Input from manufacturer on the 2nd draft assessment
"SOTAGLIFLOZIN FOR ADULT PATIENTS WITH TYPE 1 DIABETES MELLITUS AND WITH A BODY MASS INDEX (BMI) ≥ 27 KG/M2 WHO HAVE INADEQUATE GLUCOSE CONTROL USING OPTIMISED INSULIN OR INSULIN ANALOGUES"

Project ID: PTJA04

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Comments on the 2nd draft rapid assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues

The objective of this reviewer form is to standardise the process of reviewing rapid relative effectiveness assessments.

The 2nd version of the Rapid Assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues was open to review by the manufacturer [Sanofi] between 13/05/2019 and 17/05/2019.

Comments received from

Manufacturer
Sanofi.

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Comments on the 2nd draft rapid assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues

Comments from Manufacturer

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
Sanofi	General		*There are large parts of the REA report that draw on information provided to EUnetHTA as confidential appendices. These data should be removed from the final REA report before publication.* *This is particularly important when the information is taken from the NMA – which suffers from significant limitations – and is utilised in place of datza from direct head-to-head studies.*	1	The authors were not allowed to use the confidential information from the submission dossier attachments and have removed this information from the document upon request from the MAH.
Sanofi	General		*Sanofi is disappointed that a balanced presentation of the Network meta-analysis (NMA) could not be agreed on within the constraints of the current process. Sanofi had expressed concerns about the feasibility of the NMA analysis prior to undertaking the work, and considers that the limited presentation in the draft EUnetHTA report was both selective, and did not adequately qualify the limitations of the findings.* *Despite seeking to resolve this, Sanofi was informed by EUnetHTA that addition of further material and another draft review could not be accommodated, and it was agreed that EUnetHTA would limit the presentation to the base-case results only, an analysis approach considered by the EUnetHTA authors as the most appropriate given the limitations.*	1	
Sanofi	General		*Overall the document mixes 24-week and 52-week data depending on the section, and does not therefore respect the primary endpoint design of the trials. We feel this is can be misleading and confusing. 52 weeks is important, but the appropriate scientific focus should reflect the study design.*	1	Not considered a fact-check comment.
Sanofi	General		*In many places the unit is not indicated (e.g. line 851), and in places confidence intervals are not fully declared as 95% CIs*	1	Partly accepted. These were mainly altered during the medical editing process.
Sanofi	General		*Please ensure consistency in use of the terms mITT and ITT* *mITT is the appropriate term*		Accepted

Comments on the 2nd draft rapid assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
Sanofi	General		*Please ensure correct definition of documented hypoglycaemia. <55mg/dL and ≤55mg/dL are used* ≤55mg/dL is the appropriate definition		Accepted
Sanofi	General		*For the final version, the formatting issues summarized in the following should be checked and adapted throughout the document:* • *Adjustment of body text font size (e.g. lines 298-306, 473-475, 1471-1476)* • *Adjustment of table width (e.g. lines 307, 555)* • *Update and correction of hyperlinks (e.g. missing links on page 58; page break 40/41)* • *Special symbols (e.g. lines 602-604)* • *Harmonisation of blank spaces between words/numbers and unit (e.g. lines 301, 303, 363), especially consistency for „BMI ≥27 kg/m²"* • *Specification of units (e.g. lines 851, 1079)* • *Introduction of abbreviations (e.g. line 197, 286)*	3	Not considered a fact-check comment. This has been corrected during the medical editing.
Sanofi	11	194	*Please correct the mechanism of action to match with SmPC.* *Current text:* "Inhibition of SGLT1 in the small intestine leads to reduced glucose absorption, …" *Proposed text:* "Inhibition of SGLT1 in the small intestine leads to **delayed and** reduced glucose absorption, …"	1	Accepted
Sanofi			*Please correct the inconsistent wording of the sotagliflozin indication and align to the EMA label text:* *Current text:* **Title:** Sotagliflozin for ***Adult*** Patients With Type 1 Diabetes Mellitus With a Body Mass Index (BMI) ≥ 27 kg/m² ***Who Have Indadequate Glucose Control*** Using ***Optimised Insulin*** or Insulin Analogues	2	Accepted
	11 & 29	196 & 582	**Executive Summary& Scope:** Add-on treatment of patients ***≥ 18 years*** old, with Type 1 diabetes mellitus with a BMI ≥ 27 kg/m², ***who have failed to achieve adequate glycaemic control*** despite using ***optimised therapy*** with insulin or insulin analogues		Accepted

Comments on the 2nd draft rapid assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
	12 & 28	206 & 575	**Executive Summary & Objective:** (…) whether sotagliflozin (Zynquista®) add-on therapy for ***adult*** patients with T1D with a Body Mass Index (BMI) ≥ 27 kg/m^2 ***who have inadequate glucose control*** using ***optimised therapy*** with insulin or insulin analogues		Accepted
	16 & 79	361 & 456	**Executive Summary & Conclusion:** For patients with BMI ≥27 kg/m^2 ***who have failed to reach individual glycaemic targets despite optimized insulin therapy*** (…)		Accepted
	24	494	**Size of target population**: Sotagliflozin is indicated as an adjunct to insulin therapy for ***adult*** patients with T1D and a BMI ≥ 27 kg/m2 ***who have failed to achieve desired glycaemic control despite optimal insulin therapy***. *Proposed text:* Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.		Accepted
Sanofi	13	231/232	*Please correct the following statement:* "A network meta-analysis (NMA) was performed by the MAH in order to compare sotagliflozin **to both empagliflozin and dapagliflozin**" *Proposed text:* "A network meta-analysis (NMA) was performed by the MAH in order to compare sotagliflozin **to all SGLT2 inhibitors relevant in this setting**. In a systematic literature search relevant studies on empagliflozin and dapagliflozin were found and included in the NMA."	2	Not accepted. Not considered a fact-check comment.
Sanofi	13	232-234	*Please correct the following statement:* "This NMA was conducted on the entire population, rather than the BMI ≥27 kg/m^2 subgroup, due to a lack of information about this subgroup in a number of the trials."	2	The authors have included the word "comparator".

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			Proposed text: "This NMA was conducted on the entire population, rather than the BMI ≥27 kg/m^2 subgroup, due to a lack of information about this subgroup in a number of the **comparator** trials". Information on sotagliflozin trials was available.		
Sanofi	13	232/233	*Please address the incomplete statement:* Outcomes were assessed at 24±2 weeks. *To recognize:* "NMAs were carried out at 24±2 weeks and 52±2 weeks. Given that more studies reported results at 24±2 weeks, the NMAs in this report focus on outcomes at 24±2."	2	Accepted. Proposed text inserted.
Sanofi	13	273	*Please correct the omission of inTandem 3 from the evidence consideration:* *InTandem 3 should not be excluded from the main body of the assessment as it provides important information on the treatment of patients who have not experienced rigorous insulin optimization prior treatment commencement. Whatever efforts are in place to support rigorous optimization in clinical practice, it is highly likely that some patients will not achieve this, so inTandem 3 offers important insights into the effectiveness in this situation*	1	Not accepted. Not considered a fact-check comment.
Sanofi	14	292-292	*Please correct the inconsistency in use of AND vs OR in reference to Severe Hypoglycaemia OR DKA Please check and use the same wording throughout the document:* *Current text:* "(defined as proportion of patients achieving an HbA1c<7% without experiencing severe hypoglycaemia and diabetic ketoacidosis) *Proposed text:* "(defined as proportion of patients achieving an HbA1c<7% without experiencing severe hypoglycaemia **or** diabetic ketoacidosis)	2	Accepted

Comments on the 2nd draft rapid assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
Sanofi	15	307	*Please consider including an explanation of ES1 pool in the heading of the table to make it easier for the reader and add SAF-1 pool.* *Proposed text:* "Summary of relative outcomes for mITT population ES1 and SAF-1 pool (pooled analysis of inTandem1 and inTandem2) BMI ≥27 kg/m^2".	2	Accepted
Sanofi	15 & 51	307 & 908 (Tabe 1 & 17)	*Please correct the results for SBP 0.4 should a negative number – apologies but this was due to a typo in the submission file addendum.* *Current text:* (sotagliflozin 200 mg vs. insulin alone) from "-2.1 (-3.9 to 0.4), 0.018" *Proposed text:* "….-2.1 (-3.9 to -0.4), 0.018"	1	Accepted
Sanofi	15	310-312	*The assessment in the sentence below is not correct:* "A substantial number of patients seem to be excluded from analyses for several outcomes provided by the MAH and numbers fall below the mITT populations presented in the CONSORT flow diagrams of the trials." *In the InTandem studies (as well as in DEPICT and EASE studies) efficacy analyses were made on the full mITT population and safety analyses on the full safety population, with formal imputation made on missing values.* *Further discussion is provided when discussing Table 18 below.*		Authors added "change from baseline" before outcomes to clarify that this relates only to those outcomes.
Sanofi	16-17	347-349 & 367-368	*Please clarify that 0.3-0.4% (FDA) and 0.3% (EMA) are commonly used non-inferiority margins for* ***type 2 diabetes mellitus***	1	Accepted
Sanofi	16	364	*Please correct the value for placebo-adjusted changes in HbA1c for sotagliflozin 400 mg; -0.38 should be a reported as a negative number*	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			Current text: "in HbA1c by−0.24% [CI: −0.35 to −0.13] and 400 mg resulted in placebo-adjusted changes in HbA1c by 0.38 % [CI: −0.49 to −0.27]," *Proposed text:* "in HbA1c by −0.24% [CI: −0.35 to −0.13] and 400 mg resulted in placebo-adjusted changes in HbA1c by **-0.38 %** [CI: −0.49 to −0.27],		
Sanofi	16	309	*This paragraph should be revised in light of information already provided and comments made in respect of Table 18 below:* Overall, evidence for the effects of sotagliflozin versus placebo, both as add-on to optimized insulin therapy was based on two RCTs. A substantial number of patients seem to be excluded from analyses for several outcomes provided by the MAH and numbers fall below the mITT populations presented in the CONSORT flow diagrams of the trials. Since the BMI subgroup has been extracted from these study bases, the authors assume the bias that may arise from this also applies to the BMI subgroup analyses. The MAH has been asked for an explanation, and until further notice, the risk of bias has been set too high for sotagliflozin studies and similarly for several outcome measures for dapagliflozin trials. *The specific statement* *"*The MAH has been asked for an explanation, and until further notice" should not be required for the final version. *Does not reflect appropriately the collaborative nature of the interaction, nor that all requests for information have been addressed. If the authors continue to be unclear about some aspects of the data, they should request further clarification.*	1	Adapted the paragraph to better reflect the information provided by the MAH.
Sanofi	16	357	*Please correct the statement* *Current text:*	2	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			sotagliflozin will be approved.." *Proposed text:* "sotagliflozin **has been** approved…"		
Sanofi	16	364-366	*Due to a typo in the submission file addendum, the following sentence should be rephrased*: *Current text:* "The 400 mg dose also significantly improves the cardiovascular risk factors systolic blood pressure (SBP) (-3.6 mm Hg [CI: −5.3 to −1.9]) and body weight." *Proposed text:* "Both sotagliflozin doses also significantly improve the cardiovascular risk factors systolic blood pressure (SBP) (-3.6 mm Hg [CI: −5.3 to −1.9] for sotagliflozin 400mg and -2.1 [-3.9 to -0.4] for sotagliflozin 200mg) and body weight."	1	Accepted
Sanofi	18	385	*For better readability we suggest to swap the upper and lower limits of the confidence intervals in the column "Relative effect" if the lower limit of the CI is larger than the upper limit. For example we suggest changing (0.35 to 0.13 lower) to (0.13 to 0.35 lower).*	3	Accepted
Sanofi	18-20	385	*General comment on the 1st column:* *Time point considered is not consistently reported for all outcomes considered.* *General comments on columns reporting absolute effects and relative effects:* *For consistency between columns reporting "Anticipated absolute effects" and "Relative effect", we suggest presenting all effects using the symbol '-' when "lower" is mentioned.* *Results on EQ-5D-5L index score:* *Placebo-adjusted effect of Sota 400 was not reported for ES1 in the Table 31 of the submission file. If results presented in Table 2 of the EUnetHTA report come from the meta-analysis conducted, the effects of Sota 400mg are not exact: "EQ-5D-5L: 0.01 points higher (0.01 lower to 0.02 higher)" should be "EQ-5D-5L: 0.01 points higher (-0.004 lower to 0.02 higher)"*	2	Accepted Not accepted Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			Outcome Symptomatic documented hypoglycaemia: *Should be "with documented SMBG ≤ 55 mg/dL"* *not "with documented SMBG < 55 mg/dL"* *<u>Results on Severe Hypoglycaemia:</u>* *In the outcome description, "n events per 1000 person-years" should be replaced by "n events per 1000 person-years adjusted to patient's exposure"* *<u>Results on DKA</u>:* *In the outcome description, "event rate per 1000 person-years" should be replaced by "event rate per 1000 person-years adjusted to patient's exposure"* *<u>Results on SBP:</u>* *Anticipated absolute effects reported are those reported in the addendum whatever the SBP at baseline while the relative effect reported are those reported in the addendum for patients with baseline SBP ≥ 30.* *<u>Results on body Weight:</u>* *Absolute risk for Sotagliflozin 400 is not exact: "3.6 (0.3) kg lower"* *should be "3.6 (0.2) kg lower"*		Accepted Accepted Accepted Accepted
Sanofi	19 & 79	376-377 & 1476	*Could you please clarify the following:* "… but the results are very imprecise and therefore, should be interpreted with caution"		Not considered a fact-check comment. This has been corrected during the medical editing
Sanofi	21	387	*Please correct the title of this table, as it summarizes results on the mITT population, and includes inTandem3 data* *Please correct the description for Severe hypoyglycaemia. Results relate to any Severe Hypoglycaemia, not only those that are positively adjudicated -*		Partly accepted Title of table: changed.
Sanofi	21	Table 3	*The table indicates these results are from the NMA. However, the results reported appear to be from*	1	

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			diagnostic analyses supporting the NMA, taken from the appendix file, and are not the results of the NMA itself.		
Sanofi	21	Table 3	*Please correct the reporting balance in this table. Presently it is highly misleading since it does not report data for sotagliflozin 200mg, and does not consistently use the same dose for empagliflozin for all endpoint (high dose 25 mg is used for efficacy but low dose 2.5 mg is used for safety)*	1	The authors have added in a note to say "Note that most studies include multiple doses, however we focus here on the highest dose in each study. Therefore the same dose for each treatment is not used for each endpoint."
sanofi	21	DKA in Table 3	*Please correct the information by adding a footnote to reflect that the assessment relies on different definitions are used depending on the program (for example "Definite + Probable" DKA are considered positive for InTandem studies) while only "Definite" DKA are considered positive in DEPICT* *Use of the data without this qualification is misleading*	1	Accepted
sanofi	22	414-415	*Please correct the following sentence* *Current text*: "Typically, people with T1D exhibit one or more of the following symptoms: glycosuria leading to polyuria, ketosis, **rapid weight loss**, age of onset below 30 years." *Rapid weight loss only is observed at the onset of diabetes before insulin treatment, but up to half of T1D patients are overweight or obese (Ryden A, Sorstadius E, Bergenheim K et al. The Humanistic Burden of Type 1 Diabetes Mellitus in Europe: Examining Health Outcomes and the Role of Complications. PLoS One. 2016;11:e0164977)*	1	Partly accepted: "The complications of diabetes include hyperglycaemia and metabolic imbalance, and people with untreated T1D exhibit one or more of the following features: glycosuria leading to polyuria, keto-sis, rapid weight loss, and age of onset <50 years"
sanofi	22	423-424	*Please adjust following sentence to correctly recognize the limitations of current treatment options* *Current text*:	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			"today's insulin treatment allows the patient to live with near normal blood glucose levels and fluctuations" *Proposed text:* In spite of progress made in insulin therapy, up to 70% of T1D patients are uncontrolled with optimal insulin therapy and have uncontrolled fluctuations (McKnight J, Wild S, Lamb M, Cooper MN, Jones TW, Davies EA, et al. Glycaemic control of Type 1 diabetes in clinical practice early in the 21st century: an international comparison. Diabet Med. 2015;32:1036-50).		
Sanofi	11 & 22	181 & 415	*Please correct statement regarding the age of T1D onset:* *Current text in Executive summary:* „Typically, people with T1D show (…) age of onset below 50 years" *Current text in Background:* „Typically, people with T1D exhibit (…) age of onset below 30 years" *Proposed text - according to the reference cited (NICE guideline)* „below 50 years"	2	Accepted
Sanofi	22	391-393	*Please add the word „exogenous":* *Current text:* Type 1 diabetes mellitus (T1D) is a complex, autoimmune disease characterized by rapidly progressive pancreatic β-cell destruction that leads to insulin deficiency and hence a lifelong insulin dependence. *Proposed text:* Type 1 diabetes mellitus (T1D) is a complex, autoimmune disease characterized by rapidly progressive pancreatic β-cell destruction that leads to insulin deficiency and hence a lifelong ***exogenous*** insulin dependence"	3	Accepted
Sanofi	24	489-492	*Please correct/update the following paragraph:*	2	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			Current text; " Furthermore, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion on 31 January 2019 for the SGLT2 inhibitor dapagliflozin in T1D; adjunct to insulin in patients with BMI ≥ 27 kg/m2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy." *Both dapagliflozin and sotagliflozin are now approved in the European Union*		
Sanofi	25	519	*Please correct the mechanism of action to match with SmPC.* *Current text:* "Inhibition of SGLT1 in the small intestine leads to reduced glucose absorption, …" *Proposed text:* "Inhibition of SGLT1 in the small intestine leads to **delayed and** reduced glucose absorption, …"	1	Accepted
Sanofi	25-27	530-531 and Tables 4 & 5	*Please double-checked and clarify the following:* "Forxiga® is indicated in adults for the treatment of insufficiently controlled … T1D as an adjunct to insulin in patients with BMI ≥ 27 kg/m2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy." *To our knowledge only Forxiga 5 mg is approved in T1D*	1	Accepted
Sanofi	27	Table 5	*Please correct in "method of administration" and "doses" to match the SmPC:* "The recommended dose is 200 mg sotagliflozin once daily before the first meal of the day. After at least three months, if additional glycaemic control is needed, in patients tolerating sotagliflozin 200 mg, the dose may be increased to 400 mg once daily."	1	Accepted
Sanofi	34	644-645	*Please correct the statement* *Current text:* **"**A network meta-analysis (NMA) was performed in order to compare sotagliflozin **to both empagliflozin and dapagliflozin**"	3	Not accepted. Not considered a fact check. This comment has also been made previously in the document.

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			Proposed text: "A network meta-analysis (NMA) was performed in order to compare sotagliflozin **to all SGLT2 inhibitors relevant in this setting**. In a systematic literature search relevant studies on empagliflozin and dapagliflozin were found and included in the NMA."		
Sanofi	34	646-647	*Please correct the statement* *Current text:* "a lack of information about this subgroup in a number of the trials." *Proposed text:* "a lack of information about this subgroup in a number of the **comparator** trials."	3	The authors have added in the word comparator. This comment has also been made previously in the document.
Sanofi	36	701	*Please add a reference to the cited paper: Orme et al. 2017*	2	No longer relevant as this section has been removed due to confidentially reasons.
Sanofi	36	720	*Please correct* *Current text* "NMAs were carried out at 24±2 weeks and 52±2." *Proposed text* "NMAs were carried out at 24±2 weeks and 52."	2	Accepted. Note that 52±2 was included in another comment by Sanofi above. The authors have changed this to 52.
Sanofi	45	782	*Please correct the information to specify that*"[…] the submitted material also presents indirect comparisons **on the whole mITT population** in the form of […]"	3	Accepted. Authors have included the phrase "on the mITT population"
Sanofi	43	813	*Please correctly report the doses of dapagliflozine and emagliflozin*	3	Authors have added in "Note that most studies include multiple doses, however we focus here

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					on the highest dose in each study. Therefore the same dose for each treatment is not used for each endpoint."
sanofi	44	Table 13	*Please correct the text below which incorrectly indicates that insulin optimization was prevented in the controlled group in InTandem3. Only pre-randomization insulin optimization was not conducted. After randomization insulin doses were optimized to the same FPG and PPG targets as in InTandem 1-2.* *Current text:* "InTandem3 was excluded from the main body of the assessment, mainly because the study design without insulin optimisation may favour the intervention since optimal treatment with insulin in the control group is prevented." *Proposed text:* "InTandem3 was excluded from the main body of the assessment, mainly because the study design **did not include** insulin optimization **before randomization.**	1	Not considered a fact check. This was rephrased after medical editing.
Sanofi	45	840-842	*The sentence "A total of 793/782 patients were included in the trials in a 1:1:1 randomisation to either sotagliflozin 200 mg, sotagliflozin 400 mg or placebo." can be misunderstood.* *Proposed wording:* "A total of 793/782 patients were included in the inTandem1/inTandem2 trials. Patients were randomised in a 1:1:1 ratio to either sotagliflozin 200 mg, sotagliflozin 400 mg or placebo".	3	Not considered a fact check comment. This sentence was rephrased during the medical editing.
sanofi	45	847-849	*Please correct the text below which incorrecty indicates that insulin optimization was prevented in the controlled group in InTandem3. Only pre-randomization insulin optimization was not conducted. After randomization insulin doses were optimized to the same FPG and PPG targets as in InTandem 1-2.* *Current text:* "Insulin optimisation was not performed and, after randomisation, results of laboratory tests for HbA1c, FPG and urinary glucose levels were masked to trial staff." *Proposed text:* "Insulin optimisation was not performed **before randomization** and, after randomisation, results of	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			laboratory tests for HbA1c, FPG and urinary glucose levels were masked to trial staff. **Insulin doses were optimized to FPG and PPG targets based on SMBG monitoring**"		
Sanofi	45	871	*Please change:*week 24 *to* week 26 Please adapt Study duration and data cut offs of DEPICT-1 and EASE-2 in Table 14 according to text.		Accepted
Sanofi	49-50	892	***Please add*** *explanation of footnotes 1-4.*	3	Accepted
sanofi	49-50	Table 16	*Please correct the number of patients in the header for ES1, for Total insulin dose, DTSQs and DDS2 These should be the mITT population (298/305/313).* *Also, the number of patients for 2-h PPG should be corrected to the mITT population (58/59/65).*	1	Accepted
Sanofi	50 & 60	902 & 1080	*Please correct grammar:* *Current text:* **"**Since the finally approved…." *Proposed text* **"**Since **the final** approved indication…"	3	Not considered a fact-check comment. This has been rephrased during medical editing
Sanofi	50 58 60	906-907 1041,1053 1086,1094	*Hyperlink cross-reference not working*	3	Not considered a fact-check comment. These hyperlink cross references were altered during the medical editing.
Sanofi	51	908	*Please correct the description for the endpoint "Serum lipids – LDL-C *SD" to indicate that this data is based on the mITT pool.*	3	Accepted
Sanofi	51	908	*Please correct the description for the endpoint for the endpoints "Time in range" and "PPG" to indicate that this data is based on the CGM substudy.*	3	Accepted
Sanofi	51	908	*Please adjust for clarity* *Current text:*	3	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			"SBP (≥130 mmHg)" *Proposed text* "SBP (in patients with SBP ≥130 mmHg at baseline)" in order to avoid misunderstandings.		
Sanofi	52	908	*Please correctly describe for the endpoints "Hypoglycaemia (≤55 mg/dL, ≤3.0 mmol/L)", "EAIR of severe hypoglycaemia (Positively ad-judicated)" and "EAIR of DKA (positively ad-judicated)" that N, events per subject per year and Event rate (95% CI) was used instead of N and LS Mean (SE).*	3	Accepted
Sanofi	53	916	*Footnote 1: **Please add** that for inTandem trials an interactive voice/web response system (IXRS) system was used to generate the random sequence and for allocation concealment.* *Sources: CSRs [1-3]*	3	Accepted
Sanofi	53	916	*Footnote 3: We suggest changing the risk of bias regarding blinding of outcome assessment in inTandem2 and inTandem3 from uncertain to low.* At 52 weeks, 0.4% of patients receiving insulin alone (placebo) in inTandem1 and inTandem2 reported polyuria, in patients receiving 200 mg and 400 mg sotagliflozin 0.8% and 0.9% reported polyuria. In study inTandem3, 0.1% of patients receiving insulin alone (placebo) and 0.6% of patients receiving sotagliflozin 400 mg reported polyuria. Due to the **low** incidence of this PT, the risk of potential unblinding affects less than 1% of all patients in inTandem1 and inTandem2.	2	Not accepted. Not considered a fact-check comment.
Sanofi	53-54	Table 18	*Please correct the statement about missing data, and adjust any grading that relied upon the currently reported interpretation.* *The assessment about a bias due to incomplete outcome data addressed (number of patients included different from mITT) is not accurate. In the InTandem studies (as well as in DEPICT and EASE studies) efficacy analyses were made on the full mITT population and safety analyses on the full safety population, with formal imputation made on missing values. There are no major differences between the 3 programs. For the EASE program, the number of patients with actual values of HbA1c at each visit is visible in Figure 1 Panel A of Rosenstock et al, Diabetes Care 2018 Dec; 41:2560-2569.* The effect size estimates used in the NMA were from the full mITT population and addressed the issue of missing values using previously described imputation methods.	1	Not accepted. Not considered a fact-check comment.
Sanofi	53-54	Table 18	*Footnote 3 should also apply to the EASE program since empagliflozin also has a glycosuric effect*	1	Accepted
Sanofi	53-54	Table	*Please correct the recorded NA in relation to the "blinding of outcome assessment for InTandem3.*	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
		18	This study was blinded and blinded adjudication was performed		
Sanofi	53-54	Table 18	*It is unclear why risk of bias is considered low for EASE program at study level since the methodology of the 3 programs are overall very similar*	1	Not accepted. Not considered a fact-check comment.
Sanofi	55	932	***Please delete*** "e.g. younger patients with a BMI<27 kg/m^2" Sotagliflozin is not indicated for patients with BMI <27 kg/m^2 and therefore these patients were excluded in the analysis in the addendum submission file.	3	Accepted
Sanofi	56	973	*Please correct definition of net benefit* *Current text:* "achievement of HbA1c > 7 %" *Proposed text:* "achievement of HbA1c **<** 7 %".	2-3	Accepted
Sanofi	56	Section 4.8.1.1	*For clarification: please replace* *Current text:* "after 24 weeks" and "after 1 year/after 52 weeks" *Proposed text:* "**at Week 24**" by "**at Week 52**" in all places.		Not considered a fact-check comment. Has been rephrased during medical editing.
Sanofi	57	Section 4.8.1.2	*For clarification: please replace*: "after 24 weeks" *by* "**at Week 24**" in all places.	2	Not considered a fact-check comment. Has been rephrased during medical editing.
Sanofi	57	997-998	*Due to a typo in the submission file addendum, the following sentence should be rephrased:* *Current text:*	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			"The effect of the lower 200 mg dose was not statistically significant but suggested that also this dose reduces SBP (1.3 mm Hg at 24 weeks, and 2.1 mm Hg at 52 weeks)" *Proposed text:* "The effect of the lower 200 mg dose was statistically significant after 1 year (1.3 mm Hg at 24 weeks, and 2.1 mm Hg at 52 weeks)".		
Sanofi	57	1015	*Please correct the following information as this relates to the full population and can be reported for the subgroup* *Current text* "2.3 units for 200 mg, and 2.1 units for 400 mg" *Proposed text:* to "2.6 units for 200 mg and 400 mg".	1	Accepted
Sanofi	57	1016-1018	*Please correct the following text to avoid misunderstanding* *Current text* "no change was observed for the general EQ5D (low certainty of evidence Table 35 and a significant increase in the EQ-VAS score was found compared to placebo (moderate certainty of evidence Table 35)." *Proposed text* "no change was observed for the general EQ5D **index score** (low certainty of evidence Table 35**)** and a significant increase in the EQ-VAS score was found compared to placebo (moderate certainty of evidence Table 35)."	3	Accepted
Sanofi	57	1022-1024	*Please correct the following text to reflect the appropriate follow-up period* *Current text* "Pooled analysis of InTandem1-2 (BMI≥27 kg/m^2) show that total insulin dose decreased by 3.4 IU/day with 200 mg, and by 6.6 IU/day with 400 mg, compared to placebo after **52** weeks" *Proposed text*	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			"Pooled analysis of InTandem1-2 (BMI≥27 kg/m^2) show that total insulin dose decreased by 3.4 IU/day with 200 mg, and by 6.6 IU/day with 400 mg, compared to placebo after **24** weeks"		
Sanofi	56 and 57	footnote	***Please delete*** *footnote:* "May 2019The proportion of patients experiencing a net benefit (achievement of HbA1c > 7 % without DKA or SH) was increased after 24 weeks with sotagliflozin compared to placebo; 14% for 200 mg and 19.5% for 400 mg based on analysis of pooled data from all patients".	3	The footnote was deleted during the medical editing.
Sanofi	58	1059	*Please correct the definition* *Current text* "symptomatic documented hypoglycaemia (SMBG**>**55mg/dl)" *Proposed text* "symptomatic documented hypoglycaemia (SMBG**≤**55mg/dl)"	2	Accepted
Sanofi	58	1059	*Please correct the wrong value for documented hypoglycaemia.* *Current text:* "SMBG>55mg/dl" *Proposed text:* "SMBG≤55mg/dl"	2	Accepted
sanofi	58	1070-1071	*Please clarify the following sentence*: "(high certainty of evidence (low certainty of evidence, Table 33 and Table 34)"	3	Not considered a fact-check comment. Has been adapted during medical editing process.
Sanofi	59	1074	*For endpoint diarrhoea, please use a nonbreaking hyphen for the risk difference to avoid misinterpretation of the results by the reader.*	2	Accepted
Sanofi	59	1074	*Please add for endpoint genital mycotic infection in brackets that these are the results for women, analogous to the row above.*	2	Accepted
Sanofi	61	1119-1120	*Please correct the statement that indicates in Tandem3 was the only trial not to have post-insulin optimisation* *Proposed text*	3	This section is no longer included as the authors can no longer report the sensitivity analyses due

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			"However, no empagliflozin or dapagliflozin trial included post-insulin optimisation periods either."		to confidentiality reasons.
Sanofi	61	1118-1119	*The sentence about inTandem3below is not accurate and should be removed:* „It was also the only sotagliflozin trial which did not include a post-insulin optimisation period." *Only pre-randomization insulin optimization was not conducted. After randomization insulin doses were optimized to the same FPG and PPG targets as in InTandem 1-2.*	1	This section is no longer included as the authors can no longer report the sensitivity analyses due to confidentiality reasons.
Sanofi	63	Table 20	*Please correct the heading label or use footnotes to indicate how "any hypoglycemia" was defined and collected*	2	The authors have included Table 46 from the submission file detailing how hypoglycaemia was defined in each study.
Sanofi	63	Table 20	*Please correct/complete this table, as it is misleading- selectively reporting only some of the results and their corresponding rankings.* For example hypoglycaemia rates are not listed, yet for this endpoint, sotagliflozin is ranked first. The selection of presented endpoints by the authors should be made transparent. In addition we suggest adding the exact definition of the endpoints in the table.	1	Not accepted. As stated in the report, "For the crucial safety outcomes, only the NMAs for the proportion of patients experiencing an event are presented in this report. Additional NMAs examining the number of patients experiencing an event are excluded due to the similarity between the outcomes, as this outcome was reported in fewer trials so the NMAs would not be as informative." We have changed the headings in the table.

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
Sanofi	63	1159	*Please correct the table and remove the ranking of Sotagliflozin 200 mg for DKA, as this was not included in the NMA for this endpoint.*	1	Not accepted. Not considered a fact-check comment.
Sanofi	64	Table 21 Table 22 Figure 4	*Please correct* Theses tables as well as the conclusions drawn in ranking are misleading without exposing the limitations of the comparison such as consideration of the lower baseline HbA1c values in InTandem 1-2 compared to Depict and Ease programs. A strong positive relationship between baseline HbA1c and the magnitude of HbA1c change was demonstrated (Int J Clin Pract. 2011;65:602-612).	1	Not accepted. Not considered a fact-check comment.
Sanofi	67	1208-1230	*Please correct the description of "any hypoglycemia" to capture how it was defined and collected*	2	The authors have included Table 46 from the submission file detailing how hypoglycaemia was defined in each study.
Sanofi	68	1224	*Please correct Table 26 layout as the heading in the last column is truncated.*	3	This table is no longer in the document due to changes made due to confidentiality reasons.
Sanofi	70	Table 27 Table 28 Figure 10	*Please correct/complete the reporting of these data. For example, please clarify why the positive effect on severe hypoglycemia with sotagliflozin 200 and 400 mg vs placebo is not visible in this section.*	1	Not accepted. Not considered a fact-check comment.
Sanofi	71-73	1253-1278	*Please correct/complete the description of the findings and outline that assessment is constrained / misleading since different definitions for "positively-adjudicated DKA" are used depending on the program (for example "Definite + Probable" DKA are considered positive for InTandem studies) while only "Definite" DKA are considered positive in DEPICT*	1	The authors have added in the following: "We note that the MAH identifies differing definitions of DKAs across trials as

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
					being a limitation of this analysis."
Sanofi	75	1317	*Please correct the language since there is significant weight loss with both sotagliflozin 200mg and 400mg* *Current text* '… no weight gain…." *Proposed text* "….weight loss…"	1	Not accepted. Not considered a fact-check comment.
Sanofi	75	1330-1332	*Please delete the sentence in parentheses to be consistent with the SmPC* *Current text* "Even though the risk of DKA might be even higher in clinical practice **(e.g. because patients with a prior DKA in the month before enrolment were excluded)".** *Proposed text* *"*Even though the risk of DKA might be even higher in clinical practice *According to the summary of product characteristics patients should be evaluated with respect to DKA risk. Sotagliflozin should not be initiated when patients are at high risk such as patients with recent or recurrent history of DKA (1 episode in the past 3 months or more than 1 episode in the past 6 months). Therefore, it is not expected that this exclusion criteria in the studies will lead to more DKA events in clinical practice.*	3	Accepted
Sanofi	75	1330-1340	*It is unclear what the authors are trying to say here. The sentence appears to make a judgement about the treatment, more so that a simple description of the evidence.*	1	Not accepted. Not considered a fact-check comment.
Sanofi	75	1347	*We suggest using consistent units for HbA1c (% vs mmol/mol).*	3	Accepted
Sanofi	76	1349	*We suggest using consistent units for HbA1c (% vs mmol/mol).*	3	Accepted

Comments on the 2nd draft rapid assessment on sotagliflozin for adult patients with type 1 diabetes mellitus and with a body mass index (bmi) ≥ 27 kg/m2 who have inadequate glucose control using optimised insulin or insulin analogues

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
Sanofi	76	1367	*Please correct the following inconsistency* *A two level downgrade for indirectness is an inconsistent approach since in line 1354 there is only a one level downgrade for indirectness in effect on hard outcome measures.* *A one level downgrade for quality of life would be more consistent and as there is only one reason mentioned, DTSQ is not directly linked to QoL and thus 1 level downgrade.*	*1*	Not accepted. Not considered a fact-check comment.
Sanofi	76	1394-1396	*The statements here are speculative and not based on observed evidence. We propose these statements are removed*	2	Not accepted. Not considered a fact-check comment.
Sanofi	77	1400-1406	*Please correct the evidence downgrading to be consistent with the statements outlined here and reported in the literature. It is inconsistent to downgrade some endpoints for indirectness, when accepting there is strong evidence of surrogacy for the harder clinical outcomes*	1	Not accepted. Not considered a fact-check comment.
Sanofi	77	1419-1427	*Please correct the text, dapagliflozin has now EC approval in T1D, this paragraph could be adjusted* *Current text* "However, depending on the clinical trial outcomes, both drugs may obtain marketing authorisations for treatment in T1D patients in the future. Of note, in February 2019, dapagliflozin received a positive recommendation, from the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). The CHMP recommended that dapagliflozin be indicated for the adjunct treatment of insulin for certain patients with T1D (46)"	2	Accepted
Sanofi	79	1458	*Please correct the value for placebo-adjusted changes in HbA1c for sotagliflozin 400 mg.* *Current text:* "in HbA1c by−0.24% [CI: −0.35 to −0.13] and 400 mg resulted in placebo-adjusted changes in HbA1c by 0.38 % [CI: −0.49 to −0.27]," *Proposed text:* "in HbA1c by −0.24% [CI: −0.35 to −0.13] and 400 mg resulted in placebo-adjusted changes in HbA1c by **-0.38 %** [CI: −0.49 to −0.27],		Accepted
Sanofi	79	1464-1467	***Please correct*** *the following statement regarding SBP change from baseline for sotagliflozin 200mg as there was a typo in the submission file addendum.*	1	Accepted

MAH	Page	Line	Comment	Character of comment • 'major'a =1 • minor'b = 2 • 'linguistic'c =3	Reply from author
			Current text: "The 400 mg dose also significantly reduces the cardiovascular risk factors systolic blood pressure (SBP) (low certainty of evidence) and body weight (low certainty of evidence). The change in SBP is −3.6 mm Hg [CI: −5.3 to −1.9] after 1 year (the 200 mg dose appears to improve SBP as well, but not with statistical significance for the subgroup of the indication; −2.1 mm Hg [CI: −3.9 to 0.4])." *Proposed text:* "Both sotagliflozin doses also significantly reduce the cardiovascular risk factors systolic blood pressure (SBP) (low certainty of evidence) and body weight (low certainty of evidence). The change in SBP for sotagliflozin 400mg is −3.6 mm Hg [CI: −5.3 to −1.9] after 1 year, the 200 mg dose also improves SBP statistically significant, −2.1 mm Hg [CI: −3.9 to -0.4])."		
Sanofi	109-113	Table 7	*The assessment in footnote b that " EASE trials had lower attrition for change from baseline than the InTandem or DEPICT trials" and the inference that bias is lower is not accurate (see detailed answer above)*		Not accepted. Not considered a fact-check comment.

1. Lexicon Pharmaceuticals I. Clinical Study Report: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1 Diabetes Mellitus who have Inadequate Glycemic Control with Insulin Therapy (inTandem1). 2017.
2. Lexicon Pharmaceuticals I. Clinical Study Report: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel–group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of LX4211 as Adjunct Therapy in Adult Patients with Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control with Insulin Therapy (inTandem2). 2017.
3. Lexicon Pharmaceuticals I. Clinical Study Report: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Net Clinical Benefit of Sotagliflozin as Adjunct to Insulin Therapy in Type 1 Diabetes (inTandem3). 2017.