition. Therefore, at the start of this Joint Assessment an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they have the position to collect and present patient's and care-givers' views and experiences by engaging with a wide range of patients and their careers.

The open call used by EUnetHTA asks general questions to elicit patients' views on living with the disease, important outcomes to be considered in this assessment and expectations about the drug under assessment. The questions are based on the HTAi questionnaire template. For more information on the development of the HTAi questionnaire template please see their website.

The open call was published on July 9th 2018 and was closed on August 23rd 2018, in which EUnetHTA was seeking for European and national patient organisations to provide an organisational perspective on the questions in English. In all parts of the open call, the term 'patient' refers to anyone living with, or who has lived with, the condition for which the new medicine is indicated. Two patient organisations completed the survey, namely Diabetes UK (UK) and Fede (Spain).

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. In the PICO table (Table 2-3), the outcomes that are related to issues particularly emphasised by patient organisations are marked by an asterisk (*).

3.3 Collaboration with EUnetHTA WPs

For the individual rapid assessment, some collaboration with other WPs is planned: WP7 [Implementation] will be informed of the project, in order to prepare activities to improve national uptake of the final assessment. Feedback on the WP4 REA process will be asked from the involved parties by WP6 [Quality Management], and this information will be processed by WP6 to improve the quality of the process and output.

3.4 Conflict of interest and confidentiality management

Conflicts of interest will be handled according to the EUnetHTA Conflict of Interest Policy. All individuals participating in this project will sign the standardised "Declaration of Interest and Confidentiality Undertaking" (DOICU) statement.

Authors, co-authors and dedicated reviewers who declare a conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

For external experts, patients or other stakeholders involved, conflict of interest declarations are collected regarding the topic. External experts or patients who declare conflict of interest will be excluded from parts of or the whole work under this specific topic. However they still may be included in other assessments.

4 References

1. EUnetHTA_Guidelines. [Online] December 2017. http://eunethta.eu/sites/default/files/Guideline_Information_Retrieval_V1-2_2017.pdf.

2. —. Comparators & Comparisons Direct and indirect comparisons. [Online]

3. —. Endpoints sed for relative effectiveness assessment: clinical endpoints. [Online]

4. —. Levels of evidence. Internal validy of randomised controlled trials. [Online] http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/16_WP7-SG3-GL-int_val_RCTs_amend2015.pdf.

5. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014; 349:g5630.

6. Guideline direct and indirect comparisons. [Online] https://www.eunethta.eu/wp-content/uploads/2018/03/Direct_comparators_comparisons.pdf

7. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155

5 Appendix A

5.1 Selected Assessment Elements

The table shows the assessment elements and the translated research questions that will be addressed in the assessment. They are based on the assessment elements contained in the 'Model for Rapid Relative Effectiveness Assessment'. Additionally, assessment elements from other HTA Core Model Applications (for medical and surgical interventions, for diagnostic technologies or for screening) have been screened and included/ merged with the existing questions if deemed relevant.

Table 5-1: Selected Assessment Elements

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
Description and technical characteristics of technology					
B0001	Features of the technology and comparators	What is the technology and the comparator(s)?	Yes	M	What are sotagliflozin and optimised insulin therapy and SGLT-2-inhibitors?
A0020	Regulatory Status	For which indications has the technology received marketing authorisation or CE marking? [This assessment element can be placed either in the TEC OR in the CUR domain]	Yes	M	What is the approved indication of sotagliflozin?
B0002	Features of the technology and comparators	What is the claimed benefit of the technology in relation to the comparator(s)?	Yes	M	What is the claimed benefit of sotagliflozin add-on to insulin compared to insulin therapy alone? What is the claimed benefit of sotagliflozin add-on to insulin compared to any SGLT-2-inhibitor?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	Yes	NM	What is the phase of development of sotagliflozin? What is the phase of development of any SGLT-2-inhibitor?
B0004	Features of the technology	Who administers the technology and the comparator(s) and in what context and level of care are they provided?	Yes	NM	Who administers sotagliflozin, insulin, and any SGLT-2-inhibitor and in what context and level of care are they provided?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	No	NM	Not relevant, next question more appropriate.
B0009	Investments and tools required to use	What equipment and supplies are needed to use the technology	Yes	NM	What equipment and supplies are needed to use sotagliflozin, any SGLT-2-inhibitor and insulin?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
	the technology	and the comparator(s)?			
A0021	Regulatory Status	What is the reimbursement status of the technology? [This assessment element can be placed either in the TEC OR in the CUR domain]	Yes	NM	What is the reimbursement status of sotagliflozin?
Health problem and current use of technology					
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	Yes	M	What is Type 1 diabetes in the scope of this assessment?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	Yes	NM	What are the known risk factors of Type 1 diabetes?
A0004	Target Condition	What is the natural course of the disease or health condition?	Yes	M	What is the natural course of Type 1 diabetes?
A0005	Target Condition	What are the symptoms and the burden of disease or health condition for the patient?	yes	M	What are the symptoms and the burden of Type 1 diabetes?
A0006	Target Condition	What are the consequences of the disease or health condition for the society?	yes	NM	What are the consequences of Type 1 diabetes condition for the society?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	yes	NM	How is Type 1 diabetes currently diagnosed according to published guidelines and in practice? What are the possible differences between national and European guidelines?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	yes	M	How is Type 1 diabetes currently managed according to published guidelines and in practice? What are the possible differences between national and European routines? Are other add-on therapies to insulin used in T1DM according to published guidelines?
A0007	Target Population	What is the target population in this assessment?	yes	M	What is the target population in this assessment?

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
A0023	Target Population	How many people belong to the target population?	Yes	M	How many people belong to the target population?
A0011	Utilisation	How much are the technologies utilised?	No	NM	How much are sotagliflozin and any SGLT-2-inhibitor used, including a discussion on other possible therapies, used as add-on to insulin for patients with type 1 diabetes?
Clinical effectiveness					
D0001	Mortality	What is the expected beneficial effect of the intervention on mortality?	Yes	M	What is the expected beneficial effect on mortality of sotagliflozin add-on to optimised insulin compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?	yes	M	How does sotagliflozin add-on to optimised insulin affect symptoms and findings (severity, frequency) of Type 1 diabetes compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0006	Morbidity	How does the technology affect progression (or recurrence) of the disease or health condition?	yes	M	How does sotagliflozin add-on to optimised insulin therapy affect progression of Type 1 diabetes compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0011	Function	What is the effect of the technology on patients' body functions?	yes	M	What is the effect of sotagliflozin add-on to optimised insulin therapy on patients' body functions compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0016	Function	How does the use of technology affect activities of daily living?	yes	NM	How does the use of sotagliflozin add-on to optimised insulin therapy affect activities of daily living compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0012	Health-related quality of life **(Importance particularly emphasised by patient organisations)**	What is the effect of the technology on generic health-related quality of life?	yes	M	What is the effect of sotagliflozin add-on to optimised insulin therapy on generic health-related quality of life compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0013	Health-related quality of life	What is the effect of the technology on	yes	M	What is the effect of sotagliflozin add-on to optimised insulin therapy

ID	Topic	Topic Issue	Relevance in this assessment	Mandatory (M) or non-mandatory (NM)	Research question(s) or reason for non-relevance of 'mandatory' elements
	(Importance particularly emphasised by patient organisations)	disease-specific quality of life?			on diabetes-specific quality of life compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
D0017	Patient satisfaction	Were patients satisfied with the technology?	yes	NM	Were patients satisfied with the sotagliflozin add-on to optimised insulin therapy compared to optimised insulin therapy alone or compared to add-on of any SGLT-2-inhibitor to optimised insulin?
Safety					
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	yes	M	How safe is sotagliflozin add-on to optimised insulin in relation to optimised insulin therapy alone or in relation to add-on of any SGLT-2-inhibitor to optimised insulin? What is the frequency of any adverse event of sotagliflozin add-on to optimised insulin therapy compared to optimised insulin therapy alone or in relation to add-on of any SGLT-2-inhibitor to optimised insulin??
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	yes	M	Are the harms related to dosage of sotagliflozin?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	No	NM	
C0005	Patient safety	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?	yes	M	What are the susceptible patient groups that are more likely to be harmed through the use of sotagliflozin?
C0007	Patient safety	Are the technology and comparator(s) associated with user-dependent harms?	no	NM	
B0010	Safety risk management	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator(s)?	yes	NM	What kind of data/records and/or registry is needed to monitor the use of sotagliflozin and insulin?

5.2 Checklist for potential ethical, organisational, patient and social and legal aspects

1. Ethical	
1.1. Does the introduction of the new technology 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 technology to the defined, existing comparators point to any differences that may be ethically relevant?	No
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	No
(A possible incorporation into national guidelines of recommendations for the possible use of add-on to insulin therapy for patients with Type 1 diabetes would be beneficial (Sweden).)	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	No
3. Social	
3.1. Does the introduction of the new technology 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 technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology 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 technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	No