NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Sanofi**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. JDRF
   b. Association of British Clinical Diabetologists
   c. UK Clinical Pharmacy Association

4. **Expert personal perspectives** from:
   a. Professor Melanie Davies – clinical expert, nominated by Sanofi

5. **Evidence Review Group report** prepared by **BMJ Evidence**
   a. Evidence Review Group report
   b. Addendum

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response from Sanofi**
   a. Response to technical team's preferred base case
   b. Scenario analyses using population from inTandem2 with a BMI ≥ 27 kg/m², HbA1c ≥ 7% and Total Basal insulin dose > 0.4units/kg/day
   c. Scenario analyses using population from inTandem2 with a BMI ≥ 27 kg/m² and Total Basal insulin dose > 0.5units/kg/day
   d. Sensitivity analyses of adverse events using population from inTandem2 with a BMI ≥ 27 kg/m² and Total Basal insulin dose > 0.5units/kg/day

8. **Technical engagement responses from consultees and commentators:**
   - UK Clinical Pharmacy Association

9. Evidence Review Group critique of company response to technical engagement prepared by BMJ Evidence

10. **Final Technical Report**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sotagliflozin (Zynquista™) for treatment of type 1 diabetes (ID1376)

Document B

Company evidence submission

February 2019

File name	Version	Contains confidential information	Date
	FINAL	No	8th November 2019

Contents

Tables

Figures

Abbreviations

ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BHB	Beta-hydroxybutyrate
BMI	Body mass index
BNF	British National Formulary
CC	Complications and comorbidities
CDM	CORE Diabetes Model
CDR	Common Drug Review
CEA	Cost-effectiveness analyses
CFB	Change from baseline
CGM	Continuous glucose monitoring
CHF	Chronic Heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CL	Confidence Limit
CMH	Cochran-Mantel-Haenszel
CORE	Centre for Outcomes Research and Evaluation
CPRD	Clinical Practice Research Data
CrI	Credible interval
CSII	Continuous subcutaneous insulin infusion
CSR	Clinical Study Report
CT	Core treatment
CUA	Cost-utility analyses
CV	Cardiovascular
CVD	Cardiovascular disease
DAFNE	Dose Adjustment For Normal Eating
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DEXA	Dual-energy X-ray absorptiometry
DKA	Diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
EMA	European Medicines Agency
EOSI	Events of special interest
EOT	End of treatment
EW	Early withdrawal
EXT	Extension
FPG	Fasting plasma glucose
GI	Gastrointestinal
HbA_{1c}	Glycated haemoglobin
HCHS	Hospital and community health services
HCP	Heath care professional
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IDF	International Diabetes Federation
IDMC	Insulin Dose Monitoring Committee
ISPOR	International Society for Pharmacoeconomic Research
ITC	Indirect Treatment Comparison

ITT	intention-to-treat
IU	International Units
LS	Least Squares
LSM	Least squares mean
LTE	Long-term extension
LYG	Life-year gained
MD	Mean difference
MDI	Multiple daily injection
MDRD	Modification of Diet in Renal Disease
MI	Myocardial Infarction
MMRM	Mixed-effects model for repeated measures
NDA	National Diabetes Audit
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
PBAC	Pharmaceutical Benefits Advisory Committee
PICOS	Population, intervention, comparator, outcomes, and study design
PK	Pharmacokinetics
PPG	postprandial glucose
PPH	postprandial hyperglycaemia
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
PSSRU	Personal Social Services Research Unit
PT	Preferred Term
QALY	Quality-adjusted life-years
QD	Once daily
QoL	Quality of Life
QW	Once weekly
RCT	Randomised controlled trial
REM	Random effects model
RR	Rate ratio
SA	Sensitivity analyses
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT	Sodium-glucose transporter
SGLT-1/2	Sodium-glucose transporter-1/-2
SH	Severe hypoglycaemia
SLR	Systematic literature review
SMBG	Self-monitoring blood glucose
SMC	Scottish Medicines Consortium
SMDM	Society for Medical Decision Making
SoC	Standard of Care
SOC	System Organ Class
SmPC	Summary of Product Characteristics
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TEAE	Treatment-emergent adverse events
TG	Triglycerides
THIN	The Health Improvement Network
TID	Once daily
TIR	Time in Range
TTO	Time trade-off
UK PDS	UK Prospective Diabetes Study
ULN	Upper Limit of Normal

US	United States of America
UTI	Urinary tract infection
WK	Week

1. Decision problem, description of the technology and clinical care pathway

1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1.1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with T1D on insulin therapy that does not adequately control blood glucose levels	As per scope	As per scope. Please note this may be subject to adjustment until the CHMP reaches the adoption of the final label. Sanofi will communicate final label indication to NICE on CMHP opinion by 28 February 2019.
Intervention	Sotagliflozin in combination with insulin	As per scope with some exceptions	Clinical evidence is presented for the full marketing authorisation with respect to dose. The base-case for the economic analysis considers the 200 mg dose only because the 400 mg tablet will not be available at the time of launch in the UK.
Comparator(s)	Insulin therapy with or without metformin	As per scope	Insulin (primary comparator). Insulin + metformin (secondary analysis).
Outcomes	• HbA_{1c}/glycaemic control/blood glucose variability • BMI/change in body weight/waist circumference • Frequency and severity of hypoglycaemia • Changes in CV risk factors, including blood pressure and lipids • Microvascular complications of diabetes, including damage to nerve, kidney and	As per scope with some exceptions	AEs as reported in the registration studies are described in the clinical section of the submission. The main AEs that were considered in the economic base-case analysis are the number of severe and non-severe hypoglycaemic and DKA events. Based on currently available data, UTI and fractures were not considered important potential risks of sotagliflozin. Therefore, these have not been included in the economic model. Overall, the rates of genital mycotic infections were

	eye • Macrovascular complications of diabetes, including coronary artery disease, peripheral arterial disease, stroke and lower limb amputations • Mortality • Total daily insulin dose • Adverse effects of treatment, including DKA, fractures, genital infections and UTIs • Health-related quality of life		higher in female patients, but the increase occurred in both placebo and sotagliflozin patients. In nearly all, the cases were mild or moderate in severity. None of the events was reported as serious. The rate of treatment discontinuation due to genital mycotic infection was low. Therefore, genital infections have not been included in the economic model but are reported in the clinical section.

AEs, adverse event; BMI, body mass index; CHMP, Committee for Human Medicinal Products; CV, cardiovascular; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; T1D, type 1 diabetes; UTI, urinary tract infections.

1.2. Description of the technology being appraised

Table 1.2 Technology being appraised

UK approved name and brand name	Zynquista® (sotagliflozin)
Mechanism of action	Sotagliflozin is a dual inhibitor of SGLT-1 and SGLT-2 (1). Sotagliflozin improves glycaemic control, independent of insulin, in patients with T1D by both reducing glucose absorption in the intestine (SGLT-1) and enhancing glucose excretion in the urine (SGLT-2). Local intestinal inhibition of SGLT-1, the major transporter for glucose absorption, delays and reduces glucose absorption in the proximal intestine, resulting in a blunting and delay of postprandial hyperglycaemia. SGLT-2 is the predominant transporter responsible for reabsorption of glucose from the renal glomerular filtrate back into the circulation. By inhibiting SGLT-2, sotagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.
Marketing authorisation/CE mark status	The CHMP is expected on 28 February and marketing authorisation on 6th May 2019. All information regarding the indication is subject to CHMP opinion.
Indications and any restriction(s) as described in the Summary of Product Characteristics	Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with T1D, who have failed to achieve desired glycaemic control despite optimal insulin therapy. The decision to prescribe sotagliflozin should be based on an assessment of the individual patient's risk for DKA.

UK approved name and brand name	Zynquista® (sotagliflozin)
Method of administration and dosage	The recommended dose is 200 mg sotagliflozin once daily before the first meal of the day. After ≥3 months, if additional glycaemic control is needed, in patients tolerating sotagliflozin 200 mg, the dose may be increased to 400 mg once daily.
Additional tests or investigations	Before initiating treatment with sotagliflozin, it is advised that clinicians assess risk factors for DKA and ensure that ketone levels are normal. Before initiating treatment with sotagliflozin 200 mg and before increasing dose to sotagliflozin 400 mg: • Patients should be as close as possible to their glycaemic goal by diet and optimal insulin therapy. • Risk factors for DKA should be assessed and ketone levels should be evaluated as normal. If ketones are elevated (BHB reading is >0.6 mmol/L or urine ketones one plus (+)), treatment with sotagliflozin should not be initiated, nor should the dose be increased to 400 mg until the ketone levels are normal. • It is recommended that patients obtain several baseline blood or urine ketone levels over 1–2 weeks prior to initiation of sotagliflozin therapy, and patients should become familiar with how their behaviours and circumstances affect their ketone levels. • Patients must be able to perform self-management of the day-to-day aspects of their disease, including self-monitoring of blood glucose and ketones, and how to manage DKA risk. Volume depletion correction prior to initiation of sotagliflozin is recommended in patients with this condition.
List price and average cost of a course of treatment	Per 30-tablet pack is £39.20. Treatment is continued until the patient is no longer receiving benefit or unacceptable side-effects.
Patient access scheme (if applicable)	No patient access scheme is submitted with this submission.

BHB, beta-hydroxybutyrate; CHMP, Committee for Medicinal Products for Human Use; DKA, diabetic ketoacidosis; SGLT-1, sodium-glucose co-transporter type 1; SGLT-2, sodium-glucose co-transporter type 2; T1D, type 1 diabetes.

1.3. Health condition and position of the technology in the treatment pathway

Summary

- Type 1 diabetes (T1D) is a chronic disease that poses significant burden on patients and the healthcare system. In the UK, most adult patients with T1D are inadequately controlled (HbA_{1c} >6.5% as defined by NICE), overweight/obese and at increased risk for cardiometabolic complications. The cost to the NHS, mostly due to managing complications, was estimated to be £1 billion in 2010/2011.
- Insulin is the cornerstone of treatment for T1D, but it is associated with adverse events, which limits its potential for patients to reach target glycated haemoglobin and therefore requires enhancement or adjunctive therapy. After failure on optimised insulin there are no other licensed pharmacological options with proven effectiveness for patients who are unable to achieve optimal glycaemic control.
- Sotagliflozin, a dual sodium-glucose transporter-1/-2 (SGLT-1/2) inhibitor, that reduces absorption of glucose in the kidney and the gastrointestinal tract, and can help to address the unmet need in patients who have not achieved adequate glycaemic control with optimised insulin therapy alone.

1.4. Overview of type 1 diabetes in adults

Type 1 diabetes (T1D) is a disease of insulin deficiency resulting in chronic, persistent hyperglycaemia in both fasting and fed states (2). Chronic hyperglycaemia is the main risk factor for the development of diabetes-related complications, including cardiac conditions, retinopathy, nephropathy and cognitive decline (3-5). Therefore, an aim of treatment is to reduce the risk of complications arising from hyperglycaemia.

Patients with T1D must have exogenous insulin treatment, otherwise the disease is fatal. Since its introduction in the 1920s, insulin therapy has undergone several advancements in both formulation and delivery methods and is currently recommended by National Institute of Health and Care Excellence (NICE) for reducing HbA_{1c} in T1D patients (6). According to NICE, a HbA_{1c} level of ≤6.5% (48 mmol/mol) is recommended as optimum control to prevent

long-term complications as studies have found that the risk and frequency of diabetes-related comorbidities rose with higher HbA_{1c} levels and with age (6). Multiple daily injection (MDI) basal-bolus insulin regimens is the principal treatment option, with continuous subcutaneous insulin infusion (CSII) pumps recommended when MDI insulin is ineffective (6). Non−insulin adjunctive therapy with metformin in adults with inadequately controlled T1D is currently recommended in NICE guidelines for patients with BMI >25 kg/m^2 who are inadequately controlled despite optimised insulin. However, NICE states that there is uncertainty around the data supporting the value of metformin in this specific setting (6) .

Although insulin is the mainstay treatment of T1D, it is associated with weight gain and (severe) hypoglycaemia (abnormally low blood glucose level) (7-9). Rates of mild-to-moderate hypoglycaemia in clinical trials are high (40–100 events per patient per year) but may be higher in routine practice (5, 9, 10). The Diabetes Control and Complications Trial (DCCT) established that tight glycaemic control using intensive insulin therapy is associated with an increased risk of hypoglycaemia (5); however, recent studies have suggested that many severe hypoglycaemic episodes occur in patients with poor, and often chaotic, glycaemic control. It is suggested that between 30% and 50% of patients with T1D suffer from recurrent and unpredictable severe hypoglycaemia. Fear of these side-effects may promote suboptimal dosing of insulin. Reduced insulin dosing, interruption of treatment or an excessive increase in insulin need will increase the risk of diabetic ketoacidosis (DKA), a life-threatening complication associated with excess mortality (6, 9, 11).

Despite clear national HbA_{1c} targets and advances in insulin treatments, over 90% of adult T1D patients do not meet the NICE-recommended HbA_{1c} targets (Table 1.3) (12). This failure to achieve targets arises primarily because exogenous insulin delivery cannot reproduce the finely calibrated release of insulin in the body by the pancreas (12).

Table 1.3 Percentage of UK adult patients with type 1 diabetes achieving glycated haemoglobin targets

	2010/ 2011	2011/ 2012	2012/ 2013	2013/ 2014	2014/ 2015	2015/ 2016	2016/ 2017
HbA_{1c} <6.5 % (<48 mmol/mol)	6.8	6.5	7.5	8.4	8.7	8.4	8.5
HbA_{1c} ≤7.5% (≤58 mmol/mol)	28.1	27.0	27.2	29.4	29.9	29.2	30.2
HbA_{1c} ≤10.0% (≤86 mmol/mol)	82.4	81.9	83.0	84.5	84.2	84.1	NR

NR, not reported.
Adapted from the UK NHS National Diabetes Audit report (13).

HbA_{1c} is a well established surrogate marker for disease control and is the only outcome linked to long-term complications. However, over a 24-hour period, blood glucose fluctuates and HbA_{1c} measurement does not capture this glycaemic variability (14). For example, Figure 1.1 shows blood glucose over a 24-hour period in two hypothetical patients. Fluctuations in blood glucose levels outside the normal range — due to missed insulin doses, infection, stress or postprandial hyperglycaemia — are common and have an independent role in the aetiology of diabetes-related complications (15-21). A web-based survey in Germany, the UK and USA of 356 patients with T1D revealed that 61.5% of respondents reported experiencing post-prandial hyperglycaemia in the preceding week, with 30.0% experiencing three or more episodes in that time (39). Therefore, reducing day-to-day fluctuations and increasing the amount of time within the normal blood glucose range (defined as time in range) (22-24) allows patients to achieve near-normal glycaemia and may avoid long-term complications related to suboptimal glycaemic control.

Figure 1.1. Two hypothetical patients with type 1

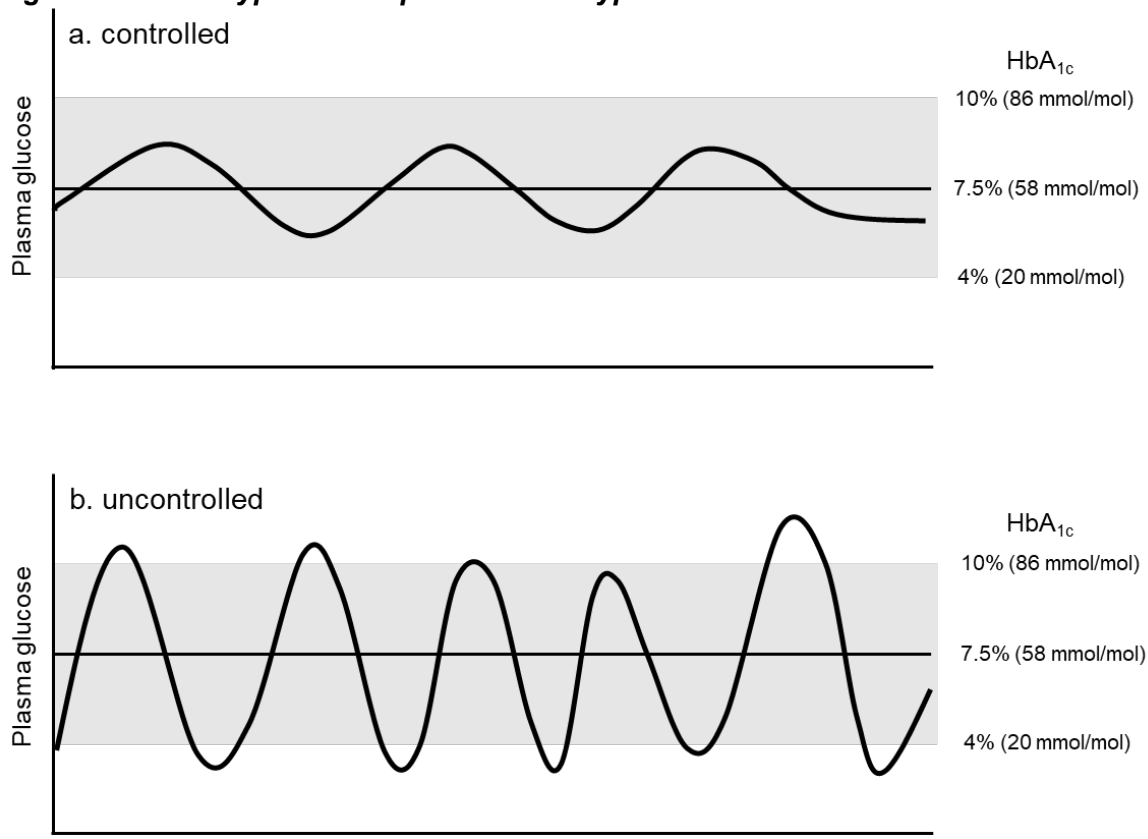


Figure shows two hypothetical patients with T1D. Both patients may have similar mean HbA_{1c} over time, but differ in terms of stability and fluctuation of plasma glucose concentrations around the mean level
HbA_{1c}, glycated haemoglobin.
Adapted from Aragona et al, 2005 (14).

The UK has the fifth highest rate of T1D in the world at present, with around 330,000 people affected (25) but the profile of the patients has changed over time which in turn has an impact on management approach. According to a recent cross-sectional study (n=5,607) using data from the Clinical Practice Research Datalink (CPRD), UK T1D patients are on average 45.6 years old, have a mean HbA_{1c} of 8.8% [standard deviation (SD) 3.6] [73 mmol/mol (SD 13)] and average body mass index (BMI) of 27.4 kg/m² (26). Therefore, the profile of the T1D patient population is changing and T1D patients after midlife tend to have a profile similar to patients with type 2 diabetes (T2D) where cardiovascular disease (CVD) is a more common comorbidity.

The challenge in managing the disease is reflected in its costs to the NHS. In 2010/2011 it was estimated that T1D cost the NHS close to £1 billion (27, 28) and managing diabetes-related complications, primarily due to uncontrolled diabetes and hypoglycaemia, accounts for 80% of these costs (27).

Therefore management of T1D requires a careful balance between reducing/avoiding the 'highs' (hyperglycaemia) and 'lows' (hypoglycaemia) over time (2), effectively increasing the time in normal glycaemic range. New treatments must evolve to improve glycaemic control without increasing the risk of hypoglycaemia.

1.5. Living with diabetes—the patient perspective

The responsibility for maintaining the delicate balance of preventing the 'highs' and 'lows' over time rests almost entirely with the patient (21). The patient is responsible for testing blood glucose, adhering to the insulin regimen and monitoring carbohydrate intake, as well as adjusting the insulin bolus dose at meal times, times of stress, or exercise. (21). Despite the patient's best efforts, a person's diabetes rarely remains static for long periods. Patients can experience periods of balanced blood glucose results one week, followed by apparently unexplainable variability the next (5, 15, 16, 18, 29, 30). Shouldering the responsibility for managing their disease imposes a significant burden on the health-related quality of life (QoL) of patients, as patients with T1D are also more likely to suffer comorbidities such as depression, stress and cognitive impairment (2, 11, 30).

In summary, for patients who are inadequately controlled despite optimised insulin, there are currently no further pharmacological options. More non-insulin treatment options are needed to achieve good glycaemic control and maintain daily blood glucose levels within normal

ranges in order to decrease the risk of micro- and macrovascular complications and improve cardiovascular outcomes. Overall, this will lead to improved long-term QoL for patients (3-5).

1.6. Sotagliflozin's place in the treatment pathway

Sotagliflozin will be the first dual sodium-glucose co-transporter type 1 (SGLT-1) and sodium-glucose co-transporter type 2 (SGLT-2) inhibitor licensed in diabetes [subject to approval by European Medicines Agency (EMA) in 2019]. It acts by reducing glucose absorption in the gastrointestinal (GI) tract (local action) and prevents glucose reabsorption in the kidneys (systemic action), thereby enhancing glucose excretion in the urine.

- SGLT-2 inhibition in the kidney has several consequences: 1) glucose is cleared from the circulation independently from insulin; 2) glucose clearance decreases with reduced levels of blood glucose, which limits the risk of severe hypoglycaemia; 3) urinary glucose excretion (UGE) lowers blood pressure through mild diuresis; and 4) UGE leads to weight loss through caloric loss.

- The primary transporter for absorption of glucose and galactose in the intestine is SGLT-1. Inhibition of SGLT-1 in the intestine may improve glucose control in several ways, namely: 1) reducing intestinal glucose absorption leading to reduced postprandial glucose (PPG); and 2) stimulation of GI peptides, such as GLP-1 and PYY, which assist in glycaemic and appetite control; and are associated with reductions in blood pressure and body weight.

- Therefore, with sotagliflozin, the desirable effects of SGLT-2 inhibition are complemented with SGLT-1 inhibition in the GI tract to produce reductions in PPG while triggering lower UGE than the more selective SGLT-2 inhibitors. Importantly, sotagliflozin's mechanism of action does not depend on endogenous insulin secretion.

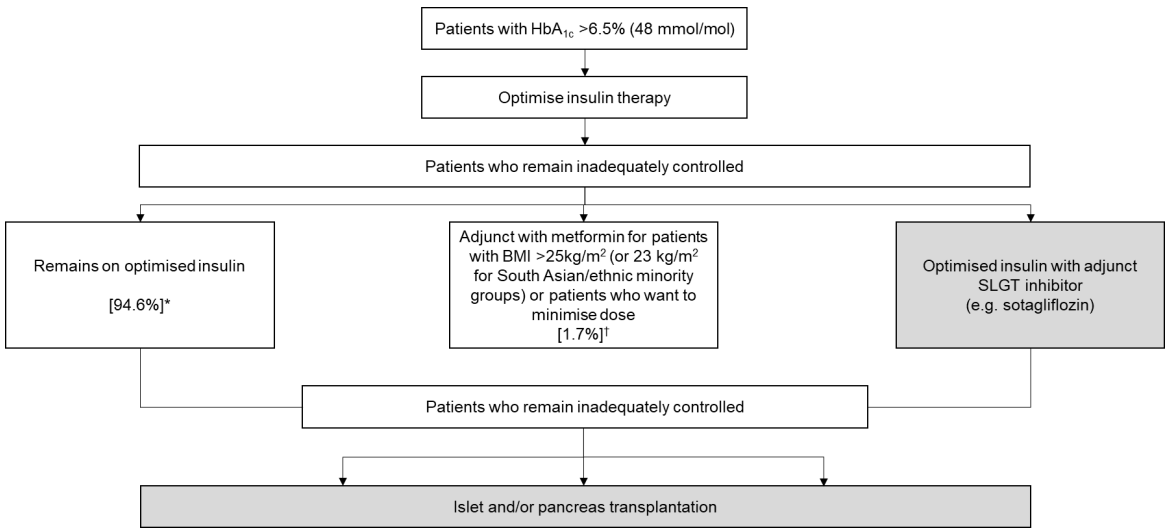
Currently, only insulin is approved for the treatment of T1D with NICE guidance being to optimise insulin therapy in patients with inadequate glycaemic control. CPRD analysis reported above (30) support the view that insulin is the primary treatment choice for patients with T1D. According to a CPRD analysis, metformin is not widely used in clinical practice. As noted above, the place of metformin in the treatment pathway is not licensed or supported by evidence of a significant impact on HbA_{1c}. Recent evidence from the REMOVAL trial

demonstrate a transient and minimal improvement on HbA_{1c} levels with metformin and showed no meaningful reduction in insulin requirement (31). Therefore, the primary comparator to sotagliflozin in this submission is optimised insulin. Metformin has been included in this submission per the NICE scope but is presented as a secondary analysis. SGLT-2 medicines (empagliflozin and dapagliflozin) are currently under review by NICE for T1D and have not been included in this submission as were not considered relevant comparators in the scope of this appraisal (30, 32, 33).

Sotagliflozin is proposed as an adjunct to insulin therapy to improve glycaemic control in adults with T1D, when insulin alone does not provide adequate glycaemic control. The schematic below shows sotagliflozin's proposed place in T1D within the UK.

Based on the anticipated licence for sotagliflozin, the eligible patient population in the UK are all patients with HbA_{1c} >6.5% (>48 mmol/mol) (i.e. inadequately controlled as defined by NICE). Appendix D describes the current NICE pathway for T1D in adults.

Figure 1.2. Proposed place in therapy for adjunctive sotagliflozin



[*n/N=5198/5618 on CSII and MDI. †n/N=94/5618 on metformin (26)]
Figure based on current NICE Type 1 Diabetes Clinical Guideline [NG17](6)
Optimised insulin could be using any mode of delivery.
Percentage use is based on baseline data from the Clinical Practice Research Datalink (CPRD) evaluate the progression of key clinical parameters for uncontrolled adult T1D patients over five years of follow-up.
BMI, Body Mass Index; NG, NICE guidance; T1D, Type 1 diabetes. SGLT, Sodium-glucose co-transporter.

1.7. Equality considerations

To the best of our knowledge, there are no equality considerations relevant to this appraisal.

2. Clinical effectiveness

Summary

- The Phase III programme comprised of three trials conducted in 2,977 patients and supported the regulatory submission for the full marketing authorisation.
- Two studies—inTandem1 and inTandem2—include the 200 mg and 400 mg dose and are relevant for this submission. inTandem3 (N=1402) was a global study of the 400 mg dose only. The summary of clinical efficacy is provided in Appendix E.
- The inTandem1 study recruited patients from the United States (N=793) and inTandem2 recruited patients from Europe (N=782). Both studies were identical in design.
- Both studies demonstrated that sotagliflozin 200 mg or 400 mg, as an adjunct to optimised insulin improved glycaemic control in patients with Type 1 diabetes (T1D) compared with T1D patients treated with insulin alone.
    - There was a statistically significant and clinically meaningful reduction in glycated haemoglobin (HbA_{1c}) from baseline with sotagliflozin compared with insulin alone at 24 weeks, which was sustained at 52 weeks, despite insulin optimisation. Reductions in HbA_{1c} were larger in patients with baseline HbA_{1c} >8.5% (69 mmol/mol).
    - The change from baseline to 24 weeks in HbA_{1c} for sotagliflozin 200 mg and 400 mg was −0.42% and −0.49% respectively in inTandem1 ($p<0.001$), and −0.39% for both doses in inTandem2 ($p<0.001$).
- Lower postprandial glucose (PPG), fasting plasma glucose (FPG), increased time in glycaemic range, and shorter time out of target range versus insulin therapy led to reduced glycaemic variability for patients. These effects are consistent with dual sodium-glucose co-transporter type 1 (SGLT-1) and type 2 (SGLT-2) inhibition.
- inTandem1 and inTandem2 demonstrated benefits in addition to HbA_{1c} reduction:
    - Mean differences in weight versus placebo were −1.98 to −3.45 kg at Week 24 and these were sustained at 52 weeks across both doses.
    - Both studies demonstrated reductions in systolic blood pressure (SBP) across both the 200 mg and 400 mg doses, in a subgroup of patients with baseline SBP ≥130 mmHg.
- Safety:
    - Overall, the incidence of treatment-emergent adverse events was similar in the sotagliflozin and placebo groups (across all Phase III studies), and the majority of patients in all groups completed the studies.
    - There was a reduction in documented severe hypoglycaemic events for sotagliflozin compared with placebo across the studies.
    - Sotagliflozin was associated with a numerically greater risk of diabetic ketoacidosis (DKA) compared with placebo. DKA is a feature of uncontrolled T1D as well as a documented issue class effect associated with inhibition of SGLT-2 (34). DKA risk can be reasonably mitigated through education about appropriate event surveillance, early identification and aggressive treatment, as outlined in the draft SmPC (Appendix C).

2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was carried out to identify relevant evidence to determine the relative efficacy, safety, and tolerability of sotagliflozin in comparison with insulin and insulin plus metformin, the comparators identified in the final scope.

The SLR was conducted for the period 1 January 1980 to 5 October 2018 in order to inform the network meta-analysis (NMA) of the comparators identified in this appraisal.

See Appendix F for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

Searches were conducted in PubMed, Embase, Cochrane CENTRAL and other sources including congress proceedings and clinical trial registries. Two reviewers undertook study selection and data extraction. The NICE method guide was used for quality assessment (35).

The SLR identified a total of 10 relevant studies. Three studies were the head-to-head sotagliflozin registration studies (inTandem1, 2 and 3) and seven studies evaluated metformin.

Two head-to-head trials of sotagliflozin versus placebo are presented in this section (inTandem1, and inTandem2) (36, 37). In Tandem3 used the 400 mg dose only (38). The 400 mg tablet will not be available at the time of launch in the UK and efficacy data from this trial does not inform the base-case for the economic analysis. The efficacy results for inTandem3 are therefore provided in Appendix F.

Sanofi confirms that there are no other studies conducted outside of the company that are relevant to the use of sotagliflozin in adults with T1D. A signed statement that all relevant data have been disclosed accompanies this submission.

The remaining seven studies inform the network meta-analysis (NMA) versus metformin, which is described further in Section 2.10

Table 2.1 Summary of studies identified in the systematic literature review and included in the network meta-analysis

Author and year	Trial acronym	Countries	Study design /Phase	Optimisation period	Randomised N	Treatment regimen	Treatment period	Length of follow-up
SGLT trials								
Buse, et al. 2017 (36) NCT02384941	inTandem1	United States, Canada	RCT/III	Insulin for 6 wk	258	Placebo (+insulin)	Baseline–24 (core) +28 (EXT) wk	52 wk + 4 wk
					261	Sotagliflozin 200 mg (+insulin)		
					263	Sotagliflozin 400 mg (+ insulin)		
Danne, et al. 2017 (37) NCT02421510	inTandem2	EU	RCT/III	Insulin for 6 wk	258	Placebo (+ insulin)	Baseline–24 (core) +28 (EXT) wk	52 wk + 4 wk
					261	Sotagliflozin 200 mg (+ insulin)		
					263	Sotagliflozin 400 mg (+ insulin)		
Garg, et al. 2017 (38) NCT02531035	inTandem3	Global	RCT/III	NA	703	Placebo (+insulin)	Baseline–24 wk	24 wk + 4 wk
					699	Sotagliflozin 400 mg (+insulin)		
Metformin trials								
Lund, et al. 2009 (39) Lund, et al. 2008 (40) NCT00118937	NA	Denmark	RCT/IV	NR	51	Placebo (+Insulin)	Baseline–12 mo (52 wk)	52 wk
					49	Metformin 500–1000 mg bid (titrate) (+Insulin)		
Jacobsen, et al. 2009 (41) NCT:NR	NA	Denmark	RCT/NR	Insulin for 4 weeks	12	Placebo (+Soluble Human Insulin + NPH Insulin)	Baseline–24 wk	24 wk
					12	Metformin 500–1000 mg (+Soluble Human Insulin + NPH Insulin)		

Petrie, et al. 2017 (31) NCT01483560	REMOVAL	Global	RCT/III	Glycaemic control for 3 months	209	Placebo (+Insulin)	Baseline–36 mo (154 wk)	154 wk
					219	Metformin 500–1000 mg bid (titrate) (+Insulin)		
Zawada, et. al. 2018 (42) NCT01889706	NR	Poland	RCT/NR	NR	74	Metformin + Insulin	Baseline–26 wk	26 wk
					40	Insulin		
Burchardt, et. al. 2013 (43) NCT:NR	NR	Poland	RCT/NR	Insulin for 1 weeks	33	Metformin + Insulin	Baseline–26 wk	26 wk
					19	Insulin		
Meyer, et al. 2002 (44) NCT:NR	NA	France	NR	NR	62	Metformin 850 mg (+ Insulin)	Baseline–24 wk	24 wk
						Placebo (+ Insulin)	Baseline-24 wk	
Pitocco, et al. 2013 (45) NCT:NR	NA	Italy	RCT/NR	NR	21	Metformin 850 mg (+ Insulin)	Baseline-24 wk	26 wk
					21	Placebo (+ Insulin)		

BID, twice a day; EXT, extension; mo, months; NA, not applicable; NR, not reported; RCT, randomised controlled trial; SGLT, sodium-glucose co-transporter; wk, weeks.

2.2. Relevant clinical effectiveness evidence

There are three robust Phase III, multicentre, randomised, double-blind, placebo-controlled trials (total of 2,977 patients) that support regulatory submission for the full marketing authorisation (36-38). Two of the studies include the 200 mg dose (inTandem1 and inTandem2) and are relevant for the submission of clinical and economic evidence, of which one study (inTandem2) is used to inform the economic analysis for sotagliflozin 200 mg as an adjunct to insulin in adults with inadequately controlled T1D compared with optimised insulin (36, 37). The clinical efficacy for inTandem3, which only includes the 400 mg dose is provided in Appendix F.

The inTandem1 and inTandem2 trials had identical designs (Figure 2.1) but with different geographical focus: inTandem1 recruited patients from North America, whereas inTandem2 recruited patients from Europe and Israel (36, 37). In order to evaluate the efficacy of sotagliflozin beyond what can be provided by insulin alone, all patients in these two studies entered a rigorous 6-week insulin optimisation period prior to randomisation, with the objective of improving glycaemic control using insulin alone. Insulin adjustment algorithms were provided to investigators in all Phase III studies, and these could be modified per clinical assessment. Key characteristics of each of these Phase III RCTs are summarised in Table 2.2 (36, 37).

Patients selected for the continuous glucose monitoring (CGM) sub-study were monitored with a blinded CGM device between Week −1 and baseline, Week 3 and Week 4, Week 11 and Week 12, and Week 23 and Week 24 (36, 37).

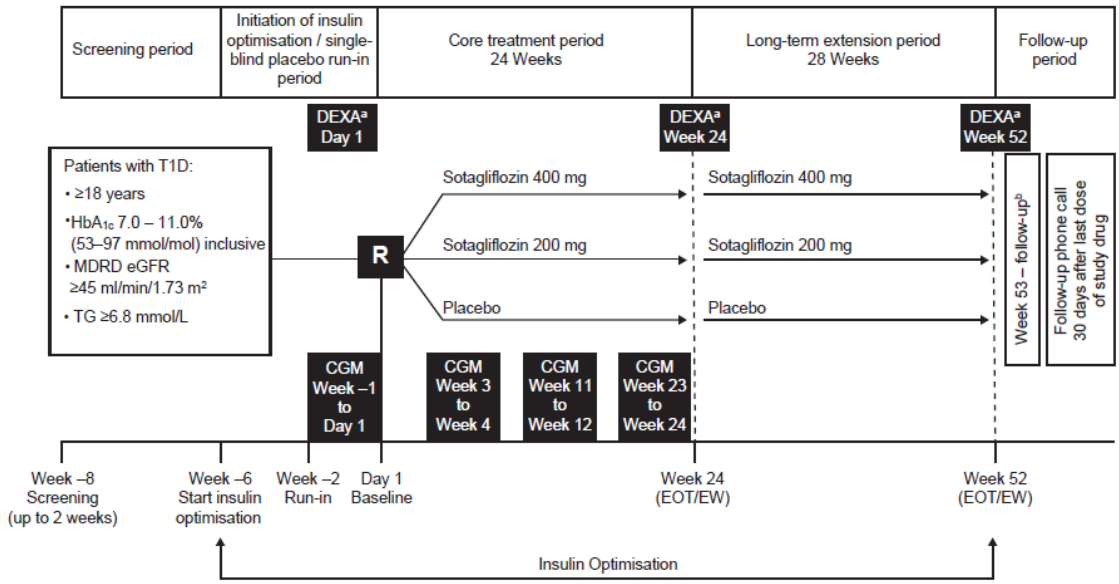
For patients selected for the dual-energy X-ray absorptiometry (DEXA) sub-study, DEXA assessments of body composition with quantitative assessment of fat mass were performed at baseline, Week 24 and Week 52. Bone density was evaluated at baseline and Week 52.

CGM and DEXA sub-studies were planned to target approximately 70 patients per treatment group in each study. Patients were recruited from selected sites that participated in either the CGM or DEXA, or both sub-studies. Due to the recruitment in each sub-study not reaching target sample sizes, the CGM and DEXA data are presented for the pooled analysis only, as pre-specified in the individual study protocols. Individual reported analyses for these endpoints can be found in the individual respective study reports for inTandem1 (46) and inTandem2 (47) and were considered exploratory. Formal analyses of the sub-

study data were based on the pooled datasets in both trials, and comparative inferences of treatment effects were drawn from the performed analyses.

The efficacy and safety of adjunctive sotagliflozin added to insulin for adults with inadequately controlled T1D was also studied in two Phase II trials: a dose ranging study (ClinicalTrials.gov Identifier: NCT02459899) and a small (N=87) trial in young-adults (18–30 years) (ClinicalTrials.gov Identifier: NCT02383940). In line with the regulatory submissions for sotagliflozin, only the Phase III studies are considered in this dossier.

Figure 2.1. Overall trial design for inTandem1 and inTandem2 (46, 47)



CGM, continuous glucose monitoring; DEXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EOT, end of treatment; EW, early withdrawal; HbA_{1c}, glycated haemoglobin; MDRD, modification of diet in renal disease; R, randomisation; T1D, type 1 diabetes; TG, triglycerides.
[a] Patients who participated in the optional DEXA sub-study were to complete the baseline DEXA −2 weeks from the Day 1 visit. The visit window for DEXA after the Day 1 visit was to be ± 2 weeks.
[b] Patients who participated in the optional CGM sub-study, and all patients who were screened after institutional review board approval of Amendment 2, were to complete the Week 53 follow-up visit.

Table 2.2 Clinical effectiveness evidence: inTandem Phase III randomised, controlled trials of adjunctive sotagliflozin added to insulin in adults with type 1 diabetes

	inTandem1 (36, 46)	**inTandem2** (37, 47)
ClinicalTrials.gov identifier	**NCT02384941**	**NCT02421510**
Study design	Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group, 24-week study with a long-term extension to Week 52 in adults with T1D in North America (inTandem1) or Europe (inTandem2)	
Population	Adults with T1D who had inadequate glycaemic control with insulin therapy administered as MDI or CSII	
Intervention(s)*	Sotagliflozin 200 mg, taken as one 200 mg tablet and one placebo tablet once daily before the first meal of the day added to an optimised insulin regimen Sotagliflozin 400 mg, taken as two 200 mg tablets once daily before the first meal of the day added to an optimised insulin regimen	
Comparator(s)	Placebo (two tablets, once daily) added to an optimised insulin regimen	
Supports application for marketing authorisation	Yes	
Used in the economic model	inTandem1 and inTandem2 have been used to inform the economic analysis.	
Rationale for use/non-use in the model	inTandem1 and inTandem2 were part of the Phase III programme of registrational trials to evaluate the use of sotagliflozin in adults with T1D	
Reported outcomes specified in the decision problem	Glycaemic control • HbA_{1c} change from baseline (primary outcome) • FPG • Time in glycaemic range (CGM sub-study) • PPG levels • Insulin dosing • Composite endpoints of glycaemic control and safety Beyond glycaemic control: • Body weight • Blood pressure • Quality of life and other patient-reported outcomes • Adverse effects of treatment.	

*The recommended dose is 200 mg sotagliflozin once daily before the first meal of the day. After ≥3 months, if additional glycaemic control is needed, in patients tolerating sotagliflozin 200 mg, the dose may be increased to 400 mg once daily (Draft SmPC – see Appendix C1).
CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injection; PPG, postprandial glucose; T1D, type 1 diabetes.

2.3. Summary of methodology of the relevant clinical effectiveness evidence

2.3.1. Trial design, eligibility, setting, treatments and outcomes in the inTandem1 and inTandem2 programme

A summary of the key elements of trial design, eligibility criteria, settings and locations, treatments and outcomes in inTandem1 and inTandem2 is given in Table 2.3

Table 2.3 Summary of trial methodology for the Phase III inTandem1 and inTandem2 studies of sotagliflozin in T1D

	inTandem1 (36, 46)	inTandem2 (37, 47)
Study design	Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre study (Figure 2.1)	
Main inclusion criteria for participants	Adult patients, ≥18 years, with a diagnosis of T1D made ≥1 year prior to informed consent. Patients who were being treated with insulin or insulin analogue delivered via CSII or MDI. Willing and able to perform SMBG and complete the study diary as required per protocol. At the screening visit, HbA_{1c} must have been between 7.0% and 11.0% (53 and 97 mmol/mol) inclusive. Females of childbearing potential must have been using an adequate method of contraception and have had a negative pregnancy test.	
Main exclusion criteria for participants	Use of any antidiabetic agent other than insulin or insulin analogue at the time of screening. Use of SGLT inhibitors within 8 weeks prior to screening. Chronic systemic corticosteroid use. T2D, or severely uncontrolled T1D as determined by the Investigator. eGFR <45 mL/min/1.73 m^2 (as determined by the four-variable MDRD equation). Fasting TG >6.77 mmol/L, although patients who failed screening based on this criterion must have had their fasting status verified, may have had TG-lowering medications adjusted, and could be re-evaluated during the screening period. Abnormal liver function i.e. AST >2 x ULN, ALT >2 x ULN, serum total bilirubin >1.5 x ULN (unless, in the opinion of the investigator and the medical monitor, the increase in bilirubin was due to Gilbert's syndrome).	

	inTandem1 (36, 46)	inTandem2 (37, 47)
	Screening BHB >0.6 mmol/L. A significant recent history of cardiac disease or hypertensive urgency/emergency, or a history of haemoglobinopathies (sickle cell anaemia, thalassemia major, sideroblastic anaemia) or other disorder that may have interfered with HbA_{1c} determination.	
Settings and locations	63 study sites in the United States and 12 study sites in Canada	96 study sites across 17 countries in Europe, including 5 in the UK
Trial drugs	Sotagliflozin 200 mg, given as two tablets (one sotagliflozin 200-mg tablet and one placebo tablet) once daily, before the first meal of the day. Sotagliflozin 400 mg, given as two sotagliflozin 200-mg tablets, once daily, before the first meal of the day. Placebo, given as two tablets (identical to sotagliflozin in appearance) once daily, before the first meal of the day.	
Treatment duration	Patients received study drug for approximately 52 weeks: 24-week double-blind core treatment period and 28-week double-blind LTE period. Following a 2-week screening period, participants underwent a single-blind, 6-week run-in period during which each participant's insulin therapy was optimised and continued throughout the study. There was a subsequent follow-up period of 30 days after the final dose of study drug.	
Primary outcomes	Demonstration of the superiority of adjunctive sotagliflozin (200 mg or 400 mg) added to insulin therapy in adults with inadequately controlled T1D vs placebo, assessed as a reduction in HbA_{1c} levels at Week 24 of treatment.	
Secondary outcomes	CFB in: proportion of patients with HbA_{1c} <7% (53 mmol/mol) and no episodes of SH and no episodes or of DKA; body weight; bolus insulin dose; FPG; DTSQ status score; and DDS2 score.	
Other objectives	Comparison of changes in sotagliflozin vs placebo for several parameters, as assessed by evaluations with specified cut points, and at specified time intervals, during the 24-week double-blind CT period and the 28-week double-blind LTE period Parameters included: HbA_{1c}; FPG; insulin dose; hypoglycaemic events; blood pressure; body weight;	

	inTandem1 (36, 46)	inTandem2 (37, 47)
	measures of kidney function; proportion of patients meeting success criteria for HbA_{1c} and insulin dose; (EQ-5D-5L; CFB in the Bristol Stool Form Scale score).	
Safety	The safety and tolerability of both doses of sotagliflozin (200 mg and 400 mg) vs placebo was assessed throughout the study to record information on SAEs, EOSI, and any AE that was ongoing at the EOT or EW visit). The PK of each dose of sotagliflozin were also assessed.	
Sub-studies	CGM: to evaluate time spent out of the target glucose range and other glycaemic targets. DEXA: to compare the effect of sotagliflozin vs placebo on total fat mass as well as additional fat mass measurements, bone mineral content, and bone density.	

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BHB, beta-hydroxybutyrate; CFB, change from baseline; CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion, CT, core treatment; DDS2, two-item Diabetes Distress Screening Scale; DEXA, dual-energy X-ray absorptiometry; DKA, diabetic ketoacidosis; DTSQ, Diabetes Treatment Satisfaction Questionnaire; eGFR, estimated glomerular filtration rate; EOSI, events of special interest; EOT, end of treatment; EQ-5D-5L, EuroQol Questionnaire 5 dimensions 5 level; EW, early withdrawal; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; LTE, long-term extension; MDI, multiple daily injection; MDRD, modification of diet in renal disease; PK, pharmacokinetic; SAE, serious adverse event; SGLT, sodium-glucose co-transporter; SH, severe hypoglycaemia; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes; TG, triglycerides; ULN, upper limit of normal

2.3.2. Baseline characteristics

Characteristics of patients in the inTandem1 and in inTandem2 trials are presented in Table 2.4 (36, 37). The patient groups were well matched within each study and there were no differences of note or that may have resulted in bias in the efficacy results.

In all studies, the mean age of the participants was 41–46 years and men and women were equally represented. The majority of participants were white and either overweight or obese (mean BMI >27 kg/m^2).

Both daily total insulin dose and ratio of bolus to total insulin dose at baseline were comparable across the treatment groups and consistent with an adult population with T1D.

Table 2.4 Summary of baseline characteristics in the inTandem1 and inTandem2 studies

	inTandem1 (36)			inTandem2 (37)		
	Sotagliflozin		Placebo	Sotagliflozin		Placebo
	200 mg (N=263)	400 mg (N=262)	(N=268)	200 mg (N=261)	400 mg (N=263)	(N=258)
Age, years mean (SD)	46.6 (13.48)	46.4 (13.12)	45.2 (12.72)	42.3 (13.59)	41.7 (13.23)	39.7 (13.42)
Female sex, n (%)	137 (52.1)	142 (54.2)	131 (48.9)	122 (46.7)	130 (49.4)	124 (48.1)
Race or ethnic group, n, (%)						
White	241 (91.6)	246 (93.9)	244 (91.0)	252 (96.6)	250 (95.1)	250 (96.9)
Black	11 (4.2)	8 (3.1)	9 (3.4)	0	0	1 (0.4)
Asian	4 (1.5)	2 (0.8)	4 (1.5)	3 (1.1)	3 (1.1)	0
Native American	1 (0.4)	0	0	0	0	0
Native Hawaiian or other Pacific Islander	2 (0.8)	0	2 (0.7)	0	0	0
Other	4 (1.5)	6 (2.3)	9 (3.4)	6 (2.3)	10 (3.8)	7 (2.7)
Diabetes parameters and other risk factors						
Duration of diabetes, years (SD)	25.0 (13.15)	24.0 (12.88)	24.2 (12.38)	18.2 (10.82)	18.9 (11.18)	18.1 (10.72)
HbA_{1c}, mmol/mol (SD)	59.7 (7.98)	59.1 (7.91)	58.9 (7.80)	61.1 (8.77)	60.8 (8.95)	61.6 (9.63)
HbA_{1c}, % (SD)	7.61 (0.73)	7.56 (0.72)	7.54 (0.71)	7.74 (0.81)	7.71 (0.82)	7.79 (0.88)
FPG, mmol/L (SD)	8.61 (3.8)	8.23 (3.5)	8.53 (3.6)	9.09 (4.13)	9.19 (3.94)	8.91 (3.63)
Weight, kg (SD)	86.96 (18.54)	86.50 (18.00)	87.30 (17.71)	81.93 (17.39)	81.97 (17.96)	81.08 (16.86)
BMI, mg/kg^2 (SD)	29.81 (5.69)	29.63 (5.30)	29.55 (5.19)	27.97 (5.28)	27.85 (4.92)	27.50 (5.17)
BMI ≥30, n. (%)	121 (46.0)	114 (43.5)	114 (42.5)	84 (32.2)	78 (29.7)	72 (27.9)

	inTandem1 (36)			inTandem2 (37)		
	Sotagliflozin		Placebo	Sotagliflozin		Placebo
	200 mg (N=263)	400 mg (N=262)	(N=268)	200 mg (N=261)	400 mg (N=263)	(N=258)
SBP, mmHg (SD)	120.0 (14.84)	119.5 (14.73)	120.9 (13.47)	123.0 (15.08)	123.1 (13.69)	123.1 (15.53)
DBP, mm Hg (SD)	76.4 (9.28)	75.3 (9.17)	76.4 (8.24)	77.4 (9.83)	76.2 (8.37)	76.3 (8.48)
SBP ≥130 mm Hg, no. (%)	60 (22.8)	60 (22.9)	64 (23.9)	86 (33.0)	80 (30.4)	85 (32.9)
Insulin use						
Daily total dose of insulin, IU/kg (SD)	0.72 (0.39)	0.72 (0.34)	0.74 (0.36)	0.73 (0.28)	0.74 (0.27)	0.75 (0.30)
Total	65.11 (42.70)	64.15 (37.64)	66.79 (41.27)	60.30 (28.96)	61.38 (28.65)	61.85 (30.86)
Basal	34.84 (23.90)	33.39 (18.96)	35.06 (19.73)	29.18 (15.81)	29.50 (14.324)	29.76 (14.42)
Bolus and corrections (SD)	30.27 (23.65)	30.75 (22.83)	31.72 (25.01)	31.12 (17.55)	31.89 (19.16)	32.08 (21.460)
Type of insulin therapy, n (%)						
Subcutaneous injections (SD)	107 (40.7)	105 (40.1)	108 (40.3)	193 (73.9)	196 (74.5)	192 (74.4)
Pump, n (%)	156 (59.3)	157 (59.9)	160 (59.7)	68 (26.1)	67 (25.5)	66 (25.6)

Data are m,ean (SD) unless otyherwise indicated.
BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose, HbA_{1c}, glycated haemoglobin SBP, systolic blood pressure; SD, standard deviation.

2.4. Statistical analysis, definition of study groups and participant flow in the relevant clinical effectiveness evidence

The primary hypothesis for the inTandem trials was that adding adjunctive sotagliflozin to insulin therapy in adults with uncontrolled T1D can help improve glycaemic control compared with placebo. Table 2.5 provides a summary of the statistical methods used in the individual inTandem1 and inTandem2 trials.

Additionally, a pooled analysis of inTandem1 and inTandem2, and of all three trials where appropriate, was planned. Unless otherwise specified, all efficacy summary analyses for the pooled groups were performed on the modified intention-to-treat (mITT) population as previously defined. The mITT patient data were analysed according to their randomised treatment. The pooled analyses of the primary and secondary endpoints followed the methods provided in the individual study plans (Table 2.5). No multiple testing adjustments were performed for the pooled analyses.

The flow of participants in the inTandem trials is summarised in the CONSORT flow diagrams in Appendix G.

Table 2.5 Summary of statistical methods used to analyse data from the inTandem1&2 trial (46, 47)

	inTandem1 and inTandem2
Sample size determination	• Assuming a true treatment difference of −0.4% and a common SD of 1.0%, 157 patients per treatment group would provide 90% power to determine if either sotagliflozin 200 mg or sotagliflozin 400 mg differed from placebo in the mean HbA_{1c} CFB to Week 24 at an overall 0.05 α-level (two-sided). • Calculation was based on the 2.5% significance level (α=0.025) assigned to each sotagliflozin comparison with placebo. • The sample size estimate was further adjusted for dropouts (primarily due to non-compliance) in a manner to reflect that the primary analysis would be conducted in the mITT patients. Assuming a 24-week dropout rate of 20%, the adjusted effect size for detection became −0.4% × (1−0.20) = −0.320%, equating to 244 patients per treatment group. • Estimates were rounded upward for a requirement of 250 patients per treatment group, or 750 total patients. • The sample size of 250 patients per arm provided the minimal detectable difference of −0.203% between either sotagliflozin groups vs placebo under the same assumptions that are specified above.
Main efficacy analysis	• Population: mITT population, defined as all randomised patients who had taken at least one dose of study drug, classified according to their randomised treatment. • Primary analysis of the primary efficacy endpoint used MMRM statistics based on the restricted maximum likelihood method for estimation. • The model included fixed, categorical effects of treatment, randomisation strata of insulin delivery method (MDI, CSII), randomisation strata of Week −2 HbA_{1c} (≤8.5%, >8.5%), time (study week) and a treatment-by-time interaction, with baseline HbA_{1c}-by-time interaction as a covariate. • The adjusted mean change in HbA_{1c} from baseline to Week 24 for each treatment group was estimated in the MMRM framework, as well as between-group differences plus 95% CIs. • For continuous secondary and other efficacy endpoints, MMRM or ANCOVA was used, with the corresponding endpoint and baseline value (including first-order interactions in the MMRM) in the model. • For binary endpoints, a CMH test, stratified by the randomisation stratification factors, was used. • Summaries for composite, net clinical benefit endpoints — i.e. HbA_{1c} <7% (53 mmol/mol) at Week 24 with associated SH, DKA, weight gain and insulin reduction benefit categories — were assessed at the end of the CT period and at the end of the overall treatment period as well. • Similar summaries were presented for other net clinical benefits at Week 24: HbA_{1c} reductions of 0.3%, 0.4% and 0.5%, with the associated SH, DKA, weight gain and insulin reduction benefit categories.
Missing data	• Missing observations at Week 24 were imputed as non-response.

	inTandem1 and inTandem2

Sub-study analysis	• CGM:
	  ○ Based on patients in the mITT population who participated in the CGM sub-study.
	  ○ Primary efficacy endpoints: CFB to Week 24 in percent time spent outside the target range (>10 to <3.9 mmol/L), above the target range (>10 mmol/L, hyperglycaemia), below the target range (<3.9 mmol/L, hypoglycaemia) and in the target range (3.9–10 mmol/L).
	  ○ Endpoints were analysed using MMRM statistics, with the corresponding endpoint and baseline value (including first-order interactions) in the model.
	• DEXA: based on patients in the mITT population who participated in the DEXA sub-study.
	  ○ Primary efficacy endpoint: CFB to Week 24 in total fat mass.
	  ○ Analysis of CFB in total fat mass was analysed using ANCOVA.
	  ○ Secondary efficacy analysis: CFB in fat mass endpoints at Weeks 24 and 52, and bone density endpoints at Week 52, analysed using ANCOVA.

Safety	• Population: safety population, defined as all randomised patients who had taken at least one dose of study drug, classified according to their actual treatment received on Day 1. • The 24-week CT period and the 28-week LTE period were used as the main study periods. • Overall treatment period by treatment group for the safety population was also analysed. • Summaries of TEAEs included the overall incidence (by SOC and PT), events by maximum intensity, events by relationship to study drug, events leading to discontinuation of study drug, EOSI and SAEs. • Vital signs, ECGs, and clinical laboratory tests were summarised descriptively at each time-point. • Changes from baseline were calculated and summarised for quantitative safety endpoints.

ANCOVA, analysis of covariance; CI, confidence interval; CFB, change from baseline; CGM, continuous glucose monitoring; CMH, Cochran-Mantel-Haenszel; CSII, continuous subcutaneous insulin infusion; CT, core treatment; DEXA, dual-energy X-ray absorptiometry; DKA, diabetic ketoacidosis; ECG, electrocardiogram; EOSI, events of special interest; $HbA_{1c,}$ glycated haemoglobin; LTE, long-term extension; MDI, multiple daily injection; mITT, modified intention-to-treat; MMRM, mixed-effects model for repeated measures; PT, preferred term; SAE, serious adverse event; SD, standard deviation, SH, severe hypoglycaemia; SOC, system organ class; TEAE, treatment-emergent adverse event.

2.5. Quality assessment of the relevant clinical effectiveness evidence

The complete quality assessment of the sotagliflozin trials (36-38) and metformin trials (39-41) used in the NMA is presented in Appendix F.

All three sotagliflozin trials contained adequate randomisation sequence generation; had adequate concealment of treatment allocation; showed similarity between groups at baseline in terms of prognostic factors; had adequate blinding of participants, care providers, and outcome assessors; and reported all pre-specified outcomes of interest.

In all trials, the pre-specified outcomes were reported in either the online protocols (e.g. ClinicalTrails.gov) or within the publications themselves. All three trials included a mITT analysis which included all randomised patients who had taken at least one dose of study drug.

2.6. Clinical effectiveness results of the relevant trials

The inTandem clinical trial programme was designed to investigate whether sotagliflozin, a dual sodium-glucose co-transporter type 1 (SGLT-1) and type 2 (SGLT-2) inhibitor, could incrementally improve glycaemic control when added to basal-bolus insulin in adult patients with uncontrolled T1D. Such an approach could reduce the risk of hypoglycaemia associated with intensive insulin therapy and would be expected to afford additional benefits beyond glycaemic control, including improvements in body weight, blood pressure and wellbeing, which could, in concert, lead to reductions in diabetes-related microvascular and macrovascular complications.

In the inTandem trials, compliance rates (defined as compliance >80%) were high: 88.6% of patients had adhered to treatment within inTandem1 and 89.4% and within inTandem2.

2.6.1. Insulin optimisation: inTandem1 and inTandem2

Both inTandem1 and inTandem2 featured a pre-treatment insulin dose optimisation period (36, 37). The rigour of this optimisation period is important when considering the results of the study and relevance to real-world clinical practice.

Starting at Week −6, the study site staff were to call the patients weekly to facilitate optimisation of insulin titration. At each visit, the investigator would determine if the average blood glucose values [using self-monitoring of blood glucose (SMBG) data] met the glycaemic goals recommended for this study. Insulin optimisation algorithm is described in Appendix H.

2.6.2. Glycaemic goals: inTandem1 and inTandem2

HbA_{1c} and blood glucose were treated to the following targets: HbA_{1c} <7% (53 mmol/mol) (HbA_{1c} was unmasked starting at the Week 24 visit), fasting/pre-prandial capillary plasma glucose 4.4–7.2 mmol/L, and 2-hour/peak postprandial capillary plasma glucose <10.0 mmol/L (48). Goals could have been adapted, based on individual patient considerations, consistent with other guidelines and study findings (49, 50).

If results did not meet the glycaemic goals recommended for these studies, then investigators were to assess the need for a change in insulin dosing. Investigators were given detailed dose adjustment algorithms to use as a guide during the study (see Appendix H for the insulin dose adjustment algorithm). Following any change in insulin dosing, a follow-up call was to be arranged within 1 week to assess response to the therapy change, and any need for additional change(s). If the individual targets varied from those listed, they were to be recorded on the insulin titration worksheet by the site staff. An insulin titration electronic case report form was to be completed at every scheduled visit to allow documentation of insulin adjustments.

The dose of basal or bolus insulin could have been reduced or modified at any time for management of hypoglycaemia. Patients who experienced hypoglycaemia as a result of a missed meal, unusual exercise or alcohol use were to receive counselling on the correction of these behaviours. If needed, additional contact was to be made available for patients to discuss dose adjustments in between scheduled site visits. During these visits (on-site or by phone), patients were to report their SMBG data, insulin doses and hypoglycaemic events to the study site staff.

The dose of double-blind study treatment was not to be adjusted at any time during the study.

An independent Insulin Dose Monitoring Committee (IDMC) comprising diabetologists and certified diabetes educators was in place to review insulin dose titration decisions made by

the investigators. The committee reviewed dossiers including SMBG data, insulin doses and insulin titration case report forms for Week −5, Week −2, Day 1, and Week 1 for all patients. After Week 1, dossiers were reviewed for those patients who were not at glycaemic goal, and for whom no insulin dose change was made, and no reason provided for an unchanged insulin dose. In addition, a random sample of 10% of all visits and all visit records for those patients who reported an event of possible DKA or severe hypoglycaemia (SH) were also reviewed.

Table 2.6 Summary of primary and secondary efficacy endpoints at Week 24 (unless otherwise stated) in the inTandem1 and inTandem2 trials (36, 37)

Endpoint*		inTandem1			inTandem2		
	Hierarchy	Placebo (N=268)	Sotagliflozin 200mg (N=263)	Sotagliflozin 400mg (N=262)	Placebo (N=258)	Sotagliflozin 200mg (N=261)	Sotagliflozin 400mg (N=263)
HbA_{1c} change from baseline	**Primary**						
% LSM ±SE		−0.07 ± 0.036	−0.43 ± 0.036	−0.48 ± 0.036	−0.02 ± 0.044	−0.39 ± 0.044	−0.37 ± 0.043
% LSM difference (SE) vs placebo		NA	−0.36 (0.047)	−0.41 (0.047)	NA	−0.37 (0.058)	−0.35 (0.058)
95% CI		NA	−0.45, −0.27	0.50, −0.32	NA	−0.48, -0.25	−0.47, −0.24
p-value		NA	<0.001	<0.001	NA	<0.001	<0.001
Net benefit	**Secondary (1st)**						
Responders, n (%)		58 (21.6)	88 (33.5)	114 (43.5)	39 (15.1)	82 (31.4)	85 (32.3)
LSM difference in % responders vs placebo		NA	11.8	21.9	NA	16.3	17.2
95% CI		NA	3.90, 19.73	13.72, 30.02	NA	9.17, 23.43	(10.06, 24.35)
p-value		NA	0.002	<0.001	NA	<0.001	<0.001
Body weight change from baseline (kg)	**Secondary (2nd)**						
LSM ±SE		−0.84 ± 0.688	−2.33 ± 0.692	−4.13 ± 0.692	−1.19 ± 0.635	−4.38 ± 0.636	−4.78 ± 0.634
LSM difference ±SE vs placebo		NA	−2.35 ± 0.256	−3.45 ± 0.256	NA	−1.98 ± 0.276	−2.58 ± 0.276
95% CI		NA	−2.85, −1.85	−3.95, −2.94	NA	−2.53, −1.44	−3.12, −2.04
p-value		NA	<0.001	<0.001	NA	<0.001	<0.001
Bolus insulin change from baseline (IU)	**Secondary (3rd)**						
LSM ±SE		−0.84 ± 0.688	−2.33 ± 0.692	−4.13 ± 0.692	−1.19 ± 0.635	−4.38 ± 0.636	−4.78 ± 0.634
LSM difference ±SE vs placebo		NA	−1.50 ± 0.917	−3.30 ± 0.916	NA	−3.20 ± 0.847	−3.59 ± 0.845
95% CI		NA	−3.30, 0.30	−5.09, −1.50	NA	−4.86, −1.53	−5.25, −1.93
p-value		NA	0.10	<0.001	NA	<0.001	<0.001

Endpoint*	Hierarchy	inTandem1			inTandem2		
		Placebo (N=268)	Sotagliflozin 200mg (N=263)	Sotagliflozin 400mg (N=262)	Placebo (N=258)	Sotagliflozin 200mg (N=261)	Sotagliflozin 400mg (N=263)
FPG change from baseline (mmol/L)	**Secondary (4th)**						
LSM ±SE		0.21 ± 0.191	−0.34 ± 0.192	−0.78 ± 0.193	0.49 ± 0.219	−0.71 ± 0.220	−0.93 ± 0.220
LSM difference ±SE vs placebo		NA	−0.55 ± 0.259	−0.99 ± 0.260	NA	−1.20 ± 0.299	−1.42 ± 0.298
95% CI		NA	−1.06, −0.04	−1.50, −0.48	NA	−1.79, −0.61	−2.01, −0.84
p-value		NA	0.034	<0.001	NA	<0.001	<0.001
PRO: DTSQ change from baseline	**Secondary (5th)**						
LSM ±SE		−0.4 ± 0.30	2.1 ± 0.31	2.1 ± 0.31	−0.1 ± 0.28	1.9 ± 0.28	1.6 ± 0.28
LSM difference ±SE vs placebo		NA	2.5 ± 0.40	2.5 ± 0.40	NA	2.0 ± 0.37	1.7 ± 0.36
95% CI		NA	1.7, 3.3	1.8, 3.3	NA	1.3, 2.7	1.0, 2.4
p-value		NA	<0.001	<0.001	NA	<0.001	<0.001
PRO: DDS2 change from baseline	**Secondary (6th)**						
LSM ±SE		0.3 ± 0.11	−0.4 ± 0.11	−0.5 ± 0.11	0.0 ± 0.12	−0.3 ± 0.12	−0.4 ± 0.11
LSM difference ±SE vs placebo		NA	−0.7 ± 0.14	−0.8 ± 0.14	NA	−0.3 ± 0.15	−0.4 ± 0.15
95% CI		NA	−0.9, −0.4	(−1.0, −0.5)	NA	−0.6, −0.0	−0.7, −0.2
p-value		NA	<0.001	<0.001	NA	0.025	0.003
SBP change from baseline to Week 12 (mmHg)	**Other**						
LSM ±SE		1.0 ± 0.66	−2.5 ± 0.67	−3.2 ± 0.66	−2.4 ± 0.68	−2.8 ± 0.67	−5.2 ± 0.67
LSM difference ±SE vs placebo		NA	−3.5 ± 0.88	−4.2 ± 0.88	NA	−0.4 ± 0.89	−2.8 ± 0.89
95% CI		NA	−5.2, -1.8	−5.9, −2.4	NA	−2.2, 1.3	−4.6, −1.1
p-value		NA	<0.001	<0.001	NA	0.64	0.001

* Net benefit is HbA_{1c} <7.0% at Week 24 and no SH or DKA from randomisation to Week 24.
CI, confidence interval; DDS2, two-item Diabetes Distress Screening Scale; DKA, diabetic ketoacidosis; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; NA, not applicable; PRO, patient-reported outcome; SBP, systolic blood pressure; SE, standard error; SH, severe hypoglycaemia

2.6.3. Glycaemic control following adjunctive sotagliflozin

2.6.3.1. Change from baseline in HbA_{1c} at Week 24

Across inTandem1 and inTandem2, both sotagliflozin groups had a highly statistically significant and clinically meaningful mean decrease in HbA_{1c} after insulin dose optimisation as described above ($p<0.001$ vs placebo) (36, 37). The mean decreases in HbA_{1c} >0.3% (3.3 mmol/mol) observed for both sotagliflozin doses on top of insulin optimisation was also considered clinically significant. The approximate 0.6% (6.6 mmol/mol) mean decrease in HbA_{1c} between screening and randomisation in all treatment groups is consistent with appropriate optimisation. Furthermore, the mean decrease in HbA_{1c} at Week 24 was observed starting with a baseline mean HbA_{1c} of approximately 7.6%, which is lower than that typically reported in previous T1D trials, where the fall in HbA_{1c} is related to baseline HbA_{1c}.

Across the entire treatment period, a greater mean HbA_{1c} reduction (primary endpoint in inTandem1 and inTandem2), was reported in the sotagliflozin group compared with placebo on top of rigorous insulin optimisation.

For each of the studies, a summary of the change from screening to baseline and the mixed-effects model for repeated measures (MMRM) analysis results of the percentage change from baseline in HbA_{1c} at Week 24 are presented in Table 2.7. A summary of the change from screening to baseline and the MMRM analysis results of the CFB in HbA_{1c} at Week 24 are presented in Appendix I for each of the studies.

Table 2.7 Change from baseline HbA_{1c} at Week 24 the inTandem1 and inTandem2 trials (36, 37, 46, 47)

Study	**inTandem1**			**inTandem2**		
HbA_{1c}	***Placebo***	***Sotagliflozin 200 mg***	***Sotagliflozin 400 mg***	***Placebo***	***Sotagliflozin 200 mg***	***Sotagliflozin 400 mg***
Screening						
N	268	263	261	257	261	262
Mean, mmol/mol	66.2	66.8	66.1	68.5	67.8	68.1
Mean, %	8.21	8.26	8.20	8.42	8.35	8.38
Baseline						
N	268	263	262	258	261	263
Mean, mmol/mol	58.9	59.7	59.1	61.6	61.1	60.8
Mean, %	7.54	7.61	7.56	7.79	7.74	7.71
Change from screening (insulin optimisation pre-study period in inTandem1 and 2), HbA_{1c} %						
N	268	263	261	257	261	262
Mean, % (SD)	−0.66 (0.567)	−0.65 (0.538)	−0.64 (0.552)	−0.64 (0.644)	−0.61 (0.666)	−0.67 (0.548)
Change from baseline at Week 24						
N	246	245	242	239	239	241
LSM, % (SE)	−0.07 (0.036)	−0.43 (0.036)	−0.48 (0.036)	−0.02 (0.044)	−0.39 (0.044)	−0.37 (0.043)
95% CI	−0.14, −0.00	−0.50, −0.36	−0.56, −0.41	−0.11, −0.07	−0.47, −0.30	−0.46, −0.29
p-value	0.038	<0.001	<0.001	0.63	<0.001	<0.001
Summary of treatment comparison, HbA_{1c} %						
LSM difference (SE) vs placebo	−	−0.36 (0.047)	−0.41 (0.047)	−	−0.37 (0.058)	−0.35 (0.058)
95% CI	−	−0.45, −0.27	−0.50, −0.32	−	−0.48, −0.25	−0.47, −0.24
p-value	−	<0.001	<0.001	−	<0.001	<0.001

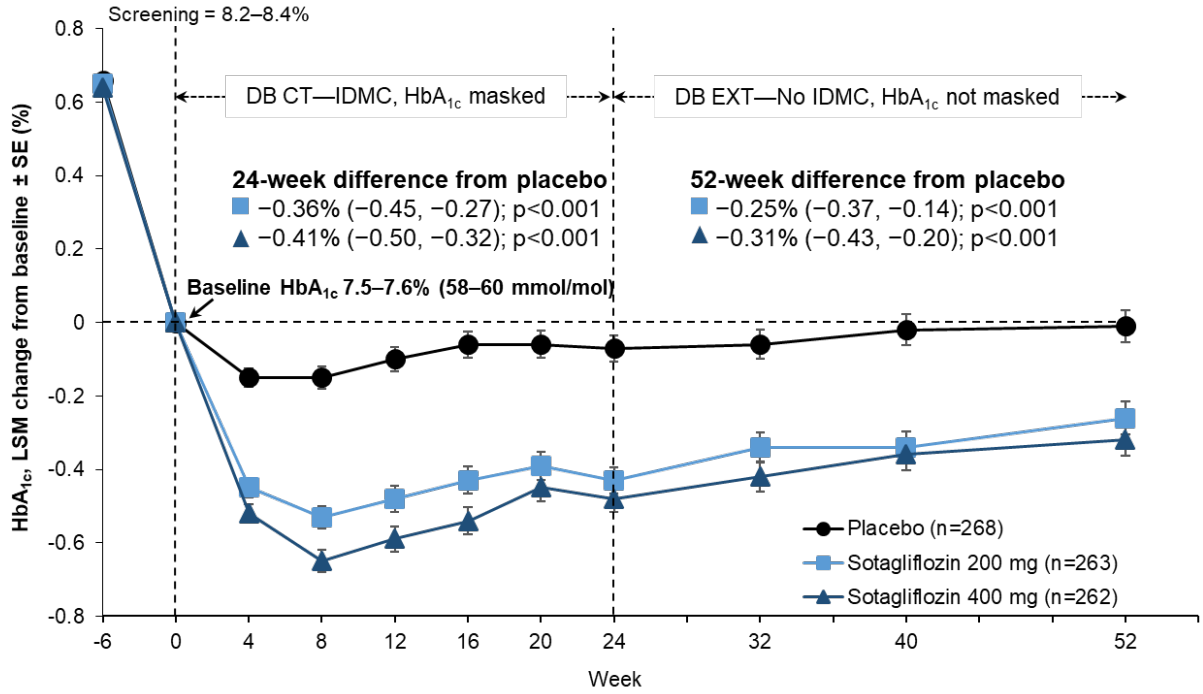
CL, confidence limit; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; SD, standard deviation; SE, standard error.

2.6.3.2. Change from baseline in glycated haemoglobin at Week 52

Reductions in HbA_{1c} from baseline were observed across the 52 weeks of the inTandem1 and inTandem2 studies (Figure 2.2 and Figure 2.3, respectively). The mean difference from placebo at Week 52 ranged between −2.3 mmol/mol and −3.5 mmol/mol (−0.21% to −0.32%).

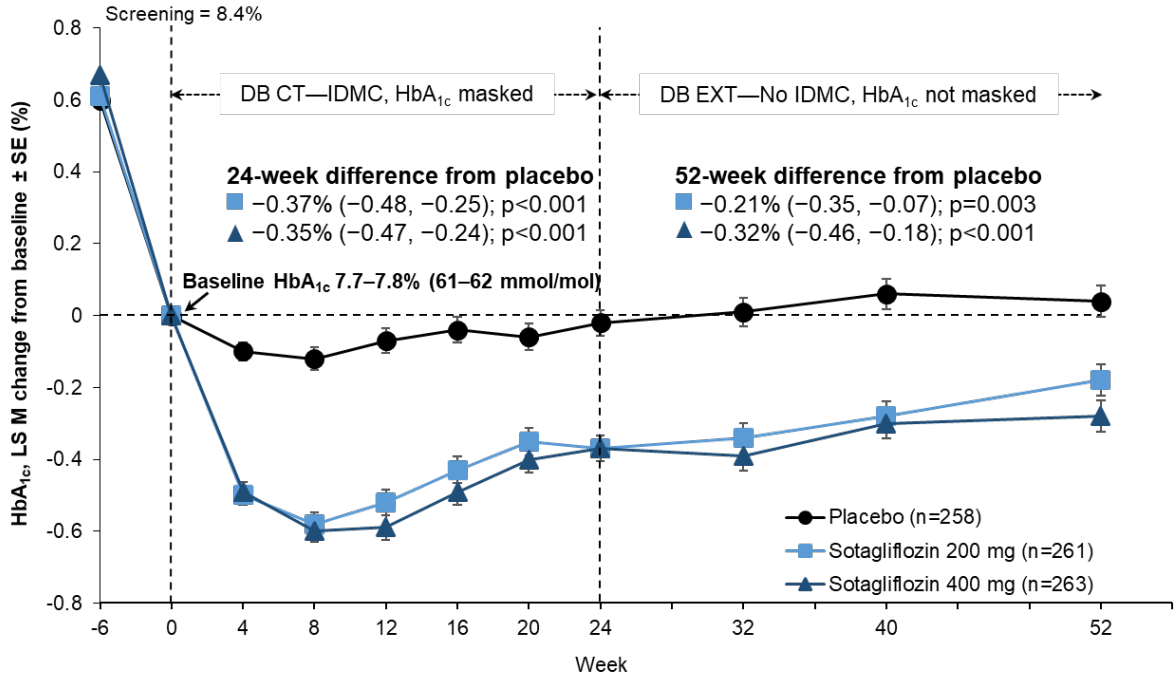
Approximately 80% of the effect was observed during the first 4 weeks and the effect was maximum at Week 8 and Week 12. However, a clinically relevant and statistically significant difference versus placebo was maintained at Week 52, in particular for the 400 mg dose. Despite changes to the study design after Week 24 (e.g. unblinding of HbA_{1c} to investigators and the discontinuation of insulin adjustment oversight by the IDMC after the Week 24 visit), the clinically meaningful and statistically significant difference from placebo confirmed the persistence of efficacy of sotagliflozin on HbA_{1c} at 1 year.

Figure 2.2. Change in HbA_{1c} from baseline to Week 52 in inTandem1 (36)



Modified intention-to-treat population. Difference from placebo (95% CL)
To convert HbA_{1c} from % to mmol/mol, use the formula (HbA_{1c} % × 10.93) − 23.5
DB, double-blind; CT, core treatment; EXT, extension; HbA_{1c}, glycated haemoglobin, IDMC, Insulin Dose Monitoring Committee; LS, least squares; SE, standard error.

Figure 2.3. Change in HbA_{1c} from baselines to Week 52 in inTandem2 (37)



Modified intention-to-treat population. Difference from placebo (95% CL)
To convert HbA_{1c} from % to mmol/mol use the formula (HbA_{1c} % x 10.93) – 23.5
DB, double-blind; CL, confidence limits; CT, core treatment; EXT, extension; HbA_{1c}, glycated haemoglobin, IDMC, Insulin Dose Monitoring Committee; LSM, least squares mean; SE, standard error.

2.6.4. *Net clinical benefit—meeting glycated haemoglobin target <7% without severe hypoglycaemia and diabetic ketoacidosis*

Net benefit, defined as the proportion of patients with HbA_{1c} <7% (53 mmol/mol) and no episode of SH or DKA from randomisation to Week 24, was the primary outcome in inTandem3 (see Appendix E) and a secondary outcome in both inTandem1 and inTandem2.

This endpoint was designed to capture the surrogate endpoint for maintenance of lower overall blood glucose, together with potential complications of diabetes. The assessment encompasses both efficacy and safety, and thus may more fully balance interpretation of key clinical outcomes in this patient population. This composite endpoint was agreed with the European Regulator.

The proportion of patients with HbA_{1c} <7.0% (53 mmol/mol) at Week 24 was the main component of this composite endpoint and represents the glycaemic target based on improved outcomes. In inTandem1 and inTandem2, despite the rigorous insulin optimisation during the 6-week run-in period, <20% of patients had reached HbA_{1c} <7.0% (53 mmol/mol) at baseline. At Week 24, 33.3–36.9% of patients treated with sotagliflozin 200 mg achieved HbA_{1c} <7.0% (53 mmol/mol), compared with 15.1–22.8% of placebo patients, a statistically

significant and clinically meaningful difference. Similar results were observed for the 400 mg dose (Table 2.8).

At Week 24, the difference versus placebo for the responders in net benefit was statistically significant and clinically meaningful in all studies and all groups, ranging from 11.8% to 16.3% with sotagliflozin 200 mg and from 17.2% to 21.9% with sotagliflozin 400 mg [p<0.001 for all groups except sotagliflozin 200 mg in inTandem1 (p=0.002)].

In inTandem1 and inTandem2, statistically significant and clinically meaningful net benefit was maintained to Week 52. The difference from placebo for the net benefit remained statistically significant in all groups in both studies, ranging between 7.2% and 13.4% (p<0.001 for all except the sotagliflozin 200 mg group in inTandem1, which was p=0.049) (Table 2.9).

Table 2.8 Analysis of net benefit at Week 24 for the inTandem1 and inTandem2 studies (36, 37)

	inTandem1			inTandem2		
	Placebo (N=268)	**Sotagliflozin 200 mg (N=263)**	**Sotagliflozin 400 mg (N=262)**	**Placebo (N=258)**	**Sotagliflozin 200 mg (N=261)**	**Sotagliflozin 400 mg (N=263)**
Components of net benefit, n (%)						
HbA_{1c} <7.0% (53 mmol/mol) at baseline	51 (19.0)	50 (19.0)	51 (19.5)	44 (17.1)	50 (19.2)	46 (17.5)
HbA_{1c} <7.0% (53 mmol/mol) at Week 24	61 (22.8)	97 (36.9)	123 (46.9)	39 (15.1)	87 (33.3)	89 (33.8)
HbA_{1c} <7% (53 mmol/mol) at Week 24 and no SH	58 (21.6)	89 (33.8)	117 (44.7)	39 (15.1)	83 (31.8)	85 (32.3)
HbA_{1c} <7.0% (53 mmol/mol) at Week 24 and no DKA	61 (22.8)	96 (36.5)	120 (45.8)	39 (15.1)	86 (33.0)	89 (33.8)
Analysis of net benefit at Week 24, n (%)						
HbA_{1c} <7.0% (53 mmol/mol) at Week 24 and no SH or DKA	58 (21.6)	*88 (33.5)*	114 (43.5)	39 (15.1)	82 (31.4)	85 (32.3)
Net benefit difference vs. placebo (95% CI)	NA	11.82 (3.90, 19.73)	21.87 (13.72, 30.02)	NA	16.30 (8.79, 23.82)	17.20 (9.67, 24.73)
p-value	NA	0.002	<0.001	NA	<0.001	<0.001

Modified intention-to-treat population
CI, confidence interval; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; NA, not applicable; SH, severe hypoglycaemia

Table 2.9 Analysis of net benefit at Week 52 in the inTandem1 and inTandem2 studies (36, 37)

	inTandem1			inTandem2		
	Placebo (N=268)	**Sotagliflozin 200 mg (N=263)**	**Sotagliflozin 400 mg (N=262)**	**Placebo (N=258)**	**Sotagliflozin 200 mg (N=261)**	**Sotagliflozin 400 mg (N=263)**
Components of net benefit, n (%)						
HbA_{1c} <7.0% (53 mmol/mol) at baseline	51 (19.0)	50 (19.0)	51 (19.5)	44 (17.1)	50 (19.2)	46 (17.5)
HbA_{1c} <7.0% (53 mmol/mol) at Week 52	56 (20.9)	79 (30.0)	93 (35.5)	40 (15.5)	71 (27.2)	73 (27.8)
HbA_{1c} <7.0% (53 mmol/mol) at Week 52 and no SH	51 (19.0)	72 (27.4)	87 (33.2)	37 (14.3)	67 (25.7)	70 (26.6)
HbA_{1c} <7.0% (53 mmol/mol) at Week 52 and no DKA	55 (20.5)	75 (28.5)	91 (34.7)	40 (15.5)	71 (27.2)	72 (27.4)
Analysis of net benefit at Week 24, n (%)						
HbA_{1c} <7.0% (53 mmol/mol) at Week 52 and no SH or DKA	51 (19.0)	69 (26.2)	85 (32.4)	37 (14.3)	67 (25.7)	70 (26.6)
Net benefit difference vs. placebo (95% CI)	NA	7.2 (−0.27, 14.68)	13.4 (5.67, 21.15)	NA	11.3 (4.13, 18.52)	12.3 (5.05, 19.50)
p-value	NA	0.049	<0.001	NA	0.001	<0.001

Modified intention-to-treat population
CI, confidence interval; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; NA, not applicable; SH, severe hypoglycaemia

2.6.5. Reducing glycaemic variability and increasing time in range

Chronic or excessive glycaemic variability outside the target range may contribute to long-term complications in T1D. A study using the Diabetes Control and Complications Trial (DCCT) data set found that occurrence of biochemical hypoglycaemia is associated with increased risk of SH. The risk of an SH event during the 3-month period was more than two-fold greater when there was at least one hypoglycaemic blood glucose measurement, and risk increased further when there was more than one hypoglycaemic blood glucose concentration (51). Therefore, treatments that control HbA_{1c} levels within target and that reduce glycaemic variability through insulin-independent mechanism offer a valuable addition to treatment options for patients. Evidence regarding sotagliflozin effects in reducing glycaemic variability can be seen in the effect on postprandial glucose (PPG) levels and time

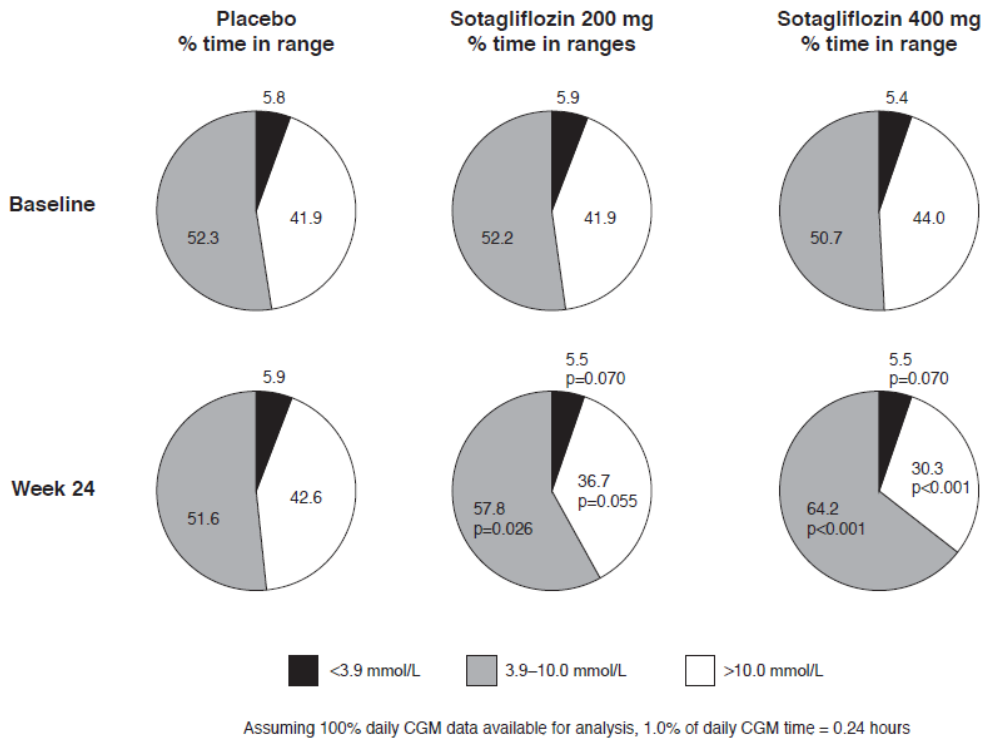
in range as well as fasting plasma glucose (FPG). The latter two outcomes are supported by changes in insulin dosing, a consequence expected with sotagliflozin's mechanism of action in the intestine and the kidney. The impact on PPG, FPG contribute to the increased time in range. A summary of these endpoints is given below.

CGM data from inTandem1 and inTandem2 were combined for analysis in a prospectively defined meta-analysis. Therefore, the results for the individual studies presented here are descriptive only. The primary endpoint for the CGM sub-study (93 placebo patients, 99 sotagliflozin 200 mg patients, and 96 sotagliflozin 400 mg patients) was the percentage of time spent inside the target range for CGM glucose (defined as 3.9–10.0 mmol/L (46, 47)). Time in range results are considered clinically relevant based on the recommendations from the DiaTribe meeting "Glycemic Outcomes Beyond A_{1c}: Standardization and Implementation" held in Bethesda, MD, United States in July 2017 (52).

The least squares mean (LSM) differences [standard error (SE)] from placebo in percent time in range at Week 24 were +5.35% (2.388) and +11.71% (2.316) for the sotagliflozin 200 mg and 400 mg dose group, ($p = 0.026$ and $p < 0.001$, respectively; Figure 2.4). Assuming 100% daily CGM data are available for analysis, 1.0% of daily CGM time corresponds to approximately 15 minutes (0.24 hours), therefore, the mean increase in percent time in range corresponds to actual increases of approximately 1.3 hours and 2.8 hours for sotagliflozin 200 mg and 400 mg, respectively compared with placebo. The increased time in range observed in the active treatment groups was associated with decreased time spent >10 mmol/L. The percentage of time spent in the hypoglycaemic range was essentially unchanged, which is of clinical significance as treatment with sotagliflozin did not make this worse.

Overall, the results suggest that patients will have fewer fluctuations in blood glucose levels by receiving adjunctive sotagliflozin. For patients, this means a reduction in physical and psychosocial 'ups and downs' that negatively impact daily living (2, 17, 30).

Figure 2.4. Percent time spent in range and outside range for continuous glucose monitoring in the pooled inTandem1 and inTandem2 results (53)



Modified intension to treat, CGM population.
CGM, continuous glucose monitoring; mITT, modified intention-to-treat

Additionally, the IDMC reviewed a total of 7,729 patient visits in inTandem1 and inTandem2. The IDMC found that after randomisation and through Week 24, the proportion of patients achieving SMBG targets in the placebo group remained stable compared with a significant increase for both fasting and postprandial targets for both sotagliflozin doses (twice as many vs placebo), consistent with sotagliflozin's dual mechanism of action. Beyond Week 24, up to Week 52, the proportion of patients meeting SMBG targets remained stable without significant further improvement.

Evaluation of reasons for not titrating the insulin dose in patients who were not at target (as assessed by the investigators) revealed a range of concerns related to hypoglycaemia, including general fear and concern, fear of nocturnal hypoglycaemia, impressions of risk and frequency, as well as avoiding and preventing future episodes.

Postprandial glucose

PPG is an important determinant of glycaemic control in the fed state and can therefore be considered a valuable marker of response to antidiabetic treatment that is influencing the glycaemic response to food and subsequent glucose absorption (2, 11, 18, 54, 55). SGLT-1 is a key mediator of PPG and is therefore an important treatment target to improve postprandial glycaemic control.

A 2-hour PPG assessment was performed after a standardised mixed meal at Day 1 and at Week 24 in patients participating in the CGM sub-study. Pooling of data from the CGM sub-studies from the inTandem1 and inTandem2 was pre-specified prior to database lock of individual studies. This pooled analysis served as the primary assessment of these results.

Overall, sotagliflozin demonstrated a clinically meaningful effect on PPG, consistent with SGLT-1 inhibition complementing SGLT-2-mediated reduction in PPG. The difference from placebo in LSM ± SE CFB in 2-hour PPG at Week 24 was −1.9 ± 0.7 mmol/L in the sotagliflozin 200 mg group and −2.3 ± 0.6 mmol/L in the sotagliflozin 400 mg group (nominal p=0.004 and p<0.001, respectively) (Table 2.10).

Table 2.10 Change from baseline in postprandial glucose with sotagliflozin versus placebo (53)

Characteristic	Placebo (N=93)	Sotagliflozin 200mg (N=89)	Sotagliflozin 400mg (N=96)
CFB in 2-hour PPG (mmol/L) after a standardised mixed meal*			
LSM PPG at baseline (SD)	12.8 (5.5)	11.8 (5.5)	11.6 (4.8)
LSM PPG at Week 24 (SD)	11.9 (4.8)	10.1 (4.4)	9.5 (3.5)
CFB in glucose (mmol/L) at Week 24			
Glucose LSM, mmol/L (SE)	−0.4 (0.5)	−2.4 (0.5)	−2.7 (0.5)
p-value	0.40	<0.001	<0.001
Summary of treatment comparison			
Glucose mmol/L LSM difference from placebo, mmol/L (SE)	NA	−1.9 (0.7)	−2.3 (0.6)
p-value		0.004	<0.001

*A standard mixed meal of Boost®, or equivalent was given as 6 mL/kg body weight up to a maximum of 360 mL (for subjects >60 kg, this is ~60 g carbohydrate, ~15 g protein, ~6 g fat and 360 calories).
CFB, change from baseline; LSM, least squares mean; NA, not applicable; PPG, postprandial glucose, SD, standard deviation; SE, standard error

Fasting plasma glucose

SGLT-2 inhibition by sotagliflozin results in glucose reduction independent of meals, with the impact on FPG as the key outcome. Levels of FPG show a gradual increase with increasing HbA_{1c} (56). Therefore, the sotagliflozin-mediated FPG reduction is expected to have the greatest effect on HbA_{1c} in those with poor glycaemic control.

In inTandem1 and inTandem2, FPG was the fourth secondary endpoint. The placebo-corrected CFB in FPG at Week 24 in inTandem1 was −0.55 mmol/L for sotagliflozin 200 mg (p=0.034) and −0.99 mmol/L for sotagliflozin 400 mg (p<0.001) (Figure 2.13). Because a preceding secondary endpoint in the hierarchy was not significant, the p-value calculated for the sotagliflozin 200 mg arm comparison is descriptive and cannot be used to declare statistical significance. In inTandem2, the placebo-corrected mean CFB in FPG at Week 24 was −1.20 mmol/L for sotagliflozin 200 mg (p<0.001) and −1.42 mmol/L for sotagliflozin 400 mg (p<0.001) (Table 2.11). In both studies, the effect of sotagliflozin on FPG remained at Week 52.

Table 2.11 Mixed model repeated measures analysis of change from baseline in fasting plasma glucose at Week 24 (36, 37)

Study	inTandem1			inTandem2		
	Placebo	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**	**Placebo**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
Baseline						
N	268	263	262	258	261	263
Mean	8.5	8.6	8.2	8.9	9.1	9.2
Change from baseline at Week 24, mmol/L						
N	245	245	242	239	237	239
LSM (SE)	0.21 (0.19)	−0.34 (0.19)	−0.78 (0.19)	0.49 (0.22)	-0.71 (0.22)	−0.93 (0.22)
95% CL	−0.17, 0.59	−0.72, 0.04	−1.16, -0.40	0.06, 0.92	−1.14, -0.28	−1.36, -0.50
p-value	0.27	0.08	<0.001	0.026	0.001	<0.001
Summary of treatment comparison						
LSM (SE) vs placebo	NA	−0.55 (0.26)	−0.99 (0.26)	NA	−1.2 (0.30)	−1.42 (0.30)
95% CL	NA	−1.06, −0.04	−1.50, −0.48	NA	−1.79, −0.61	−2.01, −0.84
p-value	NA	0.034	<0.001	NA	<0.001	<0.001

CL, confidence limit; LSM, least squares mean; NA, not applicable; SE, standard error.

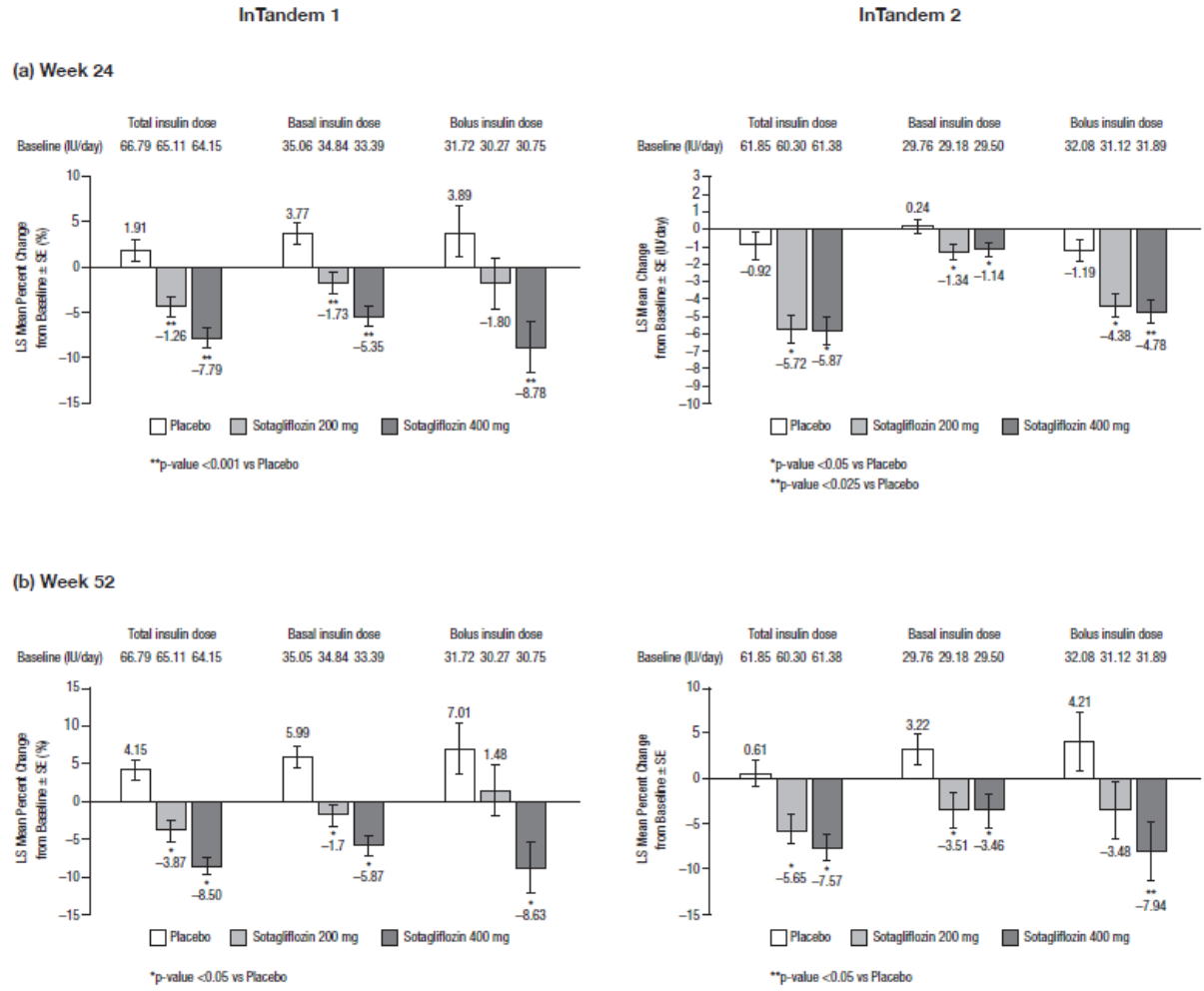
Impact on insulin dosing

The effect of sotagliflozin on reducing PPG and FPG are reflected in decreases in daily insulin doses. This is expected, based on sotagliflozin's mechanism of action in the intestine and kidney. For example, the SGLT-1-mediated response is expected to reduce bolus insulin requirements due to a blunting and delay of postprandial hyperglycaemia (PHH). Overall, the decrease in daily bolus insulin dose was statistically significant and assessed as clinically meaningful with respect to risk for hypoglycaemia (Figure 2.6). Decreases were consistent across the Phase III programme, ensuring glucose control without unnecessarily high insulin doses. Consistent with the sotagliflozin effect on SGLT-2, findings were similar, although less pronounced, for percent changes from baseline in daily basal insulin dose for the individual studies (Figure 2.5).

The LSM difference from placebo in percent change in bolus insulin dose remained clinically relevant and statistically significant in all groups in the inTandem1 and inTandem2 studies at Week 52, ranging from −5.53 to −15.63%. Because insulin is usually adjusted in increments of ≥10%, these changes were also assessed as clinically meaningful. Similar results were observed for the mean daily basal insulin dose and for the mean daily total insulin dose

As a result, the sotagliflozin draft Summary of Product Characteristics (SmPC) states that "In order to avoid hypoglycaemia with the first dose of sotagliflozin a 20% reduction in the first mealtime bolus insulin may be considered. Subsequent bolus doses should be adjusted individually based on blood glucose results" (57). No reduction in basal insulin is recommended when initiating sotagliflozin. Subsequently basal insulin should be adjusted based on blood glucose results and when needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Figure 2.5. Change from baseline in insulin doses at (a) Week 24 and (b) at Week 52 in inTandem1 and inTandem2 (36, 37)



Modified intenetion-to-treat population
LS, least squares; SE, standard error.

Concluding remarks regarding glycaemic outcomes achieved with sotagliflozin

Overall, the evidence relating to change in HbA_{1c} levels from baseline, net benefit, effects on PPG excursions and FPG means that with sotagliflozin treatment, glycaemic goals can be achieved with less glycaemic variability and lower bolus insulin doses. The decrease in daily bolus insulin dose was statistically significant and assessed as clinically meaningful with respect to risk for hypoglycaemia. Decreases were consistent across the Phase III programme in patients who were or were not taking an optimised insulin dose, ensuring glucose control without unnecessarily high insulin doses. For some patients, calculating and managing bolus dosing can be a challenge, and for others, concerns related to weight gain and hypoglycaemia can result in poor adherence (2, 11, 30, 58). Therefore, the opportunity

to reduce insulin bolus dose is considered a desirable outcome of adjunctive therapy in T1D, although it must be balanced against the risk of DKA.

2.6.6. Non-glycaemic endpoints: cardiovascular risk

The main non-glycaemic outcomes relate to weight change, systolic blood pressure (SBP) and patient-reported outcomes (PROs), in particular diabetes-related and general health-related quality of life (HRQoL). Results for the two studies are summarised in Table 2.6 (above) and are described further below.

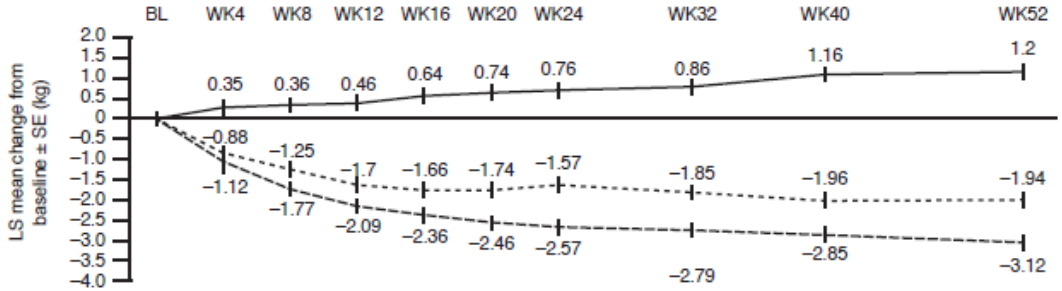
2.6.6.1. Weight change

In both inTandem1 and inTandem2, there were statistically significant and clinically relevant reductions of between 2 kg and 3.5 kg in bodyweight for patients receiving sotagliflozin (200 mg and 400 mg) over the study duration, whereas body weight of patients receiving placebo tended to increase slightly (Figure 2.6) (36, 37). Weight reductions due to sotagliflozin appeared within the first month of treatment and continued throughout the study duration, up to Week 52.

The reduction in body weight observed for both sotagliflozin doses was further supported by the results of the DEXA sub-study that described change in total fat mass in the inTandem2 trial (37). Placebo-subtracted LSM changes of −1512 g (p=0.031) and −2004 g (p=0.003) were observed for the sotagliflozin 200 mg and 400 mg groups, respectively. Similar results were observed for the inTandem1 study in North America. In both studies, a modest but statistically significant decrease in total lean mass from baseline to Week 24 was also noted for both sotagliflozin groups and confirms that the beneficial effect on body weight was mainly due to a decrease in total fat mass.

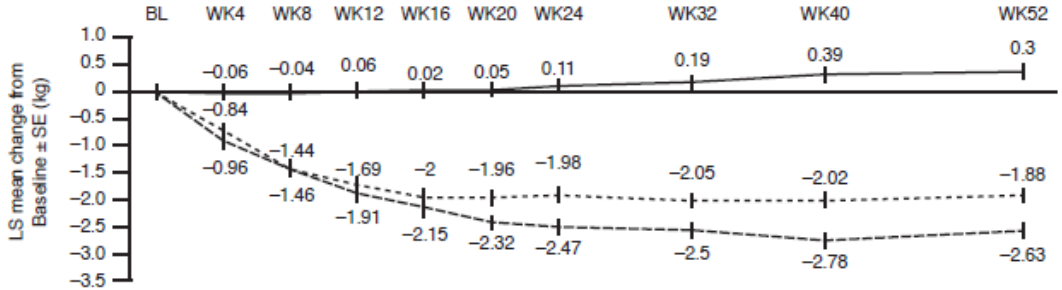
Figure 2.6. Weight changes among patient groups in the insulin-optimised inTandem1 and inTandem2 trials (36, 37)

In Tandem 1



	Difference from baseline*	P-value
Sotagliflozin 200 mg	–3.14 kg	<0.001
Sotagliflozin 400 mg	–4.32 kg	<0.001

In Tandem 2



	Difference from baseline*	P-value
Sotagliflozin 200 mg	–2.18 kg	<0.001
Sotagliflozin 400 mg	–2.93 kg	<0.001

*Placebo adjusted.

Placebo
Sotagliflozin 200 mg
Sotagliflozin 400 mg

BL, baseline; LS, least squares; SE, standard error; WK, week.

The influence of baseline BMI (<30 or ≥30 kg/m^2) on the proportion of patients with HbA_{1c} <7.0% (53 mmol/mol) was also assessed. Regardless of baseline BMI, sotagliflozin helped more patients achieve HbA_{1c} targets than placebo.

In inTandem2, in the subset of patients with baseline BMI <30 kg/m^2, 25 out of 186 patients (13.4%) in the placebo group were classed as responders [HbA_{1c} <7.0% (53 mmol/mol) at Week 24] whereas 58 out of 177 (32.8%) in the sotagliflozin 200 mg group and 65 out of 185 (35.1%) in the sotagliflozin 400 mg group were responders (difference in the percentage of responders from placebo: 19.3% and 21.7% in the sotagliflozin 200 mg and 400 mg groups, respectively; both p<0.001 vs placebo).

In the subset of patients with baseline BMI ≥30 kg/m^2, 14 (19.4%) patients in the placebo group were responders compared with 29 (34.5%) in the sotagliflozin 200 mg group and 24 (30.8%) in the sotagliflozin 400 mg group.

2.6.7. Blood pressure

Increasing blood pressure is a risk factor for increased mortality due to an elevated risk of stroke and coronary disease. In T1D, increased blood pressure is also a significant driver of diabetic nephropathy, which leads to renal failure and is the major source of premature mortality and complication costs associated with T1D (9, 11). Therefore, any adjunctive therapy that helps reduce blood pressure will offer incremental clinical value over glycaemic control alone and any influencer of diabetic renal disease would be of major significance.

A beneficial effect on SBP was also observed in the overall population, with larger reductions in SBP observed in patients with baseline SBP ≥130 mm Hg. For all these secondary efficacy endpoints, the effect was numerically greater for the sotagliflozin 400 mg dose compared with 200 mg.

Overall, adjunctive sotagliflozin resulted in significantly lower SBP than in patients receiving placebo at Week 12 (inTandem1 and inTandem2) (Table 2.6).

2.7. Health-related quality of life (HRQoL)

2.7.1. Diabetes-specific measures of HRQoL

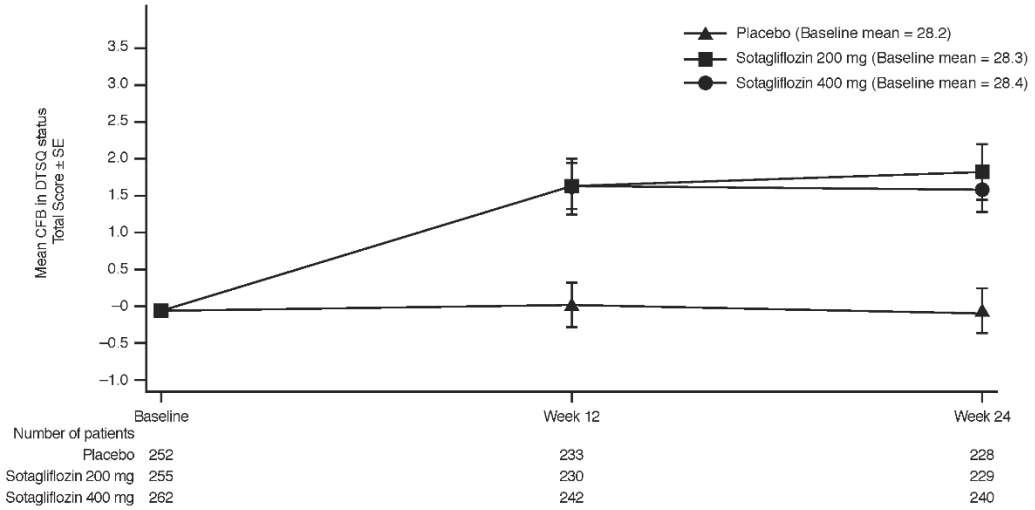
As described in Section 1.3, T1D has a profound adverse impact on the HRQoL. Therefore, there is a strong need for new interventions that normalise quality of life by reducing disease-related distress and improving treatment satisfaction.

In inTandem2, patients' satisfaction with diabetes treatment was assessed by the diabetes treatment satisfaction questionnaire (DTSQ). DTSQ significantly increased from baseline to Week 24 in both the sotagliflozin 200 mg or 400 mg treatment arm (1.9 ± 0.28 and 1.6 ± 0.28 respectively, compared with placebo −0.1 ± 0.28; p<0.001 for both comparisons) (37, 47). Similar results were observed for the inTandem1 study (36, 46).

Similarly, at Week 24, distress among sotagliflozin-treated patients, as measured by the two-item Diabetes Distress Screening Scale (DDS2), decreased by 0.3 (20.6 to 0.0; p=0.025) and 0.4 (20.7 to 20.2; p=0.003) with the 200- and 400-mg doses relative to placebo. Distress values among patients in the placebo group did not change from baseline (Figure 2.8) (37, 47). Again, similar results were observed for the inTandem1 study (36, 46).

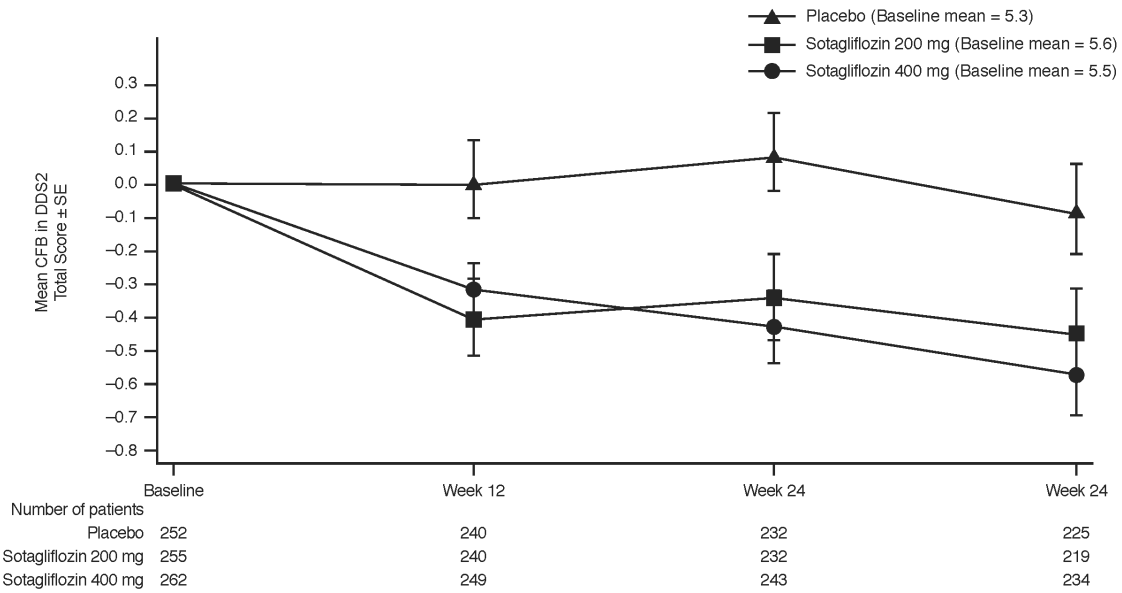
Treatment with sotagliflozin therefore lead to a reduction in distress and improvements in treatment satisfaction. Interviews conducted inTandem1 patients showed that those who demonstrated improvements in glucose stability and improved HbA_{1c} also reported improvements in their quality of life, including but not limited to a reduction in stress/worry and improvements in mood, energy, and physical functioning. These data suggest that improvement in glycaemic control can lead to meaningful improvements in patient quality of life (46).

Figure 2.7 Mean change from baseline in Diabetes Treatment Satisfaction Questionnaire status total score by study visit in inTandem2 (37, 47)



Modified intention-to-treat population
CFB, change from baseline; DTSQ, Diabetes Treatment Satisfaction Questionnaire

Figure 2.8 Mean change from baseline in the 2-item Diabetes Distress Screening Scale total score by study visit in inTandem2 (37, 47)



Modified intention-to-treat population
CFB, change from baseline; DDS2, Diabetes Distress Screening Scale 2

2.7.2. General measures of HRQoL

General HRQoL was measured using the EQ-5D instrument, in particular the index score, which measured overall health state (higher values indicate better health states) and the visual analogue scale (VAS).

EQ-5D index scores of all patients in the inTandem1 and inTandem2 trials remained similar between baseline and Week 52. In the inTandem2 trial, the LSM ± SE change from baseline at Week 52 was −0.0070 ± 0.00902 for the sotagliflozin 200 mg group, and −0.0015 ± 0.00884 for the sotagliflozin 400 mg group and not different from placebo (−0.0051 ± 0.00687) (47).

When asked to rate on a scale of 0 ('worst health you can imagine') to 100 ('best health you can imagine') on the VAS according to "how good or bad your health is today?", scores remained approximately the same for all treatment groups (LSM ± SE CFB at week 52 = −1.0 ± 1.04, p=0.35 versus baseline), the sotagliflozin 200 mg group (LSM ± SE CFB =0.3 ± 1.04, p=0.75 versus baseline), and the sotagliflozin 400 mg group (LSM ± SE CFB =0.2 ± 1.02, p=0.87 versus baseline) (47).

2.8. Subgroup analysis

2.8.1. Pre-specified subgroups: inTandem1 and inTandem2

The efficacy data from the Phase III studies were pooled to allow integrated assessments of findings across studies to provide increased precision for CGM and DEXA assessments (as discussed above) and for analysis of efficacy endpoints across several subgroups of clinical interest. The pool analysis includes efficacy data from inTandem1 and inTandem2 (24-week and 52-week data for sotagliflozin 200 mg and 400 mg) (53).

In order to increase the precision of subgroup analyses on a larger dataset, a pooled analysis was pre-planned for the following subgroups of particular interest:

- Age at study entry (<65, ≥65 to <75, ≥75 years);
- Sex (male, female);
- Race (white, non-white, unknown);
- Baseline eGFR status (<60, ≥60 to <90, and ≥90 mL/min/1.73 m^2);
- BMI categories (<25, ≥25 kg/m^2);
- Geographic region (North America [US + Canada], Outside North America);

- Insulin delivery method (CSII, non-CSII);
- Duration of T1D (<20, ≥20 years)
- Week −2 HbA_{1c} (≤8.5%, >8.5%)

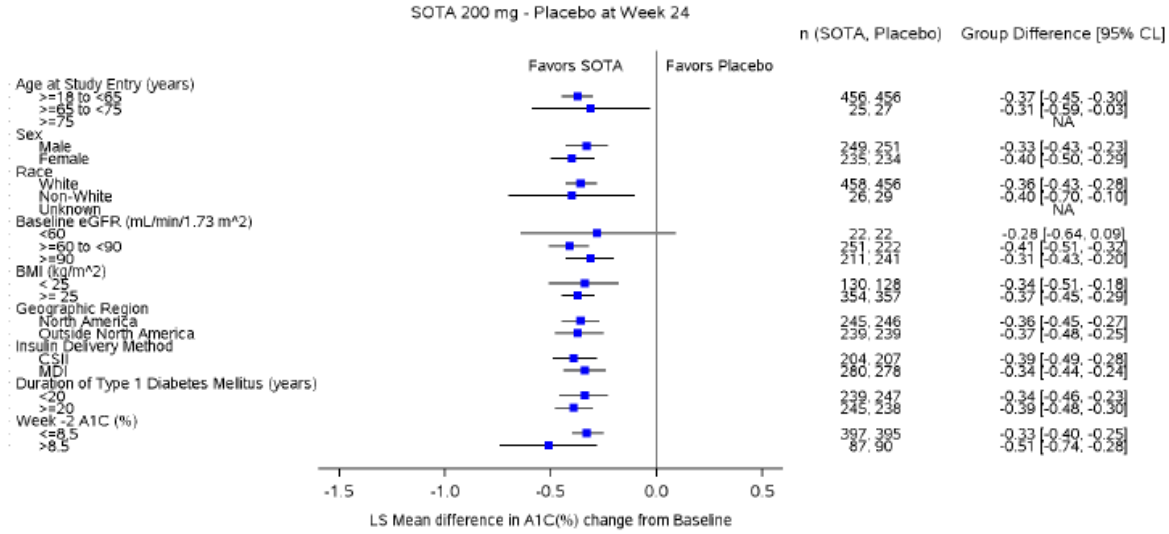
Figure 2.9 summarise the LSM difference of the CFB to Week 24 in HbA_{1c} (%) for each sotagliflozin group compared with placebo for the inTandem1 and inTandem2 pooled analysis (mITT population) for these subgroups.

Overall, in pooled analysis of inTandem1 and inTandem2 and at both doses, no clinically meaningful difference was observed between males and females, age at study entry, duration of disease, BMI, or geographic region. The effect was numerically greater in patients with CSII, but the difference was not clinically meaningful. Numerical differences observed between age categories >65 and ≤65 years or between races were more likely due to the limited number of patients in some subgroups. The efficacy cannot be reliably assessed in patients >75 years due to the very small number of patients (n=15). Clinically meaningful efficacy was observed in patients with eGFR ≥60 to <90, and ≥90 mL/min/1.73 m^2. A LSM difference compared to placebo of −0.21% to −0.28% was observed in patients with eGFR <60 mL/min/1.73 m² (53).

A similar subgroup analysis confirmed that the LS mean difference compared to placebo in net benefit was statistically significant at both doses in all subgroups of sufficient size, without meaningful difference between groups (53). These data provide support for sotagliflozin's benefit in a broad population of T1D regardless of age, sex, disease duration, BMI, and insulin delivery method.

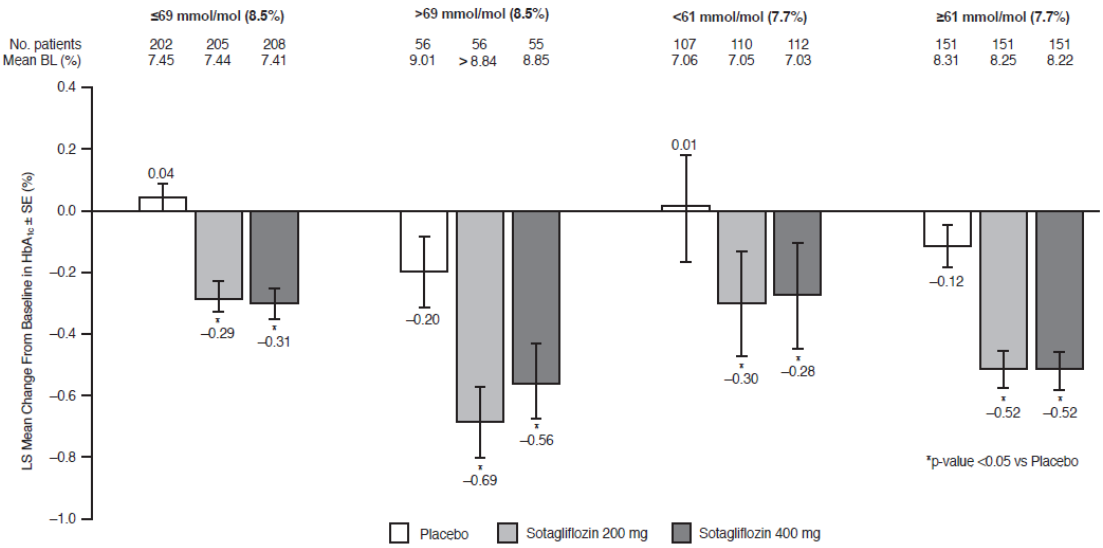
The largest decreases in HbA_{1c} were observed in patients with baseline HbA_{1c} >8.5% (69 mmol/mol) in both trials. The values for inTandem2 are shown in Figure 2.10.

Figure 2.9 Forest plot of difference in the adjusted mean change from baseline to Week 24 in glycated haemoglobin (%) of sotagliflozin 200 mg compared with placebo by subgroups for inTandem1 and inTandem2 pool (53)



Difference between mean change from baseline (%) and 95% CI; modified intention-to-treat population
A_{1c}, glycated haemoglobin; BMI, body mass index; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections; SOTA, sotagliflozin.

Figure 2.10. Least squares mean change from baseline in glycated haemoglobin at Week 24 by categorical glycated haemoglobin value at Week −2 (47)



Modified intention-to-treat, inTandem2 population
BL, baseline; LS, least squares; mITT, modified intention-to-treat; SE, standard error;

Insulin delivery (MDI or CSII): HbA_{1c} reductions at Week 24 were similar regardless of insulin delivery method in inTandem2 (47). For patients receiving insulin via CSII, the LSM

difference [95% confidence interval (CI)] from placebo in HbA_{1c} change was −0.44% (−0.66, −0.21) and −0.39% (−0.62, −0.17) for the sotagliflozin 200 mg and 400 mg groups, respectively. For those taking MDI, the LSM difference (95% CI) from placebo in HbA_{1c} change was −0.34% (−0.48, −0.21) and −0.33% (−0.47, −0.20) for the sotagliflozin 200 mg and 400 mg groups, respectively. All differences were statistically significant (p<0.001).

Finally, there was no influence of renal function on CFB in HbA_{1c} at Week 24, although there were only limited patient numbers per treatment arm in this subgroup.

Table 2.12. Subgroup analysis of mode of insulin administration in patients with glycated haemoglobin <7.0% (53 mmol/mol) and no severe hypoglycaemia or diabetic ketoacidosis (47)

Primary endpoint	Sotagliflozin (N= 699)	Placebo (N= 703)	Difference (95% CI)	p-Value
	n/N (%)	n/N (%)	percentage points	
All patients	200/699 (28.6)	107/703 (15.2)	13.4 (9.0–17.8)	<0.001
Patients who used CSII	88/275 (32.0)	45/280 (16.1)	15.9 (8.6–23.3)	<0.001
Patients who used MDI	112/424 (26.4)	62/423 (14.7)	11.8 (6.1–17.4)	<0.001

CI, confidence interval; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection;

2.9. Indirect and mixed treatment comparison

2.9.1. Feasibility assessment

As discussed in Section 2.1 a SLR was performed to support the decision problem for this appraisal with regards to the two comparators: insulin and insulin + metformin.

2.9.2. Overview

A feasibility assessment (FA) using the results of the SLR was conducted to explore the homogeneity/heterogeneity across the trials included in the evidence base (Appendix F). A summary of the key findings of the FA are reported here.

Based on the results from the FA, it was clear that the direct head-to-head randomised control trial evidence was more robust for the comparison to insulin rather than the network meta-analysis results. Therefore, inTandem2 was selected for the base-case comparison between sotagliflozin plus insulin vs. insulin therapy. A sensitivity analysis using the ITC was conducted and reported in the economic section, however these results must be interpreted with caution given the differences in the studies informing the ITC.

2.9.2.1. Feasibility assessment methodology

The NMA is built on an assumption of transitivity. In order for the assumption of transitivity to hold true, trials involving direct comparisons need to be sufficiently similar, apart from the different interventions they are evaluating. The indirect comparisons in NMA are not protected by randomisation and may be confounded by differences between the trials. Thereby, it is vital to check whether all the trials were conducted in a similar way and recruited participants with similar baseline characteristics as differences might modify the treatment effect.

2.9.2.2. Results of the feasibility assessment

The results of the FA indicated that the RCTs contributing to the NMA analyses differed in terms of methodological parameters, key baseline characteristics, and definitions of outcomes. Direct meta-analysis of included trials, placebo pooling and influence plot testing identified two outliers from HbA_{1c} at 24 weeks (inTandem3) and total insulin at 52 weeks (inTandem2) outcomes.

The NICE checklist, used for the quality assessment of included trials, found that the majority of the included trials indicated a low risk of bias among all the assessed parameters (Table 2.13). However, the high risk of bias was assessed in some key checklist parameters of one metformin study (43). This is discussed below.

- The seven-placebo-controlled metformin RCTs were published between 2002 and 2018. Method of randomisation and allocation concealment was adequate in only two studies (31, 39) while insufficient details were provided to allow definitive judgement in the remaining five studies (e.g. no information was provided on how the randomisation sequence was generated). Five studies reported that there were no significant differences in the baseline characteristics between the treatment arms. In one study baseline characteristics were not adequately reported (43) while in another study patients randomised to the metformin group initially differed from the subjects in the control group by a higher BMI (43). Five trials were double-blinded randomised trials, one study was an open-label study (43) while details regarding blinding were unclear in one study (42).

- The Burchardt et al. study protocol was not registered at ClinicalTrials.gov and was not approved by the Institutional Review Board, but it was conducted according to

the guidelines stated in the Declaration of Helsinki and was approved by the local bioethics commission. In REMOVAL, there was a discrepancy between what was written in the protocol and in the main publication (59). There was mention of using a pseudo-random number generator in the main publication, which is not mentioned in the protocol. An unclear risk was chosen as a result due to an unclear assessment. The authors were contacted for soliciting more information to better assess risk of bias, however, they were not responsive.

- There were unexpected imbalances in dropouts between groups in REMOVAL in which 27% of participants on metformin and 12% on placebo discontinued treatment during the trial, mainly due to gastrointestinal (GI) adverse effects (metformin 16% vs placebo 3%) (59). Inadequate withdrawals were also noted in Burchardt et al., two and 14 patients in each arm were lost to follow-up (43). In all trials the pre-specified outcomes, stated in online protocols (where available) or within the publications themselves, were reported. Six included an intention-to-treat, or a mITT analysis with a description on specific criteria that were modified while Burchardt et al. used only completers in efficacy and safety analysis.

Table 2.13. Quality assessment scores among the included randomised controlled trails

Study name	Year	Randomisation / allocation concealment	Baseline characteristics	Blinding	Withdrawals	Outcomes selection and reporting	Statistical analysis
inTandem1 (36)	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
inTandem2 (37)	2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
InTandem3 (38)	2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
REMOVAL (31)	2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lund et al (39)	2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Jacobsen (41)	2009	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zawada (42)	2018	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Burchardt (43)	2013	Unclear risk	High risk	High risk	High risk	Unclear risk	Low risk
Meyer (44)	2002	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk
Pitocco (45)	2012	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk

2.10. Network meta-analysis

Full details of the NMA are available in Appendix E. The NMA model is also provided as a confidential document. Despite limitations identified in the FA, an NMA was performed between sotagliflozin, insulin and metformin. Below we discuss how the NMA has been used to inform the comparison.

2.10.1. Overview

Evidence synthesis for comparison of sotagliflozin versus insulin

Based on the results from the FA, the treatment effect evidence for comparison with insulin is derived directly from the head-to-head inTandem2 study. This is due to the robustness of directly observed clinical evidence and because important qualitative and statistical variability concerns were observed in the NMA FA such as: 1) a high heterogeneity when assessing all combined studies (notably in key parameters such as HbA_{1c} and BMI) 2) a disproportionate number of patients using insulin pump combined with differences in the geographical location of the study participants (affecting mostly inTandem1 vs inTandem2), and 3) the discrepancy in the pre-trial insulin optimisation period (affecting the comparison of inTandem trials vs metformin trials).

Evidence synthesis for the comparison of sotagliflozin versus metformin

For the comparison with metformin, the NMA was used to inform the comparison, in the absence of a head-to-head comparison with sotagliflozin. All the analyses indicated that sotagliflozin performed better than metformin at the timepoints assessed. However, given the heterogeneity across the trials included in this analysis, results should be viewed with caution.

The NMA was performed specifically to meet the requirements of this appraisal however as discussed above, there was clear heterogeneity between the studies. Further discussion of the heterogeneity in methodological, baseline and outcome characteristics is provided below. The NMA results should be interpreted with caution as the adjustment of observed heterogeneity using meta-regression technique was not possible due to the limited number of studies in each outcome. See Appendix F for full details of the process and methods used in the NMA.

2.10.2. Framework for the network meta-analysis

A total of 10 studies identified in the SLR above contributed to the comparison with metformin. The results of the FA indicated that the RCTs identified differed in terms of methodological parameters, key baseline characteristics and definition of outcomes.

2.10.2.1. Methodological parameters

Among the ten included studies, the majority (N=8) were double-blind in design, while one study reported assessment in the open-label setting (43), and the information related to blinding was not reported in one study (42). Four of the 10 included studies were Phase III (36-38), and one was phase IV (39), while five studies did not report any information related to the study phase. In terms of study setting, the majority of trials were conducted in a single centre (N=6) whereas the remaining four studies were conducted in multiple centres across various countries (multicentre international). The sample size of included studies ranged from 24 (41) to 1,405 (38).

The treatment duration was 24 weeks in two studies (38, 41), 26 weeks in four studies (42-45), 52 weeks in three studies (36-38), and 154 weeks in one study (59). During the pre-randomisation period, insulin adjustment/optimisation was reported in five studies (36, 37, 41, 43, 59), no optimisation was conducted in one study [inTandem3 (38)]. The remaining four studies did not provide any information related to insulin optimisation. The optimisation period ranged from 1 week to 12 weeks prior to randomisation. Three studies [inTandem1, inTandem2 and Jacobsen, et al. 2009 (36, 37, 41)] reported optimisation of insulin during the trial period, while other studies did not report any information related to insulin optimisation during the trial. Further, four studies reported the use of pre-specified algorithms for insulin adjustment during the pre/post randomisation phase (36, 37, 41, 43)

The contributing trials varied regarding trial design, insulin optimisation, sample size, and study setting. Details of these trials are presented in Table 2.14.

Differences in baseline characteristics

Table 2.15 below provides all the key baseline characteristics reported among the included studies. The mean age among the included T1D patients ranged from 32.8 years (43) to 55.5 years (59). The studies conducted by Zawada, et al. and Burchardt, et al. included younger and the REMOVAL trial included older patients than the inTandem trials (31, 42, 43). The inTandem trials were well balanced in terms of gender distribution (~50%);

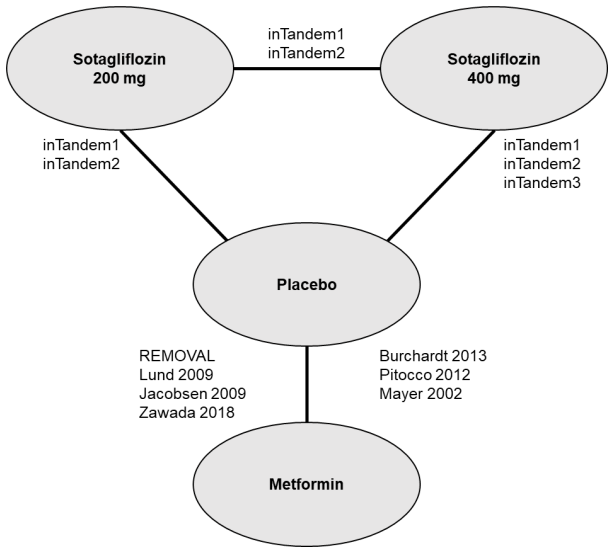
however, four trials (39, 41, 44, 59) included a slightly higher proportion of male patients. Baseline HbA_{1c} levels ranged from 7.5% (45) to 9.5% (39). Lund, et al. (2009) reported higher mean HbA_{1c} (9.5%) at baseline as compared with other included trials. Disease duration ranged from 9.0 (45) to 33.9 years (59). Three trials (42, 43, 45) assessed patients with shorter and one trial (59) assessed patients with longer disease duration as compared with inTandem trials. The included trials were sufficiently similar in terms of BMI at baseline. Lund, et al. (2009) reported slightly higher mean SBP values as compared to inTandem trials. Other parameters in which metformin trials differed from the inTandem trials include CSII pump use (44) and hypertension (43).

In summary, the contributing trials varied regarding baseline HbA_{1c}, age, gender, sample size, disease duration, and comorbidities.

2.10.2.2. Network of interlinked studies

Figure 2.11 depicts the network diagram for the secondary and sensitivity analyses verses insulin and secondary analysis verses metformin.

Figure 2.11 Network diagram for the secondary and sensitivity analyses



Note: Heterogeneity across the studies contributing to the network is not taken into account for mandatory analyses

2.10.2.3. Outcomes selected and assessed

Table 2.14 lists the outcomes of interest for the NMA, selected on the basis of their clinical relevance and outcomes reported. Table 2.15 reports the baseline characteristics of patients included in the NMA.

Table 2.14. Design and outcomes of trials included in the network meta-analysis

	inTandem1(36)	inTandem2 (37)	inTandem3 (38)	REMOVAL (31)	Lund, et al. (2009) (39)	Jacobsen, et al. (2009) (41)	Zawada, et al. (2018) (42)	Burchardt et al. (2013) (43)	Pitocco, et al. (2013)(45)	Meyer et al. (2002) (44)
Subjects randomised	793	782	1405	428	100	24	114	68	42	62
Country	United States and Canada	17 European countries	Global	Global	Denmark	Denmark	Poland	Poland	Italy	France
Phase	III	III	III	III	IV	NR	NR	NR	NR	NR
Type	Double-blind, multicentre, international	Double-blind, multicentre, international	Double-blind, multicentre, international	Double-blind, multicentre, international	Double-blind, single centre	Double-blind, single centre	Single centre	Open-label, single centre	Double-blind, single centre	Double-blind, single centre
Treatments (+ insulin)	Sotagliflozin 200/400 mg Placebo	Sotagliflozin 200/400 mg Placebo	Sotagliflozin 400 mg Placebo	Metformin Placebo	Metformin Placebo	Metformin Placebo	Metformin Placebo	Metformin Placebo	Metformin Placebo	Metformin Placebo
Trial duration	52 wk t/t + 4 wk FU	52 wk t/t + 4 wk FU	24 wk t/t + 4 wk FU	154 wk	52 wk eek	24 wk	26 wk	26 wk	26 wk	26 wk
Optimisation (run-in) period	Insulin over 6 weeks	Insulin over 6 weeks	None	Glycaemic control for 3 months	No information	Insulin for 4 weeks	No information	Insulin for 1 week	No information	No information
Outcomes										
Mean CFB HbA_{1c} (%)	24 wk 52 wk	24 wk 52 wk	24 wk	24 wk 52 wk	52 wk	24 wk	26 wk	26 wk	24 wk	-
Mean CFB body weight (kg)	24 wk 52 wk	24 wk 52 wk	24 wk	24 wk 52 wk	52 wk	24 wk	-	-	24 wk	-

	inTandem1(36)	inTandem2 (37)	inTandem3 (38)	REMOVAL (31)	Lund, et al. (2009) (39)	Jacobsen, et al. (2009) (41)	Zawada, et al. (2018) (42)	Burchardt et al. (2013) (43)	Pitocco, et al. (2013)(45)	Meyer et al. (2002) (44)
Total daily insulin dose (IU/day)	24 wk 52 wk	24 wk 52 wk	24 wk	-	52 wk	24 wk	-	-	-	24 W
Patients at HbA_{1c} target (≤7%) + no episode of SH + no episode of DKA	24 wk 52 wk	24 wk 52 wk	24 wk	-	-	-	-	-	-	-
Patients with hypoglycaemia (Any)	24 wk 52 wk	24 wk 52 wk	24 wk	-	-	-	26 wk	-	24 wk	-
Patients with SH	24 wk 52 wk	24 wk 52 wk	24 wk	-	-	-	26 wk	-	-	-
Patients with DKA	24 wk 52 wk	24 wk 52 wk	24 wk	-	-	-	26 wk	-	-	-
Any hypoglycaemic event rate	24 wk 52 wk	24 wk 52 wk	24 wk	-	-	24 wk	-	-	-	24 wk
Severe hypoglycaemic event rate	24 wk 52 wk	24 wk 52 wk	24 wk	-	52 wk	-	-	-	-	24 wk

CFB, change from baseline; DKA, diabetic ketoacidosis; FU, follow-up; HbA_{1c}, glycated haemoglobin; NR, not reported; SH, severe hypoglycaemia wk, weeks

Table 2.15. Baseline characteristics of patients included in the network meta-analysis

Trial name	Mean age (years)	Female (%)	Mean HbA_{1c} (%)	Mean BMI (kg/m^2)	Mean diabetes duration (years)	MDI (%)/CSII pump (%)	Mean SBP/DBP (mm Hg)	BMI as inclusion criteria	Hypertension (%)
inTandem1 (36)	46.1	51.7	7.6	29.7	24.4	40.4/59.6	120.1/76.1	NR	38.8
inTandem2	41.2	48.1	7.8	27.8	18.4	74.3/25.7	123.1/76.6	NR	33.2
inTandem3 (38)	42.8	50.3	8.2	28.2	20.1	60.4/39.6	121.0/76.5	≥18.5	35.3
REMOVAL (31)	55.5	41.0	8.1	28.5	33.9	66.5/33.5	129.5/72.3	>27.0	NR
Lund, et al. 2009 (39)	45.5	36.0	9.5	26.0	28.0*	NR	138.7/80.0	NR	NR
Jacobsen, et al. 2009 (41)	40.4	41.7	8.8	29.2	19.1	NR	135.3/75.1† 113.6/66.1‡	≥25.0	NR
Zawada, et al. 2018 (42)	31.0*	53.0	8.5*	28.4*	14.0*	NR	122.0/80.0	NR	NR
Burchardt, et al. 2013 (43)	32.8	51.9	8.7	28.6	15.9	NR	NR	NR	46.2
Pitocco, et al. 2012 (45)	43.5	57.1	7.5	28.0	9.0	NR	NR	NR	NR
Meyer, et al. 2002 (44)	40.5	40.3	7.6	26.1	19.3	0/100	130.0/79.0	NR	NR

*Median values; †Daytime; ‡Nocturnal.
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injection; NR, not reported; SBP, systolic blood pressure.

Definition of outcomes for hypoglycaemia

The definition of key outcomes such as hypoglycaemia events and DKA varied between the included trials Table 2.16 and Table 2.17.

Table 2.16. Definitions of hypoglycaemia across included studies

Study name	Hypoglycaemia
inTandem1(36)	Hypoglycaemic events (blood glucose level ≤3.0 mmol/L)
inTandem2(37)	Hypoglycaemic events (blood glucose level ≤3.0 mmol/L)
inTandem3(38)	Hypoglycaemic events (blood glucose level ≤3.0 mmol/L)
Zawada, et al 2018(42)	Not reported
Pitocco, et al 2012(45)	Calculated as sum of minor and major hypoglycaemic events; Minor hypoglycaemic events were defined as asymptomatic or symptomatic glucose values ≤3.88 mmol/L; Major hypoglycaemic events were defined as any event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

Table 2.17. Definitions of severe hypoglycaemia across included studies

Study name	Severe hypoglycaemia
inTandem1 (36)	Any event that required assistance from another person or during which the patient lost consciousness or had a seizure
inTandem2 (37)	Any hypoglycaemic event that required assistance from another person or during which the patient lost consciousness or had a seizure
inTandem3 (38)	Any hypoglycaemic event that required assistance from another person or resulted in the loss of consciousness or a seizure, regardless of the patient's glucose level
Zawada, et al. 2018 (42)	The occurrence of hypoglycaemia (including SH), as obtained using a questionnaire
Meyer, et al. 2002(44)	Defined by the DCCT criteria; to qualify as SH, an episode had to require assistance from another person and included coma or seizures or episodes requiring glucagon, IV dextrose, or oral carbohydrate administered by another person

DCCT, Diabetes Control and Complications Trial; IV, intravenous; SH, severe hypoglycaemia

2.10.2.4. Results of the network meta-analysis: efficacy outcomes

Sotagliflozin 200 mg as an adjunct to insulin therapy showed significantly better efficacy as compared with insulin therapy alone (placebo plus insulin) in terms of HbA_{1c} (%), body weight (kgs-absolute), and total insulin dose (IU/day-absolute) at 24 and 52 weeks (Table 2.18).

For patients treated with sotagliflozin 200 mg the expected CFB for HbA_{1c} at 24 ± 2 weeks −0.43% (95% CrL −0.61, −0.22) and the expected CFB for body weight at 24 ± 2 weeks was found to be −1.72 kg (95% CrL −2.53, −0.91).

The efficacy of sotagliflozin 200 mg was comparable with—and not significantly different from—metformin for HbA_{1c} (%) at 24 weeks. In addition, body weight (kgs) and total insulin dose (IU/day) at 24 and 52 weeks was comparable between sotagliflozin 200 mg and metformin (Table 2.18). Full details are available in Appendix F.

2.10.2.5. Results of network meta-analysis: safety outcomes

Figure 2.11 depicts the master network diagram for the UK-specific base-case analysis and a summary of the NMA for safety outcomes is provided in Table 2.19.

Sotagliflozin 200 mg and 400 mg as an adjunct to insulin therapy showed comparable safety profile to insulin therapy alone (placebo plus insulin) and combination of metformin with insulin therapy (Table 2.19). Full details are available in Appendix F.

Given the substantial differences in the trials included in the NMA, the results should be interpreted with caution, particularly as adjustment of differences in important treatment effect modifiers using a meta-regression technique was not possible due to the limited number of studies.

Table 2.18. Summary of base-case efficacy results at Weeks 24 and 52 using the random effects model

Outcome	Comparator	Base-case 24 weeks (MD CFB 95% CrI using REM)		Base-case 52 weeks (MD CFB 95% CrI using REM)	
		Sotagliflozin 200 mg	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Sotagliflozin 400 mg
CFB in HbA_{1c} (%)	Placebo	−0.38 (−0.55, −0.21)	−0.41 (−0.55, −0.27)	−0.24 (−0.45, −0.02)	−0.31 (−0.54, −0.10)
	Metformin	−0.19 (−0.41, 0.13)	−0.22 (−0.42, 0.08)	−0.23 (−0.58, 0.07)	−0.30 (−0.67, −0.01)
	Sotagliflozin 200 mg	-	−0.03 (−0.2, 0.14)	-	−0.08 (−0.3, 0.13)
	Sotagliflozin 400 mg	0.03 (−0.14, 0.20)	-	0.08 (−0.13, 0.30)	-
CFB in body weight (kg)	Placebo	−2.16 (−3.00, −1.34)	−3.01 (−3.7, −2.3)	−2.67 (−4.11, −1.24)	−3.64 (−5.06, −2.21)
	Metformin	−0.33 (−1.47, 1.19)	−1.18 (−2.24, 0.27)	−1.00 (−3.10, 1.11)	−1.97 (−4.05, −0.16)
	Sotagliflozin 200 mg	-	−0.85 (−1.67, 0.00)	-	−0.97 (−2.39, −0.46)
	Sotagliflozin 400 mg	0.85 (0.00, 1.67)	-	0.97 (−0.46, 2.39)	-
CFB in total daily insulin dose (IUday)	Placebo	−3.87 (−5.9, −1.79)	−5.44 (−7.15, −3.79)	−3.62 (−6.35, −0.91)	−5.81 (−8.56, −3.17)
	Metformin	0.87 (−3.47, 5.18)	−0.71 (−4.86, 3.44)	2.07 (−2.67, 6.84)	−0.12 (−4.94, −4.59)
	Sotagliflozin 200 mg	-	−1.58 (−3.69, 0.46)	-	−2.2 (−4.93, −0.42)
	Sotagliflozin 400 mg	1.58 (−0.46, 3.69)	-	2.2 (−0.42, 4.94)	-

CFB, change from baseline; CrI, credible interval; HbA_{1c}, glycated haemoglobin; MD, mean difference; REM, random effect model

Table 2.19. Summary of base-case safety results at Weeks 24 and 52 using the random effects model

Outcome	Time-point	Comparator	Base-case 24 weeks (OR/RR 95% CrI using REM)	
			Sotagliflozin 200 mg	Sotagliflozin 400 mg
Proportion of patients with hypoglycaemia	24 weeks	Placebo	OR: 1.06 (0.35,3.29)	OR: 1.18 (0.46,2.69)
	24 weeks	Metformin	OR: 0.97 (0.19,5.08)	OR: 1.07 (0.23,4.59)
	24 weeks	Sotagliflozin 200 mg	-	OR: 1.11 (0.35,3.26)
	24 weeks	Sotagliflozin 400 mg	OR: 0.9 (0.31,2.9)	-
Proportion of patients with SH	24 weeks	Placebo	OR: 0.98 (0.28, 3.56)	OR: 0.91 (0.3, 2.63)
	24 weeks	Metformin	OR: 5.75 (0.76, 52.05)	OR: 5.34 (0.77, 41.81)
	24 weeks	Sotagliflozin 200 mg	-	OR: 0.93 (0.24, 3.23)
	24 weeks	Sotagliflozin 400 mg	OR: 1.08 (0.31, 4.12)	-
Any hypoglycaemic events	24 weeks	Placebo	RR: 0.89 (0.44, 1.8)	RR: 0.91 (0.5, 1.66)
	24 weeks	Metformin	RR: 0.59 (0.21, 1.61)	RR: 0.6 (0.23, 1.53)
	24 weeks	Sotagliflozin 200 mg		RR: 1.02 (0.5, 2.06)
	24 weeks	Sotagliflozin 400 mg	RR: 0.98 (0.49, 2.02)	
Severe hypoglycaemic events	24 weeks	Placebo	RR: 1.48 (0.59, 3.72)	RR: 0.86 (0.38, 1.9)
	24 weeks	Metformin	RR: 0.6 (0.1, 3.36)	RR: 0.35 (0.06, 1.81)
	24 weeks	Sotagliflozin 200 mg		RR: 0.58 (0.22, 1.49)
	24 weeks	Sotagliflozin 400 mg	RR: 1.72 (0.67, 4.49)	
Severe hypoglycaemic events	52 weeks	Placebo	RR: 1.23 (0.38, 3.79)	RR: 0.67 (0.21, 2.21)
	52 weeks	Metformin	RR: 0.61 (0.08, 4.53)	RR: 0.33 (0.05, 2.58)
	52 weeks	Sotagliflozin 200 mg		RR: 0.54 (0.17, 1.8)
	52 weeks	Sotagliflozin 400 mg	RR: 1.85 (0.56, 5.73)	
Any hypoglycaemic events	No restriction	Placebo	RR: 0.85 (0.42,1.72)	RR: 0.88 (0.48,1.63)
		Metformin	RR: 0.56 (0.2,1.57)	RR: 0.58 (0.22,1.53)

		Sotagliflozin 200 mg	-	RR: 1.03 (0.51,2.12)
		Sotagliflozin 400 mg	RR: 0.97 (0.47,1.96)	-
Severe hypoglycaemic events	No restriction	Placebo	RR: 1.21 (0.72,1.96)	RR: 0.65 (0.35,1.22)
		Metformin	RR: 0.57 (0.24,1.26)	RR: 0.31 (0.12,0.75)
		Sotagliflozin 200 mg	-	RR: 0.54 (0.29,1.03)
		Sotagliflozin 400 mg	RR: 1.86 (0.98,3.4)	-

CFB, change from baseline; CrI, credible interval; REM, random effect model; RR, rate ratio; SH, severe hypoglycaemia.

2.10.3. Strengths and limitations of the NMA

Strengths:

The findings from the NMA suggested that overall sotagliflozin has a comparable efficacy and safety profile to metformin, with some outcomes showing advantages for the 400 mg dose of sotagliflozin. Sotagliflozin 400 mg added to insulin therapy showed superior and clinically meaningful reductions in HbA_{1c} (%) in comparison with insulin and a combination of insulin and metformin at 52 weeks. Consistent with head-to-head inTandem trials data, sotagliflozin plus insulin therapy showed significantly better efficacy versus insulin monotherapy. The findings of this NMA are aligned with the findings of a previously published meta-analysis of SGLT inhibitors (60). Alignment with the published evidence and all possible sensitivity analyses give decent strength and robustness to the current NMA results.

Limitations:

As highlighted during the FA, there are differences in the methodological and clinical aspects of the contributing trials. Hence, NMA results can be confounded and should be interpreted with caution. Further, there is not enough evidence in the network to account for the differences using regression-analysis techniques. However, all sensitivity analyses planned on the basis of methodological, clinical and bias assessment parameters indicated results in line with the base-case analysis. Further, the results of this NMA are in line with those from the previously published meta-analysis results of SGLT inhibitors in combination with insulin in patients with diabetes (60).

2.11. Adverse reactions

2.11.1. Safety overview: results from pooled analyses

The safety of sotagliflozin was evaluated in the three Phase III trials (36-38, 46, 47, 61).

Pooled analyses were performed to evaluate the safety across the Phase III programme. The primary safety pool used to describe common treatment-emergent adverse events (TEAEs) and assess potential risks associated with 200 mg and 400 mg sotagliflozin administration contained the two 52-week Phase III studies (i.e. inTandem1 and inTandem2). A second pool contained all three studies to assess potential risks associated with 400 mg sotagliflozin. Finally, data were pooled from all patients with T1D from Phase II

and three studies. This broad safety pool was used to describe events of special interest (EOSIs), including DKA, hypoglycaemia, volume depletion, renal events, genital mycotic infections, urinary tract infections and diarrhoea for 200 mg and 400 mg sotagliflozin.

Treatment-emergent adverse events

The most common TEAEs (i.e., occurring in ≥2% patients in either sotagliflozin group and more frequent than placebo) in inTandfem1 and inTandem2 through 52 weeks of treatment are summarised by preferred term in Table 2.20.

Overall, in the two 52-week, Phase III trials, TEAEs were frequent and the incidences were similar across treatment groups; TEAEs were reported by 374 patients (71.1%) in the placebo group, 393 patients (75.0%) in the sotagliflozin 200 mg group, and 390 patients (74.3%) in the sotagliflozin 400 mg treatment group.

Study drug-related TEAEs were reported more frequently in sotagliflozin-treated patients than in placebo-treated patients: 106 patients (20.2%) in the placebo group, 167 patients (31.9%) in the sotagliflozin 200 mg group, and 193 patients (36.8%) in the sotagliflozin 400 mg group.

TEAEs were mostly mild or moderate in severity. Severe TEAEs occurred more frequently in sotagliflozin-treated patients in inTandem1 and inTandem2, 37 patients (7.0%) in the placebo group, 50 patients (9.5%) in the sotagliflozin 200 mg group, and 48 patients (9.1%) in the sotagliflozin 400 mg group.

The overall incidence of severe study drug-related TEAEs was higher in sotagliflozin-treated patients in inTandem1 and inTandem2: 11 patients (2.1%) in the placebo group, 19 patients (3.6%) in the sotagliflozin 200 mg group, and 22 patients (4.2%) in the sotagliflozin 400 mg group.

In inTandem1 and inTandem2, a greater proportion of patients treated with sotagliflozin experienced TEAEs leading to study drug discontinuation: 20 patients (3.8%) in the placebo group, 23 patients (4.4%) in the sotagliflozin 200 mg group, and 35 patients (6.7%) in the sotagliflozin 400 mg group. Finally, a total of three patients experienced TEAEs leading to death, all in the placebo group.

Table 2.20. Overall summary of treatment-emergent adverse events through 52 weeks of treatment inTandem1 and inTandem2 (62)

	Placebo (N=526)	Sotagliflozin 200 mg (N=524)	Sotagliflozin 400 mg (N=525)	All sotagliflozin (N=1049)
Patients with TEAEs	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAE	374 (71.1)	393 (75.0)	390 (74.3)	783 (74.6)
Treatment-related TEAEs	106 (20.2)	167 (31.9)	193 (36.8)	360 (34.3)
Severe TEAEs	37 (7.0)	50 (9.5)	48 (9.1)	98 (9.3)
Severe treatment-related TEAEs	11 (2.1)	19 (3.6)	22 (4.2)	41 (3.9)
Treatment-emergent SAEs	37 (7.0)	53 (10.1)	50 (9.5)	103 (9.8)
Treatment-emergent/ treatment-related SAEs	10 (1.9)	18 (3.4)	23 (4.4)	41 (3.9)
TEAEs leading to study drug discontinuation	20 (3.8)	23 (4.4)	35 (6.7)	58 (5.5)
Treatment-related TEAEs leading to study drug discontinuation	12 (2.3)	19 (3.6)	31 (5.9)	50 (4.8)
Any TEAEs leading to death	3 (0.6)	0	0	0

SAE, serious adverse event; TEAE, treatment-emergent adverse event;

A pooled analysis of treatment-emergent EOSI was performed using data from patients in the Phase II and III programmes (Table 2.21). In summary, there was an increased incidence of DKA and mycotic infections at rates similar to those observed with SGLT-2 inhibitors (62). The incidence of volume depletion, a known risk factor for DKA, was low and of mild–moderate severity. Volume depletion did not lead to treatment discontinuation. Diarrhoea attributable to SGLT-1 inhibition in GI tract was observed, but events were generally mild or moderate, transient, and associated with only low rates of treatment discontinuation. There was no increase in the risk of renal events. Major adverse cardiovascular (CV) events occurred infrequently in the inTandem trials and there was no indication of a difference between the treatment and placebo arms. The safety data for GI events, infections, hypoglycaemia and DKA are described and discussed below.

Table 2.21. Overall summary of treatment-emergent investigator-reported events of special interest in Phase II and III trials of sotagliflozin (up to 28 weeks after the end of treatment) (62)

Event No. patients (%)	Placebo (N=1324)	Sotagliflozin, 200 mg (N=559)	Sotagliflozin, 400 mg (N= 321)	All sotagliflozin (N=1915)
At least one treatment-emergent investigator-reported EOSI	1,266 (95.6)	547 (97.9)	1,273 (96.4)	1,854 (96.8)
Volume depletion	8 (0.6)	14 (2.5)	21 (1.6)	35 (1.8)
Genital mycotic infection	30 (2.3)	49 (8.8)	111 (8.4)	161 (8.4)
Urinary tract infection	64 (4.8)	37 (6.6)	58 (4.4)	95 (5.0)
Diarrhoea	46 (3.5)	35 (6.3)	79 (6.0)	114 (6.0)
Pancreatitis	0	0	1 (0.1)	1 (0.1)
Bone fracture	25 (1.9)	15 (2.7)	14 (1.1)	31 (1.6)
Potential drug-induced liver injury	4 (0.3)	2 (0.4)	8 (0.6)	10 (0.5)
Renal event	12 (0.9)	8 (1.4)	13 (1.0)	21 (1.1)
Malignancies of special interest	2 (0.2)	2 (0.4)	4 (0.3)	6 (0.3)
Amputation	0	1 (0.2)	1 (0.1)	2 (0.1)
Venous thromboembolism	0	0	0	0
Myocardial infarction or hospitalisation for unstable angina	3 (0.2)	4 (0.7)	4 (0.3)	8 (0.4)
Stroke	3 (0.2)	1 (0.2)	2 (0.2)	3 (0.2)
Hospitalisation for heart failure	1 (0.1)	2 (0.4)	1 (0.1)	3 (0.2)
Coronary revascularisation	2 (0.2)	4 (0.7)	2 (0.2)	6 (0.3)
Cardiovascular death	2 (0.2)	0	0	0
Documented hypoglycaemia	1261 (95.2)	547 (97.9)	1264 (95.7)	1844 (96.3)
SH and/or hypoglycaemia reported as an SAE	65 (4.9)	31 (5.5)	51 (3.9)	83 (4.3)

EOSI, events of special interest; SAE, serious adverse event; SH, severe hypoglycaemia

2.11.1.1. Gastrointestinal events

GI events (particularly diarrhoea, consistent with other observations for inhibition of SGLT-1 (9, 11)) occurred more frequently in sotagliflozin-treated patients (6.0%) than those receiving placebo (3.5%) in the inTandem programme, with no dose effect for sotagliflozin. However, none of the events of diarrhoea were reported as serious, and most were considered mild and transient. Only one event was reported as severe, occurring in a female patient in the sotagliflozin 200 mg group. Overall, diarrhoea led to study drug discontinuation in just 0.4% of sotagliflozin-treated patients and 0.2% of placebo-treated patients.

2.11.1.2. Genital mycotic infections

Genital mycotic infections (associated with inhibition of SGLT-2 (9, 11)) were observed more frequently in the sotagliflozin arms (8.4%) than in the placebo arms (2.3%). Incidence of genital mycotic infection increased with increased dose of sotagliflozin in both male and female patients, but mostly among women (placebo groups: 0.8% in men vs 3.7% in women; sotagliflozin 200 mg: 2.8% in men vs 15% in women; sotagliflozin 400 mg: 3.5% in men versus 13.3% in women). However, no cases were considered serious and discontinuation rates were low (0.6% for sotagliflozin and 0.2% for placebo).

2.11.1.3. Hypoglycaemia

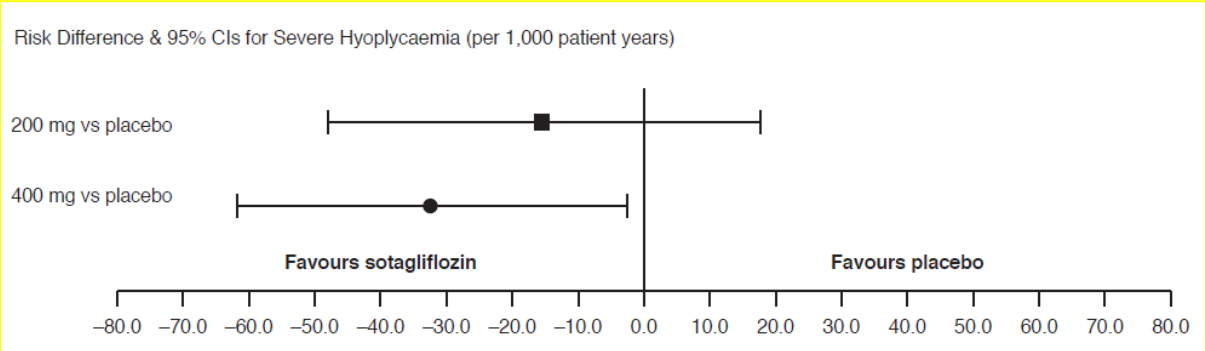
Rates of documented hypoglycaemia were similar between treatment groups overall in the inTandem programme (Table 2.22). Specifically, investigator-reported SH occurred in 56 (4.6%), 30 (5.7%), and 44 (3.6%) patients in the placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg groups, respectively. These data indicate that up-titrating sotagliflozin to 400 mg daily is not accompanied by any increase in risk of SH (Figure 2.12)

Table 2.22. Rates of treatment-emergent, positively adjudicated severe hypoglycaemia (pooled safety analysis of inTandem1, 2 and 3) (62)

	Placebo (N=1229)	Sotagliflozin 200 mg (N=524)	Sotagliflozin 400 mg (N=1224)	All Sotagliflozin (N=1748)
Total number of positively adjudicated events	72	68	58	126
Subjects with at least one event, n (%)	56 (4.6)	30 (5.7)	44 (3.6)	74 (4.2)
Exposure-adjusted incidence rate per 1,000 patient-years (95% CL)	71.97 (53.12, 90.82)	62.50 (40.13, 84.86)	56.75 (39.98, 73.52)	58.95 (45.52, 72.38)
Relative risk (95% CL) versus placebo		0.87 (0.55, 1.35)	0.79 (0.53, 1.17)	0.82 (0.58, 1.16)

CL, confidence limit

Figure 2.12. Risk differences for severe hypoglycaemia (pooled analysis of safety data from inTandem1 and inTandem2) (62)



CI, confidence interval

Analyses were performed to identify potential risk factors for positively adjudicated SH using both descriptive statistics and stepwise logistic regression (Table 2.23). In the stepwise logistic regression, using data from inTandem1 and inTandem2 (the 52-week Phase III studies with insulin optimisation) identified female gender as a risk factor for positively adjudicated SH. The use of sotagliflozin was associated with a dose-related reduction in positively adjudicated SH after adjusting for other covariates in the model. Sotagliflozin 400 mg versus placebo had an odds ratio (OR) of 0.43 [95% confidence limit (CL], 0.231–0.810). Another risk factor identified was baseline HbA_{1c}, which was assessed separately for patients on placebo, sotagliflozin 200 mg, and sotagliflozin 400 mg. All the point estimates were associated with OR <1, meaning that a high value was generally protective. A low HbA_{1c} has been recognised as a risk factor for SH (63).

Table 2.23. Risk factor analysis of treatment-emergent positively adjudicated severe hypoglycaemia: stepwise logistic regression model results using pooled safety data (Phase III studies only) (62)

Predictors	OR (95% CL)
inTandem1 vs inTandem2	1.68 (1.064, 2.661)
Sex (male vs female)	0.61 (0.396, 0.947)
Duration of T1D (<20 years vs ≥20 years)	0.71 (0.448, 1.111)
Sotagliflozin 200 mg vs placebo at mean baseline HbA_{1c} 7.6% (60 mmol/mol)	0.72 (0.434, 1.195)
Sotagliflozin 400 mg versus placebo at mean baseline $HbA_{1c,}$ 7.6% (60 mmol/mol)	0.43 (0.231, 0.810)
Baseline HbA_{1c} (%) in placebo group	0.82 (0.522, 1.286)
Baseline HbA_{1c} (%) in sotagliflozin 200 mg group	0.76 (0.447, 1.290)
Baseline HbA_{1c} (%) in sotagliflozin 400 mg group	0.38 (0.188, 0.759)

CL, confidence limit; HbA_{1c}, glycated haemoglobin; OR, odds ratio; T1D, type 1 diabetes

2.11.1.4. DKA

As described in Section 1.4, episodes of DKA are an issue of both the disease and its treatment via inhibition of SGLT-2, the mechanism of which is currently unknown (9, 11). The criteria for a confirmed diagnosis of DKA in the inTandem1, inTandem2 and inTandem3 trials was based on evidence of anion-gap metabolic acidosis-related to excessive ketone production without a satisfactory alternative cause for anion-gap acidosis (36-38). The diagnostic criteria were provided to all investigators, but a final diagnosis of metabolic acidosis, including DKA, was made by the adjudication committee. The terms used to identify possible DKA in the trials are shown in Table 2.25.

Table 2.24. Terms used to identify possible diabetic ketoacidosis (62)

Trigger terms typically associated with elevated BHB	Trigger terms that may not be associated with elevated BHB
• Acetonemia • Blood ketone body • Blood ketone body increased • Blood ketone body present • Diabetic ketoacidosis • Diabetic ketoacidotic hyperglycaemic coma • Ketoacidosis • Ketosis • Urine ketone body • Urine ketone body present	• Acidosis • Acidosis hyperchloraemic • Diabetic coma • Diabetic hyperglycaemic coma • Diabetic metabolic decompensation • Hyperglycaemic coma • Hyperglycaemic seizure • Hyperglycaemic unconsciousness • Lactic acidosis • Metabolic acidosis • Renal tubular acidosis • Uremic acidosis

BHB, beta-hydroxybutyrate.

Overall, sotagliflozin was associated with a numerically greater risk of DKA compared with placebo (Table 2.26). The reduction in insulin dose demonstrated in the inTandem trials may also contribute to cases of DKA and may in part explain the higher rates of DKA seen in CSII patients (38). As with SH, DKA occurred most frequently among those patients receiving sotagliflozin and who were not achieving glycaemic targets. However, rates of discontinuation due to DKA in the overall safety population was less than 2%.

Table 2.25. Rates of treatment-emergent, positively adjudicated metabolic acidosis (pooled safety analysis of inTandem1, 2 and 3) (62)

	Placebo (N=1307)	Sotagliflozin 200 mg (N=559)	Sotagliflozin 400 mg (N=1302)	All Sotagliflozin (N=1896)
Total number of positively adjudicated events	9	18	46	64
Treatment-related events	4	10	25	35
Severe events	2	12	31	43
Serious events	7	17	44	61
Events leading to study drug interruption	5	11	19	30
Events leading up to study drug discontinuation	1	4	20	24
Exposure-adjusted incidence rate per 1,000 patient-years (95% CL)	11.32 (3.92, 18.72)	36.87 (19.83, 53.90)	57.99 (41.23, 74.76)	49.66 (37.49, 61.82)
Relative risk (95% CL) vs placebo	-	3.26 (1.48, 7.60)	5.12 (2.59, 11.09)	4.39 (2.26, 9.36)

CL, confidence limit

Of the 64 positively adjudicated DKA cases, 24 led to study drug discontinuation (one on placebo, four on sotagliflozin 200 mg, and 19 on sotagliflozin 400 mg). It should be noted that most patients chose to resume treatment (there were five interruptions in the placebo group, 11 in the sotagliflozin 200 mg group and 19 in the sotagliflozin 400 mg group). There were no fatal cases of DKA in the T1D programme.

A manual review of positively adjudicated DKA supported and extended the understanding of DKA risk. For example, concomitant illness such as infections, injuries or surgery were reported in approximately 40% and symptoms of nausea and vomiting were reported in approximately 30% of the cases. Around 60% of the positively adjudicated DKA cases

occurred in patients using insulin pumps and one in three DKA cases was associated with pump infusion malfunction and interruption of insulin dosing. Daily insulin dose reductions of ≥20% also appeared to be associated with increased risk of DKA.

Stepwise logistic regression revealed subgroups of sotagliflozin 400 mg- and placebo-treated patients at elevated risk of DKA (Table 2.27). Prior history of DKA or ketosis, higher baseline beta-hydroxybutyrate (BHB) values, use of CSII, and higher baseline HbA_{1c} were identified as risk factors for positively adjudicated DKA and serious acidosis-related events. Treatment with sotagliflozin 400 mg was associated with positively adjudicated DKA after adjusting for other covariates in the model (OR=9.21, 95% CL 3.596 to 23.583). There were no consistent trends in DKA incidence rates by baseline estimated glomerular filtration rate (eGFR), indicating that sotagliflozin will not require dose adjustment for individuals with kidney disease.

The relationship between DKA and use of CSII in the inTandem programme likely exists because of pump-related issues. The elevated risk for DKA in patients using CSII in inTandem3 was deemed to be due to pump-related issues leading to interrupted insulin dosing (38).

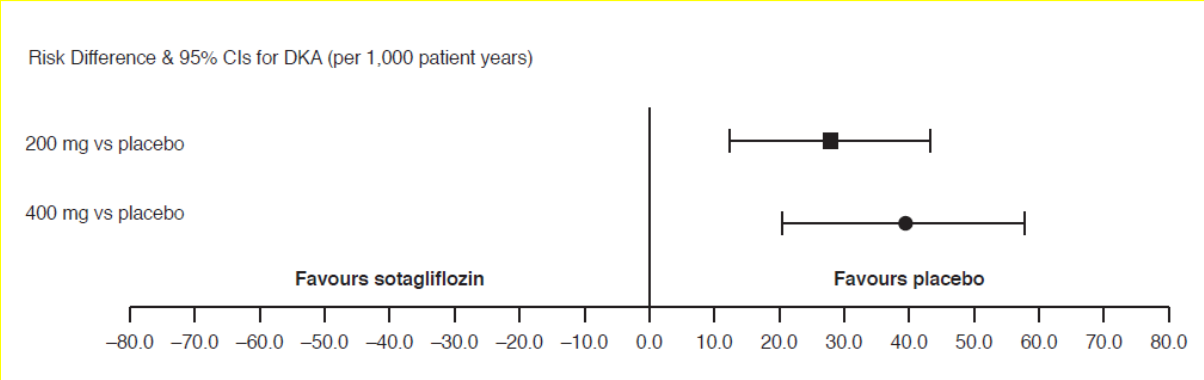
DKA risk can be reasonably mitigated through education on appropriate event surveillance, early identification and aggressive treatment. In this regard, interviews of patients in inTandem1 indicated that ketone monitoring was accepted by patients as simple and feasible (46).

Table 2.26. Risk factors for treatment-emergent positively adjudicated diabetic ketoacidosis (pooled analysis of sotagliflozin 400 mg only and placebo) (62)

Predictors	OR (95% CL)
Sotagliflozin 400 mg vs placebo	9.21 (3.596, 23.583)
Prior history of DKA or ketosis vs not	4.19 (1.741, 10.071)
Baseline BHB (mmol/L)	5.23 (1.548, 17.666)
CSII v not CSII	2.25 (1.194, 4.230)
Baseline HbA_{1c} (%)	1.43 (1.053, 1.953)
Age at study entry (years)	0.98 (0.953, 0.998)
Baseline BMI (kg/m^2)	0.95 (0.895, 1.016)
Baseline urine ketones	0.47 (0.159, 1.383)
inTandem1 vs inTandem3	0.87 (0.401, 1.871)
inTandem2 vs inTandem3	0.62 (0.273, 1.400)

BHB, beta-hydroxybutyrate; BMI, body mass index; CL, confidence limit; CSII, continuous subcutaneous insulin infusion; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; OR, odds ratio.

Figure 2.13. Risk differences for diabetic ketoacidosis (pooled analysis of safety data from inTandem1 and inTandem2) (62)



CI, confidence interval; DKA, diabetic ketoacidosis

It has been suggested that the DKA rates in the inTandem3 trial are numerically higher than those reported in the DEPICT trial in cross-study comparisons (64). However, as described by Garg and Strumph (65), these differences are explained by differences in adjudication criteria. In DEPICT, only definite cases were positively adjudicated, whereas in inTandem3, DKA cases classified 'with certainty' and 'probably' were categorised as such. Recalculating DKA rates based on only excluding 'unlikely' cases led to numerically equivalent placebo-adjusted incidences in the two trials (65), supporting the view that DKA seen in the inTandem programme is a class effect and will be common to all SGLT-2 inhibitors.

2.12. Ongoing studies

As of February 2019, there were no ongoing trials of adjunctive sotagliflozin in adults with T1D and none are planned at this time.

2.13. Innovation

Sotagliflozin represents a breakthrough in the management of T1D as an insulin−independent, adjunctive therapy. Insulin has been the mainstay of treatment since the 1920s with advancements only with regards to delivery and formulation.

Sotagliflozin is a unique oral tablet with dual SGLT-1 and SGLT-2 mechanism of action – SGLT-2 inhibition results glucose reduction through action on the kidneys (increased glycosuria) while SGLT-1 inhibition in the gut results in blunting or delay of PPG, offering a complementary insulin-independent way to reduce glucose after meals. In the inTandem2 study, sotagliflozin treatment reduces HbA_{1c} resulting in better mean glucose levels than insulin alone in a trial population similar to the current UK T1D population (i.e., older age

with significant proportions of overweight/obese patients with high SBP and uncontrolled blood glucose levels) (37). In addition, more patients treated with sotagliflozin achieved HbA_{1c} targets of <7% with the additional benefit of improved glycaemic variability, demonstrated by a greater time in optimal glucose range. At 1 year, one in five sotagliflozin-treated patients achieved HbA_{1c} <7.0% without SH, DKA, or weight gain compared with 1 in 13 patients treated with placebo. Beyond glycaemic benefits, sotagliflozin also reduced SBP and weight in adults with T1D compared with insulin alone, which may help to reduce longer term CV risk, as well as improving PROs associated with HRQoL.

The safety profile is as expected for its mode of action, with manageable DKA risk and no increase (with potential reductions) in problematic hypoglycaemia. As a once daily oral tablet, sotagliflozin offers a convenient, effective new treatment strategy that can limit the daily treatment burden to patients while providing glycaemic and non-glycaemic benefits

2.14. Interpretation of clinical effectiveness and safety evidence

Despite advances in insulin therapy, maintenance of good glycaemic control is difficult, and the disease profile is still characterised by short-term fluctuations in blood glucose levels. In the UK, <10% of patients meet the NICE-recommended target for adequate glycaemic control (HbA_{1c} ≤6.5%). Fluctuations in daily blood glucose levels (e.g. due to missed insulin doses, infection, stress or postprandial hyperglycaemia) are common and appear to have an independent role in the aetiology of diabetes-related complications (2). One of the reasons for this is because exogenous insulin delivery cannot reproduce the workings of the pancreas and the finely calibrated release of insulin in the body. In addition, insulin treatment is limited by its association with weight gain and (severe) hypoglycaemia. The fear of these side-effects may promote suboptimal dosing of insulin, which can lead to increased risk of DKA, a life-threatening complication associated with excess mortality (9, 11). Another relevant factor of increasing importance is that the patient profile is changing. Most patients with T1D tend to be closer to the profile of patients with T2D in which cardiovascular disease (CVD) is a more common comorbidity as patients live longer.

Therefore, successful T1D management may require more than insulin, through non-insulin pathways, as well as a focus on outcomes beyond traditional HbA_{1c} measures. T1D is a complex condition and management of blood glucose levels needs a multiplicity of approaches to manage the disease and to improve the quality of life for those who suffer the condition.

Data from the inTandem Phase III programme described in this submission demonstrate that sotagliflozin offered statistically significant and clinically meaningful reduction in HbA_{1c} from baseline and on top of optimised insulin in adults with inadequately controlled T1D. These effects persisted to Week 52 in the inTandem1 and inTandem2 studies. Subgroup analyses by age, sex, race, diabetes duration or geographic region confirmed the efficacy of both doses in all subgroups of sufficient sizes. Further, similar efficacy was demonstrated in patients treated with CSII or MDI.

The greatest decreases in HbA_{1c} were observed among patients with baseline HbA_{1c} values >8.5% (69 mmol/mol). Efficacy was demonstrated in both patients with mild renal impairment and patients with normal renal function and eGFR was not found to be a statistically significant predictor of the responses in any efficacy parameters in the population of patients examined.

Treatment with sotagliflozin resulted in reduced glycaemic variability and increasing time−in−range, an important emerging outcome in T1D. Compared with placebo, patients treated with 200 mg and 400 mg sotagliflozin spent respectively, 8.4% (p=0.044) and 10.4–13.4% (p<0.001) more time with glucose values in the target range (3.9–10.0 mmol/L) with potentially fewer fluctuations in blood glucose levels (36, 37). The increased time in range that was observed in the sotagliflozin groups was associated with decreased time spent in the hyperglycaemic range (>10.0 mmol/L). The percentage of time spent in the hypoglycaemic range (<3.9 or <3.0 mmol/L) was essentially unchanged, which is of clinical significance (36, 37). A study using the DCCT data set found that occurrence of biochemical hypoglycaemia was associated with increased risk of SH. The risk of an SH event during the 3-month period was more than two-fold greater when there was at least one hypoglycaemic blood glucose measurement. The risk was further increased when there was more than one hypoglycaemic blood glucose measurement (51). Therefore, it is important to avoid hypoglycaemic glucose levels as much as possible.

The 2-hour PPG levels following a standardised mixed meal were significantly reduced in both study arms compared to insulin only arm: 22.80 mmol/L (p=0.009) for 200 mg sotagliflozin and 24.20 mmol/L (p<0.001) for 400 mg sotagliflozin. This reflects clinically meaningful reductions in PPG and provide evidence in support of sotagliflozin blunting PPG excursions; with sotagliflozin treatment, glycaemic goals can be achieved with less glycaemic variability with lower insulin doses. Other endpoints assessed in the CGM sub-

study indicated a decrease in glucose variability as measured by mean daily glucose and mean amplitude of glucose excursion.

The reduction in HbA_{1c} (<7.0%) with sotagliflozin was achieved without SH and DKA. The net benefit outcome (proportion of patients who achieve the target goal of HbA_{1c} at <7.0% with no episodes of SH or DKA over the 24-week period) was designed to reflect a clinically relevant summation of the major expected benefits and risks of sotagliflozin therapy in T1D patients. Twice as many patients receiving sotagliflozin than placebo achieved the composite net benefit endpoint in inTandem2. The difference in inTandem1 was slightly less but was still statistically significant.

Benefits of sotagliflozin treatment beyond glycaemic endpoints were also demonstrated in the Phase III programme. Sotagliflozin treatment led to a decrease in body weight of around 1.6–2.7kg compared with an increase in body weight in the placebo group (36-38) which was sustained at 52 weeks (36, 37). Considering a mean BMI of approximately 28 kg/m^2 at baseline, achieving a weight loss of 3% to 5% is clinically relevant and associated with significant benefits (66). Sotagliflozin weight loss/BMI benefits are comparable to those observed with adjunctive metformin; in a recent meta-analysis of RCTs, metformin was associated with reductions in BMI (−1.14, 95% CI −2.05 to −0.24; p=0.01) (67). However, there is no clear evidence that metformin improves HbA_{1c}.

In addition to the intrinsic beneficial effect of sotagliflozin treatment, the decrease in body weight is also likely due to the mild but significant decrease in insulin doses, and especially in daily bolus doses. The decrease in daily bolus insulin dose was statistically significant and assessed as clinically meaningful with respect to risk for hypoglycaemia i.e. glucose control without unnecessarily high insulin doses (36-38).

A beneficial effect on SBP was also observed in the overall population, with larger reductions in SBP observed in patients with baseline SBP ≥130 mm Hg. For all these secondary efficacy endpoints, the effect was numerically greater for the sotagliflozin 400 mg dose compared with 200 mg.

CVD is a major cause of mortality in T1D and evidence of its risks and management is often extrapolated from studies in T2D patients (32). Although there are currently no data available describing CV outcomes with sotagliflozin in T1D, meta-analyses and real-world evidence suggest that the results of the EMPA-REG OUTCOME trial can be applied to other

agents within the class and also to patients with T1D and risk factors associated with CVD (68-71).

In terms of patient benefits, the was significant improvement in treatment satisfaction (measured by DTSQ) and disease distress (measure by DDS2) with sotagliflozin treatment.

These potential benefits in terms of microvascular complications, CV risk and SH should be contrasted with an understanding of DKA morbidity. In a pooled analysis of 52-week data from inTandem1 and inTandem2, the incidence of DKA was increased in a dose-dependent manner for sotagliflozin (2.9% and 3.8% for sotagliflozin 200 mg and 400 mg, respectively) compared with placebo (0.2%) (41). There were no deaths due to DKA in the sotagliflozin programme. DKA occurred more frequently in patients using CSII and was often attributed to pump-related issues in these patients (41). The risk of DKA can be mitigated by careful monitoring of BHB (41) and further details can be found in the Summary of Product Characteristics detailing the recommended steps to assess the DKA risk in patients initiating treatment or titrating dose on sotagliflozin.

Conclusion

Overall, sotagliflozin once daily before the first meal of the day on top of insulin, resulted in consistent and sustained glycaemic control, reduced glycaemic variability and increased time in range. Non-glycaemic benefits such as weight loss and reduced SBP equates to reduced cardiovascular risk. PROs were also improved, possibly due to patients spending more time in glycaemic target range and experiencing less glycaemic variability. The safety profile of sotagliflozin also supports its use in adult patients with T1D as an adjunct to insulin in a setting of education and monitoring for DKA, a class-related risk of SGLT inhibitors (34).

Taken together, these outcomes address important unmet needs in the management of T1D in adults in the UK.

3. Cost-effectiveness

Summary

- The cost-effectiveness of sotagliflozin 200 mg was evaluated using the CORE Diabetes Model, a validated and externally audited, patient-level, discrete, event-simulation model for populations with type 1 diabetes (T1D).
- Compared to standard of care (SoC) alone, the incremental cost-effectiveness ratio (ICER) of sotagliflozin was £8,578 per quality of life-year (QALY) gained. The results were found to be robust in probabilistic sensitivity analyses with an ICER value of £8,307 per QALY gained.
- The reduced risk of hypoglycaemia with sotagliflozin was shown to be the biggest driver of QALY benefit over placebo. BMI also played a role in driving improved quality of life.
- Compared to metformin, sotagliflozin was found to be dominant, having lower costs and resulting in greater QALYs.
- For patients with T1D, when insulin alone does not provide adequate glycaemic control, sotagliflozin as an adjunctive therapy was shown to be a cost-effective use of NHS resources compared with current standard of care.
- The cost-effectiveness results were validated using the PRIME Diabetes Model. Both models produced ICERs for sotagliflozin versus insulin below £20,000 per QALY.

3.1. Published cost-effectiveness studies

Appendix J details the methods and results of published cost-effectiveness analyses available for the technology and/or the comparator technologies.

3.1.1. Identification of studies

3.1.1.1. Systematic literature review of economic evaluations of non-insulin medicines

Methods

A systematic literature review (SLR) was undertaken to identify and summarise published cost-effectiveness analyses (CEAs) or cost-utility analyses (CUAs) for adult patients with T1D. The review could identify publications which facilitate the development of an economic

model representing the important clinical impacts of sotagliflozin and its direct comparators. Full details are described in Appendix K.

Searches were performed in MEDLINE, Embase, EconLIT, the NHS Economic Evaluation Database and the Centre for Reviews and Dissemination Health Technology Assessment (HTA) Database, through hand searches of relevant conference proceedings, and from publicly available information from NICE. Recursive searches of identified review papers were performed, and any additional relevant economic evaluations identified in the process were screened for inclusion.

Table 3.1 Population, intervention, comparator, outcomes and study design (PICOS) eligibility criteria

PICOS	Inclusion criteria	Exclusion criteria
Participants	Adult (≥18 years) patients with T1D	T2D, adolescents with T1D
Interventions/ comparators	Review of the landscape of the published literature on the models and methods implemented in cost-effectiveness and cost-utility analysis (CEA-CUA) studies of: • Sotagliflozin • Any approved non-insulin medication as an adjunct therapy to insulin • Insulin therapies	
Outcome measures	Studies must report an ICER and may report additionally the following: • Costs (total and/or incremental) • QALYs gained (total and/or incremental) Other natural effectiveness measures, e.g. life-years gained (total and/or incremental)	
Study design	Studies must be one of the following: • Full economic evaluations • CEAs • CUAs	Other types of economic models, including cost–benefit, cost-minimisation, budget impact analyses and partial evaluations

CEA, cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; PICOS, population, intervention, comparator, outcomes and study design; QALY, quality-adjusted life-year; T1D, type 1 diabetes; T2D, type 2 diabetes.

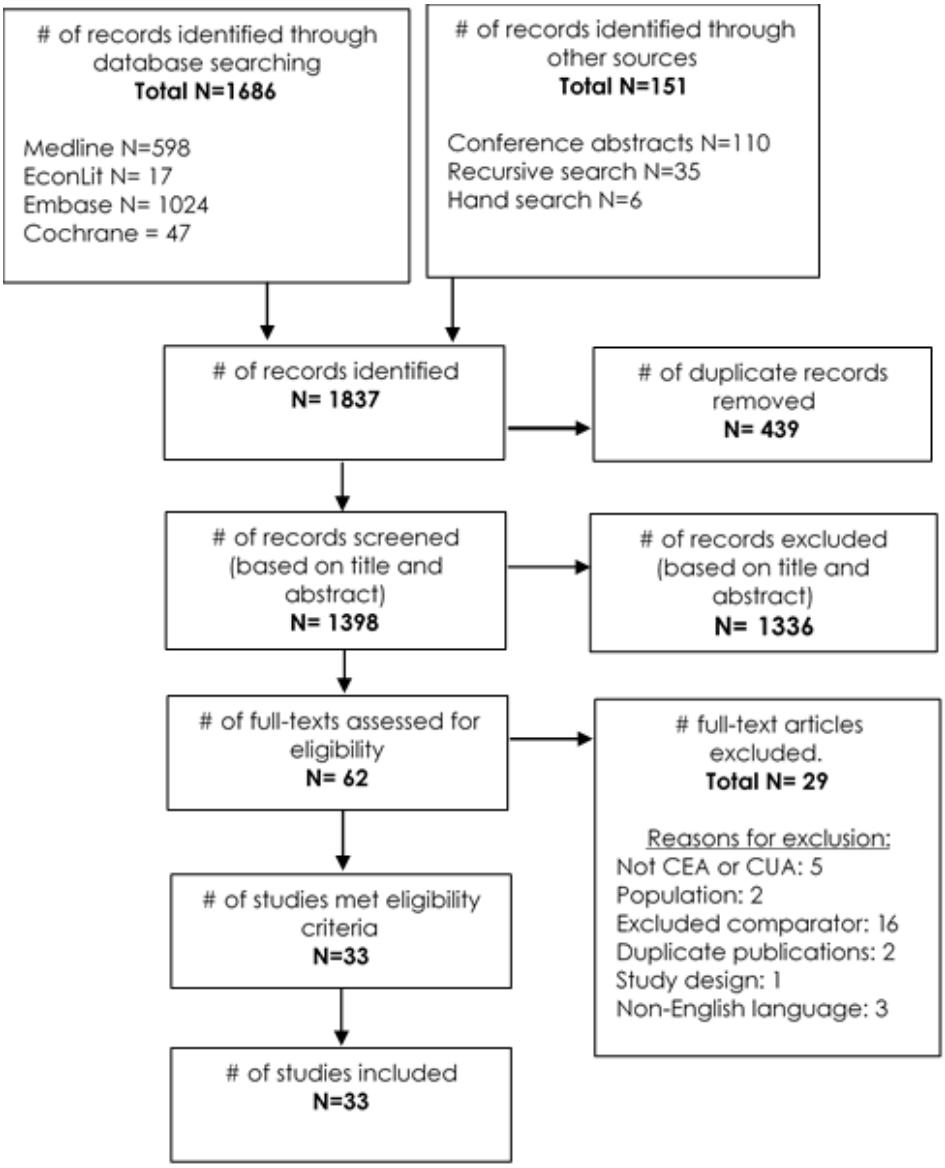
Results

A total of 33 unique CEA or CUA studies were included that examined drug therapies for adult T1D patients. These 33 studies included 22 full-text publications and 11 abstracts. Of the included evaluations, 11 used the CORE (Centre for Outcomes Research and Evaluation; Basel, Switzerland) Diabetes Model [also reported as the IQVIA (formerly IMS) CORE Diabetes Model (CDM)] with a European national health payer perspective. There

were 22 papers reporting a long-term horizon; 10 evaluations used a short-term (1-year) horizon that focused on prevention of hypoglycaemia and the short-term effects of insulin choice. The models with a short time horizon are less able to represent all clinical and cost impacts of treatment, particularly those associated with later-stage complications.

The CDM was the most-reported single model in this review. The SLR also identified the PRIME model.

Figure 3.1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the systematic literature review insulin relevant economic evaluation



CEA, cost-effectiveness analysis; CUA, cost-utility analysis.

3.2. Economic analysis

3.2.1. Model overview

Based on the results of the SLR, the base-case cost-effectiveness of sotagliflozin 200 mg and long-term projections of clinical outcomes and costs were evaluated using the CDM (72).

The CDM is a computer simulation model developed to determine the long-term health outcomes and economic consequences of interventions in T1D and T2D (73, 74). The model is accessible on a licensed basis over the internet. It is a non-product-specific diabetes policy analysis tool that performs real-time simulations considering intensive or conventional insulin therapy, oral antidiabetic drugs, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications and multi-factorial interventions.

The model has been used extensively to demonstrate the cost-effectiveness of products launching in T1D and T2D and is robustly validated through both external validation studies (e.g. through participation in the Mount Hood Challenge) and internal update and review. Since the first publication and validation of the CDM in 2004, (73) there have been a number of major updates to the model in response to evolving datasets and feedback from both peer review and HTA submission bodies. The current version of the model is version 9.0 (74).

The SLR also identified the PRIME model as an option to evaluate the cost-effectiveness of sotagliflozin. The PRIME Diabetes Model is a validated and externally audited, patient-level, discrete, event-simulation model for populations with T1D. The PRIME model was used to validate the results from the CDM. Full details on the model structure are available on request.

3.2.2. Conceptualisation of the decision problem

The economic evaluation consists of analyses of the cost-effectiveness of sotagliflozin in adults with T1D who are not adequately controlled on insulin treatment in the UK. Clinical evidence is presented for the full marketing authorisation for the 200 mg dose in the base-case as the 400 mg tablet will not be available at the time of launch in the UK. This economic evaluation is to support the use of sotagliflozin in clinical practice in England and Wales as reported below.

Patients were simulated to receive sotagliflozin 200 mg as an add-on to SoC based on clinical data from head-to-head comparisons in inTandem2. Treatment effects [e.g. decreases in glycated haemoglobin (HbA_{1c}), body mass index (BMI), systolic blood pressure (SBP), lipids and other physiological parameters] in the CDM were applied in the first year of treatment. An annual progression of these parameters was applied in subsequent years in alignment with the Diabetes Control and Complications Trial (DCCT)/ Epidemiology of Diabetes Interventions Complications (EDIC) long-term findings (7), alternative T2D risk equations if not available in T1D, or assumed zero in the case of no evidence. The current set of analyses assumes a 5-year duration of initial treatment, following which all patients switch to insulin alone (SoC). The 5-year duration of treatment is assumed to hold in combination therapy (i.e. sotagliflozin 200 mg + SoC and metformin + SoC). This assumption is explored in a sensitivity analysis (2-year treatment effect) and is consistent with previous sodium-glucose co-transporter type-2 NICE submissions in T2D (75).

Upon initial treatment discontinuation, the incremental differences in HbA_{1c}, BMI and SBP are abolished (i.e. intervention and metformin + SoC arms are set to be equal to the SoC arm). HbA_{1c} and BMI maximum levels were applied, as a lifetime increase in HbA_{1c} and BMI could lead to levels that are not clinically plausible. The following cap (maximum) values were applied:

- HbA_{1c}: After the initial treatment effect, HbA_{1c} values where allowed to naturally progress until patients reached their original baseline value, which represents both the initial starting point and the mean value of T1D patients in the UK (76). The final cap was set at 8.7%, which means a slight positive deviation of 0.1% was allowed, this to allow the treatment effect of the control (placebo + SoC) to take place, since a positive increase in HbA_{1c} values was shown after one year.

- BMI: 35 kg/m^2 as cap value, following the definition of class 2 obesity (77).

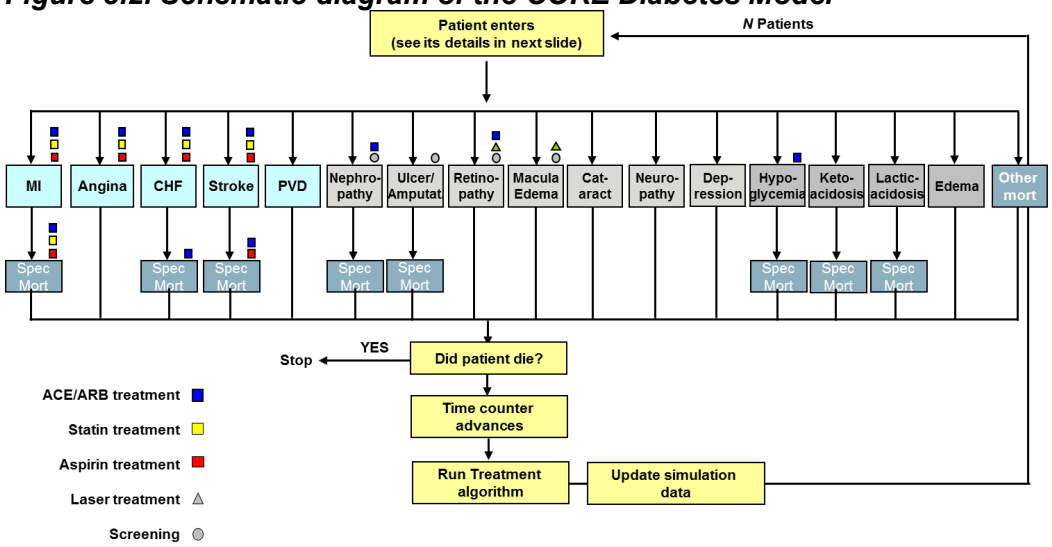
For the comparison to metformin the treatment effects from the NMA was used to inform the economic evaluation. According to the CPRD analysis metformin is not widely used in clinical practice nor is it licensed for T1D. Therefore, we do not consider metformin a relevant comparator, we report only the main results in this submission. Further details can be found in Appendix K.

3.2.3. Model structure and parameters

3.2.3.1. Model structure

Within the CDM, disease progression is based on a series of inter-dependent Markov sub-models that simulate progression of disease-related complications [angina, myocardial infarction (MI), congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation] and other causes of mortality. The model is a fixed-time increment (annual) stochastic simulation with each sub-model using time, state and diabetes type dependent probabilities. Monte Carlo simulations are performed at the individual patient-level using tracker variables to accommodate complex interactions between sub-models. The progression of relevant physiological parameters (e.g. HbA_{1c}, SBP, lipids and BMI) is simulated on the basis of long-term epidemiological data, and event risk is constantly updated on the basis of these risk factors. The model facilitates interconnectivity and interaction between the modelled complications, representing the complex and varied sequelae of diabetes. An overview of the treatment pathway considered in the CDM is illustrated in Figure 3.2. Details of risk equations for each sub-models are reported in CDM version 9 (78).

Figure 3.2. Schematic diagram of the CORE Diabetes Model



ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; CHF, chronic heart failure; MI, myocardial infarction; PVD, posterior vitreous detachment.

To run simulations, the model creates a set, or cohort, of individual patients in which each patient is associated with a set of characteristics that define them [e.g. age, age at diagnosis of T1D, gender, BMI, HbA_{1c}, SBP, total cholesterol, high-density lipoprotein cholesterol

(HDL-C) and smoking status]. During simulations, treatment-specific effects on patient characteristics of HbA_{1c}, SBP, BMI, HDL-C and total cholesterol, as well as adverse event rates for hypoglycaemia and ketoacidosis, can be applied. The model is user-editable in terms of costs and utility weights used for any given set of simulations.

Clinical and economic outcomes (means and standard deviations) are calculated within the model using a non-parametric bootstrapping approach. This process simulates the lifetime progression of diabetes in a cohort of hypothetical patients repeating the process over numerous simulations. In the base-case analyses, second-order uncertainty is not applied, and stability of outcomes is reached through a run of 1,000 patients through 1,000 iterations (74). The model reports costs, life expectancy, quality-adjusted life-year (QALY), cumulative incidence of all modelled diabetes complications, mean hypoglycaemia and ketoacidosis rates in each simulation arm, along with differences in cost, life expectancy and QALY outcomes between simulation arms and the incremental cost-effectiveness ratio (ICER).

Key features of the economic analysis are summarised in Table 3.2 in comparison with the CEA published by NICE guidelines NG17 (6).

Table 3.2. Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	NG17	**Chosen values**	**Justification**
Diabetes model used	CORE Diabetes Model	CORE Diabetes Model	Up-to-date T1D specific model, published and available to NICE
Time horizon	80 years	60 years	60 years is long enough to capture relevant differences in outcomes across strategies
Discount rate	3.5% annually	3.5% annually	Recommended discount rate for the UK setting
Treatment waning effect	Not applicable (as patients were assumed to continue therapy with insulin regimens)	Sotagliflozin/placebo therapy for 5 years assumed. No treatment waning effect included. All treatment differences abolished after Year 5 as patients return to baseline of 8.7% HbA_{1c}	It is assumed that treatment benefit on sotagliflozin persists while on therapy. No legacy benefit of sotagliflozin is assumed after 5 years

Factor	Previous appraisals	Current appraisal	
Long-term HbA_{1c} progression	Increased by 0.045% in line with DCCT data	Increased by 0.045% in line with DCCT data	Analogous approach to NG17. Varying HbA_{1c} assumption was investigated in sensitivity analysis
Source of utilities	Published sources	Updated published sources	Analogous approach to NG17
Source of costs	Published sources (generally NHS reference costs)	Updated published sources (generally NHS reference costs)	Analogous approach to NG17

NG17, Type 1 diabetes in adults: diagnosis and management (6)
DCCT, Diabetes Control and Complications Trial; EAG, external assessment group; HbA_{1c}, glycated haemoglobin; T1D, type 1 diabetes.

3.2.3.2. Time horizon, perspective and discount rates used

A time horizon of 60 years was used in the base-case as this was deemed sufficient to consider lifetime costs and outcomes. Costs and quality-adjusted life-years (QALYs) were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and incremental analysis.

3.2.3.3. Intervention technology and comparators

The analysis comprised a comparison of sotagliflozin 200 mg + SoC versus a SoC alone.

A secondary analysis comparing sotagliflozin 200 mg + SoC to metformin + SoC was also included. This analysis incorporated data from the NMA (see Section 2.10).

3.2.4. Model inputs

3.2.4.1. Patient population

For the base-case analysis, a simulated population considered to be representative of adults with T1D in the UK was derived primarily from National Diabetes Audit data described in the cost-effectiveness evaluation supporting NICE Guideline NG17 (6). The population cohort was 56.7% male, with a starting age of 42.98 years. Patients had been diagnosed with diabetes for a mean of 16.92 years, with a mean HbA_{1c} level of 8.60% at baseline. The mean baseline BMI was 27.09 kg/m^2. A summary of the baseline characteristics and complication rates used in the base-case analyses is outlined in Table 3.3.

Table 3.3. Baseline characteristics of the simulated cohort based on National Diabetes Audit data

Characteristic	Mean	SD	Source
Patient demographics			
Start age (years)	42.980	19.140	DCCT (79)
Duration of diabetes (years)	16.920	13.310	NDA (76)
Male (proportion)	0.567	–	NDA (76)
Baseline risk factors			
HbA_{1c} (%)	8.600	4.000	NDA (76)
SBP (mmHg)	128.270	16.070	NDA (76)
DBP (mmHg)	80.000	0.000	Default CDM
Total cholesterol (mg/dL)	176.500	33.000	DCCT (79)
HDL-C (mg/dL)	50.250	13.000	DCCT (79)
LDL-C (mg/dL)	109.750	29.000	DCCT (79)
Triglycerides (mg/dL)	81.500	41.000	DCCT (79)
BMI (kg/m^2)	27.090	5.770	NDA (76)
eGFR ($mL/min/1.73\ m^2$)	77.500	0.000	Default CDM
Haemoglobin (g/dL)	14.500	0.000	Default CDM
WBC ($\times 10^6$/mL)	6.800	0.000	Default CDM
Heart rate (bpm)	72.000	0.000	Default CDM
WHR	0.900	0.000	Default CDM
uACR (mg/mmol)	3.100	0.000	Default CDM
Serum/creatinine (mg/dL)	1.100	0.000	Default CDM
Serum/albumin (g/dL)	3.900	0.000	Default CDM
Proportion smokers	0.220	–	NDA (76)
Cigarettes/day	12.000	–	ONS, 2012 (80)
Alcohol consumption (oz/week)	9.000	–	WHO 2011 (77)
Racial characteristics			
White	0.920	–	NDA (76)
Black	0.030	–	NDA (76)
Hispanic	0.000	–	Assumption
Native American	0.000	–	Assumption
Asian/Pacific Islander	0.050	–	NDA (76)
Baseline cardiovascular complications			
MI	0.003	–	Health Survey for England 2011 (81)
Angina	0.004	–	Health Survey for

Characteristic	Mean	SD	Source
			England 2011 (81)
Peripheral vascular disease	0.000	–	Assumption
Stroke	0.003	–	Health Survey for England 2011(81)
Congestive heart failure	0.000	–	Assumption
Atrial fibrillation	0.000	–	Assumption
Left ventricular hypertrophy	0.000	–	Assumption
Baseline renal complications			
Microalbuminuria	0.181	–	NDA (76)
Gross proteinuria	0.000	–	Assumption
End-stage renal disease	0.000	–	Assumption
Baseline retinopathy complications			
Background diabetic retinopathy	0.0000	–	Assumption
Proliferative diabetic retinopathy	0.0000	–	Assumption
Severe visual loss	0.0000	–	Assumption
Baseline macular oedema			
Macular oedema	0.000	–	Assumption
Baseline cataract			
Macular cataract	0.000	–	Assumption
Baseline foot ulcer complications			
Uninfected ulcer	0.000	–	Assumption
Infected ulcer	0.000	–	Assumption
Healed ulcer	0.000	–	Assumption
History of amputation	0.000	–	Assumption
Baseline neuropathy			
Neuropathy	0.049	–	DCCT (79)
Baseline depression			
Depression	0.210	–	Hopkins, et al. 2012 (82)

BMI, body mass index; CDM, CORE Diabetes Model; DCCT, Diabetes Control and Complications Trial; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; ONS, Office for National Statistics; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell count; WHR, waist-to-hip ratio; uACR, urine albumin-to-creatinine ratio.

Additional simulations were also undertaken to evaluate long-term outcomes in the population of the inTandem2 trial, as summarised in Table 3.4. Of the three Phase III registration trials on sotagliflozin in T1D, inTandem2 was selected to inform the cost-effectiveness evaluation as the study was conducted across 17 countries in Europe and,

therefore, was considered more relevant to the UK setting than inTandem1 or inTandem3, which were conducted in North America and globally, with the latter only investigating the 400 mg dose of sotagliflozin.

The two populations in the NDA and in inTandem2 were similar in terms of age and duration of diabetes. The population cohort of the inTandem2 trial was 51.9% male with a mean starting age of 41.23 years. Patients had been diagnosed with diabetes for a mean of 18.4 years at baseline, with a mean HbA_{1c} level of 7.75% at baseline. Mean baseline BMI was 27.77 kg/m^2. Mean HbA_{1c} was 8.3% at screening, which is closer to the UK average. At baseline, HbA_{1c} was lower in the trial population (~7.7%) than in the NDA. This is likely due to the 6-week insulin optimisation period following recruitment. A summary of the baseline characteristics and complication rates is outlined in Appendix L.

The two populations in the NDA and in inTandem2 were similar in terms of age and duration of diabetes. The population cohort of the inTandem2 trial was 51.9% male with a mean starting age of 41.23 years. Patients had been diagnosed with diabetes for a mean of 18.4 years, with a mean HbA_{1c} level of 7.75% at baseline. Mean baseline BMI was 27.77 kg/m^2 and mean HbA_{1c} was 8.3% at screening, which is closer to the UK average. At baseline, HbA_{1c} was lower in the trial population (~7.7%) than in the NDA. This is likely due to the 6-week insulin optimisation period following recruitment. A summary of the baseline characteristics and complication rates is outlined in Appendix L.

3.3. Clinical parameters and variables

For the modelling analysis, the intervention and comparator treatments were associated with changes from baseline in risk factors applied in the first year of the simulation and event rates applied for the duration of therapy. Changes from baseline in risk factors for the base-case were derived from the inTandem2 trial.

InTandem2 was a Phase III, randomised, double-blind trial conducted in an insulin-exposed population and compared sotagliflozin 200 mg + SoC to placebo + SoC over a 52-week treatment period in patients with T1D. In comparison with other inTandem clinical developments (namely inTandem1 and inTandem3), inTandem2 was the only trial to study the 52-week effects of sotagliflozin 200 mg in a European population; therefore, characterising the UK population in a narrower way.

Adverse events associated with treatment, namely non-severe hypoglycaemia (non-SH), SH and diabetic ketoacidosis (DKA), were captured in the health economic analysis. These were sourced directly from the head-to-head inTandem2 trial.

Simulations were run comparing sotagliflozin + SoC with placebo + SoC based on the inTandem2 trial, with treatment effect data taken from the 52-week time-point wherever possible. Treatment effects for the intervention and comparator arms are summarised in Table 3.4.

Table 3.4. Treatment effects for sotagliflozin 200 mg + SoC and placebo + SoC observed in the inTandem2 trial

Physiological parameters	Mean treatment effect (SD)	
	Sotagliflozin 200 mg + SoC	Placebo + SoC
HbA_{1c} (%)	−0.210 (0.821)	0.030 (0.785)
SBP (mmHg)	−1.700 (12.530)	1.200 (11.210)
DBP (mmHg)	−1.700 (8.170)	−0.100 (7.850)
Total cholesterol (mg/dL)	9.900 (26.680)	2.700 (25.410)
LDL-C (mg/dL)	5.300 (21.860)	2.000 (20.460)
HDL-C (mg/dL)	3.300 (12.690)	1.500 (9.450)
Triglycerides (mg/dL)	6.800 (54.040)	0.600 (46.380)
BMI (kg/m^2)	−0.643 (1.357)	0.119 (1.178)
eGFR ($mL/min/1.73\ m^2$)	−1.800 (12.032)	−0.040 (10.926)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation.

The types of adverse events included in the analysis were based on those that were between Grade 3 and 5 and occurred in >5% of people in all arms of the inTandem2 trial. The main adverse events that were considered in the base-case analysis were the number of severe and non-severe hypoglycaemic and DKA events. The results of inTandem2 indicated that sotagliflozin did not lead to a substantial increase in these effects, and therefore these effects were not considered in the analysis. The increase in incidences observed in inTandem2 of diarrhoea and combined renal and urinary disorders were 0.7% (3.9% vs 4.6%) and 1.9% (3.8% vs 1.9%), respectively. The summary of these events is also presented in Appendix L.

The treatment effects were calculated using the corresponding event rates obtained in the inTandem2 trial (37). In the CDM, the number of events per 100 patient-years is required for all adverse event rates. The non-SH events were calculated by subtracting the total documented number of hypoglycaemia events, symptomatic or unknown, from the total SH events. The values for non-severe and SH events were reported as events per patient per year in the trial; therefore, a simple conversion to 100 patient-years was applied in order to fit the model (×100). The DKA events per 100 patient-years were calculated using the patients with at least one DKA event and the total number of patients per arm. Treatment effects of adverse event rates are outlined in Table 3.5.

Table 3.5 Adverse event rates in sotagliflozin 200 mg + SoC and placebo + SoC observed in the inTandem2 trial

Adverse events	Mean treatment effect	
	Sotagliflozin 200 mg + SoC	**Placebo + SoC**
Non-SH event rate per 100 patient-years	5,595	6,715
SH 1 event rate (requiring non-medical assistance) per 100 patient-years*	NA	NA
SH 2 event rate (requiring medical assistance) per 100 patient-years	8	8
Annual probability of lactic acidosis	0	0
DKA	5.857	1.264

*Where values were not reported in the trial (e.g. SH event requiring non-medical assistance, proportion of SH events requiring medical assistance), the inputs of the CORE Diabetes Model were assumed equal to 0 to align with the trial outcomes (all SH events reported in the trial required medical assistance; all hypoglycaemia not requiring medical assistance were assumed to be non-severe).
DKA, diabetic ketoacidosis; NA, not applicable; SH, severe hypoglycaemia.

For the sensitivity analysis, treatment effect data for sotagliflozin 200 mg + SoC and placebo +SoC were also taken from the NMA. These model inputs are summarised in Table 3.7 and Table 3.8. Where changes in risk factors included in the model were not available from the NMA, a value of zero was assumed in the intervention and comparator treatment arms. Rates of DKA were taken from the inTandem2 trial.

Table 3.6. Treatment effects applied to simulated patients receiving sotagliflozin 200 mg in addition to insulin based on the network meta-analysis

Treatment effects	Mean	Standard deviation	Reference
Risk factor changes			
HbA_{1c} CFB (%)	−0.271	0.164	NMA results
SBP CFB (mmHg)	0	0	Assumed (as not part of the NMA)
Total cholesterol CFB (mmol/L)	0	0	Assumed (as not part of the NMA)
High-density lipoprotein cholesterol CFB (mmol/L)	0	0	Assumed (as not part of the NMA)
BMI CFB (kg/m^2)	−0.71	0.38	NMA results
Adverse event rates			
Annual SH rate (events per patient-year)	0.269	Not required	NMA results
Annual non-SH rate (events per patient-year)	62.53	Not required	NMA results
Annual DKA rate (events per patient-year)	0.023	Not required	Patients with treatment-emergent, positively adjudicated metabolic acidosis who also had DKA (6 out of 261 patients over 52 weeks), inTandem2

BMI, body mass index; CFB, change from baseline; CSR, clinical study report; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; NMA, network meta-analysis; SBP, systolic blood pressure; SH, severe hypoglycaemia.

Table 3.7 Treatment effects applied to simulated patients receiving placebo in addition to insulin based on the network meta-analysis

Treatment effects	Mean	Standard deviation	Reference
Risk factor changes			
HbA_{1c} CFB (%)	−0.034	0.032	NMA results
SBP CFB (mmHg)	0	0	Assumed (as not part of the NMA)
Total cholesterol CFB (mmol/L)	0	0	Assumed (as not part of the NMA)
High-density lipoprotein cholesterol CFB (mmol/L)	0	0	Assumed (as not part of the NMA)
BMI CFB (kg/m^2)	0.19	0.06	NMA results
Adverse event rates			
Annual SH rate (events per patient-year)	0.188	Not required	NMA results
Annual non-SH rate (events per patient-year)	68.73	Not required	NMA results
Annual DKA rate (events per patient-year)	0	Not required	Patients with treatment-emergent, positively adjudicated metabolic acidosis who also had DKA (6 out of 261 patients over 52 weeks), inTandem2

BMI, body mass index; CFB, change from baseline; CSR, clinical study report; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; NMA, network meta-analysis; SBP, systolic blood pressure; SH, severe hypoglycaemia.

3.3.1. Long-term progression of risk factors

In years subsequent to the treatment change (i.e. first year effect), annual progressions of 0.045% and 0.2375 kg/m^2 in HbA_{1c} and BMI, respectively, are applied. These estimates are based on DCCT intensive insulin arm and have been used within NICE guidance NG17 (Appendix N) (6). The annual progression is applied until patients reach HbA_{1c} and BMI maximum thresholds of 8.7% and 35 kg/m^2, respectively, at which point HbA_{1c} and BMI stabilise. These assumptions are aligned with the definition of obesity class II (severe obesity) (83) in the case of BMI, and the baseline level of HbA_{1c} that equally represents the UK average, but with a slight 0.1% deviation to allow all treatment effects to occur in Year 1 (25).

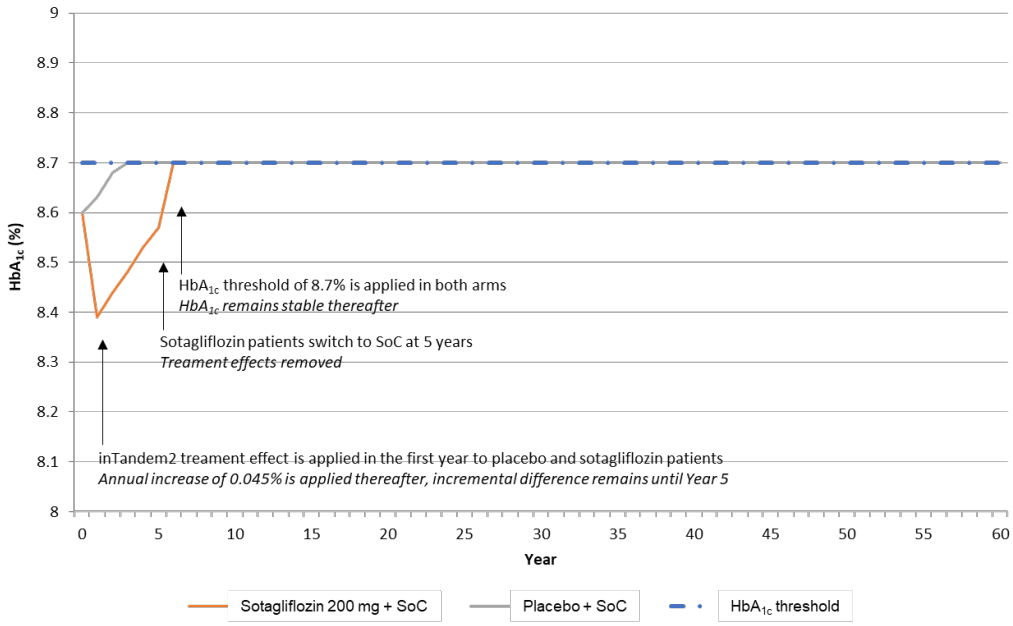
An independent critique of derived DCCT/EDIC natural progression values was performed in 2017 by the University of Sheffield resulting in an alternative estimation of these values; the new set of proposed values were analysed in a sensitivity analysis (Appendix L).

Due to a lack of available evidence in T1D, T2D progressions were applied to some parameters as required: SBP progression was assumed to follow UK Prospective Diabetes Study number 68 (84) and the total cholesterol, LDL-C, HDL-C and triglycerides progression was assumed to follow Framingham progression (85). For all other physiological parameters (eGFR, haemoglobin, white blood cell count, heart rate, DBP, waist-to-hip ratio, urinary albumin-to-creatinine ratio, serum creatinine and serum albumin), there were no annual increases applied (i.e. intervention and comparator curves converged after Year 1 and remained constant). Note that not all parameters included within the CDM analysis influence outcomes (e.g. white blood cell count, heart rate and waist-to-hip ratio are not utilised within this analysis).

For HbA_{1c}, BMI, SBP and lipid profile, after-treatment effects were applied in the first year of the simulation and the incremental differences were maintained until the time on treatment. After 5 years (and therapy switching to insulin only, as in the placebo arm), HbA_{1c} was assumed to remain constant at 8.7% (Figure 3.3). The differences in BMI, SBP and lipid profile were assumed to rebound to placebo on discontinuation of sotagliflozin therapy (Figure 3.4 and Figure 3.5)

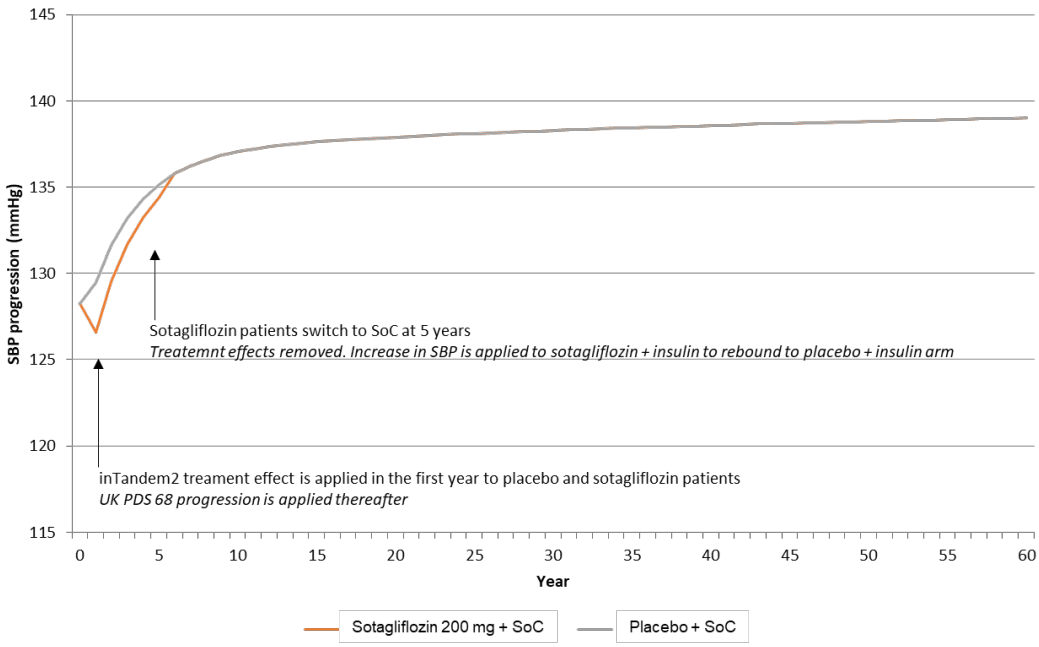
The key analysis assumptions related to the patient progression over time are outlined in Table 3.8.

Figure 3.3. Modelled glycated haemoglobin progression in the base-case analysis



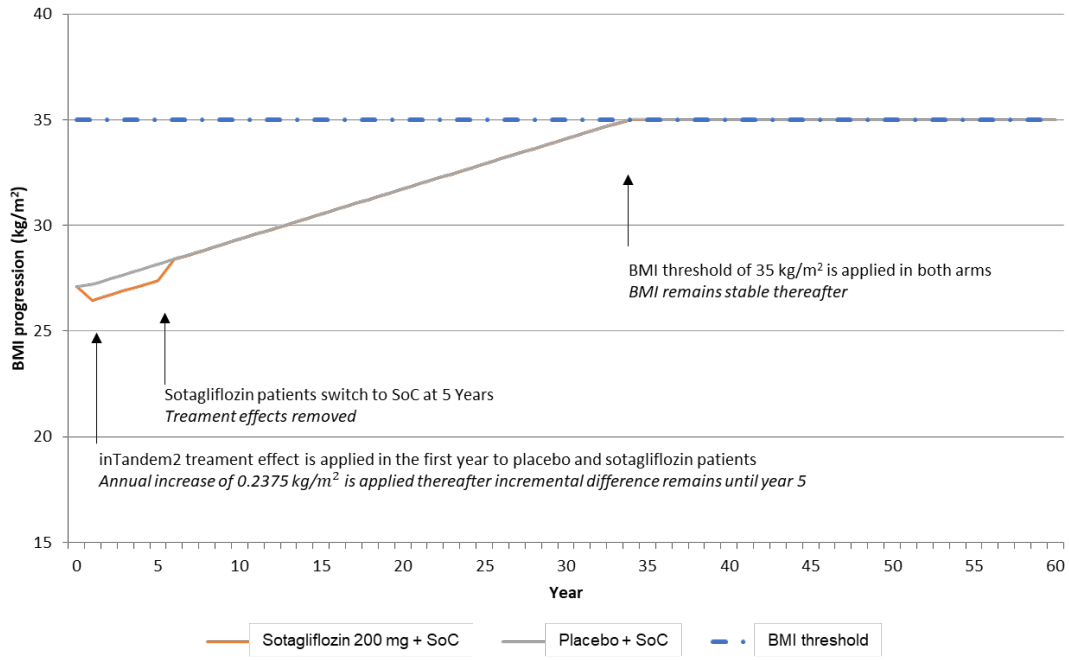
HbA_{1c}, glycated haemoglobin; SoC, standard of care.

Figure 3.4. Modelled systolic blood pressure progression in the base-case analysis



SBP, systolic blood pressure; SoC, standard of care; UK PDS, UK Prospective Diabetes Study.

Figure 3.5. Modelled body mass index progression in the base-case analysis



BMI, body mass index; SoC, standard of care.

Table 3.8 Key assumptions related to patient progression over time

Variable	Value/assumption	Source
HbA_{1c} progression	0.045% annual increase, with maximum level set to 8.7%	DCCT study (86)
BMI progression	0.2375 kg/m^2 annual increase, with maximum level set to 35 kg/m^2	DCCT study (86)
SBP progression	UK PDS 68 risk equation	Clarke, et al, 2004 (84)
Total cholesterol progression	Framingham risk equation	Framingham Heart Study (85)
LDL-C progression	Framingham risk equation	Framingham Heart Study (85)
HDL-C progression	Framingham risk equation	Framingham Heart Study (85)
Triglycerides	Framingham risk equation	Framingham Heart Study (85)

BMI, body mass index; DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UKPDS, UK Prospective Diabetes Study.

3.3.2. Management settings

Management settings include the proportion of patients on preventative medication, the proportion of patients undergoing screening, and the sensitivity and specificity of tests. Inputs were sourced from available literature with country-specific data preferred where

available and are outlined in Table 3.9. The data on sensitivity and specificity of tests is not country specific and is considered replicable across countries.

Table 3.9 Management settings

Health state	Input value	Source
Patients on preventative medication		
Proportion of primary prevention aspirin	0.590	EUROASPIRE II Study Group (87) and Kotseva, et al. 2009 (88)
Proportion of secondary prevention aspirin	0.890	Kotseva, et al. 2009 (88)
Proportion of primary prevention statins	0.470	EUROASPIRE II Study Group (87) and Kotseva, et al. (88)
Proportion of secondary prevention statins	0.840	Kotseva, et al. 2009 (88)
Proportion of primary prevention ACEi	0.210	EUROASPIRE II Study Group (87) and Kotseva, et al. 2009 (88)
Proportion of secondary prevention ACEi	0.760	Kotseva, et al. 2009 (88)
Screening and patient management		
Proportion on foot ulcer prevention programme	1.000	No UK data; assumed to be included in standard management
Proportion screened eye disease	1.000	No UK data; assumed to be included in standard management
Proportion screened for renal disease	1.000	No UK data; assumed to be included in standard management
Proportion receiving intensive insulin after MI	1.000	Bydureon NICE submission, (89)
Proportion treated with extra ulcer treatment	0.100	Bydureon NICE submission, (89)
Proportion screened for depression — no complications	0.830	Jones, et al. 2007 (90)
Prop screened for depression — complications	0.830	Jones, et al. 2007 (90)
Sensitivity and specificity of tests		
Reduction in incidence FU with prevention programme	0.690	O'Meara, et al. 2000 (91)
Improvement in ulcer healing rate with extra treatment	1.390	Kantor, et al. 2001 (92)
Reduction in amputation rate with foot care	0.690	O'Meara, et al. 2000 (91)
Sensitivity eye screening	0.920	Lopez-Bastida, et al. 2007 (93)
Specificity eye screening	0.960	Lopez-Bastida, et al. 2007 (93)
Sensitivity GRP screening	0.830	Cortes-Sanabria, et al. 2006 (94)
Sensitivity MAU screening	0.830	Cortes-Sanabria, et al. 2006 (94)
Specificity renal screening	0.960	Cortes-Sanabria, et al. 2006 (94)

ACEi, angiotensin-converting-enzyme inhibitor; FU, foot ulcer; GRP, gross renal proteinuria; MAU, microalbuminuria; MI, myocardial infarction.

3.3.3. Mortality inputs

All-cause mortality was sourced from the UK Office for National Statistics using 2014–16[1] data (95). The mortality rates for males and females in the UK are shown in Appendix L.

3.3.4. Measurement and valuation of health effects

The factors that impact the QoL in patients with T1D are listed below:

- **Diabetes-related complications:** As T1D progresses, patients are exposed to an even greater risk of complications, including CV disease, renal disease, amputation and retinopathy. The occurrence of diabetes- related complications results in significant reductions in QoL (7).

- **Change in body weight:** Sotagliflozin is associated with a reduction in patient bodyweight, which can have a positive impact on a patient's QoL.

3.3.5. Health-related quality of life data from clinical trials

No health-related quality of life (HRQoL) data from the sotagliflozin clinical trial programme were included in the health economic analysis since the trial includes impact of treatment over a short period and does not capture the significant reduction in QoL due to long-term complications. The HRQoL evidence captured in the inTandem trials has been reported in the clinical section (Table 2.6).

3.3.6. Mapping

No mapping techniques were applied in the present analysis.

3.3.7. Health-related quality of life studies

Appendix M describes how systematic searches for relevant HRQoL data were conducted to identify studies reporting utility values related to T1D and its complications. Studies reporting utility values either from direct measurement or derived from QoL instruments were included. The full results of the searches are presented in Appendix M, and only those results used in the model are reported here.

[1] 2016–17 data available as of 25 September 2018.

3.3.7.1. Health-related quality of life data used in the cost-effectiveness model

Utilities and disutilities for the health economic analysis were taken from published sources, with a focus on identifying robust diabetes-specific values appropriate for the UK setting wherever possible. All values used in the modelling analysis using the CDM model are described in Table 3.10. A multiplicative approach was used to estimate QALY in the base-case with an additive approach used as a sensitivity analysis. Health state utilities associated with T1D and its complications were based on the Peasgood, et al study (96), which estimated HRQoL or utility decrements associated T1D using data from a UK research programme on the Dose Adjustment For Normal Eating (DAFNE) education programme. The Peasgood, et al. study is the most recent study that identified studies reporting utility values of T1D-specific complications and therefore was favourable in this analysis (96). Note, when values were not available, the utilities presented in Beaudet, et al. (2014) (97) and Currie, et al. (2006) (98) were selected where necessary. The later studies are widely used across T2D cost-effectiveness models submitted to HTA agencies.

The analysis of the DAFNE research database provides utility estimates based on panel data on diabetes-related health states to populate economic models exploring the cost-effectiveness of interventions for patients with T1D. Utility and disutility inputs are outlined in Table 3.10.

3.3.7.2. Adverse events

The impact of weight gain (insulin is associated with weight gain), hyperglycaemia and DKA were captured in the model via the application of published utility estimates to the modelled incidence of AEs.

BMI, and the disutility associated with BMI gain, is a core component of the progression of diabetes complications over time and an important measure of the impact of treatment on patients. BMI disutility is also based on the Peasgood, et al. study (96). Based on the definition of obesity stated in the WHO (83) and NHS (99) a person with a BMI ≥25 kg/m^2 is considered overweight; therefore, a disutility of −0.0028 per BMI unit gain was assigned to patients with a BMI >25 kg/m^2 (a conservative assessment of the potential disutility of weight gain).

The disutility associated with non-severe hypoglycaemic events was assumed to be zero, which was consistent with the disutility used in NG17 (Appendix N of NG17 (6)).

Note, where standard error values were not reported in the Peasgood, et al. study, the standard error at baseline (i.e. standard error corresponding T1D without complication) was considered.

Table 3.10. Summary of utility values for the cost-effectiveness analysis

Health state	Input value	SE	Diabetes population	Input justification	Reference
T1D without complication	0.839	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
MI event	−0.024	0.053	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Post-MI	0.815	0.231	–	Estimation	Peasgood, et al. 2016 (100)
Angina	0.749	0.010	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Chronic heart failure	0.743	0.010	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Currie, et al. 2006 (98)
Stroke event	−0.033	0.048	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Post-stroke	0.806	0.231	T1D		Estimation
Peripheral vascular disease	0.778	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Microalbuminuria	0.000	0.000	–		Assumption
Gross renal proteinuria	0.791	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Haemodialysis	0.604	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Peritoneal dialysis	0.581	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Renal transplant	0.829	0.231	T1D	No available data in T1D; most recent	Peasgood, et al. 2016 (100)

Health state	Input value	SE	Diabetes population	Input justification	Reference
				applicable utility study in T2D was used	
BDR	0.810	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
BDR wrongly treated	0.810	0.231	T1D	Assumed equal to BDR	Peasgood, et al. 2016 (100)
PDR laser treated	0.769	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
PDR no laser	0.769	0.231	T1D	Assumed equal to PDR	Peasgood, et al. 2016 (100)
Macular oedema	0.799	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Severe vision loss	0.780	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Cataract	0.823	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Neuropathy	0.603	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Healed ulcer	0.839	0.231	T1D	Assumed zero	
Active ulcer	0.715	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Amputation, year of event	−0.117	0.052	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Post-amputation	0.722	0.231	T1D	Estimation	
NSHE 1 (daytime)	0.000	0.000	–	Assumption	
NSHE 1 (nocturnal)	0.000	0.000	–	Assumption	
SHE 1 (during daytime)	−0.002	0.001	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
SHE 1 (nocturnal)	−0.002	0.001	T1D	Assumed equal to SHE 1 (daytime)	Peasgood, et al. 2016 (100)
Ketoacidosis event	−0.009	0.010	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Oedema	−0.010	0.000	T2D	No available data in T1D, most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (97)
Post-oedema	0.829	0.231	–	Estimation	Beaudet, et al. 2014 (97)

Health state	Input value	SE	Diabetes population	Input justification	Reference
Depression not treated	0.587	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)
Depression treated	0.839	0.231	T1D	Assumed equal to baseline	Peasgood, et al. 2016 (100)
Disutility associated with 1 unit increase in BMI	−0.003	–	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (100)

BDR, background diabetic retinopathy; BMI, body mass index; MI, myocardial infarction; NSHE, non-severe hypoglycaemic event; PDR, proliferative diabetic retinopathy; SE, standard error; SHE; severe hypoglycaemic event; T1D, type 1 diabetes; T2D, type 2 diabetes.

3.4. Cost and healthcare resource use identification, measurement and valuation

The analysis perspective includes direct costs only. Direct costs encompass the costs of patient treatment for acute events and long-term illness and include the costs associated with managing the complications associated with the T1D. Costs are described below by treatment-associated costs, complication costs and management costs.

All costs from sources published before 2017 were inflated to 2017 using the 2016/2017 Personal Social Services (PSS) pay and prices index available in the Personal Social Services Research Unit (PSSRU) 2017 (101).

3.5. Intervention and comparators' costs and resource use

Treatment costs comprised drug, needle, multiple daily injection (MDI), pump costs and the costs associated with self-monitoring blood ketone (where applicable) and self-monitoring of blood glucose (SMBG).

In this analysis, a proportion of insulin pump therapy was considered at baseline as observed in the inTandem2 trial. In the trial, 74.3% of the overall population were on MDI while 25.7% were on continuous subcutaneous insulin infusion (CSII). The insulin dosages of MDI and CSII were sourced from the inTandem2 trial and are summarised in Table 3.11.

Table 3.11 Mean daily basal and bolus insulin doses in InTandem2

Delivery method	Insulin type	Placebo (IU/day)	Sotagliflozin 200 mg (IU/day)	Reference
Continuous	Bolus	30.850	28.610	inTandem2 (47)

Delivery method	Insulin type	Placebo (IU/day)	Sotagliflozin 200 mg (IU/day)	Reference
subcutaneous insulin infusion	Basal	28.380	27.850	inTandem2 (47)
Multiple daily injection	Bolus	32.510	32.000	inTandem2 (47)
	Basal	30.240	29.650	inTandem2 (47)

CSR, clinical study report.

The mean doses, as shown in Table 3.11, were conservatively assumed to be constant over time, despite the 52-week outcomes showing an insulin dose-sparing effect favouring sotagliflozin. The doses were also assumed to be equivalent across all subgroups (explored in the sensitivity analyses); this assumption will not impact results as the dose has no incremental impact between arms and no important differences are observed in the doses.

The yearly cost of the different types of insulin regimens was calculated using nationally available prices from the British National Formulary (BNF) 2018. Consistent with previous economic models in T1D (Appendix N of NG17(6)), only cartridges and pre-filled pens were used to calculate insulin costs. The sales share data by molecule were estimated using IQVIA Longitudinal Patient Database (LPD) data (102) and were used to calculate the average cost of MDI and CSII. The annual drug costs of MDI and CSII (not including related consumables) were estimated as the weighted average of the cost of each available drug multiplied by its sale share, which led to £508.90 and £468.62 for MDI and CSII respectively. Detailed breakdown of these costs is presented in Appendix L.

Needle cost was considered for the MDI proportion only; the unit cost of needles was calculated as a weighted average based on the prices of the 10 most commonly used needles according to Prescription Cost Analysis, England data (103). The weighted average needle cost was estimated to be £0.10. This was used to calculate the annual cost of needles per patient for each insulin regimen, which varied according to the frequency of insulin administration. The frequency of insulin therapies was based on NICE guidelines (NG17) for T1D in adults (6). The annual needle cost was estimated to be £151.13. A breakdown details of the cost of needles is presented in Appendix L.

The cost of sotagliflozin 200 mg and its daily dose were obtained from Sanofi. The drug acquisition costs and daily doses are summarised in Table 3.12.

Table 3.12 Drug acquisition costs

Drug	Pack price (£)	Daily dose	Annual cost (£)	Source
Sotagliflozin 200 mg	39.20	200 mg	477.30	Sanofi
SoC (MDI)	–	–	508.63	BNF 2018, inTandem2 (104), NG17 (6)
SoC (CSII)	–	–	468.62	BNF 2018, inTandem2 (104), NG17 (6)

BNF, British National Formulary; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; SoC, standard of care.

The insulin pump costs comprised the CSII, annualised pump and consumable costs. The annualised pump and consumable costs were sourced from the NG17 costing template (6) and inflated to 2018 costs. The breakdown of pump costs is summarised in Table 3.13

Table 3.13 Breakdown of pump cost

	Cost (£)	Inflated costs to 2018 (£)	Source
Consumables	1,758.00	1,813.18	NG17 (6)
Annualised pump	605.00	623.99	NG17 (6)
CSII	468.62	468.62	BNF 2018 inTandem2 (104) IQVIA LPD (102)
Total annual pump cost (£)	2,906		

CSII, continuous subcutaneous insulin infusion

The SMBG cost was calculated as a weighted average based on the prices of the 10 most commonly used lancet and strips (103). The weighted average SMGB cost was estimated to be £0.30. The number of test strips and lancets required per day was assumed to be four times for all regimens based on NICE NG17 guidance (6), and subsequently the annual cost of SMBG per patient was estimated to be £437.80 and applied in all arms. A breakdown of these costs is presented in Appendix L.

Self-monitoring blood ketone cost was calculated as a weighted average based on the prices of the most commonly used blood ketone strips according to the Prescription Cost Analysis, England data (103). The weighted average cost was estimated to be £2.00. It was assumed that blood ketone was monitored using 20 and 10 strips per year for sotagliflozin and the comparators (placebo + SoC and metformin + SoC), respectively, in alignment with the NHS ketone testing and sick day rules guideline (105, 106). The guideline states that patients with a high risk of ketones should receive two boxes of strips, while newly diagnosed patients should receive one box of strips (each box containing 10 strips) (6).

Based on these data, annual costs of blood ketone monitoring equal to £40.03 and £20.02 were applied to sotagliflozin 200 mg adjunct to SoC and the comparators, respectively. A sensitivity analysis has been performed using an extreme assumption of 100 blood ketone test strips for sotagliflozin-treated patients. This may be considered an extreme scenario given expert opinion suggests that there is no evidence that daily ketone monitoring prevents DKA (34). A breakdown of these costs is presented in Appendix L.

The yearly treatment costs per patient in each arm are outlined in Table 3.14. Note that the sum of MDI, CSI insulin and SMBG costs (sum corresponding to cost of placebo + SoC) were assumed to accrue yearly from the initiation of insulin treatment, hence, were the same for first and subsequent years.

Table 3.14 Yearly treatment costs per patient

Intervention	Annual drug cost (excluding SoC) (£)	Annual MDI cost* (£)	Annual pump cost (£)	Annual SMBG cost (£)	Annual self-monitoring blood ketone cost (£)	Total annual cost (£)
Sotagliflozin 200 mg + SoC	477.30	490.21	746.79	437.90	40.03	£2,192.23
Placebo + SoC	0.00	490.21	746.79	437.90	20.02	£1,732.48

*Costs include needle costs.
MDI, multiple daily injection; SoC, standard of care; SMBG, self-monitoring of blood glucose.

For the secondary analysis, metformin doses were calculated as a weighted average of doses administered in the trials captured in the NMA. The cost of metformin was sourced from BNF 2018 and the daily dosage was assumed to be 2000 IU, as reported consistently in the REMOVAL trial (59), Lund et al. (39) and Jacobsen IB et al. (41) studies.

3.6. Health state unit costs and resource use

Costs were estimated based on literature or local data sources. Drug acquisition costs were sourced from the BNF using 2018 costs. Screening tests for eye disease and proteinuria, and foot screening programmes were sourced from published tariffs reported in the PSSRU. With regards to the direct costs associated with management of diabetes complications, emphasis was placed on the use of costs derived from local sources and diabetes-specific sources where possible.

In the PSSRU, SH was considered as a proxy for DKA. The costs of SH and DKA were calculated based on a weighted average of admission count and non-elective spell tariff cost of diabetes with hyperglycaemic (with NHS reference cost for complications and comorbidities (CC) score 0–8+) and hypoglycaemic disorder (with CC score 5–8+), respectively. A breakdown of these costs is presented Appendix L.

Complication and management costs are summarised in Table 3.15. Where data from the literature were not available, the CDM default values were considered. These costs were inflated to 2017 using the 2016/2017 PSS pay and prices index available in PSSRU 2017 (107).

Table 3.15. Summary of direct costs associated with diabetes-related complications

Input variable	Mean cost per year (£)	Source/comments
Management costs		
Annual statins*	22.31	BNF 2018
Annual aspirin*	14.35	BNF 2018
Annual ACEi*	7.11	BNF 2018
Annual eye screening	35.00	NHS reference costs 2018 (107)
Annual screening for microalbuminuria	3.11	Lamb, et al. 2009 (108)
Annual screening for gross renal proteinuria	3.00	Lamb, et al. 2009 (108)
Stopping ACEi due to adverse event*	7.44	BNF 2018
Foot screening programme (monthly)	53.00	NHS reference costs 2018 (107)
Non-standard ulcer treatment (e.g. Regranex) (monthly based)	0.00	CDM default value
Anti-depression treatment and management	0.00	Assumption
Screening for depression	0.00	Part of standard management
Direct costs: cardiovascular complications		
MI, first year	3,419.59	NHS Reference Costs 2018, (107)
MI, second+ years	820.01	NICE CG181, 2016 (109) cost inflated to 2017
Angina, first year	1,810.85	NHS Reference Costs 2018, (107)
Angina, second+ years	299.70	NICE CG181, 2016 (109) cost inflated to 2017
CF, first year	2,964.21	NICE CG181, 2016 (109)
CF, second+ years	2,702.49	NICE CG181, 2016 (109)
Stroke, first year†	4,506.28	NHS reference costs 2018 (107)

Input variable	Mean cost per year (£)	Source/comments
Stroke, second+ years	702.86	Beaudet et al., 2011 (110), cost inflated to 2017
Stroke death within 30 days	4,962.11	Beaudet et al., 2011 (110), cost inflated to 2017
Peripheral vascular disease, first year	1,914.33	Beaudet et al., 2011 (110), cost inflated to 2017
Peripheral vascular disease, second+ years	1,914.29	Beaudet et al., 2011 (110), cost inflated to 2017
Direct costs: renal complications		
Haemodialysis, first year‡	25,116.00	NHS reference costs 2018 (107) NICE CG125, 2011 (111)
Haemodialysis, second+ years‡	25,116.00	NHS reference costs 2018 (107) NICE CG125, 2011 (111)
Peritoneal dialysis, first year*	28,105.00	NHS Reference Costs 2018, (107) and NICE CG125, 2011 (111)
Peritoneal dialysis, second+ years*	28,105.00	NHS reference costs 2018 (107) NICE CG125, 2011 (111)
Renal transplant, first year§	14,328.81	NHS reference costs 2018 (107)
Renal transplant, second+ years	8006.27	NICE CG125, 2011(111), cost was inflated to 2017
Direct costs: acute events		
Non-SH	0.00	Guideline development group: assumed to be treated at home
SH event 1: requires non-medical assistance	NA	All SHE assumed to require medical assistance
SH event 2: requires medical assistance	2,320.03	NHS reference costs 2018 (107)
DKA event‖	1,556.22	NHS reference costs 2018 (107) Assumption: diabetes with hypoglycaemic disorders, with CC scores 5–8 (weighted cost))
Lactic acid event	0.00	Assumed no cost of management required (expert opinion)
Oedema onset	0.00	Assumed no cost of management required (expert opinion)
Oedema follow-up	0.00	Assumed no cost of management required (expert opinion)
Direct costs: eye disease		
Laser treatment	700.00	NHS reference costs 2018 (107)
Cataract operation	1,388.98	NHS reference costs 2018 (107)
Following cataract operation	105.00	NHS reference costs 2018 (107)
Blindness, year of onset	7,735.41	Aflibercept NICE submission (112), cost inflated to 2017
Blindness, following years	7,662.19	Aflibercept NICE submission (112), cost inflated to 2017

Input variable	Mean cost per year (£)	Source/comments
Direct costs: neuropathy, foot ulcer, amputation		
Neuropathy, first year	26.09	BNF, 2018
Neuropathy, second+ years	26.09	BNF, 2018
Amputation (event based)	12,659.00	NHS reference costs 2018 (107)
Amputation prosthesis (event based)	15,728.68	NHS reference costs 2018 (107)
Gangrene treatment (monthly)	4,704.55	Ghatnekar et al., 2002 (113)
Healed ulcer	29.67	Ghatnekar et al., 2002 (113)
Infected ulcer (monthly)	2,697.34	Ghatnekar et al., 2002 (113)
Standard uninfected ulcer (monthly)	2,644.45	Ghatnekar et al., 2002 (113)
Healed ulcer history of amputation	26,089.71	NICE CG147, 2018 (114)

*Estimated by multiplying daily costs by 365.25.
†Cost estimated by calculating the weighted average of the costs incurred in strokes score 10–12 (HRG code AA35C) including elective in patient and non-elective long stay.
‡Calculated by multiplying the unit cost for hospital haemodialysis or filtration with access via arteriovenous fistula or graft (LD02A) with 156 sessions as stated in CG125.
§Includes the costs with Healthcare Resource Group codes LA031 and LA12A.
||DKA cost was calculated based on a weighted average of admission count and non-elective spell tariff cost of diabetes with hyperglycaemic (with CC score 0–8+) and hypoglycaemic disorder (with CC score 5–8+), respectively.
ACEi, angiotensin-converting-enzyme inhibitor; BNF, British National Formulary; CC, complications and comorbidities; CDM, CORE Diabetes Model; CHF, congestive heart failure; DKA, diabetic ketoacidosis; MI, myocardial infarction; NA, not applicable; SH, severe hypoglycaemia

3.6.1. Miscellaneous unit costs and resource use

All costs and resource use assumptions are described in Sections 3.4

3.6.1.1. Summary of base-case analysis inputs

The base-case analysis compared the long-term cost-effectiveness of sotagliflozin 200 mg + insulin with placebo + insulin based on the inTandem2 trial. All base-case settings are summarised in Table 3.16, with additional detail provided in previous sections.

Table 3.16. Summary of settings for the base-case modelling analysis

Model input	Sotagliflozin plus SoC	Placebo plus SoC
Model input	**Sotagliflozin + SoC**	
Cohort	UK T1D cohort (Table 3.3)	
Treatment	Sotagliflozin + SoC	Placebo + SoC
Treatment cost	£2,192.23 (Table 3.14)	
Complication costs	UK 2017 costs (Table 3.15)	
Adverse event costs	UK 2017 costs (Table 3.15)	
Utilities	UK-appropriate, diabetes-specific utilities (Table 3.10)	

Model input	Sotagliflozin plus SoC	Placebo plus SoC
Mortality from causes other than diabetes-related complications	UK office for national statistics using 2014-2016 data (115)	
Duration of sotagliflozin therapy	5 years then switch to comparator intervention	
Progression of risk factors	Assumed constant over time (Section 3.3.1)	
Time horizon	60 years	

T1D, type 1 diabetes.

3.7. Summary of base-case analysis inputs and assumptions

The main assumptions employed in the base-case analysis can be summarised as follows:

- Cohort characteristics were based on a previous economic evaluation by NICE and are considered to be representative of patients with T1D in the UK. This can be considered to be the most appropriate choice for a base-case analysis, but relies on the assumption that the treatment effects estimated in inTandem2 would be applicable to a population with these characteristics. For instance, it is well established that the magnitude of improvements in HbA_{1c} with therapy intensification is influenced by baseline HbA_{1c} and, in a population with a relatively high starting HbA_{1c} (such as that used in the base-case analysis), the potential benefits of intensification of therapy (such as adjunct sotagliflozin) may be greater than estimated in the clinical trial data.

- It was assumed that patients would remain on sotagliflozin for 5 years before switching to insulin therapy (as modelled in the placebo arm). This simplifying assumption was used to improve the transparency of the base-case analysis. The assumption of 5 years of therapy for all sotagliflozin patients means that the costs and benefits of therapy can be clearly evaluated (as no benefits were assumed to persist beyond the 5-year period). Alternative assumptions (e.g. a proportion of patients switch therapy every year) make it more difficult to interpret the results. Moreover, it can be considered a conservative assumption, as the legacy effect or metabolic impact of a 5-year improvement in HbA_{1c} (as documented in the DCCT) is not captured in the modelling analysis and no weight loss is assumed to persist beyond the 5 years of sotagliflozin therapy.

- The base-case analysis assumed 100% persistence with therapy in both treatment arms. This is a simplifying assumption in the absence of clinical evidence on the effects of discontinuing sotagliflozin as an adjunct to SoC. Any modelling of compliance and/or persistence would be based on a set of assumptions, which would have the potential to obfuscate the central research question under investigation with this analysis (i.e. is sotagliflozin cost-effective versus placebo when added to insulin therapy for T1D).

- It was assumed that the treatment benefit with sotagliflozin (i.e. the difference in $HbA_{1c,}$ BMI, SBP and lipid profile between the sotagliflozin and placebo arms) would be abolished on discontinuation of sotagliflozin. For example, it is reasonable to assume that the benefits observed at 52 weeks in the inTandem2 trial would persist for the duration of therapy. Alternative HbA_{1c} progression assumptions were investigated in sensitivity analyses.

- Simplifying assumptions were made on the progression of risk factors over time in the base-case analysis. This was done to simplify the interpretation of findings (i.e. the differences in long-term outcomes were associated with treatment effects applied in the modelling analysis as opposed to being due to long-term assumptions on the progression of risk factors). Alternative risk factor progression assumptions were investigated in sensitivity analyses.

An independent analysis undertaken by the University of Sheffield aimed to reproduce some of the default values in the CDM derived from the DCCT/EDIC trials (and widely used in other published T1D cost-effectiveness analyses) — specifically the annual natural progression of +0.045% in the HbA_{1c} levels, and +0.2375 kg/m^2 in the BMI, however they were unable to reproduce these values (Appendix L). The authors of this independent analysis recommended rather the use of the alternative set of 0.018% and 0.095 kg/m^2 for HbA_{1c} and BMI respectively, to explore the impact of changing these parameters these values included in a sensitivity analysis.

Finally, the need of ketone monitoring was identified as an important aspect of clinical practice for sotagliflozin patients. The frequency of ketone monitoring is highly patient specific, therefore determining a mean frequency applicable to a cohort of patients is challenging. The current analyses used the NHS sick day guideline on ketone monitoring,

stating that patients with high risk of ketones (as the case of pump users) should receive two boxes of blood strips when required while early diagnosed T1D patients should receive one box of strips. Therefore, respective mean of 20 strips and 10 strips per year were assumed for patients on sotagliflozin and placebo/metformin.

3.8. Base-case incremental cost-effectiveness analysis results

Long-term projections of costs and clinical outcomes for 5 years of therapy with sotagliflozin versus placebo showed that sotagliflozin was associated with improved clinical outcomes and increased direct costs (Table 3.17Table 3.17). Improvements in glycaemic control, SBP and BMI associated with sotagliflozin improved life expectancy by approximately 0.015 years versus placebo and QALY by approximately 0.111 QALYs versus placebo. Despite a lower risk of diabetes-related complications with sotagliflozin, direct costs were projected to be approximately £948 higher than with placebo, leading to an ICER of £8,578 per QALY gained.

Table 3.17 Summary of base-case cost-effectiveness outcomes for sotagliflozin 200 mg versus placebo

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Quality-adjusted life year (QALYs)	8.382	8.272	0.111
Life expectancy (years)	16.723	16.708	0.015
Lifetime combined costs (£)	78,366	77,418	948
ICER (Delta costs/Delta QALYs)	8,578		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care

3.8.1. Base-case breakdown of costs

Sotagliflozin 200 mg + SoC reduced the costs of complications (−£1,561) and increased the costs of treatment (£2,249), management (£3), SH events (£5) and DKA events (£252), which led to a total incremental cost difference of £948. A breakdown of direct lifetime costs by cost category is outlined in Table 3.18.

Table 3.18 Breakdown of costs (£) (sotagliflozin 200 mg + standard of care versus placebo + standard of care)

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental (£)
Total direct costs	78,366	77,418	948
Treatment	31,246	28,997	2,249
Management	1,882	1,879	3
Cardiovascular disease	4,018	4,025	−7
Renal	5,528	5,786	−258
Ulcer/amputation/neuropathy	18,267	18,809	−542
Eye	13,678	14,432	−754
Non-severe hypoglycaemia	0	0	0
Severe hypoglycaemia	3,159	3,154	5
Diabetic Ketoacidosis	588	336	252

SoC, standard of care.

Sotagliflozin 200 mg + SoC delayed the appearance of any complications versus placebo + SoC by approximately 4.3 months on average. The time alive and free of complications results are outlined in Table 3.20. Sotagliflozin 200 mg + SoC led to lower cumulative incidence of all simulated complications with the exception of cataract, posterior vitreous detachment (PVD), stroke, DKA, SH, MI events and death. The cumulative incidence of complications in each arm are outlined in Table 3.19.

Table 3.19 Life-years gained

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Any complications	4.34	3.97	0.37
Background retinopathy	11.55	11.02	0.53
Proliferative retinopathy	23.15	22.88	0.27
Microalbuminuria	16.77	16.48	0.29
Gross proteinuria	23.92	23.72	0.2
End-stage renal disease	27.91	27.8	0.11
First ulcer	23.72	23.55	0.17
Amputation	27.12	26.99	0.13
Neuropathy	16.79	16.54	0.25
Peripheral vascular disease	26.19	26.16	0.03
Congestive heart failure	28.14	28.04	0.1
Angina	25.65	25.53	0.12
Myocardial infarction	26.14	26.04	0.1
Stroke	27.84	27.74	0.1
Cataract	25.17	25.14	0.03
Macular oedema	19.65	19.27	0.38
Severe vision loss	24.09	23.81	0.28

SoC, standard of care.

Table 3.20 Cumulative incidence of complications

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Background retinopathy	79.75	80.82	−1.07
Proliferative retinopathy	27.53	28.26	−0.73
Macular oedema	47.23	48.20	−0.97
Severe vision loss	31.19	31.90	−0.71
Cataract	18.33	18.13	0.20
Microalbuminuria	46.79	48.07	−1.28
Gross proteinuria	31.78	32.41	−0.63
End-stage renal disease	12.15	12.50	−0.35
Nephropathy-related death	9.01	9.33	−0.32
Foot ulcer, first event	46.06	46.39	−0.33
Recurring foot ulcer	72.47	73.27	−0.80
First amputation	16.03	16.36	−0.33

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Amputation, recurrent ulcer	9.56	9.73	−0.17
Neuropathy	63.82	64.49	−0.67
CHF death	4.86	5.11	−0.25
CHF event	7.26	7.52	−0.26
PVD onset	17.22	16.84	0.38
Angina	20.12	20.37	−0.25
Diabetes mortality	2.71	2.72	−0.01
Stroke event	6.37	6.35	0.02
MI death	17.15	17.14	0.01
MI event	30.61	30.63	−0.02
Non-SH	1,913.07	1,951.17	−38.11
SH event 1 (requires non-medical assistance)	0.00	0.00	0.00
SH event 2 (requires medical assistance)	2.34	2.33	0.01
Nausea	0.00	0.00	0.00
Lactic acidosis	0.00	0.00	0.00
DKA	0.55	0.37	0.18

CHF, congestive heart failure; DKA, diabetic ketoacidosis; MI, myocardial infarction; PVD, posterior vitreous detachment; SH, severe hypoglycaemia; SoC, standard of care.

4. Sensitivity analyses

4.1. One-way sensitivity analyses

A number of one-way sensitivity analyses were conducted to test the robustness of model assumptions to plausible changes in key model parameters. In these, one or more inputs were changed, and the analyses were rerun to evaluate the impact on results. A list of variables that have been changed with description of the analysis are outlined in Table 4.1.

4.1.1. Results of one-way SA

In the majority of the sensitivity analyses performed, sotagliflozin 200 mg + standard of care (SoC) remained cost-effective compared with placebo + SoC, with incremental cost-effectiveness ratios (ICERs) between £3,931 per quality-adjusted life-year (QALY) and £20,737 per QALY. All of the sensitivity analyses conducted except for one [in which the network meta-analysis (NMA) treatment effects were applied to the full inTandem2 population] resulted in an ICER below the cost-effectiveness threshold of £20,000 per QALY. When using the NMA results, the higher severe hypoglycaemia (SH) events in the sotagliflozin 200 mg + SoC arm compared with the placebo + SoC arm yielded higher incremental costs (£1,976), which resulted an ICER just exceeding the threshold. Overall, for the treatment effects drawn from the NMA National Diabetes Audit (NDA) population and to the subgroup of full inTandem2 population with glycated haemoglobin (HbA_{1c}) >6.5% and body mass index (BMI) ≥25 kg/m², health-related utilities and disutilities and the change in HbA_{1c} and BMI annual increase were the main drivers of the cost-effectiveness results.

Table 4.1 Sensitivity analyses results – sotagliflozin 200mg + standard of care versus placebo + standard of care

Cohort characteristics	Treatment effects	Total costs (£)			Total QALYs			ICER (£)
		Sotagliflozin 200mg + SoC	Placebo + SoC	Incremental (£)	Sotagliflozin 200mg + SoC	Placebo + SoC	Incremental (£)	
Base-case: NDA population	InTandem2 (ITT analysis)	78,366	77,418	948	8.382	8.272	0.111	8,578
	PSA	77,909	76,962	946	8.372	8.258	0.114	8,307
Sensitivity analysis								
InTandem2	InTandem2 (ITT analysis)	76,925	75,296	1,629	10.621	10.519	0.101	16,097
NDA (base-case)	NMA	82,750	81,380	1,370	8.412	8.287	0.125	10,948
NDA (base-case)	Treatment effect: 2 years	77,758	77,418	340	8.358	8.272	0.087	3,931
NDA (base-case)	T2D disutilities Beaudet et al.2014	78,366	77,418	948	10.343	10.285	0.058	16,258
NDA (base-case)	BMI disutility excluded	78,366	77,418	948	8.621	8.518	0.103	9,175
NDA (base-case)	Economics varied by +20%	87,789	87,102	688	8.382	8.272	0.111	6,223
NDA (base-case)	Economics varied by –20%	68,942	67,734	1,208	8.382	8.272	0.111	10,932
NDA (base-case)	Blood ketone monitoring 100 strips per year	79,082	77,418	1,664	8.382	8.272	0.111	15,057
NDA (base-case)	HbA_{1c} and BMI increase of 0.018% and 0.095 m^2kg respectively	82,865	78,496	4,369	8.542	8.205	0.337	12,956
Scenario analyses								
NDA	Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5%	78,435	77,493	942	8.479	8.319	0.16	5,897

Cohort	Treatment effects	Total costs (£)			Total QALYs			ICER (£)
NDA	Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5% and BMI ≥ 25 kg/m²	75,471	74,323	1,148	10.47	10.329	0.142	8,096
NDA	Subgroup of inTandem2 population with HbA_{1c}>8.5%	74,816	76,026	-1,210	8.688	8.484	0.204	DOMINANT
Subgroup analyses								
Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5% and BMI ≥ 25 kg/m²	Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5% and BMI ≥ 25 kg/m²	77,075	76,047	1,028	10.633	10.495	0.138	6,212
Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5%	Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5%	77,075	76,047	1,028	10.633	10.495	0.138	7,427
Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5% and BMI ≥ 25 kg/m²	NMA	80,044	78,068	1,976	10.388	10.293	0.095	20,737

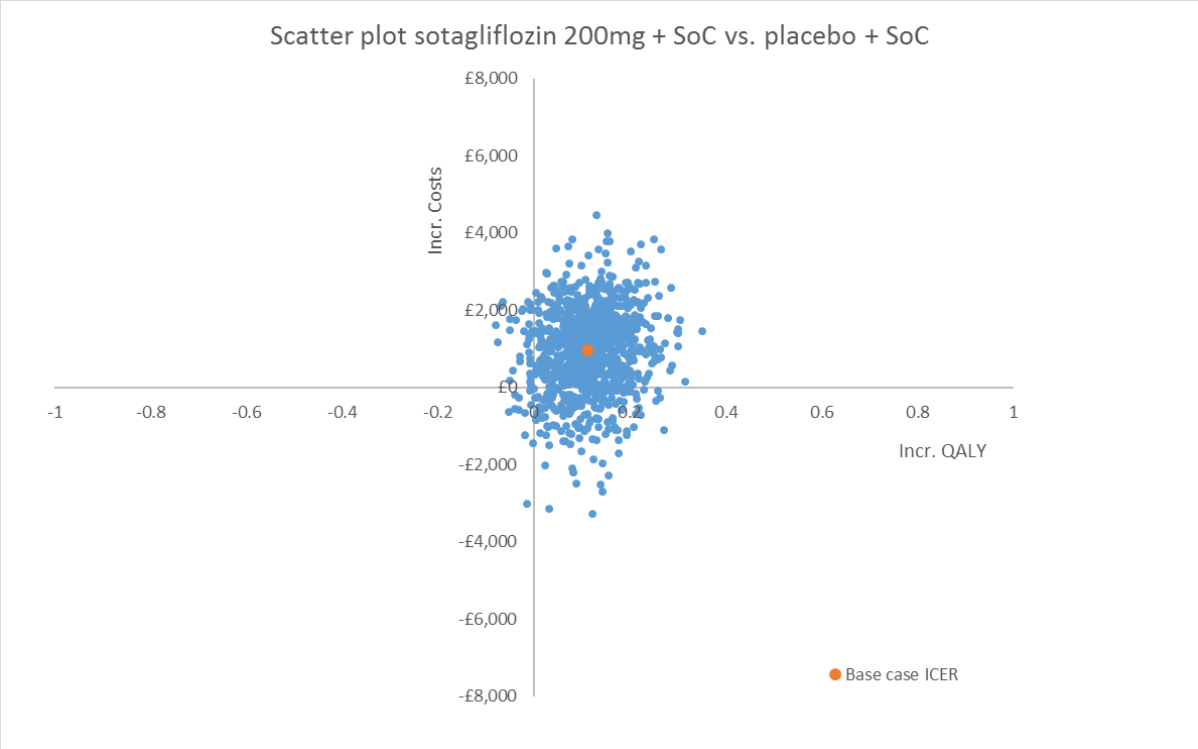
BMI, body mass index; HbA_{1c}, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; ITT, intent to treat; NDA, National Diabetes Audit; NMA, network meta-analysis; PSA, probabilistic sensitivity analysis ; QALY, quality-adjusted life-year; SoC, standard of care.

4.2. Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) were conducted to analyse the robustness of results to second-order uncertainty. A PSA was conducted utilising 10,000 patients and 1,000 iterations.

Probabilistic results were in line with deterministic results, with an average ICER of £8,307 per QALY gained. The incremental cost-effectiveness pairs for costs and QALYs gained are plotted in Figure 4.1. The north-east quadrant contained 78.2% of points and the south-east quadrant 18.4% of points.

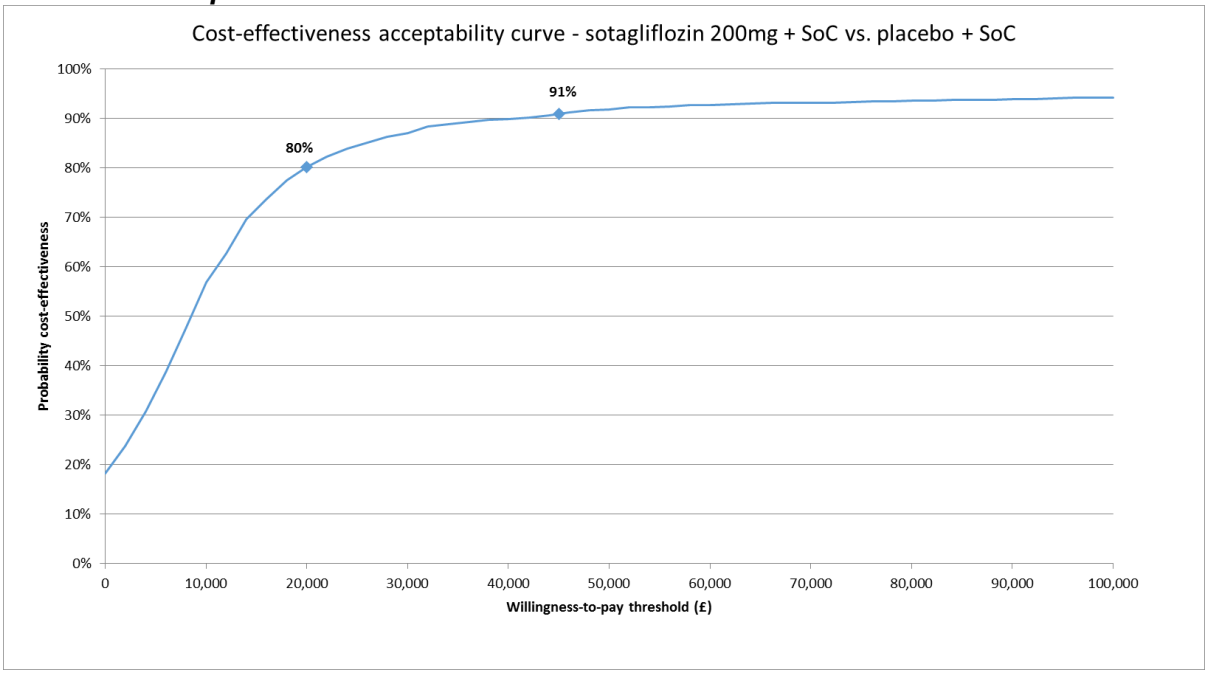
Figure 4.1: Cost-effectiveness scatter plot — sotagliflozin 200 mg + standard of care versus placebo + standard of care



ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care.

The cost-effectiveness acceptability curve is shown in Figure 4.2. At a willingness-to-pay of £20,000 per QALY there is an 80% probability of sotagliflozin 200 mg + SoC being cost-effective relative to SoC.

Figure 4.2: Cost-effectiveness acceptability curve — sotagliflozin 200 mg + standard of care versus placebo + standard of care



SoC, standard of care

4.3. Cost-effectiveness of sotagliflozin 200 mg versus metformin

On incorporation of results from the NMA, sotagliflozin 200 mg was found to be dominant (i.e. less costly and more effective) versus metformin. This outcome was driven primarily by benefits in terms of hypoglycaemia rates, along with HbA_{1c} and BMI, leading to a substantial QALY benefit and comparable lifetime direct costs (Table 4.3). The ICER for sotagliflozin 200 mg versus metformin, both for a duration of 5 years before switching to basal-bolus insulin therapy, was £156 per QALY gained based on the findings of the NMA.

Table 4.2. Summary of cost-effectiveness outcomes for sotagliflozin 200 mg versus metformin based on the network meta-analysis

	Sotagliflozin 200 mg + SoC	Metformin + SoC	Incremental
Quality-adjusted life-year (QALYs)	8.458	8.342	0.117
Life expectancy (years)	16.752	16.758	−0.006
Lifetime combined costs (£)	82,930	84,617	−1,687
ICER (Delta costs/Delta QALY)	DOMINANT		

All values are discounted unless otherwise indicated.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care.

Sotagliflozin 200 mg + SoC reduced the costs of complications (−£1,777) and of SH events (−£2,211), offsetting the additional costs of treatment (£2,045), management (£2) and DKA events (£252), which led to a total incremental difference of −£1,687. A breakdown of direct lifetime costs by cost category is outlined in Table 4.4.

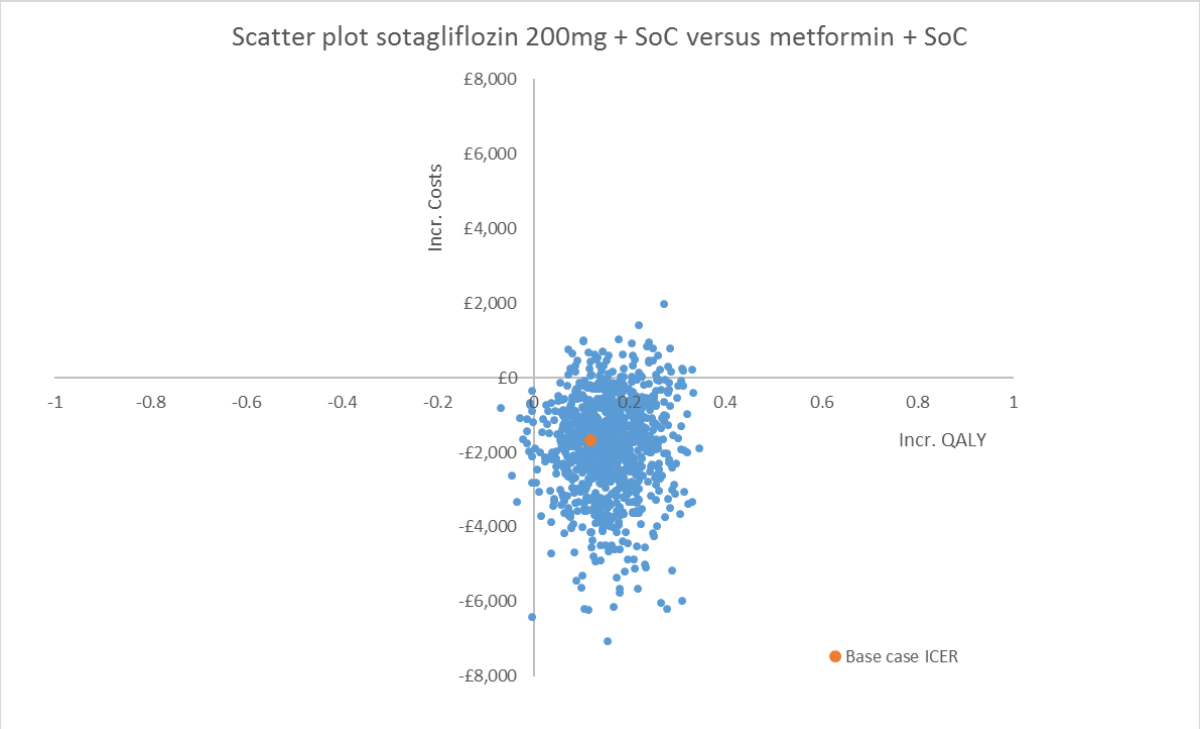
Table 4.3: Breakdown of costs (sotagliflozin 200 mg + standard of care versus placebo + standard of care)

	Sotagliflozin 200mg + SoC (£)	Placebo + SoC (£)	Incremental (£)
Total direct costs	**82,930**	**84,617**	**-1,687**
Treatment	31,294	29,249	2,045
Management	1,886	1,884	2
Cardiovascular disease	4,000	4,048	-48
Renal	5,325	5,681	-356
Ulcer/Amputation/Neuropathy	18,237	18,795	-558
Eye	13,497	14,312	-815
Non-severe hypoglycaemia	0	0	0
SHE 1 (requires non-medical assistance)	0	0	0
SHE 2 (requires medical assistance)	8,104	10,315	−2,211
Diabetic Ketoacidosis	586	334	252

SHE, severe hypoglycaemic event; SoC, Standard of care.

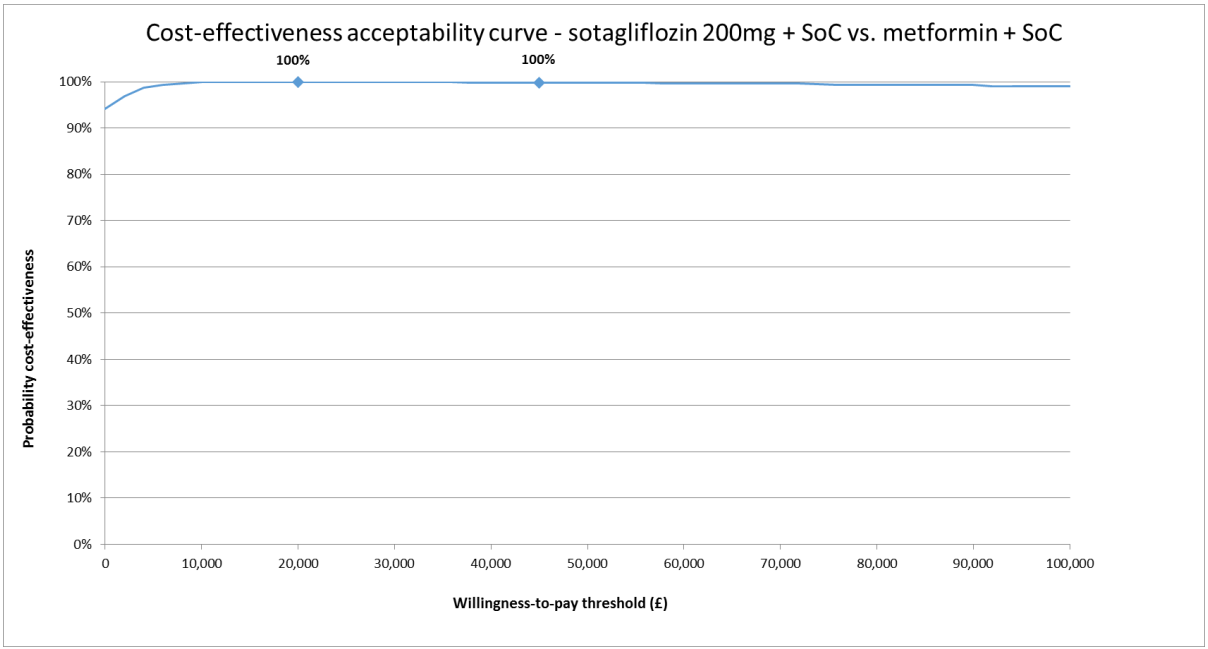
Probabilistic results were in line with deterministic results, indicating that sotagliflozin 200 mg + SoC was more effective and less costly (dominant) than metformin + SoC over a range of plausible input values. The incremental cost-effectiveness pairs for costs and QALYs gained are plotted in Figure 4.3. At a willingness-to-pay of £20,000 per QALY there is a 100% probability of sotagliflozin 200 mg + SoC being cost-effective relative to metformin + SoC (Figure 4.4).

Figure 4.3 Cost-effectiveness scatter plot – sotagliflozin 200 mg + SoC versus metformin + SoC



ICER, incremental cost-effectiveness ratio; QALY, quality of life-year; SoC, standard of care.

Figure 4.4 Cost-effectiveness acceptability curve – sotagliflozin 200mg standard of care versus metformin + standard of care



SoC, standard of care

4.3.1. Summary of the sensitivity analyses

Overall, the sensitivity analyses indicated that sotagliflozin 200 mg was cost-effective versus placebo under variation in a range of base-case assumptions. Similarly, changing cohort characteristics to match those of the inTandem2 population had only a minor impact on incremental outcomes, although survival and lifetime costs were higher overall in this analysis. Increasing the costs of sotagliflozin therapy to account for 100 ketone blood testing strips each year led to higher incremental costs (£1,664) than in the base-case analysis and a corresponding higher ICER (£15,057).

Changing assumptions around the duration of sotagliflozin therapy did not notably impact cost-effectiveness. This was due to the fact that costs and clinical benefits associated with sotagliflozin were balanced in the analysis (i.e. clinical benefits in terms of hypoglycaemia rates and HbA_{1c} were only applied in the modelling analysis during treatment with sotagliflozin and accompanied by the associated additional pharmacy costs). Using treatment effects for sotagliflozin 200 mg and placebo from the NMA produced a higher ICER than the base-case analysis. This was because although the HbA_{1c} benefit was comparable for sotagliflozin in this analysis, the benefits in terms of reduced hypoglycaemia risk were less pronounced. Indeed, the risk of SH was higher with sotagliflozin than placebo (0.269 versus 0.188 events per patient-year) in the NMA. Correspondingly, incremental quality-adjusted life-year (QALY) was lower than in the base-case, yielded higher incremental costs in the sotagliflozin 200 mg + SoC versus placebo + SoC analysis. Similarly, the lower hypoglycaemia event rates seen in the sotagliflozin 200 mg + SoC compared with metformin + SoC arm yielded an ICER below the threshold. This suggests the SH event rate is a key driver of the cost-effectiveness analysis results.

Changing assumptions on the long-term progression of HbA_{1c} in the modelling analysis had little impact on incremental outcomes. In the base-case analysis, it was assumed that HbA_{1c} levels return to the baseline level of 8.7% after 5 years of therapy with sotagliflozin (or placebo) and remained constant at that level for the remainder of the simulation. In a sensitivity analysis in which HbA_{1c} crept up by 0.018% and BMI increased by 0.095 kg/m^2 per year in both treatment arms, ICER increased to £12,956 per QALY gained, still remaining below £20,000 per QALY.

4.3.2. *PRIME — validation model (sotagliflozin vs insulin)*

To investigate the impact of structural uncertainty on the modelling analysis, the PRIME Diabetes Model (used in the base-case analysis) was used to run a simulation designed to reproduce the CORE Diabetes Model (CDM) base-case. It should be noted that there are some differences between the models in terms of long-term progression of risk factors. However, there are no differences in model inputs and assumptions related to treatment effects. The results of these simulations are summarised in Table 4.5. Full details for this analysis using the PRIME model are available on request.

Table 4.4 Comparison of cost-effectiveness outcomes with the PRIME Diabetes Model and the CORE Diabetes Model

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Difference
PRIME diabetes model outcomes			
Life expectancy (years)	17.49	17.41	0.08
QALYs	12.13	11.97	0.16
Total direct costs (£)	48,534	46,458	2,076
ICER (£ per QALY gained)	12,719		
CORE Diabetes Model Outcomes			
Life expectancy (years)	16.72	16.71	0.015
QALYs	8.38	8.27	0.11
Total direct costs (£)	78,366	77,418	948
ICER (£ per QALY gained)	8,578		

ICER, incremental cost−effectiveness ratio; LYG, life-years gained; QALYs, quality−adjusted life-years

Importantly, survival estimates were comparable across the two models. QALY was, overall, a little lower with the PRIME Diabetes Model, but the difference between treatments was greater. Both models used an additive approach to estimate QALY, and the differences in this area are assumed to be driven mainly by different approaches to calculating the effect of BMI and SH episodes on quality of life. Direct costs estimates are, overall, much higher with the CDM, where high costs were reported for diabetic foot complications and eye disease. By contrast, macrovascular complications were the biggest component of diabetes-related complication costs in the PRIME Diabetes Model simulation. Incremental costs were higher in the PRIME Diabetes Model analysis as lower overall complication costs did less to offset the acquisition costs of sotagliflozin treatment. ICERs were similar with both models

(although reached through different incremental values) and both simulations indicated that sotagliflozin is likely to be cost-effective by commonly quoted standards in the UK setting.

4.3.2.1. Subgroup analyses

Post hoc subgroup analyses were performed on the inTandem2 ITT population to identify patients with baseline HbA_{1c} ≥ 6.5%. This was performed to mirror NICE definition of inadequate control. According to NICE, inadequately controlled was defined as HbA_{1c} ≥6.5%. When the treatment effect for this group is applied to the base-case population (NDA), the ICER improves (£5,897 per QALY). A similar trend is seen when the treatment effect is applied to full ITT population with HbA_{1c} >6.5% (£7,427 per QALY). As noted above, it is well established that improvements in glycaemic control are influenced by baseline HbA_{1c} and the potential for treatment benefits may be greater in patients with relatively higher starting HbA_{1c}. This can be seen in the analysis were the treatment effects from the subgroup of patients of patients with HbA_{1c} >8.5% is applied in the model the ICER is dominant.

Post hoc analyses performed on the inTandem2 ITT population of patients with BMI >25 kg/m^2 (reflective of average T1D patients as seen in CPRD analysis) also results in a similar ICER (£ 8,096 per QALY). The ICER for patients with HbA_{1c} >6.5% and BMI >25 kg/m^2 the ICER is £6,212 per QALY.

The ICER increases when the treatment effects of the NMA are applied to the NDA population (£10,948 per QALY). Compared to £ 20,737 when applied to patients with HbA_{1c} >6.5% and BMI >25 kg/m^2. This is because the NDA cohort represents patients with baseline HbA_{1c} of 8.6% leading to increased risks of diabetic related complications due to uncontrolled risk. The BMI disutilities (starting at 25 kg/m^2) are a key reason for the difference in the ICERs for the two populations considered. Subgroup analyses are reported in Table 4.5.

Table 4.5 Subgroup analysis

	Subgroup analyses						
	Treatment effects	Total Costs (£)			Total QALYs			ICER
		Sotagliflozin 200mg + SoC	Placebo + SoC	Incremental (£)	Sotagliflozin 200mg + SoC	Placebo + SoC	Incremental (£)	
Subgroup of inTandem2 (ITT analysis) with HbA_{1c}>6.5% and BMI 25 kg/m²	Subgroup of inTandem2 (ITT analysis) with HbA_{1c} >6.5% and BMI ≥25 kg/m²	77,075	76,047	1,028	10.633	10.495	0.138	6,212
Subgroup of inTandem2 (ITT analysis) with HbA_{1c} >6.5%	Subgroup of inTandem2 (ITT analysis) with HbA_{1c} >6.5%	77,075	76,047	1,028	10.633	10.495	0.138	7,427
Subgroup of inTandem2 (ITT analysis) with HbA_{1c} >6.5% and BMI ≥25 kg/m²	NMA	80,044	78,068	1,976	10.388	10.293	0.095	20,737

BMI, body mass index; HbA_{1c}, glycated haemoglobin; ITT, intent to treat; NMA, network meta-analysis

4.3.3. Validation

The CDM model has been used extensively to demonstrate the cost-effectiveness of products launching in T1D and T2D and is robustly validated through both external validation studies (e.g. through participation in the Mount Hood Challenge) and internal update and review. The CDM is one of the few models currently available with published validations that demonstrate the reliability of outcomes (116). In addition, results from the model have been widely published, with over 80 peer-reviewed publications.

Validation to analyses performed in PRIME

Prior to initiating the present analysis, the PRIME Diabetes Model was validated in two main ways as outlined in Valentine et al. 2017 (72).

For the present analysis, the PRIME model was initiated with clinical characteristics, costs and outcomes consistent with those used in the CDM, and predicted costs and QALYs were compared over both models. The ICERs across both models were highly reliable.

4.3.4. Interpretation and conclusions of economic evidence

The CDM is the most widely adopted economic model in diabetes available to users from academia and healthcare industries, as well as healthcare payers and decision makers. In addition, results from the model have been widely published, with over 80 peer-reviewed publications.

In order to ensure UK-specific applicability within the current analyses, a comprehensive review was conducted to identify the most up-to-date data specific to the UK setting (including costs, background complications and management settings). Where appropriate, sensitivity analyses were conducted to test assumptions around key inputs, leading to a robust and credible set of analyses inputs.

Under base-case assumptions, sotagliflozin 200 mg + SoC was more effective and more costly versus placebo + SoC. Sotagliflozin 200 mg + SoC was cost-effective compared with placebo + SoC at a cost-effectiveness threshold of £20,000 per QALY. This was confirmed in all the sensitivity analyses conducted, except when using the NMA results. Under base-case assumptions, sotagliflozin 200 mg + SoC was more effective and less costly (dominant) versus metformin + SoC. Sensitivity analyses indicated that the model was robust to all of the assumptions tested.

4.3.5. Key strengths and limitations

Strengths

- Identification of precise, coherent, up-to-date, and relevant data on the many inputs required to model T1D represents a challenge. Nevertheless, the best available data were used and tested by means of sensitivity analyses. Computer simulation modelling remains the best option currently available to estimate the clinical and economic consequences of therapeutic interventions in the medium to long-term. No model can claim to be perfectly accurate but the IQVIA CDM is one of the few models currently available with published validations that demonstrate the reliability of outcomes (117).

- Consistent with previous NICE appraisals in T1D, all positive differential HbA_{1c}, BMI and SBP effects seen in the sotagliflozin arm were abolished after 5 years in the base-case (and 2 years in sensitivity analysis). For modelling this in the CDM, patients in the sotagliflozin arm had to experience a high progression of these parameters, in order to catch and bridge the gaps between intervention and control arms.

Limitations

- This economic analysis is based on parameters that are not specific to a T1D population but utilises data specific to T2D. However, the assumptions were based on established risk equations which are considered to be a reliable proxy measure of disease progression and complications outcomes.

- Due to limited treatment outcomes available from the NMA, treatments effects for only HbA_{1c} and BMI and SH events were modelled in the sotagliflozin + SoC versus metformin + SoC analyses. While these are key drivers of subsequent patient outcomes, additional information on other clinical parameters would enhance the precision of simulated patient events downstream.

- Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, consistent with previous economic modelling in T1D (Appendix N of NG17(6)), a linear disutility of non-SH was utilised. Additionally, it is believed that the

utility value associated with suffering a severe hypoglycaemic event already incorporates this disutility (98).

- Outcomes derived from the NMA data should be interpreted with care, as high statistical and qualitative heterogeneity were observed, both in the comparison versus metformin as well the inTandem trials. One of the major differences is seen in the trial design, as patients in both inTandem1 and inTandem2 underwent an exhaustive insulin optimisation period following screening, which alone reduced the HbA_{1c} levels considerably. The indirect comparison versus metformin + SoC was limited to HbA_{1c}, BMI and SH events to reflect key drivers and data limitations.

An independent analysis was undertaken using the PRIME model to explore the impact of structural uncertainty. Results of the PRIME model (using the same set of parameters and assumptions) confirm that sotagliflozin 200 mg + SoC is cost-effective versus SoC alone or SoC with adjunct metformin for patients with T1D.

5. References

1. Lapuerta P, Zambrowicz B, Strumph P, Sands A. Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. Diab Vasc Dis Res. 2015;12(2):101-10.
2. Aronoff SL, Berkowitz K, Shreiner B, Want L. Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. Diabetes Spectrum 2004;17(3):183-90.
3. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169-76.
4. Gerich JE. Physiology of glucose homeostasis. Diab Obs Metab. 2000;2(6):345-50.
5. Nathan DM, Bayless M, Cleary P, Genuth S, Gubitosi-Klug R, Lachin JM, et al. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes. 2013;62(12):3976-86.
6. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management (NG17) London: National Institute for Health and Care Excellence; 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ng17.
7. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions Complications (DCCT/EDIC) Research Group. Risk Factors for Cardiovascular Disease in Type 1 Diabetes. Diabetes. 2016;65(5):1370-9.
8. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH, et al. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care. 2008;31(7):1360-6.
9. Bode BW, Garg SK. The emerging role of adjunctive noninsulin antihyperglycemic therapy in the management of type 1 diabetes. Endocr Pract. 2016;22(2):220-30.
10. Graveling AJ, Frier BM. The risks of nocturnal hypoglycaemia in insulin-treated diabetes. Diabetes Res Clin Pract. 2017;133:30-9.
11. Ang KH, Sherr JL. Moving beyond subcutaneous insulin: the application of adjunctive therapies to the treatment of type 1 diabetes. Expert Opin Drug Deliv. 2017;14(9):1113-31.
12. Suh S, Kim JH. Glycemic Variability: How Do We Measure It and Why Is It Important? Diabetes Metab J. 2015;39(4):273-82.
13. UK NHS. National Diabetes Audit 2018 [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/clinical-audits-and-registries/our-clinical-audits-and-registries/national-diabetes-audit.
14. Aragona M, Giannarelli R, Del Prato S. Intensive insulin treatment and postprandial control in Type 1 diabetes. Acta Biomed. 2005;76 Suppl 3:26-30.
15. Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care. 2006;29(7):1486-90.
16. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care. 2008;31(11):2198-202.
17. Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia. 2008;51(2):365-71.
18. Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? Diabetes. 2005;54(1):1-7.
19. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, Group DER. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial--revisited. Diabetes. 2008;57(4):995-1001.

20. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643-53.

21. Lawton J, Rankin D, Cooke D, Elliott J, Amiel S, Heller S, et al. Patients' experiences of adjusting insulin doses when implementing flexible intensive insulin therapy: a longitudinal, qualitative investigation. Diabetes Res Clin Pract. 2012;98(2):236-42.

22. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30.

23. Byrne M, O'Connell A, Egan AM, Dinneen SF, Hynes L, O'Hara MC, et al. A core outcomes set for clinical trials of interventions for young adults with type 1 diabetes: an international, multi-perspective Delphi consensus study. Trials. 2017;18(1):602.

24. Rodbard D. Continuous Glucose Monitoring: A Review of Recent Studies Demonstrating Improved Glycemic Outcomes. Diabetes Technol Ther. 2017;19(S3):S25-S37.

25. Baxter M, Hudson R, Mahon J, Bartlett C, Samyshkin Y, Alexiou D, et al. Estimating the impact of better management of glycaemic control in adults with Type 1 and Type 2 diabetes on the number of clinical complications and the associated financial benefit (supplementary information online). Diabet Med. 2016;33(11):1575-81.

26. Sanofi. Data on file: Clinical Practice Research Datalink (CPRD) Analysis to support economic modelling activities in a UK-specific context. 2019.

27. Diabetes UK. The cost of diabetes 2014 [cited 2019 February]. Available from: https://www.diabetes.org.uk/resources-s3/2017-11/diabetes%20uk%20cost%20of%20diabetes%20report.pdf.

28. Kanavos P, van den Aardweg S, Schurer W. Diabetes expenditure, burden of disease and management in 5 EU countries London: London School of Economics; 2012 [cited 2019 February]. Available from: http://www.lse.ac.uk/business-and-consultancy/consulting/assets/documents/diabetes-expenditure-burden-of-disease-and-management-in-5-eu-countries.pdf.

29. Lachin JM, Bebu I, Bergenstal RM, Pop-Busui R, Service FJ, Zinman B, et al. Association of Glycemic Variability in Type 1 Diabetes With Progression of Microvascular Outcomes in the Diabetes Control and Complications Trial. Diabetes Care. 2017;40(6):777-83.

30. Sanofi. Data on file: Type 1 diabetes and patient unmet needs. 2017.

31. Petrie JR, Chaturvedi N, Ford I, Brouwers M, Greenlaw N, Tillin T, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 2017;5(8):597-609.

32. Sanofi. Data on file: Advisory board. Sotagliflozin within the context of UK type 1 diabetes care. 2018.

33. Sanofi. Data on file: Patient characteristic and treatment pattern for uncontrolled adult type 1 diabetes patients: a cross-sectional analysis to support economic modelling activities in a UK-specific context 2018.

34. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care. 2019.

35. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual (PMG20) 2014 [cited 2019 February]. Available from:

https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869.

36. Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care. 2018;41(9):1970-80.
37. Danne T, Cariou B, Banks P, Brandle M, Brath H, Franek E, et al. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. Diabetes Care. 2018;41(9):1981-90.
38. Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. N Engl J Med. 2017;377(24):2337-48.
39. Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, et al. Effect of adjunct metformin treatment on levels of plasma lipids in patients with type 1 diabetes. Diabetes Obes Metab. 2009;11(10):966-77.
40. Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, et al. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. PLoS One. 2008;3(10):e3363.
41. Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. Basic Clin Pharmacol Toxicol. 2009;105(3):145-9.
42. Zawada A, Naskret D, Burchardt P, Niedzwiecki P, Pilacinski S, Wierusz-Wysocka B, et al. Metformin added to intensive insulin therapy improves metabolic control in patients with type 1 diabetes and excess body fat. Pol Arch Intern Med. 2018;128(5):294-300.
43. Burchardt P, Zawada A, Tabaczewski P, Naskret D, Kaczmarek J, Marcinkaniec J, et al. Metformin added to intensive insulin therapy reduces plasma levels of glycated but not oxidized lowdensity lipoprotein in young patients with type 1 diabetes and obesity in comparison with insulin alone: a pilot study. Pol Arch Med. 2013;123(10):526-32.
44. Meyer L, Bohme P, Delbachian I, Lehert P, Cugnardey N, Drouin P, et al. The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. Diabetes Care. 2002;25(12):2153-8.
45. Pitocco D, Zaccardi F, Tarzia P, Milo M, Scavone G, Rizzo P, et al. Metformin improves endothelial function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study. Diabetes Obes Metab. 2013;15(5):427-31.
46. Sanofi. Clinical study report: inTandem1 (LX4211.309). 2017.
47. Sanofi. Clinical study report: inTandem2 (LX4211.310). 2017.
48. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.
49. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013;34(39):3035-87.
50. Lane JD, Barkauskas CE, Surwit RS, Feinglos MN. Caffeine impairs glucose metabolism in type 2 diabetes. Diabetes Care. 2004;27(8):2047-8.
51. Beck RW, Bergenstal RM, Riddlesworth TD, Kollman C. The Association of Biochemical Hypoglycemia with the Subsequent Risk of a Severe Hypoglycemic Event: Analysis of the DCCT Data Set. Diabetes Technol Ther. 2019;21(1):1-5.
52. DiaTribe. Glycemic Outcomes Beyond A1c: Standardization & Implementation' Bethesda, MD2017 [cited 2019 February]. Available from: https://diatribe.org/measuringwhatmatters.

53. Sanofi. Data on file: 2.5 Clinical overview (type 1 diabetes mellitus) sotagliflozin (SAR439954). 2018.
54. Brod M, Nikolajsen A, Weatherall J, Pfeiffer KM. Understanding Post-Prandial Hyperglycemia in Patients with Type 1 and Type 2 Diabetes: A Web-based Survey in Germany, the UK, and USA. Diabetes Therapy. 2016;7(2):335-48.
55. Brod M, Nikolajsen A, Weatherall J, Pfeiffer KM. The Economic Burden of Post-prandial Hyperglycemia (PPH) Among People with Type 1 and Type 2 Diabetes in Three Countries. Diabetes Ther 2016;7(1):75-90.
56. Monnier L, Colette C. Contributions of fasting and postprandial glucose to hemoglobin A1c. Endocr Pract 2006;12 Suppl 1:42-6.
57. Sanofi. Sotagliflozin summary of product characteristics. 2018.
58. Ahola AJ, Makimattila S, Saraheimo M, Mikkila V, Forsblom C, Freese R, et al. Many patients with Type 1 diabetes estimate their prandial insulin need inappropriately. J Diabetes 2010;2(3):194-202.
59. Petrie JR, Chaturvedi N, Ford I, Hramiak I, Hughes AD, Jenkins AJ, et al. Metformin in adults with type 1 diabetes: Design and methods of REducing with MetfOrmin Vascular Adverse Lesions (REMOVAL): An international multicentre trial. Diabetes Obes Metab. 2017;19(4):509-16.
60. Yang Y, Chen S, Pan H, Zou Y, Wang B, Wang G, et al. Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes: Systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2017;96(21):e6944.
61. Sanofi. Clinical study report: inTandem3 (LX4211.312). 2017.
62. Sanofi. Data on file: 2.7.4 Summary of clinical safety (type 1 diabetes mellitus) sotagliflozin (SAR439954). 2018.
63. Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, Davis M, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86.
64. Khoo TK, Olson KM. Effects of Sotagliflozin Added to Insulin in Type 1 Diabetes. N Engl J Med. 2018;378(10):967.
65. Garg SK, Strumph P. Effects of Sotagliflozin Added to Insulin in Type 1 Diabetes. N Engl J Med. 2018;378(10):967-8.
66. American Diabetes Association. Standards of Medical Care in Diabetes 2017;40(Suppl. 1). 2017 [cited 2019 February]. Available from: http://care.diabetesjournals.org/content/diacare/suppl/2016/12/15/40.Supplement_1.DC1/DC_40_S1_final.pdf.
67. Meng H, Zhang A, Liang Y, Hao J, Zhang X, Lu J. Effect of metformin on glycaemic control in patients with type 1 diabetes: A meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2018;34(4):e2983.
68. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28.
69. Wu JH, Foote C, Blomster J, Toyama T, Perkovic V, Sundstrom J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2016;4(5):411-9.
70. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus

Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017;136(3):249-59.

71. Toulis KA, Willis BH, Marshall T, Kumarendran B, Gokhale K, Ghosh S, et al. All-Cause Mortality in Patients With Diabetes Under Treatment With Dapagliflozin: A Population-Based, Open-Cohort Study in The Health Improvement Network Database. J Clin Endocrinol Metab. 2017;102(5):1719-25.
72. Valentine WJ, Pollock RF, Saunders R, Bae J, Norrbacka K, Boye K. The Prime Diabetes Model: Novel Methods for Estimating Long-Term Clinical and Cost Outcomes in Type 1 Diabetes Mellitus. Value Health. 2017;20(7):985-91.
73. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, 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.
74. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE Diabetes Model. Value Health. 2014;17(6):714-24.
75. National Institute for Health and Care Excellence (NICE). Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (TA390) 2016 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ta390/resources/canagliflozin-dapagliflozin-and-empagliflozin-as-monotherapies-for-treating-type-2-diabetes-pdf-82602903454405.
76. NHS. National Diabetes Audit - 2012-2013. Report 2: Care Processes and Treatment Targets [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/national-diabetes-audit-2012-2013-report-1-care-processes-and-treatment-targets.
77. World Health Organization. Health topics: Obesity [cited 2019 February]. Available from: https://www.who.int/topics/obesity/en/.
78. Sanofi. Data on file: IMS CDM Version 9. 2018.
79. Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Archives of internal medicine. 2009;169(14):1307-16.
80. Office for National Statistics. Opinions and Lifestyle Survey, Smoking Habits Amongst Adults, 2012 [cited 2019 February]. Available from: https://webarchive.nationalarchives.gov.uk/20160107053428/http://www.ons.gov.uk/ons/rel/ghs/opinions-and-lifestyle-survey/smoking-habits-amongst-adults--2012/index.html.
81. NHS. Health Survey for England - 2011. Health, social care and lifestyles [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2011-health-social-care-and-lifestyles.
82. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care. 2012;35(8):1638-42.
83. Organization WH. ObesityFeb 2019. Available from: https://www.who.int/topics/obesity/en/.
84. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004;47(10):1747-59.

85. Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol. 1987;59(14):91g-4g.

86. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. Diabetes care. 2016;39(5):686-93.

87. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. European heart journal. 2001;22(7):554-72.

88. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet (London, England). 2009;373(9667):929-40.

89. National Institute for Health and Care Excellence. Exenatide once-weekly (BYDUREON®) for the treatment of type 2 diabetes. 2011.

90. Jones LE, Doebbeling CC. Depression screening disparities among veterans with diabetes compared with the general veteran population. Diabetes care. 2007;30(9):2216-21.

91. O'Meara S, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. Health Technol Assess. 2000;4(21):1-237.

92. Kantor J, Margolis DJ. Treatment options for diabetic neuropathic foot ulcers: a cost-effectiveness analysis. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2001;27(4):347-51.

93. Lopez-Bastida J, Cabrera-Lopez F, Serrano-Aguilar P. Sensitivity and specificity of digital retinal imaging for screening diabetic retinopathy. Diabetic medicine : a journal of the British Diabetic Association. 2007;24(4):403-7.

94. Cortes-Sanabria L, Martinez-Ramirez HR, Hernandez JL, Rojas-Campos E, Canales-Munoz JL, Cueto-Manzano AM. Utility of the Dipstick Micraltest II in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension. Rev Invest Clin. 2006;58(3):190-7.

95. Office for National Statistics. National life tables: UK 2014-2016 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.

96. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Med Decis Making. 2016;36(8):1020-33.

97. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462-70.

98. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006;22(8):1523-34.

99. NHS. Overview: Obesity [cited 2019 February]. Available from: https://www.nhs.uk/conditions/obesity/.

100. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Medical Decision Making. 2016;36(8):1020-33.

101. PSSRU. Unit Costs of Health and Social Care 2017: Inflation indices [cited 2019 February]. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/.

102. IQVIA. Real-world data [cited 2019 February]. Available from: https://www.iqvia.com/solutions/real-world-value-and-outcomes/realworld-data.

103. NHS. Prescription Cost Analysis 2016 [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2016.

104. Bloomgarden Z. Sodium glucose transporter 2 inhibition: a new approach to diabetes treatment. J Diabetes. 2013;5(3):225-7.

105. NHS. Oxfordshire Clinical Commissioning Group. KETONE TESTING AND SICK DAY RULES GUIDELINE 2017 [cited 2019 January]. Available from: https://www.oxfordshireccg.nhs.uk/professional-resources/documents/clinical-guidelines/diabetes/ketone-testing-and-sick-day-rules-guidance.pdf.

106. NHS. North Central London Joint Formulary Committee. Guideline for blood glucose & ketone monitoring for adults with diabetes. 2018 [cited 2018 February]. Available from: https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/6_Blood_glucose_ketone_monitoring.pdf.

107. PSSRU. Reference costs - National schedule of reference costs 2017/2018 [cited 2019 February]. Available from: https://improvement.nhs.uk/resources/reference-costs/.

108. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? Annals of clinical biochemistry. 2009;46(Pt 3):205-17.

109. National Institute for Health and Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181) 2016 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/cg181/resources/cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-pdf-35109807660997.

110. Beaudet A, Palmer JL, Timlin L, Wilson B, Bruhn D, Boye KS, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. J Med Econ. 2011;14(3):357-66.

111. National Institute for Health and Care Excellence (NICE). Renal replacement therapy and conservative management (CG125). Updated to NG107. 2011 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ng107/resources/renal-replacement-therapy-and-conservative-management-pdf-66141542991301.

112. National Institute for Health and Care Excellence (NICE). Final appraisal determination.

Aflibercept for treating diabetic macular oedema 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ta346/documents/macular-oedema-diabetic-aflibercept-final-appraisal-determination-document2.

113. Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J Wound Care. 2002;11(2):70-4.

114. National Institute for Health and Care Excellence (NICE). Peripheral arterial disease: diagnosis and management (CG147) 2012 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/cg147/resources/peripheral-arterial-disease-diagnosis-and-management-pdf-35109575873989.

115. Office for National Statistics. National life tables, UK: 2014 to 2016 [cited 2019 February]. Available from: https://www.ons.gov.uk/releases/nationallifetablesuk2014to2016.

116. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin. 2004;20 Suppl 1:S27-S40.

117. Palmer AJ, Mount Hood 5 Modeling G, Clarke P, Gray A, Leal J, Lloyd A, et al. Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood challenge meeting. Value Health. 2013;16(4):670-85.

Addendum: Clinical and cost-effectiveness evidence for sotagliflozin for the treatment of Type 1 diabetes in patients with body mass index ≥27kg/m^2 [ID1376]

Contents

Abbreviations

AE	Adverse event
BMI	Body mass index
CGM	Continuous glucose monitoring
CSII	Continuous subcutaneous insulin infusion
m-ITT	Modified intention-to-treat
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DDS2	2-item diabetes distress screening instrument
DTSQ	Diabetes treatment satisfaction questionnaire
ERG	Expert Review Group
FPG	Fasting plasma glucose
IU	International units
HbA_{1c}	Glycated haemoglobin
MDI	Multiple daily injections
PPG	Post prandial glucose
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation;

1. Introduction:

On 28 February 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending sotagliflozin as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus (T1D) with a body mass index (BMI) ≥27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

Sanofi believe it is important for the Expert Review Group (ERG) and the NICE Committee to understand the rationale and reasoning behind the positive opinion for a patient population with a BMI of ≥27 kg/m^2 from CHMP, so that we can provide relevant analyses to the decision problem. Below are details following the D180 questions from CHMP:

QUESTION from the CHMP;

Due to the increased risk of DKA, the benefit/risk balance is considered as negative in the proposed target population. A population with a more pronounced benefit of treatment and/or a lower risk of DKA should be identified. This population could e.g. be patients with BMI ≥27kg/m^2.

Sanofi RESPONSE:

In order to identify a population of more pronounced benefit-risk, detailed efficacy and safety analyses were conducted in subgroups split by baseline BMI <27 kg/m² or ≥27kg/m². In addition to a higher BMI, overweight and obese patients with BMI ≥27kg/m² also tended to be older, to have a longer duration of disease and to have a higher SBP at baseline, and therefore presented a higher medical need that may not be addressed by insulin alone. Overall, at Week 24, the efficacy of sotagliflozin versus placebo was more pronounced in the overweight and obese subgroups, especially for the measurements of HbA_{1c}, body weight, time in range, DTSQ and DDS2. Tests of a treatment by subgroup interaction were associated with p-values <0.05 for the HbA_{1c}, body weight, and DTSQ change from baseline scores. Favourable trends for less severe hypoglycaemia, less DKA and less diarrhoea were also observed. These numerical differences, compared to patients with baseline BMI <27 kg/m², were greater for the 400 mg dose. Based on these data, the Applicant accepts the CHMP's recommendation and proposes to revise the indication in the SmPC as follows: "Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in

adults with type 1 diabetes mellitus with BMI ≥27 kg/m^2, who have failed to achieve desired glycaemic control despite optimal insulin therapy."

Full results are provided in commercial in confidence Appendix A-C.

During the regulatory review process, additional efficacy and safety subgroup analyses were conducted on the pooled dataset to address the CHMP requests, in particular in subgroups categorised by baseline BMI <27 kg/m² or ≥27 kg/m² (See commercial in confidence files Appendix A-C). These analyses confirmed a numerical trend for a better benefit-risk profile in patients with BMI ≥27 kg/m² compared to leaner patients. It should be noted that the subgroup of patients with baseline BMI ≥27 kg/m^2 is not a pre-specified subgroup of the overall study populations. No subgroup analyses were conducted combining two or more baseline characteristics since this would lead to insufficient sample size for an adequate analysis.

To summarise, this subgroup was also chosen because sotagliflozin compared to placebo was associated with more favourable efficacy results and benefit-risk ratio in the baseline BMI ≥27 kg/m^2 subgroup versus the comparisons made in the baseline BMI <27 kg/m^2.

Sotagliflozin is an innovative adjunctive therapy intended for use in adult patients with T1D with a BMI ≥27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy. It is the first dual sodium-glucose transporter-1 (SGLT-1) and sodium-glucose transporter-2 (SGLT-2) inhibitor licensed in T1D (the European Marketing Authorisation is expected no later than 6th May).

Efficacy and safety analyses are available for the main parameters (such as HbA_{1c}, net benefit, weight, systolic blood pressure (SBP) and safety) for this subgroup, (and for the residual group with baseline BMI <27 kg/m²). These results are summarised below. Please refer to the original submission dossier for the efficacy results of the three Phase III trials used to support the regulatory submission.

In line with our original submission, we present results for the inTandem1 and inTandem2 studies and the pool of these studies (ES1 pool).

2. Clinical effectiveness

Summary points

- Overall at Week 24, the efficacy of sotagliflozin versus insulin alone (placebo) was more pronounced in the subgroup of patients with baseline BMI ≥27 kg/m^2, especially for the HbA_{1c} endpoints, body weight, time in range, DTSQ and DDS2.
- Sotagliflozin as an adjunct to insulin when compared to insulin alone (placebo) in patients with baseline BMI ≥27 kg/m^2, resulted in consistent and sustained improvements in glycaemic control with patients spending more time in range and experiencing less glucose variability.
- Additional dose-dependent benefits beyond HbA_{1c} were observed: body weight loss, insulin dose reduction and lowering of blood pressure.
- Patient-reported outcomes also significantly improved.

2.1. Baseline characteristics

Key demographic and baseline characteristics for patients with baseline BMI ≥27 kg/m^2 are summarised in Table 1for inTandem1 and inTandem2 trial. For information on the total trial population, please refer to the original submission file submitted on 14th of February 2019.

Overweight and obese patients with a BMI ≥27 kg/m² tended to be older and to have a longer duration of disease compared to patients with BMI <27 kg/m².

Table 1. Summary of baseline patient demographics and clinical characteristics for inTandem1 and inTandem2 (patients with baseline BMI ≥27 kg/m^2)(1, 2)

Characteristics	inTandem1			inTandem2		
	Placebo (N=174)	Sotagliflozin 200 mg (N=170)	Sotagliflozin 400 mg (N=175)	Placebo (N=124)	Sotagliflozin 200 mg (N=135)	Sotagliflozin 400 mg (N=138)
Age in years, Mean (SD)	44.7 (11.80)	47.0 (13.52)	46.6 (12.02)	41.2 (13.47)	44.4 (11.51)	43.9 (11.82)
Female sex, n (%)	82 (47.1)	85 (50.0)	91 (52.0)	61 (49.2)	63 (46.7)	68 (49.3)
Race[1] white, n (%)	164 (94.3)	153 (90.0)	163 (93.1)	119 (96.0)	127 (94.2)	130 (94.2)

Characteristics	inTandem1			inTandem2		
	Placebo (N=174)	Sotagliflozin 200 mg (N=170)	Sotagliflozin 400 mg (N=175)	Placebo (N=124)	Sotagliflozin 200 mg (N=135)	Sotagliflozin 400 mg (N=138)
Duration of diabetes (years), n (%)						
<20	68 (39.1)	62 (36.5)	65 (37.1)	70 (56.5)	72 (53.3)	89 (64.5)
≥20 to <40	89 (51.1)	85 (50.0)	89 (50.9)	44 (35.5)	55 (40.7)	40 (29.0)
≥40	17 (9.8)	23 (13.5)	21 (12.0)	10 (8.1)	8 (5.9)	9 (6.5)
Body weight in kg, Mean (SD)	95.36 (15.815)	96.08 (15.362)	94.17 (15.652)	92.58 (14.439)	92.92 (15.335)	93.00 (16.482)
BMI (kg/m^2), Mean (SD)	32.32 (4.209)	32.97 (4.449)	32.36 (4.204)	31.61 (4.265)	31.89 (4.191)	31.45 (3.797)
Insulin delivery method[2], CSII, n(%)	104 (59.8)	103 (60.6)	112 (64.0)	34 (27.4)	37 (27.4)	35 (25.4)
Total daily insulin dose (IU/day), Mean (SD)	79.41 (45.260)	78.34 (47.014)	73.38 (41.391)	75.76 (35.687)	73.23 (32.735)	70.58 (31.157)
Bolus insulin dose (IU/day), Mean (SD)	38.67 (27.995)	36.57 (26.571)	35.09 (25.727)	39.38 (25.930)	37.13 (20.171)	36.62 (22.290)
Basal insulin dose (IU/day), Mean (SD)	40.73 (21.378)	41.77 (26.344)	38.29 (20.212)	36.37 (15.982)	36.09 (17.869)	33.90 (14.796)
HbA_{1c} (%), Mean (SD)	7.54 (0.705)	7.69 (0.699)	7.57 (0.707)	7.73 (0.822)	7.75 (0.804)	7.72 (0.789)
Baseline FPG (mg/dL), Mean (SD)	156.02 (65.370)	160.32 (72.511)	146.82 (63.426)	159.15 (67.686)	167.41 (72.143)	168.39 (70.878)
2-hour PPG (mg/dL), N[3], Mean (SD)	N=30, 215.80 (71.271)	N=28, 214.04 (100.333)	N=33, 207.12 (64.638)	N=22, 236.77 (93.817)	N=29, 213.34 (95.356)	N=29, 210.97 (100.828)
SBP (mm Hg), Mean (SD)	122.5 (12.62)	122.1 (15.08)	121.8 (14.67)	126.8 (15.96)	127.6 (14.73)	125.9 (13.82)
SBP ≥130 mm Hg[4], n (%)	48 (27.6)	46 (27.1)	50 (28.6)	51 (41.1)	55 (40.7)	58 (42.0)
DBP (mmHg), Mean (SD)	77.6 (8.09)	78.0 (9.37)	77.2 (8.15)	78.5 (8.39)	80.3 (9.61)	78.5 (8.09)
DTSQs score, Mean (SD)	N=170, 29.1 (4.62)	N=169, 28.6 (5.14)	N=172, 29.2 (4.90)	N=121, 28.2 (5.52)	N=131, 28.2 (5.18)	N=137, 28.2 (4.83)
DDS2 score, Mean (SD)	N=170, 4.9 (2.27)	N=169, 5.1 (2.00)	N=173, 4.9 (2.21)	N=122, 5.3 (2.20)	N=131, 5.7 (2.04)	N=137, 5.4 (2.01)

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; DDS2, 2-item diabetes distress screening instrument; DTSQ, diabetes treatment satisfaction questionnaire; FPG, fasting plasma glucose; IU, international units; HbA_{1c}, glycated haemoglobin; PPG, post prandial glucose; SBP, systolic blood pressure; SD, standard deviation;

In Table 2 a key demographic and baseline characteristics for patients with baseline BMI ≥27 kg/m^2 are summarised for the pooled data of inTandem1 and inTandem2 (ES1 pool).

Table 2. Summary of baseline patient demographics and clinical characteristics for pooled data (patients with baseline BMI ≥27 kg/m^2) (3)

Characteristics	ES1 pool		
	Placebo (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Age in years, Mean (SD)	43.3 (12.62)	45.9 (12.72)	45.5 (11.98)
Female sex, n (%)	143 (48.0)	148 (48.5)	159 (50.8)
Race[1]white, n (%)	283 (95.0)	280 (91.8)	293 (93.6)
Duration of diabetes (years), n (%)			
<20	138 (46.3)	134 (43.9)	154 (49.2)
≥20 to <40	133 (44.6)	140 (45.9)	129 (41.2)
≥40	27 (9.1)	31 (10.2)	30 (9.6)
Body weight in kg , Mean (SD)	94.20 (15.294)	94.68 (15.405)	93.66 (16.152)
BMI (kg/m^2), Mean (SD)	32.03 (4.240)	32.49 (4.363)	31.96 (4.049)
Insulin Delivery Method[2], CSII, n (%)	138 (46.3)	140 (45.9)	147 (47.0)
Total daily insulin dose (IU/day), Mean (SD)	N=298, 77.89 (41.519)	N=305, 76.08 (41.323)	N=312, 72.15 (37.215)
Bolus insulin dose (IU/day), Mean (SD)	38.97 (27.112)	36.82 (23.914)	35.76 (24.525)
Basal insulin dose (IU/day), Mean (SD)	38.92 (19.407)	39.26(23.120)	36.35 (18.131)
HbA_{1c} (%), Mean (SD)	7.62 (0.760)	7.72 (0.747)	7.63 (0.747)
Baseline FPG (mg/dL), Mean (SD)	157.33 (66.249)	163.46 (72.315)	156.33 (67.561)
SBP (mm Hg), Mean (SD)	124.3 (14.24)	124.6 (15.15)	123.6 (14.42)
SBP ≥130 mm Hg[4], n (%)	99 (33.2)	101 (33.1)	108 (34.5)
DBP (mm Hg), Mean (SD)	78.0 (8.21)	79.1 (9.53)	77.8 (8.14)
2-hour PPG (mg/dL), N, Mean (SD)	N=52, 224.67. (81.376)	N=57, 213.68 (96.954)	N=62, 208.92 (82.837)
DTSQs score, N, Mean (SD)	N=291, 28.7 (5.74)	N=300, 28.4 (5.15)	N=309, 28.8 (4.89)
DDS2 score, N, Mean (SD)	N=292, 5.1 (2.25)	N=300, 5.4 (2.03)	N=310, 5.1 (2.14)
Time in range (≥70 to ≤180 mg/dL), (%)	N=58, 50.683 (14.5506)	N=59, 52.155 (52.464)	N=65, 50.317 (50.801)

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DBP, diastolic blood pressure; DDS2, 2-item diabetes distress screening instrument; DTSQ, diabetes treatment satisfaction questionnaire; FPG, fasting plasma glucose; IU, international units; HbA_{1c}, glycated haemoglobin; PPG, post prandial glucose; SBP, systolic blood pressure; SD, standard deviation

2.2. Glycaemic control following adjunctive sotagliflozin

2.2.1. Change from baseline in HbA_{1c} at Week 24 and Week 52

For inTandem1 and inTandem2, the primary endpoint was the change from baseline to week 24 in HbA_{1c} in either sotagliflozin treatment group (200 mg or 400 mg) compared with insulin alone (placebo).

In the individual studies inTandem1 and inTandem2, insulin treatment was optimised before randomisation in a 6-week run-in period. Sotagliflozin 200 mg and 400 mg resulted in a clinically meaningful decrease in HbA_{1c} at Week 24. A modest decrease in HbA_{1c} in the insulin alone (placebo) group was observed at Week 24 related to the continued optimisation

of insulin. The least squares (LS) mean difference in HbA_{1c} change from baseline compared to insulin alone (placebo) at Week 24 ranged from −0.31 to −0.48% (p<0.001 in all groups).

In all studies and all efficacy pools, the change from baseline in all active groups and the difference versus insulin alone (placebo) were statistically significant (p<0.001) and clinically meaningful.

In the ES1 pool, the week 24 LS mean difference in HbA_{1c} change from baseline compared to insulin alone (placebo) was −0.39% and −0.45% for sotagliflozin 200 mg and 400 mg, respectively, (p<0.001 for both). At Week 52 the LS mean difference in HbA_{1c} change from baseline compared to insulin alone (placebo) was −0.24% and −0.38% for sotagliflozin 200 mg and 400 mg, respectively.

A summary of the results for change from baseline in HbA_{1c} is presented in Table 3

Table 3. Results summary for HbA_{1c} (%), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)(1-5)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −0.41 (0.046)	N=175, −0.54 (0.045)	N=174, −0.10 (0.045)	−0.31 (−0.43 to −0.19) <0.001	−0.44 (−0.56 to −0.32) <0.001
inTandem2	N=135, −0.46 (0.053)	N=138, −0.45 (0.052)	N=124, 0.02 (0.054)	−0.48 (−0.62 to −0.34) <0.001	−0.47 (−0.61 to −0.34) <0.001
inTandem3	–	N=379, −0.86 (0.065)	N=370, −0.32 (0.066)	–	−0.54 (−0.64, −0.44) <0.001
ES1 pool	N=305, −0.43 (0.034)	N=313, −0.50 (0.034)	N=298, −0.04 (0.034)	−0.39 (−0.48 to −0.30) <0.001	−0.45 (−0.54 to −0.36) <0.001
52 weeks					
inTandem1	N=170, −0.26 (0.056)	N=175, −0.39 (0.054)	N=174, −0.03 (0.056)	−0.23 (−0.37 to −0.08) 0.003	−0.36 (−0.51 to −0.21) <0.001
inTandem2	N=135, −0.23 (0.062)	N=138, −0.37 (0.061)	N=124, 0.04 (0.063)	−0.27 (−0.43 to −0.10) 0.002	−0.40 (−0.57 to −0.24) <0.001
ES1 pool	N=305, −0.24 (0.041)	N=313, −0.38 (0.040)	N=298, −0.00 (0.042)	−0.24 (−0.35 to −0.13) <0.001	−0.38 (−0.49 o−0.27) <0.001

CI = Confidence interval; HbA_{1c} = glycated haemoglobin; LS = Least squares; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.2.2. Net clinical benefit—meeting glycated haemoglobin target <7% without severe hypoglycaemia and diabetic ketoacidosis

Table 4: Results summary for patients with HbA_{1c} <7.0% without severe hypoglycaemia and without diabetic ketoacidosis (mITT population, patients with baseline BMI ≥27 kg/m^2)(1-4)

Study reference/ID	Sotagliflozin 200 mg n/N (%)	Sotagliflozin 400 mg n/N (%)	Insulin alone (placebo) n/N (%)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				Difference (in %) of responders (95% CI) p value	Difference (in %) of responders (95% CI) p value
24 weeks					
inTandem1	50/170 (29.4)	85/175 (48.6)	36/174 (20.7)	8.7 (-0.40 to 17.84) 0.06	27.9 (18.34 to 37.42) <0.001
inTandem2	41/135 (30.4)	46/138 (33.3)	21/124 (16.9)	13.4 (3.25 to 23.62) 0.010	16.4 (6.13 to 26.67) 0.002
inTandem3	-	109/379 (28.8)	49/370 (13.2)	-	15.5 (9.80 to 21.23) <0.001
ES 1 pool	91/305 (29.8%)	131/313 (41.9%)	57/298 (19.1%)	10.71 (3.90 to 17.51) 0.001	22.73 (15.67 to 29.78) <0.001
52 weeks					
InTandem1	39/170 (22.9%)	62/175 (35.4%)	36/174 (20.7%)	2.25 (−6.48 to 10.98) 0.602	14.74 (5.44 to 24.04) 0.002
inTandem2	33/135 (24.4%)	38/138 (27.5%)	19/124 (15.3%)	9.12 (−0.51 to 18.75) 0.059	12.21 (2.43 to 22.00) 0.014
ES 1pool	72/305 (23.6%)	100/313 (31.9%)	55/298 (18.5%)	5.15 (−1.34 to 11.64) 0.108	13.49 (6.70 to 20.28) <0.001
CI = Confidence interval¸ DKA = Diabetic ketoacidosis; HbA_{1c} = glycated haemoglobin SH = Severe hypoglycaemia					

2.2.3. Reducing glycaemic variability and increasing time in range

2.2.3.1. Time in range

inTandem1

Insulin alone (placebo)-corrected mean increase in continuous glucose monitoring (CGM) % time in range was +3.91 and +11.79% for the sotagliflozin 200 mg and 400 mg groups, respectively (nominal p-values for 200 mg and 400 mg were p=0.27 and p<0.001, respectively).

inTandem2

Insulin alone (placebo)-corrected mean increase in CGM % time in range was +14.59% and +20.07% for the sotagliflozin 200 mg and 400 mg groups respectively (nominal p-values for 200 mg and 400 mg were p=0.008 and p<0.001, respectively).

ES1 pool

Insulin alone (placebo)-corrected mean increase in CGM % time in range was +8.17% and +15.05% for the sotagliflozin 200 mg and 400 mg groups respectively (nominal p-values for 200 mg and 400 mg were p=0.007 and p<0.001, respectively).

An overall summary for percent time spent in target range (≥70 to ≤180 mg/dL) for the individual studies and the pooled analyses is presented in Table 5.

Table 5. Results summary of difference from baseline for percent time spent in target range (3.9-10.0 mmol/L [≥70 to ≤180 mg/dL]), per 24 h, (mITT population in the CGM sub-study, patients with baseline BMI ≥27 kg/m^2)(1-3)

Study reference/ID	Sotagliflozin 200 mg N, Mean (SE)	Sotagliflozin 400 mg N, Mean (SE)	Insulin alone (placebo) N, Mean (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=30, 1.874 (2.7546)	N=34, 9.758 (2.7155)	N=32, -2.033 (2.5933)	3.906 (-3.06 to 10.882) 0.27	11.791 (4.954 to 18.628) <0.001
inTandem2	N=29, 10.919 (3.6182)	N=31, 16.403 (3.1550)	N=26, -3.669 (4.1427)	14.589 (3.936; 25.242) 0.008	20.072 (10.039 to 30.106) <0.001
ES1 pool	N=59, 6.254 (2.1983)	N=65, 13.133 (2.0244)	N=58, -1.917 (2.2503)	8.171 (2.296 to 14.046) 0.007	15.051 (9.403 to 20.699) <0.001
CGM = Continuous glucose monitoring; CI = Confidence interval; LS = Least squares; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error					

2.2.3.2. Postprandial glucose

inTandem1 and inTandem2

At Week 24, the LS mean difference from insulin alone (placebo) in postprandial glucose (PPG) ranged from −38.7 mg/dL to −4.1 mg/dL. For inTandem2, the effect for sotagliflozin 400 mg compared to insulin alone (placebo) was statistically significant (p=0.046).

ES1 pool

The LS mean difference from insulin alone (placebo) in change from baseline at Week 24 in 2-hour PPG was −19.0 mg/dL (−1.1 mmol/L) for sotagliflozin 200 mg and −21.7 mg/dL (−1.2 mmol/L) for sotagliflozin 400 mg; p=0.20 and p=0.12, respectively.

An overall summary of PPG (mg/dL) for the individual studies and the pooled analyses is presented in Table 6. Two-hour PPG after a standardised mixed meal was evaluated in patients participating in the CGM sub-study of inTandem1 and inTandem2 and is primarily evaluated in the ES1 pool.

Table 6. Results summary for 2-hour PPG (mg/dL) following a standardised mixed meal, absolute difference from baseline (mITT in the CGM sub-study, patients with baseline BMI ≥27 kg/m^2)(1-3)

Study reference/ID	Sotagliflozin 200 mg N, Mean (SE)	Sotagliflozin 400 mg N, Mean (SE)	Insulin alone (placebo) N, Mean (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=30, −26.0 (18.88)	N=34, −29.0 (17.69)	N=32, −21.9 (16.17)	−4.1 (−48.3 to 40.1) 0.85	−7.1 (−47.9 to 33.8) 0.73
inTandem2	N=29, −43.8 (14.60)	N=31, −51.4 (13.44)	N=26, −12.7 (15.23)	−31.1 (−70.1 to 7.9) 0.12	−38.7 (−76.8 to −0.7) 0.046
ES1 pool	N=59, −36.8 (11.72)	N=65, −39.5 (10.72)	N=58, −17.7 (11.05)	−19.0 (−48.1 to 10.1) 0.20	−21.7 (−49.3 to 5.8) 0.12

CI = Confidence interval; LS = Least squares; LSM = Least square mean; mITT = Modified intent-to-treat; PPG = Postprandial plasma glucose; SE = Standard Error
To convert to mmol/L divide by 18.

2.2.3.3. Fasting plasma glucose

At Week 24, the LS mean difference from insulin alone (placebo) in FPG was with the exception of sotagliflozin 200 mg in inTandem1 statistically significant for all sotagliflozin groups, ranging from −20.4 to −32.0 mg/dL (−1.1 to −1.8 mmol/L). The LS mean difference from insulin alone (placebo) in inTandem1 was −9.7 mg/dL for sotagliflozin 200 mg (p=0.09).

ES1 pool

Results for the ES1 pool was consistent with the phase 3 study results. In the ES1 pool at Week 24, the LS mean difference from insulin alone (placebo) was −15.7 mg/dL (−0.9 mmol/L) and −25.0 mg/dL (−1.4 mmol/L) for the sotagliflozin 200 mg and 400 mg (p<0.001 for both).

An overall summary of FPG (mg/dL) for the individual studies and the pooled analyses is presented in Table 7.

Table 7.Results summary for FPG (mg/dL), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −6.5 (4.20)	N=175, −17.2 (4.14)	N=174, 3.2 (4.19)	−9.7 (−20.8 to 1.5) 0.09	−20.4 (−31.4 to −9.3) <0.001
inTandem2	N=135, −12.6 (5.42)	N=138, −20.9 (5.37)	N=124, 11.2 (5.52)	−23.8 (−38.4 to −9.1) 0.002	−32.0 (−46.6 to −17.5) <0.001
ES1 pool	N=305, −9.3 (3.33)	N=313, −18.6 (3.28)	N=298, 6.4 (3.36)	−15.7 (−24.7 to −6.7) <0.001	−25.0 (−33.9 to −16.1) <0.001
52 weeks					
inTandem1	N=170, −7.22 (4.975)	N=175, −16.51 (4.873)	N=174, 7.64 (5.107)	−14.85 (−28.51, −1.20) <0.0330	−24.15 (−37.66, −10.64) <0.0005
inTandem2	N=135, −7.81 (5.868)	N=138, −23.81 (5.765)	N=124, 5.78 (6.008)	−13.60 (−29.66, 2.47) −0.0970	−29.59 (−45.48, −13.69) 0.0003

CI = Confidence interval; FPG = Fasting plasma glucose; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
To convert to mmol/L divide by 18.

2.2.4. Impact on insulin dosing

Daily bolus insulin dose

inTandem1

At Week 24, the LS mean (SE) change from baseline in mean daily bolus insulin dose was -1.44 (0.995) IU/day in the insulin alone (placebo) group, −2.63 (0.998) IU/day in the sotagliflozin 200 mg group, and −5.26 (0.987) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) change from baseline was −1.19 IU/day (p=0.37) in the sotagliflozin 200 mg group and −3.82 IU/day (p=0.004) in the sotagliflozin 400 mg group.

inTandem2

At Week 24, the LS mean (SE) change from baseline in mean daily bolus insulin dose was −2.30 (1.057) IU/day in the insulin alone (placebo) group, −5.35 (1.033) IU/day in the sotagliflozin 200 mg group, and −6.61 (1.024) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) change from baseline was

−3.05 IU/day (p=0.030) for the sotagliflozin 200 mg group and −4.31 IU/day (p=0.002) for the sotagliflozin 400 mg group.

ES1 pool

The results of the pooled analyses are consistent with the results of the individual analyses at Week 24.

In the ES1 pool, the LS mean (SE) change from baseline in mean daily bolus insulin dose at Week 24 was −1.86 (0.722) IU/day in the insulin alone (placebo) group, −3.89 (0.715) IU/day in the sotagliflozin 200 mg group and −5.91 (0.705) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) change from baseline was −2.02 IU/day for sotagliflozin 200 mg (p=0.037) and −4.05 IU/day for sotagliflozin 400 mg (p<0.001).

An overall summary of daily bolus insulin dose for the individual studies and the pooled analyses is presented in Table 8.

Table 8. Results summary for mean daily bolus insulin dose (IU/day), absolute change from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −2.63 (0.998)	N=175, −5.26 (0.987)	N=174, −1.44 (0.995)	−1.19 (−3.80 to 1.43) 0.37	−3.82 (−6.40 to −1.23) 0.004
inTandem2	N=135, −5.35 (1.033)	N=138, −6.61 (1.024)	N=124, −2.30 (1.057)	−3.05 (−5.80 to −0.30) 0.030	−4.31 (−7.04 to −1.58) 0.002
ES1 pool	N=305, −3.89 (0.715)	N=313, −5.91 (0.705)	N=298, −1.86 (0.722)	−2.02 (−3.92 to −0.12) 0.037	−4.05 (−5.93 to −2.17) <0.001
52 weeks					
inTandem1	N=170, 0.11 (0.705)	N=175, −2.06 (0.694)	N=174, 3.37 (0.709)	−3.26 (−5.15, −1.37) 0.0008	−5.43 (−7.31, −3.56) <0.0001
inTandem2	N=135, −0.41 (0.757)	N=138, −1.83 (0.745)	N=124, 1.26 (0.774)	−1.67 (−3.74, 0.39) 0.1120	−3.09 (−5.14, −1.05) 0.0032
ES1 pool	N=305, −3.33 (0.783)	N=313, −6.40 (0.772)	N=298, −2.47 (0.800)	−0.86 (−2.98, 1.25) 0.423	−3.93 (−6.03, −1.84) <0.001

CI = Confidence interval; FPG = Fasting plasma glucose; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.2.4.1. Daily basal insulin dose

inTandem1

At Week 24, the LS mean (SE) change from baseline in mean daily basal insulin dose was 2.09 (0.597) IU/day in the insulin alone (placebo) group, 0.31 (0.599) IU/day in the sotagliflozin 200 mg group, and −1.44 (0.592) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) change from baseline was −1.78 IU/day (p=0.027) in the sotagliflozin 200 mg group and −3.54 IU/day (p<0.001) in the sotagliflozin 400 mg group.

inTandem2

At Week 24, the LS mean (SE) change from baseline in mean daily basal insulin dose was 0.83 (0.696) IU/day in the insulin alone (placebo) group, −0.85 (0.678) IU/day in the sotagliflozin 200 mg group, and −0.90 (0.668) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) change from baseline was −1.68 IU/day (p=0.07) for the sotagliflozin 200 mg group and −1.74 IU/day (p=0.06) for the sotagliflozin 400 mg group.

ES1 pool

Consistent results were observed in the ES1 pool with the difference between insulin alone (placebo) and sotagliflozin treatment arms at 24 weeks being LS mean reductions of −1.72 IU/day (p=0.006) and of −2.71 IU/day (p<0.001) for the sotagliflozin 200 mg and 400 mg groups respectively.

An overall summary of daily basal insulin dose for the individual studies and the pooled analyses is presented in Table 9.

Table 9.Results summary for mean daily basal insulin dose (IU/day), absolute change from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 0.31 (0.599)	N=175, −1.44 (0.592)	N=174, 2.09 (0.597)	−1.78 (−3.35 to −0.20) 0.027	−3.54 (−5.10 to −1.97) <0.001
inTandem2	N=135, −0.85 (0.678)	N=138, −0.90 (0.668)	N=124, 0.83 (0.696)	−1.68 (−3.52 to 0.16) 0.07	−1.74 (−3.56 to 0.09) 0.06
ES1 pool	N=305, −0.14 (0.453)	N=313, −1.14 (0.445)	N=298, 1.57 (0.458)	−1.72 (−2.93 to −0.50) 0.006	−2.71 (−3.92 to −1.51) <0.001
52 weeks					
inTandem1	N=170, −2.13 (1.083)	N=175, −6.46 (1.069)	N=174, −0.68 (1.094)	−1.45 (−4.34, 1.44) 0.3244	−5.77 (−8.63, −2.92) <0.0001
inTandem2	N=135, −4.55 (1.122)	N=138, −6.09 (1.115)	N=124, −4.70 (1.145)	0.15 (−2.88, 3.17) 0.9235	−1.39 (−4.40, 1.62) 0.3643
ES1 pool	N=305, −0.07 (0.523)	N=313, −1.87 (0.514)	N=298, 2.46 (0.531)	−2.53 (−3.95, −1.11) <0.001	−4.33 (0.717) (−5.74, −2.92) <0.001

CI = Confidence interval; IU = International unit; LS = Least squares; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.2.4.2. Total daily insulin dose inTandem1

At Week 24, the LS mean (SE) change from baseline in mean daily total insulin dose was 0.65 (1.232) IU/day in the insulin alone (placebo) group, −1.79 (1.237) IU/day in the sotagliflozin 200 mg group, and −6.49 (1.223) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) in the change from baseline was −2.44 IU/day (p=0.14) in the sotagliflozin 200 mg group and −7.14 IU/day (p<0.001) in the sotagliflozin 400 mg group.

inTandem2

At Week 24, the LS mean (SE) change from baseline in mean daily total insulin dose was −1.50 (1.327) IU/day in the insulin alone (placebo) group, −6.17 (1.296) IU/day in the sotagliflozin 200 mg group, and −7.42 (1.283) IU/day in the sotagliflozin 400 mg group. The difference from insulin alone (placebo) in LS mean (SE) change from baseline was −4.67 IU/day (p=0.008) for the sotagliflozin 200 mg group and −5.92 IU/day (p<0.001) for the sotagliflozin 400 mg group.

ES1 pool

Consistent results were observed in the ES1 pool (Week 24 insulin alone (placebo)-subtracted LS mean reduction of -3.43 IU/day and -6.62 IU/day for the sotagliflozin 200 mg and 400 mg groups; p=0.005 for sotagliflozin 200 mg and p<0.001 for sotagliflozin 400 mg).

An overall summary of daily bolus insulin dose for the individual studies and the pooled analyses is presented in Table 10.

Table 10. Results summary for total insulin dose (IU/day), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −1.79 (1.237)	N=175, −6.49 (1.223)	N=174, 0.65 (1.232)	−2.44 (−5.69 to 0.81) 0.14	−7.14 (−10.35 to −3.92) <0.001
inTandem2	N=135, −6.17 (1.296)	N=138, −7.42 (1.283)	N=124, −1.50 (1.327)	−4.67 (−8.13 to −1.20) 0.008	−5.92 (−9.37 to −2.48) <0.001
ES1 pool	N=305, −3.82 (0.897)	N=313, −7.01 (0.884)	N=298, −0.39 (0.906)	−3.43 (−5.82 to −1.04) 0.005	−6.62 (−8.99 to −4.25) <0.001

CI = Confidence interval; IU = International unit; LS = Least squares; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.2.5. Non-glycaemic endpoints: cardiovascular risk

The main non-glycaemic outcomes relate to weight change, SBP and patient-reported outcomes, in particular diabetes-related and general health-related quality of life (HRQoL). Results for the two individual studies and pooled analysis are described further below.

2.2.5.1. Weight change

inTandem1 and inTandem2

A clinically meaningful and highly statistically significant decrease in LS mean body weight was observed at Week 24 in all sotagliflozin groups, ranging from −3.05 kg to −1.71 kg. The LS mean difference to insulin alone (placebo) at Week 24 was –2.29 kg (inTandem1) and −2.25 kg (inTandem2) with sotagliflozin 200 mg; it was -3.54 kg (inTandem1),−3.04 kg (inTandem2) and −3.41 kg (inTandem3) with sotagliflozin 400 mg (all p<0.001). These results are clinically meaningful, especially in the light of optimised insulin treatment in inTandem1 and inTandem2.

ES1 pool

At Week 24, pooled analyses showed results consistent with the individual phase 3 studies. In the ES1 pool, the LS mean change from baseline at Week 24 was −1.93 kg, −2.98 kg and 0.34 kg for sotagliflozin 200 mg, 400 mg and insulin alone (placebo), respectively. The LS mean difference from insulin alone (placebo) in body weight change at Week 24 was −2.27 kg for 200 mg and −3.32 kg for 400 mg respectively (p<0.001 for both). At Week 52, the LS mean difference from insulin alone (placebo) was −3.01 kg and −4.46 kg with sotagliflozin 200 mg and sotagliflozin 400 mg (p<0.001 for both).

An overall summary of body weight for the individual studies and the pooled analyses is presented in Table 11.

Table 11. Results summary for body weight (kg), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −1.71 (0.253)	N=175, −2.96 (0.250)	N=174, 0.58 (0.253)	−2.29 (−2.97 to−1.61) <0.001	−3.54 (−4.22 to−2.87) <0.001
inTandem2	N=135, −2.26 (0.311)	N=138, −3.05 (0.306)	N=124, −0.01 (0.319)	−2.25 (−3.11 to−1.39) <0.001	−3.04 (−3.89 to−2.19) <0.001
ES1 pool	N=305, −1.93 (0.196)	N=313, −2.98 (0.193)	N=298, 0.34 (0.198)	−2.27 (−2.81 to−1.74) <0.001	−3.32 (−3.85 to−2.79) <0.001
52 weeks					
inTandem1	N=170, −1.91 (0.334)	N=175, −3.57 (0.328)	N=174, 1.30 (0.337)	−3.21 (−4.13 to −2.29) <0.001	−4.87 (−5.77 to −3.96) <0.001
inTandem2	N=135, −2.51 (0.392)	N=138, −3.68 (0.384)	N=124, 0.22 (0.400)	−2.72 (−3.81 to −1.64) <0.001	−3.90 (−4.97 to −2.82) <0.001
ES1 pool	N=305, −2.16 (0.254)	N=313, −3.61 (0.249)	N=298, 0.85 (0.258)	−3.01 (−3.71 to−2.31) <0.001	−4.46 (−5.15 to−3.76) <0.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.2.5.2. Blood pressure

inTandem1

At Week 24 the LS mean difference from insulin alone (placebo) in SBP was statistically significant for the sotagliflozin 400 mg group. The LS mean difference was −3.8 mm Hg (p<0.001). The LS mean difference for SBP was not statistically significant for the 200 mg dose.

inTandem2

At Week 24 the LS mean difference from insulin alone (placebo) in SBP was −1.8 mm Hg (p=0.19) for the sotagliflozin 200 mg group and −0.7 mm Hg (p=0.62) or the sotagliflozin 400 mg group.

ES1

Overall, similar results were observed for the pooled analyses of the change from baseline in SBP.

At Week 24, the difference from insulin alone (placebo) in LS mean change from baseline in SBP in ES1 pool was –1.3 mm Hg (p=0.13) for the sotagliflozin 200 mg group and −2.5 mm Hg (p=0.005) for the sotagliflozin 400 mg group. At Week 52, the difference from insulin alone (placebo) in LS mean change from baseline in SBP was −2.1 mm Hg (p=0.018) for the sotagliflozin 200 mg group and −3.6 mm Hg (p<0.001) for the sotagliflozin 400 mg group.

An overall summary of SBP (mm Hg) for the individual studies and the pooled analyses is presented in Table 12.

Table 12. Results summary for SBP (mm Hg), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −1.3 (0.84)	N=175, −4.2 (0.83)	N=174, −0.4 (0.84)	−0.9 (−3.2 to1.3) 0.40	−3.8 (−6.0 to−1.6) <0.001
inTandem2	N=135, −5.4 (1.01)	N=138, −4.2 (1.01)	N=124, −3.6 (1.04)	−1.8 (−4.5 to0.9) 0.19	−0.7 (−3.3 to2.0) 0.62
ES1 pool	N=305, −2.9 (0.64)	N=313, −4.0 (0.64)	N=298, −1.6 (0.65)	−1.3 (−3.0 to0.4) 0.13	−2.5 (−4.2 to−0.8) 0.005
52 weeks					
inTandem1	N=170, -0.4 (0.90)	N=175, -3.4 (0.88)	N=174, 0.7 (0.91)	-1.1 (-3.5 to 1.3) 0.36	-4.1 (-6.5 to -1.7) <0.001

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
inTandem2	N=135, -3.8 (0.98)	N=138, -3.4 (0.96)	N=124, -0.5 (1.00)	-3.3 (-5.9 to -0.7) 0.013	-2.9 (-5.4 to -0.3) 0.028
ES1 pool	N=305, -1.7 (0.66)	N=313, -3.2 (0.65)	N=298, 0.4 (0.67)	-2.1 (-3.9 to0.4) 0.018	-3.6 (-5.3 to-1.9) <0.001

Abbreviations: CI = Confidence interval; LS = Least squares; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error

2.2.5.3. Change from baseline in systolic blood pressure in the subset of patients with SBP ≥130 mm Hg at baseline

inTandem1 and inTandem2

At Week 24, the LS mean difference from insulin alone (placebo) in SBP for this subset of patients ranged from −3.8 mm Hg to −0.0 mm Hg.

ES1 pool

At Week 24, the LS mean difference from insulin alone (placebo) in SBP for this subset of patients was −2.4 (1.73) mm Hg for sotagliflozin 200 mg and −2.5 (1.69) mm Hg for sotagliflozin 400 mg.

An overall summary of SBP (mm Hg) in the subset of patients with SBP ≥130 mm Hg at baseline for the individual studies and the pooled analyses is presented in Table 13.

Table 13. Results summary for SBP (mm Hg) in patients with baseline SBP ≥130 mm Hg, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, Mean (SE)	Sotagliflozin 400 mg N, Mean (SE)	Insulin alone (placebo) N, Mean (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=46, −9.2 (1.89)	N=50, −11.6 (1.76)	N=48, −9.2 (1.87)	−0.0 (−5.1 to 5.0) 0.99	−2.4 (−7.3 to 2.4) 0.32
inTandem2	N=55, −10.4 (1.82)	N=58, −8.7 (1.79)	N=51; −6.7 (1.87)	−3.8 (−8.5 to 0.9) 0.12	−2.0 (−6.7 to 2.7) 0.40
ES1 pool	N=101, −10.0 (1.29)	N=108, −10.1 (1.24)	N=99, −7.6 (1.29)	−2.4 (−5.8 to 1.1) 0.18	−2.5 (−5.8 to 0.8) 0.14

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error

2.3. Health-related quality of life

2.3.1. Diabetes-specific measures of Health-related quality of life

2.3.1.1. Diabetes Distress Screening Scale (DDS2)

inTandem1 and inTandem2

At Week 24, the LS mean difference compared to insulin alone (placebo) ranged between −0.6 (p<0.001) and −0.8 (p<0.001) in all sotagliflozin groups, indicating a lower diabetes-related distress with sotagliflozin.

ES1 pool

At Week 24, the LS mean difference compared to insulin alone (placebo) was -0.6 for sotagliflozin 200 mg and −0.7 for sotagliflozin 400 mg (p<0.001 for both).

An overall summary of DDS2 total score for the individual studies is presented in Table 14.

Table 14. Results summary for DDS2 total score, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −0.4 (0.14)	N=175, −0.6 (0.13)	N=174, 0.2 (0.14)	−0.6 (−1.0 to −0.3) <0.001	−0.8 (−1.1 to −0.4) <0.001
inTandem2	N=135, −0.5 (0.15)	N=138, −0.5 (0.15)	N=124, 0.1 (0.15)	−0.6 (−1.0 to −0.2) 0.005	−0.5 (−0.9 to −0.1) 0.009
ES1 pool	N=305; −0.5 (0.10)	N=313, −0.5 (0.10)	N=298, 0.1 (0.10)	−0.6 (−0.9 to −0.3) <0.001	−0.7 (−0.9 to −0.4) <0.001
52 weeks					
inTandem1	N=170, −0.27 (0.137)	N=175, −0.50 (0.136)	N=174, 0.16 (0.141)	−0.43 (−0.79, −0.07) 0.0202	−0.65 (−1.01, −0.30) 0.0004
inTandem2	N=135, −0.50 (0.161)	N=138, −0.50 (0.155)	N=124, −0.14 (0.162)	−0.36 (−0.79, 0.06) 0.0914	−0.36 (−0.77, 0.06) 0.0893

CI = Confidence interval; DDS2 = 2-item Diabetes Distress Screening Scale; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.3.1.2. Diabetes treatment satisfaction questionnaire (DTSQ)

inTandem1 and inTandem2

At Week 24, the LS mean difference compared to insulin alone (placebo) ranged between +2.0 and +3.0 in all sotagliflozin groups (all p<0.001), indicating an improved diabetes treatment satisfaction with sotagliflozin. In the inTandem1 trial the LS mean difference (SE) compared to insulin alone (placebo) was 2.8 (0.48) for sotagliflozin 200 mg and 3.0 (0.48) for sotagliflozin 400 mg. In the inTandem2 the LS mean difference (SE) compared to insulin alone (placebo) was 2.4 (0.52) for sotagliflozin 200 mg and 2.0 (0.51) for sotagliflozin 400 mg.

ES1 pool

At Week 24, the LS mean difference compared to insulin alone (placebo) was 2.6 for both sotagliflozin 200 mg and sotagliflozin 400 mg (p<0.001 for both).

An overall summary of DTSQ score for the individual studies is presented in Table 15.

Table 15. Results summary for DTSQs score, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2) (1-3)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 2.2 (0.36)	N=175, 2.4 (0.36)	N=174, -0.6 (0.37)	2.8 (1.9 to 3.7) <0.001	3.0 (2.1 to 3.9) <0.001
inTandem2	N=135, 2.4 (0.39)	N=138, 2.0 (0.38)	N=124, 0.0 (0.40)	2.4 (1.4 to 3.4) <0.001	2.0 (1.0 to 3.0) <0.001
ES1 pool	N=305, 2.3 (0.26)	N=313, 2.2 (0.26)	N=298, -0.3 (0.27)	2.6 (1.9 to 3.3) <0.001	2.6 (1.9 to 3.3) <0.001

CI = Confidence interval; DTSQ = Diabetes Treatment Satisfaction Questionnaire; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error

2.4. Individual study results (safety outcomes)

Summary

- Overall, the safety profile of sotagliflozin supports its use as an adjunct to insulin in a setting of education and monitoring for DKA. Most of the treatment-emergent adverse events (TEAEs) were mild or moderate in intensity.
- Sotagliflozin was associated with no increase in hypoglycaemia in the subgroup of patients with baseline BMI ≥27 kg/m², and a trend to a lower incidence of SH and a lower rate of documented clinically important hypoglycaemia events (i.e. ≤55 mg/dL) compared to optimal insulin alone (placebo).
- Consistent with other SGLT2 inhibitors, the use of sotagliflozin was associated with an increased risk of DKA and ketosis-related events. In patients with baseline BMI ≥27 kg/m² a trend to lower risk of DKA was observed supporting the use of sotagliflozin in this subgorup of patients.

In the following sections only the results of the population with BMI ≥27 kg/m^2 are presented.

2.4.1. Crucial endpoints

Definitions

All data presentations and analyses in the ISS and this SCS were based on the Safety Population, which is defined as all subjects treated with at least 1 dose of study drug, unless otherwise specified. Subjects in the Safety Population were analyzed according to their actual treatment received on Day 1. Safety data were pooled into 6 safety pools of which SAF1 and SAF 3 are relevant for this appraisal. The definitions for these are shown below.

Name of study pool Studies included Population	**Treatment groups**	**Clinical studies included**
SAF-1 52-week Phase 3 studies T1DM	Placebo, sotagliflozin qd: 200 mg, 400 mg, total	inTandem 1 and inTandem 2
SAF-3 T1DM Phase 2 and 3 studies T1DM	Placebo, sotagliflozin qd: 75 mg, 200 mg, and 400 mg, total	InTandem 1, 2 and 3 203, 204, 206*

**Study 203 - Phase 2, Placebo-controlled, Proof-of-Concept Study in T1DM including 400 mg sotagliflozin or placebo administered qd for 29 days, Study 204 - Phase 2, Placebo-controlled Study in Young Adult Patients with T1DM and Elevated A1C including 400 mg sotagliflozin or placebo administered qd for 12 weeks, Study 206 - Phase 2, Placebo-controlled, Dose-ranging Study in T1DM including 75 mg, 200 mg, or 400 mg sotagliflozin or placebo administered qd for 12 weeks*

2.4.1.1. Adverse events

SAF-1 pool

Up to Week 52, adverse events (AEs) were reported by 238 patients (78.0%) in the sotagliflozin 200 mg group, 234 patients (74.8%) in the sotagliflozin 400 mg treatment group and 221 patients (74.2%) in the insulin alone (placebo) group.

2.4.1.2. Severe drug-related adverse events

SAF-1 pool

Up to Week 52, severe drug-related AEs occurred more frequently in sotagliflozin-treated patients in SAF-1 pool than in the insulin alone (placebo) group. 8 patients (2.7%) in the insulin alone (placebo) group, 9 patients (3.0%) in the sotagliflozin 200 mg group, and 14 patients (4.5%) in the sotagliflozin 400 mg group reported at least 1 severe drug-related adverse event.

2.4.1.3. Serious adverse events

SAF-1 pool

Overall, treatment-emergent serious AE (SAE) were reported more frequently in sotagliflozin-treated patients in SAF-1 pool than in the insulin alone (placebo) group. Up to Week 52, 28 patients (9.2%) in the sotagliflozin 200 mg group, 31 patients (9.9%) in the sotagliflozin 400 mg group and 22 patients (7.4%) in the insulin alone (placebo) group reported at least 1 SAE.

2.4.1.4. Adverse events leading to death

SAF-1 pool

A total of 2 patients (0.7%) experienced AE leading to death in SAF-1 pool, all in the insulin alone (placebo) group.

2.4.1.5. Adverse events leading to study drug discontinuation

SAF-1 pool

Up to weeks 52, 13 patients (4.3%) in the sotagliflozin 200 mg group, 13 patients (4.2%) in the sotagliflozin 400 mg group and 13 patients (4.4%) in the insulin alone (placebo) group reported AE leading to study drug discontinuation.

Table 16. Overview of treatment-emergent adverse events (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference	Sotagliflozin 200 mg N, n (%)	Sotagliflozin 400 mg N, n (%)	Insulin alone (placebo) N, n (%)
Total number of adverse events			
52 weeks			
SAF-1 pool	N=305, 238 (78.0)	N=313, 234 (74.8)	N=298, 221 (74.2)
Total number of severe drug-related adverse events			
52 weeks			
SAF-1 pool	N=305, 9 (3.0)	N=313, 14 (4.5)	N=298, 8 (2.7)
Total number of serious adverse events			
52 weeks			
SAF-1 pool	N=305, 28 (9.2)	N=313, 31 (9.9)	N=298, 22 (7.4)
Total number of adverse events leading to death			
52 weeks			
SAF-1 pool	N=305, 0	N=313, 0	N=298, 2 (0.7)
Total number of adverse events leading to study drug discontinuation			
52 weeks			
SAF-1 pool	N=305, 13 (4.3)	N=313, 13 (4.2)	N=298, 13 (4.4)

A treatment-emergent adverse event was defined as adverse event with start date on or after the date of first dose of double-blind study treatment and up to 30 days after date of last dose of double-blind study treatment. Some adverse events may have been attributed to the long-term effects of study drug and were included in the analysis even if the onset was more than 30 days after the last dose of study drug. The cut-off date for events of hypoglycaemia is the date of the last dose of study drug. Hypoglycaemia was considered an EOSI and reported in a specialised case report form. Investigators were asked not to submit hypoglycaemic events on the AE case report form unless the event met the criteria for an SAE or was the cause for discontinuation.
Abbreviations: CI = confidence interval; EOSI=event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; NA = Not available

2.4.1.6. Hypoglycaemia - documented blood glucose ≤55 mg/dL (≤3.0 mmol/L)

SAF-1 pool

At Week 52, the insulin alone (placebo) group showed higher event rates per subject per year for documented blood glucose ≤3.0 mmol/L (55 mg/dL) compared to the sotagliflozin groups (13.41, 14.45 and 17.87 for the sotagliflozin 200 mg, sotagliflozin 400 mg and the insulin alone (placebo) groups, respectively).

The event rate difference (95% CI) between the sotagliflozin 200 mg and 400 mg group and the insulin alone (placebo) group was −4.25 (−6.93 to −1.57) (p=0.0019) and −3.42 (−6.14 to −0.7) (p=0.0138), respectively (Table 17 [Table 44a]).

SAF-3 pool

For the SAF-3 pool (Phase III studies only), the event rate for documented blood glucose ≤3.0 mmol/L (55 mg/dL) was lower with sotagliflozin 200 mg and 400 mg compared to insulin alone (placebo) (13.41, 13.32 and 16.10 for the sotagliflozin 200 mg, sotagliflozin 400 mg and the insulin alone (placebo) groups, respectively).

The event rate difference (95% CI) between the sotagliflozin 200 mg and 400 mg group and the insulin alone (placebo) group was −1.61 (−3.66 to 0.43) (p=0.1215) and −2.49 (−4.11 to −0.88) (p=0.0024), respectively (Table 17).

Table 17: Results summary for hypoglycaemia: documented blood glucose ≤55 mg/dL by self-monitoring blood glucose (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, events per subject per year Event rate (95% CI)	Sotagliflozin 400 mg N, events per subject per year Event rate (95% CI)	Insulin alone (placebo) N, events per subject per year Event rate (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Event rate difference (95% CI) p value	Sotagliflozin 400 mg vs. insulin alone (placebo) Event rate difference (95% CI) p value
52 weeks					
SAF-1 pool	N=305, 13.41 13.75 (12.12 to 15.37)	N=313, 14.45 14.57 (12.88 to 16.6)	N=298, 17.87 17.99 (15.86 to 20.13)	−4.25 (−6.93 to −1.57) 0.0019	−3.42 (−6.14 to −0.7) 0.0138
T1D phase 3 studies only					
SAF-3 pool	N=305, 13.41 13.75 (12.12 to 15.37)	N=692, 13.32 12.86 (11.83 to13.90)	N=668, 16.10 15.36 (14.12 to 16.60)	−1.61 (−3.66 to 0.43) 0.1215	−2.49 (−4.11 to −0.88) 0.0024
CI = Confidence interval; NA = Not available					

2.4.1.7. Positively adjudicated severe hypoglycaemia inTandem trial results

An overall summary of positively adjudicated SH of the individual studies and the pooled analyses is presented in Table 18 [Table 47a].

SAF-1 pool

At Week 52, the insulin alone (placebo) group showed higher event rates per 1,000 subject-years for positively adjudicated SH compared to the sotagliflozin groups (46.51, 41.06 and 81.03 for the sotagliflozin 200 mg, sotagliflozin 400 mg and the insulin alone (placebo) groups, respectively).

The risk difference of event rates (95% CI) between the sotagliflozin 200 mg group and the insulin alone (placebo) group was −34.52 (−76.78 to 7.74). The risk difference of event rates (95% CI) between the sotagliflozin 400 mg group and the insulin alone (placebo) group was −39.98 (−81.04 to 1.09).

The relative risk of event rates (95% CI) of sotagliflozin 200 mg versus insulin alone (placebo) at Week 52 was 0.57 (0.28 to 1.14) and the relative risk of event rates (95% CI) of sotagliflozin 400 mg versus insulin alone (placebo) at Week 52 was 0.51 (0.24 to 1.02).

SAF-3

For the SAF-3 pool (Phase III studies only), the insulin alone (placebo) group also showed higher event rates per 1,000 subject-years for positively adjudicated SH compared to the sotagliflozin groups (46.51, 46.09 and 73.66 for the sotagliflozin 200 mg, sotagliflozin 400 mg and the insulin alone (placebo) groups, respectively).

The risk difference of event rates (95% CI) between the sotagliflozin 200 mg group and the insulin alone (placebo) group was −27.15 (−63.08 to 8.78). The risk difference of event rates (95% CI) between the sotagliflozin 400 mg group and the insulin alone (placebo) group was −27.57 (−59.82 to 4.68).

The relative risk of event rates (95% CI) of sotagliflozin 200 mg versus insulin alone (placebo) at Week 52 was 0.63 (0.32 to 1.19) and the relative risk of event rates (95% CI) of sotagliflozin 400 mg versus insulin alone (placebo) was 0.63 (0.36 to 1.08).

Table 18: Results summary for treatment-emergent positively adjudicated severe hypoglycaemia per subject-years of exposure (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1,000 subject-years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Relative difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Relative difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
52 weeks					
SAF-1 pool	N=305, 13 (4.3) 46.51 (21.23 to 71.80)	N=313, 12 (3.8) 41.06 (17.83 to 64.29)	N=298, 22 (7.4) 81.03 (47.17 to 114.90)	−34.52 76.78 to 7.74) 0.57 (0.28 to 1.14)	−39.98 (−81.04 to 1.09) 0.51 (0.24 to 1.02)
T1D Phase 3 studies only					
SAF-3 pool	N=305, 13 (4.3) 46.51 (21.23 to 71.80)	N=692, 21 (3.0) 46.09 (26.38 to 65.80)	N=668, 32 (4.8) 73.66 (48.14 to 99.19)	−27.15 (−63.08 to 8.78) 0.63 (0.32 to 1.19)	−27.57 (−59.82 to 4.68) 0.63 (0.36 to 1.08)
CI = Confidence interval; EAIR = Exposure-adjusted incidence rate; NA = Not available					

2.4.1.8. Positively adjudicated diabetic ketoacidosis inTandem trial results

An overall summary of positively adjudicated DKA is presented in Table 19.

SAF-1 pool

The event rate per 1,000 subject-years for positively adjudicated DKA increased with increased dose of sotagliflozin with rates of 28.62, 37.64 and 3.68 at Week 52 for the sotagliflozin 200 mg, sotagliflozin 400 mg and the insulin alone (placebo) group, respectively.

The risk difference of event rates (95% CI) between the sotagliflozin 200 mg group and the insulin alone (placebo) group Week 52 was 24.94 (3.83 to 46.05). The risk difference of event rates (95% CI) between the sotagliflozin 400 mg group and the insulin alone (placebo) group at Week 52 was 33.95 (10.57 to 57.34).

The relative risk of event rates (95% CI) of sotagliflozin 200 mg versus insulin alone (placebo) at Week 52 was 7.77 (1.24 to 173.82) and the relative risk of event rates (95% CI) of sotagliflozin 400 mg versus insulin alone (placebo) at Week 52 was 10.22 (1.74 to 221.94).

SAF-3 pool

The event rate per 1,000 subject-years for positively adjudicated DKA for SAF-3 pool (Phase II and Phase III studies excluding study 203) was 28.12 and 42.91 for the sotagliflozin 200 mg and 400 mg group and 4.50 for the insulin alone (placebo) group.

The risk difference of event rates (95% CI) between the sotagliflozin 200 mg group and the insulin alone (placebo) group was 23.63 (3.17 to 44.09). The risk difference of event rates (95% CI) between the sotagliflozin 400 mg group and the insulin alone (placebo) group was 38.41 (18.60 to 58.23).

The relative risk of event rates (95% CI) of sotagliflozin 200 mg versus insulin alone (placebo) at Week 52 was 6.25 (1.45 to 43.10) and the relative risk of event rates (95% CI) of sotagliflozin 400 mg versus insulin alone (placebo) at Week 52 was 9.54 (2.59 to 60.47).

The risk difference of event rates (95% CI) between the sotagliflozin 400 mg group and the insulin alone (placebo) group was 54.77 (32.30 to 77.23). The relative risk of event rates (95% CI) of sotagliflozin 400 mg versus insulin alone (placebo) was 8.32 (3.19 to 27.56).

Table 19 [Table 48a]: Results summary for treatment-emergent positively adjudicated DKA (safety population, patients with baseline BMI ≥27 kg/m^2) per 1,000 subject-years exposure

Study reference	Sotagliflozin 200 mg N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1,000 subject-years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
52 weeks					
SAF-1 pool	N=305, 8 (2.6) 28.62 (8.79 to 48.46)	N=313, 11 (3.5) 37.64 (15.39 to 59.88)	N=298, 1 (0.3) 3.68 (0.00 to 10.90)	24.94 (3.83 to 46.05) 7.77 (1.24 to 173.82)	33.95 (10.57 to 57.34) 10.22 (1.74 to 221.94)
T1D Phase II and III studies excluding study 203 (proof of concept study)					
SAF-3 pool	N=326, 8 (2.5) 28.12 (8.64 to 47.61)	N=738, 20 (2.7) 42.91 (24.10 to 61.72)	N=716, 2 (0.3) 4.50 (0.00 to 10.73)	23.63 (3.17 to 44.09) 6.25 (1.45 to 43.10)	38.41 (18.60 to 58.23) 9.54 (2.59 to 60.47)
CI = Confidence interval; DKA = Diabetic ketoacidosis; EAIR = Exposure-adjusted incidence rate; NA = Not available					

2.4.1.9. Most frequent adverse events

SAF-1 pool

The most frequently reported AEs by standard of care (SoC) included genital mycotic infections (in males: 6 [3.8%] in the sotagliflozin 200 mg group, 7 patients [4.5%] in the sotagliflozin 400 mg group and 1 patients [0.6%] in the insulin alone [placebo] group; in females: 32 [21.6%] in the sotagliflozin 200 mg group, 28 patients [17.6%] in the sotagliflozin 400 mg group and 9 patients [6.3%] in the insulin alone [placebo] group) and diarrhoea (16 [5.2%] in the sotagliflozin 200 mg group, 27 patients [8.6%] in the sotagliflozin 400 mg group and 20 patients [6.7%] in the insulin alone [placebo] group).

For men, the risk difference of event rates (95% CI) of genital mycotic infections between the sotagliflozin groups and the insulin alone (placebo) group was 34.16 (−1.35 to 69.67) and 40.85 (2.99 to 78.70), respectively. The relative risk of event rates (95% CI) of sotagliflozin versus insulin alone (placebo) at Week 52 was 5.96 (0.88 to 138.01) and 6.93 (1.07 to 157.36), respectively.

For women, the risk difference of event rates (95% CI) of genital mycotic infections between the sotagliflozin groups and the insulin alone (placebo) group was 168.78 (73.47 to 264.08) and 121.01 (35.94 to 206.09), respectively. The relative risk of event rates (95% CI) of sotagliflozin versus insulin alone (placebo) at Week 52 was 3.37 (1.65 to 7.46) and 2.70 (1.30 to 6.04), respectively.

The risk difference of event rates (95% CI) of diarrhoea between the sotagliflozin groups and the insulin alone (placebo) group was −16.42 (−59.19 to 26.35) and 18.71 (−28.79 to 66.22), respectively. The relative risk of event rates (95% CI) of sotagliflozin versus insulin alone (placebo) at Week 52 was 0.78 (0.40 to 1.51) and 1.25 (0.70 to 2.27), respectively (Table 20).

SAF-3 pool

For men, the risk difference of event rates (95% CI) of genital mycotic infections between the sotagliflozin groups and the insulin alone (placebo) group was 27.14 (−8.28 to 62.55) and 32.96 (1.99 to 63.93), respectively. The relative risk of event rates (95% CI) of sotagliflozin versus insulin alone (placebo) at Week 52 was 3.08 (0.77 to 15.05) and 3.52 (1.04 to 15.72), respectively.

For women, the risk difference of event rates (95% CI) of genital mycotic infections between the sotagliflozin groups and the insulin alone (placebo) group was 179.14 (89.22 to 269.07) and 176.58 (104.29 to 248.88), respectively. The relative risk of event rates (95% CI) of sotagliflozin versus insulin alone (placebo) at Week 52 was 3.76 (2.04 to 7.24) and 3.72 (2.11 to 6.92), respectively.

The risk difference of event rates (95% CI) of diarrhoea between the sotagliflozin groups and the insulin alone (placebo) group was −22.36 (-60.28 to 15.56) and 22.10 (−16.73 to 60.92), respectively. The relative risk of event rates (95% CI) of sotagliflozin versus insulin alone (placebo) at Week 52 was 0.72 (0.39 to 1.28) and 1.28 (0.83 to 2.00), respectively (Table 20).

Table 20 [Table 50a]: Overview of most frequent adverse events (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID System Organ Class Preferred Term	Sotagliflozin 200 mg N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1,000 subject-years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
SAF-1 pool (52 weeks)					
Genital mycotic infections (male)	N=157, 6 (3.8) 41.05 (8.20 to 73.89)	N=154, 7 (4.5) 47.74 (12.37 to 83.10)	N=155, 1 (0.6) 6.89 (0.00 to 20.39)	34.16 (−1.35 to 69.67) 5.96 (0.88 to 138.01)	40.85 (2.99 to 78.70) 6.93 (1.07 to 157.36)
Genital mycotic infections (female)	N=148, 32 (21.6) 240.02 (156.86 to 323.19)	N=159, 28 (17.6) 192.26 (121.05 to 263.48)	N=143, 9 (6.3) 71.25 (24.70 to 117.80)	168.78 (73.47 to 264.08) 3.37 (1.65 to 7.46)	121.01 (35.94 to 206.09) 2.70 (1.30 to 6.04)
Diarrhoea	N=305, 16 (5.2) 57.25 (29.20 to 85.30)	N=313, 27 (8.6) 92.38 (57.53 to 127.23)	N=298, 20 (6.7) 73.67 (41.38 to 105.95)	−16.42 (−59.19 to 26.35) 0.78 (0.40 to 1.51)	18.71 (−28.79 to 66.22) 1.25 (0.70 to 2.27)
SAF-3 pool (T1D Phase 2 and 3 studies)					
Genital mycotic infections (male)	N=170, 6 (3.5) 40.21 (8.04 to 72.39)	N=378, 11 (2.9) 46.04 (18.83 to 73.25)	N=359, 3 (0.8) 13.08 (0.00 to 27.87)	27.14 (−8.28 to 62.55) 3.08 (0.77 to 15.05)	32.96 (1.99 to 63.93) 3.52 (1.04 to 15.72)
Genital mycotic infections (female)	N=156, 33 (21.2) 244.01 (160.76 to 327.27)	N=368, 55 (14.9) 241.45 (177.64 to 305.27)	N=364, 14 (3.8) 64.87 (30.89 to 98.85)	179.14 (89.22 to 269.07) 3.76 (2.04 to 7.24)	176.58 (104.29 to 248.88) 3.72 (2.11 to 6.92)
Diarrhoea	N=326, 16 (4.9) 56.25 (28.69 to 83.81)	N=746, 47 (6.3) 100.70 (71.91 to 129.50)	N=723, 35 (4.8) 78.61 (52.56 to 104.65)	−22.36 (−60.28 to 15.56) 0.72 (0.39 to 1.28)	22.10 (−16.73 to 60.92) 1.28 (0.83 to 2.00)

MedDRA = Medical Dictionary for Regulatory Activities

2.4.2. Summary of the efficacy and safety

The target population for sotagliflozin treatment consists of adult patients with BMI ≥27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

All three inTandem studies presented enrolled adult patients (≥18 years) who had been diagnosed with T1D at least one year prior to obtaining informed consent for study participation. All patients were treated with insulin or insulin analogues delivered via CSII or multiple daily injections (MDI). Use of any antidiabetic agent other than insulin or insulin analogue excluded patients from participation in the study. In addition, all patients had to have an eGFR ≥45 mL/min/1.73 m^2 at the time of screening. Patients with a history of SH or DKA within one month of screening were excluded from the studies. At screening, all patients had inadequate glycaemic control with insulin therapy, defined as an HbA_{1c} between and including 7.0% and 11.0%. Patients who were ≥80% compliant during the run-in period were randomised and included into the treatment period.

It should be noted that the subgroup of patients with baseline BMI ≥27 kg/m^2 is not a pre-specified subgroup of the overall study populations. The subset of patients with BMI ≥27 kg/m^2 represent around 56% of the patients in the Phase 3 T1D study programme. In addition to a higher BMI, patients with BMI ≥27 kg/m² tended to be older, to have a longer duration of disease, and to have a higher SBP at baseline, and therefore presented a higher medical need that may not be addressed by insulin alone.

Overall, at Week 24, the efficacy of sotagliflozin versus insulin alone (placebo) was more pronounced in the subgroup of patients with baseline BMI ≥27 kg/m^2, especially for the measurements of HbA_{1c}, body weight, time in range, DTSQ and DDS2. Tests of a treatment by subgroup interaction were associated with p-values <0.05 for the HbA_{1c}, body weight, and DTSQ change from baseline scores. Favourable trends for less severe hypoglycaemia, less DKA and less diarrhoea were also observed. These numerical differences, compared to patients with baseline BMI <27 kg/m², were greater for the 400 mg dose.

Overall a more pronounced benefit of treatment and a lower risk, including a lower risk of DKA, was observed in patients with BMI ≥27 kg/m². These data support the recommendation to consider the use of sotagliflozin in overweight or obese T1D patients with a BMI ≥27 kg/m² and to revise the indication as follows: *"Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus*

with BMI ≥27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy".

3. Cost-effectiveness

3.1.1. Important changes in the evidence synthesis informing the economic analysis of sotagliflozin due to the revised patient population with a BMI ≥27kg/m^2

On February 28th 2019, the CHMP adopted a positive opinion for sotagliflozin as "an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a BMI ≥ 27 kg/m^2, who have failed to achieve adequate glycaemic control despite optimal insulin therapy". In order to provide relevant cost-effectiveness analysis consistent with the licence Sanofi has extracted data from the inTandem clinical trial programme for patients with a BMI ≥ 27 kg/m² to inform the cost-effectiveness model.

Sotagliflozin versus insulin + placebo

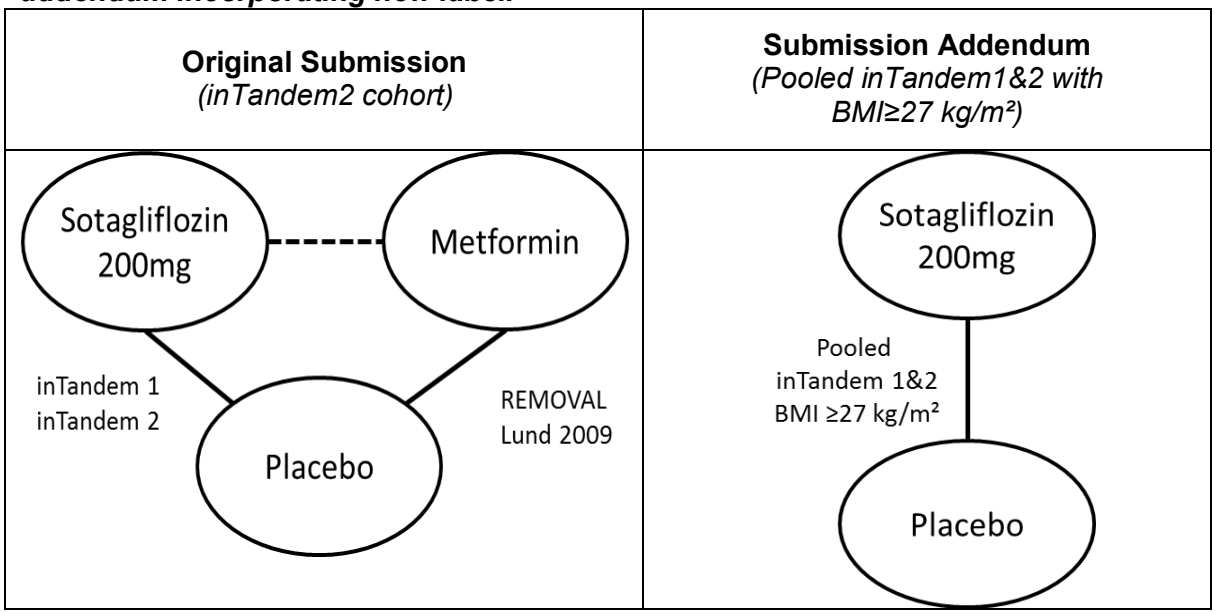
Relevant outcomes for the model inputs were based on a pooled analysis of the subgroup with BMI ≥ 27 kg/m^2 from inTandem1 and inTandem2 trials. The two trials were pooled because they were of similar design and pooling the studies increased the sample size for the evidence synthesis. To provide all possible information considering the BMI ≥ 27 kg/m² sub-population, Sanofi pooled inTandem1 and inTandem2 data, weighting the studies by both the number of patients and study precision (as measured by outcome variance), which is consistent with the common assignment of weights in a meta-analysis. Compared to a common meta-analysis approach using aggregate (cohort) estimates, pooling the data is a more comprehensive analysis that acknowledges for individual level-patient data. This technique allows an increased level of stratification by patient characteristics, and provides least square estimates as the outcome of each variable.

Sotagliflozin versus metformin

In the original submission a comparison versus metformin was presented however the change in the target population affected the complementary comparison versus metformin. As there is no evidence in the metformin trials for patients with a BMI ≥27kg/m^2 this comparison is no longer feasible. In addition, during clarification questions stage, the ERG

specifically specified that no analyses on metformin need to be provided. On this basis, metformin has been excluded in this addendum.

Figure 1. Comparison of the approach to evidence synthesis – original submission vs addendum incorporating new label.



3.1.2. Important changes in the economic analysis of sotagliflozin due to the revised patient population with a BMI ≥27kg/m^2

Following the CHMP positive opinion, the economic analysis has been updated to reflect the new licence. In addition, Sanofi took the opportunity to adopt a number of suggestions made by the ERG during the clarification stage of the appraisal. Table 21 lists the changes made to the revised base-case compared to the original company submission. All other estimates remained the same between the original submission and the revised base-case, unless otherwise indicated.

Table 21. Changes to CORE Diabetes Model

Variable	Revised company base-case (new licence)	Company base-case *(original submission)*
Population	NDA	NDA
Time horizon	60 years	60 years
Cycle length	1 year	1 year
Efficacy outcomes	inTandem1 and 2 (pooled) sub-population with BMI ≥27kg/m²	inTandem2 (ITT population)
HbA_{1c} progression	0.012% per year*	0.045% per year
BMI progression	0.094 kg/m² per year*	0.2375 kg/m² per year
eGFR progression	−1.227 (mL/min/1,73 m^2) per year*	0 (mL/min/1,73 m^2) per year
SBP progression	0.118 mmHg per year*	UKPDS risk equation
DBP progression	−0.588 mmHg*	0
Total Chol progression	−0.588 (mg/dL) per year*	Framingham risk equation
HDL progression	1.059 (mg/dL) per year*	Framingham risk equation
LDL progression	−1.412 (mg/dL) per year*	Framingham risk equation
Triglycerides progression	−1.176 (mg/dL) per year*	Framingham risk equation
Probability of. Mortality-severe hypoglycaemia	0.003% (Wolowacz et al 2015)(6) per year	5% (Ben-Ami H et al 1999)(7)
Probability of mortality-DKA	0.05% (Wolowacz et al 2015)(6) per year	2.7% (MacIsaac RJ et al. 2002)(8)
Duration of sotagliflozin treatment	5 (base-case) or 2 (SA) years treatment effect and then rebound for a convergence between treatment arms. Cost of optimised insulin treatment as rescue treatment for the rest of the time horizon. No treatment effects assumptions for rescue treatment but a constant rate of AEs. Rescue treatment as substitution in the base-case, and as addition in other SAs (up to 2, 5 years and lifetime).	

*Estimated based on 8.5 years of data (2004 to 2012/13) and using the EDIC intensive insulin arm(9)
AEs, adverse events, BMI, body mass index; DCCT, Diabetes Control and Complications Trial; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SA, sensitivity analysis; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study.

As per the original submission Sanofi have rerun the analysis as submitted in the original company dossier, we have updated the economic write up and presents the base-case and sensitivity results from the updated CORE Diabetes Model (CDM) model in section 4.8.

4. Cost-Effectiveness Analysis (full details)

Summary

- The cost-effectiveness of sotagliflozin 200 mg in patients with baseline BMI >27kg/m^2 was evaluated using the CORE Diabetes Model, a validated and externally audited, patient-level, discrete, event-simulation model for populations with T1D.

- Compared to SoC alone, the incremental cost-effectiveness ratio (ICER) of sotagliflozin was £1,934 per quality of life-year (QALY) gained. The results were found to be robust in probabilistic sensitivity analyses with an ICER value of £2434 per QALY gained. Under base-case assumptions, sotagliflozin 200 mg + SoC versus SoC and had an 89% chance of being cost-effective at a threshold of £20,000.

- In conclusion, in the licensed population with a BMI .27kg/m^2 the cost-effectiveness of sotagliflozin 200 mg + SoC versus SoC has improved versus the original submission based on the entire ITT population from inTandem2. This is in line with the EMA's decision to position the use of Sotagliflozin in T1D patients who are at the highest risk and will hence derive the most benefit from this intervention.

4.1. Published cost-effectiveness studies

Appendix J details the methods and results of published cost-effectiveness analyses available for the technology and/or the comparator technologies.

4.1.1. Identification of studies

4.1.1.1. Systematic literature review of economic evaluations of non-insulin medicines

Methods

A systematic literature review (SLR) was undertaken to identify and summarise published cost-effectiveness analyses (CEAs) or cost-utility analyses (CUAs) for adult patients with

T1D. The review could identify publications which facilitate the development of an economic model representing the important clinical impacts of sotagliflozin and its direct comparators. Full details are described in Appendix K.

Searches were performed in MEDLINE, Embase, EconLIT, the NHS Economic Evaluation Database and the Centre for Reviews and Dissemination Health Technology Assessment (HTA) Database, through hand searches of relevant conference proceedings, and from publicly available information from NICE. Recursive searches of identified review papers were performed, and any additional relevant economic evaluations identified in the process were screened for inclusion.

Table 22. Population, intervention, comparator, outcomes and study design (PICOS) eligibility criteria

PICOS	Inclusion criteria	Exclusion criteria
Participants	Adult (≥18 years) patients with T1D	T2D, adolescents with T1D
Interventions/ comparators	Review of the landscape of the published literature on the models and methods implemented in cost-effectiveness and cost-utility analysis (CEA-CUA) studies of: • Sotagliflozin • Any approved non-insulin medication as an adjunct therapy to insulin • Insulin therapies	
Outcome measures	Studies must report an ICER and may report additionally the following: • Costs (total and/or incremental) • QALYs gained (total and/or incremental) Other natural effectiveness measures, e.g. life-years gained (total and/or incremental)	
Study design	Studies must be one of the following: • Full economic evaluations • CEAs • CUAs	Other types of economic models, including cost–benefit, cost-minimisation, budget impact analyses and partial evaluations

CEA, cost-effectiveness analysis; CUA, cost-utility analysis; ICER, incremental cost-effectiveness ratio; PICOS, population, intervention, comparator, outcomes and study design; QALY, quality-adjusted life-year; T1D, type 1 diabetes; T2D, type 2 diabetes.

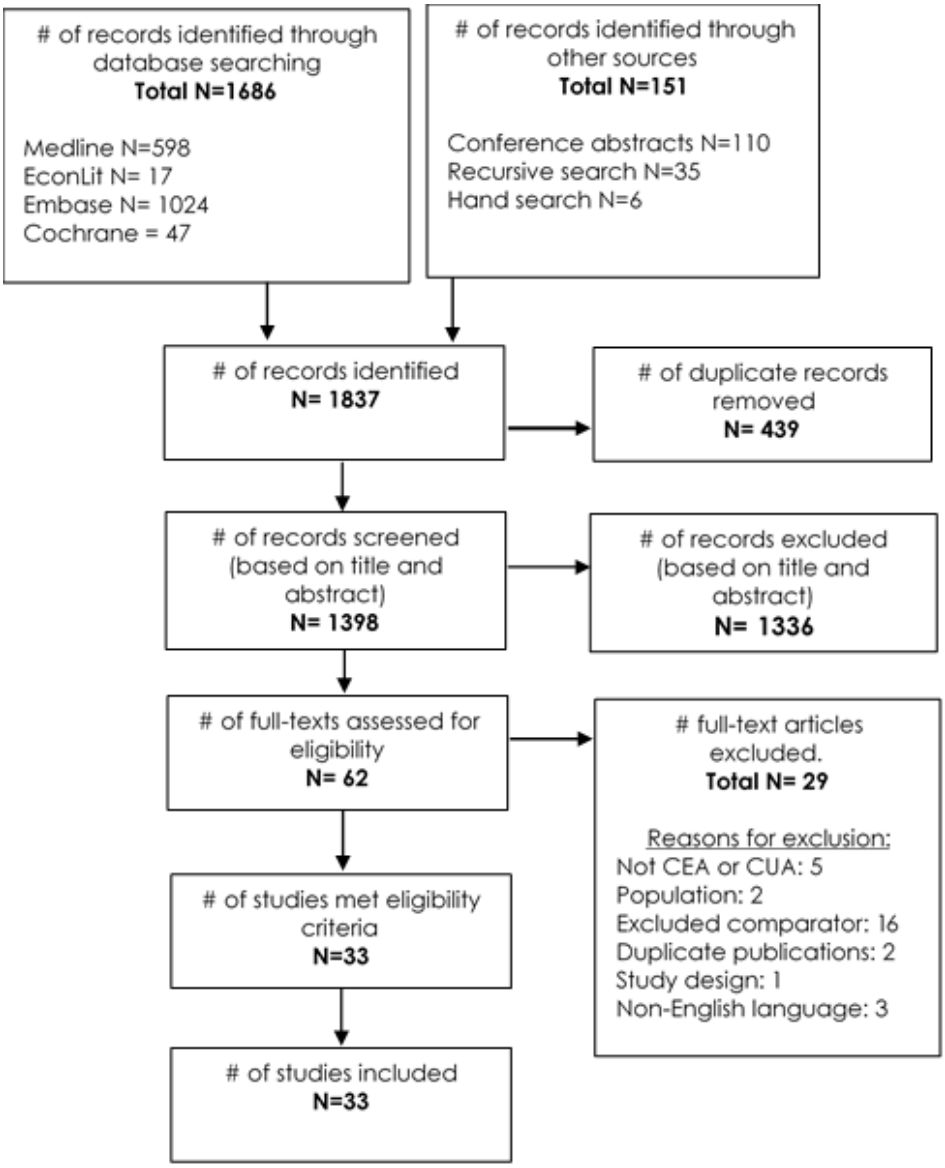
Results

A total of 33 unique CEA or CUA studies were included that examined drug therapies for adult T1D patients. These 33 studies included 22 full-text publications and 11 abstracts. Of the included evaluations, 11 used the CORE (Centre for Outcomes Research and Evaluation; Basel, Switzerland) Diabetes Model [also reported as the IQVIA (formerly IMS) CORE Diabetes Model (CDM)] with a European national health payer perspective. There

were 22 papers reporting a long-term horizon; 10 evaluations used a short-term (1-year) horizon that focused on prevention of hypoglycaemia and the short-term effects of insulin choice. The models with a short time horizon are less able to represent all clinical and cost impacts of treatment, particularly those associated with later-stage complications.

The CDM was the most-reported single model in this review. The SLR also identified the PRIME model.

Figure 2. Preferred reporting Items for systematic reviews and meta-analyses (PRISMA) diagram of the systematic literature review insulin relevant economic evaluation



CEA, cost-effectiveness analysis; CUA, *cost-utility analysis.*

4.2. Economic analysis

4.2.1. Model overview

Based on the results of the SLR, the base-case cost-effectiveness of sotagliflozin 200 mg and long-term projections of clinical outcomes and costs were evaluated using the CDM (10).

The CDM is a computer simulation model developed to determine the long-term health outcomes and economic consequences of interventions in T1D and T2D (11, 12). The model is accessible on a licensed basis over the internet. It is a non-product-specific diabetes policy analysis tool that performs real-time simulations considering intensive or conventional insulin therapy, oral antidiabetic drugs, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications and multi-factorial interventions.

The model has been used extensively to demonstrate the cost-effectiveness of products launching in T1D and T2D and is robustly validated through both external validation studies (e.g. through participation in the Mount Hood Challenge) and internal update and review. Since the first publication and validation of the CDM in 2004, (11) there have been a number of major updates to the model in response to evolving datasets and feedback from both peer review and HTA submission bodies. The current version of the model is version 9.0 (12).

4.2.2. Conceptualisation of the decision problem

The economic evaluation consists of analyses of the cost-effectiveness of sotagliflozin in adults with T1D with a BMI ≥27 kg/m^2 who are not adequately controlled on insulin treatment in the UK. Clinical evidence is presented for the full marketing authorisation for the 200 mg dose in the base-case in Appendix D. In this addendum sensitivity analysis has been provided around the 400 mg dose to estimate the cost-effectiveness of sotagliflozin in the anticipated scenario where 10% patients may be on the higher dose. It is currently anticipated that the 400 mg tablet will be made available in [redacted] at [redacted] as the 200 mg tablet and the additional costs of taking two tablets a day by a small percentage of the patients will only be for two years. This economic evaluation is to support the use of sotagliflozin in clinical practice in England and Wales as reported below.

Patients were simulated to receive sotagliflozin 200 mg as an add-on to SoC based on clinical data from head-to-head comparisons in a pooled analysis of inTandem1 and

inTandem2 with a BMI ≥27 kg/m^2 (pooled analysis). Treatment effects [e.g. decreases in HbA_{1c}, BMI, SBP, lipids and other physiological parameters] in the CDM were applied in the first year of treatment. An annual progression of these parameters was applied in subsequent years in alignment with latest (2004 to 2012/13) data from the Epidemiology of Diabetes Interventions Complications (EDIC) long-term findings (13), or assumed zero in the case of no evidence (pulse rate and waste-to-hip ratio). The current set of analyses assumes a 5-year duration of initial treatment effects applied at year one of the analysis, following by a rebound to the control arm in which all patients switch to insulin alone (SoC). The 5-year duration of treatment is assumed to hold in combination therapy (i.e. sotagliflozin 200 mg + SoC). This assumption is explored in a sensitivity analysis (2-year treatment effect) and is consistent with previous sodium-glucose co-transporter type-2 NICE submissions in T2D (14).

Upon initial treatment discontinuation, the incremental differences in HbA_{1c}, BMI, SBP, lipids and eGFR are abolished (i.e. intervention arm is set to be equal to the SoC arm). HbA_{1c} and BMI maximum levels were applied, as a lifetime increase in HbA_{1c} and BMI could potentially lead to levels that are not clinically plausible. The following cap (maximum) values were applied:

- HbA_{1c}: After the initial treatment effect, HbA_{1c} values where allowed to naturally progress until patients reached their original baseline value, which represents both the initial starting point and the mean value of T1D patients in the UK (15). The final cap was set at 8.7%, which means a slight positive deviation of 0.1% was allowed, this to allow the treatment effect of the control (placebo + SoC) to take place, since a positive increase in HbA_{1c} values were shown after one year.

- BMI: 35 kg/m^2 as cap value, following the definition of class 2 obesity (16).

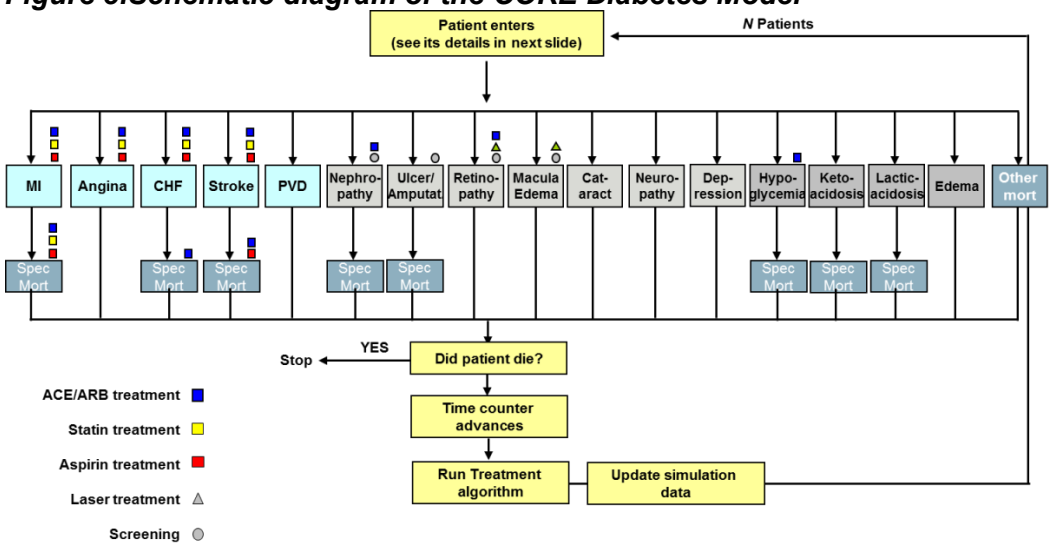
4.2.3. Model structure and parameters

4.2.3.1. Model structure

Within the CDM, disease progression is based on a series of inter-dependent Markov sub-models that simulate progression of disease-related complications [angina, myocardial infarction (MI), congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation] and other causes of mortality. The model is a fixed-time increment (annual) stochastic simulation with each sub-model using

time, state and diabetes type dependent probabilities. Monte Carlo simulations are performed at the individual patient-level using tracker variables to accommodate complex interactions between sub-models. The progression of relevant physiological parameters (e.g. HbA_{1c}, SBP, lipids and BMI) is simulated on the basis of long-term epidemiological data, and event risk is constantly updated on the basis of these risk factors. The model facilitates interconnectivity and interaction between the modelled complications, representing the complex and varied sequelae of diabetes. An overview of the treatment pathway considered in the CDM is illustrated in Figure 5. Details of risk equations for each sub-models are reported in CDM version 9 (17).

Figure 3.Schematic diagram of the CORE Diabetes Model



ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; CHF, chronic heart failure; MI, myocardial infarction; PVD, posterior vitreous detachment.

To run simulations, the model creates a set, or cohort, of individual patients in which each patient is associated with a set of characteristics that define them [e.g. age, age at diagnosis of T1D, gender, BMI, HbA_{1c}, SBP, total cholesterol, high-density lipoprotein cholesterol (HDL-C) and smoking status]. During simulations, treatment-specific effects on patient characteristics of HbA_{1c}, SBP, BMI, HDL-C and total cholesterol, as well as adverse event rates for hypoglycaemia and ketoacidosis, can be applied. The model is user-editable in terms of costs and utility weights used for any given set of simulations.

Clinical and economic outcomes (means and standard deviations) are calculated within the model using a non-parametric bootstrapping approach. This process simulates the lifetime progression of diabetes in a cohort of hypothetical patients repeating the process over

numerous simulations. In the base-case analyses, second-order uncertainty is not applied, and stability of outcomes is reached through a run of 1,000 patients through 1,000 iterations (12). The model reports costs, life expectancy, QALY, cumulative incidence of all modelled diabetes complications, mean hypoglycaemia and ketoacidosis rates in each simulation arm, along with differences in cost, life expectancy and QALY outcomes between simulation arms and the ICER.

Key features of the economic analysis are summarised in Table 24 in comparison with the CEA published by NICE guidelines NG17 (18).

Table 23. Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	NG17	Chosen values	Justification
Diabetes model used	CORE Diabetes Model	CORE Diabetes Model	Up-to-date T1D specific model, published and available to NICE
Time horizon	80 years	60 years	60 years is long enough to capture relevant differences in outcomes across strategies
Discount rate	3.5% annually	3.5% annually	Recommended discount rate for the UK setting
Treatment waning effect	Not applicable (as patients were assumed to continue therapy with insulin regimens)	Sotagliflozin/placebo therapy for 5 years assumed. No treatment waning effect included. All treatment differences abolished after Year 5 as patients return to baseline of 8.7% HbA_{1c}	It is assumed that treatment benefit on sotagliflozin persists while on therapy. No legacy benefit of sotagliflozin is assumed after 5 years
Long-term HbA_{1c} progression	Increased by 0.045% in line with DCCT data	Increased by 0.012% in line with EDIC data	Latest available evidence data cut-off from the EDIC clinical trial (2004-2012/13)
Source of utilities	Published sources (T2D specific)	Updated published sources (T1D specific mostly)	Analogous approach to NG17
Source of costs	Published sources (generally NHS reference costs)	Updated published sources (generally NHS reference costs)	Analogous approach to NG17

NG17, Type 1 diabetes in adults: diagnosis and management (18)
DCCT, Diabetes Control and Complications Trial; EAG, external assessment group; HbA_{1c}, glycated haemoglobin; T1D, type 1 diabetes.

4.2.3.2. Time horizon, perspective and discount rates used

A time horizon of 60 years was used in the base-case as this was deemed sufficient to consider lifetime costs and outcomes. Costs and QALYs were considered from a UK NHS perspective. The analysis follows the standard assumptions of the NICE reference case including discounting at 3.5% for costs and health effects, and incremental analysis.

4.2.3.3. Intervention technology and comparators

The analysis comprised a comparison of sotagliflozin 200 mg + SoC versus a SoC alone.

4.2.4. Model inputs

4.2.4.1. Patient population

For the base-case analysis, a simulated population considered to be representative of adults with T1D in the UK was derived primarily from National Diabetes Audit data described in the cost-effectiveness evaluation supporting NICE Guideline NG17 (18). The population cohort was 56.7% male, with a starting age of 42.98 years. Patients had been diagnosed with diabetes for a mean of 16.92 years, with a mean HbA_{1c} level of 8.60% at baseline. The mean baseline BMI was 27.09 kg/m^2. A summary of the baseline characteristics and complication rates used in the base-case analyses is outlined in Table 25.

Table 24. Baseline characteristics of the simulated cohort based on National Diabetes Audit data

Characteristic	Mean	SD	Source
Patient demographics			
Start age (years)	42.980	19.140	DCCT (19)
Duration of diabetes (years)	16.920	13.310	NDA (15)
Male (proportion)	0.567	–	NDA (15)
Baseline risk factors			
HbA_{1c} (%)	8.600	4.000	NDA (15)
SBP (mmHg)	128.270	16.070	NDA (15)
DBP (mmHg)	80.000	0.000	Default CDM
Total cholesterol (mg/dL)	176.500	33.000	DCCT (19)
HDL-C (mg/dL)	50.250	13.000	DCCT (19)
LDL-C (mg/dL)	109.750	29.000	DCCT (19)
Triglycerides (mg/dL)	81.500	41.000	DCCT (19)
BMI (kg/m^2)	27.090	5.770	NDA (15)
eGFR (mL/min/1.73 m^2)	77.500	0.000	Default CDM
Haemoglobin (g/dL)	14.500	0.000	Default CDM

Characteristic	Mean	SD	Source
WBC (× 10^6/mL)	6.800	0.000	Default CDM
Heart rate (bpm)	72.000	0.000	Default CDM
WHR	0.900	0.000	Default CDM
uACR (mg/mmol)	3.100	0.000	Default CDM
Serum/creatinine (mg/dL)	1.100	0.000	Default CDM
Serum/albumin (g/dL)	3.900	0.000	Default CDM
Proportion smokers	0.220	–	NDA (15)
Cigarettes/day	12.000	–	ONS, 2012 (20)
Alcohol consumption (oz/week)	9.000	–	WHO 2011 (16)
Racial characteristics			
White	0.920	–	NDA (15)
Black	0.030	–	NDA (15)
Hispanic	0.000	–	Assumption
Native American	0.000	–	Assumption
Asian/Pacific Islander	0.050	–	NDA (15)
Baseline cardiovascular complications			
MI	0.003	–	Health Survey for England 2011 (21)
Angina	0.004	–	Health Survey for England 2011 (21)
Peripheral vascular disease	0.000	–	Assumption
Stroke	0.003	–	Health Survey for England 2011(21)
Congestive heart failure	0.000	–	Assumption
Atrial fibrillation	0.000	–	Assumption
Left ventricular hypertrophy	0.000	–	Assumption
Baseline renal complications			
Microalbuminuria	0.181	–	NDA (15)
Gross proteinuria	0.000	–	Assumption
End-stage renal disease	0.000	–	Assumption
Baseline retinopathy complications			
Background diabetic retinopathy	0.0000	–	Assumption
Proliferative diabetic retinopathy	0.0000	–	Assumption
Severe visual loss	0.0000	–	Assumption
Baseline macular oedema			
Macular oedema	0.000	–	Assumption
Baseline cataract			
Macular cataract	0.000	–	Assumption

Characteristic	Mean	SD	Source
Baseline foot ulcer complications			
Uninfected ulcer	0.000	–	Assumption
Infected ulcer	0.000	–	Assumption
Healed ulcer	0.000	–	Assumption
History of amputation	0.000	–	Assumption
Baseline neuropathy			
Neuropathy	0.049	–	DCCT (19)
Baseline depression			
Depression	0.210	–	Hopkins, et al. 2012 (22)

BMI, body mass index; CDM, CORE Diabetes Model; DCCT, Diabetes Control and Complications Trial; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; ONS, Office for National Statistics; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell count; WHR, waist-to-hip ratio; uACR, urine albumin-to-creatinine ratio.

As per the ERG's request in the clarification questions the pooled analysis of patients from inTandem1 and inTandem2 with a BMI ≥27 kg/m^2 (pooled analysis) was selected to inform the cost-effectiveness evaluation. Additional simulations were undertaken to evaluate long-term outcomes in the population of the pooled analysis group, as summarised in Table 26.

The two populations in the NDA and in pooled analysis were similar in terms of age and duration of diabetes. The population cohort of the pooled analysis was 51.% male with a mean starting age of 44.87 years. Patients had been diagnosed with diabetes for a mean of 22.14 years at baseline, with a mean HbA_{1c} level of 7.66% at baseline. Mean baseline BMI was 32.16 kg/m^2. At baseline, HbA_{1c} was lower in the trial population (~7.7%) than in the NDA. This is likely due to the 6-week insulin optimisation period following recruitment. A summary of the baseline characteristics and complication rates is outlined in Appendix D.

4.3. Clinical parameters and variables

For the modelling analysis, the intervention and comparator treatments were associated with changes from baseline in risk factors applied in the first year of the simulation and event rates applied for the duration of therapy. Changes from baseline in risk factors for the base-case were derived from the pooled analysis population.

The pooled analysis was derived from Phase III, randomised, double-blind trials conducted in an insulin-exposed population and compared sotagliflozin 200 mg + SoC to placebo + SoC over a 52-week treatment period in patients with T1D.

Adverse events associated with treatment, namely non-severe hypoglycaemia (non-SH), SH and diabetic ketoacidosis (DKA), were captured in the health economic analysis. These were sourced directly from the head-to-head pooled analysis population.

Simulations were run comparing sotagliflozin + SoC with placebo + SoC based on the pooled analysis population with treatment effect data taken from the 52-week time-point wherever possible. Treatment effects for the intervention and comparator arms are summarised in Table 26.

Table 25. Treatment effects for sotagliflozin 200 mg + SoC and placebo + SoC observed in the pooled analysis population

Physiological parameters	Mean treatment effect (SD)	
	Sotagliflozin 200 mg + SoC	Placebo + SoC
HbA_{1c} (%)	−0.24 (0.04)	0.00 (0.04)
SBP (mmHg)	−1.74 (0.66)	0.40 (0.67)
DBP (mmHg)	−1.18 (0.43)	−0.18 (0.44)
Total cholesterol (mg/dL)	8.84 (1.75)	4.44 (1.80)
LDL-C (mg/dL)	5.29 (1.50)	4.07 (1.55)
HDL-C (mg/dL)	2.36 (0.59)	0.04 (0.61)
Triglycerides (mg/dL)	7.50 (3.12)	7.01 (3.21)
BMI (kg/m^2)	−0.77 (0.09)	0.28 (0.09)
eGFR ($mL/min/1.73\ m^2$)	−2.90 (0.67)	-0.43 (0.69)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation.

For the inclusion of relevant AE in the economic analysis, the AE grading scale as reported by the Common Terminology Criteria for Adverse Events (CTCAE) was considered. Sanofi excluded mild or asymptomatic (Grade 1) events, as well as moderate events where a non-invasive intervention was required (Grade 2). Following this criteria, the full list of AE considered severe (Grade 3), life-threatening (Grade 4) and death related (Grade 5) was examined, with additional focus on those where a statistical significant difference between intervention and control arm was seen. The main adverse events that were considered in the base-case analysis following this methodology were metabolic and nutrition disorders, in particular the number of severe and non-severe hypoglycaemic and DKA events. The increase in incidences observed in pooled analysis population of diarrhoea and combined renal and urinary disorders were 0.7% (3.9% vs 4.6%) and 1.9% (3.8% vs 1.9%),

respectively and were therefore not considered. The summary of these events is also presented in Appendix D.

The treatment effects were calculated using the corresponding event rates obtained in the pooled analysis population. In the CDM, the number of events per 100 patient-years is required for all adverse event rates. The values for all events were reported as events per patient per year in the trial; therefore, a simple conversion to 100 patient-years was applied in order to fit the model (×100). Treatment effects of adverse event rates are outlined in Table 27.

Table 26. Adverse event rates in sotagliflozin 200 mg + SoC and placebo + SoC observed in the pooled inTandem1& 2 (BMI >27KG/M^2)

Adverse events	Mean treatment effect	
	Sotagliflozin 200 mg + SoC	Placebo + SoC
Non-SH event rate per 100 patient-years	5280	6040
SH 1 event rate (requiring non-medical assistance) per 100 patient-years*	NA	NA
SH 2 event rate (requiring medical assistance) per 100 patient-years	8.9	11.4
Annual probability of lactic acidosis	0	0
DKA	3.2	0.4

*Where values were not reported in the trial (e.g. SH event requiring non-medical assistance, proportion of SH events requiring medical assistance), the inputs of the CORE Diabetes Model were assumed equal to 0 to align with the trial outcomes (all SH events reported in the trial required medical assistance; all hypoglycaemia not requiring medical assistance were assumed to be non-severe).
DKA, diabetic ketoacidosis; NA, not applicable; SH, severe hypoglycaemia.

4.3.1. Long-term progression of risk factors

In years subsequent to the treatment change (i.e. first year effect), annual progressions of 0.012% and 0.094 kg/m^2 in HbA_{1c} and BMI, respectively, are applied. These values are based on 8.5 years of data (2004 to 2012/13) and using the EDIC intensive insulin arm. The annual progression is applied until patients reach HbA_{1c} and BMI maximum thresholds of 8.7% and 35 kg/m^2, respectively, at which point HbA_{1c} and BMI stabilise. These assumptions are aligned with the definition of obesity class II (severe obesity) (23) in the case of BMI, and the baseline level of HbA_{1c} that equally represents the UK average, but with a slight 0.1% deviation to allow all treatment effects to occur in Year 1 (25).

The set of utilised values are based on an independent critique of derived DCCT/EDIC natural progression values performed in 2017 by the University of Sheffield, resulting in an

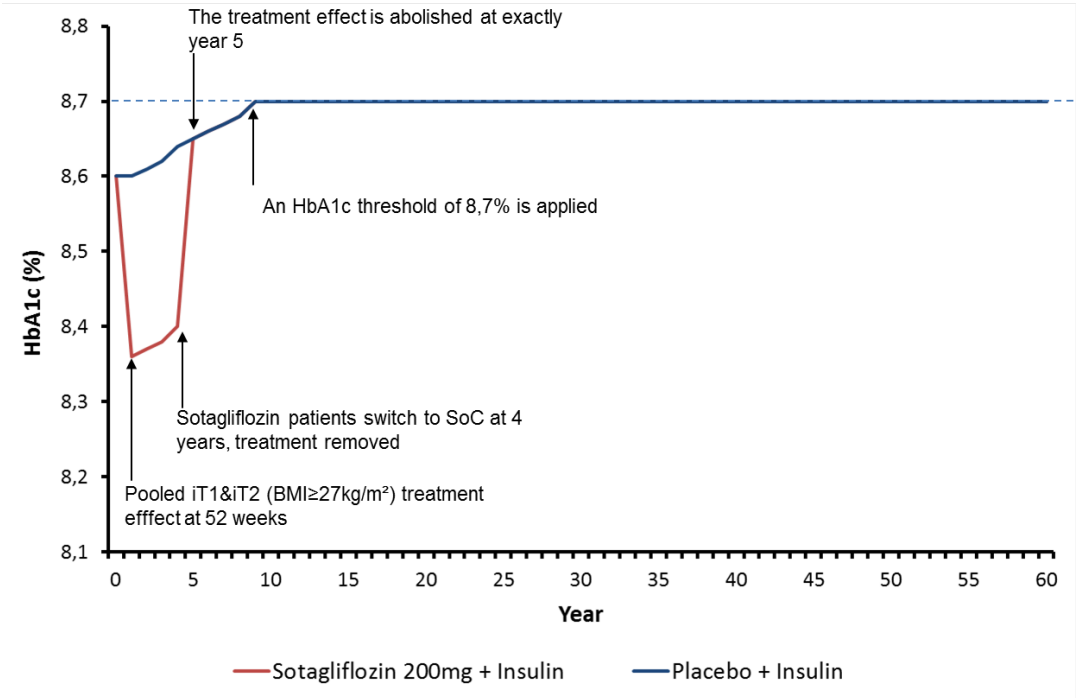
expert recommendation to use the most recent EDIC (2004-2012/13) values, rather than its predecessor the DCCT study (1983-1993).

Following the same methodology, background progression for SBP, LDL-C, HDL-C and triglycerides were informed from the EDIC intensive insulin arm. Due to data consistency reasons, the background progression for eGFR was informed from a longer DCCT/EDIC data range, namely 1993 to 2012/13.

For all the physiological parameters describe above, effects were applied in the first year of the simulation and the incremental differences were maintained until the time on treatment. After 5 years (and therapy switching to insulin only, as in the placebo arm), effects were assumed to rebound to placebo on discontinuation of sotagliflozin therapy (Figure 6 and Figure 7 and Figure 8).

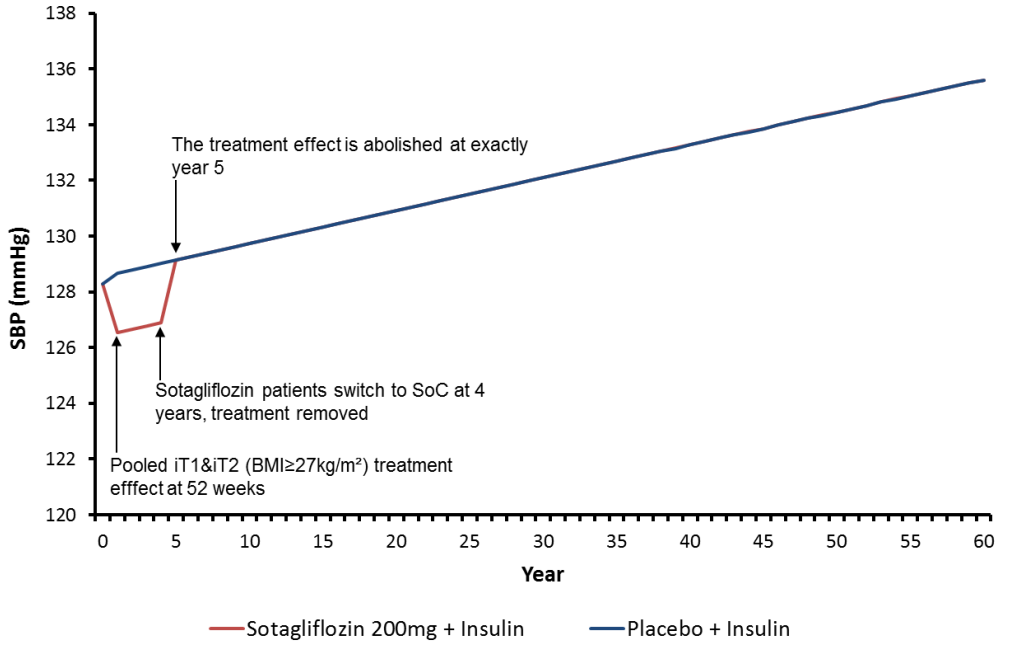
The key analysis assumptions related to the patient progression over time are outlined in Table 28.

Figure 4. Modelled glycated haemoglobin progression in the base-case analysis



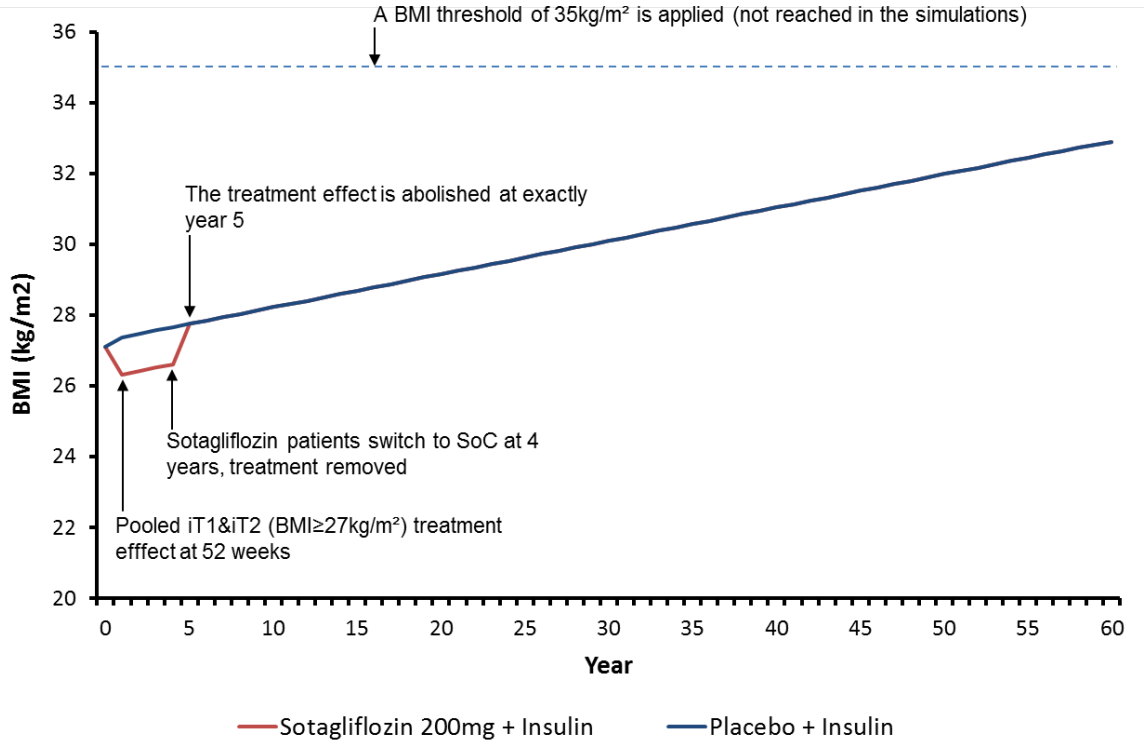
HbA_{1c}, glycated haemoglobin; SoC, standard of care.

Figure 5. Modelled systolic blood pressure progression in the base-case analysis



SBP, systolic blood pressure; SoC, standard of care; UK PDS, UK Prospective Diabetes Study.

Figure 6. Modelled body mass index progression in the base-case analysis



BMI, body mass index; SoC, standard of care.

Table 27. Key assumptions related to patient progression over time

Variable	Value/assumption
HbA_{1c} progression[1]	0.012% per year
BMI progression[1]	0.094 kg/m² per year
SBP progression[1]	0.118 mmHg per year
Total cholesterol progression[1]	−0.588 (mg/dL) per year
LDL-C progression[1]	1.412 (mg/dL) per year
HDL-C progression[1]	1.059 (mg/dL) per year
Triglycerides[1]	−1.176 (mg/dL)
eGFR	−1.227 (mL/min/1,73 m^2)
Prob. Mortality-Severe Hypo	0.003% (Wolowacz et al 2014) (6)
Prob. Mortality-DKA	0.05% (Wolowacz et al 2014) (6)

BMI, body mass index; DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; UKPDS, UK Prospective Diabetes Study.

[1] Estimated based on 8.5 years of data (2004 to 2012/13) and using the EDIC intensive insulin arm(9)

4.3.2. Management settings

Management settings include the proportion of patients on preventative medication, the proportion of patients undergoing screening, and the sensitivity and specificity of tests. Inputs were sourced from available literature with country-specific data preferred where available and are outlined in Table 29. The data on sensitivity and specificity of tests is not country specific and is considered replicable across countries.

Table 28. Management settings

Health state	Input value	Source
Patients on preventative medication		
Proportion of primary prevention aspirin	0.590	EUROASPIRE II Study Group (24) and Kotseva, et al. 2009 (25)
Proportion of secondary prevention aspirin	0.890	Kotseva, et al. 2009 (25)
Proportion of primary prevention statins	0.470	EUROASPIRE II Study Group (24) and Kotseva, et al. (25)
Proportion of secondary prevention statins	0.840	Kotseva, et al. 2009 (25)
Proportion of primary prevention ACEi	0.210	EUROASPIRE II Study Group (24) and Kotseva, et al. 2009 (25)
Proportion of secondary prevention ACEi	0.760	Kotseva, et al. 2009 (25)
Screening and patient management		
Proportion on foot ulcer prevention programme	1.000	No UK data; assumed to be included in standard management
Proportion screened eye disease	1.000	No UK data; assumed to be included in standard management
Proportion screened for renal disease	1.000	No UK data; assumed to be included in standard management
Proportion receiving intensive insulin after MI	1.000	Bydureon NICE submission, (26)
Proportion treated with extra ulcer treatment	0.100	Bydureon NICE submission, (26)
Proportion screened for depression — no complications	0.830	Jones, et al. 2007 (27)
Prop screened for depression — complications	0.830	Jones, et al. 2007 (27)
Sensitivity and specificity of tests		
Reduction in incidence FU with prevention programme	0.690	O'Meara, et al. 2000 (28)
Improvement in ulcer healing rate with extra treatment	1.390	Kantor, et al. 2001 (29)
Reduction in amputation rate with foot care	0.690	O'Meara, et al. 2000 (28)
Sensitivity eye screening	0.920	Lopez-Bastida, et al. 2007 (30)
Specificity eye screening	0.960	Lopez-Bastida, et al. 2007 (30)
Sensitivity GRP screening	0.830	Cortes-Sanabria, et al. 2006 (31)
Sensitivity MAU screening	0.830	Cortes-Sanabria, et al. 2006 (31)
Specificity renal screening	0.960	Cortes-Sanabria, et al. 2006 (31)

ACEi, angiotensin-converting-enzyme inhibitor; FU, foot ulcer; GRP, gross renal proteinuria; MAU, microalbuminuria; MI, myocardial infarction.

4.3.3. Mortality inputs

All-cause mortality was sourced from the UK Office for National Statistics using 2015–17 data (32). The mortality rates for males and females in the UK are shown in Appendix D. Other event-related mortality is applied to the following cases:

- Myocardial infraction: 39.3% for male and 36.4% for females (Sonke GS et al 1996) (33)

- Stroke: 12.4% for both males and females (Eriksson SE et al 2001)(34)
- Severe Hypoglycaemia: 0.002% to 0.004% (Wolowacz S et al 2014)(6)
- Diabetes Ketoacidosis: 0.05% (Wolowacz S et al 2014)(6)
- Foot ulcer and amputation: 0.98% for gangrene and 0.4% for amputation and ulcer (Persson U et al 2000) (35)

4.3.4. Measurement and valuation of health effects

The factors that impact the QoL in patients with T1D are listed below:

- **Diabetes-related complications:** As T1D progresses, patients are exposed to an even greater risk of complications, including CV disease, renal disease, amputation and retinopathy. The occurrence of diabetes- related complications results in significant reductions in QoL (13).

- **Change in body weight:** Sotagliflozin is associated with a reduction in patient bodyweight, which can have a positive impact on a patient's QoL.

4.3.5. Health-related quality of life data from clinical trials

No health-related quality of life (HRQoL) data from the sotagliflozin clinical trial programme were included in the health economic analysis since the trial includes impact of treatment over a short period and does not capture the significant reduction in QoL due to long-term complications. The HRQoL evidence captured in the pooled analysis population has been reported in the clinical section.

4.3.6. Mapping

No mapping techniques were applied in the present analysis.

4.3.7. Health-related quality of life studies

Appendix M describes how systematic searches for relevant HRQoL data were conducted to identify studies reporting utility values related to T1D and its complications. Studies reporting utility values either from direct measurement or derived from QoL instruments were included. The full results of the searches are presented in Appendix M, and only those results used in the model are reported here.

4.3.7.1. Health-related quality of life data used in the cost-effectiveness model

Utilities and disutilities for the health economic analysis were taken from published sources, with a focus on identifying robust diabetes-specific values appropriate for the UK setting wherever possible. All values used in the modelling analysis using the CDM model are described in **Appendix D.**. A minimum approach was used to estimate QALY in the base-case. Health state utilities associated with T1D and its complications were based on the Peasgood, et al study (36), which estimated HRQoL or utility decrements associated T1D using data from a UK research programme on the Dose Adjustment For Normal Eating (DAFNE) education programme. The Peasgood, et al. study is the most recent study that identified studies reporting utility values of T1D-specific complications and therefore was favourable in this analysis (36). Note, when values were not available, the utilities presented in Beaudet, et al. (2014) (37) and Currie, et al. (2006) (38) were selected where necessary. The later studies are widely used across T2D cost-effectiveness models submitted to HTA agencies.

The analysis of the DAFNE research database provides utility estimates based on panel data on diabetes-related health states to populate economic models exploring the cost-effectiveness of interventions for patients with T1D. Utility and disutility inputs are outlined in **Appendix D** .

4.3.7.2. Adverse events

The impact of weight gain (insulin is associated with weight gain), hyperglycaemia and DKA were captured in the model via the application of published utility estimates to the modelled incidence of AEs.

BMI, and the disutility associated with BMI gain, is a core component of the progression of diabetes complications over time and an important measure of the impact of treatment on patients. BMI disutility is also based on the Peasgood, et al. study (36). Based on the definition of obesity stated in the WHO (23) and NHS (39) a person with a BMI ≥25 kg/m^2 is considered overweight; therefore, a disutility of −0.0028 per BMI unit gain was assigned to patients with a BMI >25 kg/m^2 (a conservative assessment of the potential disutility of weight gain).

The disutility associated with non-severe hypoglycaemic events was assumed to be zero, which was consistent with the disutility used in NG17 (Appendix N of NG17 (18)).

Note, where standard error values were not reported in the Peasgood, et al. study, the standard error at baseline (i.e. standard error corresponding T1D without complication) was considered.

Table 29. Summary of utility values for the cost-effectiveness analysis

Health state	Input value	SE	Diabetes population	Input justification	Reference
T1D without complication	0.839	0.231	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
MI event	−0.024	0.053	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Post-MI	0.815	0.231	–	Estimation	Peasgood, et al. 2016 (40)
Angina	0.749	0.010	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Chronic heart failure	0.743	0.010	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Currie, et al. 2006 (38)
Stroke event	−0.033	0.048	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Post-stroke	0.806	0.231	T1D		Estimation
Peripheral vascular disease	0.778	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Microalbuminuria	0.000	0.000	–		Assumption
Gross renal proteinuria	0.791	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Haemodialysis	0.604	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Peritoneal dialysis	0.581	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Renal transplant	0.829	0.231	T1D	No available data in T1D; most recent applicable utility study in T2D was used	Peasgood, et al. 2016 (40)

Health state	Input value	SE	Diabetes population	Input justification	Reference
BDR	0.810	0.231	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
BDR wrongly treated	0.810	0.231	T1D	Assumed equal to BDR	Peasgood, et al. 2016 (40)
PDR laser treated	0.769	0.231	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
PDR no laser	0.769	0.231	T1D	Assumed equal to PDR	Peasgood, et al. 2016 (40)
Macular oedema	0.799	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Severe vision loss	0.780	0.231	T1D	Most recent applicable utility study in T1D	Peasgood, et al. 2016 (40)
Cataract	0.823	0.231	T2D	No available data in T1D; most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)
Neuropathy	0.603	0.231	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Healed ulcer	0.839	0.231	T1D	Assumed zero	
Active ulcer	0.715	0.231	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Amputation, year of event	−0.117	0.052	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Post-amputation	0.722	0.231	T1D	Estimation	
NSHE 1 (daytime)	0.000	0.000	–	Assumption	
NSHE 1 (nocturnal)	0.000	0.000	–	Assumption	
SHE 1 (during daytime)	−0.002	0.001	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
SHE 1 (nocturnal)	−0.002	0.001	T1D	Assumed equal to SHE 1 (daytime)	Peasgood, et al. 2016 (40)
Ketoacidosis event	−0.009	0.010	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Oedema	−0.010	0.000	T2D	No available data in T1D, most recent applicable utility study in T2D was used	Beaudet, et al. 2014 (37)

Health state	Input value	SE	Diabetes population	Input justification	Reference
Post-oedema	0.829	0.231	–	Estimation	Beaudet, et al. 2014 (37)
Depression not treated	0.587	0.231	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)
Depression treated	0.839	0.231	T1D	Assumed equal to baseline	Peasgood, et al. 2016 (40)
Disutility associated with 1 unit increase in BMI	−0.003	–	T1D	Most recent applicable utility study in T1D, UK specific and EQ5D	Peasgood, et al. 2016 (40)

BDR, background diabetic retinopathy; BMI, body mass index; MI, myocardial infarction; NSHE, non-severe hypoglycaemic event; PDR, proliferative diabetic retinopathy; SE, standard error; SHE; severe hypoglycaemic event; T1D, type 1 diabetes; T2D, type 2 diabetes.

4.4. Cost and healthcare resource use identification, measurement and valuation

The analysis perspective includes direct costs only. Direct costs encompass the costs of patient treatment for acute events and long-term illness and include the costs associated with managing the complications associated with the T1D. Costs are described below by treatment-associated costs, complication costs and management costs.

All costs from sources published before 2017 were inflated to 2017 using the 2016/2017 Personal Social Services (PSS) pay and prices index available in the Personal Social Services Research Unit (PSSRU) 2017 (41).

4.5. Intervention and comparators' costs and resource use

Treatment costs comprised drug, needle, MDI, pump costs and the costs associated with self-monitoring blood ketone (where applicable) and self-monitoring of blood glucose (SMBG).

In this analysis, a proportion of insulin pump therapy was considered at baseline as observed in the inTandem clinical trials. Given the high proportion of insulin pump users seen in pooled inTandem1 and inTandem2 (BMI >27 kg/m^2) of 46.4%, the previously submitted case of inTandem2 was conservatively hold in the addendum (25.7% of patients using insulin pump). The insulin dosages were sourced from the pooled analysis population and are summarised in Table 31.

Table 30. Mean daily basal and bolus insulin doses in InTandem2

Delivery method	Insulin type	Placebo (IU/day)	Sotagliflozin 200 mg (IU/day)	Reference
Continuous subcutaneous insulin infusion	Bolus	30.850	28.610	inTandem2 (42)
	Basal	28.380	27.850	inTandem2 (42)
Multiple daily injection	Bolus	32.510	32.000	inTandem2 (42)
	Basal	30.240	29.650	inTandem2 (42)

The mean doses, as shown in Table 31, were conservatively assumed to be constant over time, despite the 52-week outcomes showing an insulin dose-sparing effect favouring sotagliflozin. The doses were also assumed to be equivalent across all subgroups (explored in the sensitivity analyses); this assumption will not impact results as the dose has no incremental impact between arms and no important differences are observed in the doses.

The yearly cost of insulin was calculated using nationally available prices from the British National Formulary (BNF) 2018. Consistent with previous economic models in T1D (Appendix N of NG17(18)), only cartridges and pre-filled pens were used to calculate insulin costs. The sales share data by molecule were estimated using IQVIA Longitudinal Patient Database (LPD) data (43) and were used to calculate the average cost. The annual drug costs were estimated as the weighted average of the cost of each available drug multiplied by its sale share, which led to £508.90 and £468.62 for MDI and CSII respectively

Needle cost was considered; the unit cost of needles was calculated as a weighted average based on the prices of the 10 most commonly used needles according to Prescription Cost Analysis, England data (44). The weighted average needle cost was estimated to be £0.10. This was used to calculate the annual cost of needles per patient for each insulin regimen, which varied according to the frequency of insulin administration. The frequency of insulin therapies was based on NICE guidelines (NG17) for T1D in adults (18). The annual needle cost was estimated to be £151.13. A breakdown details of the cost of needles is presented in Appendix D.

The cost of sotagliflozin 200 mg and its daily dose were obtained from Sanofi. The drug acquisition costs and daily doses are summarised in Table 32.

Table 31. Drug acquisition costs

Drug	Pack price (£)	Daily dose	Annual cost (£)	Source
Sotagliflozin 200 mg	39.20	200 mg	477.30	Sanofi
SoC (MDI)	–	–	508.63	BNF 2018, inTandem2 (45), NG17 (18)
SoC (CSII)	–	–	468.62	BNF 2018, inTandem2 (45), NG17 (18)

BNF, British National Formulary; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injection; SoC, standard of care.

The insulin pump costs comprised the CSII, annualised pump and consumable costs. The annualised pump and consumable costs were sourced from the NG17 costing template (18) and inflated to 2018 costs. The breakdown of pump costs is summarised in Table 33.

Table 32. Breakdown of pump cost

	Cost (£)	Inflated costs to 2018 (£)	Source
Consumables	1,758.00	1,813.18	NG17 (18)
Annualised pump	605.00	623.99	NG17 (18)
CSII	468.62	468.62	BNF 2018 inTandem2 (45) IQVIA LPD (43)
Total annual pump cost (£)	2,906		

CSII, continuous subcutaneous insulin infusion

The SMBG cost was calculated as a weighted average based on the prices of the 10 most commonly used lancet and strips (44). The weighted average SMGB cost was estimated to be £0.30. The number of test strips and lancets required per day was assumed to be four times for all regimens based on NICE NG17 guidance (18), and subsequently the annual cost of SMBG per patient was estimated to be £437.80 and applied in all arms. A breakdown of these costs is presented in Appendix D.

Self-monitoring blood ketone cost was calculated as a weighted average based on the prices of the most commonly used blood ketone strips according to the Prescription Cost Analysis, England data (44). The weighted average cost was estimated to be £2.00. It was assumed that blood ketone was monitored using 20 and 10 strips per year for sotagliflozin and the comparators (placebo + SoC and metformin + SoC), respectively, in alignment with the NHS ketone testing and sick day rules guideline (46, 47). The guideline states that patients with a high risk of ketones should receive two boxes of strips, while newly diagnosed patients should receive one box of strips (each box containing 10 strips) (18). Based on these data, annual costs of blood ketone monitoring equal to £40.03 (two boxes)

and £20.02 (one box) were applied to sotagliflozin 200 mg adjunct to SoC and the comparators, respectively. A sensitivity analysis has been performed using an extreme assumption of 100 blood ketone test strips for sotagliflozin-treated patients. This may be considered an extreme scenario given expert opinion suggests that there is no evidence that daily ketone monitoring prevents DKA (48). A breakdown of these costs is presented in Appendix D.

The yearly treatment costs per patient in each arm are outlined in Table 34. Note that the sum of MDI, CSI insulin and SMBG costs (sum corresponding to cost of placebo + SoC) were assumed to accrue yearly from the initiation of insulin treatment, hence, were the same for first and subsequent years.

Table 33. Yearly treatment costs per patient

Intervention	Annual drug cost (excluding SoC) (£)	Annual MDI cost* (£)	Annual pump cost (£)	Annual SMBG cost (£)	Annual self-monitoring blood ketone cost (£)	Total annual cost (£)
Sotagliflozin 200 mg + SoC	477.30	490.21	746.79	437.90	40.03	£2,192.23
Placebo + SoC	0.00	490.21	746.79	437.90	20.02	£1,732.48

*Costs include needle costs.
MDI, multiple daily injection; SoC, standard of care; SMBG, self-monitoring of blood glucose.

4.6. Health state unit costs and resource use

Costs were estimated based on literature or local data sources. Drug acquisition costs were sourced from the BNF using 2018 costs. Screening tests for eye disease and proteinuria, and foot screening programmes were sourced from published tariffs reported in the PSSRU. With regards to the direct costs associated with management of diabetes complications, emphasis was placed on the use of costs derived from local sources and diabetes-specific sources where possible.

In the PSSRU, SH was considered as a proxy for DKA. The costs of SH and DKA were calculated based on a weighted average of admission count and non-elective spell tariff cost of diabetes with hyperglycaemic (with NHS reference cost for complications and comorbidities (CC) score 0–8+) and hypoglycaemic disorder (with CC score 5–8+), respectively. A breakdown of these costs is presented Appendix D.

Complication and management costs are summarised in Table 35**.** Where data from the literature were not available, the CDM default values were considered. These costs were inflated to 2017 using the 2016/2017 PSS pay and prices index available in PSSRU 2017 (49).

Table 34. Summary of direct costs associated with diabetes-related complications

Input variable	Mean cost per year (£)	Source/comments
Management costs		
Annual statins*	22.31	BNF 2018
Annual aspirin*	14.35	BNF 2018
Annual ACEi*	7.11	BNF 2018
Annual eye screening	35.00	NHS reference costs 2018 (49)
Annual screening for microalbuminuria	3.11	Lamb, et al. 2009 (50)
Annual screening for gross renal proteinuria	3.00	Lamb, et al. 2009 (50)
Stopping ACEi due to adverse event*	7.44	BNF 2018
Foot screening programme (monthly)	53.00	NHS reference costs 2018 (49)
Non-standard ulcer treatment (e.g. Regranex) (monthly based)	0.00	CDM default value
Anti-depression treatment and management	0.00	Assumption
Screening for depression	0.00	Part of standard management
Direct costs: cardiovascular complications		
MI, first year	3,419.59	NHS Reference Costs 2018, (49)
MI, second+ years	820.01	NICE CG181, 2016 (51) cost inflated to 2017
Angina, first year	1,810.85	NHS Reference Costs 2018, (49)
Angina, second+ years	299.70	NICE CG181, 2016 (51) cost inflated to 2017
CF, first year	2,964.21	NICE CG181, 2016 (51)
CF, second+ years	2,702.49	NICE CG181, 2016 (51)
Stroke, first year†	4,506.28	NHS reference costs 2018 (49)
Stroke, second+ years	702.86	Beaudet et al., 2011 (52), cost inflated to 2017
Stroke death within 30 days	4,962.11	Beaudet et al., 2011 (52), cost inflated to 2017
Peripheral vascular disease, first year	1,914.33	Beaudet et al., 2011 (52), cost inflated to 2017
Peripheral vascular disease, second+ years	1,914.29	Beaudet et al., 2011 (52), cost inflated to 2017

Input variable	Mean cost per year (£)	Source/comments
Direct costs: renal complications		
Haemodialysis, first year‡	25,116.00	NHS reference costs 2018 (49) NICE CG125, 2011 (53)
Haemodialysis, second+ years‡	25,116.00	NHS reference costs 2018 (49) NICE CG125, 2011 (53)
Peritoneal dialysis, first year*	28,105.00	NHS Reference Costs 2018, (49) and NICE CG125, 2011 (53)
Peritoneal dialysis, second+ years*	28,105.00	NHS reference costs 2018 (49) NICE CG125, 2011 (53)
Renal transplant, first year§	14,328.81	NHS reference costs 2018 (49)
Renal transplant, second+ years	8006.27	NICE CG125, 2011(53), cost was inflated to 2017
Direct costs: acute events		
Non-SH	0.00	Guideline development group: assumed to be treated at home
SH event 1: requires non-medical assistance	NA	All SHE assumed to require medical assistance
SH event 2: requires medical assistance	2,320.03	NHS reference costs 2018 (49)
DKA event‖	1,556.22	NHS reference costs 2018 (49) Assumption: diabetes with hypoglycaemic disorders, with CC scores 5–8 (weighted cost))
Lactic acid event	0.00	Assumed no cost of management required (expert opinion)
Oedema onset	0.00	Assumed no cost of management required (expert opinion)
Oedema follow-up	0.00	Assumed no cost of management required (expert opinion)
Direct costs: eye disease		
Laser treatment	700.00	NHS reference costs 2018 (49)
Cataract operation	1,388.98	NHS reference costs 2018 (49)
Following cataract operation	105.00	NHS reference costs 2018 (49)
Blindness, year of onset	7,735.41	Aflibercept NICE submission (54), cost inflated to 2017
Blindness, following years	7,662.19	Aflibercept NICE submission (54), cost inflated to 2017
Direct costs: neuropathy, foot ulcer, amputation		
Neuropathy, first year	26.09	BNF, 2018
Neuropathy, second+ years	26.09	BNF, 2018
Amputation (event based)	12,659.00	NHS reference costs 2018 (49)
Amputation prosthesis (event based)	15,728.68	NHS reference costs 2018 (49)
Gangrene treatment (monthly)	4,704.55	Ghatnekar et al., 2002 (55)
Healed ulcer	29.67	Ghatnekar et al., 2002 (55)

Input variable	Mean cost per year (£)	Source/comments
Infected ulcer (monthly)	2,697.34	Ghatnekar et al., 2002 (55)
Standard uninfected ulcer (monthly)	2,644.45	Ghatnekar et al., 2002 (55)
Healed ulcer history of amputation	26,089.71	NICE CG147, 2018 (56)

*Estimated by multiplying daily costs by 365.25.
†Cost estimated by calculating the weighted average of the costs incurred in strokes score 10–12 (HRG code AA35C) including elective in patient and non-elective long stay.
‡Calculated by multiplying the unit cost for hospital haemodialysis or filtration with access via arteriovenous fistula or graft (LD02A) with 156 sessions as stated in CG125.
§Includes the costs with Healthcare Resource Group codes LA031 and LA12A.
‖DKA cost was calculated based on a weighted average of admission count and non-elective spell tariff cost of diabetes with hyperglycaemic (with CC score 0–8+) and hypoglycaemic disorder (with CC score 5–8+), respectively.
ACEi, angiotensin-converting-enzyme inhibitor; BNF, British National Formulary; CC, complications and comorbidities; CDM, CORE Diabetes Model; CHF, congestive heart failure; DKA, diabetic ketoacidosis; MI, myocardial infarction; NA, not applicable; SH, severe hypoglycaemia

4.6.1. Miscellaneous unit costs and resource use

All costs and resource use assumptions are described in Sections 4.5

4.6.1.1. Summary of base-case analysis inputs

The base-case analysis compared the long-term cost-effectiveness of sotagliflozin 200 mg + insulin with placebo + insulin based on the inTandem2 trial. All base-case settings are summarised in Table 36, with additional detail provided in previous sections.

Table 35. Summary of settings for the base-case modelling analysis

Model input	Sotagliflozin plus SoC	Placebo plus SoC
Model input	Sotagliflozin + SoC	
Cohort	UK T1D cohort (Table 25)	
Treatment	Sotagliflozin + SoC	Placebo + SoC
Treatment cost	£2,192.23 (Table 34)	
Complication costs	UK 2017 costs (Table 35)	
Adverse event costs	UK 2017 costs (Table 35)	
Utilities	UK-appropriate, diabetes-specific utilities (Table 30)	
Mortality from causes other than diabetes-related complications	UK office for national statistics using 2015-2017 data (57)	
Duration of sotagliflozin therapy	5 years then switch to comparator intervention	
Progression of risk factors	Assumed constant over time, a maximum cap value of 8.7% and 35 kg/m² applied to HbA_{1c} and BMI respectively (Section 4.4.1)	
Time horizon	60 years	

T1D, type 1 diabetes.

4.7. Summary of base-case analysis inputs and assumptions

The main assumptions employed in the base-case analysis can be summarised as follows:

- Cohort characteristics were based on a previous economic evaluation by NICE and are considered to be representative of patients with T1D in the UK. This can be considered to be the most appropriate choice for a base-case analysis, but relies on the assumption that the treatment effects estimated in pooled analysis population would be applicable to a population with these characteristics. For instance, it is well established that the magnitude of improvements in HbA_{1c} with therapy intensification is influenced by baseline HbA_{1c} and, in a population with a relatively high starting HbA_{1c} (such as that used in the base-case analysis), the potential benefits of intensification of therapy (such as adjunct sotagliflozin) may be greater than estimated in the clinical trial data.

- It was assumed that patients would remain on sotagliflozin for 5 years before switching to insulin therapy (as modelled in the placebo arm). This simplifying assumption was used to improve the transparency of the base-case analysis. The assumption of 5 years of therapy for all sotagliflozin patients means that the costs and benefits of therapy can be clearly evaluated (as no benefits were assumed to persist beyond the 5-year period). Alternative assumptions (e.g. a proportion of patients switch therapy every year) make it more difficult to interpret the results. Moreover, it can be considered a conservative assumption, as the legacy effect or metabolic impact of a 5-year improvement in HbA_{1c} (as documented in the DCCT) is not captured in the modelling analysis and no weight loss is assumed to persist beyond the 5 years of sotagliflozin therapy.

    - The base-case analysis assumed 100% persistence with therapy in both treatment arms. This is a simplifying assumption in the absence of clinical evidence on the effects of discontinuing sotagliflozin as an adjunct to SoC. Any modelling of compliance and/or persistence would be based on a set of assumptions, which would have the potential to obfuscate the central research question under investigation with this analysis (i.e. is sotagliflozin cost-effective versus placebo when added to insulin therapy for T1D).

    - It was assumed that the treatment benefit with sotagliflozin (i.e. the difference in $HbA_{1c,}$ BMI, SBP and lipid profile between the sotagliflozin and placebo

arms) would be abolished on discontinuation of sotagliflozin. For example, it is reasonable to assume that the benefits observed at 52 weeks in the pooled analysis would persist for the duration of therapy. Alternative HbA_{1c} progression assumptions were investigated in sensitivity analyses.

- Simplifying assumptions were made on the progression of risk factors over time in the base-case analysis. This was done to simplify the interpretation of findings (i.e. the differences in long-term outcomes were associated with treatment effects applied in the modelling analysis as opposed to being due to long-term assumptions on the progression of risk factors). Alternative risk factor progression assumptions were investigated in sensitivity analyses.

An independent analysis undertaken by the University of Sheffield aimed to reproduce some of the default values in the CDM derived from the DCCT/EDIC trials (and widely used in other published T1D cost-effectiveness analyses) — specifically the annual natural progression of +0.045% in the HbA_{1c} levels, and +0.2375 kg/m^2 in the BMI, however they were unable to reproduce these values (Appendix D). The authors of this independent analysis recommended rather the use of the most updated EDIC evidence (2004-2012/13) for HbA_{1c} and BMI. Consistent with this approach, all yearly background progression where estimated from the intensive EDIC insulin arm, as it was considered to represent the most accurate practice (conventional insulin therapy is no longer recommended for T1DM patients).

Finally, the need of ketone monitoring was identified as an important aspect of clinical practice for sotagliflozin patients. The frequency of ketone monitoring is highly patient specific, therefore determining a mean frequency applicable to a cohort of patients is challenging. The current analyses used the NHS sick day guideline on ketone monitoring, stating that patients with high risk of ketones (as the case of pump users) should receive two boxes of blood strips when required while early diagnosed T1D patients should receive one box of strips. Therefore, a mean of 20 strips and 10 strips per year were assumed for patients on sotagliflozin and placebo respectively.

4.8. Base-case incremental cost-effectiveness analysis results

Long-term projections of costs and clinical outcomes for 5 years of therapy with sotagliflozin versus placebo showed that sotagliflozin was associated with improved clinical outcomes and increased direct costs (Table 37). Improvements in glycaemic control, SBP and BMI

associated with sotagliflozin improved life expectancy by approximately 0.029 years versus placebo and QALY by approximately 0.108 QALYs versus placebo. Despite a lower risk of diabetes-related complications with sotagliflozin, direct costs were projected to be approximately £209 higher than with placebo, leading to an ICER of £1,934 per QALY gained.

Table 36. Summary of base-case cost-effectiveness outcomes for sotagliflozin 200 mg versus placebo

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Quality-adjusted life-year (QALYs)	8.803	8.695	0.108
Life expectancy (years)	17.223	17.194	0.029
Lifetime combined costs (£)	78,940	78,731	209
ICER (Delta costs/Delta QALYs)	£1934		

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care

4.8.1. Base-case breakdown of costs

Sotagliflozin 200 mg + SoC reduced the costs of complications (−£1,561) and increased the costs of treatment (£2,249), management (£3), SH events (£5) and DKA events (£252), which led to a total incremental cost difference of £948. A breakdown of direct lifetime costs by cost category is outlined in Table 38

Table 37. Breakdown of costs (£) (sotagliflozin 200 mg + standard of care versus placebo + standard of care)

	Sotagliflozin 200 mg + SoC	**Placebo + SoC**	**Incremental (£)**
Total direct costs	78,940	78,731	209
Treatment	31,655	29,794	1,861
Management	1,934	1,931	3
Cardiovascular disease	3,220	3,269	−49
Renal	4,993	5,093	−100
Ulcer/amputation/neuropathy	18,725	19,387	−662
Eye	13,718	14,521	−803
Non-severe hypoglycaemia	0	0	0
Severe hypoglycaemia	4,469	4,626	−157
Diabetic Ketoacidosis	227	110	117

SoC, standard of care.

Sotagliflozin 200 mg + SoC delayed the appearance of any complications versus placebo + SoC by approximately 4.8 months on average. The time alive and free of complications

results are outlined in Table 39. Sotagliflozin 200 mg + SoC led to lower cumulative incidence of all simulated complications with the exception of cataract, posterior vitreous detachment (PVD), stroke, DKA, SH, MI events and death. The cumulative incidence of complications in each arm are outlined in Table 40.

Table 38. Life-years gained

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Any complications	4.76	4.37	0.39
Background retinopathy	12.55	11.95	0.6
Proliferative retinopathy	24.66	24.3	0.36
Microalbuminuria	17.91	17.62	0.29
Gross proteinuria	25.4	25.17	0.23
End-stage renal disease	29.4	29.27	0.13
First ulcer	25.03	24.79	0.24
Amputation	28.49	28.33	0.16
Neuropathy	18.13	17.77	0.36
Peripheral vascular disease	27.97	27.86	0.11
Congestive heart failure	29.57	29.42	0.15
Angina	27.9	27.78	0.12
Myocardial infarction	28.34	28.21	0.13
Stroke	29.4	29.26	0.14
Cataract	26.32	26.27	0.05
Macular oedema	20.98	20.6	0.38
Severe vision loss	25.38	25.05	0.33

SoC, standard of care.

Table 39. Cumulative incidence of complications

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
Background retinopathy	78.82	80.02	−1.2
Proliferative retinopathy	26.03	26.72	−0.69
Macular oedema	46.26	46.82	−0.56
Severe vision loss	31.18	32.12	−0.94
Cataract	19.14	18.94	0.2
Microalbuminuria	45.6	46.66	−1.06
Gross proteinuria	30.66	31.06	−0.4

	Sotagliflozin 200 mg + SoC	Placebo + SoC	Incremental
End-stage renal disease	11.32	11.46	−0.14
Nephropathy-related death	8.53	8.62	−0.09
Foot ulcer, first event	46.28	47.03	−0.75
Recurring foot ulcer	74.19	75.74	−1.55
First amputation	16.62	17.01	−0.39
Amputation, recurrent ulcer	9.99	10.36	−0.37
Neuropathy	62.69	63.69	−1
CHF death	5.07	5.39	−0.32
CHF event	7.09	7.6	−0.51
PVD onset	14.26	14.13	0.13
Angina	11.52	11.59	−0.07
Diabetes mortality	2.24	2.28	−0.04
Stroke event	4.79	4.93	−0.14
MI death	9.93	10.13	−0.2
MI event	17.93	18.15	−0.22
Non-SH	1828.251	1843.128	−14.877
SH event 1 (requires non-medical assistance)	0	0	0
SH event 2 (requires medical assistance)	3.419	3.482	−0.063
Nausea	0	0	0
Lactic acidosis	0	0	0
DKA	0.207	0.123	0.084

CHF, congestive heart failure; DKA, diabetic ketoacidosis; MI, myocardial infarction; PVD, posterior vitreous detachment; SH, severe hypoglycaemia; SoC, standard of care.

5. Sensitivity analyses

5.1. One-way sensitivity analyses

A number of one-way sensitivity analyses were conducted to test the robustness of model assumptions to plausible changes in key model parameters. In these, one or more inputs were changed, and the analyses were rerun to evaluate the impact on results. A list of variables that have been changed with description of the analysis are outlined in Table 41.

5.1.1. Results of one-way SA

In the sensitivity analyses performed, sotagliflozin 200 mg + SoC remained cost-effective compared with placebo + SoC, with ICERs between being dominant and £10,012 per QALY. All of the sensitivity analyses conducted resulted in an ICER below the cost-effectiveness threshold of £20,000 per QALY.

Similarly, changing cohort characteristics to match those of the pooled analysis population still produced a cost-effective ICER of £10,012 at a willingness-to-pay threshold of £20,000. Increasing the costs of sotagliflozin therapy to account for 100 ketone blood testing strips each year led to higher incremental costs (£793) than in the base-case analysis and a corresponding higher ICER (£7347).

Changing assumptions around the duration of sotagliflozin therapy did not meaningfully impact cost-effectiveness. This was due to the fact that costs and clinical benefits associated with sotagliflozin were balanced in the analysis (i.e. clinical benefits in terms of hypoglycaemia rates and HbA_{1c} were only applied in the modelling analysis during treatment with sotagliflozin and accompanied by the associated additional pharmacy costs).

Table 40. Sensitivity analyses results – sotagliflozin 200mg + standard of care versus placebo + standard of care

Comparison	Name in the CORE Diabetes Model	Lifetime combined costs (GBP)			Quality-adjusted life-years (QALYs)			ICER
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	
Base-case								
Base-case	S200vsPla-iT1&2-NDA-NICE-BC	78,940	78,731	209	8,803	8,695	0,108	**1,934**
Sotagliflozin 200mg + SoC versus Placebo + SoC **PSA**	S200vsPla-NDA-NICE-PSA	78,593	78,300	293	8.782	8.661	0.12	**2,434**
Sensitivity Analyses								
Tx effects & costs 2 years	S200vsPla-iT1&2-NDA-NICE-SA1	78,913	78,735	178	8.733	8.695	0.038	**4,654**
Type 2 DM utility values	S200vsPla-iT1&2-NDA-NICE-SA2	78,940	78,731	209	8.612	8.495	0.116	**1,796**
No BMI disutility	S200vsPla-iT1&2-NDA-NICE-SA3	78,940	78,731	209	8.970	8.869	0.101	**2,073**
Economics +20%	S200vsPla-iT1&2-NDA-NICE-SA4	88,397	88,519	-122	8.802	8.694	0.108	**DOMINANT**
Economics -20%	S200vsPla-iT1&2-NDA-NICE-SA5	69,483	68,944	539	8.802	8.694	0.108	**4,997**
Increased frequency of ketone monitoring (100 strips/year)	S200vsPla-iT1&2-NDA-NICE-SA6	79,524	78,731	793	8.803	8.695	0.108	**7,347**
Price of Sotagliflozin +10%	S200vsPla-iT1&2-NDA-NICE-SA7	79,114	78,731	383	8.803	8.695	0.108	**3,548**
Study Cohort (Pooled inTandem1 & inTandem2 with BMI≥27 kg/m²)	S200vsPla-NICE-B2	72,126	71,511	615	10.490	10.428	0.061	**10,012**

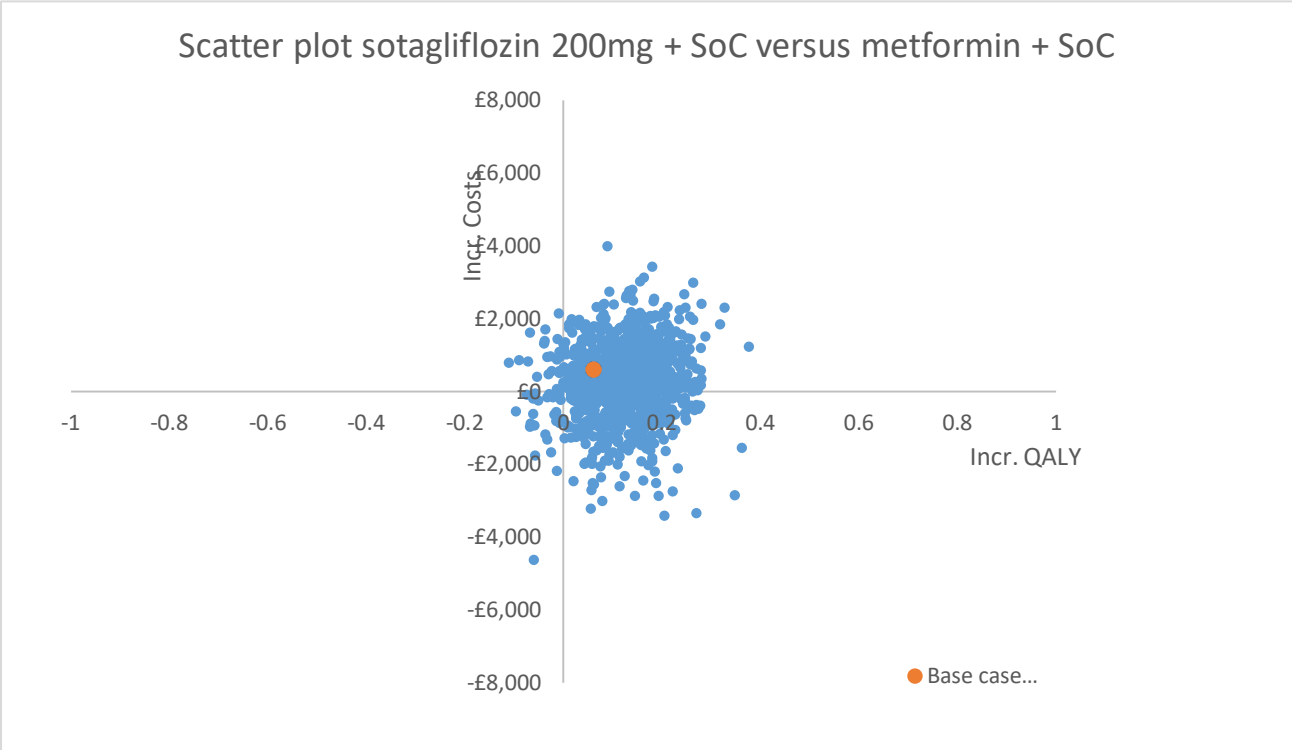
BMI, body mass index; HbA_{1c}, glycated haemoglobin; ICER, incremental cost-effectiveness ratio; ITT, intent-to-treat; NDA, National Diabetes Audit; NMA, network meta-analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SoC, standard of care.

5.2. Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) were conducted to analyse the robustness of results to second-order uncertainty. A PSA was conducted utilising 10,000 patients and 1,000 iterations.

Probabilistic results were in line with deterministic results, with an average ICER of £2,434 per QALY gained. The incremental cost-effectiveness pairs for costs and QALYs gained are plotted in Figure 9. The north-east quadrant contained 60.6% of points and the south-east quadrant 34% of points.

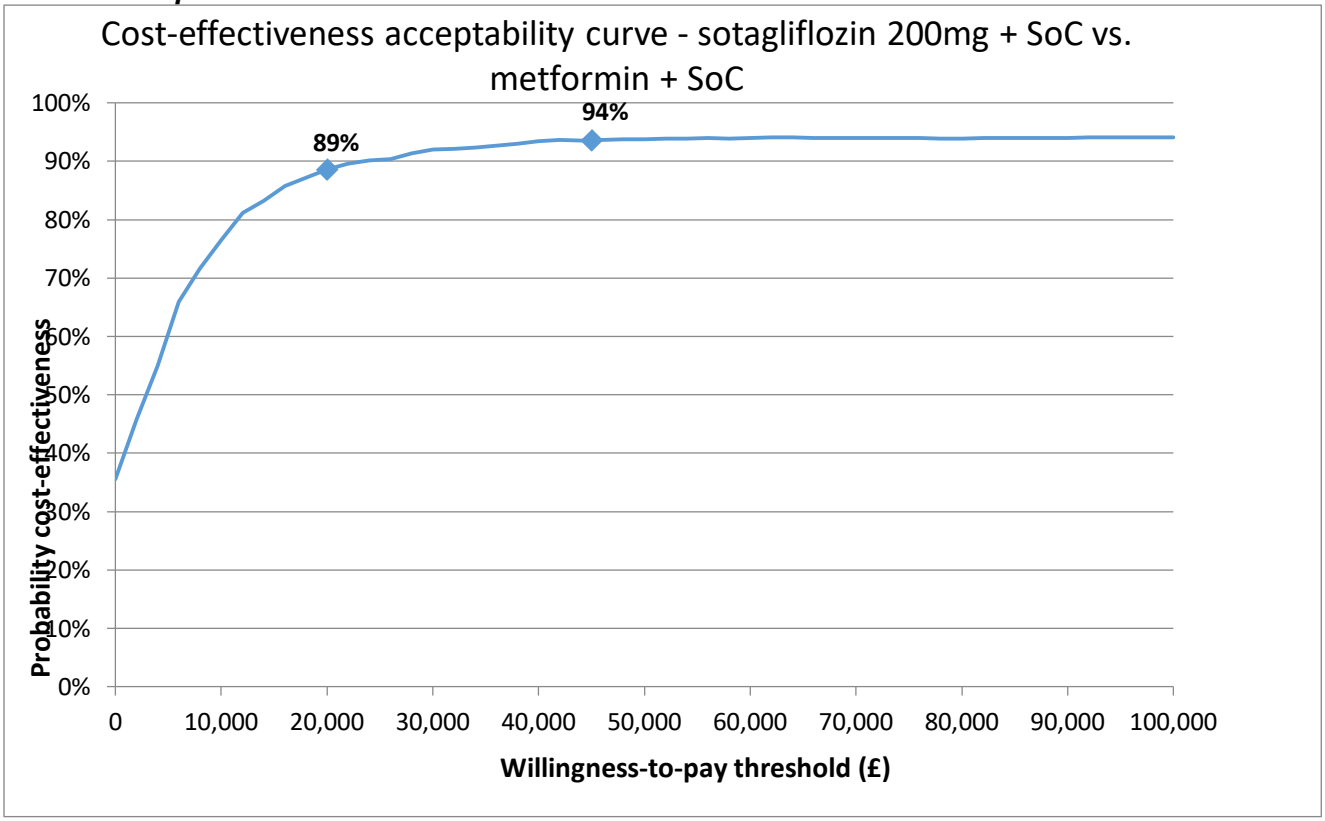
Figure 7. Cost-effectiveness scatter plot — sotagliflozin 200 mg + standard of care versus placebo + standard of care



ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SoC, standard of care.

The cost-effectiveness acceptability curve is shown in Figure 10. At a willingness-to-pay of £20,000 per QALY there is an 89% probability of sotagliflozin 200 mg + SoC being cost-effective relative to SoC.

Figure 8. Cost-effectiveness acceptability curve — sotagliflozin 200 mg + standard of care versus placebo + standard of care



SoC, standard of care

5.2.1. Validation

The CDM model has been used extensively to demonstrate the cost-effectiveness of products launching in T1D and T2D and is robustly validated through both external validation studies (e.g. through participation in the Mount Hood Challenge) and internal update and review. The CDM is one of the few models currently available with published validations that demonstrate the reliability of outcomes (58). In addition, results from the model have been widely published, with over 80 peer-reviewed publications.

5.2.2. Interpretation and conclusions of economic evidence

The CDM is the most widely adopted economic model in diabetes available to users from academia and healthcare industries, as well as healthcare payers and decision-makers. In addition, results from the model have been widely published, with over 80 peer-reviewed publications.

In order to enable NICE to address the decision question Sanofi has incorporated all model adjustments as suggested in the ERG clarification questions in the current submission and as already alluded in the previous submission a comprehensive review was conducted to

identify the most up-to-date data specific to the UK setting (including costs, background complications and management settings). Sanofi have also provide sensitivity analyses to test assumptions around key inputs, leading to a robust and credible set of analyses inputs.

Under base-case assumptions, sotagliflozin 200 mg + SoC was more effective and more costly versus placebo + SoC. Sotagliflozin 200 mg + SoC was cost-effective compared with placebo + SoC at a cost-effectiveness threshold of £20,000 per QALY. This was confirmed in all the sensitivity analyses conducted. Sensitivity analyses indicated that the model was robust to all of the assumptions tested.

In conclusion, in the licensed population with a BMI .27kg/m^2 the cost-effectiveness of sotagliflozin 200 mg + SoC versus SoC has improved versus the original submission based on the entire ITT population from inTandem2. This is in line with the EMA's decision to position the use of Sotagliflozin in T1D patients who are at the highest risk and will hence derive the most benefit from this intervention.

5.2.3. Key strengths and limitations

Strengths

- Identification of precise, coherent, up-to-date, and relevant data on the many inputs required to model T1D represents a challenge. However, Sanofi have implemented all model modifications as suggested by the ERG, have employed the best available data and have tested by means of sensitivity analyses. Computer simulation modelling remains the best option currently available to estimate the clinical and economic consequences of therapeutic interventions in the medium to long-term. No model can claim to be perfectly accurate but the IQVIA CDM is one of the few models currently available with published validations that demonstrate the reliability of outcomes (59).

- Consistent with previous NICE appraisals in T1D, all positive differential HbA_{1c}, BMI and SBP effects seen in the sotagliflozin arm were abolished after 5 years in the base-case (and 2 years in sensitivity analysis). For modelling this in the CDM, patients in the sotagliflozin arm had to experience a high progression of these parameters, in order to catch and bridge the gaps between intervention and control arms.

Limitations

- This economic analysis is based on parameters that are not specific to a T1D population but utilises data specific to T2D. However, the assumptions were based on established risk equations which are considered to be a reliable proxy measure of disease progression and complications outcomes.

- Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, consistent with previous economic modelling in T1D (Appendix N of NG17(18)), a linear disutility of non-SH was utilised. Additionally, it is believed that the utility value associated with suffering a severe hypoglycaemic event already incorporates this disutility (38).

References

1. Sanofi. Data on File. LX4211-309-SG13-BMI 27- All results-20190318. 2019.
2. Sanofi. Data on File. LX4211-310-SG13-BMI 27- All results-20190318. 2019.
3. Sanofi. Data on File. LX4211-Pool-309-310-SG13-BMI 27- All results-20190318. 2019.
4. Sanofi. Data on File. LX4211-312-SG13-BMI 27- All results-20190318 2019.
5. Sanofi. Data on File. LX4211-Pool-309-310-312 -SG13-BMI 27- All results-20190318. 2019.
6. Wolowacz S, Pearson I, Shannon P, Chubb B, Gundgaard J, Davies M, et al. Development and validation of a cost-utility model for Type 1 diabetes mellitus. Diabet Med. 2015;32(8):1023-35.
7. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Glibenclamide-induced hypoglycemic coma in 51 older patients with type 2 diabetes mellitus. J Am Geriatr Soc. 1999;47(5):631-3.
8. MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C, Jerums G. Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. Intern Med J. 2002;32(8):379-85.
9. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. Diabetes Care. 2016;39(5):686-93.
10. Valentine WJ, Pollock RF, Saunders R, Bae J, Norrbacka K, Boye K. The Prime Diabetes Model: Novel Methods for Estimating Long-Term Clinical and Cost Outcomes in Type 1 Diabetes Mellitus. Value Health. 2017;20(7):985-91.
11. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, 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.
12. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE Diabetes Model. Value Health. 2014;17(6):714-24.
13. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions Complications (DCCT/EDIC) Research Group. Risk Factors for Cardiovascular Disease in Type 1 Diabetes. Diabetes. 2016;65(5):1370-9.
14. National Institute for Health and Care Excellence (NICE). Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes (TA390) 2016 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ta390/resources/canagliflozin-dapagliflozin-and-empagliflozin-as-monotherapies-for-treating-type-2-diabetes-pdf-82602903454405.
15. NHS. National Diabetes Audit - 2012-2013. Report 2: Care Processes and Treatment Targets [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/national-diabetes-audit-2012-2013-report-1-care-processes-and-treatment-targets.
16. World Health Organization. Health topics: Obesity [cited 2019 February]. Available from: https://www.who.int/topics/obesity/en/.
17. Sanofi. Data on file: IMS CDM Version 9. 2018.
18. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management (NG17) London: National Institute for Health and Care Excellence; 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ng17.

19. Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Archives of internal medicine. 2009;169(14):1307-16.
20. Office for National Statistics. Opinions and Lifestyle Survey, Smoking Habits Amongst Adults, 2012 [cited 2019 February]. Available from: https://webarchive.nationalarchives.gov.uk/20160107053428/http://www.ons.gov.uk/ons/rel/ghs/opinions-and-lifestyle-survey/smoking-habits-amongst-adults--2012/index.html.
21. NHS. Health Survey for England - 2011. Health, social care and lifestyles [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2011-health-social-care-and-lifestyles.
22. Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M, et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care. 2012;35(8):1638-42.
23. Organization WH. ObesityFeb 2019. Available from: https://www.who.int/topics/obesity/en/.
24. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme. European heart journal. 2001;22(7):554-72.
25. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet (London, England). 2009;373(9667):929-40.
26. National Institute for Health and Care Excellence. Exenatide once-weekly (BYDUREON®) for the treatment of type 2 diabetes. 2011.
27. Jones LE, Doebbeling CC. Depression screening disparities among veterans with diabetes compared with the general veteran population. Diabetes care. 2007;30(9):2216-21.
28. O'Meara S, Cullum N, Majid M, Sheldon T. Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. Health Technol Assess. 2000;4(21):1-237.
29. Kantor J, Margolis DJ. Treatment options for diabetic neuropathic foot ulcers: a cost-effectiveness analysis. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2001;27(4):347-51.
30. Lopez-Bastida J, Cabrera-Lopez F, Serrano-Aguilar P. Sensitivity and specificity of digital retinal imaging for screening diabetic retinopathy. Diabetic medicine : a journal of the British Diabetic Association. 2007;24(4):403-7.
31. Cortes-Sanabria L, Martinez-Ramirez HR, Hernandez JL, Rojas-Campos E, Canales-Munoz JL, Cueto-Manzano AM. Utility of the Dipstick Micraltest II in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension. Rev Invest Clin. 2006;58(3):190-7.
32. Office for National Statistics. National life tables: UK 2014-2016 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.
33. Sonke GS, Beaglehole R, Stewart AW, Jackson R, Stewart FM. Sex differences in case fatality before and after admission to hospital after acute cardiac events: analysis of community based coronary heart disease register. BMJ. 1996;313(7061):853-5.
34. Eriksson SE, Olsson JE. Survival and recurrent strokes in patients with different subtypes of stroke: a fourteen-year follow-up study. Cerebrovasc Dis. 2001;12(3):171-80.

35. Persson U, Willis M, Odegaard K, Apelqvist J. The cost-effectiveness of treating diabetic lower extremity ulcers with becaplermin (Regranex): a core model with an application using Swedish cost data. Value Health. 2000;3 Suppl 1:39-46.
36. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Med Decis Making. 2016;36(8):1020-33.
37. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462-70.
38. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006;22(8):1523-34.
39. NHS. Overview: Obesity [cited 2019 February]. Available from: https://www.nhs.uk/conditions/obesity/.
40. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Medical Decision Making. 2016;36(8):1020-33.
41. PSSRU. Unit Costs of Health and Social Care 2017: Inflation indices [cited 2019 February]. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/.
42. Sanofi. Clinical study report: inTandem2 (LX4211.310). 2017.
43. IQVIA. Real-world data [cited 2019 February]. Available from: https://www.iqvia.com/solutions/real-world-value-and-outcomes/realworld-data.
44. NHS. Prescription Cost Analysis 2016 [cited 2019 February]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2016.
45. Bloomgarden Z. Sodium glucose transporter 2 inhibition: a new approach to diabetes treatment. J Diabetes. 2013;5(3):225-7.
46. NHS. Oxfordshire Clinical Commissioning Group. KETONE TESTING AND SICK DAY RULES GUIDELINE 2017 [cited 2019 January]. Available from: https://www.oxfordshireccg.nhs.uk/professional-resources/documents/clinical-guidelines/diabetes/ketone-testing-and-sick-day-rules-guidance.pdf.
47. NHS. North Central London Joint Formulary Committee. Guideline for blood glucose & ketone monitoring for adults with diabetes. 2018 [cited 2018 February]. Available from: https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/6_Blood_glucose_ketone_monitoring.pdf.
48. Danne T, Garg S, Peters AL, Buse JB, Mathieu C, Pettus JH, et al. International Consensus on Risk Management of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Treated with Sodium-Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care. 2019.
49. PSSRU. Reference costs - National schedule of reference costs 2017/2018 [cited 2019 February]. Available from: https://improvement.nhs.uk/resources/reference-costs/.
50. Lamb EJ, MacKenzie F, Stevens PE. How should proteinuria be detected and measured? Annals of clinical biochemistry. 2009;46(Pt 3):205-17.
51. National Institute for Health and Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181) 2016 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/cg181/resources/cardiovascular-disease-risk-assessment-and-reduction-including-lipid-modification-pdf-35109807660997.
52. Beaudet A, Palmer JL, Timlin L, Wilson B, Bruhn D, Boye KS, et al. Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. J Med Econ. 2011;14(3):357-66.
53. National Institute for Health and Care Excellence (NICE). Renal replacement therapy and conservative management (CG125). Updated to NG107. 2011 [cited 2019 February].

Available from: https://www.nice.org.uk/guidance/ng107/resources/renal-replacement-therapy-and-conservative-management-pdf-66141542991301.
54. National Institute for Health and Care Excellence (NICE). Final appraisal determination.
Aflibercept for treating diabetic macular oedema 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ta346/documents/macular-oedema-diabetic-aflibercept-final-appraisal-determination-document2.
55. Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J Wound Care. 2002;11(2):70-4.
56. National Institute for Health and Care Excellence (NICE). Peripheral arterial disease: diagnosis and management (CG147) 2012 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/cg147/resources/peripheral-arterial-disease-diagnosis-and-management-pdf-35109575873989.
57. Office for National Statistics. National life tables, UK: 2014 to 2016 [cited 2019 February]. Available from: https://www.ons.gov.uk/releases/nationallifetablesuk2014to2016.
58. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. Curr Med Res Opin. 2004;20 Suppl 1:S27-S40.
59. Palmer AJ, Mount Hood 5 Modeling G, Clarke P, Gray A, Leal J, Lloyd A, et al. Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood challenge meeting. Value Health. 2013;16(4):670-85.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sotagliflozin, in combination with insulin, for treating type 1 diabetes ID1376

Clarification questions

March 2019

File name	Version	Contains confidential information	Date
ID1376 clarification questions CIC REDACTED_AIC_30.05.2019	CIC REDACTED	**Yes**	30.05.2019

Section A: Clarification on effectiveness data

The ERG notes that the CHMP positive opinion is for both doses of sotagliflozin and covers a population that is narrower than the population reported in the company submission. As such, the ERG would like to see clinical effectiveness results for the population with BMI ≥ 27 kg/m^2 for both the 200 mg and 400 mg dose.

Following the advice of clinical experts, the ERG would also like to see the population further refined using trial stratification factors for insulin delivery and screening HbA$_{1c}$ to better reflect patients in the UK who are likely to be considered for treatment with sotagliflozin. Experts have advised that the small proportion of patients using continuous subcutaneous insulin infusions (CSII) in the UK are unlikely to be offered sotagliflozin for safety reasons, and that baseline glycaemic control is much worse in UK clinical practice than in the inTandem trials.

A1. Priority question: Please provide full clinical effectiveness results at Week 24 for inTandem1, inTandem2 and inTandem3 and Week 52 for inTandem1 and inTandem2 (including all clinical inputs for the economic model) for:

a) the subgroup of patients in each arm with BMI ≥ 27 kg/m^2

HbA$_{1c}$

Table 1. Results summary for HbA$_{1c}$ (%), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −0.41 (0.046)	N=175, −0.54 (0.045)	N=174, −0.10 (0.045)	−0.31 (−0.43 to −0.19) <0.001	−0.44 (−0.56 to −0.32) <0.001
inTandem2	N=135, −0.46 (0.053)	N=138, −0.45 (0.052)	N=124, 0.02 (0.054)	−0.48 (−0.62 to −0.34) <0.001	−0.47 (−0.61 to −0.34) <0.001
inTandem3	-	N=379, −0.86 (0.065)	N=370, −0.32 (0.066)	-	−0.54 (−0.64, −0.44) <0.001
52 weeks					
inTandem1	N=170, −0.257 (0.056)	N=175, −0.391 (0.054)	N=174, −0.03(0.056)	−0.23 (−0.37 to −0.08) 0.003	−0.360 (−0.51 to −0.21) <0.001
inTandem2	N=135, −0.229 (0.062)	N=138, −0.365 (0.061)	N=124, 0.036 (0.063)	−0.27 (−0.433 to −0.099) 0.002	−0.402 (0.000)

Table 2. Results summary for patients with HbA_{1c} <7.0% without SH and without DKA (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg n/N (%)	Sotagliflozin 400 mg n/N (%)	Insulin alone (placebo) n/N (%)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				Difference (in %) of responders (95% CI) p value	Difference (in %) of responders (95% CI) p value
24 weeks					
inTandem1	50/170 (29.4)	85/175 (48.6)	36/174 (20.7)	8.7 (−0.40 to 17.84) 0.06	27.9 (18.34 to 37.42) <0.001
inTandem2	41/135 (30.4)	46/138 (33.3)	21/124 (16.9)	13.4 (3.25 to 23.62) 0.010	16.4 (6.13 to 26.67) 0.002
inTandem3		109/379 (28.8)	49/370 (13.2)		15.5 (9.80 to 21.23) <0.001
52 weeks					
inTandem1	50/170 (29.4%)	85/175 (48.6%)	36/174 (20.7%)	8.72 (−0.40 to 17.84) 0.052	27.88 (18.34 to 37.42) <0.001
inTandem2	33/135 (24.4%)	38/138 (27.5%)	19/124 (15.3%)	9.12 (−0.51 to 18.75) 0.059	12.21 (2.43 to 22.00) 0.014

CI = Confidence interval¸ DKA = Diabetic ketoacidosis; HbA_{1c} = Glycated haemoglobin; SH = Severe hypoglycaemia
Ref: Confidential documents 1-3

Body weight

Table 3. Results summary for body weight (kg), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −1.71 (0.253)	N=175, −2.96 (0.250)	N=174, 0.58 (0.253)	−2.29 (−2.97 to−1.61) <0.001	−3.54 (−4.22 to−2.87) <0.001
inTandem2	N=135, −2.26 (0.311)	N=138, −3.05 (0.306)	N=124, −0.01 (0.319)	−2.25 (−3.11 to−1.39) <0.001	−3.04 (−3.89 to−2.19) <0.001
inTandem3	-	N=379, −2.80 (0.277)	N=370, 0.61 (0.280)	-	−3.41 (−3.90 to−2.93) <0.001
52 weeks					
inTandem1	N=170, −1.91 (0.334)	N=175, −3.57 (0.328)	N=174, 1.30 (0.337)	−3.21 (−4.13 to −2.29) <0.001	−4.87 (−5.77 to −3.96) <0.001
inTandem2	N=135, −2.51 (0.392)	N=138, −3.68 (0.384)	N=124, 0.22 (0.400)	−2.72 (−3.81 to −1.64) <0.001	−3.90 (−4.97 to −2.82) <0.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-3

Daily basal and bolus insulin (IU) – missing 52 weeks

Table 4. Results summary for mean daily bolus insulin dose (IU/day), absolute change from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −2.63 (0.998)	N=175, −5.26 (0.987)	N=174, −1.44 (0.995)	−1.19 (−3.80 to 1.43) 0.37	−3.82 (−6.40 to −1.23) 0.004
inTandem2	N=135, −5.35 (1.033)	N=138, −6.61 (1.024)	N=124, −2.30 (1.057)	−3.05 (−5.80 to −0.30) 0.030	−4.31 (−7.04 to −1.58) 0.002
inTandem3	-	N=379, −5.83 (1.498)	N=370, −2.09 (1.526)	-	−3.74 (−5.65 to −1.83) <0.001
52 weeks					
inTandem1	N=170, 0.11 (0.705)	N=175, −2.06 (0.694)	N=174, 3.37 (0.709)	−3.26 (−5.15, −1.37) 0.0008	−5.43 (−7.31, −3.56) <0.0001
inTandem2	N=135, −0.41 (0.757)	N=138, −1.83 (0.745)	N=124, 1.26 (0.774)	−1.67 (−3.74, 0.39) 0.1120	−3.09 (−5.14, −1.05) 0.0032

CI = Confidence interval; IU = International unit; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-3

Table 5. Results summary for mean daily basal insulin dose (IU/day), absolute change from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 0.31 (0.599)	N=175, −1.44 (0.592)	N=174, 2.09 (0.597)	−1.78 (−3.35 to −0.20) 0.027	−3.54 (−5.10 to −1.97) <0.001
inTandem2	N=135, −0.85 (0.678)	N=138, −0.90 (0.668)	N=124, 0.83 (0.696)	−1.68 (−3.52 to 0.16) 0.07	−1.74 (−3.56 to 0.09) 0.06
inTandem3	-	N=379, −0.82 (0.913)	N=370, 2.21 (0.930)	-	−3.02 (−4.20, −1.85) <0.001
52 weeks					
inTandem1	N=170, −2.13 (1.083)	N=175, −6.46 (1.069)	N=174, −0.68 (1.094)	−1.45 (−4.34, 1.44) 0.3244	−5.77 (−8.63, −2.92) <0.0001
inTandem2	N=135, −4.55 (1.122)	N=138, −6.09 (1.115)	N=124, −4.70 (1.145)	0.15 (−2.88, 3.17) 0.9235	−1.39 (−4.40, 1.62) 0.3643

CI = Confidence interval; IU = International unit; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-3

Fasting plasma glucose

Table 6. Results summary for FPG (mg/dL), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −6.5 (4.20)	N=175, −17.2 (4.14)	N=174, 3.2 (4.19)	−9.7 (−20.8 to 1.5) 0.09	−20.4 (−31.4 to −9.3) <0.001
inTandem2	N=135, −12.6 (5.42)	N=138, −20.9 (5.37)	N=124, 11.2 (5.52)	−23.8 (−38.4 to −9.1) 0.002	−32.0 (−46.6 to −17.5) <0.001
inTandem3	-	N=379, −23.5 (6.34)	N=370, 0.8 (6.46)	-	−24.3 (−33.5 to −15.1) <0.001
52 weeks					
inTandem1	N=170, −7.22 (4.975)	N=175, −16.51 (4.873)	N=174, 7.64 (5.107)	−14.85 (−28.51, −1.20) <0.0330	−24.15 (−37.66, −10.64) <0.0005
inTandem2	N=135, −7.81 (5.868)	N=138, −23.81 (5.765)	N=124, 5.78 (6.008)	−13.60 (−29.66, 2.47) −0.0970	−29.59 (−45.48, −13.69) 0.0003

CI = Confidence interval; FPG = Fasting plasma glucose; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-3

Patient reported outcomes (DTSQ and DDS2)

Table 7. Results summary for DDS2 total score, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −0.4 (0.14)	N=175, −0.6 (0.13)	N=174, 0.2 (0.14)	−0.6 (−1.0 to −0.3) <0.001	−0.8 (−1.1 to −0.4) <0.001
inTandem2	N=135, −0.5 (0.15)	N=138, −0.5 (0.15)	N=124, 0.1 (0.15)	−0.6 (−1.0 to −0.2) 0.005	−0.5 (−0.9 to −0.1) 0.009
52 weeks					
inTandem1	N=170, −0.27 (0.137)	N=175, −0.50 (0.136)	N=174, 0.16 (0.141)	−0.43 (−0.79, −0.07) 0.0202	−0.65 (−1.01, −0.30) 0.0004
inTandem2	N=135, −0.50 (0.161)	N=138, −0.50 (0.155)	N=124, −0.14 (0.162)	−0.36 (−0.79, 0.06) 0.0914	−0.36 (−0.77, 0.06) 0.0893

CI = Confidence interval; DTSQ = diabetes treatment satisfaction questionnaire; DDS2 = 2-item Diabetes Distress Screening Scale; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-3

Table 8. Results summary for DTSQs score, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 2.2 (0.36)	N=175, 2.4 (0.36)	N=174, −0.6 (0.37)	2.8 (1.9 to 3.7) <0.001	3.0 (2.1 to 3.9) <0.001
inTandem2	N=135, 2.4 (0.39)	N=138, 2.0 (0.38)	N=124, 0.0 (0.40)	2.4 (1.4 to 3.4) <0.001	2.0 (1.0 to 3.0) <0.001

CI = Confidence interval; DTSQ = Diabetes Treatment Satisfaction Questionnaire; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-2

Systolic blood pressure

Table 9. Results summary for SBP (mm Hg), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −1.3 (0.84)	N=175, −4.2 (0.83)	N=174, −0.4 (0.84)	−0.9 (−3.2 to1.3) 0.40	−3.8 (−6.0 to−1.6) <0.001
inTandem2	N=135, −5.4 (1.01)	N=138, −4.2 (1.01)	N=124, −3.6 (1.04)	−1.8 (−4.5 to 0.9) 0.19	−0.7 (−3.3 to 2.0) 0.62
inTandem3	-	N=379, −3.8 (1.19)	N=370, −0.6 (1.22)	−	−3.2 (−4.7 to−1.6) <0.001
52 weeks					
inTandem1	N=170, −0.4 (0.90)	N=175, −3.4 (0.88)	N=174, 0.7 (0.91)	−1.1 (−3.5 to 1.3) 0.36	−4.1 (−6.5 to −1.7) <0.001
inTandem2	N=135, −3.8 (0.98)	N=138, −3.4 (0.96)	N=124, −0.5 (1.00)	−3.3 (−5.9 to −0.7) 0.013	−2.9 (−5.4 to −0.3) 0.028

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

Table 10. Results summary for SBP (mm Hg) in patients with baseline SBP ≥130 mm Hg, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, Mean (SE)	Sotagliflozin 400 mg N, Mean (SE)	Insulin alone (placebo) N, Mean (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=46, −9.2 (1.89)	N=50, −11.6 (1.76)	N=48, −9.2 (1.87)	−0.0 (−5.1 to 5.0) 0.99	−2.4 (−7.3 to 2.4) 0.32
inTandem2	N=55, −10.4 (1.82)	N=58, −8.7 (1.79)	N=51; −6.7 (1.87)	−3.8 (−8.5 to 0.9) 0.12	−2.0 (−6.7 to 2.7) 0.40
inTandem3	-	N=133, −7.1 (3.34)	N=132, −4.6 (3.26)	-	−2.5 (−5.4 to 0.3) 0.08

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

Diastolic blood pressure (mmHg)

Table 11. Results summary for DBP (mm Hg), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −0.80 (0.53)	N=175, −1.59 (0.53)	N=174, −0.19 (0.53)	−0.61 (−2.6 to −0.55) 0.003	−1.40 (−2.77 to −0.03) <0.05
inTandem2	N=135, −2.36 (0.63)	N=138, −1.21 (0.63)	N=124, −1.60 (0.65)	−0.76 (−2.44 to 0.93) 0.38	0.39 (−1.28 to 2.06) 0.64
inTandem3	–	N=379, −1.33 (0.39)	N=370, 0.58 (0.39)	–	−1.91 (−2.95 to −0.88) <0.001
52 weeks					
inTandem1	N=170, −0.69 (0.58)	N=175, −1.89 (0.57)	N=174, 0.22 (0.59)	−0.91 (−2.45 to 0.63) 0.25	−2.08 (−3.60 to −0.55) 0.01
inTandem2	N=135, −2.20 (0.67)	N=138, −1.80 (0.65)	N=124, −1.07 (0.68)	−1.13 (−2.91 to 0.66) 0.22	−0.73 (−2.49 to 1.03) 0.42

CI = Confidence interval; DBP = Diastolic blood pressure; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-3

Total cholesterol (mg/dL)

Table 12. Results summary for total cholesterol (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo) LSM (95% CI) p value	Sotagliflozin 400 mg vs. insulin alone (placebo) LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 7.04 (2.24)	N=175, 7.13 (2.21)	N=174, 6.56 (2.22)	0.48 (−5.23 to 6.19) 0.87	0.57 (−5.06 to 6.20) 0.84
inTandem2	N=135, 6.56 (2.54)	N=138 7.67 (2.50)	N=124 1.96 (2.59)	4.61 (−1.98 to 11.19) 0.17	5.72 (−0.79 to 12.23) 0.09
inTandem3	–		N=370, −0.82 (1.49)	–	6.59 (2.71 to 10.46) <0.001
52 weeks					
inTandem1	N=170, 8.86 (2.33)	N=175, 14.00 (2.31)	N=174, 6.45 (2.39)	2.41 (−3.75 to 8.58) 0.44	7.55 (1.44 to 13.66) 0.02
inTandem2	N=135, 8.13 (2.73)	N=138, 10.12 (2.70)	N=124, 1.15 (2.81)	6.98 (−0.28 to 14.23)	8.97 (1.78 to 16.16) 0.01

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

LDL-C (mg/dL)

Table 13. Results summary for LDL-C (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo) LSM (95% CI) p value	Sotagliflozin 400 mg vs. insulin alone (placebo) LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 5.10 (1.90)	N=175, 6.28 (1.88)	N=174, 5.93 (1.89)	−0.83 (−5.65 to 3.99) 0.73	0.34 (−4.41 to 5.10) 0.89
inTandem2	N=135, 4.52 (2.25)	N=138, 4.61 (2.21)	N=124, 2.66 (2.34)	1.86 (−4.11 to 7.83) 0.54	1.95 (−3.95 to 7.86) 0.52
52 weeks					
inTandem1	N=170, 5.33 (2.05)	N=175, 8.93 (2.04)	N=174, 5.70 (2.09)	−0.36 (−5.77 to 5.04) 0.89	3.23 (−2.14 to 8.60) 0.24
inTandem2	N=135, 5.05 (2.23)	N=138, 5.82 (2.24)	N=124, 1.86 (2.33)	3.19 (−2.81 to 9.19) 0.30	3.96 (−2.03 to 9.94) 0.19

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

HDL-C (mg/dL)

Table 14. Results summary for HDL-C (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 1.86 (0.75)	N=175, 1.68 (0.74)	N=174, −1.57 (0.75)	3.43 (1.50 to 5.36) 0.001	3.26 (1.35 to 5.16) 0.001
inTandem2	N=135, 1.85 (0.84)	N=138, 1.57 (0.82)	N=124, −1.41 (0.85)	3.26 (1.06 to 5.45) 0.004	2.98 (0.81 to 5.14) 0.007
inTandem3		N=379, 1.74 (0.49)	N=370, −1.70 (0.49)		3.44 (2.16 to 4.71) <0.001
52 weeks					
inTandem1	N=170, 3.15 (0.78)	N=175, 4.19 (0.77)	N=174, −0.26 (0.79)	3.41 (1.37 to 5.46) 0.001	4.45 (2.43 to 6.48) <0.001
inTandem2	N=135, 1.56 (0.93)	N=138, 2.11 (0.92)	N=124, 0.52 (0.96)	1.04 (−1.47 to 3.55) 0.417	1.59 (−0.89 to 4.04) 0.209

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

Triglycerides (mg/dL)

Table 15. Results summary for triglycerides (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, 2.59 (4.21)	N=175, −3.94 (4.11)	N=174, 11.56 (4.17)	−8.97 (−20.10 to 2.16) 0.114	−15.50 (−26.45 to −4.55) 0.006
inTandem2	N=135, 1.79 (5.38)	N=138, 7.68 (5.26)	N=124, 16.19 (5.44)	−14.40 (−28.38 to −0.42) 0.043	−8.51 (−22.29 to 5.28) 0.226
inTandem3		N=379, −3.61 (3.64)	N=370, 4.54 (3.63)		−8.16 (−17.58 to 1.26) 0.089
52 weeks					
inTandem1	N=170, 4.70 (3.19)	N=175, 3.00 (3.16)	N=174, 6.59 (3.27)	−1.89 (−10.34 to 6.56) 0.660	−3.59 (−11.97 to 4.79) 0.400
inTandem2	N=135, 8.43 (5.79)	N=138, 14.89 (5.73)	N=124, 3.88 (5.98)	4.55 (−10.95 to 20.05) 0.564	11.00 (−4.39 to 26.39) 0.161

Abbreviations: CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

BMI (kg/m^2)

Table 16.Results summary for body mass index (kg/m^2), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −0.61 (0.09)	N=175, −1.03 (0.09)	N=174, 0.16 (0.09)	−0.77 (−1.01 to −0.53) <0.001	−1.19 (−1.43 to −0.95) <0.001
inTandem2	N=135, −0.81 (0.11)	N=138, −1.02 (0.10)	N=124, −0.03 (0.11)	−0.78 (−1.07 to −0.49) <0.001	−0.99 (−1.28 to −0.70) <0.001
inTandem3		N=379, −0.90 (0.06)	N=370, 0.28 (0.06)		−1.18 (−1.35 to −1.01) <0.001
52 weeks					
inTandem1	N=170, −0.66 (0.12)	N=175, −1.24 (0.11)	N=174, 0.44 (0.12)	−1.09 (−1.41 to −0.78) <0.001	−1.68 (−1.99 to −1.37) <0.001
inTandem2	N=135, −0.92 (0.14)	N=138, −1.25 (0.13)	N=124, 0.07 (0.14)	−0.98 (−1.36 to −0.60) <0.001	−1.32 (−1.69 to −0.94) <0.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

eGFR (mL/min/1.73 m^2)

Table 17. Results summary for eGFR (mL/min/1.73 m^2), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1	N=170, −2.04 (0.82)	N=175, −2.99 (0.81)	N=174, −0.42 (0.81)	−1.61 −3.74 to 0.51 0.136	−2.57 (−4.68 to 0.47) 0.017
inTandem2	N=135, −3.02 (0.98)	N=138, −1.34 (0.97)	N=124, −0.87 (1.00)	−2.14 (−4.76 to 0.47) 0.108	−0.47 (−3.07 to 2.12) 0.721
inTandem3		N=379, −1.85 (0.71)	N=370, −1.78 (0.70)		−0.05 (−1.91 to 1.81) 0.958
52 weeks					
inTandem1	N=170, −2.60 (0.87)	N=175, −2.60 (0.86)	N=174, −0.91 (0.89)	−1.70 (−4.01 to 0.63) 0.153	−1.69 (−3.99 to 0.61) 0.150
inTandem2	N=135, −3.30 (1.06)	N=138, 0.46 (1.04)	N=124, 0.24 (1.01)	−3.54 (−6.40 to −0.68) 0.015	0.23 (−2.60 to 3.05) 0.874

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-3

EQ-5D index scores and VAS

Table 18. Mixed Model Repeated Measures analysis of change from baseline in EQ-5D Index value at Week 52 mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
52 weeks					
inTandem1	N=170, −0.00 (0.009)	N=175, 0.01 (0.009)	N=174, −0.00 (0.009)	0.00 (−0.02, 0.02) 0.9143	−0.01 (−0.01, 0.03) 0.4361
inTandem2	N=135, −0.02 (0.012)	N=138, −0.01 (0.012)	N=124, −0.02 (0.013)	0.00 (−0.03, 0.03) 0.9806	0.00 (−0.03, 0.03) 0.8938

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SE = Standard Error
Ref: Confidential documents 1-2

Table 19. Mixed Model Repeated Measures analysis of change from baseline in EQ-5D VAS at Week 52 mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
52 weeks					
inTandem1	N=170, −0.77 (1.055)	N=175, 2.40 (1.055)	N=174, −0.29 (1.062)	−0.48 (−3.11, 2.16) 0.7224	2.70 (0.09, 5.31) 0.0429
inTandem2	N=135, 2.12 (1.308)	N=138, 1.09 (1.274)	N=124, −0.71 (1.355)	2.83 (−0.52, 6.17) 0.0972	1.80 (−1.49, 5.09) 0.2825

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent-to-treat; SBP = Systolic blood pressure; SE = Standard Error
Ref: Confidential documents 1-2

b) the subgroup of patients in each arm with BMI ≥ 27 kg/m^2 who were within the upper HbA_{1c} category (>8.5% for inTandem1 and 2, >9% for inTandem3) and using multiple daily injections (MDI).

For continuous measures, please provide the number of patients, mean change from baseline and standard deviation for all three treatment groups and the treatment effect of each dose versus placebo:

- **HbA_{1c} (%)**
- **Net benefit**
- **Body weight (kg)**
- **Daily basal and bolus insulin (IU)**
- **FPG**
- **DTSQ**
- **DDS2**
- **SBP (mmHg)**
- **DBP (mmHg)**
- **Total cholesterol (mg/dL)**
- **LDL-C (mg/dL)**
- **HDL-C (mg/dL)**
- **Triglycerides (mg/dL)**
- **BMI (kg/m^2)**
- **eGFR (mL/min/1.73 m^2)**
- **EQ-5D index scores and VAS**

As discussed in the clarification questions meeting on 14 March, with NICE and the ERG, the data from sotagliflozin phase III clinical programme means that stratification by BMI is more relevant as it identifies patients with higher unmet need, who are most likely to derive clinical benefit, and therefore the best risk/benefit ratio. Sanofi believe it is important for the ERG and the NICE Committee to understand the rationale and reasoning behind the positive opinion for a patient population with a BMI of ≥ 27kg/m^2 from CHMP, so that we can provide relevant analyses to the decision problem. Below are details following the D180 questions from CHMP:

[redacted]

[redacted]

Full results are provided in commercial in confidence in Appendix E.

During the regulatory review process, additional efficacy and safety subgroup analyses were conducted on the pooled dataset to address the Committee for Medicinal Products for Human Use (CHMP) requests, in particular in subgroups categorised by baseline BMI <27 kg/m² or ≥27 kg/m² (See commercial in confidence file Appendix D). These analyses confirmed a numerical trend for a better benefit-risk profile in patients with BMI ≥27 kg/m² compared to leaner patients. It should be noted that the subgroup of patients with baseline BMI ≥27 kg/m2 is not a pre-specified subgroup of the overall study populations. No subgroup analyses were conducted combining two or more baseline characteristics since this would lead to insufficient sample size for an adequate analysis.

Considering the requested subgroup analyses in patients with BMI ≥27 kg/m², using MDI and with baseline HbA_{1c} >8.5%, and considering these baseline characteristics are evenly distributed, combining the three criteria would therefore select 6.9% of the patients, i.e. approximately 30 patients in each arm. The same trend would apply for the combined subgroup analyses in patients with BMI ≥27 kg/m², not using pump and with baseline HbA_{1c} >9.0% in the inTandem3 data. These very small sample sizes will not allow meaningful subgroup analyses (see Table 20 to Table 22). Therefore, we have presented the different elements requested separately to address the ERG question.

Subgroup analyses of change in HbA_{1c} (primary endpoint for both inTandem1 and inTandem2 and main secondary endpoint for inTandem3) were pre-specified in the statistical analysis plan, and results are included in the original company submission. Analyses were performed on pooled datasets to ensure adequate sample size. They included analyses by BMI categories (<25, ≥25 kg/m²), insulin delivery method (CSII, non-CSII) and Week −2 HbA_{1c} (≤8.5%, >8.5%).

The difference compared to placebo was numerically greater in patients with HbA_{1c} >8.5% at Week −2 compared with those ≤8.5%, and the least squared mean (LSM) difference between sotagliflozin 400 mg and placebo was numerically greater in patients with baseline BMI >25 kg/m^2 compared with those ≤25 kg/m^2. No clinically meaningful difference was observed depending on insulin delivery method (see Table 23).

Table 20. Patient numbers per subgroups requested by ERG (inTandem1)

	Placebo		Sotagliflozin 200 mg		Sotagliflozin 400 mg		All	
	N	%	N	%	N	%	N	%
Whole population	268	100	263	100	262	100	793	100
BMI ≥ 27 kg/m²	174	64.9	170	64.6	175	66.8	519	65.4
BMI ≥ 27 kg/m² & HbA_{1c} >8.5%	31	11.6	31	11.8	26	9.9	88	11.1
BMI ≥ 27 kg/m² & HbA_{1c} >8.5% & MDI user	16	6	14	5.3	13	5	43	5.4

BMI, body mass index; HbA_{1c}, Glycated haemoglobin; ERG, expert review group; MDI, Multiple daily injection
Ref: Confidential documents 1-5

Table 21. Patient numbers per subgroups requested by ERG (inTandem2)

	Placebo		Sotagliflozin 200 mg		Sotagliflozin 400 mg		All	
	N	%	N	%	N	%	N	%
Whole population	258	100	261	100	263	100	782	100
BMI ≥ 27 kg/m²	124	48.1	135	51.7	138	52.5	397	50.8
BMI ≥ 27 kg/m² & HbA_{1c} >8.5%	27	10.5	31	11.9	31	11.8	89	11.4
BMI ≥ 27 kg/m² & HbA_{1c} >8.5% & MDI user	19	7.4	22	8.4	24	9.1	65	8.3

BMI, body mass index; HbA_{1c}, Glycated haemoglobin; ERG, expert review group; MDI, Multiple daily injection
Ref: Confidential documents 1-5

Table 22. Patient numbers per subgroups requested by ERG (inTandem3)

	Placebo		Sotagliflozin 200 mg		Sotagliflozin 400 mg		All	
	N	%	N	%	N	%	N	%
Whole population	703	100	699	100	1402	100	703	100
BMI ≥ 27 kg/m²	370	52.6	379	54.2	749	53.4	370	52.6
BMI ≥ 27 kg/m² & HbA_{1c} >9%	89	12.7	85	12.2	174	12.4	89	12.7
BMI ≥ 27 kg/m² & HbA_{1c} >9% & MDI user	61	8.7	58	8.3	119	8.5	61	8.7

BMI, body mass index; HbA_{1c}, Glycated haemoglobin; ERG, expert review group; MDI, Multiple daily injection
Ref: Confidential documents 1-3

As highlighted above, in order to address this question and provide meaningful results to the ERG, we provide results for various subgroup analyses of the primary/secondary efficacy

variable for various categories of baseline characteristics and randomisation stratification factors in the three individual Phase III studies. In Table 23 a summary of subgroup analyses for HbA_{1c} is given for insulin delivery method, week −2 HbA_{1c}, and baseline eGFR (for all studies) as well as for BMI (for inTandem3 and ES1 and ES2 pool only). Overall, these subgroup analyses confirm that the LSM difference in HbA_{1c} change compared to insulin alone (placebo) observed in the main analysis is also statistically significant at both doses in all subgroups of sufficient size.

Table 23. Results summary for HbA_{1c} (%) by subgroup, difference from baseline (mITT population)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
inTandem1					
Insulin delivery method: CSII	N=144, −0.47 (0.047)	N=144, −0.54 (0.047)	N=144, −0.10 (0.046)	−0.37 (−0.49 to −0.25) <0.001	−0.44 (−0.56 to −0.33) <0.001
Insulin delivery method: MDI	N=101, −0.39 (0.057)	N=98, −0.41 (0.057)	N=102, −0.05 (0.056)	−0.34 (−0.48 to −0.19) <0.001	−0.36 (−0.51 to −0.21) <0.001
Week −2 HbA_{1c}: ≤8.5%	N=212, −0.35 (0.033)	N=209, −0.42 (0.033)	N=209, −0.03 (0.033)	−0.32 (−0.41 to −0.23) <0.001	−0.39 (−0.48 to −0.30) <0.001
Week −2 HbA_{1c}: >8.5%	N=33, −0.83 (0.122)	N=33, −0.78 (0.123)	N=37, −0.27 (0.116)	−0.56 (−0.89 to −0.22) 0.001	−0.51 (−0.84 to −0.17) 0.004
Baseline eGFR (mL/min/1.73 m^2): ≥45 to <60	N=14, −0.63 (0.148)	N=15, −0.91 (0.150)	N=12, −0.49 (0.148)	−0.14 (−0.55 to 0.27) 0.49	−0.42 (−0.84 to −0.01) 0.044
Baseline eGFR (mL/min/1.73 m^2): ≥60	N=231, −0.41 (0.037)	N=226, −0.45 (0.037)	N=233, −0.04 (0.037)	−0.37 (−0.46 to −0.28) <0.001	−0.41 (−0.51 to −0.32) <0.001
inTandem2					
Insulin delivery method: CSII	N=60, −0.34 (0.085)	N=58, −0.29 (0.085)	N=63, 0.10 (0.083)	−0.44 (−0.66 to −0.21) <0.001	−0.39 (−0.62 to −0.17) <0.001
Insulin delivery method: MDI	N=179, −0.41 (0.050)	N=183, −0.40 (0.049)	N=176, −0.06 (0.051)	−0.34 (−0.48 to −0.21) <0.001	−0.33 (−0.47 to −0.20) <0.001
Week −2 HbA_{1c}: ≤8.5%	N=185, −0.29 (0.043)	N=189, −0.31 (0.043)	N=186, 0.04 (0.043)	−0.33 (−0.45 to −0.21) <0.001	−0.35 (−0.47 to −0.23) <0.001
Week −2 HbA_{1c}: >8.5%	N=54, −0.69 (0.113)	N=52, −0.56 (0.114)	N=53, −0.20 (0.115)	−0.49 (−0.81 to −0.18) 0.002	−0.36 (−0.68 to −0.05) 0.025
Baseline eGFR (mL/min/1.73 m^2): ≥45 to <60	N=8, −0.79 (0.307)	N=8, −0.27 (0.299)	N=8, −0.36 (0.305)	−0.43 (−1.21 to 0.34) 0.26	0.08 (−0.70 to 0.87) 0.83
Baseline eGFR (mL/min/1.73 m^2): ≥60	N=231, −0.37 (0.044)	N=233, −0.38 (0.044)	N=230, −0.01 (0.044)	−0.36 (−0.47 to −0.24) <0.001	−0.36 (−0.48 to −0.25) <0.001
inTandem3					
Insulin delivery method: CSII		N=254, −0.78 (0.048)	N=250, −0.30 (0.047)		−0.48 (−0.60 to −0.36) <0.001

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo) LSM (95% CI) p value	Sotagliflozin 400 mg vs. insulin alone (placebo) LSM (95% CI) p value
Insulin delivery method: MDII		N=373, −0.81 (0.042)	N=378, −0.35 (0.041)		−0.45 (−0.56 to −0.34) <0.001
BMI (kg/m^2): <25		N=186, −0.69 (0.066)	N=193, −0.36 (0.064)		−0.32 (−0.49 to −0.15) <0.001
BMI (kg/m^2): ≥25		N=441, −0.83 (0.034)	N=435, −0.31 (0.034)		−0.52 (−0.61 to −0.44) <0.001
Week −2 HbA_{1c}: <7.7%		N=144, −0.43 (0.157)	N=160, −0.01 (0.158)		−0.41 (−0.54 to −0.29) <0.001
Week −2 HbA_{1c}: ≥7.7%		N=483, −0.88 (0.037)	N=468, −0.41 (0.037)		−0.47 (−0.57 to −0.37) <0.001
Week −2 HbA_{1c}: ≤8.5%		N=389, −0.69 (0.075)	N=379, −0.26 (0.076)		−0.43 (−0.51 to −0.35) <0.001
Week −2 HbA_{1c}: >8.5%		N=238, −0.97 (0.060)	N=249, −0.47 (0.059)		−0.49 (−0.65 to −0.33) <0.001
Week −2 HbA_{1c}: ≤9.0%		N=485, −0.69 (0.028)	N=476, −0.24 (0.028)		−0.45 (−0.52 to −0.37) <0.001
Week −2 HbA_{1c}: >9.0%		N=142, −1.08 (0.088)	N=152, −0.58 (0.086)		−0.50 (−0.74 to −0.26) <0.001
Baseline eGFR (mL/min/1.73 m^2): ≥45 to <60		N=25, −0.68 (0.179)	N=34, −0.55 (0.156)		−0.13 (−0.56 to 0.31) 0.57
Baseline eGFR (mL/min/1.73 m^2): ≥60		N=601, −0.79 (0.032)	N=591, −0.32 (0.032)		−0.47 (−0.56 to −0.39) <0.001

BMI = Body mass index; CI = Confidence interval;1a insulin infusion; eGFR = Estimated glomerular filtration rate; HbA_{1c} = Glycated haemoglobin; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error; MDI = Multiple daily injections

Ref: Confidential documents 1-3

Table 24: Results summary for HbA_{1c} (%) by subgroup, difference from baseline (mITT population)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo) LSM (95% CI) p value	Sotagliflozin 400 mg vs. insulin alone (placebo) LSM (95% CI) p value
ES1 pool					
Insulin delivery method: CSII	N=204, −0.41 (0.042)	N=202, −0.45 (0.042)	N=207, −0.02 (0.042)	−0.39 (−0.49 to −0.28) <0.001	−0.43 (−0.54 to −0.33) <0.001
Insulin delivery method: MDII	N=280, −0.41 (0.038)	N=281, −0.41 (0.038)	N=278, −0.06 (0.038)	−0.34 (−0.44 to −0.24) <0.001	−0.35 (−0.45 to −0.24) <0.001
BMI (kg/m^2): <25	N=130, −0.33 (0.064)	N=115, −0.31 (0.067)	N=128, 0.01 (0.065)	−0.34 (−0.51 to −0.18) <0.001	−0.32 (−0.49 to −0.14) <0.001
BMI (kg/m^2): ≥25	N=354, −0.44 (0.031)	N=368, −0.47 (0.030)	N=357, −0.07 (0.030)	−0.37 (−0.45 to −0.29) <0.001	−0.40 (−0.48 to −0.32) <0.001

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
Week −2 HbA_{1c}: ≤8.5%	N=397, −0.32 (0.027)	N=398, −0.37 (0.026)	N=395, 0.00 (0.027)	−0.33 (−0.40 to −0.25) <0.001	−0.37 (−0.45 to −0.30) <0.001
Week −2 HbA_{1c}: >8.5%	N=87, −0.76 (0.084)	N=85, −0.67 (0.084)	N=90, −0.25 (0.082)	−0.51 (−0.74 to −0.28) <0.001	−0.42 (−0.65 to −0.19) <0.001
Baseline eGFR (mL/min/1.73 m^2): <60	N=22, −0.66 (0.139)	N=24, −0.60 (0.131)	N=22, −0.38 (0.135)	−0.28 (−0.64 to 0.09) 0.14	−0.21 (−0.57 to 0.14) 0.24
Baseline eGFR (mL/min/1.73 m^2): ≥60 to <90	N=251, −0.41 (0.037)	N=236, −0.50 (0.038)	N=222, −0.00 (0.039)	−0.41 (−0.51 to −0.32) <0.001	−0.50 (−0.59 to −0.40) <0.001
Baseline eGFR (mL/min/1.73 m^2): ≥90	N=211, −0.37 (0.044)	N=223, −0.32 (0.043)	N=241, −0.06 (0.042)	−0.31 (−0.43 to −0.20) <0.001	−0.27 (−0.38 to −0.15) <0.001
ES2 pool					
Insulin delivery method: CSII		N=456, −0.58 (0.032)	N=457, −0.13 (0.032)		−0.45 (−0.54 to −0.37) <0.001
Insulin delivery method: MDII		N=654, −0.60 (0.029)	N=656, −0.19 (0.029)		−0.41 (−0.48 to −0.33) <0.001
BMI (kg/m^2): <25		N=298, −0.49 (0.048)	N=309, −0.17 (0.047)		−0.32 (−0.44 to −0.19) <0.001
BMI (kg/m^2): ≥25		N=812, −0.63 (0.023)	N=804, −0.17 (0.023)		−0.47 (−0.53 to −0.41) <0.001
Week −2 HbA_{1c}: ≤8.5%		N=787, −0.48 (0.020)	N=774, −0.08 (0.020)		−0.40 (−0.46 to −0.35) <0.001
Week −2 HbA_{1c}: >8.5%		N=323, −0.86 (0.052)	N=339, −0.39 (0.051)		−0.47 (−0.61 to −0.34) <0.001
Baseline eGFR (mL/min/1.73 m^2): <60		N=50, −0.65 (0.107)	N=59, −0.44 (0.100)		−0.21 (−0.48 to 0.06) 0.13
Baseline eGFR (mL/min/1.73 m^2): ≥60 to <90		N=523, −0.61 (0.028)	N=498, −0.14 (0.029)		−0.47 (−0.54 to −0.40) <0.001
Baseline eGFR (mL/min/1.73 m^2): ≥90		N=537, −0.56 (0.033)	N=556, −0.16 (0.032)		−0.40 (−0.49 to −0.31) <0.001
52 weeks					
ES1 pool					
Insulin delivery method: CSII	N=195, −0.22 (0.054)	N=190, −0.29 (0.054)	N=190, 0.07 (0.054)	−0.29 (−0.43 to −0.15) <0.001	−0.37 (−0.51 to −0.22) <0.001
Insulin delivery method: MDII	N=265, −0.22 (0.044)	N=264, −0.31 (0.043)	N=258, −0.03 (0.044)	−0.19 (−0.30 to −0.07) 0.002	−0.28 (−0.40 to −0.16) <0.001
Baseline eGFR (mL/min/1.73 m^2): <60	N=22, −0.55 (0.136)	N=22, −0.33 (0.132)	N=19, −0.42 (0.139)	−0.13 (−0.50 to 0.24) 0.49	0.09 (−0.28 to 0.45) 0.63
Baseline eGFR (mL/min/1.73 m^2): ≥60 to <90	N=240, −0.27 (0.043)	N=220, −0.35 (0.045)	N=207, 0.01 (0.046)	−0.28 (−0.40 to −0.16) <0.001	−0.36 (−0.48 to −0.25) <0.001
Baseline eGFR (mL/min/1.73 m^2): ≥90	N=198, −0.12 (0.055)	N=212, −0.25 (0.054)	N=222, 0.05 (0.052)	−0.17 (−0.32 to −0.03) 0.019	−0.31 (−0.45 to −0.16) <0.001

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
BMI (kg/m^2): <25	N=121, −0.10 (0.078)	N=102, −0.15 (0.082)	N=121, 0.14 (0.078)	−0.24 (−0.45 to −0.04) 0.021	−0.29 (−0.51 to −0.07) 0.008
BMI (kg/m^2): ≥25	N=339, −0.27 (0.037)	N=352, −0.36 (0.036)	N=327, −0.04 (0.037)	−0.23 (−0.32 to −0.13) <0.001	−0.32 (−0.41 to −0.22) <0.001
Week −2 HbA_{1c}: ≤8.5%	N=379, −0.16 (0.033)	N=375, −0.26 (0.033)	N=366, 0.05 (0.033)	−0.21 (−0.31 to −0.12) <0.001	−0.32 (−0.41 to −0.22) <0.001
Week −2 HbA_{1c}: >8.5%	N=81, −0.47 (0.100)	N=79, −0.48 (0.101)	N=82, −0.16 (0.099)	−0.31 (−0.59 to −0.04) 0.027	−0.32 (−0.60 to −0.05) 0.022

BMI = Body mass index; CI = Confidence interval; CSII = Continuous subcutaneous insulin infusion; eGFR = Estimated glomerular filtration rate; HbA_{1c} = Glycated haemoglobin; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error; MDII = Multiple daily injections

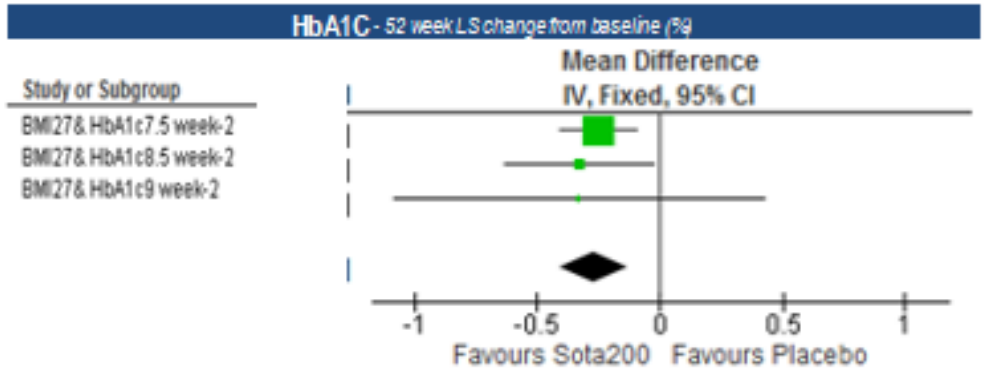
Ref: Confidential documents 1-3

Meta-analysis

To test the hypothesis that stratification factor for HbA1c does impact treatment effects on selected important endpoints (HbA1c, BMI, SBP, SH & DKA) from a statistical point of view, a meta-analysis was conducted in the label population. This demonstrated that HbA_{1c} cut-offs of 7.5%, 8.5% and 9% had no significant impact on the endpoint parameters mentioned above. With this being the case, it can be assumed that stratification factor for HbA1c will have limited impact upon ICER values.

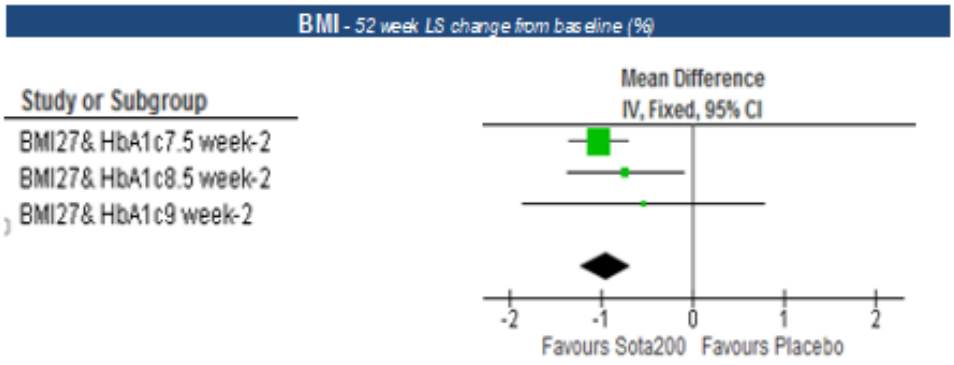
Figure 1 to Figure 5 show the forest plots from the meta-analysis performed to assess the correlation between HbA_{1c} cut-off and the effects on trial endpoints.

Figure 1. HbA_{1c} least squares mean change from baseline at Week 52



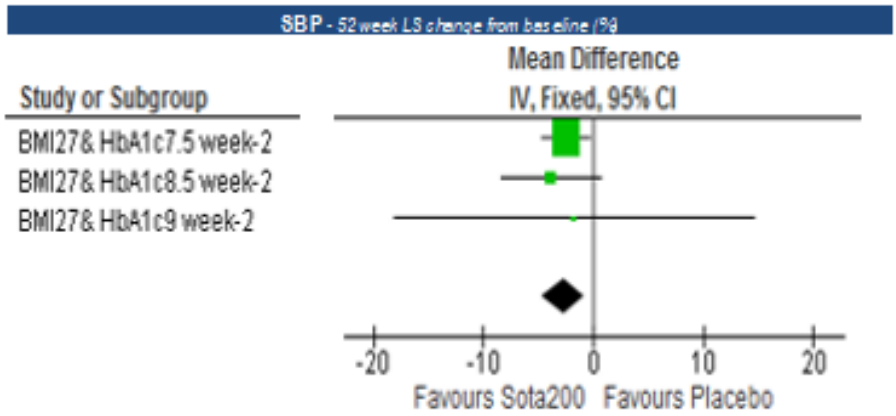
CI, confidence interval; HbA1c, Glycated haemoglobin; LS, least squares; Sota, sotagliflozin

Figure 2. BMI least squares mean change from baseline at Week 52



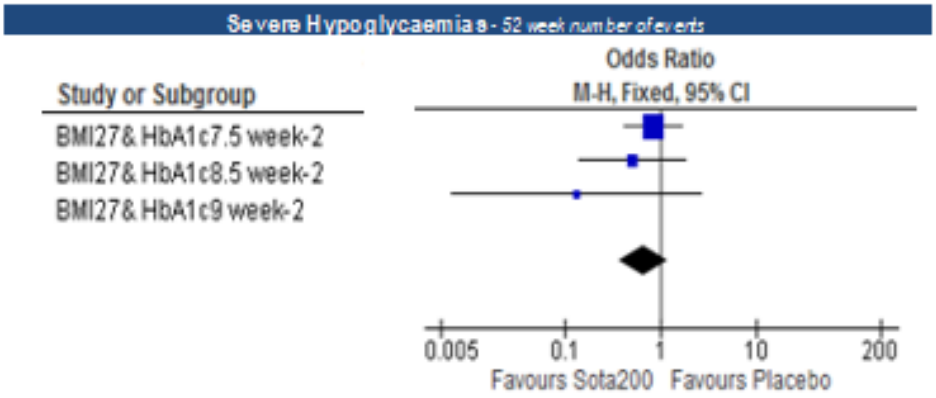
BMI, body mass index; CI, confidence interval; LS, least squares; Sota, sotagliflozin

Figure 3. Systolic blood pressure least squares mean change from baseline at Week 52



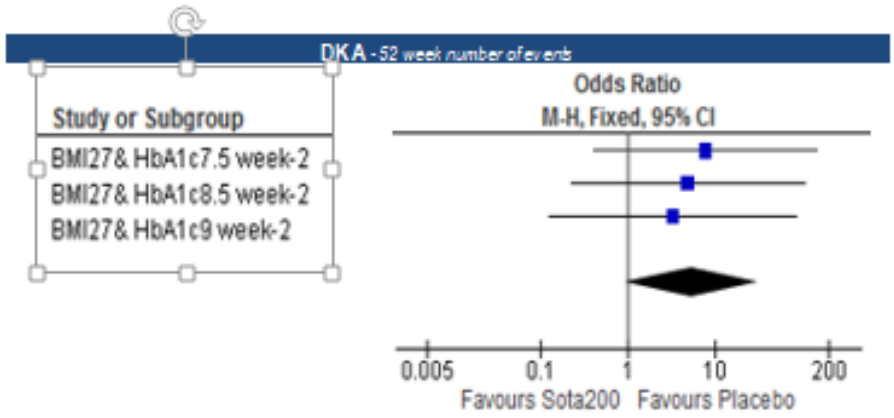
HbA_{1c}, Glycated LS, CI, confidence interval; LS, least squares; SBP, systolic blood pressure; Sota, sotagliflozin

Figure 4. Severe hypoglycaemia number of events at Week 52



CI, confidence interval; LS, least squares; SBP, systolic blood pressure; Sota, sotagliflozin

Figure 5. Diabetic ketoacidosis number of events at Week 52



CI, confidence interval; LS, least squares; SBP, systolic blood pressure; Sota, sotagliflozin

As can be seen from above the stratification factor for HbA1c had no statistically significant effect on important trial outcomes.

For reasons outlined above, for the remaining questions, Sanofi have focussed on addressing the question with respect to population defined in A1a i.e. the licensed and most relevant patient population under review in the appraisal.

A2. Priority question: Please provide the following safety results (and any additional safety inputs required for the economic model) for inTandem1, inTandem2 and inTandem3 for the two populations defined in A1a and A1b. Please provide results as the number of patients who had at least one event, the total number of events, number of evaluable patients, patient years, and the rate/patient per year:

- **Severe hypoglycaemia (any, requiring medical assistance, requiring non-medical assistance)**
- **Non-severe hypoglycaemia**
- **DKA**

Population A1a (separate trial data)

Table 25. inTandem1 (24 weeks): Diabetic ketoacidosis

Type	Insulin alone (placebo) N=174	Sotagliflozin 200 mg N=170	Sotagliflozin 400 mg N=175
Total patient years of exposure	76.0	76.1	78.9
Treatment emergent adjudicated DKA during the core treatment period			
Number of patients with the events, n (%)	0	1 (0.6%)	5 (2.9%)
Number of patients with the events per 100 patient years	0.0	1.3	6.3
Number of events	0	1	5
Number of events per 100 patient years	0.0	1.3	6.3
DKA, diabetic ketoacidosis; Ref Confidential documents 1			

Table 26. inTandem1 (24 weeks): Non-severe hypoglycaemia

Type	Insulin alone (placebo) N=174	Sotagliflozin 200 mg N=170	Sotagliflozin 400 mg N=175
Total patient years of exposure	76.0	76.1	78.9
Non-documented symptomatic hypoglycaemia during the core treatment period	159 (91.4%)	152 (89.4%)	166 (94.9%)
Number of patients with the events, n (%)	209.2	199.7	210.4
Number of patients with the events per 100 patient years	479.5	420.7	462.1
Number of events	4975	4207	4621
Number of events per 100 patient years	6309	5528	5857
DKA, diabetic ketoacidosis; Ref Confidential documents 1			

Table 27. inTandem1 (24 weeks): Severe hypoglycaemia

Type	Insulin alone (placebo) N=174	Sotagliflozin 200 mg N=170	Sotagliflozin 400 mg N=175
Total patient years of exposure	76.0	76.1	78.9
Severe hypoglycaemia during the core treatment period			
Number of patients with the events, n (%)	12 (6.9%)	5 (2.9%)	7 (4.0%)
Number of patients with the events per 100 patient years	15.8	6.6	8.9
Number of events	14	11	8
Number of events per 100 patient years	18.4	14.5	10.1
Ref Confidential documents 1			

Table 28. inTandem1 (52 weeks) – diabetic ketoacidosis

Type	Insulin alone (placebo) N=174	Sotagliflozin 200 mg N=170	Sotagliflozin 400 mg N=175
Total patient years of exposure	154.3	157.2	163.5
Treatment emergent adjudicated DKA during the core & long-term treatment period			
Number of patients with the events, n (%)	1 (0.6%)	6 (3.5%)	6 (3.4%)
Number of patients with the events per 100 patient years	0.6	3.8	3.7
Number of events	1	7	6
Number of events per 100 patient years	0.6	4.5	3.7
DKA, diabetic ketoacidosis; Ref Confidential documents 1			

Table 29. inTandem1 (52 weeks) Non-severe hypoglycaemia

Type	Insulin alone (placebo) N=174	Sotagliflozin 200 mg N=170	Sotagliflozin 400 mg N=175
Total patient years of exposure	154.3	157.2	163.5
Non-severe documented symptomatic hypoglycaemia during the core and long-term treatment period			
Number of patients with the events, n (%)	164 (94.3%)	157 (92.4%)	168 (96.0%)
Number of patients with the events per 100 patient years	106.3	99.9	102.8
Number of events	9504	8044	8942
Number of events per 100 patient years	6159	5117	5469
Ref Confidential documents 1			

Table 30. inTandem1 (52 weeks): Severe hypoglycaemia

Type	Insulin alone (placebo) N=174	Sotagliflozin 200 mg N=170	Sotagliflozin 400 mg N=175
Total patient years of exposure	154.3	157.2	163.5
Severe hypoglycaemia during the core and long-term treatment period			
Number of patients with the events, n (%)	17 (9.8%)	8 (4.7%)	9 (5.1%)
Number of patients with the events per 100 patient years	11.0	5.1	5.5
Number of events	22	18	11
Number of events per 100 patient years	14.3	11.5	6.7
Ref Confidential documents 1			

Table 31. inTandem2 (24 weeks): diabetic ketoacidosis

Type	Insulin alone (placebo) N=124	Sotagliflozin 200 mg N=135	Sotagliflozin 400 mg N=138
Total patient years of exposure	56.8	59.2	62.2
Treatment emergent adjudicated DKA during the core treatment period			
Number of patients with the events, n (%)	0	0	2 (1.4%)
Number of patients with the events per 100 patient years	0.0	0.0	3.2
Number of events	0	0	2
Number of events per 100 patient years	0.0	0.0	3.2
DKA, diabetic ketoacidosis; Ref Confidential documents 1			

Table 32. inTandem2 (24 weeks): Non-severe hypoglycaemia

Type	Insulin alone (placebo) N=124	Sotagliflozin 200 mg N=135	Sotagliflozin 400 mg N=138
Total patient years of exposure	56.8	59.2	62.2
Non-severe documented symptomatic hypoglycaemia during the core treatment period			
Number of patients with the events, n (%)	106 (85.5%)	119 (88.1%)	117 (84.8%)
Number of patients with the events per 100 patient years	186.6	201.0	188.1
Number of events	3552	3585	3299
Number of events per 100 patient years	6254	6056	5304
Ref Confidential documents 1			

Table 33. inTandem2 (24 weeks): Severe hypoglycaemia

Type	Insulin alone (placebo) N=124	Sotagliflozin 200 mg N=135	Sotagliflozin 400 mg N=138
Total patient years of exposure	56.8	59.2	62.2
Severe hypoglycaemia during the core treatment period			
Number of patients with the events, n (%)	4 (3.2%)	4 (3.0%)	4 (2.9%)
Number of patients with the events per 100 patient years	7.0	6.8	6.4
Number of events	5	4	6
Number of events per 100 patient years	8.8	6.8	9.6
Ref Confidential documents 1			

Table 34. inTandem2 (52 weeks): diabetic ketoacidosis

Type	Insulin alone (placebo) N=124	Sotagliflozin 200 mg N=135	Sotagliflozin 400 mg N=138
Total patient years of exposure	118.0	123.1	129.6
Treatment emergent adjudicated DKA during the core and long-term treatment period			
Number of patients with the events, n (%)	0	2 (1.5%)	5 (3.6%)
Number of patients with the events per 100 patient years	0.0	1.6	3.9
Number of events	0	2	5
Number of events per 100 patient years	0.0	1.6	3.9
DKA, diabetic ketoacidosis; Ref Confidential documents 2			

Table 35. inTandem2 (52 weeks): Non-severe hypoglycaemia

Type	Insulin alone (placebo) N=124	Sotagliflozin 200 mg N=135	Sotagliflozin 400 mg N=138
Total patient years of exposure	118.0	123.1	129.6
Non-severe documented symptomatic hypoglycaemia during the core and long-term treatment period			
Number of patients with the events, n (%)	112 (90.3%)	122 (90.4%)	124 (89.9%)
Number of patients with the events per 100 patient years	94.9	99.1	95.7
Number of events	6943	6555	5970
Number of events per 100 patient years	5884	5325	4607
Ref Confidential documents 2			

Table 36. inTandem2 (52 weeks): Severe hypoglycaemia

Type	Insulin alone (placebo) N=124	Sotagliflozin 200 mg N=135	Sotagliflozin 400 mg N=138
Total patient years of exposure	118.0	123.1	129.6
Severe hypoglycaemia during the core and long-term treatment period			
Number of patients with the events, n (%)	7 (5.6%)	5 (3.7%)	4 (2.9%)
Number of patients with the events per 100 patient years	5.9	4.1	3.1
Number of events	9	7	7
Number of events per 100 patient years	7.6	5.7	5.4
Ref Confidential documents 2			

Table 37. inTandem3 (24 weeks) DKA

Type	Insulin alone (placebo) N=370	Sotagliflozin 400 mg N=379
Total patient years of exposure	163.9	164.4
Treatment emergent adjudicated DKA during the core treatment period		
Number of patients with the events, n (%)	1 (0.3%)	7 (1.8%)
Number of patients with the events per 100 patient years	0.6	4.3
Number of events	1	7
Number of events per 100 patient years	0.6	4.3
DKA, diabetic ketoacidosis; Ref Confidential documents 3		

Table 38. inTandem3 (24 weeks): Non-severe hypoglycaemia

Type	Insulin alone (placebo) N=370	Sotagliflozin 400 mg N=379
Total patient years of exposure	163.9	164.4
Non-severe documented symptomatic hypoglycaemia during the core treatment period		
Number of patients with the events, n (%)	311 (84.1%)	333 (87.9%)
Number of patients with the events per 100 patient years	189.7	202.6
Number of events	7881	7302
Number of events per 100 patient years	4808	4442
Ref Confidential documents 3		

Table 39. inTandem3 (24 weeks): Severe hypoglycaemia

Type	Insulin alone (placebo) N=370	Sotagliflozin 400 mg N=379
Total patient years of exposure	163.9	164.4
Severe hypoglycaemia during the core treatment period		
Number of patients with the events, n (%)	11 (3.0%)	10 (2.6%)
Number of patients with the events per 100 patient years	6.7	6.1
Number of events	14	13
Number of events per 100 patient years	8.5	7.9
Ref Confidential documents 3		

A3. Priority question: Please provide full baseline characteristics (demographics, diabetic parameters and other risk factors) for inTandem1, inTandem2 and inTandem3 for the populations defined in A1a and A1b. (separately and pooled).

Population A1a: subgroup of patients with BMI >27kg/m^2 (separately)

Table 40. Summary of baseline patient demographics and clinical characteristics for inTandem1, inTandem2 and inTandem3 (patients with baseline BMI ≥27 kg/m^2)

Characteristics	inTandem1			inTandem2			inTandem3	
	Placebo (N=174)	Sotagliflozin 200 mg (N=170)	Sotagliflozin 400 mg (N=175)	Placebo (N=124)	Sotagliflozin 200 mg (N=135)	Sotagliflozin 400 mg (N=138)	Placebo (N=370)	Sotagliflozin 400 mg (N=379)
Age in years, Mean (SD)	44.7 (11.80)	47.0 (13.52)	46.6 (12.02)	41.2 (13.47)	44.4 (11.51)	43.9 (11.82)	44.7 (12.51)	44.9 (13.39)
Female sex, n (%)	82 (47.1)	85 (50.0)	91 (52.0)	61 (49.2)	63 (46.7)	68 (49.3)	188 (50.8)	181 (47.8)
Race[1] white, n (%)	164 (94.3)	153 (90.0)	163 (93.1)	119 (96.0)	127 (94.2)	130 (94.2)	334 (90.3)	340 (89.7)
Duration of diabetes (years), n (%)								
<20	68 (39.1)	62 (36.5)	65 (37.1)	70 (56.5)	72 (53.3)	89 (64.5)	188 (50.8)	195 (51.5)
≥20 to <40	89 (51.1)	85 (50.0)	89 (50.9)	44 (35.5)	55 (40.7)	40 (29.0)	152 (41.1)	152 (40.1)
≥40	17 (9.8)	23 (13.5)	21 (12.0)	10 (8.1)	8 (5.9)	9 (6.5)	30 (8.1)	32 (8.4)
Body weight in kg, Mean (SD)	95.36 (15.815)	96.08 (15.362)	94.17 (15.652)	92.58 (14.439)	92.92 (15.335)	93.00 (16.482)	92.22 (15.084)	93.17 (14.400)
BMI (kg/m^2), Mean (SD)	32.32 (4.209)	32.97 (4.449)	32.36 (4.204)	31.61 (4.265)	31.89 (4.191)	31.45 (3.797)	31.87 (4.178)	31.94 (3.958)
Insulin delivery method[2], CSII, n (%)	104 (59.8)	103 (60.6)	112 (64.0)	34 (27.4)	37 (27.4)	35 (25.4)	156 (42.2)	156 (41.2)
Total daily insulin dose (IU/day), Mean (SD)	79.41 (45.260)	78.34 (47.014)	73.38 (41.391)	N=124, 75.76 (35.687)	N=135, 73.23 (32.735)	N=137, 70.58 (31.157)	68.25 (32.730)	66.46 (31.278)
Bolus insulin dose (IU/day), Mean (SD)	38.67 (27.995)	36.57 (26.571)	35.09 (25.727)	N=124, 39.38 (25.930)	N=135, 37.13 (20.171)	N=137, 36.62 (22.290)	N=369, 33.84 (21.477)	N=379, 32.19 (19.245)
Basal insulin dose (IU/day), Mean (SD)	40.73 (21.378)	41.77 (26.344)	38.29 (20.212)	36.37 (15.982)	36.09 (17.869)	33.90 (14.796)	N=369, 34.41 (17.459)	N=379, 34.26 (18.270)
HbA_{1c} (%), Mean (SD)	7.54 (0.705)	7.69 (0.699)	7.57 (0.707)	7.73 (0.822)	7.75 (0.804)	7.72 (0.789)	8.21 (0.928)	8.19 (0.884)
Baseline FPG (mg/dL), Mean (SD)	156.02 (65.370)	160.32 (72.511)	146.82 (63.426)	159.15 (67.686)	167.41 (72.143)	168.39 (70.878)	162.97 (65.985)	162.98 (70.089)
2-hour PPG (mg/dL), N[3], Mean (SD)	N=30, 215.80 (71.271)	N=28, 214.04 (100.333)	N=33, 207.12 (64.638)	N=22, 236.77 (93.817)	N=29, 213.34 (95.356)	N=29, 210.97 (100.828)		

Characteristics	inTandem1			inTandem2			inTandem3	
	Placebo (N=174)	Sotagliflozin 200 mg (N=170)	Sotagliflozin 400 mg (N=175)	Placebo (N=124)	Sotagliflozin 200 mg (N=135)	Sotagliflozin 400 mg (N=138)	Placebo (N=370)	Sotagliflozin 400 mg (N=379)
SBP (mm Hg), Mean (SD)	122.5 (12.62)	122.1 (15.08)	121.8 (14.67)	126.8 (15.96)	127.6 (14.73)	125.9 (13.82)	124.5 (14.32)	125.2 (14.51)
SBP ≥130 mm Hg[4], n (%)	48 (27.6)	46 (27.1)	50 (28.6)	51 (41.1)	55 (40.7)	58 (42.0)	132 (35.7)	133 (35.1)
DBP (mmHg), Mean (SD)	77.6 (8.09)	78.0 (9.37)	77.2 (8.15)	78.5 (8.39)	80.3 (9.61)	78.5 (8.09)	78.4 (8.93)	78.1 (8.49)
DTSQs score, Mean (SD)	N=170, 29.1 (4.62)	N=169, 28.6 (5.14)	N=172, 29.2 (4.90)	N=121, 28.2 (5.52)	N=131, 28.2 (5.18)	N=137, 28.2 (4.83)		
DDS2 score, Mean (SD)	N=170, 4.9 (2.27)	N=169, 5.1 (2.00)	N=173, 4.9 (2.21)	N=122, 5.3 (2.20)	N=131, 5.7 (2.04)	N=137, 5.4 (2.01)		

1: Only the most frequent category was presented; 2: Only the category CSII was presented, all other patients were in category non-CSII; 3: 2hr-PPG was evaluated only in the CGM population in studies inTandem1 and inTandem2; 4: Only the category SBP ≥130 mm Hg was presented
Abbreviations: BMI = body mass index; CGM = Continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DBP = diastolic blood pressure; DDS2 = 2-item Diabetes Distress Screening Scale; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; FPG = fasting plasma glucose; HbA_{1c} = glycated haemoglobin; IU = international unit; mITT = modified intent-to-treat; PPG = Postprandial plasma glucose; SBP = systolic blood pressure; SD = standard deviation;
Ref Confidentiail documents 1-3

Population A1a: subgroup of patients with BMI >27kg/m^2 (pooled)

Table 41. Summary of baseline patient demographics and clinical characteristics for pooled data (patients with baseline BMI ≥27 kg/m^2)

Characteristics	ES1 pool			ES2 pool	
	Placebo (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)	Placebo (N=668)	Sotagliflozin 400 mg (N=692)
Age in years, Mean (SD)	43.3 (12.62)	45.9 (12.72)	45.5 (11.98)	44.1 (12.57)	45.1 (12.77)
Female sex, n (%)	143 (48.0)	148 (48.5)	159 (50.8)	331 (49.6)	340 (49.1)
Race[1]white, n (%)	283 (95.0)	280 (91.8)	293 (93.6)	617 (92.4)	633 (91.5)
Duration of diabetes (years), n (%)					
<20	138 (46.3)	134 (43.9)	154 (49.2)	326 (48.8)	349 (50.4)
≥20 to <40	133 (44.6)	140 (45.9)	129 (41.2)	285 (42.7)	281 (40.6)
≥40	27 (9.1)	31 (10.2)	30 (9.6)	57 (8.5)	62 (9.0)
Body weight in kg, Mean (SD)	94.20 (15.294)	94.68 (15.405)	93.66 (16.152)	93.10 (15.198)	93.39 (15.208)
BMI (kg/m^2), Mean (SD)	32.03 (4.240)	32.49 (4.363)	31.96 (4.049)	31.94 (4.203)	31.95 (3.996)
Insulin delivery method[2], CSII, n (%)	138 (46.3)	140 (45.9)	147 (47.0)	294 (44.0)	303 (43.8)
Total daily insulin dose (IU/day), Mean (SD)	N=298, 77.89 (41.519)	N=305, 76.08 (41.323)	N=312, 72.15 (37.215)	N=667, 72.56 (37.197)	N=691, 69.03 (34.179)
Bolus insulin dose (IU/day), Mean (SD)	38.97 (27.112)	36.82 (23.914)	35.76 (24.525)	N=667, 36.13 (24.273)	N=691, 33.81 (21.706)
Basal insulin dose (IU/day), Mean (SD)	38.92 (19.407)	39.26(23.120)	36.35 (18.131)	N=667, 36.42 (18.477)	N=692, 35.21 (18.224)
HbA_{1c} (%), Mean (SD)	7.62 (0.760)	7.72 (0.747)	7.63 (0.747)	7.94 (0.905)	7.94 (0.869)
Baseline FPG (mg/dL), Mean (SD)	157.33 (66.249)	163.46 (72.315)	156.33 (67.561)	160.45 (66.113)	159.97 (68.987)
SBP (mm Hg), Mean (SD)	124.3 (14.24)	124.6 (15.15)	123.6 (14.42)	N=667, 124.4 (14.27)	N=692, 124.5 (14.48)
SBP ≥130 mm Hg[4], n (%)	99 (33.2)	101 (33.1)	108 (34.5)	231 (34.6)	241 (34.8)
DBP (mm Hg), Mean (SD)	78.0 (8.21)	79.1 (9.53)	77.8 (8.14)	N=667, 78.2 (8.61)	N=692, 78.0 (8.33)
2-hour PPG (mg/dL), N, Mean (SD)	N=52, 224.67. (81.376)	N=57, 213.68 (96.954)	N=62, 208.92 (82.837)	N=52, 224.67 (81.376)	N=62, 208.92 (82.837)

Characteristics	ES1 pool			ES2 pool	
	Placebo (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)	Placebo (N=668)	Sotagliflozin 400 mg (N=692)
DTSQs score, Mean (SD)	N=291, 28.7 (5.74)	N=300, 28.4 (5.15)	N=309, 28.8 (4.89)		
DDS2 score, Mean (SD)	N=292, 5.1 (2.25)	N=300, 5.4 (2.03)	N=310, 5.1 (2.14)		
Time in range (≥70 to ≤180 mg/dL), (%)	N=58, 50.683 (14.5506)	N=59, 52.155 (52.464)	N=65, 50.317 (50.801)		

ES1 pool: inTandem1 and inTandem2 pooled data
ES2 pool: inTandem1, inTandem2 and inTandem3 pooled data
1: Only the most frequent category was presented
2: Only the category CSII was presented, all other patients were in category non-CSII
3: 2hr-PPG was evaluated only in the CGM population in studies inTandem1 and inTandem2
4: Only the category SBP ≥130 mm Hg was presented
Abbreviations: BMI = Body mass index; CGM = Continuous glucose monitoring; CSII = Continuous subcutaneous insulin infusion; DBP = Diastolic blood pressure; FPG = Fasting plasma glucose; HbA_{1c} = Glycated haemoglobin; IU = International unit; PPG = Postprandial plasma glucose; SBP = Systolic blood pressure; SD = Standard deviation
Ref: Confidential documents 1-3

A4. Priority question: Please provide efficacy and safety results for sotagliflozin 200 mg, sotagliflozin 400 mg and placebo (insulin alone) from pooled analyses of the inTandem trials for the following populations:

a) **The population defined in A1a for all three inTandem trials at 24 weeks [Population ES1 (200 mg inTandem1 and inTandem2) and ES2 (400 mg from inTandem1 inTandem2 and inTandem3)]**

b) **The population defined in A1a for inTandem1 and inTandem2 at 52 weeks (Population ES1)**

Table 42. Results summary for HbA_{1c} (%), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −0.43 (0.034)	N=313, −0.50 (0.034)	N=298, −0.04 (0.034)	−0.39 (−0.48, −0.30) <0.001	−0.45 (−0.54, −0.36) <0.001
ES2 pool		N=692, −0.65 (0.026)	N=668, −0.15 (0.026)		−0.50 (−0.57 to −0.43) <0.001
52 weeks					
ES1 pool	N=305, −0.24 (0.041)	N=313, −0.38 (0.040)	N=298, −0.00 (0.042)	−0.24 (−0.35 to −0.13) <0.001	−0.38 (−0.49 o−0.27) <0.001

CI = Confidence interval; HbA_{1c} = Glycated haemoglobin; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

Table 43. Results summary for patients with HbA_{1c} <7.0% without SH and without DKA (mITT population, patients with baseline BMI ≥27 kg/m^2)−+

Study reference/ID	Sotagliflozin 200 mg n/N (%)	Sotagliflozin 400 mg n/N (%)	Insulin alone (placebo) n/N (%)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				Difference (in %) of responders (95% CI) p value	Difference (in %) of responders (95% CI) p value
24 weeks					
ES1 pool	91/305 (29.8%)	131/313 (41.9%)	57/298 (19.1%)	10.71 (3.90 to 17.51) 0.001	22.73 (15.67 to 29.78) <0.001
ES2 pool		240/692 (34.7%)	106/668 (15.9%)		18.81 (14.31 to 23.31) <0.001
52 weeks					
ES1 pool	72/305 (23.6%)	100/313 (31.9%)	55/298 (18.5%)	5.15 (−1.34 to 11.64) 0.108	13.49 (6.70 to 20.28) <0.001

CI = Confidence interval¸ DKA = Diabetic ketoacidosis; HbA_{1c} = Glycated haemoglobin; SH = Severe hypoglycaemia
Ref Confidential documents 4-5

Patient reported outcomes

Table 44. Results summary for DDS2 total score, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305; −0.5 (0.10)	N=313, −0.5 (0.10)	N=298, 0.1 (0.10)	−0.6 (−0.9 to −0.3) <0.001	−0.7 (−0.9 to −0.4) <0.001

CI = Confidence interval; DDS2 = 2-item Diabetes Distress Screening Scale; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

Table 45. Results summary for DTSQs score, difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, 2.3 (0.26)	N=313, 2.2 (0.26)	N=298, −0.3 (0.27)	2.6 (1.9 to 3.3) <0.001	2.6 (1.9 to 3.3) <0.001

CI = Confidence interval; DTSQ = Diabetes Treatment Satisfaction Questionnaire; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

Body weight

Table 46. Results summary for body weight (kg), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −1.93 (0.196)	N=313, −2.98 (0.193)	N=298, 0.34 (0.198)	−2.27 (−2.81 to−1.74) <0.001	−3.32 (−3.85 to−2.79) <0.001
ES2 pool		N=692, −2.79 (0.131)	N=668, 0.59 (0.133)		−3.38 (−3.73 to−3.02) <0.001
52 weeks					
ES1 pool	N=305, −2.16 (0.254)	N=313, −3.61 (0.249)	N=298, 0.85 (0.258)	−3.01 (−3.71 to−2.31) <0.001	−4.46 (−5.15 to−3.76) <0.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

SBP

Table 47. Results summary for SBP (mm Hg), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −2.9 (0.64)	N=313, −4.0 (0.64)	N=298, −1.6 (0.65)	−1.3 (−3.0 to0.4) 0.13	−2.5 (−4.2 to−0.8) 0.005
ES2 pool		N=692, −3.5 (0.44)	N=668, −0.6 (0.44)		−2.9 (−4.0 to−1.7) <0.001
52 weeks					
ES1 pool	N=305, −1.7 (0.66)	N=313, −3.2 (0.65)	N=298, 0.4 (0.67)	−2.1 (−3.9 to0.4) 0.018	−3.6 (−5.3 to−1.9) <0.001

Abbreviations: CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

Daily basal and bolus insulin (IU)

Table 48. Results summary for mean daily bolus insulin dose (IU/day), absolute change from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −3.89 (0.715)	N=313, −5.91 (0.705)	N=298, −1.86 (0.722)	−2.02 (−3.92 to −0.12) 0.037	−4.05 (−5.93 to −2.17) <0.001
ES2 pool		N=692, −5.50 (0.506)	N=668, −1.63 (0.514)		−3.86 (−5.19 to −2.54) <0.001
52 weeks					
ES1 pool	N=305, −3.33 (0.783)	N=313, −6.40 (0.772)	N=298, −2.47 (0.800)	−0.86 (−2.98, 1.25) 0.423	−3.93 (−6.03, −1.84) <0.001

CI = Confidence interval; IU = International unit; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

Table 49. Results summary for mean daily basal insulin dose (IU/day), absolute change from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −0.14 (0.453)	N=313, −1.14 (0.445)	N=298, 1.57 (0.458)	−1.72 (−2.93 to −0.50) 0.006	−2.71 (−3.92 to −1.51) <0.001
ES2 pool		N=692, −1.28 (0.311)	N=668, 1.68 (0.316)		−2.96 (−3.78 to −2.13) <0.001
52 weeks					
ES1 pool					

CI = Confidence interval; IU = International unit; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

FPG

Table 50.Results summary for FPG (mg/dL), absolute difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −9.3 (3.33)	N=313, −18.6 (3.28)	N=298, 6.4 (3.36)	−15.7 (−24.7 to −6.7) <0.001	−25.0 (−33.9 to −16.1) <0.001
ES2 pool		N=692, −18.5 (2.45)	N=668, 6.1 (2.48)		−24.7 (−31.2 to −18.1) <0.001
52 weeks					
ES1 pool	N=305, −7.65 (3.774)	N=313, −19.60 (3.694)	N=298, 6.82 (3.868)	−14.46 (−24.83, −4.10) 0.006	−26.42 (−36.66, −16.18) <0.001

CI = Confidence interval; FPG = Fasting plasma glucose; LSM = Least square mean; mITT = Modified intent−to−treat; SE = Standard Error
Ref Confidential documents 4-5

DBP

Table 51. Results summary for DBP (mm Hg), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −1.29 (0.407)	N=313, −1.22 (0.402)	N=298, −0.62 (0.411)	−0.67 (−1.75, 0.41) 0.226	−0.60 (−1.67, 0.47) 0.272
ES2 pool		N=692 −1.2 (0.28)	N= 668 0.1 (0.29)		−1.3 (0.38) (−2.1, −0.6) <.001
52 weeks					
ES1 pool	N=305, −1.18 (0.434)	N=313, −1.65 (0.426)	N=298, −0.18 (0.442)	−1.00 (−2.16, 0.17) 0.093	−1.46 (−2.62, −0.31) 0.013

Abbreviations: CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

Total cholesterol (mg/dL)

Table 52. Results summary for total cholesterol (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, 7.36 (1.658)	N=313, 7.91 (1.629)	N=298, 5.04 (1.670)	2.32 (−1.98, 6.62) 0.290	2.87 (−1.38, 7.11) 0.186
ES2 pool		N=692 7.3 (1.13)	N=668 2.5 (1.15)		4.9 (2.0, 7.8) <0.001
52 weeks					
ES1 pool	N=305, 8.84 (1.752)	N=313, 12.63 (1.729)	N=298, 4.44 (1.803)	4.40 (−0.28, 9.08) 0.065	8.18 (3.55, 12.82) <.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

LDL−C (mg/dL)

Table 53. Results summary for LDL−C (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, 5.08 (1.434)	N=313, 5.80 (1.408)	N=298, 4.74 (1.460)	0.35 (−3.40, 4.09) 0.856	1.06 (−2.63, 4.75) 0.573
ES2 pool		N=692 5.6 (0.95)	N=668 2.6 (0.97)		3.0 (0.5, 5.4) 0.017
52 weeks					
ES1 pool	N=305, 5.29 (1.497)	N=313, 7.71 (1.490)	N=298, 4.07 (1.549)	1.22 (−2.79, 5.23) 0.551	3.64 (−0.35, 7.63) 0.074

Abbreviations: CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

HDL−C (mg/dL)

Table 54. Results summary for HDL−C (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, 1.74 (0.554)	N= 313, 1.58 (0.543)	N=298, −1.55 (0.558)	3.29 (1.85, 4.74) <0.001	3.13 (1.70, 4.56) <0.001
ES2 pool		N=692 1.7 (0.37)	N=668 −1.6 (0.38)		3.3 (0.48) (2.4, 4.3) <.001
52 weeks					
ES1 pool	N=305, 2.36 (0.592)	N=313, 3.24 (0.586)	N=298, 0.04 (0.609)	2.32 (0.73, 3.90) 0.004	3.19 (1.62, 4.76) <0.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

Triglycerides (mg/dL)

Table 55. Results summary for triglycerides (mg/dL), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, 4.02 (3.319)	N=313, 3.17 (3.240)	N=298, 15.50 (3.327)	−11.48 (−20.19, −2.77) 0.001	−12.32 (−20.90, −3.74) 0.005
ES2 pool		N=692 0.7 (2.59)	N=668 11.0 (2.64)		−10.3 (−16.9, −3.7) 0.002
52 weeks					
ES1 pool	N=305, 7.50 (3.115)	N=313, 9.97 (3.077)	N=298, 7.01 (3.209)	0.48 (−7.85, 8.82) 0.909	2.95 (−5.31, 11.22) 0.483

Abbreviations: CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

BMI (kg/m^2)

Table 56. Results summary for body mass index (kg/m^2), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −0.69 (0.068)	N=313, −1.02 (0.067)	N=298, 0.09 (0.069)	−0.78 (−0.97, −0.60) <0.001	−1.11 (−1.29, −0.93) <0.001
ES2 pool		N= 692 −1.0 (0.05)	N= 668 0.2 (0.05)		−1.1 (0.06) (−1.3, −1.0) <.001
52 weeks					
ES1 pool	N=305, −0.77 (0.088)	N=313, −1.24 (0.086)	N=298, 0.28 (0.089)	−1.05 (−1.29, −0.81) <0.001	−1.53 (−1.77, −1.29) <0.001

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

eGFR (mL/min/1.73 m^2)

Table 57. Results summary for eGFR (mL/min/1.73 m^2), difference from baseline (mITT population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, LSM (SE)	Sotagliflozin 400 mg N, LSM (SE)	Insulin alone (placebo) N, LSM (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				LSM (95% CI) p value	LSM (95% CI) p value
24 weeks					
ES1 pool	N=305, −2.50 (0.621)	N=313, −2.31 (0.614)	N=298, −0.66 (0.627)	−1.84 (−3.49, −0.19) 0.029	−1.65 (−3.28, −0.01) 0.048
ES2 pool		N=692 −1.9 (0.49)	N=668 −1.1 (0.49)		−0.8 (−2.1, 0.5) 0.231
52 weeks					
ES1 pool	N=305, −1.25 (0.657)	N=313, −2.90 (0.667)	N=298, −0.43 (0.686)	−2.47 (−4.28, −0.67) 0.007	−0.83 (−2.61, 0.96) 0.364

CI = Confidence interval; LSM = Least square mean; mITT = Modified intent−to−treat; SBP = Systolic blood pressure; SE = Standard Error
Ref Confidential documents 4-5

Pooled safety results for population A1a

Table 58. Results summary for hypoglycaemia: documented blood glucose ≤55 mg/dL by SMBG (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, events per subject per year Event rate (95% CI)	Sotagliflozin 400 mg N, events per subject per year Event rate (95% CI)	Insulin alone (placebo) N, events per subject per year Event rate (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
				Event rate difference (95% CI) p value	Event rate difference (95% CI) p value
52 weeks					
SAF−1 pool	N=305, 13.41 13.75 (12.12 to 15.37)	N=313, 14.45 14.57 (12.88 to 16.6)	N=298, 17.87 17.99 (15.86 to 20.13)	−4.25 (−6.93 to −1.57) 0.0019	−3.42 (−6.14 to −0.7) 0.0138
T1D Phase III studies only					
SAF−3 pool	N=305, 13.41 13.75 (12.12 to 15.37)	N=692, 13.32 12.86 (11.83 to13.90)	N=668, 16.10 15.36 (14.12 to 16.60)	−1.61 (−3.66 to 0.43) 0.1215	−2.49 (−4.11 to −0.88) 0.0024

CI = Confidence interval; SMBG = Self-monitoring of blood glucose; T1D = type 1 diabetes
Ref Confidential documents 4-5

Table 59. Results summary for treatment−emergent positively adjudicated severe hypoglycaemia per subject−years of exposure (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID	Sotagliflozin 200 mg N, n (%) EAIR per 1,000 subject−years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1,000 subject−years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject−years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Relative difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Relative difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
52 weeks					
SAF−1 pool	N=305, 13 (4.3) 46.51 (21.23 to 71.80)	N=313, 12 (3.8) 41.06 (17.83 to 64.29)	N=298, 22 (7.4) 81.03 (47.17 to 114.90)	−34.52 (−76.78 to 7.74) 0.57 (0.28 to 1.14)	−39.98 (−81.04 to 1.09) 0.51 (0.24 to 1.02)
T1D Phase 3 studies only					
SAF−3 pool	N=305, 13 (4.3) 46.51 (21.23 to 71.80)	N=692, 21 (3.0) 46.09 (26.38 to 65.80)	N=668, 32 (4.8) 73.66 (48.14 to 99.19)	−27.15 (−63.08 to 8.78) 0.63 (0.32 to 1.19)	−27.57 (−59.82 to 4.68) 0.63 (0.36 to 1.08)

CI = Confidence interval; EAIR = Exposure−adjusted incidence rate; NA = Not available
Ref Confidential documents 4-5

Table 60. Results summary for treatment−emergent positively adjudicated DKA (safety population, patients with baseline BMI ≥27 kg/m^2) per 1,000 subject years exposure

Study reference	Sotagliflozin 200 mg N, n (%) EAIR per 1,000 subject−years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1,000 subject−years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject−years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
52 weeks					
SAF−1 pool	N=305, 8 (2.6) 28.62 (8.79 to 48.46)	N=313, 11 (3.5) 37.64 (15.39 to 59.88)	N=298, 1 (0.3) 3.68 (0.00 to 10.90)	24.94 (3.83 to 46.05) 7.77 (1.24 to 173.82)	33.95 (10.57 to 57.34) 10.22 (1.74 to 221.94)
T1D Phase 2 and 3 studies excluding Study 203					
SAF−3 pool	N=326, 8 (2.5) 28.12 (8.64 to 47.61)	N=738, 20 (2.7) 42.91 (24.10 to 61.72)	N=716, 2 (0.3) 4.50 (0.00 to 10.73)	23.63 (3.17 to 44.09) 6.25 (1.45 to 43.10)	38.41 (18.60 to 58.23) 9.54 (2.59 to 60.47)

CI = Confidence interval; DKA = Diabetic ketoacidosis; EAIR = Exposure−adjusted incidence rate; T1D, type 1 diabetes
Ref Confidential documents 4-5

Table 61. Overview of most frequent adverse events (safety population, patients with baseline BMI ≥27 kg/m^2)

Study reference/ID System Organ Class Preferred Term	Sotagliflozin 200 mg N, n (%) EAIR per 1,000 subject−years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1,000 subject−years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject−years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
SAF−1 pool (52 weeks)					
Genital mycotic infections (male)	N=157, 6 (3.8) 41.05 (8.20 to 73.89)	N=154, 7 (4.5) 47.74 (12.37 to 83.10)	N=155, 1 (0.6) 6.89 (0.00 to 20.39)	34.16 (−1.35 to 69.67) 5.96 (0.88 to 138.01)	40.85 (2.99 to 78.70) 6.93 (1.07 to 157.36)
Genital mycotic infections (female)	N=148, 32 (21.6) 240.02 (156.86 to 323.19)	N=159, 28 (17.6) 192.26 (121.05 to 263.48)	N=143, 9 (6.3) 71.25 (24.70 to 117.80)	168.78 (73.47 to 264.08) 3.37 (1.65 to 7.46)	121.01 (35.94 to 206.09) 2.70 (1.30 to 6.04)
Diarrhoea	N=305, 16 (5.2) 57.25 (29.20 to 85.30)	N=313, 27 (8.6) 92.38 (57.53 to 127.23)	N=298, 20 (6.7) 73.67 (41.38 to 105.95)	−16.42 (−59.19 to 26.35) 0.78 (0.40 to 1.51)	18.71 (−28.79 to 66.22) 1.25 (0.70 to 2.27)
SAF−3 pool (T1D Phase 2 and 3 studies)					
Genital mycotic infections (male)	N=170, 6 (3.5) 40.21 (8.04 to 72.39)	N=378, 11 (2.9) 46.04 (18.83 to 73.25)	N=359, 3 (0.8) 13.08 (0.00 to 27.87)	27.14 (−8.28 to 62.55) 3.08 (0.77 to 15.05)	32.96 (1.99 to 63.93) 3.52 (1.04 to 15.72)
Genital mycotic infections (female)	N=156, 33 (21.2) 244.01 (160.76 to 327.27)	N=368, 55 (14.9) 241.45 (177.64 to 305.27)	N=364, 14 (3.8) 64.87 (30.89 to 98.85)	179.14 (89.22 to 269.07) 3.76 (2.04 to 7.24)	176.58 (104.29 to 248.88) 3.72 (2.11 to 6.92)
Diarrhoea	N=326, 16 (4.9) 56.25 (28.69 to 83.81)	N=746, 47 (6.3) 100.70 (71.91 to 129.50)	N=723, 35 (4.8) 78.61 (52.56 to 104.65)	−22.36 (−60.28 to 15.56) 0.72 (0.39 to 1.28)	22.10 (−16.73 to 60.92) 1.28 (0.83 to 2.00)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities
Ref Confidential documents 4-5

Population A1a (pooled analyses of inTandem1 and inTandem2)

Table 62. Severe hypoglycaemia − During the core treatment period

Type	Insulin alone (placebo) (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Total patient years of exposure	132.8	135.4	141.1
Severe hypoglycaemia			
Number of patients with events, n (%)	16 (5.4%)	9 (3.0%)	11 (3.5%)
Number of patients with events per patient years	0.120	0.066	0.078
Number of events	19	15	14
Number of events per patient years	0.143	0.111	0.099
Ref Confidential documents 4-5			

Table 63. Severe hypoglycaemia − During the core & long−term treatment periods

Type	Insulin alone (placebo) (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Total patient years of exposure	272.3	280.3	293.1
Severe hypoglycaemia			
Number of patients with events, n (%)	24 (8.1%)	13 (4.3%)	13 (4.2%)
Number of patients with events per patient years	0.088	0.046	0.044
Number of events	31	25	18
Number of events per patient years	0.114	0.089	0.061
Ref Confidential documents 4-5			

Table 64. Non-severe documented symptomatic hypoglycaemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) − During the core treatment period

Type	Insulin alone (placebo) (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Total patient years of exposure	132.8	135.4	141.1
Non-severe documented symptomatic hypoglycaemia			
Number of patients with events, n (%)	265 (88.9%)	271 (88.9%)	283 (90.4%)
Number of patients with events per patient years	1.995	2.001	2.006
Number of events	8347	7792	7920
Number of events per patient years	62.85	57.55	56.13
Ref Confidential documents 4-5			

Table 65. Non-severe documented symptomatic hypoglycaemia (plasma glucose ≤70 mg/dL [3.9 mmol/L]) − During the core & long−term treatment periods

Type	Insulin alone (placebo) (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Total patient years of exposure	272.3	280.3	293.1
Non-severe documented symptomatic hypoglycaemia			
Number of patients with events, n (%)	276 (92.6%)	279 (91.5%)	292 (93.3%)
Number of patients with events per patient years	1.014	0.995	0.996
Number of events	16447	14599	14912
Number of events per patient years	60.40	52.08	50.88
Ref Confidential documents 4-5			

Table 66. Treatment emergent Adjudicated DKA − During the Core treatment period

Type	Insulin alone (placebo) (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Total patient years of exposure	132.8	135.4	141.1
Treatment emergent Adjudicated DKA			
Number of patients with events, n (%)	0	1 (0.3%)	7 (2.2%)
Number of patients with events per patient years	0.000	0.007	0.050
Number of events	0	1	7
Number of events per patient years	0.000	0.007	0.050
Ref Confidential documents 4-5			

Table 67. Treatment emergent Adjudicated DKA − During the core and long−term treatment periods

Type	Insulin alone (placebo) (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
Total patient years of exposure	272.3	280.3	293.1
Treatment emergent Adjudicated DKA			
Number of patients with events, n (%)	1 (0.3%)	8 (2.6%)	11 (3.5%)
Number of patients with events per patient years	0.004	0.029	0.038
Number of events	1	9	11
Number of events per patient years	0.004	0.032	0.038
Ref Confidential documents 4-5			

Note. Incorporation of studies to provide a comparison with metformin is not required.

For A5 c) and d) please refer to A1.

A5. Priority question: Please provide least squares mean change from baseline graphs for efficacy endpoints other than HbA_{1c} presumed to persist for 5 years in the economic model (HbA_{1c}, BMI, SBP and lipid profile) for the populations defined in A1a and A1b.

Please see progression graphs in Appendix B provided as commercial in confidence.

Table 68. least squares mean change from baseline for efficacy endpoints for population A1a.

Variable	Placebo		Sotagliflozin 200 mg	
	Mean	SE	Mean	SE
Insulin − Mean daily basal dose (IU)				
LSM change from baseline to 52weeks	2.45	0.53	−0.07	0.52
Insulin − Mean daily bolus dose (IU)				
LSM change from baseline to 52weeks	−2.47	0.80	−3.33	0.78
HbA_{1c} (%) CV				
LSM change from baseline to 52weeks	0.00	0.04	−0.24	0.04
BMI (kg/m^2)				

LSM change from baseline to 52weeks	0.28	0.09	−0.77	0.09
Systolic Blood Pressure − Derived average (mmHg)				
LSM change from baseline to 52 weeks	0.40	0.67	−1.74	0.66
Diastolic Blood Pressure − Derived average (mg/dL)				
LSM change from baseline to 52weeks	−0.18	0.44	−1.18	0.43
Cholesterol (mg/dL)				
LSM change from baseline to 52weeks	4.44	1.80	8.84	1.75
LDL-C (mg/dL)				
LSM change from baseline to 52weeks	4.07	1.55	5.29	1.50
HD-C (mg/dL) CV				
LSM change from baseline to 52weeks	0.04	0.61	2.36	0.59
Triglycerides (mg/dL)				
LSM change from baseline to 52weeks	7.01	3.21	7.50	3.12
Glomerular Filtration Rate (mL/min/1.73 m^2) CV				
LSM change from baseline to 52weeks	−0.43	0.69	−2.90	0.67
BMI, Body mass index; DL-C, high-density lipoprotein cholesterol; IU, international units; LDL-C, low-density lipoprotein cholesterol; LSM, least squares mean Ref: Confidential docs 4-5				

A6. For the populations defined in A1a and A1b, please provide the number of people with eGFR > 60 at baseline.

Table 69. the number of patients in inTandem1,2 and 3 trials with an eGFR > 60.

	Placebo (n,%)	Sotagliflozin 200 mg (n,%)	Sotagliflozin 400 mg (n,%)	All (n,%)
inTandem1	163 (93.7%)	161 (94.7%)	162 (92.6%)	486 (93.6%)
inTandem2	120 (96.8%)	131 (97.0%)	131 (94.9%)	382 (96.2%)
inTandem3	346 (93.5%)		356 (93.9%)	702 (93.7%)
Ref: Confidential docs 4-5				

A7. Please provide a summary of concomitant medications taken by patients in each group of all three inTandem trials for the populations defined in A1a and A1b.

Summary of concomitant medicines from the inTandem inTandem2 and inTandem 3 are provided in Appendix A.

A8. If the information was collected, please provide the proportions of patients in each group of all three inTandem trials for the populations defined in A1a and A1b who had attended structured education such as DAFNE.

This information was not collected during the inTandem trials.

A9. The company submission page 10 states that the 400 mg tablet will not be available at the time of launch in the UK.

a) Please clarify when the 400 mg tablet is expected to be available.

b) Will there be a difference in price between the 400 mg and 200 mg tablets?

a. The [redacted] is anticipated to be available at the time of the launch in T2D currently expected in [redacted].

[redacted]It is currently anticipated that there will be [redacted] between the [redacted] [redacted]

A10. The draft summary of product characteristics states: '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.' What proportion of patients are expected to require dose escalation?

In our global forecast, based upon market insights, we anticipate around 10% of patients will be titrated to the 400 mg dose. Although the summary of product characteristics states dose escalation may be recommended in some circumstances, the clinical trial programme did not permit dose escalation between the 200 mg and 400 mg; study participants who began on the 200 mg study arm (or 400 mg study arm) remained on study arm until the end of the study. Therefore, we cannot calculate the proportion of patients who may require a dose escalation to 400 mg from the inTandem trials.

In order to address this question, it is plausible to consider that patients with very high BMI (>35 kg/m^2) as this group may be a proxy for patients who could benefit from escalation of dose to the 400 mg tablet. By virtue of having a higher BMI these patients will probably have higher body weight and thereby may require the higher dose. Clinically these patients may be on higher insulin doses which increases risk for further weight gain and related co−morbidities. Sotagliflozin, may improve glycaemic control in such patients on individualised insulin regimens through a mechanism independent of insulin.

In the UK, a recent study using the Clinical Practice Research Datalink (N=5,607) found that adult T1D patients [defined as having HbA_{1c} >6.5% (>48 mmol/mol)] had an average BMI of 27.4 kg/m^2; 18% are overweight (BMI 25 −30), 38% are obese (BMI 30−35) and 9% are extremely obese (BMI>35). Therefore, for simplicity in one scenario for B2, we assumed 10% of patients will escalate to the 400 mg dose.

This proportion is in line with general recommendations about using lowest effective dose in the largest group of patients [1] and is also is in line with Sanofi own internal estimates for populations requiring dose escalation.

Section B: Clarification on cost−effectiveness data

For all scenarios requested, please provide results using the CORE Diabetes Model (CDM) and PRIME Diabetes Model. Please save the results of each scenario in both models with clear files names relating to the question number

For all scenarios requested, please provide results for the two populations outlined in A1a and A1b using the pooled effectiveness analyses outlined in question A4. Please provide these for both the 200 mg and 400 mg doses.

If the company base-case analysis is revised, please outline the new assumptions and provide updated results, including sensitivity analyses.

Treatment effectiveness

B1. Priority question: Please provide a comprehensive comparison of the CORE Diabetes Model and PRIME Diabetes Model, outlining any differences in structure, inputs and assumptions made. Please highlight the strengths and weaknesses of the two models and justify the decision to use the CORE Diabetes Model over the PRIME Diabetes Model for the primary analysis.

Sanofi comment

For the purposes of responding to the ERGs clarification questions Sanofi has aligned this economic analysis to the population reflecting the CHMP positive opinion (BMI ≥27kg/m^2), as well as the pooled evidence from clinical trials as requested by the ERG. Sanofi has adapted the model to reflect the A4a population using both cohort characteristics and pooled effects for all cost-effectiveness calculations in this response

Table 70 lists the inputs as requested by the ERG for the purposes of responding to the clarification questions, also displayed are company's base-case for the addendum and for the original submission.

Table 70. Model inputs

Variable	Base-case (ERG requests) *(Clarification Questions)*	Company's new base-case *(Addendum)*	Company base-case *(Original Submission)*
Population	inTandem1 and 2 (pooled) Subpopulation with BMI ≥27kg/m²	NDA	NDA
Efficacy outcomes	inTandem1 and 2 (pooled) Subpopulation with BMI≥27kg/m²	inTandem1 and 2 (pooled) Subpopulation with BMI≥27kg/m²	inTandem2
HbA_{1c} progression[1]	0.012% per year	0.012% per year	0.045% per year
BMI progression[1]	0.094 kg/m² per year	0.094 kg/m² per year	0.2375 kg/m² per year
eGFR progression[1]	−1.227 (mL/min/1,73 m^2) per year	−1.227 (mL/min/1,73 m^2) per year	0 (mL/min/1,73 m^2) per year
SBP progression[1]	0.118 mmHg per year	0.118 mmHg per year	UKPDS risk equation
DBP progression[1]	−0.588 mmHg	−0.588 mmHg	0
Total Cholesterol progression[1]	−0.588 (mg/dL)	−0.588 (mg/dL)	Framingham risk equation
HDL-C progression[1]	1.059 (mg/dL)	1.059 (mg/dL)	Framingham risk equation
LDL-C progression[1]	−1.412 (mg/dL)	−1.412 (mg/dL)	Framingham risk equation
Tryglycerides progression[1]	−1.176 (mg/dL)	−1.176 (mg/dL)	Framingham risk equation
Probability mortality severe hypoglycaemia	0.003% (Wolowacz et al. 2014)	0.003% (Wolowacz et al. 2014)	5% (Ben−Ami H et al 1999)
Probability mortality DKA	0.05% (Wolowacz et al. 2014)	0.05% (Wolowacz et al. 2014)	2.7% (MacIsaac RJ. et al. 2002)
ICER (base-case)	£10,012	£1934	£8578

BMI, body mass index; DKA, diabetic ketoacidosis ICER, incremential cost-effectiveness ratio; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HbA_{1c} Glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; NDA, no data available; SBP, systolic blood pressure;

NDA – National Diabetes Audit sourced from National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management (NG17) London: National Institute for Health and Care Excellence; 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ng17.

The cost-effectiveness of sotagliflozin when employing the ERG requested inputs are presented in Table 71.

Table 71. Results incorporating the ERG requested changes to the model inputs and using the A1a population (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin vs Placebo	S200vsPla−NICE−B2	72,126	71,511	615	10.490	10.428	0.061	10,012
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 72 Results incorporating the ERG requested changes to the model inputs and using the A1a population (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin vs Placebo	S200vsPla−NICE−B2	55,479	53,785	+1,694	9.31	9.16	+0.15	11,338
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

However, Sanofi still considers the NDA data to best reflect the UK patient population as it is derived from real world UK practice and therefore represents the best evidence on which to evaluate sotagliflozin's cost-effectiveness. Therefore, using the NDA data to inform the baseline cohort is still part of company's base-case as presented in Table 73 below and in the addendum.

.

Table 73 Base-case results incorporating the ERG requested changes to the model inputs and using NDA to inform the baseline cohort (New company base−case) (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin vs Placebo	S200vsPla−NDA-NICE−BC	78,940	78,731	209	8.803	8.695	0.108	**£1,934**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

B1. Priority question: Please provide a comprehensive comparison of the CORE Diabetes Model and PRIME Diabetes Model, outlining any differences in structure, inputs and assumptions made. Please highlight the strengths and weaknesses of the two models and justify the decision to use the CORE Diabetes Model over the PRIME Diabetes Model for the primary analysis.

Please provide further explanation on the "differences between the models in terms of long−term progression of risk factors" highlighted on page 131 of the company submission.

Table 74 Comparison of CORE Diabetes Model and PRIME Diabetes Model

	CORE Diabetes Model	PRIME Diabetes Model
Key assumptions	• Markov sub−models using a Monte Carlo simulation • Close cohort model • Discrete−time handling • Fixed states	• Patient−level simulation • Closed cohort model • Complication risk derived from conventional risk factors and patient characteristics • Capable of first and second order Monte Carlo simulation • Individual controllers with semi−Markov structure used to estimate risk of mortality, complications and adverse events for each simulated patient in each cycle
Strengths	• Disease−specific with unique T1D risk factors. • Product−generic and company independent model. • Double validation for T1D and T2D.	• Based on systematic literature review in T1D • Product and company independent tool • Validation published in 2017 • Risk of complication onset based exclusively on data from T1D populations • Developed in line with good research practice guidelines from ISPOR • Uses model averaging to overcomes conventional limitations in estimating CVD risk • Code has been externally audited • Covariance matrices for cohort generation and risk factor progression
Weaknesses	• No T1D specific risk equations incorporated.	• Only head−to−head (two arm) comparisons possible • Uses discrete health states, in combination where a patient has multiple complications, to estimate costs and utility score • External validation not possible for certain complications (due to limited published data) • No risk adjustment for ethnicity captured • Model relies on data primarily from Europe and North America, broader generalizability not tested
Time horizon	Lifetime (60 years) – user modifiable.	60 years (user modifiable) to match the CDM analysis

Cycle length	1 year	1 year
Half cycle correction	None	Not included
Baseline characteristics of simulated patients	Pooled inTandem1 & inTandem2 Post−Hoc Analysis in patients with BMI > 27kg/m^2)	PooledinTandem1 and inTandem2 post−hoc analysis in patients with BMI >27 kg/m^2
Baseline age	44.87 years (SD 12.48)	44.87 years (SD 12.48)
Ethnicity/race	White – 93% Black – 2% Native American – 0.1% Asian or Pacific Islander – 1.5% Others – 3.4%	Not modelled
BMI/Weight (kg)	32.16 kg/m^2 (SD 4.22)	BMI 32.16 kg/m^2 (SD 4.22)
Duration of diabetes	22.14 years (SD 11.91)	22.14 years (SD 11.91)
HbA_{1c} & lipids (%)	HbA_{1c} = 7.66% (SD 0.75) HDL-C = 60.67mg/dL (SD17.24) LDL-C = 97.15mg/dL (SD 31.06) TC = 178.41mg/dL (SD 36.64) Triglycerides = 101.79mg/dL (SD 58.76)	HbA_{1c} 7.66% (SD 0.75) HDL−C 1.57 mmol/L (SD 0.45) LDL−C 2.51 mmol/L (SD 0.80) TC 4.61 mmol/L (SD 0.95)
Blood pressure	124.15 mm Hg (SD 14.6)	124.15 mm Hg (SD 14.6)
Smoking status	1.2%	1.2% smokers
Comorbidities	Yes (CVD, renal, retinopathy, macular oedema, ulcer, neuropathy and depression diseases) *Full list of comorbidities described in the baseline cohort characteristics.*	Baseline comorbidities were captured in the modelling analysis. Please see the table of baseline cohort characteristics in the response to question B2.
Physical activity	Not considered	Not modelled
Baseline treatment	Optimised insulin treatment (basal−bolus)	Optimised insulin treatment (basal−bolus)
Treatment intervention		
Type of treatment	Medical oral treatment	Medical oral treatment

Treatment algorithm for HbA_{1c} evolution over time	Mean yearly progression observed in 2004−2012/13 EDIC data intensive insulin arm (= 0,012% per annum)	In line with the original submission, sotagliflozin was stopped after 5 years independent of HbA_{1c} level. Optimised basal bolus therapy was continued in both treatment arms over patients' lifetimes. HbA_{1c} progression is described below
Treatment algorithm for other conditions (e.g. hypertension, dyslipidemia and excess weight)	**Mean yearly progression (EDIC 2004−2012/13 intensive insulin arm)** BMI (kg/m^2) = 0,094 SBP (mmHg) = 0,118 DBP (mmHg) = −0,588 TC (mg/dL) = −0,588 LDL-C (mg/dL) = −1,412 HDL-C (mg/dL) = 1,059 Triglycerides (mg/dL) = −1,18 eGFR (mL/min/1,73 m^2) = −1,23* **(1993 to 2012/13 estimation, data from 2004 NA)*	Risk factor progression for HbA_{1c} and BMI were based on recommendations from NICE (clinical expert input) and all other risk factors were held constant (to aid transparency and, as risk factor progression was identical in both treatment arms, risk factor progression had no direct bearing on cost−effectiveness). HbA_{1c} annual progression +0.018% BMI annual progression +0.095 $kg.m^{-2}$
Treatment initial effects on baseline biomarkers	Applied the 1st year of treatment only to: HbA_{1c}, BMI, SBP, DBP, TG, LDL-C, HDL-C, Triglycerides and eGFR.	Treatment effects were applied in the first year of the simulation based on the results of the pooled inTandem1 and inTandem2 post−hoc analysis in patients with BMI > 27 kg/m^2 to the following modifiable risk factors/adverse event rates: • HbA_{1c} • SBP • TC • HDL-C • BMI • Severe hypoglycaemia rates • Non−severe hypoglycaemia rates • Diabetic ketoacidosis Details are provided in the response to question B2
Rules for treatment intensification (e.g. the cut−off HbA_{1c} level to switch the treatment, the type	5 (base−case) or 2 (sensitivity analysis) years treatment effect and then rebound for a convergence between treatment arms. Cost of optimised insulin treatment as rescue treatment for the rest of the time horizon. No	Analogous to the CDM approach: treatment with sotagliflozin was stopped after 5 years (or 2 years in sensitivity analysis), with patients reverting to optimised basal−bolus insulin therapy identical to the placebo arm.

of new treatment, and whether the rescue treatment is an addition or substitution to the standard treatment)	treatment effects assumptions for rescue treatment but a constant rate of AEs. Rescue treatment as substitution in the base-case, and as addition in other sensitivity analyses (up to 2, 5 years and lifetime).	After stopping sotagliflozin, there were no risk factor, adverse event rate or cost differences between the two treatment arms.
Long−term effects, adverse effects, treatment adherence and persistence, and residual effects after the discontinuation of the treatment	**AEs**: Constant while on treatment **Treatment efficacy**: Applied to year one only **Treatment adherence**: assumed 100% **Residual effects after discontinuation**: None, physiological curves forced to converge.	Adherence and persistence were assumed to be 100% through the simulation. No long−term effects on risk factors or adverse events associated with sotagliflozin were modelled beyond the duration of sotagliflozin therapy.
Trajectory of biomarkers, BMI, smoking, and any other factors that are affected by treatment	Mean yearly progression observed in the intensive insulin arm of EDIC (2004−2012/13) for HbA_{1c}, BMI, SBP, DBP TC, HDL-C, LDL-C and Triglycerides. Same approach but 1993−2012/13 data from DCCT/EDIC for eGFR.	Differences in modifiable risk factors and adverse event rates were maintained for the duration of sotagliflozin therapy, with no differences assumed between treatment arms thereafter. Trajectories for risk factor progression are described above.
Cost		
Differentiated by acute event in first year and subsequent years	Yes, accounted in the model.	Yes, captured in the model based on UK−specific published sources and expressed in 2017 GBP (as detailed in the original submission).
Cost of intervention and other costs (e.g. managing complications, adverse events and diagnostics)	Yes, accounted in the model.	Yes, captured in the model based on UK−specific published costs and resource use/insulin doses reported in the inTandem2 trial at Week 52
Health state utilities		
Operational mechanics of the assignment of utility values (i.e. utility or disutility−oriented)	Disutility oriented.	Additive approach with state utilities defined by complication history and disutilities added in each year a complication or adverse event occurs.
Management of multi−health conditions	Sub−Markov states acting independently. QALY estimation method set to account for the worst event (minimal approach).	For patients with multiple complications, the lowest applicable health state utility associated with relevant complications is applied (analogous to the CDM).

General model characteristics		
Choice of mortality table and any specific event−related mortality	**Mortality table**: UK Office for National Statistics (2015−2017). **MI**: Sonke GS. et al. 1996 **Stroke**: Eriksson SE et al. 2001 **Severe. Hypo** : Wolowacz et al. 2015 **DKA** : Wolowacz et al. 2015 **Foot ulcer and amputation**: Persson U et al. 2000	Background mortality risk was using cause−subtracted life tables derived from World Health Organization data from 2015 for the UK setting. Other mortality risk were based on the following data sources: MI – Lung et al. 2014[i] Angina – Bottle et al. 2009[ii] Stroke – Lung et al. 2014[i] Nephropathy – USRDS 2014 mortality estimates indexed by age[iii] Severe hypoglycaemia − DCCT[iv] Ketoacidosis – Wright et al. 2009[v]
Prediction of complications (including incidence of nephropathy): Choice and source of risk equations	DCCT/EDIC (Nathan DM. et al. 2005) derived risks based on HbA_{1c} and SBP levels.	Multiple sources as described in Valentine et al. 2017[vi] and online supplementary materials http://dx.doi.org/10.1016/j.jval.2016.12.001
Microvascular event rates: retinopathy and macular oedema	Applied as risk reductions for a relative lower 10% HbA_{1c} (EDIC): Retinopathy: RR=50 Macular oedema RR=50 Absolute RR of 13 for 10mmHg lower SBP for all microvascular complications.	Retinopathy modelling was informed by WESDR (Klein et al. 2008)[vii] with risk of progression/regression adjusted based on gender, HbA1c, BMI, duration of diabetes, severity of retinopathy, proteinuria, and SBP. Additional detail is provided in the Valentine et al. 2017 supplementary materials.
Microvascular event rates:	Applied as risk reductions for a relative lower 10% HbA_{1c} (EDIC) for BDR, PDR, severe vision loss, macular oedema, GRP, ESRD and neuropathy. Absolute RR of 13 for 10mmHg lower SBP for all microvascular complications.	Multiple sources as described in Valentine et al. 2017[viii] and online supplementary materials http://dx.doi.org/10.1016/j.jval.2016.12.001
Number of Monte−Carlo simulations conducted and justification	1’000,000 model iterations (1000 patient cohort with 1000 bootstrap simulations) as seen to provide outcome stability.	500,000 individual simulation patients were modelled characteristics sampled from distributions at baseline, and treatment effects sampled from distributions, were simulated using first order Monte Carlo simulation

		(random walk). Model testing indicated that population outcomes were stable with sample sizes over 300,000 simulated patients. When PSA is implemented, in addition to sampling from distributions around all baseline cohort characteristics and treatment effects, the model samples from distributions around an additional 397 internal model coefficients and parameters, including beta coefficients, hazard ratios, odds ratios and transition probabilities.
Components of model uncertainty being simulated (e.g. risk equations, risk factor trajectories, costs, and treatment effect) number of simulations and justification	**Baseline cohort characteristics**: Variability accounting for SE **Economics:** Fixed ±20% variation. **Utility estimated**: Variability accounting for SE **Treatment effects (all)**: Variability accounting for SE **PSA**: 2nd order sampling 1'000,000 model iterations (1000 patient cohort and 1000 bootstrap simulations) as seen to provide outcome stability.	Simulated patient characteristics and treatment effects are sampled from distributions (above). The model supports covariance in terms of patient characteristics and risk factor progression, but this was not used in the present analysis in the interests of transparency (and matching the CDM analysis) Risk factor progression based on analysis of patient level data is supported for HbA_{1c} and based on published studies for other risk factors. However, in the interests of transparency (given the complex nature of these interactions), this was not used in the present analysis

AE, adverse events; BMI, body mass index; CDM, CORE Diabetes Model; CVD, cardiovascular risk; DBP, diastolic blood pressure; DCCT, The Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; EDIC, Epidemiology of Diabetes Interventions and Complications; eGFR, estimated glomerular filtration rate; HbA_{1c}, Glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; NA, not available; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; SBP, systolic blood pressure; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes; TC, total cholesterol;

B2. Priority question: Please run cost−effectiveness analyses for the 200 mg and 400 mg dose of sotagliflozin using effectiveness results requested in A4d. Please use the pooled baseline characteristics for the subgroup as requested in A3 to inform the simulated cohort, rather than the NDA or DCCT (Table 3.3 in the company submission). For the 400 mg dose, please describe the methods to account for stepping−up from a 200 mg starting dose. Those methods could potentially include data from the population requested in A4c.

To align the economic analysis to the population reflecting the CHMP positive opinion (BMI ≥27kg/m^2), as well as the pooled evidence from clinical trials as requested by the ERG, Sanofi has adapted the base-case analysis to reflect the A1a population using both cohort characteristics and pooled effects for this and all upcoming priority questions.

[redacted] In order to address the question on dose escalation we apply 110% price increase to our base-case to reflect potentially 10% of patients who may require dose escalation to the 400 mg dose (see question A10). In this analysis we apply the efficacy inputs for the 200 mg dose (and not the 400 mg dose) which is a conservative estimate regarding the efficacy.

Table 75. ICER outcome where cost of Sotagliflozin is set at 110% to account for some patients potentially needing 400 mg dose (CDM Analysis) A1a population and under the context of 5 years treatment effect duration (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg efficacy costs at 110%	S200vsPla−NICE−Sota+10%	72,300	71,511	789	10.490	10.428	0.061	**12,843**

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 76. ICER outcome where cost of Sotagliflozin is set at 110% to account for some patients potentially needing 400 mg dose (PRIME Analysis) A1a population and under the context of 5 years treatment effect duration (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg efficacy costs at 110%	S200vsPla−NICE−Sota+10%	55,696	53,785	+1,911	9.31	9.16	+0.15	12,792
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

B3. Priority question: Please provide a scenario where the simulated cohort (the base-case analysis) is based on the population in the inTandem2 trial (Table L.1 in Appendix L) rather than the NDA or DCCT (Table 3.3 in the company submission).

Here we provide analysis based on the clinical inputs for the new base-case population (BMI≥27) and the baseline characteristics from the same population using the pooled data for inTandem1 and inTandem2 (as per population A1a).

Table 77. ICER outcomes of Sotagliflozin 200 mg vs placebo in the A1a inTandem2 population (baseline cohort) and under the context of 5 year treatment duration (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B2	72,126	71,511	615	10.490	10.428	0.061	**10,012**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 78. ICER outcomes of Sotagliflozin 200 mg vs placebo in the A1a inTandem2 population (baseline cohort) and under the context of 5 year treatment duration (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B2	55,479	53,785	+1,694	9.31	9.16	+0.15	11,338

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

B4. Priority question: Please clarify when patients discontinued sotagliflozin in the sensitivity analysis "Treatment effect: 2 years" in Table 4.1 of the company submission. Please provide results when sotagliflozin treatment effects rebound to placebo after 2 years assuming sotagliflozin treatment is continued for:

a) **2 years**

b) **5 years**

c) **Lifetime**

In response to the first part of the question, treatment effects are discontinued at 2 years. For B4 a) see NICE−B4 2 years, for b) see NICE−B4 5 years in below table. As discussed at the clarification meeting applying lifetime costs after discontinuation of treatment benefit at 2 years would represent a scenario that is not appropriate to model as not in line with either the anticipated decisions of physicians given the risk/benefit profile of this class of medicines, effective use of NHS resources in line with the NHS Long-Term Plan, nor in line with the market authorisation which supports safe clinical decision making for this medicine.

Table 79. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 2-year treatment effect duration, and 2 years and 5 years treatment costs (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotaglifozin 200 mg vs placebo	S200vsPla−NICE−B4 (2yrs)	72,301	71,512	790	10.459	10.428	0.031	**25,638**
Sotaglifozin 200 mg vs placebo	S200vsPla−NICE−B4 (5yrs)	72,750	71,512	1,238	10.475	10.428	0.047	**26,463**

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

Table 80. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 2-year treatment effect duration, and 2 years and 5 years treatment costs (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)	Quality−adjusted life years (QALYs)	ICER (GBP)

		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotaglifozin 200 mg vs placebo	S200vsPla−NICE−B4 (2yrs)	54,508	53,785	+724	9.23	9.16	+0.08	9,504
Sotaglifozin 200 mg vs placebo	S200vsPla−NICE−B4(5yrs)	54,893	53,785	+1,108	9.24	9.16	+0.08	13,295
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

B5. The longest follow up in the inTandem trials is 52 weeks. Please provide a scenario where the treatment effect for sotagliflozin wanes after 1 year and returns to placebo after 2 years.

The outcomes of this scenario align with those presented in NICE priority question B4, where the treatment effects rebound to the placebo arm in year 2. The applied treatment costs were consistently removed with the treatment effect.

Table 81. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 2 years treatment effect duration (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B4 (2yrs)	72,301	71,512	790	10.459	10.428	0.031	**25,638**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 82. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 2 years treatment effect duration (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B4 (2yrs)	54,468	53,785	+638	9.20	9.16	+0.05	**14,919**

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

B6. Priority question: Please provide a scenario where sotagliflozin treatment is continued for lifetime and the treatment effects rebound to placebo after 5 years.

See explanation above.B7. Priority question: Please provide clinical evidence to justify the assumption that eGFR does not progress over a patient's lifetime.

For the CDM Sanofi has updated the previous utilised mean yearly progression, by replacing 0 with −1.227 mL/min/1.73m². This new value was estimated using the 18 year data from the EDIC evidence (end of DCCT in 1993 to end of EDIC 2012). Sanofi would have ideally used the change from years 2004 to 2012/13, but this variable was not consistently reported in 2004.

Table 83. New estimated eGFR mean yearly change, used as natural progression value

Variable	End of DCCT	EDIC year 18	Mean yearly change[2]
	year 1993	*year 2012/13*[1]	
eGFR (mL/min/1.73m^2)	116	93.3	−1.227

Reference
Nathan David, The Diabetes Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. Diabetes Care vol 37. 2014
Notes
[1] the EDIC study started in 1994 and reported outcomes are from year 18 of the study and therefore year 2012
[2] Estimated based on 19 years of data (1993 to 2012)

Note: Please note that all new presented outcomes already reflect this later change.

eGFR is not a risk factor used in the PRIME Diabetes Model.

B8. Priority question: Please provide a scenario where BMI progression is capped at the baseline BMI in 80% of the cohort.

a) Please explain how this proportion can be varied in the CORE Diabetes Model and PRIME Diabetes Model

The CORE Diabetes Model (CDM) only allows for full cohort (100%) estimation of differences in parameter progressions. Therefore, Sanofi performed a more conservative simulation capping the BMI progression at baseline value (32.16 kg/m^2) for all patients with the outcomes displayed below.

Table 84. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 5 years treatment effect duration and no progression of BMI (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B8	72,126	71,511	615	10.560	10.500	0.060	**10,246**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

For the PRIME model, the results of the requested simulation in question B8 are presented below. This functionality has been added to the PRIME Diabetes Model interface and can be modified by users in the 'COUNTRY' element in the field marked '*Proportion of patients whose BMI is capped at baseline (%)*'.

Table 85. Summary of cost−effectiveness outcomes for sotagliflozin 200 mg versus placebo assuming BMI is capped at baseline levels in 80% of patients (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B8	55,389	53,564	+1825	9.35	9.21	0.144	12,649
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

B9. Priority question: Please provide a scenario where 50% of severe hypoglycaemic events require medical assistance and 50% of severe hypoglycaemic events do not require medical assistance. Do not assume hypoglycaemia not requiring medical assistance is non−severe.

As requested, Sanofi have run this analysis, it was conservatively assumed that the 50% of severe hypoglycaemic events not requiring hospitalisation incurred zero cost and therefore the cost of severe hypoglycaemic events was halved in the model. The result of this simulation is displayed in the Table 86 below. Sanofi notes however, that the study protocol definition of severe hypoglycaemic events, that has been used to inform the economic analysis, states that all severe events do result in hospitalisation.

Table 86. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 5 years treatment effect duration and the assumption of 50% of the severe hypoglycaemia events leading to hospitalisation (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B9	69,865	69,176	689	10.490	10.428	0.061	**11,218**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

For the PRIME Diabetes Model, it was assumed that 50% of severe hypoglycaemic events led to hospitalisation (group 3 in Hammer et al. [2009], Table 5) incurring a cost of GBP 999 and 50% did not require medical assistance (group 1 in Hammer et al., Table 5) and cost GBP 32 (both inflated to 2017 values).[ix]

Table 87. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 5 years treatment effect duration and the assumption of 50% of the severe hypoglycaemia events leading to hospitalisation (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B9	55,630	53,946	+1,685	9.31	9.16	+0.15	11,275
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

B10. Please explain the discrepancies in the diabetic ketoacidosis event rates per patient−year obtained from the inTandem2 trial reported in the company submission:

a) Sotagliflozin 200 mg: 0.05857 and 0.023 in Tables 3.5 and 3.6, respectively

b) Placebo: 0.01264 and 0 in Tables 3.5 and 3.7, respectively

The first set of inputs described in points a) and b) for sotagliflozin and placebo (0.0587 and 0.01264) represent the inTandem2 general population in head to head comparisons. These set of values were also utilised to inform the company original model base-case and sensitivity analyses (multiplied by 100 to fit the correct model input style).

Furthermore, the set of 0.023 and 0 for sotagliflozin and placebo respectively, are network meta-analysis estimates (NMA) obtained pooling sotagliflozin 200 mg arms from our three inTandem trials, and placebo arms from all included trials in our network of evidence. Of note, placebo arms pooled together included placebo arms from metformin trials.

Due to the latest modifications in response to these questions and in order to understand better the previous values, following table compares the previous and new rates of adverse events informing the economic model.

Table 88. Comparison of adverse event rates per 100 patient years in the general inTandem2 vs the A1a specific populations

Adverse event	inTandem2 only (whole population)		A1a Population − Pooled inTandem1 & inTandem2 (BMI≥27kg/m^2)	
	Placebo	Sotagliflozin 200 mg	Placebo	Sotagliflozin 200 mg
Non−Severe Hypoglycaemic events (/100 patient years)	6,715	5,595	6,040	5,280
Severe Hypoglycaemic events (/100 patient years)	8.0	8.0	11.4	8.9
Diabetes Ketoacidosis (/100 patient years)	1.26	5.86	0.4	3.2

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

B11. Clinical experts advised the ERG that the annual progressions in HbA_{1c} and BMI taken from the DCCT are too high, therefore the ERG suggests that the estimates obtained from the University of Sheffield are used to inform the base-case analysis (annual progressions of 0.018% and 0.095 kg/m^2 for HbA_{1c} and BMI, respectively).

Following this recommendation, Sanofi adjusted all new presented scenarios. Furthermore, all physiological trajectories were revised using the same approach and dataset. A slight change is applied to best represent current clinical practice: as patients in the conventional arm received training and intensive insulin therapy in 1993, Sanofi only used data from the DCCT/EDIC intensive insulin to estimate the values (since this arm better represents the current T1D practice). The following underlying trajectories were estimated and utilised in all analyses:

Table 89. New estimated mean yearly background progressions from the EDIC clinical trial

Variable	EDIC year 11 Intensive insulin arm	EDIC year 19−20 Intensive insulin arm	New estimated mean yearly change[1]
	year 2004	*year 2012/13*	
HbA_{1c} (%)	7.9	8	0.012
BMI (kg/m^2)	28.2	29	0.094
SBP (mmHg)	120	121	0.118
DBP (mmHg)	75	70	−0.588
Total cholesterol (mg/dL)	182	177	−0.588
HDL-C (mg/dL)	54	63	1.059
LDL-C (mg/dL)	110	98	−1.412
Triglycerides (mg/dL)	92	82	−1.176

Reference
DCCT/EDIC Research Group. Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30−Year Follow−up. Diabetes Care. 2016 May;39(5):686−93 – Data in Appendix
Notes
[1] Estimated based on 8.5 years of data (2004 to 2012/13)

BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure

Health−related quality of life

B12. Priority question: On page 107 in the company submission it states, "A multiplicative approach was used to estimate QALY in the base−case with an additive approach used as a sensitivity analysis." However, text on page 131 referring to table 4.4 states that 'Both models [PRIME and CORE] used an additive approach to estimate QALY'.

a) **Please clarify which approach was used to estimate QALYs in the base-case**

The CDM model approach in all presented scenarios is the minimum QALY estimation approach. In the following point b, we explain the main difference and justification of the base-case.

b) **The CORE Diabetes Model refers to the CORE default (minimum approach), please clarify if the minimum approach was used to inform the base-case analysis in the CORE Diabetes Model and how this differs from the additive approach**

The choice of the best QALY estimation approach is related to the number of different conditions affecting simultaneously the patient's health-related quality of life. T1D is related to several conditions and comorbidities making the choice of QALY estimation an important consideration in the economic model.

The multiplicative approach treats the disutility related to each event linearly and constantly, but also proportionally to the current utility score of the patient. In the practice, a patient with a lower score will face a smaller disutility than one with a higher one, since the estimation will be based on a weighted multiplication of the event disutility and the current utility value. The additive QALY estimation approach is essentially equivalent, but does not account for the current utility score, resulting in a worse total average score at the end of the time horizon of the study.

The minimum approach acknowledges only the condition that affected the patient's quality of life the most (the worst one), and then makes an aggregate estimate between all simulated patients.

Sanofi chose the minimum QALY estimation approach to avoid a potential overestimation of the health benefits, and to avoid accounting for health events that might have occurred in the past and that would no longer affect the patient's current quality of life due to recovery or

rehabilitation. The minimum approach is also the most conservative approach to utility estimation.

c) Please provide results of the multiplicative approach if the multiplicative approach was not used to inform the base-case analysis

The following analysis was estimated as requested using the multiplicative QALY estimation approach.

Table 90. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 5 years treatment effect duration and the assumption of a multiplicative QALY estimation approach (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B12c	72,126	71,511	615	11.114	11.049	0.066	**9,371**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

For the PRIME Diabetes Model simulations, an additive approach was used to estimate quality−adjusted life expectancy. In any given year of the simulation, each patient is assigned a state utility based on their medical history. For patients with no complications, this would be 0.839. Where a patient has a history of complications, the state utility is evaluated by adding the greatest disutility available from the patient's pre−existing conditions (e.g. for a patient with a history of angina (disutility −0.028) and history of stroke (disutility −0.165), the stroke disutility is greatest and wold be added to state utility (0.839−0.165 = 0.674). For each event occurring in that year of the simulation, then the disutilities for each event that occurs are then added to return the utility score for that year (e.g. 0.674 + MI (−0.065) + non−severe hypo (−0.004) = 0.605).

No simulations were performed using a multiplicative approach to estimate quality−adjusted life expectancy. This functionality is in beta−testing with the PRIME Diabetes Model and has not yet been rigorously tested.

B13. Priority question: Please ensure the approach to estimate utility values from Beaudet et al. 2014 is consistent.

a) **Please clarify how utility inputs for angina, haemodialysis, oedema and post−oedema were estimated from Beaudet et al. 2014.**

When estimating in the economic model a scenario using T2D utility/disutility factors, Sanofi also changed the starting value to represent this population in a narrower way utilising following model inputs and estimations.

Table 91. Estimation of quality estimated inputted in the CORE Diabetes Model from the study of Beaudet et al. 2014

Health State	Reported Utility/Disutility *(Beaudet et al. 2014)*	Final Model Input
T2D without complications	0.785	0.785
Angina	−0.09 *(Ischemic heart disease)*	0.695 (−0.09+0.785)
Haemodialysis	−0.164	0.621 (−0.164+0.785)
Oedema	−0.04 *(moderate macular edema)*	Event based – one off deduction of −0.04
Post−oedema	*Event based – return to previous utility*	*Event based – return to previous utility*

T2D, type 2 diabetes

b) **Please clarify why the utility associated with peritoneal dialysis is estimated from Table 2 (0.581) rather than Table 3 (0.839−0.204=0.635) in Beaudet et al. 2014.**

The disutility related to a peritoneal dialysis is −0.204 as reported by Beaudet et al. 2014. This value can lead to two different utility estimates depending on the context being evaluated as following:

a) In the base-case analysis Sanofi aimed to use as many T1D values as possible, estimating the final utility value of peritoneal dialysis using the baseline T1D value: 0.839 – 0.204 = 0.635.

b) In the context of a sensitivity analysis with T2D values only, the baseline utility score of 0.785 (also reported by Beaudet et al. 2014) returns the different post−event utility estimate of 0.785 – 0.204 = 0.581. This value was applied only in the context of this sensitivity analysis.

B14. Priority question: Please provide the absolute mean, standard deviation and range of EQ−5D index scores collected from all patients in the inTandem2 trial at baseline, Week 24 and Week 52.

EQ−5D was not collected at 24 weeks, EQ−5D at 52 weeks is presented below in Table 92.

Table 92. EQ-5D at Week 52 patients with baseline BMI ≥27 kg/m^2

	Placebo (N=124)	Sotagliflozin 200 mg (N=135)	Sotagliflozin (N=138)
Baseline			
N (%)	122 (98.4)	131 (97.0)	137 (99.3%)
Mean (SD)	0.85 (0.153)	0.84 (0.165)	0.83 (0.171)
Week 52			
N (%)	117 (94.4)	125 (92.6)	134 (97.1%)
Mean (SD)	0.85 (0.146)	0.83 (0.161)	0.83 (0.167)
Change from baseline at Week 52			
LSM (SE)	−0.02 (0.013)	−0.02 (0.012)	−0.01 (0.012)
95% CI for change from baseline	(−0.04, 0.01)	(−0.04, 0.01)	(−0.04, 0.01)
p value	0.2083	0.2042	0.2470
Summary of treatment comparison			
LSM (SE) from placebo		0.00 (0.016)	0.00 (0.016)
95% CI for difference		(−0.03, 0.03)	(−0.03, 0.03)
p value		0.9806	0.8938

CI, confidence interval; LSM, least squares mean; SD, standard deviation; SE, standard error

B15. Priority question: Please clarify if the disutilities for severe hypoglycaemia and diabetic ketoacidosis (−0.002 and −0.009, respectively) from Peasgood et al. 2016 are applied per year or per event in the economic models.

In the CDM the disutilities for severe hypoglycaemia and diabetic ketoacidosis are applied in the model in a "per event" basis.

For the PRIME Diabetes Model These utilities are applied per event in the PRIME Diabetes Model. For each event, the corresponding disutility is accrued by the patient experiencing the event.

B16. In the PRIME Diabetes Model, the per−unit disutility associated with a BMI over 25 kg/m^2 is set to 0. Please correct this input to reflect the value in the company submission (−0.0028)

The assertion here is incorrect. The BMI disutility was applied in all of the simulations run using the PRIME Diabetes Model unless otherwise indicated. It is notable that the BMI utility in the PRIME Diabetes Model is stored in the UTILITIES element (this is in contrast to the CDM where any BMI−related utilities are specific to individual treatment definition), which may have been the source of confusion.

B17. In the CORE Diabetes Model, please clarify if per−unit disutility associated with a BMI over 25 kg/m^2 −0.0038 (the CORE default) or −0.0028 (Peasgood et al. 2016).

a) If necessary, please correct this input to reflect the value in the company submission (−0.0028) and present updated results from the model.

In the base-case Sanofi used the disutility of −0.0028 per BMI unit over 25 kg/m² (Peasgood et al. 2016). The single exception is the scenario where T2 disutilities were utilised, in that case the factor of −0.006 was applied (Beaudet et al 2014).

B18. Please provide a scenario using a disutility of −0.006 for a 1 unit increase in BMI above 25 kg/m^2 (Beaudet et al. 2014)

The following ICER analysis was conducted as requested using a disutility of −0.006 for a 1 unit increase in BMI above 25kg/m². The cost-effectiveness results are outlined in following table.

Table 93. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 5 years treatment effect duration and the assumption of −0.006 decreasd utility per unit of BMI increase (kg/m²) (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B18	72,126	71,511	615	10.019	9.948	0.071	**8,659**
CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

Table 94. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 5 years treatment effect duration and the assumption of −0.006 decreasd utility per unit of BMI increase (kg/m²) (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B18	55,479	53,785	+1,694	9.06	8.90	+0.16	10,790
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year								

B19. Please provide the durations associated with each complication included in Table 3.10 of the company submission.

Within the CDM all events are assumed to occur instantaneously upon cycle start and incur an instant event-based disutility or move to lower utility state (depending on the event). For some events following their occurrence there is a permanent utility impact (post−event states). Given the minimum utility approach undertaken in the model if a patient is in several post−event states (for example they have undergone a cardiac event and an amputation) the state with the lowest utility is assumed to represent the patient (there is no additional long−term utility impact for having undergone two events). The table below describes which events are one−off and have no long-term utility impact and which have a permanent utility impact following the event.

Utilities are primarily sourced from Peasgood et al. 2016, consistent with NG17, which used regression analysis to estimate the utility impact of complications in a UK DAFNE cohort. The study did not report the duration of individual events.

Table 95. Event utilities

Event	Event type
Non−severe Hypoglycaemia Event	One−off event disutility (no long−term utility impact)
Severe Hypoglycaemia Event	One−off event disutility (no long−term utility impact)
Ketoacidosis	One−off event disutility (no long−term utility impact)
Angina	Permanent utility impact (no one−off event disutility)
Congestive Heart Failure	Permanent utility impact (no one−off event disutility)
Peripheral vascular disease	Permanent utility impact (no one−off event disutility)
Haemodialysis	Permanent utility impact (no one−off event disutility)
Peritoneal Dialysis	Permanent utility impact (no one−off event disutility)
Renal transplant	Permanent utility impact (no one−off event disutility)
Neuropathy	Permanent utility impact (no one−off event disutility)
Microalbuminuria	Permanent utility impact (no one−off event disutility)
Gross renal proteinuria	Permanent utility impact (no one−off event disutility)
Background diabetic retinopathy	Permanent utility impact (no one−off event disutility)
BDR wrongly treated	Permanent utility impact (no one−off event disutility)
Proliferative diabetic retinopathy laser treated	Permanent utility impact (no one−off event disutility)
Proliferative diabetic retinopathy no laser	Permanent utility impact (no one−off event disutility)
Macular oedema	Permanent utility impact (no one−off event disutility)
Severe vision loss	Permanent utility impact (no one−off event disutility)
Cataract	Permanent utility impact (no one−off event disutility)
Active ulcer	For duration of active ulcer (see clinical settings ‘Foot ulcer and amputation’) for probabilities associated with ulcer
Healed ulcer	No utility impact
Myocardial Infarction	One−off event disutility followed by permanent utility impact
Stroke	One−off event disutility followed by permanent utility impact
Amputation	One−off event disutility followed by permanent utility impact
Oedema	One−off event disutility followed by permanent utility impact

For the PRIME Diabetes Model, the following table outlines the durations associated with utilities.

Table 96. Summary of utility values for cost−effectiveness analysis

Health state	Mean utility (variance)	Duration of application
T1D with no complications	0.839 (SD 0.231)	Applied as a state utility in each year the patient has no history of complications
Angina, year of onset	−0.028 (SE 0.022)	Applied only in the year of onset
Angina, subsequent years	−0.028 (SE 0.022)	Applied in each year after onset*
Congestive heart failure, year of onset	−0.101 (SE 0.032)	Applied only in the year of onset
Congestive heart failure, subsequent years	−0.101 (SE 0.032)	Applied in each year after onset*
Myocardial infarction, year of onset	−0.065 (SE 0.030)	Applied only in the year of onset
Myocardial infarction, subsequent years	−0.065 (SE 0.030)	Applied in each year after onset*
Stroke, year of onset	−0.165 (SE 0.035)	Applied only in the year of onset
Stroke, subsequent years	−0.165 (SE 0.035)	Applied in each year after onset*
Microvascular complications (not including renal and eye complications)		
Amputation, year of onset	−0.1172 (SE 0.055)	Applied only in the year of onset
Amputation, subsequent years	−0.1172 (SE 0.055)	Applied in each year after onset*
Neuropathy, year of onset	−0.0497 (SE 0.043)	Applied only in the year of onset
Neuropathy, subsequent years	−0.0497 (SE 0.043)	Applied in each year after onset*
Renal complications		
Microalbuminuria, year of onset	0	Applied only in the year of onset
Microalbuminuria, subsequent years	0	Applied in each year the patient has this complication*
Overt nephropathy, year of onset	−0.0277 (SE 0.032)	Applied only in the year of onset
Overt nephropathy, subsequent years	−0.0277 (SE 0.032)	Applied in each year the patient has this complication*
Haemodialysis, year of onset	−0.14 (SE 0.016)	Applied only in the year of onset
Haemodialysis, subsequent years	−0.14 (SE 0.016)	Applied in each year the patient has this complication*
Peritoneal dialysis, year of onset	−0.14 (SE 0.016)	Applied only in the year of onset
Peritoneal dialysis, subsequent years	−0.14 (SE 0.016)	Applied in each year the patient has this complication*
Renal transplant, year of onset	−0.086 (SE 0.016)	Applied only in the year of onset
Renal transplant, subsequent years	−0.086 (SE 0.016)	Applied in each year the patient has this complication*
Eye complications		
Macular edema, year of onset	0	Applied only in the year of onset
Macular edema, subsequent years	0	Applied in each year the patient has this complication*
Mild non−proliferative retinopathy, year of onset	−0.0544 (SE 0.023)	Applied only in the year of onset

Health state	Mean utility (variance)	Duration of application
Mild non−proliferative retinopathy, subsequent years	−0.0544 (SE 0.023)	Applied in each year the patient has this complication*
Moderate non−proliferative retinopathy, year of onset	−0.0544 (SE 0.023)	Applied only in the year of onset
Moderate non−proliferative retinopathy, subsequent years	−0.0544 (SE 0.023)	Applied in each year the patient has this complication*
Severe non−proliferative retinopathy, year of onset	−0.0544 (SE 0.023)	Applied only in the year of onset
Severe non−proliferative retinopathy, subsequent years	−0.0544 (SE 0.023)	Applied in each year the patient has this complication*
Proliferative retinopathy, year of onset	−0.0288 (SE 0.026)	Applied only in the year of onset
Proliferative retinopathy, subsequent years	−0.0288 (SE 0.026)	Applied in each year the patient has this complication*
Severe vision loss, year of onset	−0.208 (SE 0.013)	Applied only in the year of onset
Severe vision loss, subsequent years	−0.208 (SE 0.013)	Applied in each year the patient has this complication*
Adverse events		
Non−severe hypoglycaemia	−0.004 (95%CI 0.001 to 0.006)	Applied for each event that occurs
Severe hypoglycaemia	−0.047 (95%CI 0.033 to 0.062)	Applied for each event that occurs
Ketoacidosis	−0.0119 (SE 0.011)	Applied for each event that occurs
Other		
Each unit of BMI over 25 kg/m^2	−0.0028 (SE 0.002)	Applied in each year of the simulation

* only applied provided there are no greater disutility associated with history of other diabetes−related complications (see response to B12)

BMI, body mass index; SE, standard error; T1D, type 1 diabetes;

B20. Please clarify if the uncertainty around utility estimates has been incorporated into the PSA. If not, please update the PSA to include this uncertainty.

The uncertainty around utility estimates has been incorporated into the PSA. The PSA sampled from utility values based on standard error values reported in Peasgood et al. 2016 study. The standard error values are outlined in economics sheet “SAN−UK−inTandem−BC” in the CDM.

When PSA is implemented in the PRIME Diabetes Model, in addition to sampling from distributions around all baseline cohort characteristics and treatment effects, the model samples from distributions around an additional 397 internal model coefficients and parameters, including beta coefficients, hazard ratios, odds ratios and transition probabilities. No sampling was performed around utilities or costs in the simulations presented (although the model has this functionality).

Resource use

B21. Priority question: Please explain why the cost of managing severe hypoglycaemic events is not informed by NICE CG17 (Hammer et al. 2009).

The cost of managing severe hypoglycaemic events reported in Hammer et al. 2009 were based on 2007 costs. A literature search was conducted to identify more recent sources and the documents for T1D in adults and NG17−diagnosis and management was identified. The severe hypoglycaemia event costs in NG17 were sourced from the NHS reference cost 2015−2016, these costs were updated to 2017 using the NHS reference cost 2017−2018.

Nonetheless, an economic analysis was conducted using severe hypoglycaemia event costs reported in Hammer et al. and the cost−effectiveness results are outlined in response to question B22.

B22. Priority question: Please provide scenarios using Hammer et al. 2009 to inform the cost of managing severe hypoglycaemic events (inflated to 2017 prices) assuming:

a) **All severe hypoglycaemic events require medical assistance (base-case assumption)**

b) **50% of severe hypoglycaemic events require medical assistance (see B8)**

The following two analyses were conducted using the suggested source of information. The original reported value of £849 (direct cost of severe hypoglycaemic events in patients treated in hospital in the UK) was inflated from 2007 to be aligned with the current model estimates (2017/2018), resulting in a final inflated cost of £999. Sanofi furthermore explored as suggested the outcomes in both scenarios of hospitalisation: 100% and 50% proportion.

Table 97. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 5 years treatment effect duration and severe hypoglycaemia costs from Hammer et al. 2009 under the contexts of 100% and 50% of the cohort with the event requiring hospitalisation (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B22 (1hosp)	69,551	68,852	699	10.490	10.428	0.061	**11,386**
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B22(1_2hosp)	68,577	67,846	731	10.490	10.428	0.061	**11,905**

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

For the PRIME Diabetes Model analysis, it was assumed that 50% of severe hypoglycaemic events led to hospitalisation (group 3 in Hammer et al. [2009],Table 5) incurring a cost of GBP 999 and 50% did not require medical assistance (group 1 in Hammer et al., Table 5) and cost GBP 32 (both inflated to 2017 values)

Table 98. ICER outcomes of sotagliflozin 200 mg vs placebo in the A1a population and under the context of 5 years treatment effect duration and severe hypoglycaemia costs from Hammer et al. 2009 under the contexts of 100% and 50% of the cohort with the event requiring hospitalisation (PRIME Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B22 (1hosp)	56,466	54,833	+1,633	9.31	9.16	+0.15	**10,927**
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B22 (1_2hosp)	55,630	53,946	+1,685	9.31	9.16	+0.15	**11,275**

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

B23. Priority question: Please clarify why Diabetes with Hypoglycaemic Disorders (severe hypoglycaemic events) in NHS Reference Costs with CC score 0−2 (KB01F) and CC score 3−4 (KB01E) have not been used to inform the cost of severe hypoglycaemic events.

The severe hypoglycaemic events were assumed to be moderate to highly severe, therefore the cost of severe hypoglycaemic events considered in the base-case analysis was based on NHS Reference Costs with CC score 5−8+ (reflecting severe cases).

B24. Priority question: Please provide scenarios using a weighted average of all CC scores (0 to 8+) associated with Diabetes with Hypoglycaemic Disorders in NHS Reference Costs to inform the cost of managing severe hypoglycaemic events assuming:

a) **All severe hypoglycaemic events require medical assistance (base-case assumption)**

b) **50% of severe hypoglycaemic events require medical assistance (see B8)**

As requested, an analysis of sotagliflozin 200 mg + standard of care (SOC) versus placebo + SOC was conducted using a weighted average cost of severe hypoglycaemia events based on NHS reference costs with CC score 0−8+ and are presented in response to question B24. Weighting was applied dependent on the level of activity observed in the NHS reference costs. The average cost of severe hypoglycaemia event was estimated to be £2,121.02. The cost calculation details are outlined in following table.

Table 99. Estimation of the weighted cost of severe hypoglycaemia from the NHS reference costs

	Non-elective long stay	
Secondary Uses Service Healthcare Resource Group (SUS HRG)	**Activity (finished consultant episodes)**	**Unit cost**
Diabetes with Hypoglycaemic Disorders, with CC Score 0−2 (KB01F)	303	£1,179
Diabetes with Hypoglycaemic Disorders, with CC Score 3−4 (KB01E)	913	£1,425
Diabetes with Hypoglycaemic Disorders, with CC Score 5−7 (KB01D)	1,984	£1,820
Diabetes with Hypoglycaemic Disorders, with CC Score 8+ (KB01C)	3,487	£2,556
Weighted average cost	**£2,121.02**	

The following analyses were estimated using this new suggested source, and for the scenarios of 100% and 50% severe hypoglycaemia hospitalisation.

Table 100. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 5 years treatment effect duration and NHS scores 0−8+ as source cost for severe hypoglycaemia under the context of 100% and 50% of the patients with the event requiring hospitalisation (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality−adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B24 (1hosp)	71,738	71,110	627	10.490	10.428	0.061	**10,219**
Sotagliflozin 200 mg vs placebo	S200vsPla−NICE−B24 (1_2hosp)	69,671	68,976	695	10.490	10.428	0.061	**11,322**

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

B25. Priority question: In the CORE Diabetes Model − 'Treatment Cost Group' - 'SAN-UK-inTandem2/NMA' there are 43 'DCCT Conventional' treatments and one 'SAN-UK-iT2-TxS200-HighKetone' treatment.

a) **Please add comments to each of the 43 'DCCT Conventional' treatments so the user can distinguish between them**

b) **Please clarify what the costs associated with each of the 43 'DCCT Conventional' treatments and 'SAN-UK-iT2-TxS200-HighKetone' treatment include and their sources**

c) **Please clarify why ''DCCT Conventional' does not appear as a treatment in the 'Treatment Cost Group' 'SAN-UK-inTandem2-HighKetone'**

There was a glitch in the CDM group assignment which meant that the treatment assignment names in the CDM were not visible to NICE, this has been rectified for these responses. The treatment sheet names and costs for all previously submitted analyses are outlined in Table 101.

Table 101. Treatment sheet names and costs in the CORE Diabetes Model

Treatment	C treatment year 1	C treatment years 2+
SAN-UK-iT2-TxS200-BC	2192.23	2192.23
SAN-UK-iT2-TxPla-BC	1694.91	1694.91
SAN-UK-NICE&iT2-R1S200-BC	1694.91	1694.91
SAN-UK-NICE&iT2-RPla-BC	1694.91	1694.91
SAN-UK-iT2-R1S200-BC	1694.91	1694.91
SAN-UK-iT2-RPla-BC	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-TxS200-BC	2192.23	2192.23
SAN-UK-iT2-A1c>6.5-TxPla-BC	1694.91	1694.91
SAN-UK-NICE&iT2-A1c>6.5-R1S200-BC	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-R1S200-BC	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-BMI-TxS200-BC	2192.23	2192.23
SAN-UK-iT2-A1c>6.5.BMI-RPla-BC	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-BMI-TxPla-BC	1694.91	1694.91
SAN-UK-NICE&iT2-A1c>6.5-BMI-R1S200-BC	1694.91	1694.91
SAN-UK-NICE&iT2-A1c>6.5-BMI-RPla-BC	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-BMI-R1S200-BC	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-BMI-RPla-BC	1694.91	1694.91
SAN-UK-iT2-A1c>8.5-TxS200-BC	2192.23	2192.23
SAN-UK-iT2-A1c>8.5-TxPla-BC	1694.91	1694.91
SAN-UK-NICE&iT2-A1c>8.5-R1S200-BC	1694.91	1694.91
SAN-UK-NICE&iT2-A1c>8.5-RPla-BC	1694.91	1694.91
SAN-UK-iT2-TxS200-SA-2yTx	2192.23	2192.23
SAN-UK-NICE&iT2-R1S200-SA-2yTx	1694.91	1694.91
SAN-UK-iT2-A1c>6.5-RPla-BC	1694.91	1694.91
SAN-UK-NICE&iT2-A1c>6.5-RPla-BC	1694.91	1694.91
SAN-UK-iT2-TxPla-SA-HbA1c/BMInewprog	1694.91	1694.91
SAN-UK-iT2-TxS200-SA-HbA1c/BMInewprog	2192.23	2192.23
SAN-UK-NMA/BC-TxS200-BC	2192.23	2192.23
SAN-UK-NMA/BC-TxPlaS200-BC	1694.91	1694.91
SAN-UK-NICE&NMA/BC-R1S200-BC	1694.91	1694.91
SAN-UK-NICE&NMA/BC-RPla-BC	1694.91	1694.91
SAN-UK-iT2&NMA/BC-R1S200-BC	1694.91	1694.91
SAN-UK-It2&NMA/BC-RPla-BC	1694.91	1694.91
SAN-UK-NMA/BC-R1S200-BC	1694.91	1694.91
SAN-UK-NMA/BC-TxMet-S200-BC	1732.48	1732.48
SAN-UK-NMA/BC-R1Met-S200-BC	1694.91	1694.91
SAN-UK-NMA/BC-TxS200-SA-2yTx	2192.23	2192.23
SAN-UK-NMA/BC-TxMet-S200-SA-2yrTx	1732.48	1732.48
SAN-UK-NMA/BC-TxS200-SA-2yrTx	2192.23	2192.23
SAN-UK-NMA-TxMet-SA-HbA1c/BMInewprog	1732.48	1732.48
SAN-UK-NMA-TxS200-SA-HbA1c/BMInewprog	2192.23	2192.23
SAN-UK-iT2/BC-R1S200-BC	1694.91	1694.91
SAN-UK-NMA/BC-R1S200-2yr-SA	1694.91	1694.91

B26. Please clarify why treatment-specific (healthcare professional) monitoring costs have not been included in the economic analysis.

The current monitoring items considered in the analysis (ketone monitoring and self-glucose) were assumed to be undertaken by the patient following the normal practice. Even though a regular medical follow-up of the patient can be considered, its incremental value would equally affect all interventional arms.

B27. In the company submission it states, "The mean doses, as shown in Table 3.11, were conservatively assumed to be constant over time, despite the 52-week outcomes showing an insulin dose-sparing effect favouring sotagliflozin. The doses were also assumed to be equivalent across all subgroups (explored in the sensitivity analyses)". Please provide the results of the sensitivity analyses.

The 52 weeks outcomes of inTandem1 and inTandem2 indeed showed an insulin dose sparing in the sotagliflozin arm that would unequivocally lower the treatment costs of sotagliflozin. Sanofi performed the suggested simulation leaving this beneficial effect (52 weeks) during the same duration of the treatment effects (this analysis assumes a 10% insulin sparing effect).

Table 102. ICER outcomes of Sotagliflozin 200 mg vs Placebo in the A1a population and under the context of 5 years treatment effect duration and the assumption of the insulin dose adjustment seen after the 52 weeks clinical trial outcomes (CDM Analysis)

Comparison	CDM name	Lifetime combined costs (GBP)			Quality-adjusted life years (QALYs)			ICER (GBP)
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Sotagliflozin 200 mg vs placebo	S200vsPla-NICE-B27	71,988	71,511	477	10.490	10.428	0.061	**7,772**

CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

B28. Please clarify if the uncertainty around costs estimates (such as those from NHS reference costs) has been incorporated into the PSA. If not, please update the PSA to include this uncertainty.

The PSA does consider uncertainty around costs estimates. The model is set to vary the initial cost input around a user-defined percent variation. The current model default was set to variate costs around ±20% of the original cost input for the PSA. This is specified in economics sheet "SAN-UK-inTandem-BC" under "SAMPLING FOR PROBABILISTIC SENSITIVITY ANALYSIS" in the CORE Diabetes Model.

Section C: Textual clarification and additional points

C1. In the CORE Diabetes Model 'My Simulations', please clarify which 'Simulation name' corresponds to each analysis reported in Table 4.1 of the company submission.

Sanofi would like to apologise, there was an oversight and the 'Simulation name' corresponding to each analysis reported in Table 4.1 was not provided by our modelling team. This will be available shortly and we will submit as soon available. We have attached a Table 103 displaying the "simulation" and description of the simulation for all the analysis presented in these clarification questions.

Table 103. Simulation name" and analysis report name for the new simulations

Comparison	Sheet	Lifetime combined costs (GBP)			Quality-adjusted life years (QALYs)			ICER
		Intervention	Comparator	Incremental	Intervention	Comparator	Incremental	(Delta costs/Delta QALY)
Tx effects 5 years and treatment costs 5 years	S200vsPla-NICE-B2	72,126	71,511	615	10.490	10.428	0.061	10,012
BMI cap at baseline (100% of the cohort)	S200vsPla-NICE-B8	72,126	71,511	615	10.560	10.500	0.060	10,246
S200 **vs** Pla	S200vsPla-NICE-B4 (2yrs)	72,301	71,512	790	10.459	10.428	0.031	25,638
S200 **vs** Pla	S200vsPla-NICE-B4(5yrs)	72,750	71,512	1,238	10.475	10.428	0.047	26,463
Prop sever hypo who require hospitalisation only 50%	S200vsPla-NICE-B9	69,865	69,176	689	10.490	10.428	0.061	11,218
Insuline doses adjusted after year 1 (Trial results) and until Tx discontinuation at year 5	S200vsPla-NICE-B27	71,988	71,511	477	10.490	10.428	0.061	7,772
QALY estimation method to be changed to Multiplicative Approach	S200vsPla-NICE-B12c	72,126	71,511	615	11.114	11.049	0.066	9,371
BMI disutility -0,006 per unit (Beaudet et al. 2014)	S200vsPla-NICE-B18	72,126	71,511	615	10.019	9.948	0.071	8,659
Cost of sev hypo Hammer et al. 2009 (NICE CG17) and prop hospitalisation 100%	S200vsPla-NICE-B22 (1hosp)	69,551	68,852	699	10.490	10.428	0.061	11,386
Cost of sev hypo Hammer et al. 2009 (NICE CG17) and prop hospitalisation 50%	S200vsPla-NICE-B22(1_2hosp)	68,577	67,846	731	10.490	10.428	0.061	11,905
Cost of sev hypo NHC reference costs with CC scores 0 to 8 and prop hospitalisation 100%	S200vsPla-NICE-B24 (1hosp)	71,738	71,110	627	10.490	10.428	0.061	10,219
Cost of sev hypo NHC reference costs with CC scores 0 to 8 and prop hospitalisation 50%	S200vsPla-NICE-B24(1_2hosp)	69,671	68,976	695	10.490	10.428	0.061	11,322
Sotagliflozin 200 mg cost was increased by 10%	S200vsPla-NICE-Sota+10%	72,300	71,511	789	10.490	10.428	0.061	12,843

C2. Please confirm that the subheading for the latter half of Table 2.9 should read, "Analysis of net benefit at Week 52, n (%)", rather than Week 24.

Yes, Sanofi would like to apologise for this typological error and would like to clarify that this should read **"Analysis of net benefit at Week 52, n (%)"**

C3. In the company submission it states, "The types of adverse events included in the analysis were based on those that were between Grade 3 and 5". Please clarify how adverse event Grades relate to severity of adverse events reported in Section 2.11 of the company submission (or provide the relevant clinical study report table numbers).

Following the AE grading scale, as reported by the Common Terminology Criteria for Adverse Events, Sanofi excluded mild or asymptomatic (Grade 1) events, as well as moderate events where a non-invasive intervention was required (Grade 2). Following this criteria, the full list of AE considered severe (Grade 3), life-threatening (Grade 4) and death related (Grade 5) was examined, with additional focus on those where a statistical significant difference between intervention and control arm was seen. As seen in following table, only metabolism and nutrition disorders (comprising DKA, Hypoglycaemia and Ketosis) were taken in account.

Table 104 Summary of Treatment-Emergent Serious Adverse Events (52 weeks) – inTandem2

Event	Placebo		Sotagliflozin 200 mg	
	N=	258	N=	261
	n	%	n	%
Cardiac Disorders	1	0,4%	2	0,8%
Endocrine disorders	0	0,0%	0	0,0%
Eye disorders	2	0,8%	1	0,4%
Gastrointestinal disorders	0	0,0%	2	0,8%
General disorders and administration site conditions	0	0,0%	2	0,8%
Hepatobiliary disorders	0	0,0%	1	0,4%
Infections and infestations	2	0,8%	7	2,7%
Injury, poisoning and procedural complications	2	0,8%	1	0,4%
Metabolism and nutrition disorders	1	0,4%	9	3,4%
Musculoskeletal and connective tissue disorders	2	0,8%	0	0,0%
Neoplasm benign, malignant and unspecified	2	0,8%	3	1,1%
Nervous system disorders	7	2,7%	3	1,1%
Pregnancy, puerperium and perinatal conditions	1	0,4%	0	0,0%
Renal and urinary disorders	0	0,0%	0	0,0%
Reproductive system and breast disorders	0	0,0%	1	0,4%
Skin and subcutaneous tissue disorders	1	0,4%	1	0,4%
Reference: inTandem2 Clinical Study Report P249				

For model inputs we have employed the adverse events from the pooled analysis of inTandem1 and inTandem2 (ES 1) which are presented below in Table 105.

Table 105. Model inputs for adverse events

Variable	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Non-severe documented symptomatic hypoglycaemia (plasma glucose ≤ 70 mg/dL [3.9 mmol/L]) (core + long-term extension)			
Number of events	16447	14599	14912
Even rate per 100 patient years	6040	5280	5088
Severe hypoglycaemia (core + long-term extension)			
Number of events	31	25	18
Even rate per 100 patient years	11.4	8.9	6.1
DKA during the overall (core + long-term extension)			
Number of events	1	9	11
Even rate per 100 patient years	0.4	3.2	3.8

C4. Please explain the assumptions underlying the sensitivity analysis, "T2D disutilities Beaudet et al. 2014" in Table 4.1 of the company submission.

The recent article published by Peasgood et al. in 2016 allow a more accurate estimation of health-related quality of life in patients with T1D using an EQ5D elicitation method. Articles publishing values for T2D are however more numerous, and the systematic literature review and final list of suggested values by Beaudet and collaborators in 2014 has been widely referenced in both T2D and T1D models.

C5. Please provide the independent analysis undertaken by the University of Sheffield that aimed to reproduce some of the default values in the CORE Diabetes Model derived from the DCCT/EDIC trials. This analysis is not referenced in the company submission.

Please see confidential reference folder provided

C6. Please update the UK Office for National Statistics life tables to the 2015-2017 data.

Sanofi has updated for all new presented simulations the mortality table to reflect this more up to date dataset from the UK Office for National Statistics.

C7. Please provide reference 85: Wilson PW, Castelli WP, Kannel WB. Coronary risk prediction in adults (the Framingham Heart Study). Am J Cardiol. 1987;59(14):91g-4g.

Please find this reference enclosed.

C8. Please clarify which resources (or related links) in the National Diabetes Audit - 2012-2013. Report 2: Care Processes and Treatment Targets (reference 76) have been used to inform the data in Table 3.3 of the company submission.

In the context of representing a T1D baseline cohort specific to the UK population, Sanofi utilised the baseline characteristics described by the clinical guideline for Type 1 Diabetes in adults (National Clinical Guideline Centre 2014). The document presents a total of ten baseline characteristics sourced from the National Diabetes Audit 2012-2013 as described in following table.

Please note that despite the existence of the 2017-18 updated report from the National Diabetes Audit, the description of such characteristics is no longer available in the report.

Table 106. Sourced values from the 2012/13 National Diabetes Audit (as reported by the Type 1 diabetes: diagnosis and management of type 1 diabetes in adults Clinical guideline)

Variable	Mean (SD)
Duration of diabetes	16.92 (13.31)
Proportion male	56.7%
HbA_{1c} (%)	8.6 (4)
Systolic blood pressure	128.27 (16.07)
Body mass index (kg/m^2)	27.09 (5.77)
Proportion smoker (%)	22%
Proportion White	92%
Proportion Black	3%
Proportion Asian	5%
Proportion albuminuria	18.1%
Reference: National Clinical Guideline Centre. Type 1 diabetes: diagnosis and management of type 1 diabetes in adults Clinical guideline. 2014 https://www.nice.org.uk/guidance/NG17/documents/type-1-diabetes-update-appendices-h-u2	

C9. Please clarify if the findings from the National Diabetes Audit - 2013-13 represent the most up-to-date data available to inform Table 3.3 of the company submission.

In the context of representing a T1DM baseline cohort narrow to the UK population, Sanofi utilised the baseline characteristics described by the clinical guideline for type 1 Diabetes in adults (National Clinical Guideline Centre 2014). The document presents a total of ten baseline characteristics sourced from the National Diabetes Audit 2012-2013. Despite the existence of the 2017-18 updated report from the National Diabetes Audit, the description of such characteristics is no longer available in the report. Sanofi can confirm that this does represent the most up to date data available.

Supporting documents

Confidential documents

1) Results inTandem1, BMI ≥27 (CIC_A_inTandem1_BMI 27 - All results.doc)
2) Results inTandem2, BMI ≥27 (CIC_B_inTandem2_BMI 27 - All results)
3) Results inTandem3, BMI ≥27 (CIC_C_inTandem3_BMI 27 - All results)
4) Results pooled inTandem1 and inTandem2, BMI ≥27 (CIC_D_Pooled_BMI27 iT1_iT2-All results)
5) Results pooled inTandem1, inTandem2 and inTandem3, BMI ≥27 (CIC_E_PoolediT1_iT2_iT3- All results) Table
6) Appendix A – Concomitant medications (CIC_F_Appendix A_concomicant meds.doc)
7) Appendix B – Progression graphs (CIC_G_Appendix B_progression graphs.doc)
8) Appendix C _ ScHARR critique (CIC_H_Appendix C_ ScHARR Critique of economic evidence)
9) Appendix D _CIC_I_BMI Forest Plots (CIC_I_Appendix D BMI Forest plots)
10) Appendix E_Response to CHMP (CIC_J_Appendix E Response to CHMP)

References

Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462-70.

Hammer M, Lammert M, Mejias SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. Journal of Medical Economics. 2009; 12(4):281-290

---

[i] Lung TW, Petrie D, Herman WH, Palmer AJ, Svensson AM, Eliasson B, Clarke PM. Severe hypoglycemia and mortality after cardiovascular events for type 1 diabetic patients in Sweden. Diabetes Care. 2014;37(11):2974-81.

[ii] Bottle A, Millett C, Khunti K, Majeed A. Trends in cardiovascular admissions and procedures for people with and without diabetes in England, 1996-2005. Diabetologia. 2009;52(1):74-80.

[iii] 2016 USRDS Annual Data Report Volume 2 – ESRD in the United States. Available at: https://www.usrds.org/2016/download/v2_c06_Mortality_16.pdf. Accessed on January 12, 2017

[iv] The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes. 1997;46(2):271–86.

[v] Wright J, Ruck K, Rabbitts R, et al. Diabetic ketoacidosis (DKA) in Birmingham, UK, 2000-2009: an evaluation of risk factors for recurrence and mortality. Br J Diabetes Vasc Dis. 2009;9:278-82.. B

[vi] Valentine WJ, Pollock RF, Saunders R, Bae J, Norrbacka K, Boye K. The Prime Diabetes Model: Novel Methods for Estimating Long-Term Clinical and Cost Outcomes in Type 1 Diabetes Mellitus. Value Health. 2017; 20(7): 985-991

[vii] Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology. 2008;115(11):1859-68.

[viii] Valentine WJ, Pollock RF, Saunders R, Bae J, Norrbacka K, Boye K. The Prime Diabetes Model: Novel Methods for Estimating Long-Term Clinical and Cost Outcomes in Type 1 Diabetes Mellitus. Value Health. 2017; 20(7): 985-991

[ix] Hammer M, Lammert M, Mejías SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. J Med Econ. 2009; 12(4): 281-90

NICE National Institute for Health and Care Excellence

Patient organisation submission

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	JDRF, the type 1 diabetes charity
3. Job title or position	Senior Policy and Public Affairs Officer
4a. Brief description of the organisation (including who funds it). How many members does it have?	JDRF is a medical research charity committed to eradicating type 1 diabetes and its effects for everyone in the UK with type 1, and at risk of developing it.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Internal teams at JDRF who work regularly with people with type 1 diabetes and the research papers referenced below.
Living with the condition	
6. What is it like to live with the condition? What do carers	Type 1 diabetes is a day by day, hour by hour challenge, and the management of the condition can be demanding, impacting on quality of life. People living with the condition can find the constant risks and

experience when caring for someone with the condition?	requirements of dosage adjustment to have a considerable psycho-social impact on wellbeing.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Whilst care in many areas is good, there is much frustration at the postcode lottery of NHS treatments for diabetes care. This is particularly the case around access to medical devices to optimise self-management of type 1 diabetes.
8. Is there an unmet need for patients with this condition?	Yes. There is no other therapy for type 1 diabetes other than insulin, however it is extremely difficult to achieve consistently in-range glucose levels, the most recent National Diabetes Audit shows that only 30% of people with type 1 diabetes achieve their target HbA1c[i]. Therefore SGLT-1 and SGLT-2 inhibitors could help some people with type 1 diabetes if they are able to manage the risks, and their healthcare teams are able to support them to do so.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	It is our view that this drug can offer a significant and substantial impact on health-related benefits. Reducing hypoglycaemia and improving HbA1c are priorities for patients with type 1 diabetes. Of the top ten type 1 diabetes treatment uncertainties in the James Lind Alliance report from May 2011[ii], three patient defined priorities focused on management of blood glucose levels to avoid hypoglycaemia, reducing long term adverse effects and managing fluctuations in blood glucose levels. Three recent trials showed Sotagliflozin when used with insulin can reduce hypoglycaemia and can lower HbA1c levels. The three recent trials are Tandem1[iii], Tandem2[iv] and Tandem3[v].

	Sotagliflozin can reduce hypoglycaemia: - inTandem1: severe hypos occurred in 17 (6.5%) participants from each of the 200mg and 400mg groups, and 26 (9.7%) participants who received placebo. - inTandem2: severe hypos occurred in 13 (5%) participants of each the placebo and 200mg groups, and 6 (2.3%) participants of the 400mg group. - InTandem3: rate of documented hypoglycaemia under 3.1 mmol/l or below was lower in the sotagliflozin group than the placebo group. Sotagliflozin can reduce HbA1c levels: - inTandem1: from a baseline HbA1c average of 7.57 %, there were 0.36% and 0.41%-point reductions after 24 weeks for the 200mg and 400mg doses respectively compared with placebo. At 52 weeks, there were 0.25% (200mg) and 0.31% (400mg) point reductions from baseline for 200mg and 400mg respectively, compared with placebo. - inTandem2: from baseline HbA1c average 7.8%, there were 0.37% and 0.35%-point reductions after 24 weeks for the 200mg and 400mg groups respectively compared with placebo. At 52 weeks, there were 0.21% and 0.32%-point reductions from baseline for 200mg and 400mg respectively, compared with placebo. - inTandem1: among people with a baseline HbA1c of 7% or over, an HbA1c of under 7% was achieved by 18.4%, 27.7% and 35.43% of people receiving placebo, 200mg or 400mg respectively, at 52 weeks. - inTandem2: among people with a baseline HbA1c of 7% or over, an HbA1c of under 7% was achieved by 8.8%, 20.2% and 21.6% of people receiving placebo, 200mg or 400mg respectively, at 52 weeks. - inTandem3: More people achieved an HbA1c of under 7% by 24 weeks in the 400mg sotagliflozin group (29.6%) than in placebo (15.8%) - inTandem3: 28.6% (200/699) of people in the 400mg group achieved an HbA1c of under 7% in 24 weeks without severe hypos or DKA, compared with 15.2% (107/703) in the placebo group.

	- inTandem2: 15%, 31% and 32% of people from the placebo, 200mg and 400mg groups respectively reached an HbA1c of under 7% without severe hypos or DKA by 24 weeks. Findings from the Diabetes Control and Complications Trial (DCCT) showed that reduction of HbA1c can lead to fewer long term complications in those with type 1 diabetes[vi], thus ultimately saving the NHS money.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The three Tandem studies found the following increased risks, of which the highest concern to people with type 1 diabetes will be the increased risk of DKA: Sotagliflozin increases risk of DKA: - inTandem1: 1 (0.4%), 9 (3.4%) and 11 (4.2%) participants experienced DKA for the placebo, 200mg and 400mg groups respectively. - inTandem2: 0 DKA in placebo, 6 (2.3%) participants of 200mg and 9 participants (3.4%) of 400mg - inTandem3: More DKA in 400mg group (21 people, 3%) than in placebo (4 people, 0.6%) Sotagliflozin increases genital fungal (i.e. yeast) infections: - inTandem1: 9 (3.4%), 24 (9.1%) and 34 (13%) of participants from the placebo, 200mg and 400mg groups respectively experienced genital fungal infections. - inTandem2: 6 (2.3%), 24 (9.2%) and 29 (11%) of participants from the placebo, 200mg and 400mg groups respectively experienced genital fungal infections. - inTandem3: 45 (6.4%) affected people in the sotagliflozin 400mg group, compared with 15 (2.1%) in the placebo group. Sotagliflozin increases cases of diarrhoea:

	- inTandem 1: 18 (6.7%), 22 (8.4%) and 27 (10.3%) of participants from the placebo, 200mg and 400mg groups respectively experienced diarrhoea. - inTandem2: 9 (3.5%), 12 (4.6%) and 19 (7.2%) of people from the placebo, 200mg and 400mg groups respectively experienced diarrhoea. - inTandem3: diarrhoea in 29 people (4.1%) in the sotagliflozin 400mg group and 16 (2.3%) in the placebo group. Different people with type 1 diabetes will have differing views on the risk of infection and diarrhoea, but the primary concern will be on the increased risk of DKA.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	A study found that SGLT inihibitor adjunct therapy was not recommended for patients with HbA1c >75mmol/mol (9%) and history of DKA.[vii] Therefore, people more at risk of diabetic ketoacidosis (typically women and those on insulin pumps) might benefit less from this treatment.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	There is no other therapy for type 1 diabetes other than insulin, however it is extremely difficult to achieve consistently in-range glucose levels, therefore dual SGLT-1 and SGLT-2 inhibitors cold help some people with type 1 diabetes if they are able to manage the risks, and their healthcare teams are able to support them to do so. Patients would need to be aware of the risk and symptoms of diabetic ketoacidosis (DKA), particularly as this class of drug can mask the initial symptoms, such as more frequent urination.
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • There is no other therapy for type 1 diabetes other than insulin, however it is extremely difficult to achieve consistently in-range glucose levels, therefore SGLT-1 and SGLT-2 inhibitors could help some people with type 1 diabetes. • Better management of HbA1c, and more time in range can lead to less long term complications in those with type 1 diabetes,	

ultimately saving the NHS money.

- There is an increased risk of diabetic ketoacidosis, genital fungal infections and diarrhoea with this treatment.
- People more at risk of diabetic ketoacidosis might benefit less from this treatment.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

X **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

[i] National Diabetes Audit, 2016-17 Report 1: Care Processes and Treatment Targets, March 2018: https://files.digital.nhs.uk/pdf/s/k/national_diabetes_audit_2016-17_report_1__care_processes_and_treatment_targets.pdf

[ii] James Lind Alliance, (2011) Setting priorities for type 1 diabetes research – workshop http://www.jla.nihr.ac.uk/priority-setting-partnerships/diabetes-type-1/downloads/Diabetes-Type-1-PSP-workshop-report.pdf

[iii] Buse et al. (2018) Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1. Diabetes Care 41(9): 1970-1980.

[iv] Danne et al. (2018) HbA1c and hypoglycaemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. Diabetes Care 41(9): 1981-1990.

[v] Garg et al. (2017) Effects of sotagliflozin added to insulin in patients with type 1 diabetes. New England Journal of Medicine 377(24): 2337-2348.

[vi] Diabetes controls and complications trial (DCCT) (1993) https://clinicaltrials.gov/ct2/show/NCT00360815?term=Diabetes+control+and+complications+trial&rank=1

[vii] McCrimmon and Henry (2018) SGLT inhibitor adjunct therapy in type 1 diabetes, August 2018: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6133151/

NICE National Institute for Health and Care Excellence

Professional organisation submission

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Association of British Clinical Diabetologists**

3. Job title or position	**Secretary** Consultant diabetologist
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Clinical Diabetologists is the national organisation of Consultant Physicians in Britain who specialise in Diabetes Mellitus. Most are also Acute General Physicians, and many are also Specialists in Endocrinology and Lipid Metabolism. ABCD was established in 1997 with the principal objective of ensuring high quality care for all UK diabetes patients ABCD is essentially a professional organisation committed to the preservation and support of diabetes specialist care services ABCD believes that local diabetes specialists are uniquely qualified to provide guidance and leadership for district diabetes services ABCD membership was initially open only to UK consultant diabetologists but was later extended to include specialist registrars. **Aims and Objectives** • To ensure the highest quality of care for diabetic patients both in hospitals and in primary care. • To promote awareness of and interest in diabetes mellitus and diabetes care both locally and nationally. • To provide a resource of information about diabetes care for purchasers and others. • To provide high quality training in diabetes care for Specialist Registrars training for a CCST in Diabetes and Endocrinology and other medical staff involved in the care of diabetic patients. • To encourage clinical research in diabetes mellitus in hospital clinics and jointly with primary care diabetes clinics.

	• To support diabetologists dealing with management issues as they apply to the provision of diabetes services.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Improve glycaemic control in patients with type 1 diabetes and decrease risk of micro and macrovascular complications
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Fall in HbA1c (>0.3%) towards individually set goal without additional incidence of hypoglycaemia, any movement nearer to optimal body mass index, improved quality of life

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Lack of patient education and lack of healthcare professional education around management of type 1 diabetes in general and specifically around potential additional risk of hypoglycaemia, dehydration, de escalation of insulin therapy, risk of diabetic ketoacidosis and interaction with other therapies for complications of type 1 diabetes eg renal impairment and cardiac failure
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Structured pt education and insulin either as injection or via an insulin pump
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes https://www.nice.org.uk/guidance/NG17
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	ABCD advocate that a person with type 1 diabetes should be under the shared care of Primary Care and a Diabetes Specialist team should the person wish to be.
• What impact would the technology have on the	It would have an augmentative role to insulin, offering the potential of getting HbA1c to target and de-

current pathway of care?	escalating insulin requirements
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	No – currently only used in type 2 diabetes
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Only under diabetes specialist team support initially, as ongoing emerging evidence around SGL2 inhibitors precipitating diabetic ketoacidosis in type 2 diabetes and evidence free zone in type 1 diabetes.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Education of patients and diabetes specialist teams
11. Do you expect the technology to provide clinically meaningful benefits compared	Yes – potential decreaseHbA1c towards individually set goal, movement nearer to optimal body mass index, improved quality of life, de escalation of insulin therapy but not without risk as documented above

with current care?	
• Do you expect the technology to increase length of life more than current care?	DCCT trial offers evidence that better glycaemic control decreases risk of complications
• Do you expect the technology to increase health-related quality of life more than current care?	Insulin can cause weight gain, with the BMI of the population in general going up, so to, it is the type 1 population, so the option to use sotagliflozin has the potential to off set weight gain
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More likely to benefit:Type 1 with raised BMI and / or on large doses of insulin, those with incipient heart failure or treated heart failure where diuretics could potentially be down titrated. Higher risk pts: those with chronic renal disease, heart failure, frequent DKA
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	Neither easier or more difficult, just different and potential need for additional blood testing at start of therapy and checking of renal function. Patient may need additional input from specialist team around insulin titration, sick day rule

care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Would advocate cessation of therapy if no benefit after 6 months
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year	Evidence for another SGL2 inhibitor (empagloflozin) demonstrates improvement in triglyceride profile with potentially can positively influence diabetic complications. However at this time, this cannot be extrapolated to sotagliflozin

(QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
• Is the technology a 'step-change' in the management of the condition?	No – its augmentative
• Does the use of the technology address any particular unmet need of the patient population?	Potential to help with weight loss
17. How do any side effects or adverse effects of the technology affect the management of the condition	Increased risk of acute kidney injury, hypoglycaemia, diabetic ketoacidosis, exacerbation of chronic kidney disease, destabilization of congestive cardiac failure

and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials are not the same as "real life" practise – monitoring and support is more intensive
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Clinically significant fall in HbA1c
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	emerging evidence around SGL2 inhibitors precipitating diabetic ketoacidosis in type 2 diabetes and evidence free zone in type 1 diabetes

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	Evidence for another SGL2 inhibitor (empagloflozin) demonstrates improvement in triglyceride profile with potentially can positively influence diabetic complications. However at this time, this cannot be extrapolated to sotagliflozin
21. How do data on real-world experience compare with the trial data?	
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	no

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- SGL2 inhibitors in general have the potential to augment insulin treatment in patients with type 1 diabetes
- Use is not without risk, so needs to be support by a diabetes specialist team
- there is evidence that a comparator SGL2 inhibitor has a more beneficial lipid profile
- improved glycaemic control without increased risk of hypoglycaemia should decrease risk of diabetes related complications in the long term
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Professional organisation submission

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**United Kingdom Clinical Pharmacy Association (UKCPA)** Diabetes & Endocrinology Group

3. Job title or position	**Diabetes Specialist Pharmacist**
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The vision of the UKCPA is to maintain and enhance the pharmacy professional reputation in all areas of the organisation. The organisation strives for its members to be recognised as experts in the use of medicines by colleagues in medical, nursing and allied health professional disciplines. The UKCPA also supports its members to be in a position to work with and influence national strategies for the treatment of acute and long term health conditions. The Diabetes & Endocrinology committee consists of expert pharmacists in the clinical area who have been collectively contributed to the development of national diabetes guidance and strategic work to continue to improve and maintain high quality diabetes care across the NHS. The organisation is supported by the industry and its members to deliver its services and education events.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of	Treatment is aimed at using insulin regimens to achieve as optimal a level of blood-glucose control as is feasible, while avoiding or reducing the frequency of hypoglycaemic episodes, in order to minimise the risk

treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	of long-term microvascular and macrovascular complications. Diabetic complications can often be prevented or delayed by active management of the disease. The target for glycaemic control should be individualised for each patient, taking into account factors such as daily activities, aspirations, likelihood of complications, adherence to treatment, comorbidities, occupation and history of hypoglycaemia. A target HbA1c concentration of 48 mmol/mol (6.5%) or lower is recommended in patients with type 1 diabetes. The ideal treatment for type 1 diabetes should enable patients to maintain a glycated haemoglobin level lower than 53mmol/mol (7.0%) without weight gain or an increased risk of hypoglycaemia and diabetic ketoacidosis (DKA).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Successful treatment response include reduction in: HbA1c levels towards individualised target (5-10mmol/mol HbA1c reduction), episodes of hypoglycaemia, symptoms of hyperglycaemia, risk of developing macrovascular and microvascular complications. Minimising weight gain and increasing quality of life (such as anxiety from fear of hypoglycaemia) are also considered to be beneficial treatment responses.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	In most patients with type 1 diabetes, adequate glycaemic control is not achieved with insulin therapy alone. Weight gain and hypoglycaemic events are common barriers to achieving optimised glycaemic targets. Nationally, a significant proportion of people with type 1 diabetes are not meeting the NICE three treatment targets (HbA1c, blood pressure, and serum cholesterol), which can lead to increased risk of developing diabetic complications.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Insulin therapy is the mainstay treatment for people with type 1 diabetes. Patients who have a BMI of 25 kg/m2 or above (23 kg/m2 or above for patients of South Asian or related ethnicity) who exhibit insulin resistance or wish to improve their blood-glucose control while minimising their effective insulin dose, may benefit from metformin hydrochloride [unlicensed indication] as an addition to insulin therapy (NICE NG17)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE NG17 Type 1 diabetes in adults: diagnosis and management SIGN guideline 154 Pharmacological management of glycaemic control in people with type 2 diabetes Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In most parts of the country, the care pathway is well defined. People diagnosed with type 1 diabetes are referred to and should have access to and/or be under the management of the diabetes specialist team. Patients with type 1 diabetes should be offered carbohydrate-counting training as part of a structured education programme. No difference regarding ideal treatment (i.e. insulin) although which insulin and target aims vary.
• What impact would the technology have on the current pathway of care?	It will potentially benefit people with type 1 diabetes whose glycaemic control is suboptimised on insulin therapy despite efforts have been taken to improve diabetes control including optimising insulin treatment regimens, lifestyle modification, and medication adherence, and avoidance of hypoglycaemia. It will also benefit those who are experiencing significant weight gain with insulin therapy with which weight loss or avoidance of weight gain will benefit weight-related co-morbidities.
10. Will the technology be used (or is it already used) in the same way as current care	Yes – secondary care initiated as part of a specialist team.

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Increased spend on additional oral medication (sotagliflozin). Currently only insulin is prescribed. Monitoring (ketone testing) also essential and increases cost.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It will be used in secondary care/specialist type 1 diabetes clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training for specialists managing this patient group to ensure that the patient benefits and risks of this technology are fully understood. Investment in ketone testing.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, see question 9 above (What impact would the technology have on the current pathway of care?)
• Do you expect the technology to increase length of life more than	The use of SGLT2 inhibitors (empagliflozin and canagliflozin) in type 2 diabetes has demonstrated superiority as an adjunct to standard care in reducing cardiovascular mortality. No cardiovascular outcomes trials have yet been conducted for the SGLT2 inhibitors on people with type 1 diabetes on insulin therapy.

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	It is expected this treatment will increase health-related quality of life, based on trial evidence has demonstrated reduction in body weight and postprandial glucose excursions. Treatment has also shown to reduce insulin doses, which could lead to reduced risk of hypoglycaemia. (See 'Source of evidence' section below)
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Those with type 1 diabetes who are overweight or obese would benefit with the weight loss or reduced weight gain in conjunction with insulin therapy. Less effective – those at increased risk of DKA.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	Closer monitoring of blood pressure is required in those who concurrently taking anti-hypertensive and diuretic treatments to avoid hypotension and dehydration, particularly for elderly patients. Initiation of treatment in moderate and severe renal impairment is currently contraindicated with SGLT2 inhibitors in type 2 diabetes. Patients with type 1 diabetes are at a higher risk of developing DKA. In inTandem3 trial, the rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% [21 patients] and 0.6% [4 patients], respectively). Patients and HCPs must be aware of the risk of DKA associated with the use of an SGLT2 inhibitor. Patients must receive counselling on recognising signs and symptoms of DKA and when

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	to seek medical attention, and on the sick day guidance with taking an SGLT2 inhibitor. Ketone monitoring is essential.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment with an SGLT2 inhibitor should be stopped if DKA associated with its use occurs or is suspected. It is recommended for patients with HbA1c less than 8.5% (less than 69 mmol/mol) to reduce their daily insulin dose by 20%, with special caution to avoid insulin withdrawal to minimise the risk of euglycaemic diabetic ketoacidosis. (Ref: Gomez-Peralta F. et al. Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes. *Diabetes Ther*. 2017 Oct; 8(5): 953–962.)
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a	Sotagliflozin is an oral inhibitor of sodium–glucose cotransporters 1 and 2. With the additional mechanism of action on reducing intestinal glucose absorption due to SGLT1 inhibition, sotagliflozin differentiates from SGLT2 inhibitors by reducing postprandial glucose excursion and insulin secretion, as well as by increasing

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	GLP-1 secretion. Sotagliflozin is as effective as SGLT2 inhibitors on HbA1C reduction, with a similar safety profile in short-term studies. Sotagliflozin was first assessed in type 2 diabetes, it has been assessed in as an adjuvant treatment in patients with type 1 diabetes in a phase 1 (inTandem1), phase 2 (inTandem2), and phase 3 trial (inTandem3). In inTandem3[1], a significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved the primary end point of a HbA1c level lower than 7.0% at week 24, with no episodes of severe hypoglycemia or diabetic ketoacidosis after randomization. (200 of 699 patients [28.6%] vs. 107 of 703 [15.2%], P<0.001). The mean change from baseline was significantly greater in the sotagliflozin group than in the placebo group for HbA1c (difference, −0.46 percentage points), weight (−2.98 kg), systolic blood pressure (−3.5 mm Hg), and mean daily bolus dose of insulin (−2.8 units per day) (P≤0.002 for all comparisons). The rate of severe hypoglycemia was similar in the sotagliflozin group and the placebo group (3.0% [21 patients] and 2.4% [17], respectively). The rate of documented hypoglycemia with a blood glucose level of 55 mg per deciliter (3.1 mmol per liter) or below was significantly lower in the sotagliflozin group than in the placebo group. 1. Garg S.K., et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. *N Engl J Med* 2017; 377:2337-2348
• Is the technology a 'step-change' in the management of the condition?	Yes, the use of sotagliflozin as an adjunct to insulin therapy introduces a novel therapeutic adjunct in the treatment of type 1 diabetes. First licensed adjunctive therapy in T1DM.

• Does the use of the technology address any particular unmet need of the patient population?	Yes, it addresses two of the three NICE treatment targets (HbA1c and blood pressure), reduction in rates of hypoglycaemia and body weight.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	inTandem3 - The rate of one or more positively adjudicated episodes of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group overall (3.0% vs. 0.6%), as well as among those who used an insulin pump (4.4% vs. 0.7%) and those who did not use an insulin pump (2.1% vs. 0.5%).The trial regimen was discontinued due to an adjudicated diabetic ketoacidosis event in 11 patients (1.6%) in the sotagliflozin group and in 1 (0.1%) in the placebo group. inTandem1 - There were also more episodes of diabetic ketoacidosis with sotagliflozin 200 mg (3.4%) and 400 mg (4.2%) compared with placebo (0.4%). Other recognised side effects of SGLT2 inhibitors include genitourinary infections, Fournier's gangrene, lower limb amputations (Canagliflozin).
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, inTandem3 is a double-blind trial, which was conducted at 133 centers worldwide. It randomly assigned 1402 patients with type 1 diabetes who were receiving treatment with any insulin therapy (pump or injections) to receive sotagliflozin (400 mg per day) or placebo for 24 weeks. Men and nonpregnant women 18 years of age or older who had had type 1 diabetes for at least 1 year were eligible for participation in the trial if they met the following inclusion criteria: treatment with insulin at a stable basal

	dose for at least 2 weeks before the screening visit, a glycated hemoglobin level of 7.0 to 11.0%, and a body-mass index of at least 18.5. inTandem1 - double-blind, 52-week North American trial, 793 adults with type 1 diabetes who were being treated with multiple daily insulin injections (40%) or an insulin pump (60%) were randomized to placebo (n = 268), sotagliflozin 200 mg (n=263), or sotagliflozin 400 mg (n=262) once daily. Prior to randomisation, participants underwent a 6-week insulin optimization phase. Patients were not excluded from the trial if their HbA1c dropped by > 0.5% or to > 7.5% during the optimization phase, which differentiated this trial from several others investigating similar agents. At week 52, patients taking sotagliflozin had significantly reduced HbA1c, weight, bolus insulin, fasting plasma glucose, and patient distress, compared to placebo. For weight loss, the least squares mean difference, compared to placebo, was -3.14 kg ± 0.34; P< .001 for the 200 mg dose and -4.32 kg ± 0.35; P< .001, for the 400 mg dose. Among patients with systolic blood pressure > 130 mm Hg at baseline, blood pressure also dropped significantly at 24 and 52 weeks. inTandem2 - double-blind, 52-week European study, 782 adults with Type 1 diabetes treated with multiple daily insulin injections or pump therapy were randomized 1:1:1 to placebo (n=258), sotagliflozin (SOTA) 200 mg (n=261) or SOTA 400 mg (n=263) once daily after 6 weeks of insulin optimisation.
• If not, how could the results be extrapolated to the UK setting?	n/a
• What, in your view, are the most important	Reduction in HbA1c, body weight, rate of hypoglycaemia, all of which were measured in the inTandem3

outcomes, and were they measured in the trials?	trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	HbA1c level is the standard marker for monitoring of long term glycaemic control. The reduction in HbA1c has been associated with reduction in risk of developing diabetic complications such as myocardial infarction, stroke, cardiovascular mortality, peripheral vascular disease, nephropathy, and retinopathy.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	Following comments received in the draft scope consultation NICE decided to split the Multiple Technology Appraisal (MTA) of three drugs Dapagliflozin, empagliflozin and sotagliflozin for treating type 1 diabetes [ID1217], into three separate Single Technology Appraisals (STAs). The STAs are: [ID1478] – dapagliflozin (https://www.nice.org.uk/guidance/indevelopment/gid-ta10374) [ID1376] – sotagliflozin (https://www.nice.org.uk/guidance/indevelopment/gid-ta10376) [ID1275] – empagliflozin

	(https://www.nice.org.uk/guidance/indevelopment/gid-ta10375). The efficacy and safety of canagliflozin has been assessed as add-on to insulin in adults with type 1 diabetes in a phase 2 study. Canagliflozin provided reductions in HbA1c, body weight, and insulin dose with no increase in hypoglycemia, but increased rates of ketone-related AEs, including DKA, in adults with type 1 diabetes inadequately controlled with insulin. Henry R.R., et al. Efficacy and Safety of Canagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, as Add-On to Insulin in Patients With Type 1 Diabetes. *Diabetes Care* 2015; dc151730.
21. How do data on real-world experience compare with the trial data?	No real world data yet
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Yes, the number of patients of black, asian and minority ethnic groups included in these trials is small. The majority of patients studied in these trials were overweight, with an average BMI of 28 kg/m^2. Hence, the trial results may not be applicable to people who are underweight or obese.
22b. Consider whether these issues are different from issues	No, these issues are not different, it is standard in diabetes trials.

with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- The SGLT2 inhibitors have demonstrated efficacy and safety in the treatment of type 2 diabetes.
- Canagliflozin and Sotagliflozin have both demonstrated efficacy in reducing HbA1c and body weight as an adjunct to insulin in patients with type 1 diabetes.
- Canagliflozin and Sotagliflozin as an add-on to insulin in patient with type 1 diabetes have shown an increase in ketone-related adverse events including DKA.
- Sotagliflozin as an adjunct to insulin in patients with type 1 diabetes has demonstrated reduction in blood pressure, insulin dose, and rates of hypoglycaemia.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Professor Melanie J Davies

Name of your organisation
University Hospitals of Leicester NHS Trust and University Of Leicester

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Sotagliflozin is the first dual inhibitor of SGLT1 and SGLT2. It is an oral medication which reduced renal glucose reabsorption but also delays glucose absorption in the proximal intestine through local SGLT1 inhibition. SGLT2 inhibitors are licensed and have been used routinely in the management of Type 2 Diabetes. Dapagliflozin is a selective SGLT2 inhibitor which recently received authorisation by the EMA to be used as an adjunct treatment to insulin in patients with Type 1 Diabetes Mellitus and Dapagliflozin, a selective SGLT2 inhibitor has also has been appraised by NICE with a recommendation that it can used in Type 1 patients with diabetes. Sotagliflozin has also been authorized in the EU by the EMA to be used with insulin to treat patients with Type 1 Diabetes but in patients with a BMI of at least 27.

The theoretical benefits of a dual inhibitor of SGLT1 and SGLT2 is that the SGLT1 action in the gut may blunt and reduce post prandial hyperglycaemia. There is also a theoretical mitigation of DKA risk by reducing glucose absorption in the proximal intestine and thereby reducing urine glucose excretion and association water and electrolyte loss. Also by increasing glucagon like peptide secretion from the gut thereby reducing glucagon and preserving basal insulin requirement.

References:

Sands AT et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. Diabetes Care 2015;38:1181-1188

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Zambrowicz B et al. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycaemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. Clin Pharmacol Ther 2012;92:158-169

Meek TH et al. Evidence that in uncontrolled diabetes, hyperglucagonemia is required for ketosis but not for increased heptic glucose production or hyperglycaemia. Diabetes 2015;64:2376-2387

Garg M et al. Liraglutide acutely suppresses glucagon, lipolysis and ketogenesis in type 1 diabetes. Diabetes Obes Metab 2017; 19:1306-1311

Bonner C et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells rigers glucagon secretion. Nat Med 2015;21:512-517

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

There continues to be an unmet need in type 1 diabetes with some patients unable to reach A1c targets with continuing issues of glycaemic variability and some patients also have increased cardiovascular risk factors including being overweight or obese and hypertension. There is a place for adjunct therapy to insulin in some patients with type 1 diabetes and there have been a series of programmes with either selective SGLT2 inhibitors (Dapagliflozin in the DEPICT programme and Empagliflozin in the EASE programme) which have demonstrated some benefits in

improved glycaemic control and a weight advantage. So for example in DEPICT1 there was approximately a 0.4% A1c advantage, approximately 3 kg weight advantage, improved glycaemic variability, as assessed by the mean amplitude of glucose excursion. Similar benefits have been demonstrated in the InTANDEM trials with sotagliflozin which have been conducted in the US and Europe. In InTANDEM 1 for which I was a co-investigator and presented the results at the American Diabetes Association, there was a 0.46% advantage in A1c reduction, a 3kg weight advantage, a reduction in systolic blood pressure of 3.5mm/Hg. There was no increase in hypoglycaemia and in fact a reduction in the rate of hypoglycaemia with glucose levels less 3.1mmol. In all studies however there has been noted to be an increase in the rate of diabetic ketoacidosis and in the InTANDEM 3 study this was increased 5 fold with a rate of 3% in the placebo group and 0.6% in the group treated with sotagliflozin. A further meta-analysis of sotagliflozin of the 6 RCTs which included over 3000 patients showed there was a reduction in A1c of 0.34, reduction in fasting glucose, around a 9% reduction in the total daily insulin dose, CGMS showed increased time in range, reduced body weight of approximately 3.4%, reduction in systolic blood pressure and a reduction in the albumin to creatinine ratio. There was reduced hypoglycaemic events however the relative risk of keto acidosis was increased (3.9) and as is known with this class of drugs there was an increase in genital infections. In this study the initial A1c and basal insulin dose adjustment were the factors associated with the increased risk of DKA. To put this in context, the risk of sotagliflozin of ketoacidosis was 18/1000 and genitourinary infection was 73/1000[(1)]. Overall the programme of phase 3 programmes of selective SGLT2s and sotagliflozin have been conducted in reasonably generalizable population. The InTANDEM programme, InTANDEM 1 and 2 were conducted in the USA and Europe. InTANDEM 3 was a global and more pragmatic trial, UK sites were involved. Of course in any clinical trials patients whilst broadly representative of the patient groups will not completely reflect challenges in the wider population. The main question regarding sotagliflozin and indeed the selective SGLT2 inhibitors is mitigating the increased risk of DKA. DKA is known to be a risk in type 1 diabetes. In the type 1 exchange registry in the US, prevalence is around 5% in adults aged between 18 – 25 but in less than 2% of older patients. DKA rates are known to be higher with a higher A1c at baseline particularly above 9% and in around 2.3% of pump users and 4.3% of those using MDI. It's been consistently shown in the phase 3 programmes that DKA rates tend to be higher with adjunct therapy with selective SGLT2 and sotagliflozin in those using insulin pumps. It should also be noted that whilst clinical trials often present the ideal patient scenario the risk for mitigating DKA in DEPICT, EASE and the InTANDEM programmes were not necessarily ideal and although patients were issued with keto meters there was no real defined protocol for managing sickness and reducing the risk of DKA. There have now been a number of publications for example[(2-4)]

These broadly have similar principles ie the importance of patient selection including over the age of 18, being able to adherent to their prescribed insulin regime, able to perform glucose monitoring and willing and able to perform ketone testing, of received education and training, have access to ketone testing materials, low or moderate use of alcohol, no use of illicit drugs and access to a trained clinician. The importance of initiation of dosing in SGLT2s, are starting with a lower dose, access to ketone monitoring, stopping SGLT2s in the event of sickness with the administration of bolus insulin, consuming carbohydrates and hydrating. Consensus would suggest

with appropriate selection and support of patients and implementation of DKA mitigation strategies that there is a benefit to patients with the availability of sotagliflozin and other selective SGLT2 especially in clinics managing type 1 diabetes.

References:

1 Musso et al. Efficacy and safety of dual SGLT1/2 inhibitor sotagliflozin in type 1 diabetes: meta-analysis of randomised controlled trials. BMJ 2019;365:l1328.

2 Danne et al. International Consensus on Risk Management of Diabetic ketoacidosis in Patients with Type 1 Diabetes Treated With Sodium Glucose Cotransporter (SGLT) Inhibitors. Diabetes Care 2019;42:1147-1154

3 Goldenberg et al. Sodium-glucose co-transporter inhibitors, their role in type 1 diabetes treatment and a risk of mitigation strategy for preventing diabetic ketoacidosis: The STOP DKA Protocol. Diab Obes Metab June 10;1-11

4 Garg S et al. Strategy for Mitigating DKA Risk in Patients with Type 1 Diabetes on Adjunctive Treatment with SGLT Inhibitors: A STICH Protocol. Diabetes Technol Ther. 2018 Sep;20(9):571-575

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As previously pointed out in the section of the advantage and disadvantages, the implementation issues relate to the appropriate selection of patients and both the training and support of the specialist team using this technology but also ensuring that adequate mitigation strategies for DKA are implemented and audited. These have been outlined in the previous section.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376]

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 127657

BMJ Technology Assessment Group

Title: Sotagliflozin, in combination with insulin, for treating type 1 diabetes

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

Authors: Steven J Edwards, Director of Health Technology Assessment, BMJ-TAG, London

Kayleigh Kew, Senior Health Technology Assessment Analyst, BMJ-TAG, London

Peter Cain, Senior Health Economist, BMJ-TAG, London

Victoria Wakefield, Principle Health Technology Assessment Analyst, BMJ-TAG, London

Gemma Marceniuk, Associate Health Economist, BMJ-TAG, London

Correspondence to: Steve Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JR.

Date completed: 26/04/2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 127657

Declared competing interests of the authors:
Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Acknowledgements:
The ERG would like to thank Dr Paul O'Hare (Reader in Medicine, Warwick Medical School and Honorary Consultant in Diabetes, University Hospital of Coventry and Warwickshire), and Professor Andrew Collier (Consultant Physician and Honorary Associate Clinical Professor, University Hospital, Ayr) for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Kew KM, Cain P, Wakefield V, Marceniuk G. Sotagliflozin, in combination with insulin, for treating type 1 diabetes: A Single Technology Appraisal. BMJ Technology Assessment Group, 2019.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Kayleigh Kew	Lead for the critical appraisal of the company's submission, systematic literature review and clinical evidence; drafting the clinical summary, critique of the decision problem, clinical effectiveness results, and clinical conclusions of the report.
Victoria Wakefield	Support in the critical appraisal of the company's submission and clinical evidence; drafting the background; and reviewing and revising the clinical sections of the report.
Peter Cain	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

TABLE OF CONTENTS

LIST OF BOXES

LIST OF TABLES

LIST OF FIGURES

TABLE OF ABBREVIATIONS

Abbreviation	In full
AE	Adverse event
BMI	Body Mass Index
CC	Complications and comorbidities score
CDM	Core Diabetes Model
CGM	Continuous glucose monitoring
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CPRD	Clinical Practice Research Datalink
CRD-HTA	Centre for Review and Dissemination Health Technology Assessment Database
CS	Company's submission
CSII	Continuous subcutaneous insulin infusion
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVD	Cardiovascular disease
DAFNE	Dose Adjustment for Normal Eating education programme
DCCT	Diabetes Control and Complications Trial
DEXA	Dual-energy X-ray absorptiometry
DBP	Diastolic blood pressure
DDS2	Diabetes Distress Screening Scale (2 items)
DKA	Diabetic ketoacidosis
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EDIC	Epidemiology of Diabetes Interventions and Complications follow-up study
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D	EuroQol 5-dimensions
ERG	Evidence Review Group
EOSI	Events of special interest
FPG	Fasting plasma glucose
HbA_{1c}	Glycated haemoglobin
HDL-C	High-density lipoprotein
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LDL-C	Low-density lipoprotein
LPD	Longitudinal Patient Database
MCID	Minimal clinically important difference
MDI	Multiple daily injections
MI	Myocardial infarction
NDA	National Diabetes Audit
NICE	National Institute for Health and Care Excellence
NHS EED	National Health Services Economic Evaluation Database
NMA	Network meta-analysis
PSA	Probabilistic sensitivity analysis

PSSRU	Personal Social Service Research Unit
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
SAE	Serious adverse event
SBP	Systolic blood pressure
ScHARR	School of Health and Related Research, University of Sheffield
SD	Standard deviation
SE	Standard error
SGLT	Sodium-glucose co-transporter
SH	Severe hypoglycaemia
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary tract infection
VAS	Visual analogue scale

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of sotagliflozin (Zynquista®; Sanofi) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of sotagliflozin, in combination with insulin, in the treatment of type 1 diabetes (T1D). The ERG considered the company's description of the underlying health condition and overview of current service provision appropriate and relevant to the decision problem.

Sotagliflozin received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for a European marking authorisation for adults with T1D and Body Mass Index (BMI) ≥ 27 kg/m^2 who are on insulin therapy that does not adequately control blood glucose levels. The proposed marketing authorisation was confirmed after the scope was finalised and is narrower than the population defined in the NICE final scope, because the CHMP asked the company to identify a subgroup of patients for whom the benefits of sotagliflozin would outweigh the increased risk of diabetic ketoacidosis (DKA). The company provided an updated submission to align the population with the expected marketing authorisation once the CHMP positive opinion was adopted.

The Evidence Review Group (ERG) considers evidence submitted by the company broadly in line with the decision problem outlined by NICE but highlights discrepancies between the trial populations and patients who are likely to be eligible for sotagliflozin should it be approved for use in the NHS. The population of key trials had lower glycated haemoglobin (HbA_{1c}) and more often used continuous subcutaneous insulin infusion (CSII) pumps than patients in the UK. The ERG's clinical experts expect that eligibility will be more selective in clinical practice than in the trials to maximise benefits and minimise the risk of rare but serious adverse events.

Sotagliflozin has been studied at 200 mg and 400 mg and the CHMP positive opinion is not limited by dose, but the company state that the 400 mg tablet will not be available at launch in the UK. Furthermore, the 400 mg dose was not delivered in line with the draft summary of product characteristics (SmPC) in the trials, which recommends a starting dose of 200 mg a day, which can be increased to 400 mg after at least three months if additional glycaemic control is needed. [redacted], but the ERG notes that escalation to 400 mg will be possible by prescribing two 200 mg tablets which would double the acquisition cost before the 400 mg tablet is available. The draft SmPC states that sotagliflozin will likely not be recommended for patients aged over 75 years, those with estimated glomerular filtration rate (eGFR) ≤ 45 mL/min/1.73 m^2 or those at high risk of DKA (for which assessment and monitoring criteria are outlined), which is in line with the key trials underpinning the submission.

Insulin alone was treated as the primary comparator, which the ERG's clinical experts consider appropriate. Metformin in addition to insulin was also listed as a comparator in the NICE final scope, but it is rarely used in the UK in combination with insulin for patients with T1D, is not licensed for that indication, and showed little benefit in the recent REMOVAL trial.

Outcomes from key trials were in line with those outlined in the NICE final scope, except for some complications of diabetes, which were not reported as effects of special interests in the trials (e.g. damage to the nerves and eyes).

1.2 Summary of clinical effectiveness evidence submitted by the company

The company's primary clinical evidence is based on pooled data from the twin inTandem1 (North America) and inTandem2 (Europe and Israel) trials, which were designed to evaluate the efficacy and safety of sotagliflozin at two doses (200 mg and 400 mg daily) versus placebo as adjunct treatment to optimised insulin. Patients were eligible for inclusion if they were ≥18 years old, diagnosed with T1D for at least a year, and were taking insulin or an insulin analogue via CSII pump or multiple daily injections (MDI). The primary outcome was change in HbA_{1c} (%) after 24 weeks and the trials also included a long-term extension to 52 weeks.

A third phase III randomised controlled trial (RCT) of sotagliflozin for patients with T1D (inTandem3) more closely reflects UK clinical practice regarding baseline HbA_{1c} because it did not optimise insulin rigorously prior to initiation of treatment; however, it was not included in the primary pooled analyses because it did not study the 200 mg dose or follow patients beyond 24 weeks.

The company's primary population for clinical effectiveness and safety was a pooled population of patients with BMI ≥ 27 kg/m^2 from inTandem1 and inTandem2 (n = 916; hereafter referred to as the primary population) to align the trials with the likely marketing authorisation for sotagliflozin. The ERG explored differences in results across the range of analyses submitted (e.g. individual trials, intention to treat [ITT] population, pooled results including inTandem3 and/or phase II trials).

Within the primary population, sotagliflozin 200 mg led to greater improvements in HbA_{1c} (%) from week 0 to 52 weeks versus insulin alone (difference in least squares mean change –0.24% 95% confidence interval [CI]: –0.35 to –0.13), and there was a larger benefit of the 400 mg dose (–0.38%; 95% CI: –0.49 to –0.27). Improvement in HbA_{1c} was larger in the inTandem3 trial (400 mg at 24 weeks only) that did not optimise insulin prior to treatment initiation, and so the relative treatment effect of sotagliflozin may be underestimated to some extent by the twin trials. The effect of sotagliflozin 200 mg and 400 mg on HbA_{1c} was statistically significant compared with insulin alone across all but one subgroup at 24 and 52 weeks (eGFR < 60 mL/min/1.73 m^2).

Within the primary population, sotagliflozin also led to clinically significant reductions in BMI and body weight compared with insulin alone. The difference versus insulin alone in BMI change from baseline to week 52 was –1.05 kg/m^2 for sotagliflozin 200 mg (95% CI: –1.29 to –0.81) and –1.53 kg/m^2 (CI: –1.77 to –1.29) for sotagliflozin 400 mg; differences versus insulin alone for body weight were –3.01 kg for 200 mg (95% CI: –3.71 to –2.31) and –4.46 kg for 400 mg (CI: –5.15 to –3.76).

There was not a consistent pattern of benefit for either dose of sotagliflozin at either timepoint for the primary population across measures of cardiovascular risk (systolic blood pressure [SBP], diastolic blood pressure [DBP], total cholesterol, high- and low-density lipoprotein [HDL-C and LDL-C], triglycerides). Where statistically significant benefits over insulin alone were noted, they were mostly small and unlikely to be clinically meaningful (e.g. SBP benefits of –2.5 mmHg and –3.6 mmHg at 24 and 52 weeks and DBP benefit of –1.46 mmHg at 52 weeks for sotagliflozin 400 mg). The benefits of sotagliflozin were most consistent across dose and timepoint for HDL and triglycerides.

Within the primary population, sotagliflozin led to modest but statistically significant reductions in bolus insulin dose over insulin alone of –2.02 IU/day (95% CI –3.92 to –0.12) for sotagliflozin 200 mg and –4.05 IU/day (95% CI –5.93 to –2.17) for sotagliflozin 400 mg, which was maintained at 52 weeks for sotagliflozin 400 mg. Small statistically significant benefits were also noted in basal insulin dose for both doses of sotagliflozin compared with insulin alone at 24 weeks, which were maintained or improved at 52 weeks.

Both doses of sotagliflozin led to statistically significant improvements within the primary population on the 2-item Diabetes Distress Screening Scale (DDS2) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at 24 weeks compared with insulin alone, but there was very little change over time on the EQ-5D.

Most patients in the primary population had at least one episode of non-severe hypoglycaemia (91.5–93.3%) and rates of severe hypoglycaemia (SH) were 4.3%, 4.2% and 8.1% for sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone, respectively. The ERG's clinical experts noted that rates of SH in the trials are higher than expected in UK clinical practice, and the lower rates of SH with sotagliflozin compared with insulin alone (which were not statistically significant) likely reflect changes in insulin dose during the trials because sotagliflozin works independently of insulin.

In the primary population, approximately three quarters of each group experienced at least one treatment-emergent adverse event (TEAE). The rate of severe treatment-related TEAEs and TEAEs leading to study drug discontinuation was less than 5% in all groups, although rates of treatment-emergent serious adverse events (SAEs) were somewhat higher in the sotagliflozin groups (~9–10%)

than for insulin alone (~7.0%). Three patients experienced TEAEs leading to death during inTandem1 and inTandem2, which were all in the placebo group.

Within the primary population, 2.6%, 3.5% and 0.3% of patients receiving sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone had at least one episode of DKA during 52 weeks of treatment, none of which were fatal. DKA occurred more frequently in patients using CSII pumps so might be lower in the UK because CSII use is lower than in the trials. The ERG's clinical experts expressed that they would not consider those with CSII pumps, poorly controlled diabetes, high alcohol intake, or low BMI eligible for treatment with sotagliflozin due to their elevated risk of DKA.

More patients on either dose of sotagliflozin had genital infections than those on insulin alone, particularly females (21.6%, 17.6% and 6.3% for sotagliflozin 200 mg, 400 mg, and insulin alone, respectively), differences in rates of diarrhoea were not statistically significant (8.6%, 5.2% and 6.7%), and rates of UTIs were similar between groups (4.4–6.6%). Volume depletion was rare in all groups but occurred more frequently in patients treated with sotagliflozin 200 mg (2.5%) and sotagliflozin 400 mg (1.6%) than insulin alone (0.6%). Low rates of diabetes-related complications were reported across the trials in all groups (<1%), but eye and nerve complications (specified in the NICE final scope) were not included in the list of events of special interest for the inTandem trial programme.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Evidence submitted by the company is broadly in line with the decision problem outlined by NICE, but the population of key trials had lower HbA_{1c} and more often used CSII pumps than patients in the UK. After the CHMP issued a positive opinion for sotagliflozin, the company aligned the population with the expected marketing authorisation for sotagliflozin (patients with BMI ≥ 27 kg/m^2);

The primary analyses focused on head-to-head evidence for sotagliflozin versus insulin alone, but a secondary analysis was provided to compare sotagliflozin with metformin. On the advice of clinical experts, the ERG agrees with the company that metformin is not a relevant comparator, and the ERG considers the NMA flawed due to important clinical differences between trials. Dapagliflozin (SGLT-2) would be a relevant comparator but it is currently in the NICE technology appraisal process (ID1478) and final guidance is not expected until August 2019.

The ERG's clinical experts outlined a target population in whom they expect the risk benefit profile of sotagliflozin to be most favourable, which is narrower than the population of the inTandem1 and inTandem2 trials: BMI > 30, eGFR >60, insulin via MDI, HbA_{1c} > 8.5%, high cardiovascular risk, carbohydrate intake > 80 mg/day and willing to monitor blood glucose and urine ketones. Clinical

data are not available for the clinical experts' target population; this was not possible because it resulted in too few patients in each group for robust analysis of outcomes.

The primary population with BMI ≥ 27 kg/m^2 used for the clinical analyses comprises approximately 58% of the randomised population of the inTandem1 and inTandem2 trials; statistical power to detect a difference in the primary outcome is maintained when the two trials are pooled but randomisation is broken because BMI was not a stratification factor.

In the primary population, more patients used CSII pumps (46%) and had better controlled HbA_{1c} (mean 7.6%) than in UK clinical practice (~15% and 8.8%, respectively), which affects the applicability of both efficacy and safety outcomes. The trials optimised insulin therapy from 6 weeks before baseline, which would not occur in practice, resulting in HbA_{1c} < 7% for 17.1–19.5% of patients at the start of treatment.

Subgroup analyses on the ITT population for change in HbA_{1c} show a somewhat smaller effect of sotagliflozin versus insulin alone in the subgroup of patients using MDI compared with CSII at 52 weeks, and a larger effect for the 200 mg dose in patients with HbA_{1c} >8.5% compared with ≤8.5% at 24 and 52 weeks. Confidence intervals were overlapping across subgroups, but the potential overestimate of benefit caused by higher CSII use in the trials may be mitigated by patients in the UK having higher HbA_{1c} than patients in the trials; furthermore, forest plots submitted by the company for other outcomes showed high correlation between 52-week effects for HbA_{1c}, BMI, SBP, SH and DKA at different HbA_{1c} cut-offs (7%, 8.5% and 9%) within the BMI subpopulation.

The trials do not provide evidence for the durability of initial treatment effects and were not designed to determine cardiovascular benefits of sotagliflozin in T1D. Improvements in HbA_{1c}, BMI and body weight were all consistently statistically significant for both doses, but showed different patterns over time; the effect of sotagliflozin appears to wane over time for HbA1c, net benefit and eGFR, and stabilise or increase over time for BMI, body weight, and some measures of cardiovascular risk. There was inconsistency in absolute and relative treatment effects for various outcomes depending on the timepoint (24 or 52 weeks) and the study(ies) used for analysis, including HbA_{1c}, basal and bolus insulin dose, HRQoL and SH.

Patients who received sotagliflozin 400 mg in the trials did not escalate from 200 mg after at least three months when additional glycaemic control was needed, as recommended in the draft SmPC, so assumptions were made for the economic model. The 400 mg dose appears to have larger or more sustained benefits for some outcomes (e.g. HbA_{1c}, bolus insulin dose) and the ERG considers it unreasonable to assume sotagliflozin 200 mg and sotagliflozin 400 mg have the same adverse effect profile. However, there is uncertainty about the criteria by which patients will be deemed suitable for

dose escalation, and whether the 400 mg dose will be given as two 200 mg tablets until the 400 mg tablet is available, which would double the acquisition cost.

The ERG's clinical experts expressed concern regarding the lack of clear guidance for treatment discontinuation when, "the patient is no longer receiving benefit" and dose escalation, "if additional glycaemic control is needed". The absence of clear guidance could lead to dose escalation in a larger proportion of patients than the company propose in their submission, and indefinite continuation of treatment where HbA_{1c} has returned to the baseline level but the longer-term weight and cardiovascular benefits are unknown.

1.4 Summary of cost effectiveness evidence submitted by the company

The company submitted an economic analysis based on a web-based modelling platform – the CORE Diabetes Model (CDM) – to assess the cost-effectiveness of sotagliflozin in combination with insulin, compared to insulin alone, in patients with T1D. The model is complex and takes into account the risk of multiple long-term complications of T1D depending on various physiological parameters such as HbA_{1c}, BMI and lipids. These parameters are influenced by treatment for the first year – based on data from the inTandem trials – after which time assumptions are made about the duration of treatment effects, and alternative data sources are used to estimate the progression of these parameters beyond those assumptions.

After clarification questions the company made a number of changes to their preferred base case relating to the progression of physiological parameters. These were initially informed by the Framingham risk equations within the CDM for lipids, but the company updated these to linear progressions based on annual rates observed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study – an observational follow-up to the DCCT trial. For HbA1c and BMI the company updated the applied progressions based on EDIC data rather than DCCT data in their original submission.

The risks of cardiovascular (CV) complications were informed largely by the United Kingdom Prospective Diabetes Study 68 (UKPDS 68) – a study based on type 2 diabetes (T2D) patients. This study provides a range of risk equations, derived from UKPDS data, that predict the risk of each of a number of CV complications based on various risk factors, such as HbA1c, BMI, lipids, and the presence of existing complications. The risks produced by these equations were weighted by composite CV risks estimated from the EDIC study data.

The risks of CV complications are updated at each annual model cycle based on changes in HbA_{1c} and SBP based on risk reductions estimated from the EDIC study. The same risk reductions are applied to each complication, as these risk reductions relate to a composite measure of CV risk. The risks of

microvascular complications were also informed by data from the EDIC study, and similarly updated at each model cycle as per the CV risks.

The company also provided an alternative set of analyses using the PRIME Diabetes Model as a validation exercise to test structural uncertainty. PRIME had a similar overall structure but included fewer complications (although some of the missing ones were not used in the CDM) and had different assumptions regarding progression of physiological parameters. Alternative sources of risk data were also used, based on T1D populations, many of which were based on Swedish registry data.

In terms of the utilities, the company did not consider the utility data collected in the inTandem trials as the trials assessed the impact of treatment over a short period and did not capture the full impact on HRQoL due to long-term complications. For this reason, utility data for the economic analysis were taken from published sources. In both the original CS and addendum to that submission supplied to the ERG at the clarification stage, the company stated that utility data were taken from Peasgood *et al.* 2016 wherever possible. The Peasgood study estimated the utilities and disutilities associated with T1D using data from a UK research programme on the Dose Adjustment For Normal Eating (DAFNE) education programme. When utility data were not reported in Peasgood, *et al.* 2016, the company also stated that data from Beaudet *et al.* 2014 and Currie *et al.* 2006, both undertaken in patients with T2D, were used to inform the economic analysis. However, when the ERG checked the utility inputs in the revised analyses provided at the clarification stage, the ERG found that the company employed utility values in PRIME, "*Based on ScHARR settings review in November 2018*".

The models included the costs of patient treatment for acute events and long-term illness and the costs associated with managing the complications associated with the T1D. Costs associated with the intervention and comparator treatments comprised of the drug, needle, MDI, pump costs (including CSII) and the costs associated with self-monitoring blood ketone and self-monitoring of blood glucose (SMBG). In both the original CS and addendum to that submission supplied to the ERG at the clarification stage, the company obtained resource use estimates and unit costs from the same UK sources including: NICE guidance for T1D in adults (NG17), NHS Prescription Cost Analysis data, IQVIA Longitudinal Patient Database real-world data, NHS Reference Costs 2016-17, and the BNF. However, when the ERG checked the inputs in the revised analyses provided at the clarification stage, the ERG found that the company used alternative costs in the PRIME model without reference or justification.

The company's base case results are given in Table A, and the results of the PRIME model using the company's preferred assumptions are given in Table B.

Table A. Company's base case results (sotagliflozin 200 mg in combination with insulin versus insulin alone; adapted from Table 37 of the company's addendum)

Treatment	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£78,731	17.194	8.695	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£78,940	17.223	8.803	£209	0.029	0.108	£1,934
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table B. Results of company's revised base-case analysis in PRIME corrected by the ERG

Treatment	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£52,458	17.263	11.598	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£54,176	17.282	11.693	£1,718	0.018	0.095	£18,117
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the use of the CDM to be reasonable given that the functioning is likely to be sound as it has been widely used and validated by various modellers – in particular at the Mount Hood Diabetes Challenge Network. However, the ERG notes that the "black box" nature of the model makes it difficult to fully critique the workings of the model and to fully assess whether the model functions as described by the company. Using the PRIME model as a validation, when applying the inputs and assumptions as in the company's preferred base case, resulted in quite different outputs. Therefore, the ERG is concerned that this demonstrates uncertainty in the model structure and that the results of both models should be considered with caution. Assessing the validity of the outcomes with clinical experts may mitigate the uncertainty if the CDM model demonstrates more plausible outputs.

In terms of the treatment effects applied, the data from the inTandem trials only provides data up to 52 weeks, after which the company extrapolate the effects for 5 years. The ERG considers this to be very uncertain, in particular for the effect of HbA_{1c}, which appears to be returning towards the comparator arm in the trial results. If the same trend continues, the treatment effect will have been lost by the second or third year. This is not necessarily the case for BMI and lipids, which may have a retained effect for the duration of treatment. An additional point regarding the effects in the company's base case is that they allow HbA_{1c} to continue rising by 0.1% in the comparator group. This effectively increases the relative effect, thus, overestimating the treatment effect.

The ERG considers the company's use of the EDIC study to inform the progressions of physiological parameters to be reasonable given that it is a recent source of data relating to patients who have T1D.

The risks of CV disease may be somewhat simplified given that the adjustments applied relating to HbA1c changes – and SBP changes are based on changes to the risk of a composite measure of CV disease rather than each individual complication. This is also the case for the microvascular complications.

The ERG also had some key concerns relating to the application of utilities in the model. In Peasgood *et al.* 2016, the disutility per 1 unit increase above 25kg/m² varied from -0.0052 in the fixed-effects model to -0.0028 in the random-effects model and the company chose the smaller estimate from the random-effects model in each of their analyses. However, the ERG notes that the disutility for a 1 unit increase above 25kg/m² in Beaudet *et al.* 2014 (-0.006) was similar to the fixed-effects estimate in the Peasgood *et al*. 2016. Moreover, fixed-effect estimates were preferred by the authors in the Peasgood study. The impact of using a larger disutility decreased the ICER by approximately £3,000 in PRIME (keeping all other preferred assumptions from the CDM base case) demonstrating that BMI is an important measure of the impact of treatment on patients and a key driver in the model.

Another issue noted by the ERG was that the inputs in the revised analyses using PRIME, provided at the clarification stage, were based on inputs from a ScHARR 2018 review. No rationale for this change, nor the ScHARR 2018 review, were provided to the ERG. Therefore, the ERG cannot validate the utility data employed by the company. However, the ERG was provided with the ScHARR 2019 review at the clarification stage to explore its recommendations on annual HbA_{1c} and BMI progressions. Following this, the ERG questions why the company chose the 2018 review instead of the updated 2019 review to inform their revised analyses, and why the company did not apply the results from either ScHARR review in the CDM? As a result, the ERG would like further clarity on whether the decision to include the ScHARR 2018 review was made in PRIME erroneously. Overall, the ERG's preferred utility inputs are based on the recommendations in the ScHARR 2019 review because the review includes inputs from Beaudet *et al.* 2014, which addresses the discrepancies seen in the CS and includes estimates from the authors preferred statistical model (the fixed-effects model) in Peasgood *et al.* 2016.

In terms of the estimation of QALYs, the company provided a response to the ERG's clarification question to explain that the minimum QALY approach was used in the CDM, while an additive QALY approach was used in PRIME (in the absence of a minimum approach). When the company provided the results using a multiplicative approach in the CDM, the ICER decreased by approximately £1,000. The company did not provide results using a multiplicative approach in PRIME and when the ERG explored a scenario using the multiplicative approach (keeping all other preferred assumptions from the CDM base case), the impact was to increase the ICER by approximately £4,000. Overall, the ERG's preference is to use the multiplicative approach, and this is supported by the NICE Decision Support Unit technical support document 12, which suggests that the

multiplicative approach should be adopted when multiple evidence sources are used to obtain utility values.

The ERG noted some discrepancies in costs used in the updated PRIME model compared to the CDM based on the revised analyses provided at the clarification stage. No sources of cost data or rationale for the changes were provided to the ERG and given that the company did not mention the alternative inputs for the PRIME model in the addendum to the CS, the ERG focussed its critique on the cost inputs used to inform the original and revised CDM. However, the ERG would like further clarity on whether those changes were made in PRIME erroneously or not.

A key area of uncertainty relating to costs in the company's base case was the assumption of the duration of treatment at 5 years. Clinical experts advised the ERG that sotagliflozin would be stopped in the event of unacceptable side-effects. However, they anticipated that patients are likely to be kept on treatment indefinitely after an initial benefit is achieved, as it will be difficult to isolate continued drug effects from changes in patient-related factors (e.g. diet, exercise, management of insulin). Moreover, if sotagliflozin was stopped there would be concerns as to whether a patient's condition would deteriorate. The ERG notes the impact of applying treatment costs for lifetime increases the ICER to over £100,000 per QALY. This demonstrates potentially serious uncertainty in the company's results.

A final issue regarding treatment costs related to the costs of severe hypoglycaemia (SH). In the inTandem2 trial SH was defined as, "*any hypoglycaemic event that required assistance from another person or during which the patient lost consciousness or had a seizure*". The company then assumed that all SH events required medical assistance and the ERG has two concerns with this. Firstly, the cost to treat SH in the company's analysis (£2,320) was approximately seven times higher than that employed by NG17 (taken from Hammer *et al.* 2009) to treat "*major hypoglycaemic events*" (£333 in 2014 prices). Secondly, the ERG disagrees with the company that "*assistance from another person*" translates into medical assistance. This view was also reiterated by the ERG's clinical experts who advised the ERG that around 50% of SH events would require medical assistance. Compared to the base case results, the ERG's preferred scenario that comprised of lower hospitalisation rates (50%) and lower treatment costs (Hammer *et al.* 2009[1]) had a small increase on the ICER.

The ERG was unable to run analyses using the CDM as this returned an error message, and PRIME appeared to have restrictions in what the ERG could modify. Therefore, the ERG could not implement its preferred base case analysis in either model. The ERG's preferred assumptions are: to use the simulated population based on the pooled trial data that informed the treatment effectiveness; to apply SH costs based on Hammer *et al.* 2009 and assume 50% of patients are hospitalised; using multiplicative utilities based on values from the ScHARR 2019 review; and, apply treatment effects

for HbA_{1c} for just 2 years, while all other effects are maintained for the treatment duration of 5 years. The ERG was able to present a similar analysis but with the HbA_{1c} effect removed at 3 years and other treatment effects removed after a further year, along with treatment costs. This resulted in an ICER of £18,134, a slight increase compared to the PRIME model results using the company's preferred assumptions.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Clinical

- The inTandem1 and inTandem2 trials provide high quality, head-to-head evidence for sotagliflozin (plus insulin) versus insulin alone (placebo) in line with the decision problem: randomisation procedures were robust, treatments were blinded, statistical analyses were appropriate and prespecified, dropouts were low and balanced, and insulin dose titrations, SH, DKA and other adverse events were all adjudicated by independent committees;

- Analyses were submitted in line with the expected marketing authorisation for all three trials individually and pooled, which allowed the ERG to explore the robustness of treatment effects across different underlying populations.

Economic

- The company's base case analysis was based on a validated online model that has be used for variously economic evaluations in both T1D and T2D. In particular, it was used to inform a number of analyses in the NICE T1D guideline (NG17);

- The PRIME diabetes model was also used to assess structural uncertainty. This is another online model that also has published validation studies.

1.6.2 Weaknesses and areas of uncertainty

Clinical

- There is no evidence for the efficacy and safety of sotagliflozin beyond 52 weeks, and treatment cessation criteria for judging clinical benefit are not specified in the draft SmPC;

- Evidence for the 400 mg dose from the clinical trial programme does not reflect the draft SmPC guidance to escalate to 400 mg after at least three months if additional glycaemic control is needed. There is uncertainty about the criteria by which patients will be deemed

suitable for dose escalation and whether the 400 mg dose would be given as two 200 mg tablets until the 400 mg tablet is available, which would double the acquisition cost.

- Key discrepancies between the trial populations and patients in the UK mean the treatment effect of sotagliflozin may be overestimated in terms of insulin delivery (because a larger effect is seen with CSII which are rarely used in the UK), but underestimated in terms of baseline HbA_{1c};

- The size of absolute and relative treatment effects varies for various outcomes depending on the timepoint (24 or 52 weeks) and the study(ies) used for analysis, including HbA_{1c}, basal and bolus insulin dose, HRQoL and SH;

- Clinical experts expect that patient eligibility for sotagliflozin may be more selective in clinical practice than in the trials to maximise the potential for benefit and minimise the risk of rare but serious adverse effects (e.g. BMI > 30, eGFR >60, insulin via MDI, HbA_{1c} > 8.5%, high cardiovascular risk, carbohydrate intake > 80 mg/day and willing to monitor blood glucose and urine ketones).

Economic

- The economic model, although based on a frequently used and thoroughly validated model, is a web-based platform with a "black box" nature. This makes it difficult for the ERG to confidently critique the analyses performed by the company.

- The use of a second model gives some way of challenging the outputs of the chosen model. However, this model also has a "black box" nature, making it difficult to assess how the functioning differs between the models, and exactly what differences impact the outputs.

- The modelling is based on a large degree of extrapolation with observed treatment effects only informing the first annual cycle. Further to this, the complications downstream are reliant on a number of data sources, which adds additional layers of uncertainty. The outputs in terms of incidence rates of complications should be assessed by clinical experts when considering the validity of the results. Differences in outputs in the CDM compared to PRIME is an additional source of uncertainty in the overall results. Clinical validation of the outputs may provide more confidence in the results of a particular model.

- There were a number of discrepancies between the model and what was described in the company's submission, as well as between the revised analyses and the addendum. There

were also inconsistencies between model inputs between the two models making it difficult to critique.

- The ERG was unable to run analyses in the CDM despite raising the issues with the developer, and the PRIME model did not appear to be fully modifiable, which restricted the analyses that the ERG could perform.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Economic

The ERG was not able to run analyses using the CDM as an error message was returned. This occurred even when replicating the company's base case analysis. However, the ERG performed analyses with PRIME, although there appeared to be some restrictions with this model too. In particular, the ERG was not able to fully modify the changes to treatment effects over time. The scenarios performed by the ERG are as follows:

- A simulated cohort informed by the pooled analysis population (see Section 5.4.2);
- Alternative utility values from the Beaudet *et al.* 2014 study including all other utility inputs reported in the CS (see Section 5.4.8.1.2);
- Alternative utility values from a ScHARR 2019 review (see Section 5.4.8.1.4);
- Multiplicative QALY estimation approaches (see Section 5.4.8.1.5);
- Alternative durations of sotagliflozin treatment (see Section 5.4.9.3.1);
- Alternative costs to manage SH from Hammer *et al.* 2009 (see Section 5.4.9.3.2).

The results of the ERG's scenario analyses in PRIME are given in Table C.

Table C. ERG scenarios in the PRIME model

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Analysis using the preferred assumptions from the CDM base case (addendum inputs) including BMI correction					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£54,176	11.693	£1,718	0.095	£18,117
QALY estimation: multiplicative					
Placebo	£52,458	12.043	-	-	-
Sotagliflozin	£54,176	12.120	£1,718	0.077	£22,359
Simulated cohort informed by the pooled analysis population					
Placebo	£48,924	10.557	-	-	-
Sotagliflozin	£50,569	10.656	£1,645	0.099	£16,539

Alternative Beaudet *et al.* 2014 disutility values (QALY estimation: additive)					
Placebo	£52,458	11.624	-	-	-
Sotagliflozin	£54,176	11.718	£1,718	0.094	£18,241
Alternative Beaudet *et al.* 2014 disutility values (QALY estimation: multiplicative)					
Placebo	£52,458	12.059	-	-	-
Sotagliflozin	£54,176	12.136	£1,718	0.076	£22,470
ScHARR 2018 utility values (QALY estimation: additive)					
Placebo	£52,458	8.498	-	-	-
Sotagliflozin	£54,176	8.693	£1,718	0.194	£8,834
ScHARR 2018 utility values (QALY estimation: multiplicative)					
Placebo	£52,458	9.746	-	-	-
Sotagliflozin	£54,176	9.895	£1,718	0.149	£11,515
ScHARR 2019 utility values (QALY estimation: additive)					
Placebo	£52,458	12.342	-	-	-
Sotagliflozin	£54,176	12.423	£1,718	0.081	£21,204
ScHARR 2019 utility values (QALY estimation: multiplicative)					
Placebo	£52,458	12.610	-	-	-
Sotagliflozin	£54,176	12.677	£1,718	0.067	£25,472
1-year waning effects to 2-year placebo effects and 2-year costs					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£53,202	11.640	£745	0.042	£17,854
2-year effects and 2-year costs					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£53,155	11.652	£697	0.054	£13,000
2-year effects and 5-year costs					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£53,481	11.665	£1,023	0.066	£15,452
Lifetime costs					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£59,715	11.693	£7,257	0.095	£76,532
2-year effects and lifetime costs					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£59,855	11.652	£7,397	0.054	£137,943
Cost of SH (Hammer *et al.* 2009 & 100% hospitalised)					
Placebo	£54,435	11.598	-	-	-
Sotagliflozin	£56,164	11.693	£1,729	0.095	£18,230
Cost of SH (Hammer *et al.* 2009 & 50% hospitalised)					
Placebo	£53,505	11.598	-	-	-
Sotagliflozin	£55,288	11.693	£1,782	0.095	£18,797
Simulated cohort informed by the pooled analysis population plus ScHARR 2019 utility values (QALY estimation: additive)					
Placebo	£48,924	11.318	-	-	-
Sotagliflozin	£50,569	11.406	£1,645	0.089	£18,585
Simulated cohort informed by the pooled analysis population plus ScHARR 2019 utility values (QALY estimation: multiplicative)					
Placebo	£48,924	11.684	-	-	-
Sotagliflozin	£50,569	11.758	£1,645	0.074	£22,187

Simulated cohort informed by the pooled analysis population plus cost of SH (Hammer *et al.* 2009 & 50% hospitalised)					
Placebo	£49,922	10.557	-	-	-
Sotagliflozin	£51,627	10.656	£1,705	0.099	£17,147
Simulated cohort informed by the pooled analysis population plus cost of SH (Hammer *et al.* 2009 & 50% hospitalised) plus ScHARR 2019 utility values (QALY estimation: multiplicative)					
Placebo	£49,922	11.684	-	-	-
Sotagliflozin	£51,627	11.758	£1,705	0.074	£23,003

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

The company provide an overview of the key aspects of type 1 diabetes mellitus (T1D) including: incidence and prevalence, complications, insulin therapy, and the impact of T1D on patients in Section B.1.3 to B.1.5 of the company's submission (CS). The final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) defines the population of interest as adults with T1D who are on insulin therapy that does not adequately control blood glucose levels.[2] However, wording for the intended marketing authorisation for sotagliflozin confirmed after the scope was finalised defines a narrower population limited to patients with Body Mass Index (BMI) $\geq$ 27 kg/m^2.[3] The licensed population is likely to be limited to those with BMI $\geq$ 27 kg/m^2 after the Committee for Medicinal Products for Human Use (CHMP) asked the company to identify a subgroup of patients for whom the benefits of sotagliflozin would outweigh the increased risk of diabetic ketoacidosis (DKA; company's response to clarification). The applicability of the evidence provided by the company in relation to the decision problem and likely marketing authorisation are discussed in Section 3.1.

The Evidence Review Group (ERG) considers the overview of T1D presented by the company appropriate and relevant to the decision problem but provides additional detail to outline the pathogenesis of T1D and DKA, and the importance of insulin therapy in disease management. A synopsis of information from the CS together with supplemental detail from the ERG is as follows:

- T1D is an autoimmune condition where the insulin-producing beta cells in the pancreas are destroyed leaving the body unable to produce enough insulin to adequately regulate blood glucose levels; without treatment it can be fatal;[4, 5]

- The UK currently has the fifth highest rate of T1D in the world with around 330,000 people affected, but the approach to management has changed over time with changes in the profile of patients;[6]

- A recent cross-sectional study (n=5,607) using data from the Clinical Practice Research Datalink (CPRD) found that the population of patients with T1D in the UK have a mean age of 45.6 years, mean glycated haemoglobin (HbA_{1c}) of 8.8% (standard deviation [SD] 3.6), and mean BMI of 27.4 kg/m^2;[7]

- Insulin is the mainstay of treatment for T1D and most patients in the UK self-administer basal-bolus regimens via multiple daily injections (MDI). Insulin via continuous subcutaneous insulin infusion (CSII) pumps are recommended when MDI provide insufficient

glycaemic control,[8] although use of CSII for T1D remains low in England and Wales (approximately 15%, overall with substantial geographic variation from <5% to >40%);[9]

- Patients are responsible for testing blood glucose, adhering to the insulin regimen and monitoring carbohydrate intake, as well as adjusting the insulin bolus dose at meal times, times of stress, or exercise.[10]

- Management of T1D requires a careful balance between reducing/avoiding the 'highs' (hyperglycaemia) and 'lows' (hypoglycaemia) and maximising the time in normal glycaemic range.[5] Fluctuations in blood glucose levels outside the normal range are common and may occur due to missed insulin doses, infection, stress or postprandial hyperglycaemia;[10-16]

- Chronic hyperglycaemia is the main risk factor for the development of diabetes-related complications, including retinopathy, nephropathy and neuropathy, and is implicated in cardiovascular and cerebrovascular disease.; T1D treatment aims to reduce the risk of long-term complications arising from hyperglycaemia;[17-19]

- Insulin is associated with weight gain and hypoglycaemia. Rates of mild-to-moderate hypoglycaemia in clinical trials are high (40–100 events per patient per year) but may be higher in routine practice;[19-23] Fear of hypoglycaemia may cause patients to suboptimal insulin dosing which increases the risk of DKA, a life threatening complication of T1D. Excessive alcohol intake and low BMI can also increase the risk of DKA;[8, 22, 24, 25]

- The Diabetes Control and Complications Trial (DCCT) established that tight glycaemic control using intensive insulin therapy is associated with an increased risk of hypoglycaemia; however, recent studies have suggested severe hypoglycaemic episodes also occur frequently in patients with poor, and often chaotic, glycaemic control;[19]

- HbA_{1c} is a well-established surrogate marker for disease control in T1D and is the only outcome linked to long-term complications. However, over a 24-hour period, blood glucose fluctuates and the longer term nature of HbA_{1c} does not capture this glycaemic variability;[26]

- NICE recommends an HbA_{1c} target level of ≤6.5% (48 mmol/mol) to prevent long-term complications because the risk and frequency of diabetes-related comorbidities rises with HbA_{1c} and age.[8] However, over 90% of adults with T1D do not meet the NICE-recommended HbA_{1c} targets;[27]

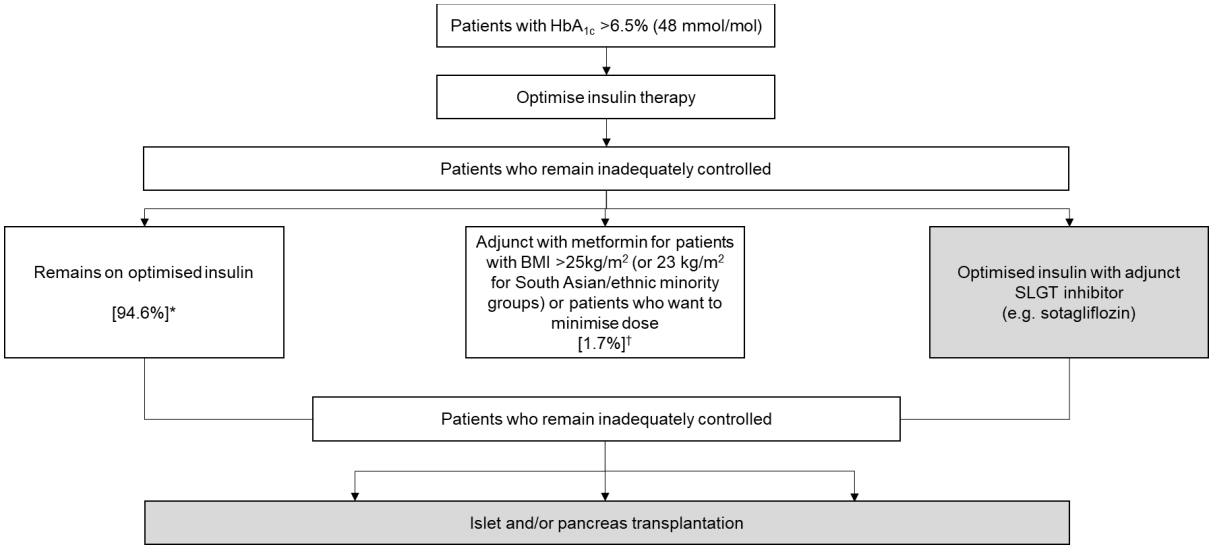
2.2 Critique of company's overview of current service provision

The company also provided a summary of the current clinical pathway for T1D (CS Section B.1.6) and the NICE pathways for T1D in adults, insulin therapy for adults with diabetes, and managing cardiovascular risk in adults with T1D (CS Appendix D). As outlined by the company, type and regimen of insulin is tailored to each patients' preferences and requirements, with the aim of maintaining target HbA_{1c} level of 6.5% or lower to minimise the risk of long-term vascular complications (NICE T1D guideline NG17).[8] However, the ERG's clinical experts reported that in the UK a target of 6.5% is rarely reached; target HbA_{1c} in clinical practice is tailored to each patient and often closer to 7.5% to minimise the risk of recurrent hypoglycaemia.

The NICE guideline recommends considering metformin as an adjunct to insulin for adults with T1D and BMI $\geq$ 25 kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups) who want to improve their blood glucose control while minimising their effective insulin dose.[8] However, metformin is not licensed for use with insulin in T1D and there is uncertainty around its effectiveness in this indication.[28] The ERG's clinical experts agree with the company's assertion that metformin is rarely used with insulin for patients with T1D in the UK, but acknowledged some geographical variation in practice. The appropriateness of metformin as a comparator for sotagliflozin is discussed in Section 3.3.

Sotagliflozin is the first dual sodium-glucose co-transporter type 1 and 2 (SGLT-1/2) inhibitor to receive a positive opinion for adults with T1D from the CHMP. The ERG notes that the single SGLT-2 inhibitor dapagliflozin has also recently received a CHMP positive opinion and is currently in the NICE appraisal process for the same indication as sotagliflozin (ID1478).[29] Sotagliflozin acts by reducing glucose absorption in the gastrointestinal tract (local action) and prevents glucose reabsorption in the kidneys (systemic action), thereby enhancing glucose excretion in the urine. Figure 1 depicts the company's proposed placement of sotagliflozin in the treatment pathway of adults with T1D in the UK although the ERG notes that the eligible population has narrowed to patients with BMI $\geq$ 27 kg/m^2 since the initial submission.[3]

Figure 1. Proposed placement of adjunctive sotagliflozin (reproduced from CS, Figure 1.2)



[*n/N=5198/5618 on CSII and MDI. †n/N=94/5618 on metformin [7]]
Figure based on current NICE Type 1 Diabetes Clinical Guideline [NG17][28]
Optimised insulin could be using any mode of delivery.
Percentage use is based on baseline data from the Clinical Practice Research Datalink (CPRD) evaluate the progression of key clinical parameters for uncontrolled adult T1D patients over five years of follow-up.
BMI, Body Mass Index; NG, NICE guidance; T1D, Type 1 diabetes. SGLT, Sodium-glucose co-transporter.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

In the original evidence submission, the company provided a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE; CS, Table 1.1 pg. 10),[2] together with a description of how closely their submitted evidence reflects the scope. The original evidence submission was in line with the NICE final scope, which did not limit the population by Body Mass Index (BMI). After confirmation of the Committee for Human Medicinal Products for Human Use (CHMP) positive, the company submitted new analyses and an addendum based on evidence in line with the narrower BMI $\geq$ 27 kg/m^2 population who will be eligible for sotagliflozin. A summary of the original and updated evidence submissions by the company is provided in Table 1, and the ERG's concerns regarding the applicability of the evidence are explained further in the sections that follow.

Table 1. Summary of decision problem as outlined in the company's submission (adapted from CS, Table 1.1, pg. 10)

	Final scope issued by NICE	Original submission	Updated submission	ERG comment
Population	Adults with T1D on insulin therapy that does not adequately control blood glucose levels	Clinical evidence based on the inTandem1 and inTandem2 trials (ITT). Economic model based on inTandem2 (ITT) results and baseline risks of hypothetical UK cohort.	Clinical evidence for subpopulation of inTandem1, 2 and 3 with BMI ≥27kg/m² (separately and pooled) in line with CHMP opinion. Economic model based on pooled inTandem1 and 2 52-week subpopulation data and baseline risks of UK cohort.	BMI ≥27kg/m² subpopulation results appropriate. Some concerns regarding applicability of baseline HbA_{1c} and CSII use in trials compared with UK. No one trial considered most appropriate. Clinical experts outlined target population as HbA_{1c} > 8.5%, BMI > 30, eGFR > 60 and MDI.
Intervention	Sotagliflozin in combination with insulin	Clinical evidence presented for both doses. Economic analysis for 200 mg dose only because 400 mg tablet will not be available at UK launch.	Clinical evidence presented for both doses. Cost-effectiveness of 400 mg dose estimated from 200 mg results, assuming 10% of patients require dose increase from 200 to 400 mg.	CHMP opinion does not limit by dose. Assumptions needed for 400 mg because trials did not step up from 200 mg as outlined in draft SmPC.
Comparator(s)	Insulin therapy with or without metformin	Insulin (primary) Insulin + metformin (secondary analysis NMA)	No change	ERG agrees metformin not a relevant comparator. Insulin more closely manage in trials than UK practice.
Outcomes	• HbA_{1c}/glycaemic control/blood glucose variability • BMI/body weight/waist circumference • Frequency and severity of hypoglycaemia • Changes in CV risk factors, including blood pressure and lipids • Microvascular complications of diabetes, including damage to nerve, kidney and eye • Macrovascular complications of diabetes, incl. coronary artery disease, peripheral arterial disease, stroke and lower limb amputations • Mortality • Total daily insulin dose • AEs of treatment, including DKA, fractures, genital infections and UTIs • Health-related quality of life	All except some microvascular complications. Selected AEs reflected in economic model. (rationale provided in CS, Table 1.1)	No change in efficacy and safety outcomes reflected in model, only in model assumptions and scenarios (e.g. rates of progression, durability of treatment effects and duration of treatment). Primary efficacy results based on subpopulation with BMI ≥27kg/m²; some safety results based on full populations of several phase II and III T1D sotagliflozin trials.	All relevant outcomes reported in original submission submitted for the BMI ≥ 27 kg/m^2 subpopulation, except some microvascular complications. Modelling assumptions and inTandem efficacy and safety inputs for model critiqued in Section 5.

Abbreviations used in table: AEs, adverse events; BMI, body mass index; CHMP, Committee for Medicinal Products for Human Use; CS, company's submission; CV, cardiovascular; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; NICE, National Institute for Health and Care Excellence; SmPC, summary of product characteristics; T1D, type 1 diabetes; UTI, urinary tract infections.

3.1 Population

The final scope issued by NICE outlines the population for this technology appraisal to be adults with type 1 diabetes (T1D) on insulin therapy that does not adequately control blood glucose levels, and the CHMP positive opinion limits the population to those with BMI of ≥ 27 kg/m^2. The original evidence submission was in line with the NICE final scope, and updated analyses were provided after the clarification stage to align the population with the proposed marketing authorisation.

The primary clinical effectiveness data in the original and updated submission were derived from twin phase III randomised controlled trials (RCTs), inTandem1 (n = 793) and inTandem2 (n = 782). The twin trials were designed to evaluate the efficacy and safety of sotagliflozin at two doses (200 mg and 400 mg daily) versus placebo as adjunct treatment to optimised insulin. The primary follow-up was 24 weeks and the trials also included a 28-week long-term extension (total follow-up 52 weeks). Adults ≥18 years were eligible for inclusion in inTandem 1 and inTandem2 if they had been diagnosed with T1D for at least a year and were taking insulin or an insulin analogue via continuous subcutaneous insulin infusion (CSII, also known as a pump) or multiple daily injections (MDI).

The company excluded a third large phase III RCT of sotagliflozin, inTandem3 (n = 1,402), because it only studied the 400 mg dose of sotagliflozin versus placebo (insulin alone). The company state that the 400 mg tablet will not be available at the time of launch in the UK [redacted]. The ERG highlights that, should sotagliflozin be approved for use in the NHS, escalation to 400 mg would be possible by prescribing two 200 mg tablets, which would double the acquisition cost until the 400 mg tablet is available. Unlike the twin trials, inTandem3 followed patients for 24 weeks with no long-term extension and did not include a rigorous 6-week insulin optimisation phase before randomisation, but the trials are otherwise similar in design and population.

The original submission reported clinical effectiveness results for the intention-to-treat (ITT) populations of the inTandem1 and inTandem2 trials and used results of inTandem2 as the primary inputs for the economic model; the inTandem2 trial was assumed to be more applicable to patients in England and Wales because it was conducted in Europe. After clarification, a range of analyses were provided for the BMI ≥27 kg/m^2 subpopulation, comprising approximately 57% of the full populations of the phase III inTandem trials, for both doses of sotagliflozin at 24 and 52 weeks. It should be noted that BMI was not a stratification factor in the inTandem1 and inTandem2 trials and was stratified using a different cut-off in the inTandem3 trial, so the benefits of randomisation are lost.

The ERG's clinical experts outlined BMI as an important factor when considering a patient's suitability for sotagliflozin, along with HbA_{1c}, insulin delivery, and estimated glomerular filtration rate (eGFR). The ERG's clinical experts outlined that the target group of patients are those with BMI > 30, eGFR >60, insulin delivered by MDI, and glycated haemoglobin (HbA_{1c}) > 8.5% despite efforts to control blood glucose with insulin alone to ensure patients most likely to see benefit and avoid risks. Experts also suggest that carbohydrate intake (ideally > 80/day) and willingness to monitor blood glucose and urine ketones would also be considered when deciding eligibility. As such, the eligibility criteria outlined by the experts suggest that even the population limited to those with the BMI $\geq$ 27 kg/m^2 is wider than the patient group who might be considered eligible in UK clinical practice. It was further noted that the trial populations are likely to represent a group of highly motivated patients with optimal self-management behaviours, meaning their baseline HbA_{1c} and risk of diabetic ketoacidosis (DKA) and hypoglycaemia are all likely to be lower than those of patients in the UK.

A key difference between the inTandem trials and patients in the UK is the baseline level of glycaemic control, which could affect the applicability of both efficacy and safety outcomes to patients in the UK. The clinical experts outlined that glycaemic control for patients with T1D in the UK is among the worst in Europe and HbA_{1c} is generally between 8 and 9%, with only 8.5% of patients achieving the NICE-defined target of 6.5%, and 30.2% achieving $\leq$7.5%.[30] The inTandem trials recruited adults with HbA_{1c} between 7% and 11% at screening, but insulin therapy optimisation starting 6 weeks before baseline in the inTandem1 and inTandem2 trials resulted adequate glycaemic control for 17.1–19.5% of patients at the start of treatment (HbA_{1c} <7%; see Section 2.1). The inTandem3 trial did not optimise insulin in the same way and has baseline HbA_{1c} closer to what is expected in UK clinical practice (see Section 4.2.2) but did not study the 200 mg dose of sotagliflozin or include a 52-week follow-up. The ERG's clinical experts explained that sotagliflozin would be considered for patients with high HbA_{1c} despite efforts to improve control with insulin, but rigorous insulin optimisation prior to treatment initiation would not be practical in UK clinical practice.

Inclusion of patients taking insulin via CSII introduced another key discrepancy between the trials and UK clinical practice, because fewer patients with T1D in the UK use CSII than was the case in the inTandem trials, particularly the trial conducted in North America (inTandem1). Approximately 60% of the people in inTandem1 were using CSII compared with 26% in the European inTandem2 trial, and approximately 15% in England and Wales (National Diabetes Audit [NDA] Insulin Pump Report), which has remained relatively stable since 2012.[9] However, the NDA acknowledges substantial variation of pump usage across centres (<5% to >40%), as well as higher pump usage among younger people with diabetes (25.9% of those under 30 years), and higher usage in England (15.6%) than Wales (6.7%). The ERG's clinical experts indicated that, while the percentage of people

using pumps in the UK may be higher in the group of patients with poor glycaemic control on MDI, they would be reluctant to start anyone using a pump on sotagliflozin; CSII generally leads to better glycaemic control but patients may be more susceptible to DKA if the pump malfunctions or becomes blocked and insulin delivery is interrupted.

Following the differences between the trial populations and UK patients who are likely to be considered for treatment with sotagliflozin, the ERG requested to see results from all trials limited first to the subpopulation of patients with BMI ≥ 27 kg/m^2 and then further to patients with HbA_{1c} > 8.5% (>9% for inTandem3) and using MDI. The additional factors were chosen because they were stratification factors in the trials, whereas eGFR, also highlighted by the clinical experts, was not. Nonetheless, data provided by the company at the clarification stage confirmed that > 93% of patients in the trials had eGFR > 60 (company's response to clarification, Table 69). The ERG hoped that by pooling the trials and limiting to patients with those characteristics, a relevant population could be studied while maintaining statistical power. However, the company outlined that patient numbers were too small when the populations were limited in the way requested by the ERG, and instead submitted a range of subgroup analyses within the BMI ≥ 27 kg/m^2 population to explore the effect of baseline HbA_{1c} and method of insulin delivery on the risk benefit profile of sotagliflozin.

3.2 Intervention

The NICE final scope outlines the intervention to be sotagliflozin (Zynquista®) in combination with insulin.[2] No restrictions were outlined in the scope with regards to the dose of sotagliflozin or the type, dose or delivery of insulin.

The company submitted clinical effectiveness and safety evidence for sotagliflozin 200 mg and 400 mg per day for T1D from the phase III inTandem trials, but initially only conducted cost-effectiveness analyses for the lower dose, stating that the 400 mg tablet will not be available at launch in the UK. The company explained that data for the 400 mg dose in the available trials does not reflect the draft summary of product characteristics (SmPC; submitted as CS Appendix C), which recommends a starting dose of 200 mg and possible escalation to 400 mg after at least three months if additional glycaemic control is needed. Patients in the trials were randomised to 200 mg or 400 mg with no dose change in either group and so, at the clarification stage, the company provided cost-effectiveness analyses for sotagliflozin 400 mg using trial data for the 200 mg dose, assuming 10% of patients would require dose escalation to 400 mg. The ERG highlights that, should sotagliflozin be approved for use in the NHS, escalation to 400 mg would be possible by taking two 200 mg tablets, which would double the acquisition cost until the 400 mg tablet [redacted] is available. The company assume that dose escalation is most likely for patients with BMI >35 kg/m^2 who make up 9% of adult

patients with T1D, (Clinical Practice Research Datalink [CPRD]) and are more likely to be on higher insulin doses, and at higher risk of further weight gain and related co-morbidities (company response to clarification, pg. 45).

The draft SmPC outlines a set of criteria to consider before initiating treatment with sotagliflozin 200 mg and before increasing the dose to 400 mg but does not advise how adequate glycaemic control should be judged to trigger a dose increase. Eligibility criteria include the assessment of risk factors for DKA, normal blood or urine ketone levels based on several baseline evaluations over 1–2 weeks, patient familiarity with how their behaviours and circumstances affect their ketone levels and willingness to perform adequate self-management (blood glucose and ketones, DKA risk management), and volume depletion correction. The criteria reflect how eligibility was assessed in the inTandem trials before treatment initiation with either dose but, as above, the trials do not reflect how patient suitability for the 400 mg dose will be assessed in practice for those already taking the 200 mg dose.

The draft SmPC states that treatment should be continued until the patient is no longer receiving benefit or until unacceptable side-effects. The ERG's clinical experts stated that they would stop sotagliflozin in the event of unacceptable side-effects but would find it difficult to judge when a patient was no longer receiving benefit, as this is likely to be unknown. The experts anticipated that, unless no change in HbA_{1c} or weight was observed after starting treatment, patients may be kept on treatment indefinitely. Changes in patient behaviours over time (e.g. diet, exercise, management of insulin) could cancel out any ongoing treatment benefit, but clinicians may be hesitant to discontinue treatment to avoid further deterioration. Even in cases where HbA_{1c} returns to the level at treatment initiation (or above) after a year or more, a clinician might be reluctant to stop treatment due to the potential long-term benefits of the drug (e.g. cardiovascular outcomes).

The ERG also consulted clinical experts about the applicability of insulin therapy and additional care received in the trials to UK clinical practice. The experts considered mean daily doses of insulin received in the trials reflective of what patients receive in practice, but highlighted that few patients in England and Wales use CSII (pumps) compared with the trials (as described in Section 3.1). Minimal information was reported about the package of care received by patients in the trials, which is likely to be highly variable given the number of countries and centres involved, making it difficult to assess similarity with UK practice.

In summary, evidence submitted by the company for the lower dose of sotagliflozin (200 mg) is likely to reflect how the intervention will be given in England and Wales, although it is unclear how the stopping rule will be applied in practice, and therefore how long patients will remain on treatment. Evidence from clinical trials for the higher 400 mg dose does not reflect the draft SmPC

recommendation to step up from the 200 mg starting dose, so cost-effectiveness analyses require assumptions to estimate the real-world efficacy and safety. For both doses, the modifying effect of insulin delivery method was explored given the differences noted between the trials and UK clinical practice.

3.3 Comparators

The NICE final scope listed the comparator for this appraisal as insulin therapy with or without metformin.[2] The company's primary effectiveness results are based on inTandem1 and inTandem2, which provide a comparison of sotagliflozin 200 mg and 400 mg versus placebo, with optimised insulin as the background treatment in all groups. Hereafter, the placebo comparator of the trials is referred to as insulin alone. The company did not consider metformin in addition to insulin a relevant comparator but submitted evidence to cover the scope as a secondary analysis. The supplementary clinical effectiveness analysis provides comparisons of sotagliflozin 200 mg and 400 mg in addition to insulin versus metformin added to insulin and insulin alone via network meta-analyses (NMA) of inTandem1, inTandem2 and inTandem3 and seven placebo-controlled trials of metformin.

On the advice of clinical experts, the ERG does not consider metformin a relevant comparator for sotagliflozin. Metformin is recommended by NICE as an adjunct to insulin for people with T1D who have BMI > 25 kg/m^2 (>23 kg/m^2 for South Asian/ethnic minority) but results of a recent large placebo-controlled trial do not support its use to improve glycaemic control in adults with T1D.[31] Metformin may have a role in managing cardiovascular risk, as it does for patients with T2D, but the company's analysis of CPRD data found it is rarely used for T1D in the UK (1.7%).[7] The company conducted a secondary analysis to provide estimates of sotagliflozin versus metformin but highlight substantial clinical and statistical heterogeneity within the studies required to make the comparison (see CS Appendices, Table F.25).

The ERG agrees with the company that direct comparative results from the inTandem trials constitute the most reliable evidence for sotagliflozin in addition to insulin versus insulin alone, which should be considered the primary comparator. However, the methods of insulin adjustment in the inTandem trials, and particularly the rigorous insulin optimisation phase in inTandem1 and inTandem2, reflect more closely managed insulin therapy and better controlled HbA_{1c} than is generally possible in UK clinical practice. The ERG considers results for the subset of patients in the inTandem trials who were using MDI for insulin delivery most representative of insulin as it is used in the UK. However, differences in optimisation of insulin by trial investigators and optimal self-management by patients in a trial setting should be considered when applying results of the inTandem trials to patients with T1D in the UK.

The ERG notes that another sodium glucose cotransporter (SGLT) inhibitor, dapagliflozin, is currently in the NICE technology appraisal process for the same T1D indication as sotagliflozin (ID1478),[29] which would be a direct comparator for sotagliflozin in addition to insulin. However, final guidance is not expected until August 2019, and so it cannot be considered a comparator for the purposes of this STA.

3.4 Outcomes

The company presents direct evidence for adjunctive sotagliflozin 200 mg and 400 mg versus insulin alone, in addition to insulin, covering all outcomes listed in the final scope issued by NICE.[2] Outcomes presented in the submission from the phase III inTandem trials compared with those listed in the scope are shown in Table 2. The ERG notes that the primary endpoint for inTandem1, 2 and 3 was 24 weeks, but some outcomes were also reported after an extension period at 52 weeks of follow-up for inTandem 1 and 2.

Net benefit was an additional outcome submitted by the company that was reported in all three inTandem trials as a composite measure of key safety and efficacy endpoints. Net benefit was defined as the proportion of patients with HbA_{1c} < 7% and no episodes of severe hypoglycaemia (SH) or DKA, which was reported at week 24 for all three trials and week 52 for inTandem 1 and inTandem2. The company also presented additional outcomes from two sub-studies conducted in a subset of patients across inTandem1 and inTandem2: glucose variability outcomes from a continuous glucose monitoring sub-study (n = 288) and total fat mass and bone density from a dual-energy X-ray absorptiometry (DEXA) sub-study (n = 243). The ERG considers outcomes from the sub-studies secondary to the main results of the inTandem trials and does not provide a full critique of the methods and results from the sub-studies in following sections.

Microvascular and macrovascular complications as listed in the NICE final scope were not reported separately but were included in the submission of safety data across the phase III inTandem studies and, for some events of special interest (EOSI), including data from phase II trials of sotagliflozin. The ERG notes that the list of study-defined EOSI did not include the nerve and eye complications listed under microvascular complications in the NICE final scope, but other microvascular and macrovascular complications were reported. Safety data were reported for adverse events of any cause, including diabetes-related complications, and for those judged to be related to the study drug. The company outlined reasoning for only including DKA and severe and non-SH in the economic model which, after consultation with clinical experts, the ERG considered reasonable; the other specific adverse events (AEs) of treatment listed in the scope (genital mycotic infections, fractures

and urinary tract infections [UTI]) were rare and were not expected to have an important impact on cost-effectiveness.

Data were submitted for disease-specific and generic measures of health-related quality of life (HRQoL). Results from the EuroQol 5 dimensions (EQ-5D) were reported at the later 52-week follow-up but were not used as the basis of HRQoL estimates in the economic model.

Table 2. Outcomes presented by the company compared with the NICE scope

Outcome listed in scope	Outcomes presented in the submission
HbA_{1c}/glycaemic control/blood glucose variability	• HbA_{1c} change from baseline (week 24 and 52) • % with HbA1c < 7% (week 24) • Net benefit (% with HbA_{1c} < 7%, no SH, no DKA at week 24 and 52) • Fasting plasma glucose change from baseline (mmol/L) • % time in glycaemic range (3.9–10.0 mmol/L) • Post-prandial plasma glucose change from baseline (mmol/L)
BMI/change in body weight/waist circumference	• Body weight change from baseline (kg) to week 24 and 52 • BMI change from baseline (kg/m^2) to week 24 and 52 • Total fat mass change from baseline (DEXA)*
Frequency and severity of hypoglycaemia	• Hypoglycaemia reported as treatment-emergent adverse effect (TEAE)
Changes in CV risk factors, including blood pressure and lipids	• SBP change from baseline to week 12 (mmHg) • Change in total cholesterol, HDL-C, LDL-C, triglycerides
Microvascular complications of diabetes, including damage to nerve, kidney and eye	• TEAEs occurring in ≥2% patients in any group (mild, moderate, severe), covering all but nerve and eye damage. Reported as pooled rates across the inTandem phase III trials and three phase II trials
Macrovascular complications of diabetes, including coronary artery disease, peripheral arterial disease, stroke and lower limb amputations	
Total daily insulin dose	• Insulin change from baseline (IU; total, basal and bolus) to week 24 and 52
Mortality	• TEAEs leading to death at week 52
Adverse effects of treatment, including DKA, fractures, genital infections and UTIs	• Study drug-related TEAEs occurring in ≥2% patients in any group (mild, moderate, severe), covering all those listed • Events of special interest (EOSI) – gastrointestinal, genital mycotic infections, hypoglycaemia and DKA • Bristol Stool Form Scale change from baseline
Health-related quality of life	• DTSQ status score change from baseline to week 24 • DDS2 score change from baseline to week 24 • EQ-5D-5L change from baseline to week 52

Abbreviations: CV, cardiovascular; DDS2, two-item Diabetes Distress Screening Scale; DKA, diabetic ketoacidosis; DTSQ, Diabetes Treatment Satisfaction Questionnaire; HbA_{1c}, glycated haemoglobin; HDL-C/LDL-C, high- and low-density lipoproteins; SBP, systolic blood pressure; SH, severe hypoglycaemia; UTI, urinary tract infection.
*time in glycaemic range and total fat mass were based on sub-study pooled analyses from inTandem1 and inTandem2

Based on advice from clinical experts, the ERG considers that the outcomes presented in the submission cover those listed in the NICE final scope, except for some diabetes-related complications, and that they are clinically relevant to the decision problem.

3.5 Other relevant factors

The ERG agrees with the company that there are no known equity considerations relevant to this appraisal. No subgroups were defined in the NICE final scope, but various subgroup analyses were prespecified in the inTandem trials for the primary outcome: change from baseline to week 24 in HbA_{1c}. Pooled results for all prespecified subgroup analyses for the modified intention-to-treat (ITT) populations of inTandem1 and inTandem2 were provided in the original submission. The company did not submit a patient access scheme for sotagliflozin.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company carried out a systematic literature review (SLR) to identify evidence to determine the efficacy and safety of sotagliflozin, in addition to insulin, versus the comparators listed in the final scope issued by the National Institute for Health and Care Excellence (NICE).[2] Full details of the methods and results of the SLR were provided in Appendix F of the submission, which the evidence review group (ERG) have reviewed and summarised in Table 3.

The main purpose of the SLR was to identify all relevant trials for the network meta-analysis (NMA) which was a secondary analysis conducted to provide an indirect comparison of adjunct sotagliflozin 200 mg and 400 mg daily with metformin. As stated in the previous section, the ERG does not consider metformin a relevant comparator for sotagliflozin and agrees that direct evidence from the inTandem trials should constitute the primary analysis (see Section 3.3). The ERG's critique of clinical and cost-effectiveness focuses on the direct evidence from which the comparison with insulin alone is derived (Section 4.2), and provides only a brief comment about the NMA conducted to compare sotagliflozin with metformin (Section 4.4).

Table 3. Summary of ERG's critique of the company's methods of review

Review step	CS Section	ERG critique
Data sources	CS Appendix F.1.1.1 to F.1.1.4 (pgs 41–44)	Comprehensive sources and dates searched: Embase, MEDLINE, MEDLINE In-Process, CENTRAL (up to October 2018), DARE (up to 2015, no longer updated), diabetes conference proceedings (ADA, EASD, IDF 2015 to 2018), trial registries for ongoing trials (ct.gov, EUCTR and WHO ICTRP), NICE and SMC websites, SR reference lists.
Search terms	CS Appendix F.1.1.6 (Tables F.2–F.12, pgs 44–65)	Terms and limits appropriate to decision problem: First phase combined terms for population, drug and class of intervention (sotagliflozin, SGLT-1/2) comparator (metformin) and pathway (2nd line/poor control). Limited to RCTs, humans, English language Jan 1980–Nov 2017. Second phase updated to Oct 2018 and added pramlintide terms (not relevant to this appraisal).
Inclusion criteria	CS Appendix F.1.1.7, Table F.13 (pg. 66)	Criteria in line with decision problem. P: adults ≥18 years, T1D inadequately controlled on insulin. I: Sotagliflozin as adjunct to insulin C: Any approved/late-phase SGLT-2 or 1/2 inhibitor or non-insulin drug as adjunct to insulin, or insulin alone. O: Any listed outcome at minimum 16 weeks (covers NICE scope) Other: Any setting, phase III/IV RCTs (II only if no III/IV), in English, Jan 1980–Oct 2018, any country.
Screening	CS Appendix F.1.1.8 (pg. 68)	Screened in accordance with PRISMA statement Title/abstract screen and full text screen by two independent reviewers according to CS Appendix Table F.13. Exclusion codes applied. Discrepancies resolved by a third independent reviewer.
Data extraction	CS Appendix F.1.1.8 (pg. 68)	Standardised template completed by two independent, highly trained reviewers. Discrepancies resolved by a third independent reviewer. Studies compiled, and multiple publications referenced. Quality control procedures to verify accuracy and completeness.

Quality assessment	CS Appendix F.2.4.1 (pgs 94–96)	All studies assessed according to NICE checklist in manufacturer's template.

Abbreviations: ADA, American Diabetes Association; CENTRAL, Cochrane Central Register of Controlled Trials; CS, company's submission; ct.gov, clinicaltrials.gov; DARE, Database of Abstracts of Reviews of Effects; EASD, European Association for the Study of Diabetes; ERG, Evidence Review Group; EUCTR, European Union Clinical Trials Register; IDF, International Diabetes Federation congress; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses; RCT, randomised controlled trial; SGLT, sodium glucose cotransporter; SMC, Scottish Medicine Consortium; T1D, type 1 diabetes; T2D, type 2 diabetes; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

The ERG considers the data sources, search terms, and inclusion criteria sufficiently comprehensive to identify evidence relevant to the decision problem, both in terms of sotagliflozin trials for the primary analysis and metformin trials required for the NMA. The ERG is satisfied with the company's approach to only consider evidence from phase II trials where none was available from phase III or IV trials and notes that the European marketing authorisation for sotagliflozin was based on the three phase III inTandem trials.[32-34] Two phase II studies of adjunct sotagliflozin in the relevant population were highlighted by the company and contribute only to pooled safety analyses: a dose ranging study (NCT02459899; N = 141)[35] and a small study of young adults (NCT02383940; N = 87).[36] The ERG notes that both phase II studies were randomised but their smaller size and less relevant designs regarding dose and population mean they are less applicable to the decision problem than the phase III inTandem trials forming the basis of the company's submission.

A flow diagram was provided in the CS Appendices (Figure F.1) detailing the study inclusion process for different health technology assessments (UK, USA, rest of the world). The numbers reported in the flow diagram are in line with the company's description of the SLR, which outlined that 10 of the 17 included randomised controlled trials (RCTs) were relevant to the scope of this appraisal. The remaining seven RCTs provide evidence for comparators that are not available in England and Wales (pramlintide, dapagliflozin, empagliflozin).

The company quality-assessed the key sotagliflozin trials and the metformin trials included in the NMA against the checklist included in the NICE template for company submissions of evidence to the Single Technology Appraisal (STA) process. The ERG validated the quality assessment for inTandem1, 2 and 3 only, because they formed the basis of the company's and the ERG's preferred analysis. A summary table of the company's risk of bias judgements and ERG's validation is provided in Section 4.2.1.

In summary, the ERG considers the company's definition of the review question relevant and their application of methods sufficiently robust that all relevant RCTs have been identified.

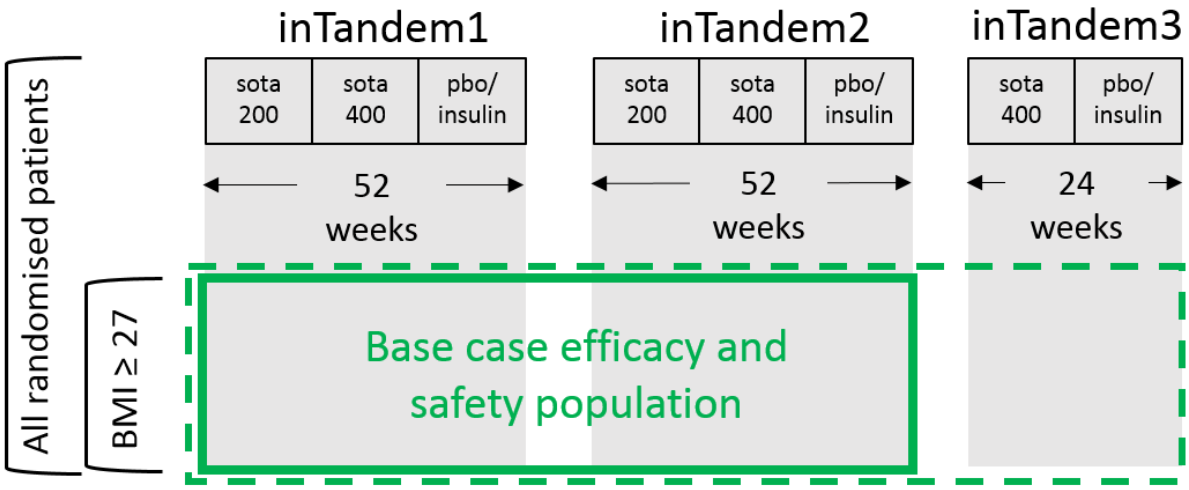
4.2 Critique of the sotagliflozin inTandem trials, their analysis and interpretation

The company presented results from twin RCTs as evidence of clinical effectiveness: one trial was conducted in North America (inTandem1) and one in Europe and Israel (inTandem2) but the trials were otherwise identical in design. The trials randomised adults with T1D to sotagliflozin 200 mg daily, sotagliflozin 400 mg daily, or placebo, but the company use data for the 200 mg dose to represent both doses in the economic model. The trials provide direct evidence for sotagliflozin versus insulin alone, the primary comparator (see Section 3.3), because all groups received optimised insulin as background therapy in addition to the randomised treatment. A third placebo-controlled trial, inTandem3, only studied the 400 mg dose of sotagliflozin and was not included in the company's primary clinical effectiveness evidence in the original or updated submission. The company states that the 400 mg tablet will not be available at the time of launch in the UK and the way 400 mg was studied in all trials does not represent how it will be given in UK clinical practice. The ERG provides a critique of all three inTandem trials because 400 mg could be prescribed as two 200 mg tablets until the 400 mg tablet is available and inTandem3 was included in a range of secondary analyses and the Committee for Medicinal Products for Human USE (CHMP) positive opinion is not limited by dose.

In their original submission, the company chose the intention-to-treat (ITT) population of the European inTandem2 trial as the primary safety and effectiveness inputs for the economic analysis of sotagliflozin 200 mg versus insulin alone. After the CHMP positive opinion was issued, results for the pooled subpopulation of patients with BMI $\geq$ 27 kg/m^2 across inTandem1 and inTandem2 subsequently became the primary clinical effectiveness inputs for the economic model (shown by the solid green box in Figure 2). However, a range of alternative analyses were submitted to assess the impact of design and population differences between results of the three inTandem trials (Figure 2). The ERG considers the BMI $\geq$ 27 kg/m^2 subpopulation most appropriate for decision making in line with the likely marketing authorisation but notes that none of the trials used BMI as a stratification factor, so the benefits of randomisation are lost.

The ERG notes that some safety analyses (treatment-emergent adverse events [TEAE], including rates of microvascular and macrovascular complications) are based on pooled data from the inTandem phase III studies and phase II studies of sotagliflozin for T1D to increase the number of patients included. The ERG considers the approach reasonable but notes that, where the full populations were used, the TEAE profile of sotagliflozin may not be representative of the subpopulation with Body Mass Index (BMI) $\geq$ 27 kg/m^2 on which clinical effectiveness estimates are based.

Figure 2. Clinical effectiveness analysis options



Key: green box illustrates the company's base case efficacy and safety population. The dashed green line illustrates the pooled population including inTandem3, for which results are only available for the 400 mg dose and at 24 weeks.
Abbreviations: BMI, body mass index; pbo, placebo (insulin); sota 200/sota 400, sotagliflozin 200 mg/day and 400 mg/day.

The three inTandem trials comprised the phase III programme for sotagliflozin in T1D, which underpinned the company's submission for marketing authorisation from the European Medicines Agency (EMA). Together, the three trials included 2,977 people with T1D and sought to evaluate the efficacy and safety of sotagliflozin in combination with optimised insulin versus insulin alone (placebo), of whom 1,665 had baseline BMI ≥ 27 kg/m^2 (Table 4). The primary differences between the twin inTandem1 and 2 trials and inTandem3 were length of follow-up, doses studied, and the rigorous 6-week pre-randomisation insulin optimisation in the inTandem1 and 2 trials. Table 4 gives an overview of the inTandem phase III trials and Table 5 outlines the company's quality assessments with comments from the ERG. The ERG's critique of each trial's conduct, population baseline characteristics, and statistical approach is provided in the sections that follow.

Table 4. Summary of the inTandem phase III trial designs

Trial IDs	Countries	Study design	Insulin	Eligibility	N	BMI ≥ 27 kg/m^2, N (%)	Treatment regimen	Treatment period (weeks)	Total follow-up (weeks)	Outcomes
inTandem1 (Buse *et al.* 2017) NCT02384941	USAs, Canada	Phase III RCT, double-blind	Via MDI or CSII. Optimised from Week -6 to 52.	• Adults >18 years • T1D for ≥ 1 year • HbA_{1c} 7–11% • willing/able to perform SMBG • BHB ≤ 0.6 mmol/L • eGFR<45 ml/min/1.73 m^2 • normal liver function • fasting TG > 6.77 mmol/L • no pregnancy • no significant recent cardiac disease or hypertensive emergency • no other antidiabetic agent, recent SGLT2i or chronic OCS.	268	170 (64.6)	Placebo (+insulin)	0–24 (core) 28-wk extension	52 + 4	• change in HbA_{1c} at wk 24 (primary) • % with HbA_{1c} < 7%, no DKA, no SH • body weight • bolus insulin dose • FPG • DTSQ status score • DDS2 score • hypoglycaemic events • SBP • kidney function • EQ-5D-5L • Bristol Stool Form • adverse events
					263	175 (66.8)	Sotagliflozin 200 mg (+insulin)			
					262	174 (64.9)	Sotagliflozin 400 mg (+ insulin)			
inTandem2 (Danne *et al.* 2017) NCT02421510	Europe and Israel	Phase III RCT, double-blind	Via MDI or CSII. Optimised from Week -6 to 52.		258	135 (51.7)	Placebo (+ insulin)	0–24 (core) 28-wk extension	52 + 4	
					261	138 (52.5)	Sotagliflozin 200 mg (+ insulin)			
					263	124 (48.1)	Sotagliflozin 400 mg (+ insulin)			
inTandem3 (Garg *et al.* 2017) NCT02531035	Global	Phase III RCT, double-blind	Via MDI or CSII	As for inTandem1 and 2, plus: • BMI > 18.5 kg/m^2 and • stable non-fast-acting insulin dose (±20%) for 2 weeks prior to screening.	703	379 (54.2)	Placebo (+insulin)	0–24 wks	24 + 4	As for inTandem1 and 2 except: • % with HbA_{1c} < 7%, no DKA, no SH (primary) • additional composites • no HRQoL endpoints
					699	370 (52.6)	Sotagliflozin 400 mg (+insulin)			

Abbreviations: BHB, beta-hydroxybutyrate; DDS2, two-item Diabetes Distress Screening Scale; DKA, diabetic ketoacidosis; DTSQ, Diabetes Treatment Satisfaction Questionnaire; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol Questionnaire 5 dimensions 5 level; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; IDs, identifiers; N, number of patients randomised; SCS, systemic corticosteroid; RCT, randomised controlled trial; SBP, systolic blood pressure; SGLT2i, sodium glucose transporter inhibitor; SH, severe hypoglycaemia; SMBG, self-monitor blood glucose; TG, triglycerides; wk, week.

Table 5. ERG critique of the company's quality assessment of the inTandem phase III trials (based on the NICE checklist)

Aspect of trial design or conduct	Company quality assessment			ERG comments
	inTandem1	inTandem2	inTandem3	
Randomisation/allocation concealment	Low risk	Low risk	Low risk	ERG agrees low risk. [redacted] Information taken from the clinical study reports.
Balance of baseline characteristics	Low risk	Low risk	Low risk	ERG agrees low risk. Baseline characteristics in the ITT population well balanced between groups in all trials. Imbalances highlighted within trials for the BMI subpopulation are unlikely to impact relative treatment effects (see Section 4.2.2).
Blinding of study treatment	Low risk	Low risk	Low risk	ERG agrees low risk. All double-blind, placebo-controlled trials, though better detection bias measures for inTandem 1 and 2 than 3 by use of independent clinical endpoint committee and insulin data monitoring committee.
Withdrawals	Low risk	Low risk	Low risk	ERG agrees low risk. CS Appendix G. Dropout relatively low and balanced in all trials. Somewhat higher rates due to AEs in the sotagliflozin 400 mg groups (see CS Appendix G and text to follow). Mixed-effect model for repeated measures used for continuous outcomes likely to have minimised potential biases from missing data.[37]
Outcome selection and reporting	Low risk	Low risk	Low risk	ERG agrees low risk. Some outcomes not measured at the 52-week follow up for inTandem1 and 2 (e.g. quality of life), but those of primary interest were available and additional results were submitted after the clarification stage (separately and pooled).
Statistical analysis	Low risk	Low risk	Low risk	ERG agrees low risk. Original primary analyses of all trials based on modified ITT population, comprising all randomised patients who took at least 1 dose of study drug. Post-clarification analyses limited to BMI ≥ 27 kg/m^2 (discussed below). ERG satisfied with company's prespecified approach and additional post-hoc analyses conducted after the clarification stage (see 4.2.3).

Abbreviations: AEs, adverse events; CS, company submission; ERG, Evidence Review Group; ITT, intention to treat; NICE, National Institute for Health and Care Excellence.

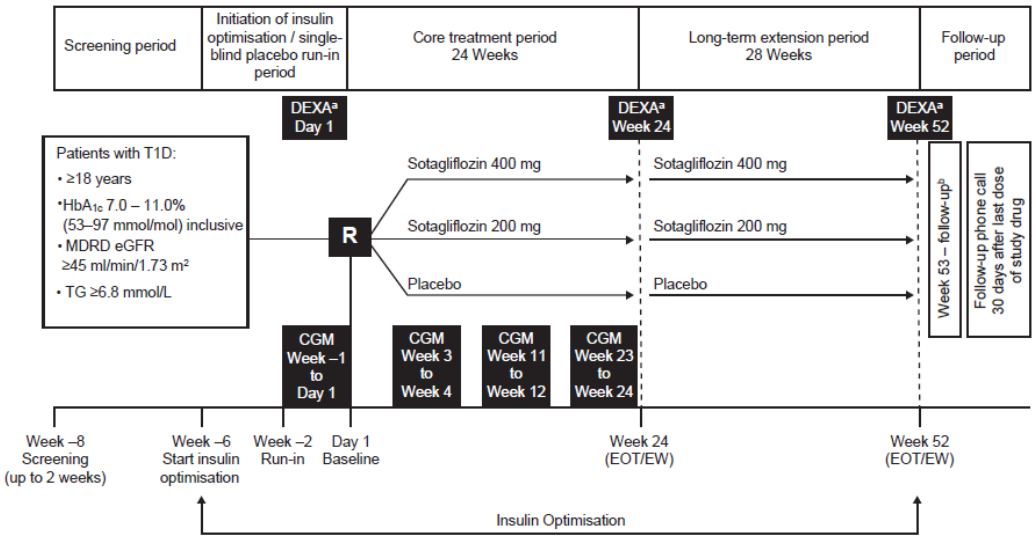
4.2.1 Trial conduct

4.2.1.1 inTandem1 and inTandem2

The inTandem1 and inTandem2 trials evaluated sotagliflozin at two doses for adults with T1D in addition to optimised insulin via multiple daily injections (MDI) or continuous subcutaneous insulin infusion pump (CSII) (Table 4). The twin trials were phase III multicentre, double-blind, placebo-controlled trials and had a 24-week core treatment period followed by a 28-week long-term extension. The inTandem1 trial randomised 793 patients across 75 sites in the USA and Canada of whom 519 had BMI ≥ 27 kg/m^2 (65.4%). The inTandem2 trial randomised 782 patients across 96 sites in Europe and Israel (five in the UK), of whom 397 had BMI ≥ 27 kg/m^2 (50.8%). Randomisation was in a 1:1:1 ratio and stratified by insulin delivery method (MDI, CSII) and screening glycated haemoglobin (HbA_{1c} ≤ 8.5%, > 8.5%). Randomisation was not stratified by BMI, and so randomisation does not hold for the subset of patients with BMI ≥ 27 kg/m^2 required to assess sotagliflozin in line with its likely marketing authorisation.

After a 2-week screening period to confirm eligibility, patients underwent 6-weeks of single-blind insulin optimisation before randomisation to sotagliflozin 200 mg daily (one active tablet plus one placebo), sotagliflozin 400 mg daily (two active tablets), or placebo (two placebo tablets; Figure 3). The ERG's concerns regarding the applicability of the intervention to how it will be used in clinical practice, particularly for the 400 mg dose, are outlined in Section 3.2. Insulin was optimised in all groups throughout the treatment period to evaluate the efficacy of sotagliflozin beyond what can be provided by insulin alone. The ERG's clinical experts expect insulin optimisation prior to treatment initiation and modification during treatment (CS, Appendix H) to be much less rigorous in clinical practice.

Figure 3. Overall trial design for inTandem 1 and inTandem2 (reproduced from CS, Figure 2.1, pg. 24)



CGM, continuous glucose monitoring; DEXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EOT, end of treatment; EW, early withdrawal; HbA_{1c}, glycated haemoglobin; MDRD, modification of diet in renal disease; R, randomisation; T1D, type 1 diabetes; TG, triglycerides.
a Patients who participated in the optional DEXA sub-study were to complete the baseline DEXA −2 weeks from the Day 1 visit. The visit window for DEXA after the Day 1 visit was to be ± 2 weeks.
b Patients who participated in the optional CGM sub-study, and all patients who were screened after institutional review board approval of Amendment 2, were to complete the Week 53 follow-up visit.

Eligibility criteria and insulin optimisation in the trials resulted in a population that had better glycaemic control at the start of treatment than would be the case in the UK (Section 3.1). Patients were eligible if their HbA_{1c} measurement in the 2-week screening period was between 7% and 11% but the subsequent insulin optimisation period meant approximately 20% had adequately controlled HbA_{1c} < 7% at randomisation, making them ineligible for sotagliflozin in line with the indication outlined by the CHMP.[3] The ERG's clinical experts considered patient eligibility criteria reasonable (summarised in Table 4, more detail in CS Table 2.3) but highlighted that the population is broader than the anticipated target population in UK clinical practice (BMI > 30, estimated glomerular filtration rate [eGFR] >60, insulin delivered by MDI, and HbA_{1c} above 8.5% despite efforts to control blood glucose with insulin alone; see Section 3.1).

The primary outcome in both trials was HbA_{1c} change from baseline and the first secondary outcome was a composite 'net benefit' outcome defined as the proportion of patients with HbA_{1c} < 7% and no episodes of severe hypoglycaemia (SH) or diabetic ketoacidosis (DKA). The primary endpoint for all efficacy outcomes was 24 weeks but most were also measured at 52 weeks after the extension period. The ERG considers the choice of outcomes in the trials to be appropriate and in line with the decision problem of interest to this STA but highlights that the 52-week endpoint does not capture the proposed long-term cardiovascular benefits of sotagliflozin. The list of outcomes measured in the trials compared with the NICE final scope is available in Table 2.

Blinding was maintained throughout the treatment periods and patients then received a phone call to capture adverse events that occurred within 30 days of the last dose of study drug (Figure 3). Three independent committees were employed to minimise the potential for bias in the measurement of key endpoints:

- a blinded independent clinical endpoint committee to adjudicate SH, DKA, major cardiovascular events, drug-induced liver injury and deaths;
- a blinded independent insulin dose monitoring committee comprising diabetologists and certified diabetes educators, who reviewed insulin titration decisions from -6 to 24 IU/day to determine consistency of insulin adjustments with self-monitoring of blood glucose;
- an unblinded independent data monitoring committee who reviewed adverse events.

Withdrawals were relatively low and balanced in both studies and unlikely to have introduced attrition bias (text and flow diagrams available in CS Appendix G). Overall, 89.7% of the inTandem1 population and 91.4% of the inTandem2 population completed the 24-week core treatment period, and 84.1% and 86.7% completed the long-term extension. Dropouts were balanced across groups for both trials: 18.7%, 13.3% and 15.6% from the placebo and sotagliflozin 200 mg and 400 mg groups in inTandem1 and 12.8%, 13.4% and 13.7% in inTandem2, respectively. Discontinuation due to adverse events over the full treatment period was somewhat higher in the 400 mg group of inTandem1 (n = 17; 6.5%) and inTandem2 (n = 18; 6.8%) than for the sotagliflozin 200 mg and placebo groups (n = 9 to 13; 3.5–4.9%), but other reasons for discontinuation were similar.

The trials included two sub-studies that included patients recruited at selected sites. The continuous glucose monitoring (CGM) sub-study included approximately 18% of participants across inTandem1 and inTandem2 (n = 288; CS Appendices, Figure G.1 and G.2) and used blinded monitoring over four 1-week periods (Figure 3) to assess the effect of sotagliflozin on glucose variability. The dual-energy X-ray absorptiometry (DEXA) sub-study included approximately 15% of participants across both studies (n = 243) and investigated the effect of sotagliflozin on fat mass (weeks 0, 24 and 52) and bone density (weeks 0 and 52). None of the outcomes which were the focus of the sub-studies are required to meet the NICE final scope, so the ERG provides only a brief critique as supplementary information with the clinical effectiveness results.

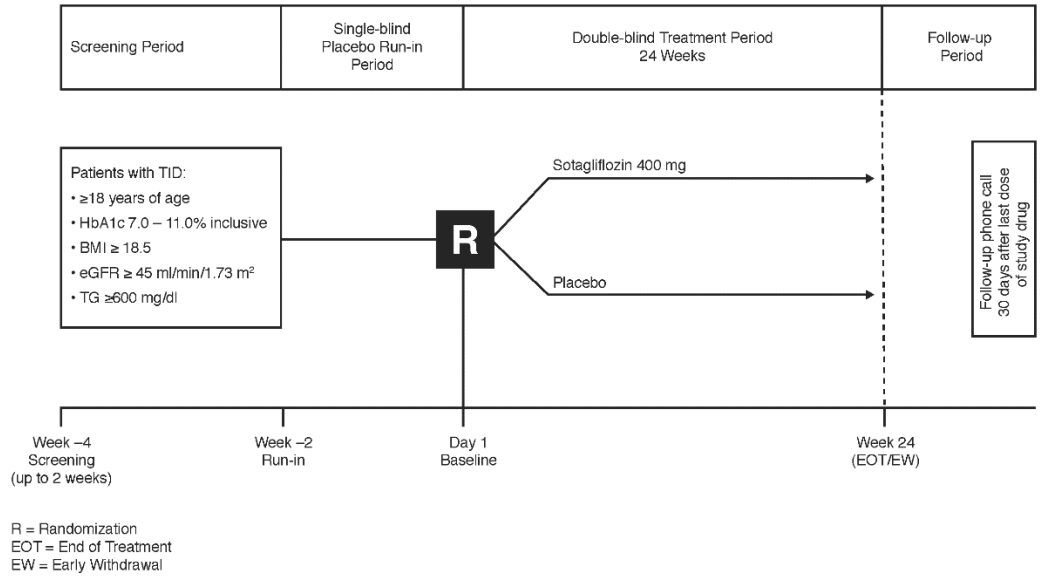
4.2.1.2 inTandem3

The inTandem3 trial was designed to evaluate sotagliflozin at the higher 400 mg daily dose for adults with T1D in addition to insulin via MDI or CSII (Table 4). Like inTandem1 and inTandem2, it was a phase III multicentre, double-blind, and placebo-controlled trial with a 24-week core treatment period, but inTandem3 did not have a long-term extension. The inTandem3 trial randomised 1,402 patients

across 133 sites in 19 countries globally, of whom 749 had BMI ≥ 27 kg/m^2 (53.4%), and approximately a third of patients were recruited in Europe. Randomisation was in a 1:1 ratio and stratified by BMI at screening (< 25 kg/m^2, ≥ 25 kg/m^2), insulin delivery method (MDI, CSII) and screening HbA_{1c} (≤ 9%, > 9%). While randomisation was stratified by BMI, it was not at the same cut-off as the subpopulation required to assess sotagliflozin in line with its likely marketing authorisation, so the benefits of randomisation are lost.

Patients were randomised to sotagliflozin 400 mg daily (two active tablets) or placebo (two placebo tablets; Figure 3) and the ERG had the same concerns as for the twin trials regarding the applicability of evidence for the 400 mg dose because it was not stepped up from 200 mg as recommended in the draft SmPC (Section 3.2).

Figure 4. Overall trial design for inTandem3 (reproduced from CS Appendix E, Figure E.1)



Abbreviations: BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; EOT, end of treatment; EW, early withdrawal; HbA_{1c}, glycated haemoglobin; R, randomisation; T1D, type 1 diabetes; TG, triglycerides.

Baseline HbA_{1c} eligibility was the same for all three trials (7–11%) but inTandem3 may better reflect clinical practice because insulin was not optimised rigorously before treatment, meaning the baseline levels are closer to what would be anticipated in the UK (see Section 4.2.2). As for the twin trials, the ERG's clinical experts considered other patient eligibility criteria reasonable (summarised in Table 4) but highlighted that the population is somewhat broader than the anticipated target population in UK clinical practice (Section 3.1).

The primary outcome was the composite 'net benefit' outcome used as the first secondary outcome for inTandem1 and inTandem2 (proportion of patients with HbA_{1c} < 7% and no episodes of SH or DKA at 24 weeks). Other outcomes were similar to the twin trials but inTandem3 did not measure quality of life (Table 4). The ERG considers the choice of outcomes in the trials appropriate and in line with the decision problem but highlights that inTandem3 could not be included in analyses of the

longer 52-week endpoint because it only followed patients for 24 weeks. As such, the trial does not evaluate the longevity of initial benefits (e.g. glycaemic control and BMI) or the proposed long-term cardiovascular benefits of sotagliflozin.

As for inTandem1 and inTandem2, blinding was maintained throughout the treatment period and patients then received a phone call to capture adverse events that occurred within 30 days of the last dose of study drug (Figure 3). The inTandem3 trial employed an unblinded independent data monitoring committee to review adverse events, but differed in the following procedures to manage insulin and minimise bias in outcome measurement:

- investigators were blinded to laboratory tests for HbA_{1c} and fasting plasma and urinary glucose levels after randomisation, but were informed about HbA_{1c} >11% after week 16 to inform treatment changes;
- there was no blinded independent insulin dose monitoring committee to determine whether insulin adjustments were consistent with self-monitoring of blood glucose;
- there was no blinded independent clinical endpoint committee to adjudicate SH, DKA, major cardiovascular events, drug-induced liver injury and deaths.

Overall, 87.5% of the randomised population completed the study, and the dropout rate was balanced between groups (11.5% of the placebo group and 13.6% of the sotagliflozin group). However, more people in the sotagliflozin 400 mg group dropped out due to adverse events than in the placebo group (2.3% vs 6.4%), whereas there were somewhat more patient decision withdrawals in the placebo group (6.2% vs 4.6%); other reasons for discontinuation were relatively balanced.

4.2.2 Baseline characteristics

Baseline characteristics were provided for the ITT populations of the three phase III inTandem trials (CS, Table 2.4 and CS Appendix, Table E.3) and for the subpopulation with BMI ≥ 27 kg/m^2. The ERG's critique focuses on the baseline characteristics of the pooled inTandem1 and inTandem2 subpopulation with BMI ≥ 27 kg/m^2, on which the company's primary estimates of effectiveness are based. Baseline characteristics of each phase III inTandem trial (BMI ≥ 27 kg/m^2) are reproduced for reference in Appendix 10, and important variation is noted in the summary below.

In the economic model, treatment effects are derived from the pooled inTandem1 and inTandem2 trials but starting values are taken from a simulated cohort of UK patients based primarily on characteristics from the National Diabetes Audit (NDA) data described in NICE Guideline NG17.[8] The ERG has explored differences between the trial baseline characteristics and the simulated cohort to determine whether it is reasonable to apply inTandem treatment effects to a different population.

Randomisation is broken by limiting the population to those with BMI ≥ 27 kg/m^2, but the ERG does not note any key imbalances between treatment groups in the pooled inTandem1 and inTandem2 population from which treatment effects are derived for the company's base case (Table 6).

Table 6. Pooled baseline characteristics for primary efficacy population (inTandem1 and inTandem2 BMI ≥27 kg/m^2) and simulated cohort

	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)	Insulin alone (N = 298)	Simulated cohort
Age in years, Mean (SD)	45.9 (12.72)	45.5 (11.98)	43.3 (12.62)	42.98 (19.14)
Female sex, n (%)	148 (48.5)	159 (50.8)	143 (48.0)	(43.3)
Race white, n (%)	280 (91.8)	293 (93.6)	283 (95.0)	92.0
Duration of diabetes (years), n (%) <20	134 (43.9)	154 (49.2)	138 (46.3)	Mean 16.92 (SD 13.3)
≥20 to <40	140 (45.9)	129 (41.2)	133 (44.6)	
≥40	31 (10.2)	30 (9.6)	27 (9.1)	
Body weight in kg, Mean (SD)	94.68 (15.405)	93.66 (16.152)	94.20 (15.294)	-
BMI (kg/m^2), Mean (SD)	32.49 (4.363)	31.96 (4.049)	32.03 (4.240)	27.09 (5.77)
Insulin delivery method2, CSII, n (%)	140 (45.9)	147 (47.0)	138 (46.3)	-
Total daily insulin dose (IU/day), Mean (SD)	76.08 (41.323)	72.15 (37.215)	77.89 (41.519)	-
Bolus insulin dose (IU/day), Mean (SD)	36.82 (23.914)	35.76 (24.525)	38.97 (27.112)	-
Basal insulin dose (IU/day), Mean (SD)	39.26(23.120)	36.35 (18.131)	38.92 (19.407)	-
HbA_{1c} (%), Mean (SD)	7.72 (0.747)	7.63 (0.747)	7.62 (0.760)	8.60 (4.00)
Baseline FPG (mg/dL), Mean (SD)	163.46 (72.315)	156.33 (67.561)	157.33 (66.249)	
SBP (mm Hg), Mean (SD)	124.6 (15.15)	123.6 (14.42)	124.3 (14.24)	128.27 (16.07)
SBP ≥130 mm Hg4, n (%)	101 (33.1)	108 (34.5)	99 (33.2)	-
DBP (mm Hg), Mean (SD)	79.1 (9.53)	77.8 (8.14)	78.0 (8.21)	80.0 (0.00)
2-hour PPG (mg/dL), N, Mean (SD)	N=57 213.68 (96.954)	N=62 208.92 (82.837)	N=52 224.67. (81.376)	-
DTSQs score, Mean (SD)	N=300, 28.4 (5.15)	N=309, 28.8 (4.89)	N=291, 28.7 (5.74)	-
DDS2 score, Mean (SD)	N=300, 5.4 (2.03)	N=310, 5.1 (2.14)	N=292, 5.1 (2.25)	-
Time in range (≥70 to ≤180 mg/dL), (%)	N=59 52.155 (52.464)	N=65 50.317 (50.801)	N=58 50.683 (14.5506)	-

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose, HbA_{1c}, glycated haemoglobin; ITT, intention-to-treat population; IU, international unit; n, number of patients; SBP, systolic blood pressure; SOTA, sotagliflozin; SD, standard deviation.

A summary of important differences noted by the ERG between groups and between the pooled trials and the simulated cohort are given below. Individual trial baseline characteristics for the subpopulation with BMI ≥ 27 kg/m^2 are provided in Appendix 10.

- Mean age was somewhat lower in the placebo group (43.3 years) of the pooled population than the active treatment groups (45.5–45.9 years), but the ERG considers the trial population

comparable to Clinical Practice Research Datalink (CPRD) data for patients with T1D in the UK (mean 45.6 years), and the simulated cohort (42.98 years). In each trial, mean age ranged from 41 to 47 years (Table 49)

- Duration of diabetes was only reported categorically but showed some imbalance across groups in the pooled population, and the data indicate more longstanding disease in the trials than the simulated cohort (mean 16.9 years). Across trials, the inTandem2 and inTandem3 populations had less longstanding disease (approximately 58% and 51% < 20 years) than inTandem1 (37% < 20 years), and imbalance between groups was most notable within inTandem2 (Table 49);

- Mean weight in the pooled population was around 94 kg and mean BMI was 32 kg/m^2, whereas starting BMI for the simulated cohort is 27.09 kg/m^2. Mean weight within treatment groups of each trial ranged from 92.2 to 96.1 kg and mean BMI was between 31 and 33 4 kg/m^2; mean weight and BMI is higher than the UK average for patients with T1D (27.4 4 kg/m^2) because the subpopulation was limited to those with BMI ≥ 27 kg/m^2;

- CSII pump usage was higher in the pooled population (~46%) than in UK practice (~15%), although uptake has been highly variable across the UK (see Section 3.1).[9] Upwards of 60% of the inTandem1 population used insulin pumps compared with approximately 27% of inTandem2 and 41% of inTandem3;

- Total daily insulin doses were highest in inTandem1 (North America), which may reflect the heavier population in that trial; the ERG's clinical experts considered the doses of the pooled population reflective of similar patients in the UK;

- Mean HbA_{1c} % in the pooled population (7.62–7.72%) is lower than expected in UK clinical practice (8.8%) and was lower after 6 weeks of insulin optimisation. Some imbalance between groups is noted in the inTandem1 trial, and baseline values in the inTandem3 trial, which did not optimise insulin prior to baseline, are closer to the UK mean (Table 49)

- Mean fasting plasma glucose (FPG) was 156–163 mmol/mL in the pooled population. Baseline means were imbalanced between groups inTandem1 and inTandem2, but standard deviations suggest values were highly variable between patients;

- Mean blood pressure was approximately 124/78 in the pooled population, which is comparable to the simulated cohort starting values. Mean systolic and diastolic blood pressure (SBP and DBP) across the trials ranged from 121.8 to 127.6 and 77.2 to 80.3, respectively;

the percentage of patients with SBP ≥ 130 was highest in inTandem2 (~41%), followed by inTandem3 (~35%) and inTandem1 (~27%);

Information provided by the company at the clarification stage indicated that approximately 40% of patients in each phase III inTandem trial were on non-insulin concomitant therapies (company response to clarification, Appendix A). The most common were renin-angiotensin system and lipid modifying agents (see summary in Appendix 9.4). In general, more patients received concomitant therapies in the inTandem1 trial (North America) compared with the inTandem2 (Europe) or inTandem3 (global) trials. The ERG notes that a small proportion of patients (<2%) also received concomitant metformin (including metformin hydrochloride) or sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g. canagliflozin and dapagliflozin) during the trials, even though they may have been randomised to sotagliflozin. However, due to the small patient numbers using concomitant metformin and SGLT2 inhibitors it is unlikely to have had much, if any impact on the study results.

Imbalances in percentage female, duration of diabetes, FPG, and weight within and between the trials do not suggest a pattern that would systematically favour one group over another within a trial or impact differences between treatment when results of inTandem1 and inTandem2 are pooled. Most notably, baseline HbA_{1c} in inTandem3 is closer to what would be expected in UK clinical practice than inTandem1 and 2 because insulin optimisation over and above usual efforts to control HbA_{1c} prior to treatment initiation would not be feasible in the NHS. However, inTandem3 did not assess sotagliflozin 200 mg or include a 52-week follow-up, and so it cannot alone provide the data required to assess clinical and cost-effectiveness. The ERG highlights differences in absolute and relative treatment effects between the primary pooled population (inTandem1 and inTandem2) and inTandem3 in Section 4.3. Subgroup analyses are also explored in Section 4.3.7 to assess the moderating effect of key factors that differ between the pooled population and the simulated cohort of patients onto which effects are applied in the economic model (HbA_{1c}, BMI, insulin delivery).

4.2.3 Description and critique of statistical approach used

A summary of the statistical approach taken by the company in their original and updated submission is provided in Table 7. Where appropriate, the ERG includes a comment about the analyses it deems most appropriate and a reference to the relevant sections of the CS and the company's response to clarification for more information. Statistical analyses summarised in the table focus on inTandem1 and inTandem2, the studies from which efficacy and safety estimates for the economic model are derived. Results from inTandem3 were incorporated in pooled 24-week analyses but do not contribute to the 52-week estimates supporting the economic analysis.

The main difference in statistical approach between the original and updated submissions is the underlying population used for analysis. Primary analyses for the original submission were based on

52-week ITT data from inTandem2 (efficacy) or pooled ITT data from inTandem1 and inTandem2 (safety). Primary efficacy and safety analyses in the updated submission are based on pooled inTandem1 and inTandem2 52-week data for the subpopulation of patients with BMI ≥ 27 kg/m^2. The ERG notes that BMI was not a randomisation stratification factor in any trial and a different cut-off of 30 kg/m^2 was used for prespecified BMI subgroup analyses. The ERG notes that assumptions underlying the power calculation for inTandem1 and inTandem2 are broken for trial-based results of the BMI ≥ 27 kg/m^2 subpopulation but are met when the two trials are pooled. As such, the ERG agrees with the company's approach to use pooled estimates for the BMI subpopulation as the primary analyses to align the population with the indication for sotagliflozin.

The ERG requested *post-hoc* analyses limiting the population further by insulin delivery method (MDI) and screening HbA_{1c} (≥ 8.5%) to explore potential differences in treatment effects for the population likely to receive sotagliflozin should it be recommended for use in the NHS (see Section 3.1). The company indicated that doing so would result in very small sample sizes even when trials were pooled (company response to clarification, Tables 20–22), and instead conducted a set of subgroup analyses to show consistency of effect for the key outcomes. A critique is provided by the ERG in Section 4.3.7.

Overall, the ERG is satisfied with the statistical approach taken in the inTandem trials that was prespecified in the analysis plan, which it understands was applied in the same way for the updated submission (BMI ≥ 27 kg/m^2 subpopulations) as for initial submission (ITT trial populations). The range of supplemental analyses provided allow the robustness of effect estimates to be explored across key effect modifiers highlighted by the ERG's clinical experts. The outcomes available and timepoints at which they are reported are in line with those prespecified in the trial analysis plans and the method of analysis for continuous endpoints is likely to have minimised potential biases from missing data.[37]

Table 7. Summary of the company's statistical approach with critique from the ERG

Analysis	CS Section	Summary and ERG critique
Sample size calculation	CS, Table 2.5 (pgs 33–34) and subpopulation numbers reported in results tables from company response to CQ	Power assumptions do not hold for individual trial subpopulations with BMI ≥ 27 kg/m^2 but 90% power is maintained if trials are pooled. inTandem1 and 2 (inputs for economic model): 90% power to determine difference from placebo of either dose in mean HbA_{1c} at 24 weeks (overall two-sided α=0.05) required 244 patients per treatment group, assuming: • true treatment difference of −0.4% and common SD of 1.0%; • 157 patients per treatment group, adjusted for 20% dropout at 24 weeks to reflect primary analysis being conducted in the mITT.
Efficacy analysis	CS, Table 2.5 (pgs 33–34)	Original primary analyses: inTandem1 and 2 pooled mITT at 52 weeks (all randomised patients who had taken at least one dose of study drug). Updated primary analyses: post-hoc inTandem1 and 2 BMI ≥ 27 kg/m^2 subpopulation pooled at 52-weeks (ERG agrees most appropriate). Also provided: trial results for ITT and subpopulation, and subpopulation 24-week data pooled with inTandem3.

		• inTandem 1 and 2 HbA_{1c} analysed with MMRM (other endpoints MMRM or ANCOVA) based on restricted maximum likelihood; fixed, categorical effects of treatment, randomisation strata, study week and treatment-by-time interaction, with baseline HbA_{1c} -by-time interaction as a covariate; • binary endpoints used a CMH test with randomisation strata.
Safety analysis	CS, Table 2.5 (pgs 33–34)	Original primary analyses: inTandem1 and 2 pooled at 52 weeks (all randomised patients, ≥ 1 dose of actual treatment received on day 1). Updated primary analyses: as for efficacy analyses (ERG agrees most appropriate); some safety data not in model based on pooled phase II/III. Also submitted: trial results for ITT and subpopulation, subpopulations pooled with inTandem3, and ITT pooled with inTandem3 and phase I/II data. • 24-week core period and end of 28-week extension (inTandem1+2 only); • TEAE reporting prespecified (e.g. overall incidence by system organ class and preferred term, maximum intensity, special interest); • number of patients with events and exposure-adjusted rates reported.
Missing data	CS, Table 2.5 (pgs 33–34)	Minimal information provided but amount and balance of dropout at 24 and 52 weeks unlikely to impact relative treatment effects (see Section 4.2.1). Missing observations at Week 24 were imputed as non-response and use of MMRM appropriate to minimise bias due to missing data.
Sub-study analysis	CS, Table 2.5 (pgs 33–34)	CGM (N = 288) and DEXA (N = 243) sub-studies of inTandem1 and 2 supplement main analyses; provided for BMI subpopulation. CGM outcomes include change in % time spent outside, above, below and within range at week 24; analysed using MMRM including corresponding endpoint and baseline values. DEXA outcomes include change to Week 24 in total fat mass, fat mass and bone density at weeks 52; analysed using ANCOVA.
Subgroup analysis	CS Section 2.8 (pgs 57–60) and company response to CQ (pgs 15–21)	Original submission: prespecified subgroup analyses of HbA_{1c} based on ITT pooled 24-week data from inTandem1 and 2. Updated submission: prespecified ITT subgroups at 24-weeks for all three trials separately and pooled plus post-hoc analyses to explore treatment effects at different HbA_{1c} cut-offs within the BMI ≥ 27 kg/m^2 subpopulation.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; CGM, continuous glucose monitoring; CMH, Cochran-Mantel-Haenszel; CQ, clarification questions; CSII, continuous subcutaneous insulin infusion; CS, company's submission; DEXA, dual-energy X-ray absorptiometry; DKA, diabetic ketoacidosis; ECG, electrocardiogram; HbA_{1c}, glycated haemoglobin; MDI, multiple daily injection; mITT, modified intention-to-treat; MMRM, mixed-effects model for repeated measures; SD, standard deviation, TEAE, treatment-emergent adverse event.
Nb: CGM target range predefined as 3.9–10 mmol/L; randomisation strata for inTandem1 and 2 were MDI/CSII and HbA_{1c} week −2 ≤8.5%/>8.5%.

4.3 Clinical effectiveness results

The ERG has focussed its critique on the efficacy analyses chosen by the company to inform its base case (inTandem1 and inTandem2 pooled subpopulation with BMI ≥ 27 kg/m^2), which are summarised for reference in Table 8 (compiled from Tables 42–57 in the company's response to clarification). In the sections that follow, the ERG highlights differences in results across the range of analyses submitted (e.g. individual trials, ITT population, pooled results including inTandem3 and/or phase II trials), with a comment about which may be most applicable to patients in the UK.

Differences between the efficacy and safety of sotagliflozin 200 mg and 400 mg are explored to assess the appropriateness of the company's choice to use data for 200 mg for both doses in the economic model. The trials randomised patients to stable doses of 200 mg or 400 mg but, in the

economic model, the company assume that all patients start sotagliflozin at 200 mg in line with the draft SmPC, and that 10% will escalate to 400 mg.

In general, the primary results shown in Table 8 suggest modest benefits of sotagliflozin compared with insulin alone for various outcomes, which are generally more pronounced for the 400 mg dose than the 200 mg dose. Treatment effect wanes between 24 and 52 weeks for some outcomes (HbA_{1c}, net benefit, eGFR) and increases for others (BMI, weight, and measures of cardiovascular risk), and the trials cannot inform assumptions of treatment effect durability beyond the first year.

Table 8. Primary efficacy results (pooled BMI ≥ 27 kg/m^2 subpopulations of inTandem1 and inTandem2 [N = 916])

Outcome	wks	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Difference (95% CI) p-value*	
					200 mg vs insulin alone	400 mg vs insulin alone
HbA_{1c} (%)	24	−0.43 (0.03)	−0.50 (0.03)	−0.04 (0.03)	**−0.39 (−0.48, −0.30) <0.001**	**−0.45 (−0.54, −0.36) <0.001**
	52	−0.24 (0.04)	−0.38 (0.04)	−0.00 (0.04)	**−0.24 (−0.35, −0.13) <0.001**	**−0.38 (−0.49, −0.27) <0.001**
FPG (mg/dL)	24	−9.3 (3.33)	−18.6 (3.28)	6.4 (3.36)	**−15.7 (−24.7 to −6.7) <0.001**	**−25.0 (−33.9, −16.1) <0.001**
	52	−7.65 (3.77)	−19.60 (3.69)	6.82 (3.87)	**−14.46 (−24.83 to −4.10) 0.006**	**−26.42 (−36.66, −16.18) <0.001**
Patients with net benefit out of total (%)	24	91/305 (29.8%)	131/313 (41.9%)	57/298 (19.1%)	**10.71 (3.90, 17.51) 0.001**	**22.73 (15.67, 29.78) <0.001**
	52	73/305 (23.6%)	100/313 (31.9%)	55/298 (18.5%)	5.15 (−1.34, 11.64) 0.108	**13.49 (6.70, 20.28) <0.001**
Body weight, kg	24	−1.93 (0.2)	−2.98 (0.19)	0.34 (0.20)	**−2.27 (−2.81. −1.74) <0.001**	**−3.32 (−3.85, −2.79) <0.001**
	52	−2.16 (0.25)	−3.61 (0.25)	0.85 (0.26)	**−3.01 (−3.71, −2.31) <0.001**	**−4.46 (−5.15, −3.76) <0.001**
BMI (kg/m^2)	24	−0.69 (0.07)	−1.02 (0.07)	0.09 (0.07)	**−0.78 (−0.97, −0.60) <0.001**	**−1.11(−1.29, −0.93) <0.001**
	52	−0.77 (0.09)	−1.24 (0.09)	0.28 (0.09)	**−1.05 (−1.29, −0.81) <0.001**	**−1.53 (−1.77, −1.29) <0.001**
SBP (mmHg)	24	−2.9 (0.64)	−4.0 (0.64)	−1.6 (0.65)	−1.3 (−3.0, 0.4) 0.13	**−2.5 (−4.2, −0.8) 0.005**
	52	−1.7 (0.66)	−3.2 (0.65)	0.4 (0.67)	−2.1 (−3.9, 0.4) 0.018	**−3.6 (−5.3, −1.9) <0.001**
Total cholesterol (mg/dL)	24	7.36 (1.66)	7.91 (1.63)	5.04 (1.67)	2.32 (−1.98, 6.62) 0.290	2.87 (−1.38, 7.11) 0.186
	52	8.84 (1.75)	12.63 (1.73)	4.44 (1.80)	4.40 (−0.28, 9.08) 0.065	**8.18 (3.55, 12.82) <0.001**
Bolus insulin (IU/day)	24	−3.89 (0.72)	−5.91 (0.71)	−1.86 (0.72)	**−2.02 (−3.92, −0.12) 0.037**	**−4.05 (−5.93, −2.17) <0.001**
	52	−3.33 (0.78)	−6.40 (0.77)	−2.47 (0.80)	−0.86 (−2.98, 1.25) 0.423	**−3.93 (−6.03, −1.84) <0.001**
Basal insulin (IU/day)	24	−0.14 (0.45)	−1.14 (0.45)	1.57 (0.46)	**−1.72 (−2.93, −0.50) 0.006**	**−2.71 (−3.92, −1.51) <0.001**
	52	−0.07 (0.52)	−1.87 (0.514)	2.46 (0.53)	**−2.53 (−3.95, −1.11) <0.001**	**−4.33 (−5.74, −2.92) <0.001**
DDS2	24	−0.5 (0.10)	−0.5 (0.10)	0.1 (0.10)	**−0.6 (−0.9, −0.3) <0.001**	**−0.7 (−0.9, −0.4) <0.001**
DTSQs	24	2.3 (0.26)	2.2 (0.26)	−0.3 (0.27)	**2.6 (1.9, 3.3) <0.001**	**2.6 (1.9, 3.3) <0.001**

Results are change from baseline least mean squares with standard error except for net benefit (proportion with HbA_{1c} < 7% and no severe hypoglycaemia or diabetic ketoacidosis) which is reported as the % of responders. Statistically significant differences are indicated in **bold**. Data are collated from the company's response to clarification, Tables 42–56.
Abbreviations: CFB, change from baseline; CI, confidence interval; DBP, diastolic blood pressure; DDS2, 2-item Diabetes Distress Screening Scale; DTSQ, Diabetes Treatment Satisfaction Questionnaire; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; IU/day, international units per day; LSM, least square mean; mg/dL, milligram per decilitre; mm/Hg, millimetre of mercury; SE, standard error; SPG, systolic blood pressure.

4.3.1 HbA_{1c}/glycaemic control/blood glucose variability

The difference in least squares mean change in HbA_{1c} (%) from 0 to 52 weeks for the company's primary population was –0.24% for sotagliflozin 200 mg versus insulin alone (95% confidence interval [CI]: –0.35 to –0.13) and –0.38% (95% CI: -0.49 to -0.27) for sotagliflozin 400 mg versus insulin alone (Table 9). The benefits of both doses versus insulin alone are statistically significant across all the analyses conducted (p-values from <0.001 to 0.003; company's response to clarification, Tables 1 and 42), although benefits are smaller at 52 weeks than at 24 weeks. Results for the full trial populations on which the initial submission was based show a similar pattern of effects that are slightly smaller in magnitude than those for the BMI ≥ 27 kg/m^2 subpopulation; HbA_{1c} (%) change from baseline at 52 weeks for sotagliflozin 200 mg vs insulin alone was -0.25 and -0.21 for inTandem1 and inTandem2, respectively (CS Figures 2.2 and 2.3).

Table 9. HbA_{1c} (%) change from baseline analyses for the BMI ≥ 27 kg/m^2 subpopulation

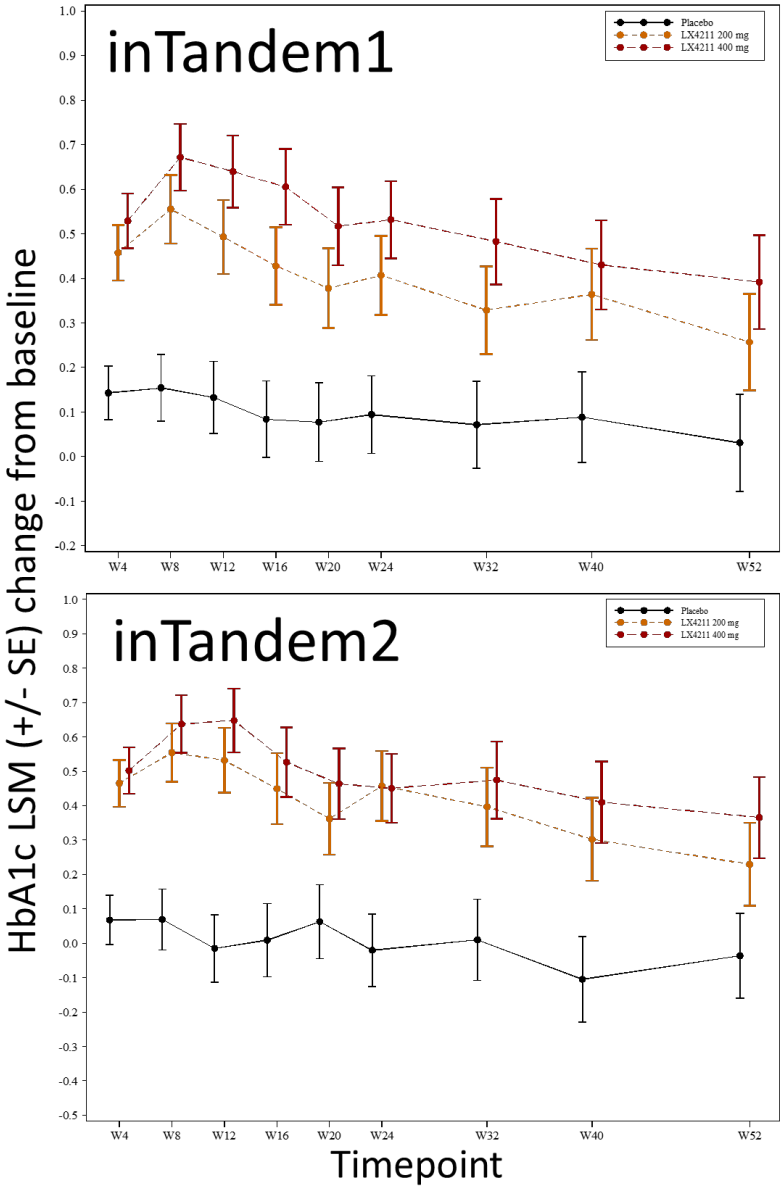
Analysis	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Primary efficacy population – inTandem1 and inTandem2 pooled					
24 weeks	−0.43 (0.03)	−0.50 (0.03)	−0.04 (0.03)	**−0.39 (−0.48, −0.30)**	**−0.45 (−0.54, −0.36)**
52 weeks	−0.24 (0.04)	−0.38 (0.04)	−0.00 (0.04)	**−0.24 (−0.35, −0.13)**	**−0.38 (−0.49, −0.27)**
Alternative analyses – 24 weeks					
inTandem1	−0.41 (0.05)	−0.54 (0.05)	−0.10 (0.05)	**−0.31 (−0.43, −0.19)**	**−0.44 (−0.56, −0.32)**
inTandem2	−0.46 (0.05)	−0.45 (0.05)	0.02 (0.05)	**−0.48 (−0.62, −0.34)**	**−0.47 (−0.61, −0.34)**
inTandem3	−	−0.86 (0.07)	−0.32 (0.07)	−	**−0.54 (−0.64, −0.44)**
All pooled	−	−0.65 (0.03)	−0.15 (0.03)	−	**−0.50 (−0.57, −0.43)**
Alternative analyses – 52 weeks					
inTandem1	−0.26 (0.06)	−0.39 (0.05)	−0.03 (0.06)	**−0.23 (−0.37, −0.08)**	**−0.36 (−0.51, −0.21)**
inTandem2	−0.23 (0.06)	−0.37 (0.06)	0.036 (0.06)	**−0.27 (−0.43, −0.10)**	**−0.40 (0.00)**

Data collated from the company's response to clarification, Tables 1 and 42. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean.

HbA_{1c} changes from baseline are noticeably larger for inTandem3 than for inTandem1 and inTandem2, which is likely related to pre-randomisation insulin optimisation in inTandem1 and inTandem2. The optimisation resulted in mean HbA_{1c} reductions of 0.6% to a baseline mean of approximately 7.6% (CS, Table 2.7, pg. 41), which limits the potential for HbA_{1c} improvement during treatment in all groups. The ERG's clinical experts suggested optimisation over and above usual efforts to control HbA_{1c} is unlikely to happy prior to initiation of sotagliflozin in the NHS, meaning inTandem3 may better reflect UK clinical practice. However, inTandem3 did not assess the 200 mg dose and did not measure outcomes at 52 weeks. Nonetheless, comparing results across the analyses for sotagliflozin 400 mg versus placebo suggests the relative treatment effect of sotagliflozin versus insulin alone may be underestimated to some extent by the twin trials in which insulin was optimised prior to treatment.

HbA_{1c} shows a consistent pattern of larger benefits of sotagliflozin at 400 mg across analyses. Consequently, the ERG agrees with the company that using 200 mg efficacy data as a proxy for sotagliflozin 400 mg in the economic model is conservative. However, the ERG considers the company's assumption that treatment effects observed at 52 weeks will persist for five years unlikely given the nature of change in HbA_{1c} observed in the trials (Figure 5). Scenario analyses requested by the ERG to test alternative assumptions are discussed in the cost-effectiveness sections, and subgroup analyses to explore the effect of baseline characteristics between the trials and patients in the UK are presented in Section 4.3.7.

Figure 5. HbA_{1c} (%) change from baseline for the BMI ≥ 27 kg/m^2 subpopulation (adapted from company's response to CQ Appendix B, Figures 1 and 9)



Abbreviations: CQ, clarification questions; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; SE, standard error.
Post-Baseline LSM are obtained from mixed-effect model for repeated measures with treatment, randomization strata of insulin delivery and Week -2 A1C [<=8.5 %, >8.5 %], time and a treatment-by-time as fixed categorical effects and baseline HDL-C-by-time interaction as a covariate.

As for HbA_{1c}, sotagliflozin showed benefits for other glycaemic outcomes in the primary efficacy population that were more distinct for the 400 mg dose than for 200 mg. However, the benefits were more variable across the alternative analyses and did not consistently show the same reduction in effect between week 24 and 52. For example, there was a benefit in fasting plasma glucose (FPG) for sotagliflozin 200 mg versus insulin alone of –15.7 mg/dL at week 24 (95% CI: –24.7 to –6.7) and –14.46 mg/dL at week 52 (95% CI: –24.83 to –4.10) for the primary population, but the same outcome was twice as large for inTandem2 alone than inTandem1 (–23.8 vs –9.7 mg/dL; Table 10). The ERG also notes important variation in the percentage of patients with net benefit across studies and analyses, defined as the proportion of patients with good HbA_{1c} control (< 7%) and no episodes of SH or DKA. The difference in percentage response between sotagliflozin 400 mg dose and insulin alone in inTandem1 at 24 weeks (27.9%) was around double the difference observed for inTandem2 (16.4%) and inTandem3 (15.5%). The difference between trials in net benefit, which persisted at 52 weeks (company response to clarification, Table 2), may be at least partially explained by the lower baseline HbA_{1c} in inTandem1.

Table 10. Fasting plasma glucose change from baseline (BMI ≥ 27 kg/m^2 subpopulation)

Analysis	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Primary efficacy population 24 weeks – fasting plasma glucose change from baseline					
24 weeks	−9.3 (3.33)	−18.6 (3.28)	6.4 (3.36)	**−15.7 (−24.7, −6.7)**	**−25.0 (−33.9, −16.1)**
52 weeks	−7.65 (3.77)	−19.6 (3.69)	6.82 (3.87)	**−14.46 (−24.83, −4.10)**	**−26.42 (−36.66, −16.18)**
Alternative analyses – 24 weeks					
inTandem1	−6.5 (4.20)	−17.2 (4.14)	3.2 (4.19)	−9.7 (−20.8, 1.5)	**−20.4 (−31.4, −9.3)**
inTandem2	−12.6 (5.42)	−20.9 (5.37)	11.2 (5.52)	**−23.8 (−38.4, −9.1)**	**−32.0 (−46.6, −17.5)**
inTandem3	−	−23.5 (6.34)	0.8 (6.46)	−	**−24.3 (−33.5, −15.1)**
All studies	−	−18.5 (2.45)	6.1 (2.48)	−	**−24.7 (−31.2, −18.1)**
Alternative analyses – 52 weeks					
inTandem1	−7.22 (4.98)	−16.51 (4.87)	7.64 (5.11)	**−14.85 (−28.51, −1.20)**	**−24.15 (−37.66, −10.64)**
inTandem2	−7.81 (5.87)	−23.81 (5.77)	5.78 (6.01)	−13.60 (−29.66, 2.47)	**−29.59 (−45.48, −13.69)**

Data collated from the company's response to clarification, Tables 6 and 50. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean.

Differences between sotagliflozin and insulin alone were mostly statistically significant for both doses across all analyses at both timepoints. However, differences in magnitude and clinical significance of effects between studies and pooled analyses may have important impacts on cost-effectiveness and may reflect study differences highlighted in Section 4.2.2. Furthermore, the pattern of reduced effect between 24 and 52 weeks, which is more apparent for HbA_{1c} and net benefit than FPG, suggests it is unreasonable to assume durability of all effects beyond one year in the economic model.

Glucose variability outcomes at week 24 for the subset of patients who took part in the continuous glucose monitoring sub-study (inTandem1 and inTandem2) were also provided for the subpopulation

with BMI ≥ 27 kg/m^2 (Addendum, Tables 5 and 6). Results for change in time spent in target glycaemic range (3.9–10.0 mmol/L) and post-prandial glucose showed a similar pattern to FPG of much larger benefits compared with insulin alone for inTandem2 than inTandem1. Pooled results indicated statistically significant mean benefits over insulin alone of 8.17% for sotagliflozin 200 mg (p= 0.007) and 15.05% for sotagliflozin 400 mg (p < 0.001) for percentage of time spent in target range, and non-significant benefits of –19.0 mg/dL (p = 0.20) and –21.7 mg/dL (p = 0.12) for post-prandial glucose.

4.3.2 BMI/body weight/waist circumference

The ERG considers that evidence submitted by the company demonstrates consistent and clinically significant benefits of sotagliflozin compared with insulin alone for BMI and body weight, regardless of the population analysed. For the primary efficacy population, the difference in BMI change from baseline to week 52 was –1.05 kg/m^2 for sotagliflozin 200 mg versus insulin alone (95% CI: –1.29 to –0.81) and –1.53 kg/m^2 (CI: –1.77 to –1.29) for sotagliflozin 400 mg versus insulin alone (Table 11). The benefits of both doses versus insulin alone are statistically significant across all the analyses conducted (p-values < 0.001; company's response to clarification, Tables 16 and 56) and are larger at 52 weeks than at 24 weeks. Differences between groups for all randomised patients were not provided in the initial submission with which to compare results for the subpopulation with BMI ≥ 27 kg/m^2.

Table 11. BMI change from baseline (BMI ≥ 27 kg/m^2 subpopulation)

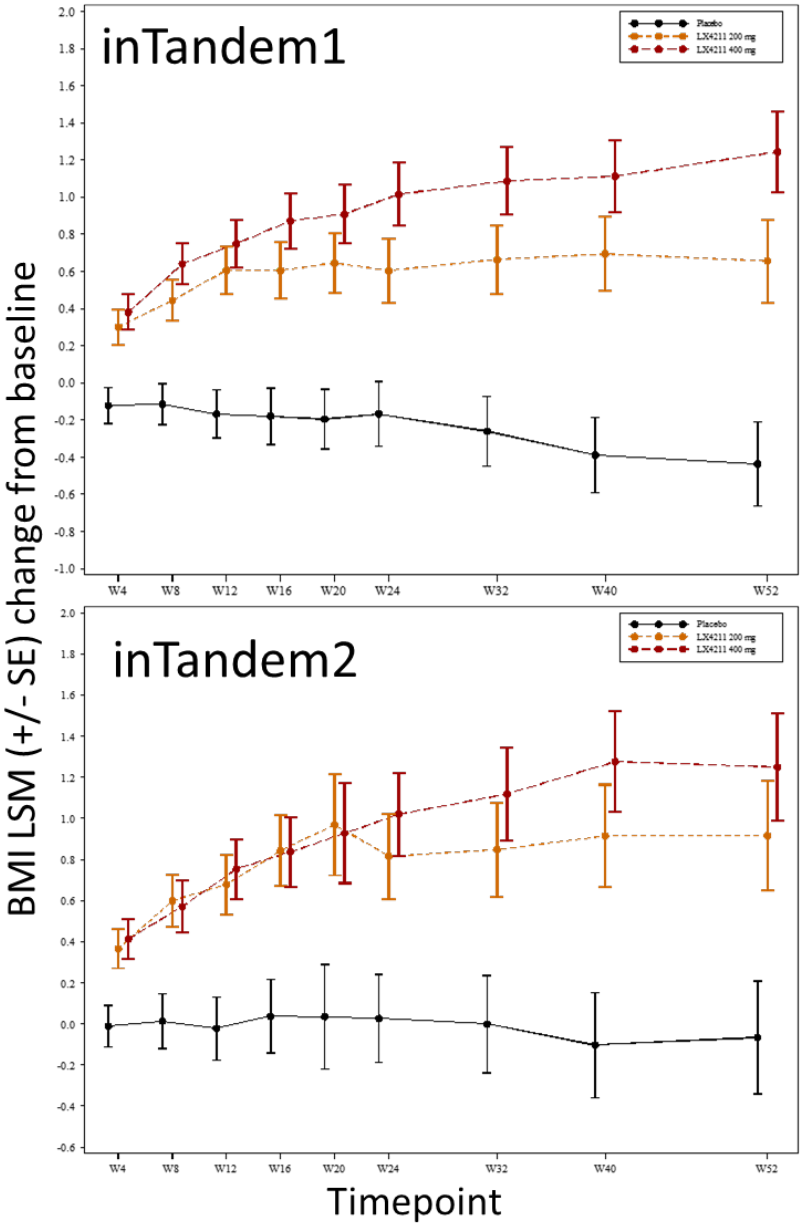
Analysis	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Primary efficacy population – inTandem1 and inTandem2 pooled					
24 weeks	−0.69 (0.07)	−1.02 (0.07)	0.09 (0.07)	**−0.78 (−0.97, −0.60)**	**−1.11 (−1.29, −0.93)**
52 weeks	−0.77 (0.09)	−1.24 (0.09)	0.28 (0.09)	**−1.05 (−1.29, −0.81)**	**−1.53 (−1.77, −1.29)**
Alternative analyses – 24 weeks					
inTandem1	−0.61 (0.09)	−1.03 (0.09)	0.16 (0.09)	**−0.77 (−1.01, −0.53)**	**−1.19 (−1.43, −0.95)**
inTandem2	−0.81 (0.11)	−1.02 (0.10)	−0.03 (0.11)	**−0.78 (−1.07, −0.49)**	**−0.99 (−1.28, −0.70)**
inTandem3	−	−0.90 (0.06)	0.28 (0.06)	−	**−1.18 (−1.35, −1.01)**
All pooled	−	−1.0 (0.05)	0.2 (0.05)	−	**−1.1 (−1.3, −1.0)**
Alternative analyses – 52 weeks					
inTandem1	−0.66 (0.12)	−1.24 (0.11)	0.44 (0.12)	**−1.09 (−1.41, −0.78)**	**−1.68 (−1.99, −1.37)**
inTandem2	−0.92 (0.14)	−1.25 (0.13)	0.07 (0.14)	**−0.98 (−1.36, −0.60)**	**−1.32 (−1.69, −0.94)**

Data collated from the company's response to clarification, Tables 16 and 56. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean.

The effect of treatment on BMI does not show the same waning between weeks 24 and 52 as for HbA_{1c} (Figure 6). BMI appears to stabilise in the sotagliflozin 200 mg groups (shown in orange) and begin to deteriorate in patients taking insulin alone (shown in black) between weeks 24 and 52 weeks; however, it is unclear whether the curves for sotagliflozin 200 mg and insulin alone will converge

thereafter or if the treatment benefit persists beyond 52 weeks as the company assume in the economic model.

Figure 6. BMI (kg/m^2) change from baseline for the BMI ≥ 27 kg/m^2 subpopulation (adapted from company's response to CQ Appendix B, Figures 2 and 10)



Abbreviations: CQ, clarification questions; LSM, least squares mean; SE, standard error.
Post-Baseline LSM are obtained from mixed-effect model for repeated measures with treatment, randomization strata of insulin delivery and Week -2 A1C [<=8.5 %, >8.5 %], time and a treatment-by-time as fixed categorical effects and baseline HDL-C-by-time interaction as a covariate.

The difference in body weight change from baseline to week 52 was –3.01 kg for sotagliflozin 200 mg versus insulin alone (95% CI: –3.71 to –2.31) and –4.46 kg (CI: –5.15 to –3.76) for sotagliflozin 400 mg versus insulin alone (Table 11). The benefits of both doses versus insulin alone are statistically significant across all the analyses conducted (p-values < 0.001; company's response to

clarification, Tables 3 and 46) and, as for BMI, benefits are larger at 52 weeks than at 24 weeks. Change in body weight reported for each group of inTandem1 and inTandem2 was similar for all randomised patients (CS Figure 2.6) and those with BMI ≥ 27 kg/m^2.

Table 12. Body weight change from baseline (BMI ≥ 27 kg/m^2 subpopulation)

Analysis	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Primary efficacy population – inTandem1 and inTandem2 pooled					
24 weeks	−1.93 (0.20)	−2.98 (0.19)	0.34 (0.20)	−2.27 (−2.81, −1.74)	−3.32 (−3.85, −2.79)
52 weeks	−2.16 (0.25)	−3.61 (0.25)	0.85 (0.258)	−3.01(−3.71, −2.31)	−4.46 (−5.15 to−3.76)
Alternative analyses – 24 weeks					
inTandem1	−1.71 (0.25)	−2.96 (0.25)	0.58 (0.253)	−2.29 (−2.97, −1.61)	−3.54 (−4.22, −2.87)
inTandem2	−2.26 (0.31)	−3.05 (0.31)	−0.01 (0.32)	−2.25 (−3.11, −1.39)	−3.04 (−3.89, −2.19)
inTandem3	−	−2.80 (0.28)	0.61 (0.280)	−	−3.41 (−3.90, −2.93)
All pooled	−	−2.79 (0.13)	0.59 (0.133)	−	−3.38 (−3.73, −3.02)
Alternative analyses – 52 weeks					
inTandem1	−1.91 (0.33)	−3.57 (0.33)	1.30 (0.337)	−3.21 (−4.13, −2.29)	−4.87 (−5.77, −3.96)
inTandem2	−2.51 (0.39)	−3.68 (0.38)	0.22 (0.400)	−2.72 (−3.81, −1.64)	−3.90 (−4.97, −2.82)

Data collated from the company's response to clarification, Tables 3 and 46. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean.

The ERG agrees with the company that the benefits of sotagliflozin on BMI and body weight are further supported by modest but statistically significant benefits on total fat mass from the DEXA sub-study (CS, pg. 52), although results were not requested for the BMI ≥ 27 kg/m^2 subpopulation.

4.3.3 Cardiovascular risk factors

Various cardiovascular (CV) measures were reported by the company, all of which are reflected in the economic model (SBP, DBP, total cholesterol, high- and low-density lipoprotein [HDL-C and LDL-C], and triglycerides). Statistically significant cardiovascular benefits of sotagliflozin versus insulin alone for the primary efficacy population are indicated in bold in Table 13, which are discussed below with reference to the results of alternative analyses where differences were noted by the ERG. Given the number of outcomes, the ERG has not reproduced results of alternative analyses. Full results for the subpopulation of each inTandem trial with BMI ≥ 27 kg/m^2 were provided in Tables 9 and 11–15 of the company's response to clarification, and all pooled results were provided in Tables 47 and 51–55.

Table 13. CV risk factors change from baseline (inTandem1 and inTandem2 pooled BMI ≥ 27 kg/m^2 subpopulation)

Outcome	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 vs insulin alone	Sotagliflozin 400 vs insulin alone
Primary efficacy population 24 weeks – inTandem1 and inTandem2 pooled					
SBP mmHg	−2.9 (0.64)	−4.0 (0.64)	−1.6 (0.65)	−1.3 (−3.0, 0.4)	**−2.5 (−4.2, −0.8)**
DBP mmHg	−1.29 (0.41)	−1.22 (0.40)	−0.62 (0.41)	−0.67 (−1.75, 0.41)	−0.60 (−1.67, 0.47)
Total cholesterol	7.36 (1.66)	7.91 (1.63)	5.04 (1.67)	2.32 (−1.98, 6.62)	2.87 (−1.38, 7.11)
LDL-C	5.08 (1.434)	5.80 (1.41)	4.74 (1.46)	0.35 (−3.40, 4.09)	1.06 (−2.63, 4.75)
HDL-C	1.74 (0.55)	1.58 (0.54)	−1.55 (0.56)	**3.29 (1.85, 4.74)**	**3.13 (1.70, 4.56)**
Triglycerides	4.02 (3.32)	3.17 (3.24)	15.50 (3.33)	**−11.48 (−20.19, −2.77)**	**−12.32 (−20.90, −3.74)**
Primary efficacy population 52 weeks – inTandem1 and inTandem2 pooled					
SBP mmHg	−1.7 (0.66)	−3.2 (0.65)	0.4 (0.67)	−2.1 (−3.9, 0.4)	**−3.6 (−5.3, −1.9)**
DBP mmHg	−1.18 (0.43)	−1.65 (0.43)	−0.18 (0.44)	−1.00 (−2.16, 0.17)	**−1.46 (−2.62, −0.31)**
Total cholesterol	8.84 (1.75)	12.63 (1.73)	4.44 (1.80)	4.40 (−0.28, 9.08)	**8.18 (3.55, 12.82)**
LDL-C	5.29 (1.497)	7.71 (1.49)	4.07 (1.55)	1.22 (−2.79, 5.23)	3.64 (−0.35, 7.63)
HDL-C	2.36 (0.59)	3.24 (0.59)	0.04 (0.61)	**2.32 (0.73, 3.90)**	**3.19 (1.62, 4.76)**
Triglycerides	7.50 (3.1125)	9.97 (3.08)	7.01 (3.209)	0.48 (−7.85, 8.82)	2.95 (−5.31, 11.22)

Data collated from the company's response to clarification, Tables 47 and 51–55. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; mmHg, millimetre of mercury.

Overall, there was not a consistent pattern of benefit for either dose at either timepoint and, where results were statistically significant, they may not be clinically meaningful. Point estimates were often larger for sotagliflozin 400 mg than the 200 mg dose, and at 52 weeks than 24 weeks (Table 13). The ERG notes some variation in treatment effects versus insulin alone between the three inTandem trials but notes that the overlap in confidence intervals suggests variation between trials is unlikely to be clinically or statistically meaningful (company's response to clarification, Table 9). Progression graphs provided by the company in Appendix B of their response to clarification illustrate overlapping confidence intervals between groups at most timepoints within each inTandem trial (Figures 3–7 for inTandem1, 11–16 for inTandem2 and 19–24 for inTandem3).

There was a modest but statistically significant benefit on SBP for sotagliflozin 400 mg versus insulin alone (–2.5 mmHg, p = 0.005 and –3.6 mmHg, p < 0.001 at 24 and 52 weeks, respectively), which is not apparent for the 200 mg dose (p = 0.13 and p = 0.018; company response to clarification, Table 47). The ERG did not note any consistent differences between the pooled estimates for the primary population at 24 weeks and the pooled estimates including inTandem3 (company response to clarification, Tables 51–55). Differences in DBP versus insulin alone were not statistically significant for either dose at 24 weeks, or for sotagliflozin 200 mg at 52 weeks (company response to clarification, Table 51), and the statistically significant benefit of sotagliflozin 400 mg versus insulin

alone at 52 weeks is unlikely to be clinically meaningful (–1.46 mmHg; Table 13). The same pattern of small or non-statistically significant effects was true for the differences observed in total cholesterol (company response to CQ, Table 52) and LDL-C (company response to clarification, Table 53). However, differences in HDL-C for both doses versus insulin alone were statistically significant at both timepoints (Table 13 and company response to clarification, Table 54), and differences in triglycerides versus insulin alone were observed for both doses at week 24 but not week 52 (company response to clarification, Table 55).

The ERG considers there to be some evidence of cardiovascular benefit by 52 weeks for sotagliflozin compared with insulin alone, primarily for sotagliflozin 400 mg, but effects are mostly small and inconsistent across the outcomes measured. The general pattern of increasing effect between 24 and 52 weeks does not rule out the possibility that sotagliflozin has longer term cardiovascular benefits, although there is no direct evidence to support durability of effects beyond the trial endpoints. The ERG notes the dose effect for these outcomes and considers the use of data for sotagliflozin 200 mg to be a conservative estimate for sotagliflozin 400 mg in the economic model.

4.3.4 Insulin dose

Change from baseline to week 24 and 52 in bolus and basal insulin dose are shown for the primary efficacy population and alternative analyses in Table 14 (statistically significant differences between sotagliflozin and insulin alone indicated in bold). At 24 weeks, there were modest but statistically significant reductions in bolus insulin dose of –2.02 IU/day (95% CI –3.92 to –0.12) for sotagliflozin 200 mg and -4.05 IU/day (95% CI -5.93 to -2.17) for sotagliflozin 400 mg versus insulin alone in the primary efficacy population. The mean reduction in bolus insulin dose compared with insulin alone was maintained at 52 weeks for sotagliflozin 400 mg (−3.93 IU/day, 95% CI: −6.03, −1.84), but not for 200 mg (−0.86 IU/day, 95% CI: −2.98, 1.25). Changes in basal insulin dose for the primary efficacy population were statistically significant for both doses compared with insulin alone at 24 and 52 weeks, but changes were also small. Unlike change in bolus insulin dose, the reduction in basal doses compared with insulin alone were somewhat larger at 52 weeks than at 24 weeks for both doses (Table 14).

Table 14. Bolus and basal insulin change from baseline (BMI ≥ 27 kg/m^2 subpopulation)

Analysis	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Change in bolus insulin (IU/day) primary efficacy population – inTandem1 and inTandem2 pooled					
24 weeks	−3.89 (0.72)	−5.91 (0.71)	−1.86 (0.72)	**−2.02 (−3.92, −0.12)**	**−4.05 (−5.93, −2.17)**
52 weeks	−3.33 (0.78)	−6.40 (0.77)	−2.47 (0.80)	−0.86 (−2.98, 1.25)	**−3.93 (−6.03, −1.84)**
Change in basal insulin (IU/day) primary efficacy population – inTandem1 and inTandem2 pooled					
24 weeks	−0.14 (0.45)	−1.14 (0.45)	1.57 (0.46)	**−1.72 (−2.93, −0.50)**	**−2.71 (−3.92, −1.51)**

52 weeks	−0.07 (0.52)	−1.87 (0.514)	2.46 (0.53)	**−2.53 (−3.95, −1.11)**	**−4.33 (−5.74, −2.92)**
Bolus insulin – 24 weeks					
inTandem1	−2.63 (1.00)	−5.26 (0.99)	−1.44 (1.00)	−1.19 (−3.80, 1.43)	**−3.82 (−6.40, −1.23)**
inTandem2	−5.35 (1.03)	−6.61 (1.02)	−2.30 (1.06)	**−3.05 (−5.80, −0.30)**	**−4.31 (−7.04, −1.58)**
inTandem3	-	−5.83 (1.50)	−2.09 (1.53)	-	**−3.74 (−5.65, −1.83)**
All trials pooled	-	−5.50 (0.51)	−1.63 (0.51)	-	**−3.86 (−5.19, −2.54)**
Basal insulin – 24 weeks					
inTandem1	0.31 (0.60)	−1.44 (0.59)	2.09 (0.60)	**−1.78 (−3.35, −0.20)**	**−3.54 (−5.10, −1.97)**
inTandem2	−0.85 (0.68)	−0.90 (0.67)	0.83 (0.70)	−1.68 (−3.52, 0.16)	−1.74 (−3.56, 0.09)
inTandem3	-	−0.82 (0.91)	2.21 (0.93)	-	**−3.02 (−4.20, −1.85)**
All trials pooled	-	−1.28 (0.31)	1.68 (0.32)	-	**−2.96 (−3.78, −2.13)**
Bolus insulin – 52 weeks					
inTandem1	0.11 (0.71)	−2.06 (0.69)	3.37 (0.71)	**−3.26 (−5.15, −1.37)**	**−5.43 (−7.31, −3.56)**
inTandem2	−0.41 (0.76)	−1.83 (0.75)	1.26 (0.77)	−1.67 (−3.74, 0.39)	**−3.09 (−5.14, −1.05)**
Basal insulin – 52 weeks					
inTandem1	−2.13 (1.08)	−6.46 (1.07)	−0.68 (1.09)	−1.45 (−4.34, 1.44)	**−5.77(−8.63, −2.92)**
inTandem2	−4.55 (1.12)	−6.09 (1.12)	−4.70 (1.15)	0.15 (−2.88, 3.17)	−1.39 (−4.40, 1.62)

Data collated from the company's response to clarification, Tables 4–5 and 48–49. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: BMI, body mass index; IU, international unit; LSM, least squares mean; SE, standard error.

Across the alternative analyses, differences are noted between inTandem1 and inTandem2 at 52 weeks. Reductions in bolus and basal insulin dose were larger for both doses of sotagliflozin versus insulin alone in the inTandem1 trial than inTandem2, despite relatively similar baseline doses in each trial (Table 49). The ERG does not consider variation in insulin dose reductions across the analyses clinically significant given the magnitude of dose reduction across the analyses and overlapping confidence intervals, and the data are not used in the economic model.

4.3.5 Health-related quality of life

Health-related quality of life (HRQoL) data were collected in the inTandem1 and inTandem2 trials using the 2-item Diabetes Distress Screening Scale (DDS2) and the EQ-5D-5L. Additionally, the twin trials measured satisfaction with treatment using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). No HRQoL data were collected during inTandem3.

Based on a minimal clinically important difference (MCID) of 0.19,38 results indicate clinically meaningful improvements in the sotagliflozin 200 mg and 400 mg groups at 24 weeks, which were statistically significant compared with insulin alone for the primary efficacy population (Table 15). The differences observed were statistically significant for both doses in both trials individually at 24 weeks and in the inTandem1 trial at 52 weeks, but not for either dose in the inTandem2 trial at 52 weeks. An MCID was not identified for the DTSQ which was only measured at 24 weeks, but statistically significant improvements of between 2.0 and 3.0 compared with insulin alone were observed across the pooled results and individual trials for both doses (Table 15).

Differences in EQ-5D index scores and visual analogue scale (VAS) indicate very little change over the course of the studies in any group, although there was a statistically significant improvement in VAS for sotagliflozin 400 mg compared with insulin alone in the inTandem1 trial (Table 15).

Table 15. Patient-reported outcomes (BMI ≥ 27 kg/m^2 subpopulation)

Outcome	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Primary efficacy population – inTandem1 and inTandem2 pooled					
DDS2 – 24 weeks	−0.5 (0.10)	−0.5 (0.10)	0.1 (0.10)	**−0.6 (−0.9, −0.3)**	**−0.7 (−0.9, −0.4)**
DTSQ – 24 weeks	2.3 (0.26)	2.2 (0.26)	−0.3 (0.27)	**2.6 (1.9 to 3.3)**	**2.6 (1.9, 3.3)**
Individual trial results 24 weeks					
DDS2 inTandem1	−0.4 (0.14)	−0.6 (0.13)	0.2 (0.14)	**−0.6 (−1.0, −0.3)**	**−0.8 (−1.1, −0.4)**
DDS2 inTandem2	−0.5 (0.15)	−0.5 (0.15)	0.1 (0.15)	**−0.6 (−1.0, −0.2)**	**−0.5 (−0.9, −0.1)**
DTSQ inTandem1	2.2 (0.36)	2.4 (0.36)	−0.6 (0.37)	**2.8 (1.9 to 3.7)**	**3.0 (2.1 to 3.9)**
DTSQ inTandem2	2.4 (0.39)	2.0 (0.38)	0.0 (0.40)	**2.4 (1.4 to 3.4)**	**2.0 (1.0 to 3.0)**
Individual trial results 52 weeks					
DDS2 inTandem1	−0.27 (0.14)	−0.50 (0.14)	0.16 (0.14)	**−0.43 (−0.79, −0.07)**	**−0.65 (−1.01, −0.30)**
DDS2 inTandem2	−0.50 (0.16)	−0.50 (0.16)	−0.14 (0.16)	−0.36 (−0.79, 0.06)	−0.36 (−0.77, 0.06)
EQ-5D IS inTandem1	−0.00 (0.01)	0.01 (0.01)	−0.00 (0.01)	0.00 (−0.02, 0.02)	−0.01 (−0.01, 0.03)
EQ-5D IS inTandem2	−0.02 (0.01)	−0.01 (0.01)	−0.02 (0.01)	0.00 (−0.03, 0.03)	0.00 (−0.03, 0.03)
EQ-5D VAS inTandem1	−0.77 (1.06)	2.40 (1.06)	−0.29 (1.06)	−0.48 (−3.11, 2.16)	**2.70 (0.09, 5.31)**
EQ-5D VAS inTandem2	2.12 (1.31)	1.09 (1.27)	−0.71 (1.36)	2.83 (−0.52, 6.17)	1.80 (−1.49, 5.09)

Data collated from the company's response to clarification, Tables 7–8, 18–19 and 44–45. Statistically significant differences are indicated in **bold**. Results rounded to two decimal places.
Abbreviations: CI, confidence interval; DTSQ, Diabetes Treatment Satisfaction Questionnaire; DDS2, 2-item Diabetes Distress Screening Scale; IS, index score; LSM, least square mean; mITT, modified intent-to-treat; SE, standard error.

4.3.6 Safety

A draft summary of product characteristics (SmPC) was submitted by the company as Appendix C of the original submission before the population was limited to patients with BMI ≥ 27 kg/m^2, but data for key events relevant to the economic model (hypoglycaemia, DKA) were provided for the subpopulation with BMI ≥ 27 kg/m^2. The draft SmPC states that sotagliflozin is not recommended for patients aged 75 years or older, or those with eGFR ≤ 45 mL/min/1.73 m^2 or high risk of DKA. Female genital mycotic infections are listed as very common, and adverse reactions listed as common are male genital mycotic infections, UTIs, DKA, volume depletion, diarrhoea, flatulence, and renal and urinary disorders (increased urination, increased blood creatinine, decreased eGFR, and increased blood ketone body, serum lipids and haematocrit).

The ERG provides a summary and critique of the available safety data with reference to the draft SmPC and highlights any differences in event frequency or severity between the full populations and the BMI ≥ 27 kg/m^2 subpopulation where both were available. Safety data are described in the following subsections in line with outcomes defined in the NICE final scope:

- Frequency and severity of hypoglycaemia;
- Adverse effects of treatment (DKA, fractures, genital infections and UTI);
- Treatment-emergent adverse events (TEAEs), including microvascular (damage to nerve, kidney and eye) and macrovascular complications of diabetes (coronary artery disease, peripheral arterial disease, stroke and lower limb amputations);
- Mortality.

4.3.6.1 Frequency and severity of hypoglycaemia (BMI ≥ 27 kg/m^2 subpopulation)

Proportions of patients with SH in the primary pooled analysis were 4.3%, 4.2% and 8.1% for sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone, respectively, and equivalent proportions having non-SH were 91.5%, 93.3% and 92.6% (Table 16, from company response to clarification, tables 63 and 65). The ERG noted slight discrepancies in SH event rates between tables provided by the company (e.g. between table 59 and tables 63 and 64), but the extent of differences did not change conclusions. Although fewer patients taking sotagliflozin 200 mg and 400 mg had SH than patients taking insulin alone, the risk differences (RD) between exposure-adjusted rates suggest the differences are not statistically significant (RD for sotagliflozin 200 mg vs insulin alone −34.52, 95% CI: −76.78 to 7.74; RD for sotagliflozin 400 mg vs insulin alone −39.98, 95% CI: −81.04 to 1.09; Addendum, Table 18).

The ERG's clinical experts explained that sotagliflozin is not expected to affect the rate of SH or non-SH because it works independently of insulin, and so the lower rates of SH with sotagliflozin compared with insulin alone may reflect insulin dose reductions in the sotagliflozin groups (Section 4.3.4). The clinical experts also noted that the rates of SH observed in the trials are higher than expected in UK clinical practice.

Table 16. Hypoglycaemia over 52-week treatment period (inTandem1 and inTandem2 pooled BMI ≥ 27 kg/m^2 subpopulation)

	Sotagliflozin 200 mg (N = 305)		**Sotagliflozin 400 mg (N = 313)**		**Insulin alone (N = 298)**	
	SH	**Non-SH**	**SH**	**Non-SH**	**SH**	**Non-SH**
Total patient years of exposure	280.3		293.1		272.3	
N patients with events, n (%)	13	279	13	292	24	276

	(4.3%)	(91.5%)	(4.2%)	(93.3%)	(8.1%)	(92.6%)
N patients with events per patient years	0.046	0.995	0.044	0.996	0.088	1.014
N events	25	14599	18	14912	31	16447
N events per patient years	0.089	52.08	0.061	50.88	0.114	60.40
Data provided by the company in their response to clarification, compiled by the ERG All results have been rounded to 2 decimal places. Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; N, number; SH, severe hypoglycaemia.						

Results for individual studies were also provided in the company's response to clarification (Tables 29–30 and 35–36), which showed similar proportions of patients having non-SH for both studies but somewhat higher proportions of SH during inTandem1 (4.7–9.8%) than during inTandem2 (2.9–5.6%). Results for the larger pool of phase II and III trials (BMI ≥27 kg/m^2) provided more data for the 400 mg dose and placebo groups and showed somewhat lower rates of SH than inTandem1 and inTandem2 alone (3.0% and 4.8%, respectively).

The ERG does not consider the data to show a dose effect of sotagliflozin for SH or non-SH, and therefore considers data for the 200 mg dose as a reasonable proxy for 400 mg in the economic model for this outcome.

4.3.6.2 Adverse effects of treatment (BMI ≥ 27 kg/m^2 subpopulation)

DKA, genital mycotic infections and diarrhoea were treated as adverse effects of special interest (EOSI) in the inTandem trials. DKA has emerged as a class effect of SGLT-2 inhibitors and was adjudicated by an independent committee during inTandem1 and inTandem2. The draft SmPC outlines criteria for DKA risk assessment before initiation of treatment or dose increase, and recommends ketone monitoring during treatment to reduce the risk of DKA (see Section 3.2 and CS Appendix C). The ERG's clinical experts highlighted that a small group of patients tend to experience recurrent DKA in clinical practice (often those with poorly controlled diabetes, high alcohol intake or low BMI), and these patients would not be considered eligible for treatment with sotagliflozin.

Within the primary population, the proportions of patients with at least one episode of DKA in the primary pooled analysis were 2.6%, 3.5% and 0.3% for sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone, respectively (Table 17). Risk differences and relative risks for each dose versus placebo indicate the difference in exposure-adjusted rates were statistically significant (company response to clarification, Table 60). The company highlight that approximately 60% of all DKA episodes in the phase III trials occurred in patients using insulin pumps, and a third of cases were associated with pump malfunctions (CS, pg. 81–82). The association is in line with advice from clinical experts that patients using CSII would be less likely to be given sotagliflozin in the UK and suggests risk of DKA with sotagliflozin would be lower in the UK than observed in the trials.

Table 17. Treatment-related adverse events of special interest (52-week treatment period – inTandem1 and inTandem2 pooled BMI ≥ 27 kg/m^2 subpopulation)

	Sotagliflozin 200 mg		Sotagliflozin 400 mg		Insulin alone	
	n/N (%)	EAIR/1000 PY (95% CI)	n/N (%)	EAIR/1000 PY (95% CI)	n/N (%)	EAIR/1000 PY (95% CI)
DKA	8/305 (2.6)	28.62 (8.79 to 48.46)	11/313 (3.5)	37.64 (15.39 to 59.88)	1/298 (0.3)	3.68 (0.00 to 10.90)
Male genital mycotic infections	6/157 (3.8)	41.05 (8.20 to 73.89)	7/154 (4.5)	47.74 (12.37 to 83.10)	1/155 (0.6)	5.96 (0.88 to 138.01)
Female genital mycotic infections	32/148 (21.6)	240.02 (156.86 to 323.19)	28/159 (17.6)	192.26 (121.05 to 263.48)	9/143 (6.3)	71.25 (24.70 to 117.80)
Diarrhoea	16/305 (5.2)	57.25 (29.20 to 85.30)	27/313 (8.6)	92.38 (57.53 to 127.23)	20/298 (6.7)	73.67 (41.38 to 105.95)

Results rounded to two decimal places.
Abbreviations: BMI, body mass index; EAIR, exposure-adjusted incidence rate; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; N, number; PY, patient years.

Higher proportions of patients on either dose of sotagliflozin had genital infections than those on insulin alone, particularly for females (21.6%, 17.6% and 6.3% for sotagliflozin 200 mg, 400 mg, and insulin alone, respectively; Table 17). Diarrhoea occurred more frequently in patients taking sotagliflozin 400 mg (8.6%) than the 200 mg dose (5.2%) or insulin alone (6.7%), but differences in exposure-adjusted risk difference and relative risk were not statistically significant (company response to clarification, Table 61). The ERG reviewed alternative results for genital mycotic infections and diarrhoea from the larger pool of phase II and phase III studies (BMI ≥27 kg/m^2; company response to clarification, Tables 60–61) and considers results consistent with those for the primary safety population. Risk differences between the two doses were not presented but, based on the available data for EOSI, the ERG considers it unreasonable to assume sotagliflozin 200 mg and sotagliflozin 400 mg have the same adverse effect profile in the economic model.

4.3.6.3 Treatment-emergent adverse events

An overview of TEAEs during the 52-week treatment period of inTandem1 and inTandem2 (pooled) for the BMI ≥27 kg/m^2 subpopulation and all randomised patients is shown in Table 18. Approximately three quarters of each group experienced at least one TEAE in the BMI ≥ 27 kg/m2 subpopulation, and rates were generally similar to those observed for all randomised patients. The rate of severe treatment-related TEAEs and TEAEs leading to study drug discontinuation was less than 5% in all groups and similar in both populations. Rates of treatment-emergent serious adverse events (SAEs) were somewhat higher in the sotagliflozin groups (~9–10%) than for insulin alone (~7.0%). The ERG notes that investigators were asked not to submit hypoglycaemic events on the AE case report form unless the event met the criteria for an SAE or was the cause for discontinuation (CS Addendum, Table 16).

Table 18. Summary of treatment emergent adverse events during 52-week treatment period of inTandem1 and inTandem2

	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone
BMI ≥ 27 kg/m^2 subpopulation			
N patients	305	313	298
Any TEAE	238 (78.0)	234 (74.8)	221 (74.2)
Severe treatment-related TEAEs	9 (3.0)	14 (4.5)	8 (2.7)
Treatment-emergent SAEs	28 (9.2)	31 (9.9)	22 (7.4)
TEAEs leading to study drug discontinuation	13 (4.3)	13 (4.2)	13 (4.4)
All randomised patients			
N patients	524	525	526
Any TEAE	393 (75.0)	390 (74.3)	374 (71.1)
Treatment-related TEAEs	167 (31.9)	193 (36.8)	106 (20.2)
Severe TEAEs	50 (9.5)	48 (9.1)	37 (7.0)
Severe treatment-related TEAEs	19 (3.6)	22 (4.2)	11 (2.1)
Treatment-emergent SAEs	53 (10.1)	50 (9.5)	37 (7.0)
Treatment-emergent/ treatment-related SAEs	18 (3.4)	23 (4.4)	10 (1.9)
TEAEs leading to study drug discontinuation	23 (4.4)	35 (6.7)	20 (3.8)
Treatment-related TEAEs leading to study drug discontinuation	19 (3.6)	31 (5.9)	12 (2.3)

Abbreviations: n, number of patients; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Data reproduced from CS, Table 2.20 and Addendum, Table 16

Data for specific microvascular and macrovascular complications of diabetes are only available from the overall TEAE tables in the original submission (CS, Table 2.21), which are based on the larger pool of inTandem phase III (1, 2 and 3) and phase II trials[35, 36] (Table 19). The ERG highlights that the larger pool is unrestricted by BMI, and so results may differ for the population with BMI ≥ 27 kg/m^2.

Microvascular complications listed in the NICE final scope were damage to the nerves, kidneys and eyes (e.g. diabetic retinopathy, macular oedema, nephropathy, neuropathy). Rates of renal events were similar across groups (0.9–1.4%), but eye and nerve complications were not included in the list of events of special interest for the inTandem trial programme.

Macrovascular complications listed in the NICE final scope were coronary artery disease, peripheral arterial disease, stroke and lower limb amputations. Low rates were reported across the trials in all groups (0–0.7%), and the ERG does not consider any of the differences clinically meaningful.

Within the other events reported, there were more cases of genital mycotic infections in the sotagliflozin groups (8.4–8.8%) than for insulin alone (2.3%), although the proportions of each group with UTI do not indicate a difference between groups (4.4–6.6%). Volume depletion was rare in all groups but occurred more frequently in patients treated with sotagliflozin 200 mg (2.5%) and sotagliflozin 400 mg (1.6%) than insulin alone (0.6%); the ERG notes that the draft SmPC recommends correction of volume depletion before initiation of sotagliflozin (CS, Appendix C).

Table 19. Specific treatment-emergent adverse events (inTandem phase III trials plus phase II T1D trials)

	Sotagliflozin 200 mg (N = 559)	Sotagliflozin 400 mg (N = 1321)	Insulin alone (N = 1324)
	n/N (%)	n/N (%)	n/N (%)
At least one treatment-emergent investigator-reported EOSI	547 (97.9)	1,273 (96.4)	1,266 (95.6)
Hypoglycaemia			
Documented hypoglycaemia	547 (97.9)	1264 (95.7)	1261 (95.2)
SH and/or hypoglycaemia reported as an SAE	31 (5.5)	51 (3.9)	65 (4.9)
Microvascular and macrovascular complications			
Renal event	8 (1.4)	13 (1.0)	12 (0.9)
Amputation	1 (0.2)	1 (0.1)	0
Venous thromboembolism	0	0	0
Myocardial infarction or hospitalisation for unstable angina	4 (0.7)	4 (0.3)	3 (0.2)
Stroke	1 (0.2)	2 (0.2)	3 (0.2)
Hospitalisation for heart failure	2 (0.4)	1 (0.1)	1 (0.1)
Coronary revascularisation	4 (0.7)	2 (0.2)	2 (0.2)
Cardiovascular death	0	0	2 (0.2)
Other events			
Volume depletion	14 (2.5)	21 (1.6)	8 (0.6)
Genital mycotic infection	49 (8.8)	111 (8.4)	30 (2.3)
Urinary tract infection	37 (6.6)	58 (4.4)	64 (4.8)
Diarrhoea	35 (6.3)	79 (6.0)	46 (3.5)
Pancreatitis	0	1 (0.1)	0
Bone fracture	15 (2.7)	14 (1.1)	25 (1.9)
Potential drug-induced liver injury	2 (0.4)	8 (0.6)	4 (0.3)
Malignancies of special interest	2 (0.4)	4 (0.3)	2 (0.2)

Data provided by the company in their response to clarification, compiled by the ERG.
Abbreviations: BMI, body mass index; HbA_{1c}, glycated haemoglobin; LSM, least squares mean; N, number.

4.3.6.4 Mortality

In the original submission, the company reported that three patients experienced TEAEs leading to death in inTandem1 and inTandem2, which were all in the placebo group. No deaths across the whole trial programme have been caused by DKA (CS, pg. 87).

4.3.7 Subgroup analyses

No subgroups were outlined in the NICE final scope, but the ERG considered it necessary to explore subgroups for insulin delivery (CSII and MDI) and baseline HbA_{1c} in light of differences highlighted by clinical experts between the inTandem trials and patients in the UK. The company outlined that limiting the population to patients using MDI and with HbA_{1c} closer to the UK mean (> 8.5%) would result in very small numbers of patients per group, and so conducted subgroup analyses on the full populations rather than the subpopulation of interest with BMI ≥ 27 kg/m^2. Results of subgroup

analyses using the pooled full populations of inTandem1 and inTandem2 are shown in Table 20; trial-based subgroup analyses (full populations) are available in Table 23 of the company's response to clarification.

The effect of sotagliflozin 200 mg and 400 mg on HbA_{1c} was statistically significant compared with insulin alone across all subgroups at 24 and 52 weeks except for the small subgroup of patients with eGFR < 60 mL/min/1.73 m^2 (Table 20). The difference between sotagliflozin 200 mg and insulin alone ranged from –0.28 to –0.51 at 24 weeks and from –0.13 to –0.31 at 52 weeks across subgroups. All confidence intervals were overlapping, but differences between sotagliflozin and insulin alone appear less pronounced in the subgroup of patients using MDI compared with CSII at 52 weeks, and more pronounced for the 200 mg dose in patients with HbA_{1c} >8.5% compared with ≤8.5% at 24 and 52 weeks. Consequently, the potential overestimate of benefit caused by higher CSII use in the trials may be mitigated by patients in the UK having higher HbA_{1c} than patients in the trials.

Table 20. HbA_{1c} (%) subgroup results (pooled full populations of inTandem1 and inTandem2)

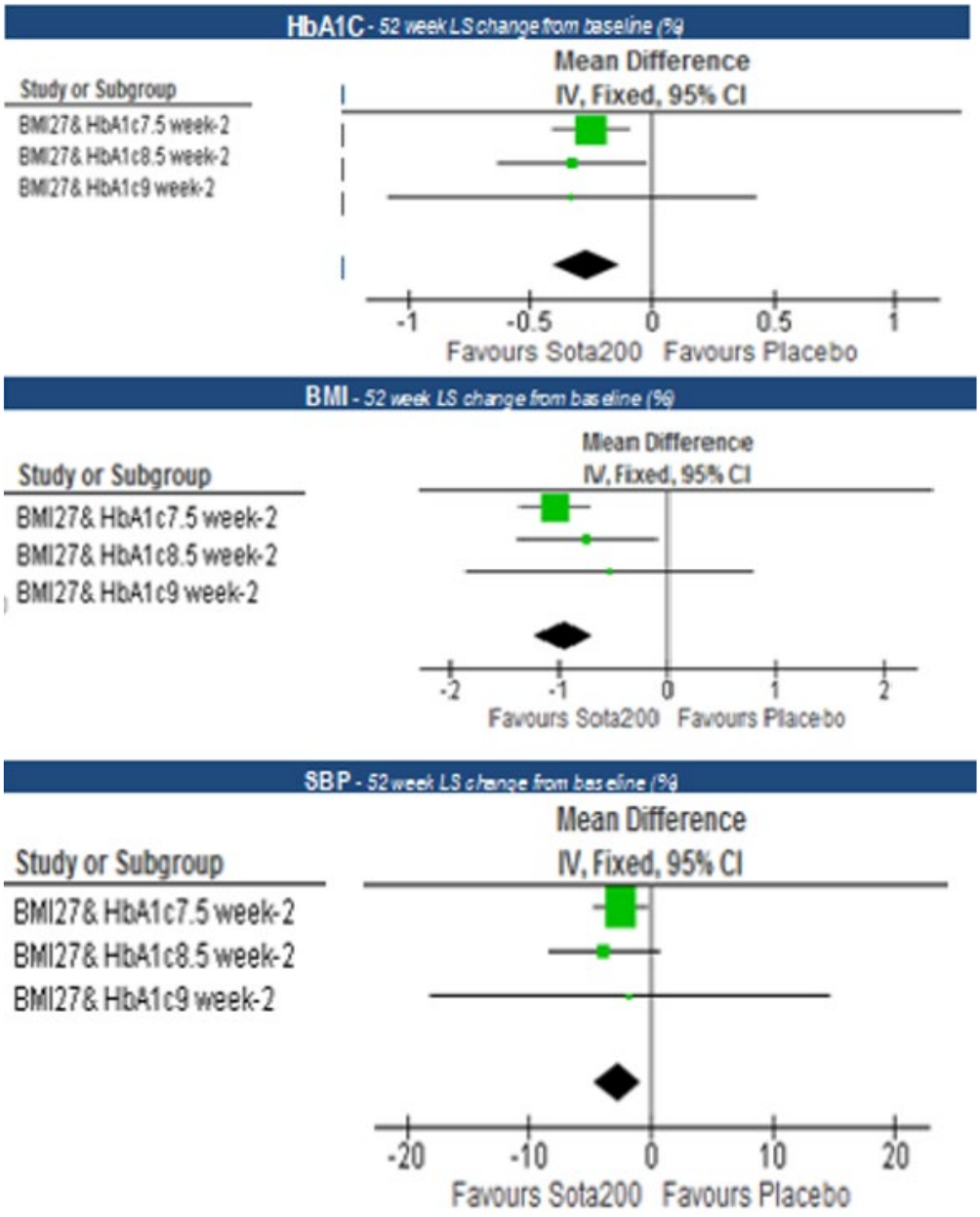
Subgroup	N	LSM change from baseline (95% CI)			LSM difference between groups (95% CI)	
		Sota 200 mg	Sota 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
24 weeks						
CSII	613	−0.41 (0.042)	−0.45 (0.042)	−0.02 (0.042)	**−0.39 (−0.49 to −0.28) <0.001**	**−0.43 (−0.54 to −0.33) <0.001**
MDI	839	−0.41 (0.038)	−0.41 (0.038)	−0.06 (0.038)	**−0.34 (−0.44 to −0.24) <0.001**	**−0.35 (−0.45 to −0.24) <0.001**
HbA_{1c} ≤8.5%	1190	−0.32 (0.027)	−0.37 (0.026)	0.00 (0.027)	**−0.33 (−0.40 to −0.25) <0.001**	**−0.37 (−0.45 to −0.30) <0.001**
HbA_{1c} >8.5%	262	−0.76 (0.084)	−0.67 (0.084)	−0.25 (0.082)	**−0.51 (−0.74 to −0.28) <0.001**	**−0.42 (−0.65 to −0.19) <0.001**
BMI <25	373	−0.33 (0.064)	−0.31 (0.067)	0.01 (0.065)	**−0.34 (−0.51 to −0.18) <0.001**	**−0.32 (−0.49 to −0.14) <0.001**
BMI ≥25	779	−0.44 (0.031)	−0.47 (0.030)	−0.07 (0.030)	**−0.37 (−0.45 to −0.29) <0.001**	**−0.40 (−0.48 to −0.32) <0.001**
eGFR <60	68	−0.66 (0.139)	−0.60 (0.131)	−0.38 (0.135)	−0.28 (−0.64 to 0.09) 0.14	−0.21 (−0.57 to 0.14) 0.24
eGFR ≥60 to <90	709	−0.41 (0.037)	−0.50 (0.038)	−0.00 (0.039)	**−0.41 (−0.51 to −0.32) <0.001**	**−0.50(−0.59 to −0.40) <0.001**
eGFR ≥90	675	−0.37 (0.044)	−0.32 (0.043)	−0.06 (0.042)	**−0.31 (−0.43 to −0.20) <0.001**	**−0.27 (−0.38 to −0.15) <0.001**
52 weeks						
CSII	575	−0.22 (0.054)	−0.29 (0.054)	0.07 (0.054)	**−0.29 (−0.43 to −0.15) <0.001**	**−0.37 (−0.51 to −0.22) <0.001**
MDI	787	−0.22 (0.044)	−0.31 (0.043)	−0.03 (0.044)	**−0.19 (−0.30 to −0.07) 0.002**	**−0.28 (−0.40 to −0.16) <0.001**
HbA_{1c} ≤8.5%	1120	−0.16 (0.033)	−0.26 (0.033)	0.05 (0.033)	**−0.21 (−0.31 to −0.12) <0.001**	**−0.32 (−0.41 to −0.22) <0.001**
HbA_{1c} >8.5%	242	−0.47 (0.100)	−0.48 (0.101)	−0.16 (0.099)	**−0.31 (−0.59 to −0.04) 0.027**	**−0.32 (−0.60 to −0.05) 0.022**

BMI <25	344	−0.10 (0.078)	−0.15 (0.082)	0.14 (0.078)	**−0.24 (−0.45 to −0.04) 0.021**	**−0.29 (−0.51 to −0.07) 0.008**
BMI ≥25	1018	−0.27 (0.037)	−0.36 (0.036)	−0.04 (0.037)	**−0.23 (−0.32 to −0.13) <0.001**	**−0.32 (−0.41 to −0.22) <0.001**
eGFR <60	63	−0.55 (0.136)	−0.33 (0.132)	−0.42 (0.139)	−0.13 (−0.50 to 0.24) 0.49	0.09 (−0.28 to 0.45) 0.63
eGFR ≥60 to <90	667	−0.27 (0.043)	−0.35 (0.045)	0.01 (0.046)	**−0.28 (−0.40 to −0.16) <0.001**	**−0.36 (−0.48 to −0.25) <0.001**
eGFR ≥90	632	−0.12 (0.055)	−0.25 (0.054)	0.05 (0.052)	**−0.17 (−0.32 to −0.03) 0.019**	**−0.31 (−0.45 to −0.16) <0.001**

HbA_{1c} cut-off are based on Week -2 (screening) values whereas eGFR (mL/min/1.73 m2) and BMI (kg/m2) are Week 0 values (baseline).
Abbreviations: BMI, body mass index; CI, confidence interval; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; LSM, least square mean; mITT, modified intent−to−treat; SE, standard error; MDI, multiple daily injections; sota, sotagliflozin.

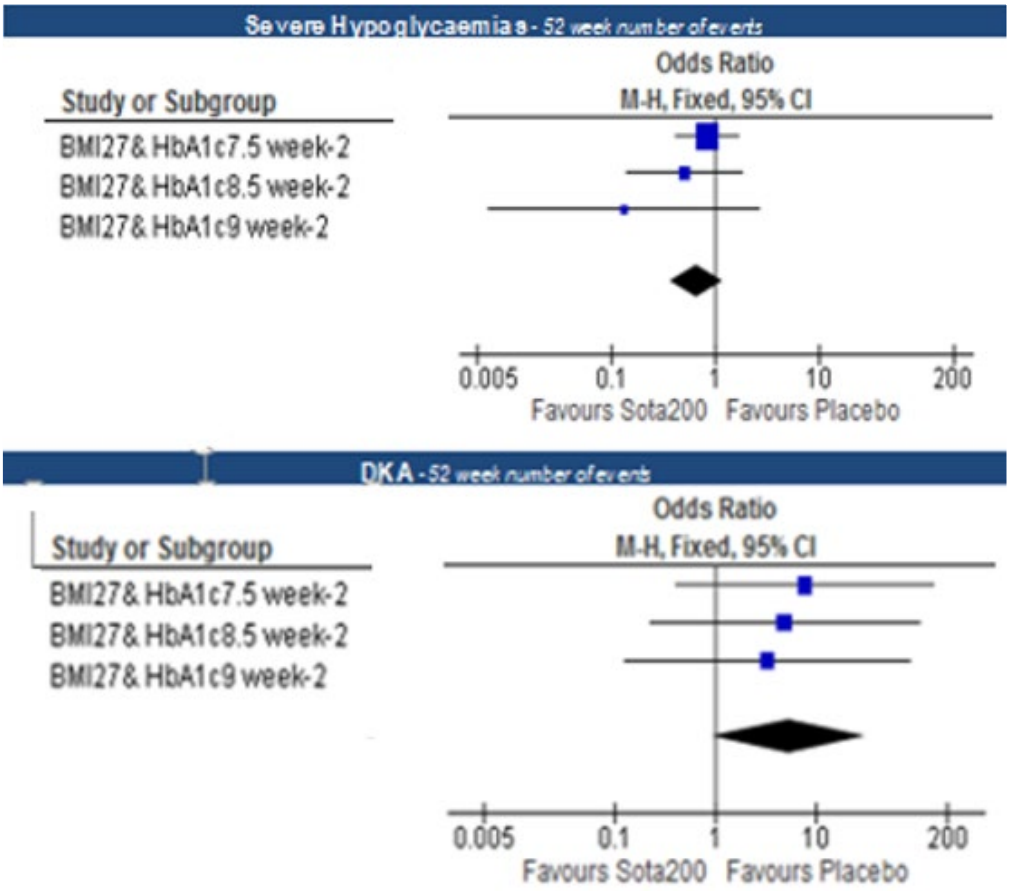
Subgroup analyses using the full trial populations or the BMI ≥ 27 kg/m^2 subpopulation were not conducted for any other outcome, but the company submitted forest plots to show correlation between 52-week HbA_{1c}, BMI, SBP, SH and DKA at different HbA_{1c} cut-offs (7%, 8.5% and 9%) within the BMI subpopulation. The HbA_{1c} 8.5% cut-off is likely to be more reflective of patients in the UK most likely to receive sotagliflozin, and the ERG does not consider the forest plots to show any meaningful differences between effects for that cut-off and the lower cut-off of 7.5%.

Figure 7. Impact of HbA_{1c} cut-off on key efficacy endpoints within the BMI ≥ 27 kg/m^2 subpopulation (adapted from company response to clarification, Figures 1–3)



Abbreviations: BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated haemoglobin; M-H, Mantel–Haenszel.

Figure 8. Impact of HbA_{1c} cut-off on SH and DKA within the BMI ≥ 27 kg/m^2 subpopulation (adapted from company response to clarification, Figures 4–5)

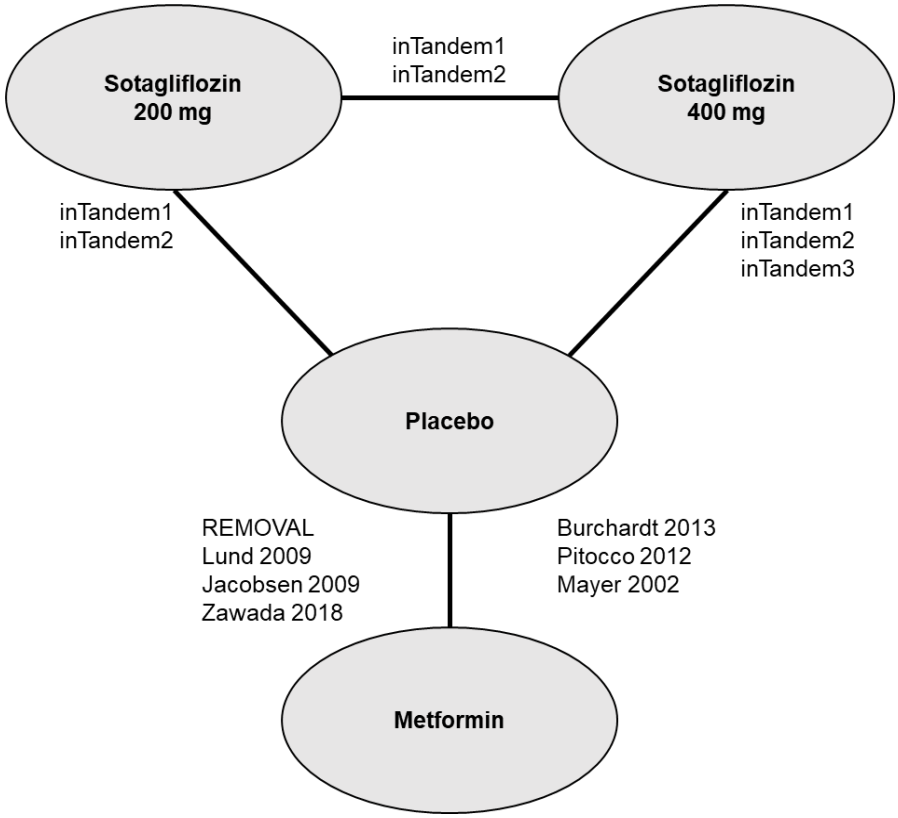


Abbreviations: BMI, body mass index; CI, confidence interval; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; M-H, Mantel–Haenszel; SH, severe hypoglycaemia.

4.4 Critique of the indirect comparison of sotagliflozin versus metformin (secondary analysis)

The company conducted an NMA of 10 trials identified in the SLR as a secondary analysis to compare sotagliflozin with metformin as adjunct therapy to insulin (Figure 9 and CS, Section 2.10. A feasibility assessment described in the CS Appendix (F.2.2–F.2.4) identified key sources heterogeneity in the methodology, baseline characteristics and outcomes across the trials (e.g. baseline HbA_{1c}, BMI and pump usage, geographical location, and pre-trial insulin optimisation). Furthermore, the populations of the seven metformin trials could not be limited to patients with BMI ≥ 27 kg/m^2, as was done for the inTandem phase III trials in line with the proposed marking authorisation for sotagliflozin. Moreover, the ERG agrees with the company that sotagliflozin in addition to insulin versus insulin alone is the most clinically relevant comparison, which is informed by head-to-head evidence from the phase III inTandem trials. Consequently, the ERG does not consider the analysis appropriate or necessary to inform the assessment of sotagliflozin for T1D.

Figure 9. Network diagram for the secondary analysis (reproduced from CS, Figure 2.11)



4.5 Summary of the clinical effectiveness evidence

- Sotagliflozin received a positive opinion from the CHMP for a European marking authorisation for adults with T1D and BMI ≥ 27 kg/m^2 who are on insulin therapy that does not adequately control blood glucose levels.[3] The proposed marketing authorisation was confirmed after the scope was finalised and is narrower than the population defined in the NICE final scope, because the CHMP asked the company to identify a subgroup of patients for whom the benefits of sotagliflozin would outweigh the increased risk of DKA;

- The draft SmPC recommends a starting dose of 200 mg a day which can be increased to 400 mg after at least three months if additional glycaemic control is needed. [redacted], but escalation to 400 mg will be possible by prescribing two 200 mg tablets before the 400 mg dose is available, which would double the acquisition cost. Sotagliflozin will likely not be recommended for patients aged over 75 years, those with eGFR ≤ 45 mL/min/1.73 m^2 or those at high risk of DKA (for which assessment and monitoring criteria are outlined);

- The company's primary clinical evidence is based on the inTandem1 (North America) and inTandem2 (Europe and Israel) trials, which were designed to evaluate the efficacy and safety

of sotagliflozin at two doses (200 mg and 400 mg daily) versus placebo as adjunct treatment to optimised insulin. Patients were eligible for inclusion if they were ≥18 years old, diagnosed with T1D for at least a year, and were taking insulin or an insulin analogue via CSII pump or MDI. The primary outcome was change in HbA_{1c} (%) after 24 weeks and the trials also included a long-term extension to 52 weeks;

- A third phase III RCT of sotagliflozin for patients with T1D (inTandem3; n = 1,402) more closely reflects UK clinical practice regarding baseline HbA_{1c} because it did not optimise insulin prior to initiation of treatment; however, it was not included in the primary analyses because it did not study the 200 mg dose or follow patients beyond 24 weeks;

- The company's primary population for clinical effectiveness and safety was a pooled population of patients with BMI ≥ 27 kg/m^2 from inTandem1 and inTandem2 (n = 916) to align the trials with the likely marketing authorisation for sotagliflozin. The ERG explored differences in results across the range of analyses submitted (e.g. individual trials, ITT population, pooled results including inTandem3 and/or phase II trials);

- The inTandem1 and inTandem2 trials provide high quality, head-to-head evidence for sotagliflozin (plus insulin) versus insulin alone (placebo) in line with the decision problem: randomisation procedures were robust, treatments were blinded, statistical analyses were appropriate and prespecified, dropouts were low and balanced, and insulin dose titrations, SH, DKA and other adverse events were all adjudicated by independent committees;

- Within the primary population, sotagliflozin 200 mg led to greater improvements in HbA_{1c} (%) at 52 weeks versus insulin alone (difference in least squares mean change –0.24% 95% confidence interval [CI]: –0.35 to –0.13), and there was a larger benefit of the 400 mg dose (–0.38%; 95% CI: –0.49 to –0.27). Improvement in HbA_{1c} was larger in the inTandem3 trial (400 mg at 24 weeks only) that did not optimise insulin before treatment, and so the relative treatment effect of sotagliflozin may be underestimated to some extent by the twin trials. The effect of sotagliflozin 200 mg and 400 mg on HbA_{1c} was statistically significant compared with insulin alone across all but one subgroup at 24 and 52 weeks (eGFR < 60 mL/min/1.73 m^2 (Table 20);

- Within the primary population, sotagliflozin led to clinically significant reductions in BMI (Table 11) and body weight (Table 12) compared with insulin alone. The difference versus insulin alone in BMI change from baseline to week 52 was –1.05 kg/m^2 for sotagliflozin 200 mg (95% CI: –1.29 to –0.81) and –1.53 kg/m^2 (CI: –1.77 to –1.29) for sotagliflozin 400 mg;

differences versus insulin alone for body weight were –3.01 kg for 200 mg (95% CI: –3.71 to –2.31) and –4.46 kg for 400 mg (CI: –5.15 to –3.76);

- There was not a consistent pattern of benefit for either dose of sotagliflozin at either timepoint for the primary population across measures of cardiovascular risk (SBP, DBP, total cholesterol, HDL-C, LDL-C, triglycerides; see Table 13). Where statistically significant benefits over insulin alone were noted, they were mostly small and unlikely to be clinically meaningful (e.g. SBP benefits of –2.5 mmHg and –3.6 mmHg at 24 and 52 weeks and DBP benefit of –1.46 mmHg at 52 weeks for sotagliflozin 400 mg). The benefits of sotagliflozin were most consistent across dose and timepoint for HDL-C and triglycerides;

- Within the primary population, sotagliflozin led to modest but statistically significant reductions in bolus insulin dose over insulin alone of –2.02 IU/day (95% CI –3.92 to –0.12) for sotagliflozin 200 mg and –4.05 IU/day (95% CI –5.93 to –2.17) for sotagliflozin 400 mg, which was maintained at 52 weeks for sotagliflozin 400 mg. Small statistically significant benefits were also noted in basal insulin dose for both doses of sotagliflozin compared with insulin alone at 24 weeks, which were maintained or improved at 52 weeks;

- Both doses of sotagliflozin led to statistically significant improvements within the primary population on the 2-item Diabetes Distress Screening Scale (DDS2) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) at 24 weeks compared with insulin alone, but there was very little change over time on the EQ-5D (index scores or VAS; Table 15);

- Most patients in the primary population had at least one episode of non-SH (91.5–93.3%) and rates of SH were 4.3%, 4.2% and 8.1% for sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone, respectively (Table 16). The ERG's clinical experts noted that rates of SH in the trials are higher than expected in UK clinical practice, and the lower rates of SH with sotagliflozin compared with insulin alone (which were not statistically significant) likely reflect changes in insulin dose during the trials because sotagliflozin works independently of insulin;

- In the primary population, approximately three quarters of each group experienced at least one TEAE. The rate of severe treatment-related TEAEs and TEAEs leading to study drug discontinuation was less than 5% in all groups, although rates of treatment-emergent serious adverse events (SAEs) were somewhat higher in the sotagliflozin groups (~9–10%) than for insulin alone (~7.0%). Three patients experienced TEAEs leading to death during inTandem1 and inTandem2, which were all in the placebo group;

- Within the primary population, 2.6%, 3.5% and 0.3% of patients receiving sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone had at least one episode of DKA during 52 weeks of treatment (Table 17), none of which were fatal. DKA occurred more frequently in patients using CSII pumps so might be lower in the UK because CSII use is lower than in the trials. The ERG's clinical experts would not consider those with CSII, poorly controlled diabetes, high alcohol intake, or low BMI eligible for treatment with sotagliflozin due to their elevated risk of DKA;

- More patients on either dose of sotagliflozin had genital infections than those on insulin alone, particularly females (21.6%, 17.6% and 6.3% for sotagliflozin 200 mg, 400 mg, and insulin alone, respectively), differences in rates of diarrhoea were not statistically significant (8.6%, 5.2% and 6.7%; Table 17), and rates of UTIs were similar between groups (4.4–6.6%). Volume depletion was rare in all groups but occurred more frequently in patients treated with sotagliflozin 200 mg (2.5%) and sotagliflozin 400 mg (1.6%) than insulin alone (0.6%). Low rates of diabetes-related complications were reported across the trials in all groups (<1%), but eye and nerve complications (specified in the NICE final scope) were not included in the list of events of special interest for the inTandem trial programme;

4.5.1 Clinical issues

- A secondary analysis was provided to compare sotagliflozin with metformin, but the ERG agrees with the company that it is not a relevant comparator, and the ERG considers the NMA flawed due to important clinical differences between trials. Dapagliflozin (SGLT-2) would be a relevant comparator but it is currently in the NICE technology appraisal process (ID1478)[29] and final guidance is not expected until August 2019;

- The ERG's clinical experts outlined a target population in whom they expect the risk benefit profile of sotagliflozin to be most favourable, which is narrower than the population of the inTandem1 and inTandem2 trials: BMI > 30, eGFR >60, insulin via MDI, HbA_{1c} > 8.5%, high cardiovascular risk, carbohydrate intake > 80 mg/day and willing to monitor blood glucose and urine ketones. Clinical data are not available for the clinical experts' target population because there were too few patients in each group for a robust analysis of outcomes;

- The primary population with BMI ≥ 27 kg/m^2 used for the clinical analyses comprises approximately 58% of the randomised population of the inTandem1 and inTandem2 trials; statistical power to detect a difference in the primary outcome is maintained when the two trials are pooled but randomisation is broken because BMI was not a stratification factor;

- In the primary population, more patients used CSII pumps (46%) and had better controlled HbA_{1c} (mean 7.6%) than in UK clinical practice (~15% and 8.8%, respectively), which affects the applicability of both efficacy and safety outcomes. The trials optimised insulin therapy from 6 weeks before baseline, which would not occur in practice, resulting in HbA_{1c} < 7% for 17.1–19.5% of patients at the start of treatment;

- ITT subgroup analyses for change in HbA_{1c} show a somewhat smaller effect of sotagliflozin versus insulin alone in the subgroup of patients using MDI compared with CSII at 52 weeks, and a larger effect for the 200 mg dose in patients with HbA_{1c} >8.5% compared with ≤8.5% at 24 and 52 weeks. Confidence intervals were overlapping across subgroups, but the potential overestimate of benefit caused by higher CSII use in the trials may be mitigated by patients in the UK having higher HbA_{1c} than patients in the trials; furthermore, forest plots submitted by the company for other outcomes showed high correlation between 52-week effects for HbA_{1c}, BMI, SBP, SH and DKA at different HbA_{1c} cut-offs (7%, 8.5% and 9%) within the BMI subpopulation;

- The trials do not provide evidence for the durability of initial treatment effects and were not designed to determine cardiovascular benefits of sotagliflozin in T1D. Improvements in HbA_{1c}, BMI and body weight were all consistently statistically significant for both doses, but showed different patterns over time; the effect of sotagliflozin appears to wane over time for HbA1c, net benefit and eGFR, and stabilise or increase over time for BMI, body weight, and some measures of cardiovascular risk. There was inconsistency in absolute and relative treatment effects for various outcomes depending on the timepoint (24 or 52 weeks) and the study(ies) used for analysis, including HbA_{1c}, basal and bolus insulin dose, HRQoL and SH;

- Patients who received sotagliflozin 400 mg in the trials did not escalate from 200 mg after at least three months when additional glycaemic control was needed, as recommended in the draft SmPC, so assumptions were made for the economic model. The 400 mg dose appears to have larger or more sustained benefits for some outcomes (e.g. HbA_{1c}, bolus insulin dose) and the ERG considers it unreasonable to assume sotagliflozin 200 mg and sotagliflozin 400 mg have the same adverse effect profile. However, there is uncertainty about the criteria by which patients will be deemed suitable for dose escalation, and whether the 400 mg dose will be given as two 200 mg tablets until the 400 mg tablet is available, which would double the acquisition cost.

- Some safety analyses are on a larger pool of phase II and III sotagliflozin studies so may not reflect absolute rates and differences from placebo (insulin alone) in the population of interest who have BMI ≥ 27 kg/m^2; some microvascular complications listed in the NICE final scope

were not included in the list of events of special interest reported for the inTandem trial programme (e.g. damage to the nerves and eyes);

- The ERG's clinical experts expressed concern regarding the lack of clear guidance for treatment discontinuation, when "the patient is no longer receiving benefit" and dose escalation, "if additional glycaemic control is needed". The absence of clear guidance could lead to dose escalation in a larger proportion of patients than the company propose in their submission, and indefinite continuation of treatment where HbA_{1c} has returned to the baseline level but the longer-term weight and cardiovascular benefits are unknown.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and de novo economic evaluation submitted by the company. The company provided a written submission of the economic evidence along with access to the web-based economic model. Table 21 summarises the location of the key economic information within the company's submission (CS).

Table 21. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	3.1
Model structure	3.2.3
Technology	3.2.3.3
Clinical parameters and variables	3.3
Measurement and valuation of health effects and adverse events	3.3.4
Resource identification, valuation and measurement	3.4
Results	3.8
Sensitivity analysis	4
Validation	4.3.3
Subgroup analysis	4.3.2.1
Strengths and weaknesses of economic evaluation	4.3.5
Abbreviations: CS, company submission.	

5.2 Summary of the company's key results

The company's base case analysis results, based on the CORE Diabetes Model, are given in Table 22.

Table 22. Company's base case results (sotagliflozin 200 mg in combination with insulin versus insulin alone) (adapted from Table 37 of the company's addendum)

Treatment	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£78,731	17.194	8.695	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£78,940	17.223	8.803	£209	0.029	0.108	£1,934
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

The company's probabilistic sensitivity analysis resulted in an incremental cost-effectiveness ratio (ICER) of £2,434. The probability that sotagliflozin was cost-effective at the £20,000 per quality-adjusted life-year (QALY) was 89%.

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review (SLR) to identify economic and health-related quality of life (HRQoL) evidence in adult patients with type 1 diabetes (T1D). Searches were conducted from November to December of 2017 in the following electronic databases: MEDLINE; Embase; EconLIT; National Health Services Economic Evaluation Database (NHS EED) and Centre for Reviews and Dissemination Health Technology Assessment Database (CRD-HTA). In addition, conference proceedings (between 2015 and 2017), the NICE website and reference lists of identified eligible studies were searched.

Search strategies are provided in the CS Appendix K and M for economic evidence and HRQoL evidence, respectively. In summary, search terms for economic evidence combined the population (adult patients with T1D) with treatment (insulin and sodium-glucose transporter [SGLT] inhibitors) and economic terms, while the search terms for HRQoL evidence combined the population (adult patients with T1D) with quality of life terms, which the ERG considers to be appropriate.

Economic evaluations were restricted to publication dates from the year 2000, while studies reporting HRQoL data were considered from the year 1990. Results of both searches were also restricted to English language studies.

In summary, a total of 33 unique economic evaluations (cost-effectiveness analysis or cost-utility analysis) met the eligibility criteria reported in Table K.6 of the CS Appendix. These 33 studies included 22 full-text publications and 11 abstracts. Of the included evaluations, 11 used the Core Diabetes Model (CDM), one used the PRIME Diabetes Model (hereon referred to as PRIME) and the remaining evaluations used models developed by the authors of the publication. The methods and baseline characteristics of the included studies are given in Tables K.9 and K.10 of the CS Appendix, respectively. Quality assessments of the study design, data collection and methods employed in each study are given in Tables K.11, K.12 and K.13 of the CS Appendix, respectively.

For HRQoL evidence, the company considered papers with a combined population (i.e., T1D and T2D patients) and only included studies that reported utility values from one of the listed instruments in Table M.6 of the CS Appendix. This resulted in a total of 65 included studies reporting utility data. However, 12 of those studies, including 11 cost-utility analyses, were not primary sources of utility data.

Of the 53 primary sources of utility data, 34 were undertaken in patients with T1D, while 19 did not specify the type of diabetes. A summary of those 53 studies is given in Table M.12 of the CS Appendix and the disutility associated with specific patient and disease characteristics is given in

Table M.13 of the CS Appendix. Quality assessments of the primary sources are given in Table M.14 of the CS Appendix.

Although the ERG considers the searches carried out by the company to be appropriate, the company did not report results from the economic evaluations or provide details in the quality assessments to enable a comprehensive comparison of the economic models. The company's chosen economic model for the primary analysis (the CDM) is outlined and critiqued in detail in Section 5.4.4.

The company did not undertake a search to identify cost or resource use data. However, the ERG does not consider this to be an issue given that the company used reliable UK sources, or default values in the CDM to inform their analysis. Sources of resource use and cost data are described in greater detail in Section 5.4.9.

Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases. However, the ERG was able to cross-check the company's utility, cost and resource use inputs with the NICE guideline for T1D in adults (NG17).[8] When the ERG made its comparisons with NG17, it was satisfied that the best available evidence was used to inform utility inputs in the model (Section 5.4.8.1). However, as explained in Section 5.4.9.3, the ERG found large discrepancies in the cost to treat severe hypoglycaemia (SH).

5.4 Overview and critique of company's economic evaluation

5.4.1 NICE reference case checklist

Table 23 summarises the ERG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.

Table 23. NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes. However, the analysis presented for the 400mg dose of sotagliflozin was not performed using data for that dose.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes. As well as insulin therapy, the company also included metformin as a comparator. Metformin is not considered as UK clinical practice, but no relevant treatments were excluded from the analysis.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs	Yes – 60 years.

	and outcomes	
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes. The various utilities sourced for the downstream complications of T1D, were all based on the EQ-5D questionnaire. The trial data were not applied in the model as this did not capture the true impact on quality of life because of the follow-up period of just 52 weeks.
Benefit valuation	Time-trade off or standard gamble	Yes – EQ-5D.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes. The economic model was stochastic, but second order sampling was also incorporated to provide a PSA with 10,000 samples.
Abbreviations in the table: EQ-5D, EuroQoL 5-dimension; HRQoL, health-related quality-of-life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.		

5.4.2 Population

The company's submission intended to represent adults with T1D in the UK. To achieve this, baseline characteristics in the simulated cohort in the CDM and PRIME Diabetes model were largely taken from data included in the National Diabetes Audit (NDA) and Diabetes Control and Complications Trial (DCCT).[39, 40] However, as treatment effectiveness data was taken from the pooled analysis of inTandem1 and inTandem2 trial in the company's updated analysis, the ERG considers that baseline characteristics from those trials may be more appropriate.[33] To assess the impact of this issue, the ERG requested the company to conduct a scenario that used the same baseline characterises from which the effectiveness data were derived.

The ERG also notes that the Committee for Medicinal Products for Human Use (CHMP)[3] adopted a positive opinion that covers a population that is narrower (patients with body mass index (BMI) ≥27 kg/m^2) than the inTandem trials.[32-34] While the mean BMI in the inTandem trials was >27 kg/m^2, the trials included a number of patients with BMI<27 kg/m^2 that would not be covered by the marketing authorisation. The ERG considers that any population put forward by the company for consideration

by the committee should reflect CHMP advice, and therefore, the ERG requested cost-effectiveness analyses for the population with a BMI ≥ 27 kg/m^2.

In their original submission, the company used results from inTandem2 as the primary clinical inputs for treatment effectiveness in their base case economic analysis.[33] This was on the basis that inTandem2 was conducted in Europe and, therefore, considered by the company to be more applicable to patients in England and Wales than inTandem1, which was conducted in North America.[32] However, clinical experts advised the ERG that the number of patients receiving continuous subcutaneous insulin infusions (CSII) in the inTandem2 trial (26%) was too high and that the small proportion of patients using CSII in the UK (approximately 15% in England and Wales according to the NDA Insulin Pump Report)[9] are unlikely to be offered sotagliflozin for safety reasons. They also added that baseline glycaemic control is much worse in UK clinical practice than in the inTandem trials. Therefore, to better reflect patients in the UK who are likely to be considered for treatment with sotagliflozin, the ERG requested the company to pool the inTandem trials and provide cost-effectiveness analyses for patients with a BMI ≥ 27 kg/m^2 who were within the upper glycated haemoglobin (HbA_{1c}) stratification factor (>8.5%) and using multiple daily injections (MDI). However, in response to the ERG's clarification question, the company explained that patient numbers were too small when the populations were limited and pooled in the way requested by the ERG. Instead, the company submitted a revised analysis that pooled inTandem1 and inTandem2 for patients with a BMI ≥ 27 kg/m^2 to reflect the population in the recent marketing authorisation. The key differences in baseline characteristics are discussed in Section 4.2.2.

5.4.3 Interventions and comparators

The company's primary analysis comprised a comparison of sotagliflozin 200 mg in combination with insulin versus insulin alone. A secondary analysis comparing sotagliflozin 200 mg in combination with insulin to metformin in combination with insulin was also included.

The inTandem trials were designed to evaluate the efficacy and safety of sotagliflozin at two doses (200 mg and 400 mg daily) versus placebo as adjunct treatment to optimised insulin.[32-34] However, the company did not initially provide a cost-effectiveness analysis for the 400 mg dose because the 400 mg tablet would not be available at the time of launch in the UK. The ERG disagrees with the company's decision to omit cost-effectiveness evidence for the 400 mg dose given that the CHMP positive opinion is for the 200 mg dose and 400 mg dose of sotagliflozin.[3] As such, the ERG requested cost-effectiveness results for the 400 mg dose during the clarification stage.

In response to the ERG's clarification question, the company provided an analysis for the 400 mg dose but used outcomes for the 200 mg dose to inform the economic analysis. As such, patients are assumed to receive the same benefits and harms they would have done should they have remained on

the 200 mg starting dose. As explained in Section 4.3 the ERG agrees with the company that using 200 mg efficacy data as a proxy for sotagliflozin 400 mg in the economic model is conservative. However, the ERG considers it potentially unreasonable to assume sotagliflozin 200 mg and sotagliflozin 400 mg have the same adverse effect profile. In summary, it is the ERG's opinion that there is too much uncertainty on how treatment effectiveness for the 400 mg is estimated in the model, therefore, caution should be taken in interpreting the current 400 mg dose cost-effectiveness analysis using the 200 mg dose data.

Metformin has been included in this submission per the NICE final scope. However, the ERG's clinical experts do not consider metformin a relevant comparator for sotagliflozin because metformin does not have marketing authorisation for this indication and there is no evidence it improves glycaemic control in the UK for T1D.[31] For these reasons, the ERG considers that the comparison with metformin in combination with insulin is not relevant to the decision problem and, therefore, will focus the critique only on the comparisons with insulin. This comparison is discussed further in Section 4.4.

5.4.4 Modelling approach and model structure

The company's base case analysis was performed using version 9 of the CDM. This model is a non-product-specific web-based platform allowing economic evaluations of a variety of different interventions for both T1D and T2D. It has been used extensively for economic evaluations of therapies for T1D, including the NG17, and is regularly validated during the Mount Hood Challenge – a conference for diabetes-focused health economic modellers from around the world to test the validity of the model. A key publication on the validation of the CDM is given by McEwan *et al.* 2014.[41]

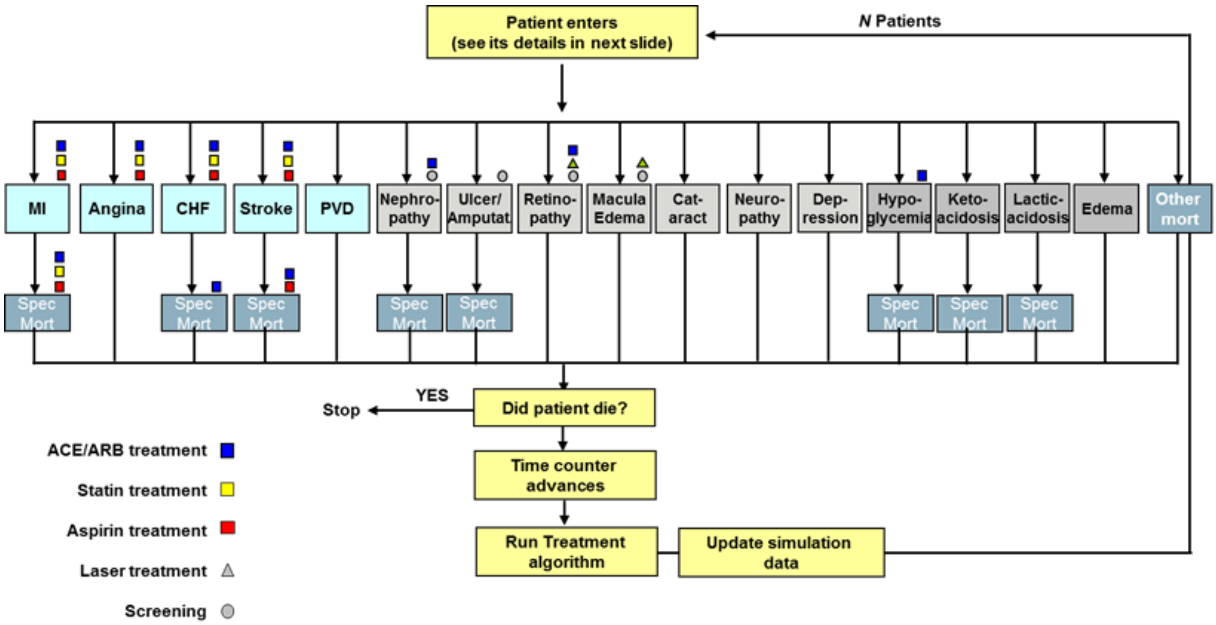
The structure of the CDM has four key aspects: simulation of a baseline cohort; modelling the progression of physiological parameters over time; estimating the risk of complications based on physiological parameters; and, modelling the long-term impacts on costs and quality-adjusted life-years (QALYs) of each complication through a set of Markov sub-models. Details of the cohort simulation are given in Section 5.4.2, while the modelling of physiological parameter progression and the risk of complications is discussed in Section 5.4.5. The remainder of this section will, therefore, focus on the structure of the Markov sub-models.

The CDM is based on a set of 17 Markov sub-models, each of which represents the disease progression of a particular complication (See Figure 10) over time. Patients pass through each of the sub-models at each annual cycle and the event risks in each sub-model are based on baseline characteristics and physiological parameters that progress over time. These are discussed further in

Section 5.4.5. Tracker variables are also used to allow complex interactions between the sub-models to accurately reflect the comorbid nature of T1D complications.

The model is a stochastic simulation that inputs a hypothetical cohort of patients individually. The company used a cohort of 1,000 patients based on data from the NDA, as discussed in Section 5.4.2, and performed 1,000 simulations for each analysis. A patient's risk of each complication is updated in each (annual) model cycle based on the progression of the physiological parameters and previous occurrences of complications. The time horizon of the model is 60 years, as specified by the company. A diagram of the model structure, showing each of the complications modelled, is given in Figure 10.

Figure 10. Schematic structure for the CORE Diabetes Model



Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; CHF, chronic heart failure; MI, myocardial infarction; PVD, posterior vitreous detachment.

5.4.4.1 Alternative PRIME Diabetes Model (Validation)

The company also provided an alternative analysis to assess structural uncertainty for validation purposes, using PRIME. Although the company did not provide a full description of PRIME in their original submission, in response to the ERG's clarification questions, the company provided a tabular comparison of the main aspects of PRIME and the CDM (Table 74 of the company's clarification response document).

The structure of PRIME appears to be similar to the CDM in that it generates a simulated cohort to define baseline characteristics including key risk factors and pre-existing complications. This cohort then follows through a series of Markov sub-models that represent each of the complications over time. Similarly, physiological parameter progressions are used to update the risk of complications in each annual cycle of the model, and the time horizon of the analysis in PRIME was also set to 60 years as per the CDM.

PRIME appears to have fewer sub-models, with just 12 compared to the CDM's 17 – the missing health states being, peripheral vascular disease (PVD), cataract, depression, lactic acidosis and oedema. A schematic of the PRIME model structure is given in Figure 11.

Progressions of physiological parameters and risks of complications used in the PRIME model are discussed in Section 5.4.5.3.

Figure 11. Schematic of the PRIME model structure (Valentine *et al.* 2017)

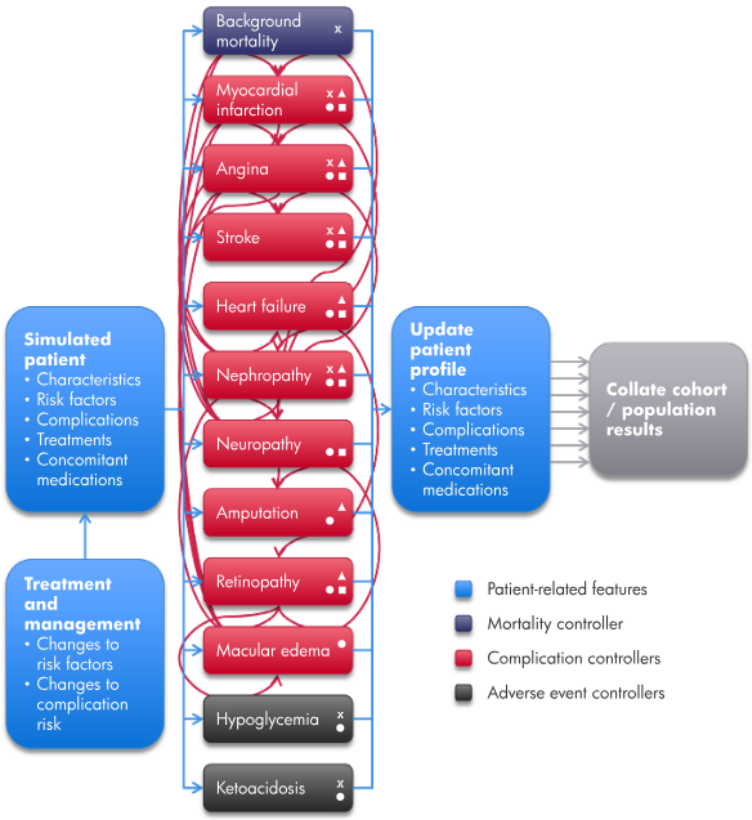


Fig. 1 – Schematic diagram of the PRIME Diabetes Model. Interactions between complication controllers are indicated by red arrows. X, risk of mortality is associated with this complication controller; ▲, SBP is a direct risk factor; ●, HbA_{1c} is a direct risk factor; ■, BMI is a direct risk factor. BMI, body mass index; HbA_{1c}, glycated hemoglobin; SBP, systolic blood pressure.

5.4.4.2 ERG critique

The ERG considers the company's base case model to have strengths in the fact that it was developed based on a thoroughly validated and widely used published online model. The model structure, therefore, is likely to be sound. The ERG would like to highlight the difficulty in providing a thorough independent critique of the model structure itself due to the "black box" nature of this online model. However, the ERG considers a comparison with PRIME, that the company used for validation purposes, to be a useful exercise in challenging the validity of the CDM structure that was chosen by the company.

The company's original submission gave very little detail regarding the structure of PRIME; however, after clarification, the company provided a table of information outlining the key differences (Table 74 of the clarification response document) between the two models. Although in some areas it was difficult to fully evaluate how, in practice, the functioning of the two models differed, the ERG considers the key differences that may impact whether either of the models could be considered to have a more appropriate structure.

Like CDM, the ERG notes that the PRIME model is also an online model that has accompanying published validation studies. It also appears to have a similar structure to the CDM in that it is a patient simulation in which the risks of complications are calculated at each annual cycle based on baseline characteristics and risk factors such as glycated haemoglobin (HbA_{1c}) and body mass index (BMI). All baseline characteristics were able to be set the same in PRIME, with the exception of ethnicity, which is not an option within PRIME. However, given that 93% of the population in the CDM were specified by the company as white, the ERG does not consider the lack of modelling the effects of the higher risk ethnicities to have an impact on the model results.

Three of the sub-models that were not part of the PRIME model were not used as part of the CDM analysis. These were: lactic acidosis, oedema and depression. Therefore, the only sub-model that differed between the two models was the inclusion of PVD in the CDM. However, the CDM does not give a breakdown of the results for PVD and, therefore, the ERG cannot estimate the impact that the exclusion of PVD may have on the results.

Other key differences between the models relate to sources of data to inform physiological parameter progressions and mortality risks relating to complications. These are discussed further in Section 5.4.5. In terms of the model structure itself, the ERG does not have any reason to suggest that the CDM is not an appropriate choice of model structure.

5.4.5 Treatment effectiveness

The company's model is dependent on the progression over time of a number of physiological parameters. These parameters influence the risk of complications throughout the model, and therefore, differences between these parameters in different treatment groups drive the benefits in the model.

In response to clarification questions, the company made substantial changes to their preferred base case analysis. For clarity, the approach taken to estimate treatment effectiveness in the original submission and the key changes made in the updated analyses are described separately in Section 5.4.5.1 and 5.4.5.2, respectively.

5.4.5.1 Original submission

The company's chosen model, the CDM, relies on predicting the risk of the multiple complications of T1D based on a number of risk factors. The key factors used to predict these risks in the company's model are: HbA_{1c}, BMI, systolic blood pressure (SBP), total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides. These risk factors are affected by treatment and progress over time. Other risk factors are included within the CDM but were not affected by treatment and were kept constant from baseline onwards.

In the company's base case analysis, baseline risk factors were informed by the NDA data. These were adjusted in the first model cycle (first year) by treatment effects observed at 52 weeks in the inTandem2 trial. After the first year, the company estimated the expected progression of these physiological parameters over time based on various other data sources and assumptions. Each of the key physiological parameter progressions are described in Section 5.4.5.1.1. The prediction of risks of complications derived from these physiological parameters is described in Section 5.4.5.1.2.

5.4.5.1.1 Physiological parameter progression

In the company's original submission, the company used data from the intensive insulin group of the DCCT to inform progression of HbA_{1c} and BMI, which estimated annual increases of 0.045% and 0.2375kg/m^2, respectively. The company considered that lifetime progressions of these values would result in implausible estimates in the long term and, therefore, chose to cap the values.

The company capped BMI at 35kg/m^2 in both treatment groups as this represents the definition of class II obesity (severe obesity). After 5 years from baseline, at which point sotagliflozin treatment was stopped, the BMI treatment effect for sotagliflozin was removed and patients were assumed to rebound to the BMI in the insulin group the following year, after which the progression continued until the cap of 35kg/m^2.

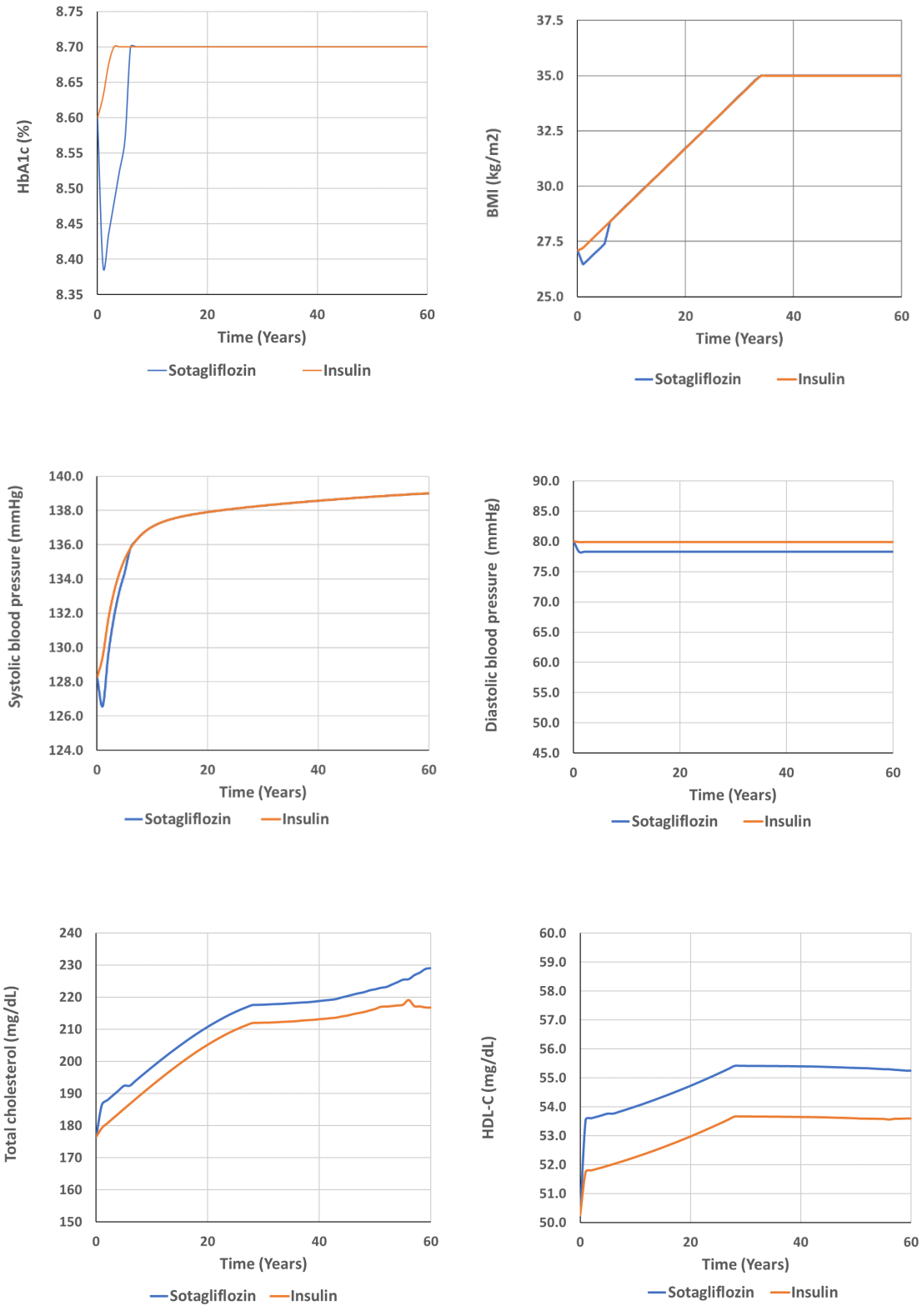
For HbA_{1c}, the company considered a slight increase of 0.1% above the baseline to be a plausible cap, as this allowed the treatment effect for the insulin group (0.03%) to be applied in the first year. The company assumed that the HbA_{1c} treatment effect for sotagliflozin was removed after 5 years when patients stopped treatment. Therefore, HbA_{1c} rebounded to that of the insulin group in the following year, after which point it progressed until the cap. The company assumed that the resulting capped value of 8.7% was maintained for the remainder of the time horizon up to 60 years in both treatment groups.

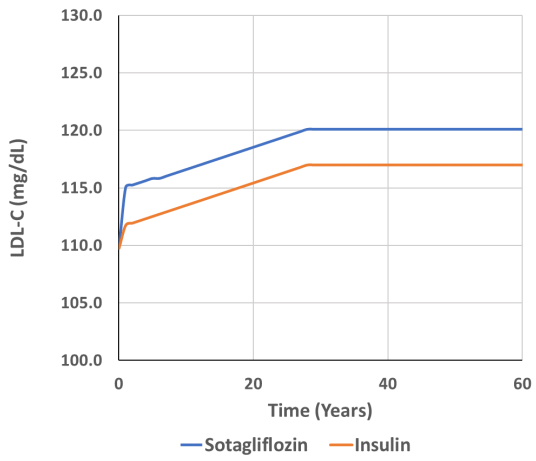
SBP progression following on from the treatment effects applied in the first year, was initially estimated using the United Kingdom Prospective Diabetes Study 68 (UKPDS 68) risk equation option within the CDM.[42] The treatment effect was maintained for the duration of treatment with sotagliflozin (5 years), after which point SBP in the sotagliflozin group was assumed to rebound to that of the insulin group.

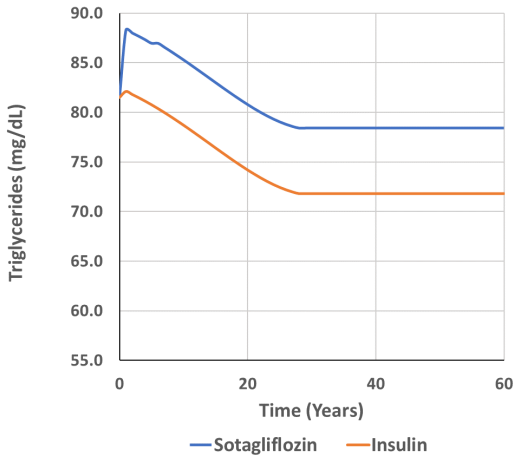
Lipid measurements, consisting of total cholesterol, HDL-C, LDL-C and triglycerides, were informed by the Framingham progressions, which are also an option to select within the CDM. As with the other parameters, the company stated that all lipid-related treatment effects for sotagliflozin were assumed to be removed after the 5-year treatment period. After this, the company stated that lipids were assumed to be equal to the insulin group.

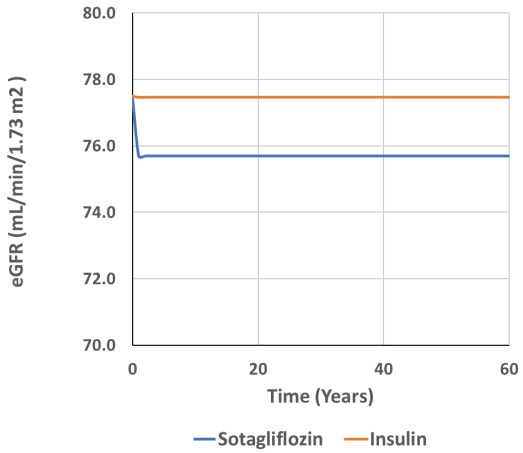
The company stated in their original submission that there were no annual increases for all other physiological parameters, namely: estimated glomerular filtration rate (eGFR); haemoglobin; white blood cell count; heart rate; diastolic blood pressure (DBP); waist-to-hip ratio; urinary albumin-to-creatinine ratio; serum creatinine; and, serum albumin. That is, the values for the sotagliflozin and insulin treatment groups converged after the first year and remained constant for the remainder of the time horizon. However, the data in the company's base case analysis using the CDM appeared to contradict these statements for eGFR and DBP, which showed that the treatment effects were maintained for a lifetime. The progression data used in the company's base case for eGFR and DBP, along with the other described progressions, is shown in Figure 12, respectively.

Figure 12. Physiological parameter progression in company's original base case (reproduced from the CDM)









5.4.5.1.2 Complication risk prediction

The model contains baseline probabilities of key complications, which are adjusted with risk reductions relating to changes in physiological parameters. The model differentiates between cardiovascular (CV) complications and microvascular complications.

For the CV complications of myocardial infarction (MI), stroke, heart failure and angina, the model has a number of in-built risk equation models, such as UKPDS 68, derived from T2D data. This was the key basis on which CV risks were based.

The UKPDS 68 study provides equations, derived using data from a cohort of 3,867 T2D patients, to estimate the risks of ischaemic heart disease (IHD), MI, congestive heart failure (CHF), stroke, amputation, blindness and renal failure. Depending on the risk factor being estimated, these equations take into account characteristics such as age, sex, smoking status, BMI, HbA_{1c}, SBP, ratio of total cholesterol to HDL-C, peripheral vascular disease (PVD), atrial fibrillation (AF), IHD, CHF and blindness. The coefficients of the UKPDS risk equations are given in Table 24.

Table 24. Coefficients for UKPDS 68 risk equations (reproduced from Clarke *et al.* 2004).

Complication	IHD	MI	CHF	Stroke	Amputation	Blindness	Renal failure
λ	−5.310 (0.174)	−4.977 (0.160)	−8.018 (0.408)	−7.163 (0.342)	−8.718 (0.613)	−6.464 (0.326)	−10.016 (0.939)
ρ	1.150 (0.067)	1.257 (0.060)	1.711 (0.158)	1.497 (0.126)	1.451 (0.232)	1.154 (0.121)	1.865 (0.387)
AGE	0.031 (0.008)	0.055 (0.006)	0.093 (0.016)	0.085 (0.014)		0.069 (0.014)	
FEMALE	−0.471 (0.143)	−0.826 (0.103)		−0.516 (0.171)			
AC		−1.312 (0.341)					
SMOK		0.346 (0.097)		0.355 (0.179)			
BMI			0.066 (0.017)				
HBA1C	0.125 (0.035)	0.118 (0.025)	0.157 (0.057)	0.128 (0.042)	0.435 (0.066)	0.221 (0.050)	
SBP	0.098 (0.037)	0.101 (0.026)	0.114 (0.056)	0.276 (0.042)	0.228 (0.075)		0.404 (0.106)
TOTAL:HDL				0.113 (0.025)			
Ln (TOTAL:HDL)	1.498 (0.202)	1.190 (0.169)					
PVD					2.436 (0.521)		
ATRFIB				1.428 (0.472)			
IHD		0.914 (0.150)					
CHF		1.558 (0.202)		1.742 (0.287)			
BLIND					1.812 (0.462)		2.082 (0.551)

Abbreviations: AC, afro-Caribbean; ATRFIB, atrial fibrillation; BLIND, blindness; BMI, body mass index; CHF, congestive heart failure; HDL, high-density lipoprotein; IHD, ischaemic heart disease; MI, myocardial infarction; PVD, peripheral vascular disease; SBP, systolic blood pressure; SMOK, smoking status.

It also provides equations for stroke and MI fatality, diabetes mortality, and other death, as well as equations to estimate the progression of HbA_{1c}, SBP, and total cholesterol.

The current version of the CDM (Version 9) allows risks to be based on a composite CV risk, which is then used to weight the risks estimated by UKPDS 68, or to apply the UKPDS 68 risk equations directly. The former was the approach taken by the company.

The company's composite baseline risk of cardiovascular disease (CVD) was taken from the Epidemiology of Diabetes Interventions and Complications (EDIC) study – an observational follow-up of the DCCT,[19] incorporating: nonfatal MI or stroke; cardiovascular death; confirmed angina or revascularisation (angioplasty, stent, or bypass); and, all adjudicated or silent MI readings on echocardiogram (ECG). Time dependent probabilities determined from EDIC study data were applied in the model, and these are shown in Table 25. These probabilities were considered to represent the MI, stroke and IHD endpoints of the CDM. The composite risks were weighted by risks determined by the UKPDS 68 outcomes model to determine the risk of each endpoint.

Table 25. Time dependent composite probabilities of CVD

Duration of T1D (Years)	Probability of CVD
0-5	0.00000
6-10	0.00042
11-15	0.00382
16-20	0.00302
21-25	0.00372
26+	0.00832

Abbreviations: CVD, cardiovascular disease; T1D, type 1 diabetes.

To incorporate treatment effects on the risk of complications, absolute risk reductions of 20% were applied for every 10% reduction in HbA_{1c}, for CVD outcomes. This risk reduction was based on data from the EDIC study.

Baseline risk of microvascular events was informed similarly using EDIC data. These were adjusted based on progressions in HbA_{1c} and SBP levels over time. Retinopathy and macular oedema were associated with an absolute risk reduction of 50% for every 10% reduction in HbA_{1c}, while all microvascular events were associated with an absolute risk reduction of 13% for every 10% reduction in SBP. A summary of the key model inputs for the CDM is given in Table 26.

Table 26. Summary of parameter values applied in the CDM (reprodcued from the CDM)

Parameter	Value
Reduction in risk for 10% reduction in HbA_{1c}	
Background diabetic retinopathy	50%
Proliferative diabetic retinopathy	50%
Macular oedema	50%

Microalbuminuria	50%
End-stage renal disease	0%
Neuropathy	45%
Myocardial infarction	20%
Heart failure	20%
Stroke	20%
Angina	20%
Reduction in risk for 1% reduction in HbA_{1c}	
Gross-proteinuria	20%
Cataract	0%
Haemodialysis mortality	12%
Peritoneal mortality	12%
Renal transplant mortality	0%
1^{st} ulcer	17%
Reduction in risk for 10mmHg reduction in SBP	
All microvascular complications	13%
Myocardial infarction adjustments	
Proportion with MI having initial coronary heart disease (CHD) event, female.	0.36
Proportion with MI having an initial CHD event, male.	0.52
Proportion with MI having a subsequent CHD event, female.	0.47
Proportion with MI having a subsequent CHD event, male.	0.45
Relative risk of MI with microalbuminuria	1
Relative risk of MI with gross proteinuria	1
Relative risk of MI with end-stage renal disease	1
Myocardial infarction mortality	
Probability of sudden death after MI, male	0.39
Probability of sudden death after MI, female	0.36
Stroke adjustments	
Relative risk of stroke with microalbuminuria	1
Relative risk of stroke with gross proteinuria	1
Relative risk of stroke with end-stage renal disease	1
Stroke mortality	
Probability of death following 1^{st} stroke	0.12
Probability of death following recurrent stroke	0.42
Angina	
Proportion with initial CHD event angina, female	0.62
Proportion with initial CHD event angina, male	0.42
Proportion with subsequent CHD event angina, female	0.36
Proportion with subsequent CHD event angina, male	0.30
Relative risk of angina with microalbuminuria	1
Relative risk of angina with gross proteinuria	1
Relative risk of angina with end-stage renal disease	1
Congestive heart failure	
Relative risk of heart failure with microalbuminuria	1
Relative risk of heart failure with gross proteinuria	1
Relative risk of heart failure with end-stage renal disease	1

Relative risk of heart failure death if diabetic, male	1
Relative risk of heart failure death if diabetic, female	1.7
Adverse events	
Probability of death from major hypoglycaemic event	0.003
Probability of death from ketoacidosis	0.05
Foot ulcer and amputation	
Probability of amputation if gangrene	0.182
Probability of gangrene healing	0.308
Probability of death following gangrene	0.010
Probability of death with history of amputation	0.004
Probability of death following healed ulcer	0.004
Probability of recurrent uninfected ulcer	0.039
Probability of amputation following infected ulcer	0.004
Probability of infected ulcer leading to healed amputation	0.045
Probability of infected ulcer leading to death	0.001
Probability of infected ulcer leading to gangrene	0.008
Probability of infected ulcer becoming uninfected	0.1397
Probability of recurrent amputation	0.008
Probability of uninfected ulcer leading to death	0.004
Probability of uninfected ulcer becoming infected	0.047
Probability of uninfected ulcer becoming healed	0.079
Probability of developing an ulcer with neither neuropathy or CVD	0.00025
Probability of developing an ulcer with either neuropathy or CVD	0.00609
Probability of developing an ulcer with both neuropathy and CVD	0.00609
Depression	
Relative risk of death if depression	1.33
Relative risk of depression if neuropathy	3.1
Relative risk of depression if stroke	6.3
Relative risk of depression if amputation	1
Others	
Probability of background diabetic retinopathy leading to severe vision loss.	0.015
Probability of reversal of neuropathy	0

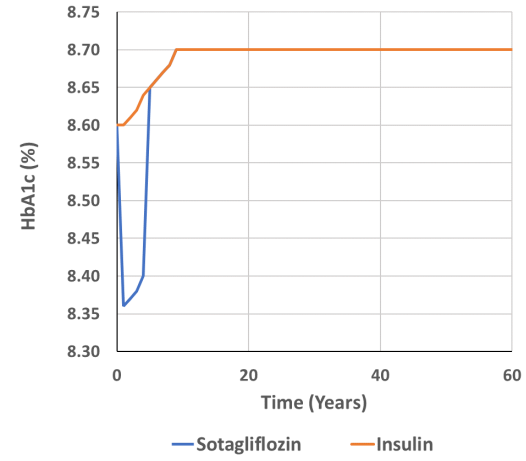
5.4.5.2 Post-clarification

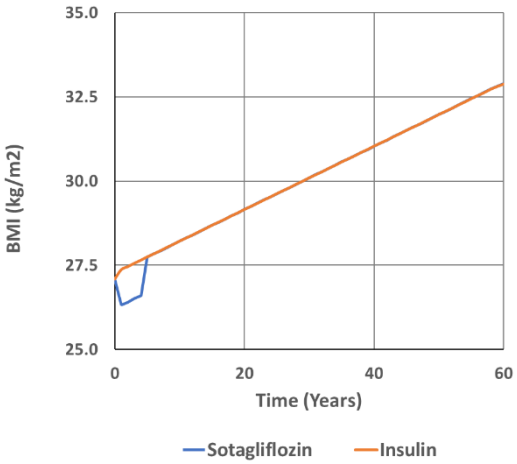
In response to clarification questions, the company provided an updated base case analysis. This analysis was still based on the CDM but used different sources of data to inform the treatment effects and the progression of physiological parameters over time.

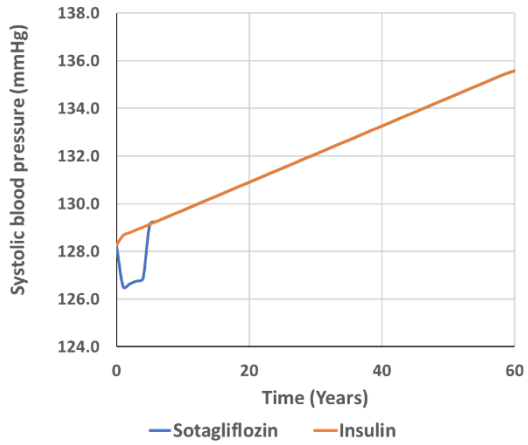
The company updated the efficacy outcomes to those based on the pooled inTandem1 and inTandem2 trials for patients who have a BMI $\geq$ 27kg/m^2. This analysis was more aligned with the likely marketing authorisation. The company also chose to change the progressions over time for all the key physiological parameters, based on alternative sources of data.

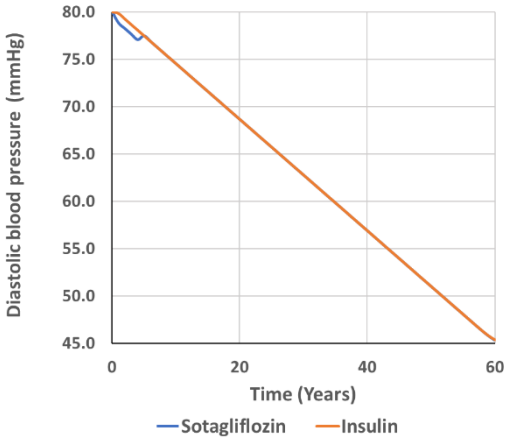
The company's updated base case analysis is now based on linear trends estimated from the outcomes of the EDIC study. The EDIC study provides more recent data than the DCCT and shows a slower progression of HbA_{1c} with an annual increase of 0.012%. The progression of BMI was also shown to be greatly reduced compared to the company's original submission, with an annual increase of $0.094kg/m^2$. The same data source was used to inform the annual changes for SBP, DBP, lipids and eGFR. The new progressions for all parameters in the company's revised base case analysis are shown in Figure 13.

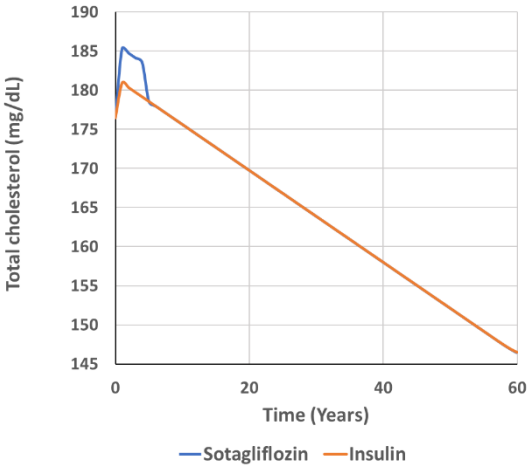
Figure 13. Physiological parameter progression in the company's updated base case (reprodcued from the CDM)

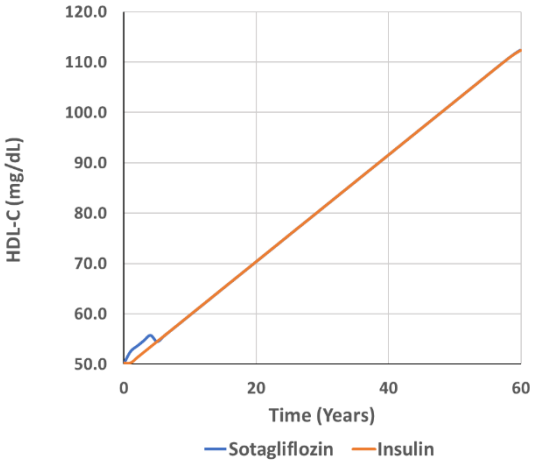


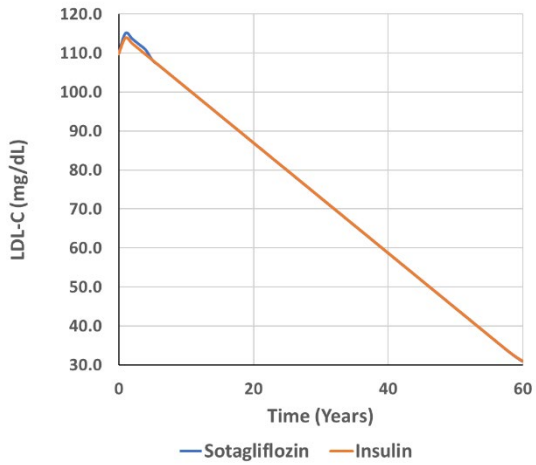


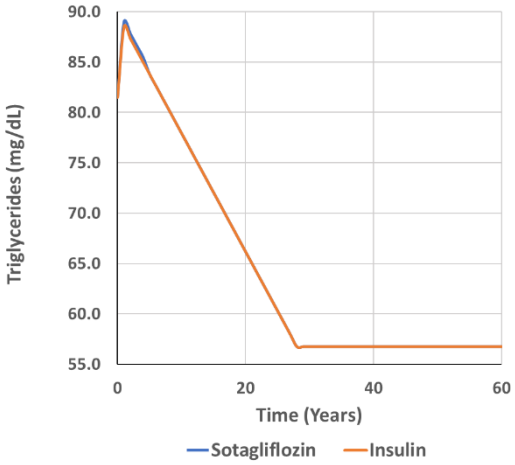


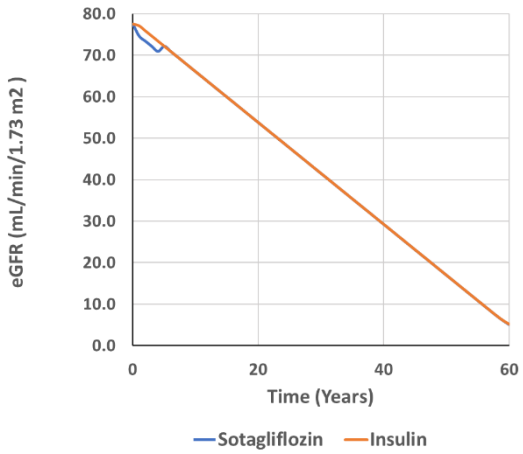












All of the company's revisions to the base case analysis in terms of treatment effectiveness are summarised in Table 27.

Table 27. Company's base case model input changes (Adapted from Table 70 of the company's clarification response document)

Variable	Company's original base-case	Company's new base-case
Population	NDA	NDA
Efficacy outcomes	inTandem2	inTandem1 and 2 (pooled) Subpopulation with BMI≥27kg/m²
HbA_{1c} progression	0.045% per year	0.012% per year
BMI progression	0.2375 kg/m² per year	0.094 kg/m² per year
eGFR progression	0 (mL/min/1,73 m2) per year	−1.227 (mL/min/1,73 m^2) per year
SBP progression	UKPDS risk equation	0.118 mmHg per year
DBP progression	0	−0.588 mmHg
Total Cholesterol progression	Framingham risk equation	−0.588 (mg/dL)
HDL-C progression	Framingham risk equation	1.059 (mg/dL)
LDL-C progression	Framingham risk equation	−1.412 (mg/dL)
Triglycerides progression	Framingham risk equation	−1.176 (mg/dL)

ICER (base-case)	£8578	£1934
Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis ICER, incremental cost-effectiveness ratio; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HbA_{1c} Glycated haemoglobin; LDL-C, low-density lipoprotein cholesterol; NDA, no data available; SBP, systolic blood pressure; NDA – National Diabetes Audit sourced from National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management (NG17) London: National Institute for Health and Care Excellence; 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ng17		

The company provided an economic analysis for the 400mg dose of sotagliflozin; however, this was based on the same data as the 200 mg analysis as a conservative assumption. Therefore, the treatment effectiveness of the 400mg dose is not described further here. However, the impact of this assumption is discussed in 5.4.5.4.

A comparison of the incidences over time for each complication for the company's original base case and their updated base case are shown graphically in Figure 14 to Figure 20, while the impact on costs is shown in Figure 21 to Figure 23.

Figure 14. Eye disease incidence

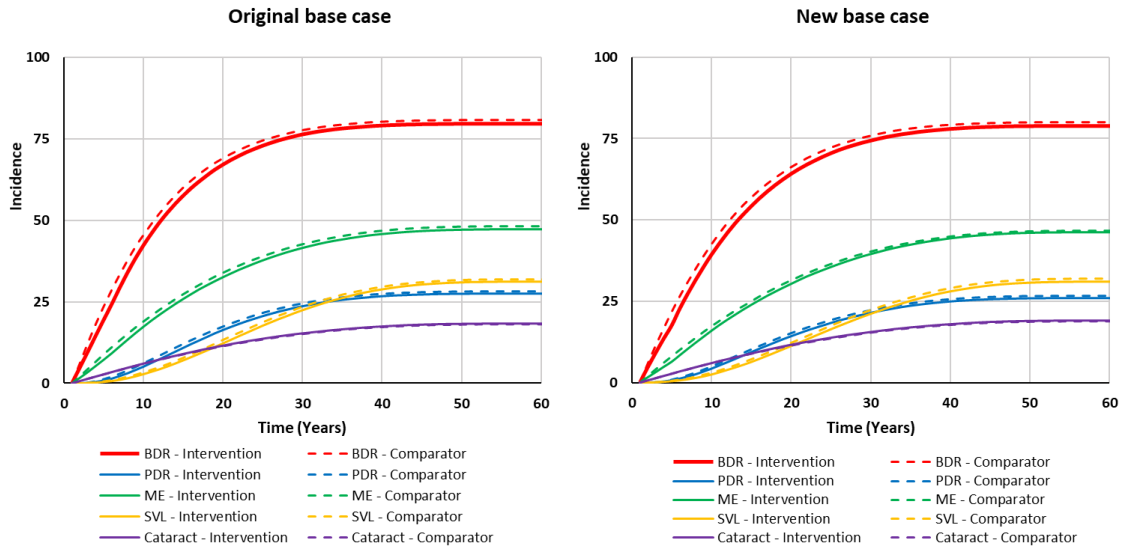


Figure 15. Renal disease incidence

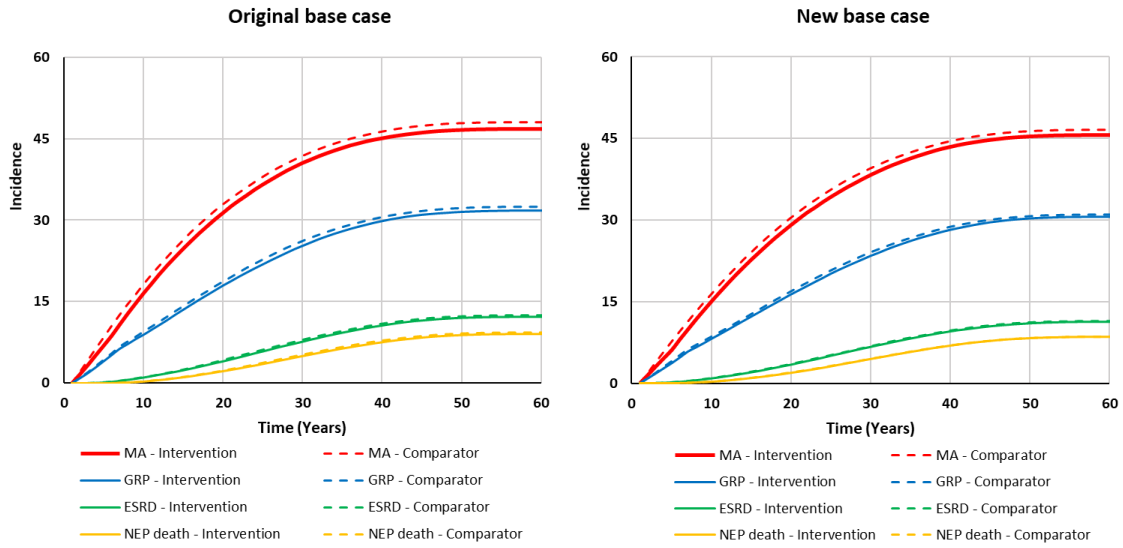


Figure 16. Ulcer incidence

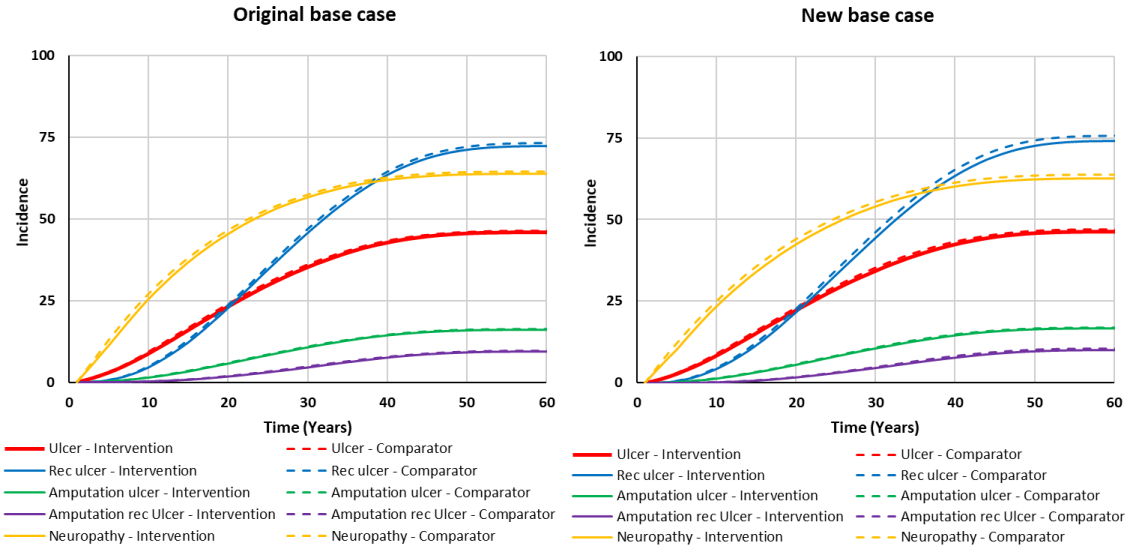


Figure 17. CVD disease incidence (1 of 2)

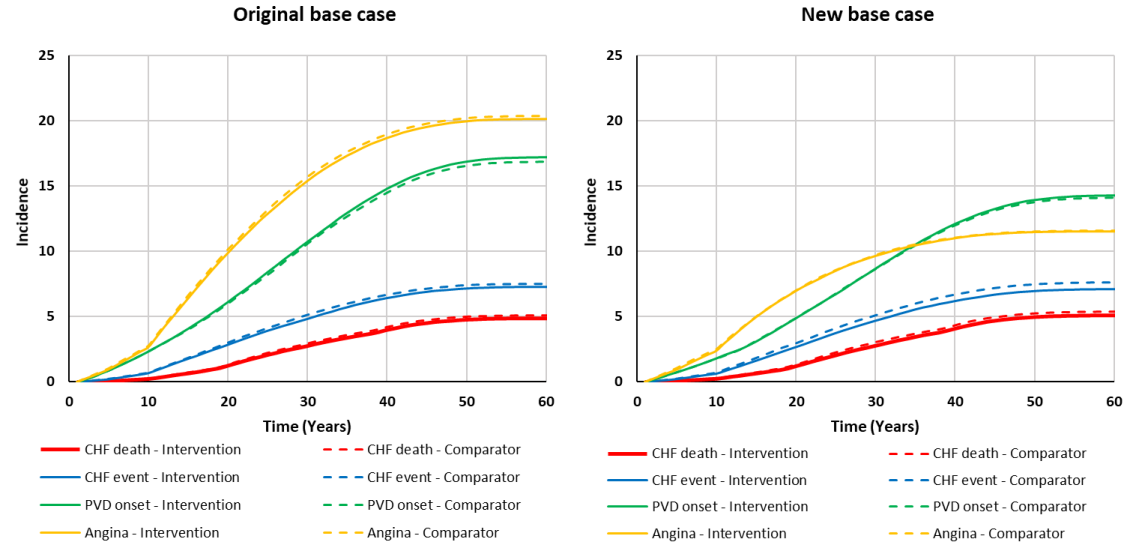


Figure 18. CVD incidence (2 of 2)

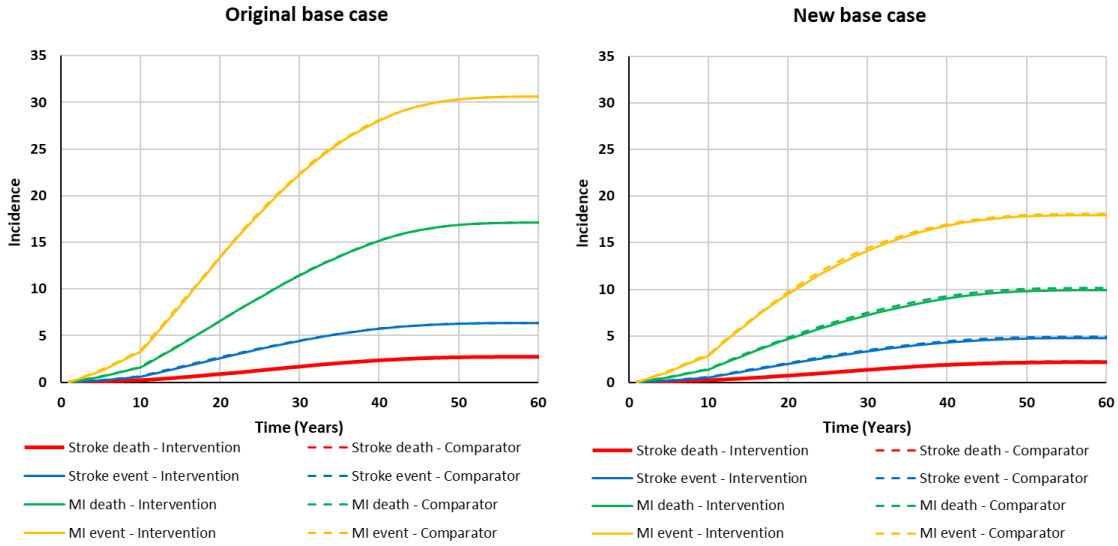


Figure 19. AE incidence (1 of 2)

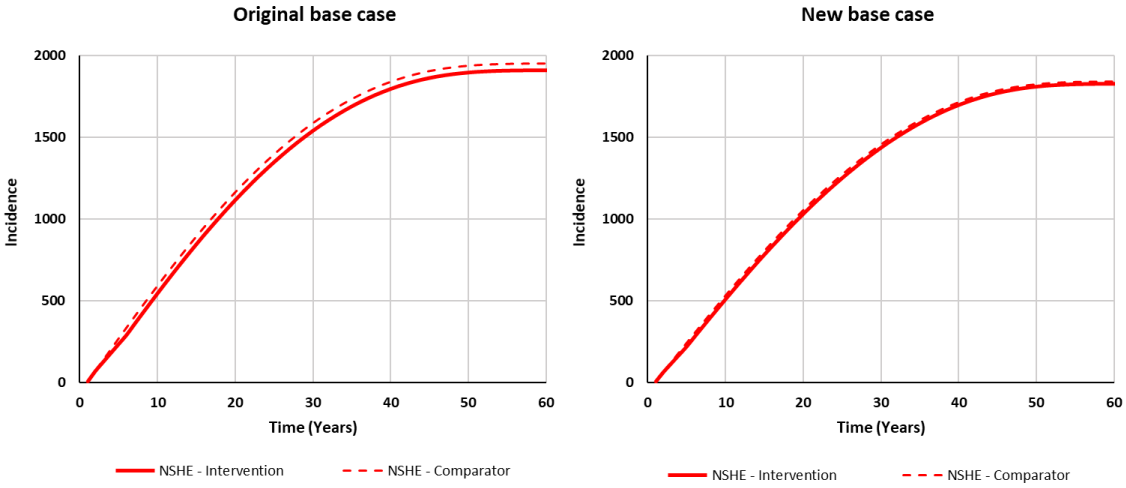


Figure 20. AE incidence (2 of 2)

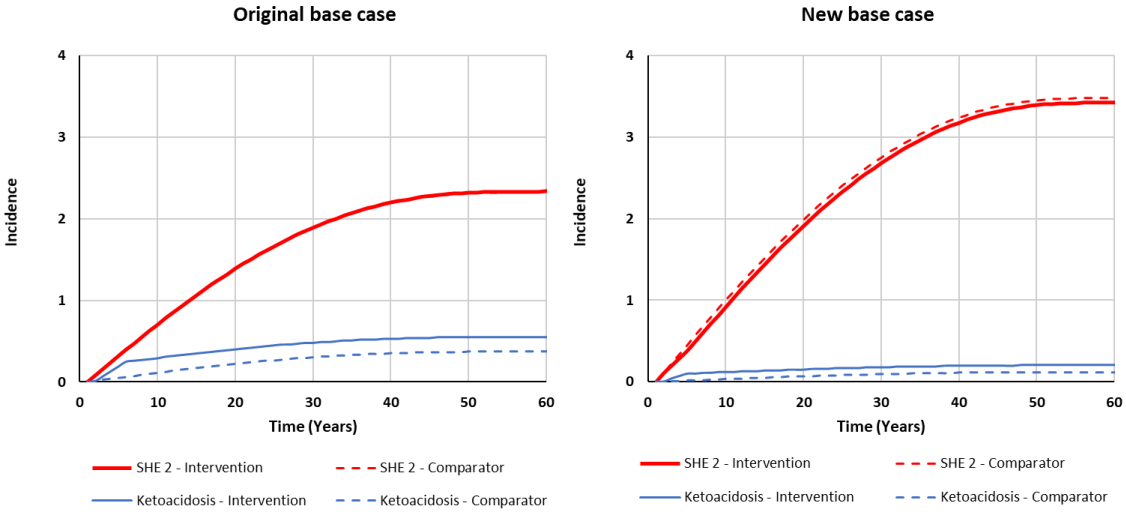


Figure 21. Cost breakdown (1 of 3)

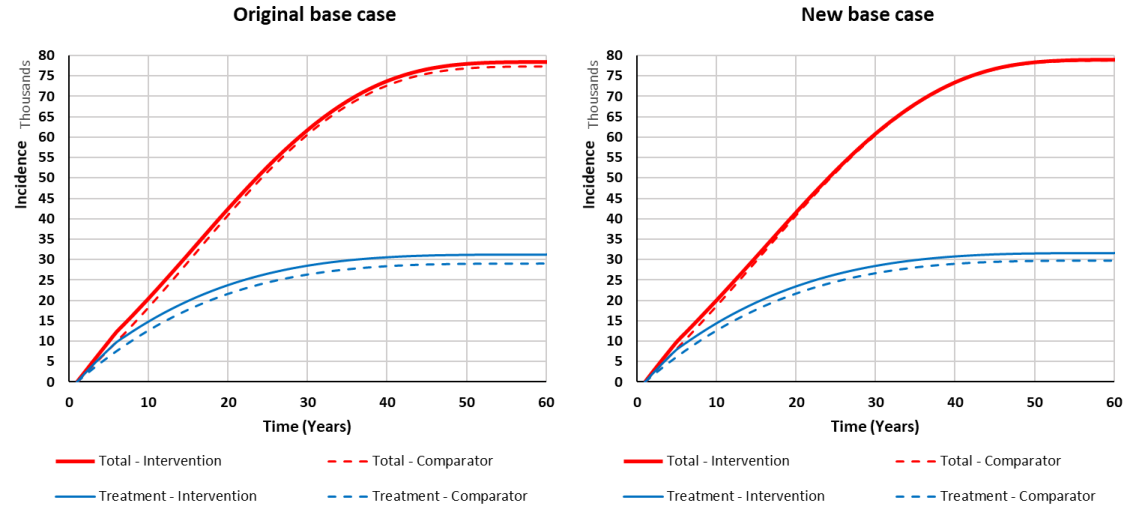


Figure 22. Cost breakdown (2 of 3)

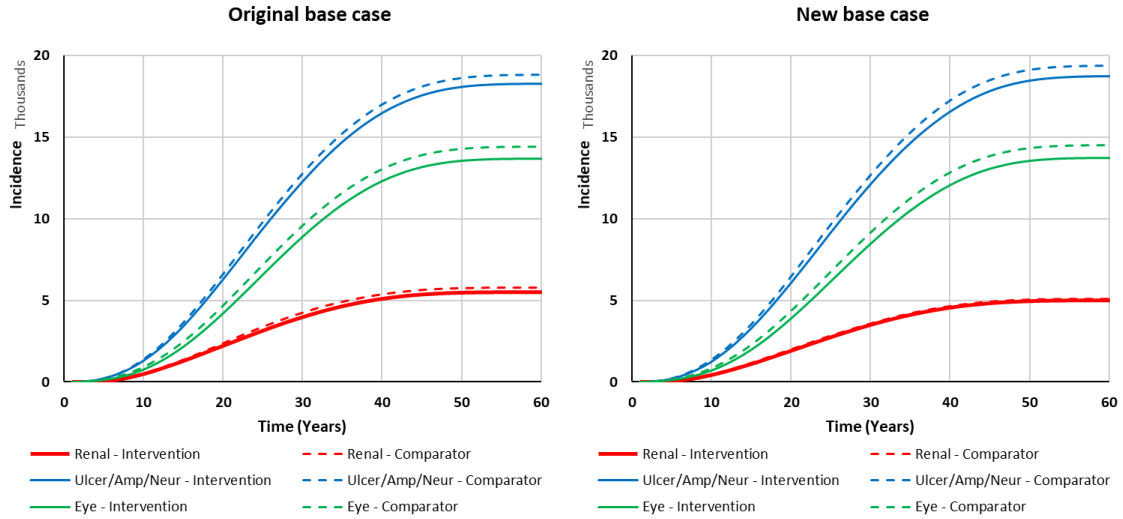
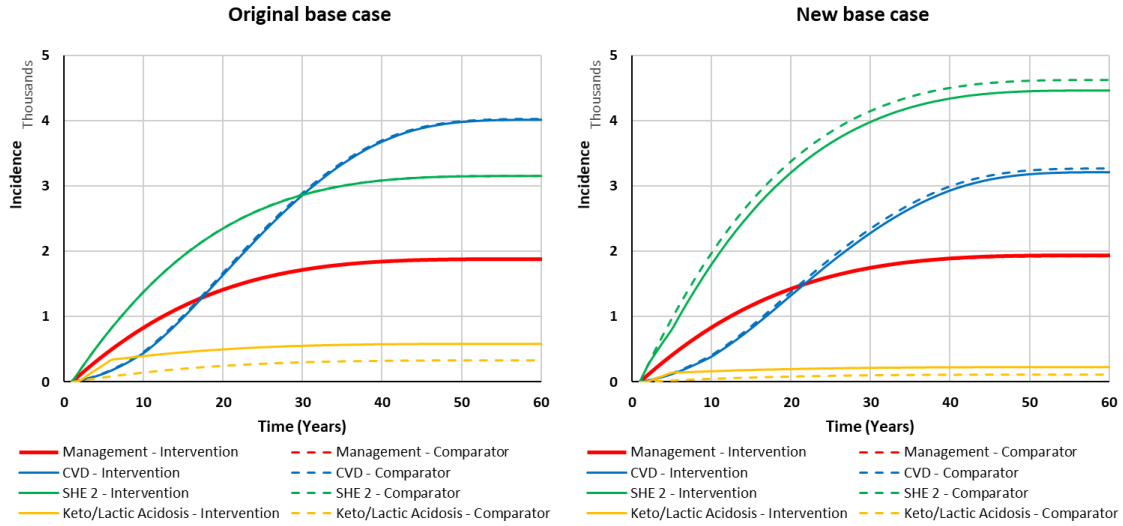


Figure 23. Cost breakdown (3 of 3)



5.4.5.3 PRIME model

The company used PRIME as a validation tool to consider the difference in the results that this alternative model might have. The company stated that although there were differences between the CDM and PRIME with respect to the long-term progression of risk factors, there were no differences in the treatment effects applied in the two models. The company stated that risk factor progression for HbA_{1c} and BMI was based on recommendations from NICE (clinical expert input) while all other risk factors were held constant. The company highlighted that the progressions were identical in each

treatment group, and therefore, did not impact on cost effectiveness. For HbA_{1c}, the company applied an annual progression of 0.018%, while for BMI they applied a progression of 0.095kg/m^2.

The risks of MI, angina and stroke were derived from various studies in T1D,[43-48] which provided risk equations to estimate patient specific risks for each complication. These risks were then weighted depending on the similarity between the cohort used to derive the risk equations and the cohort to which they are applied in the model.

Heart failure risks were derived from the Swedish National Diabetes Register (SNDR),[49] a cohort of 20,985 patients with a mean age of 38.6 years; mean HbA_{1c} of 8.18% and with a mean time since diagnosis of 23.1 years. The base rate of HF used in PRIME was 1.42 per 1,000 patient years, derived from the SNDR study for patients with HbA_{1c} less than 6.5%. A Cox proportional hazards model was fitted to these data to estimate patient specific hazard ratios (HRs), which were applied to the base rate in the PRIME model.

Nephropathy risks were derived from DCCT and EDIC data and relate to microalbuminuria, overt nephropathy and end-stage renal disease (ESRD). Progression risks were determined by factors such as HbA_{1c}, age, duration of diabetes and presence of retinopathy.

The annual onset of neuropathy was informed by the EuroDiab cohort.[50] The patient specific risks were adjusted according to duration of diabetes, HbA_{1c}, change in HbA_{1c} in the previous year, BMI, smoking status, hypertension, retinopathy status and presence of CVD.

The risk of (non-traumatic lower extremity) amputation was estimated separately for males and females and was based on data from the Swedish Diabetes Registry.[51] This data is adjusted based on a multi-variate analysis of 25-year amputation data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR).[52]

The WESDR study was also used to inform the risk of retinopathy.[53] PRIME uses standard categories of no retinopathy, mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, proliferative diabetic retinopathy (PDR), and blindness, although the risk of progressions relates to the 12-point Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity scheme used by Klein et al. 2008.[53] Progression of diabetic retinopathy was defined as a 2-step progression on the ETDRS scale. The key risk factors of progression were sex, HbA_{1c} level, and increases in HbA_{1c}. The onset of PDR was affected by HbA_{1c}, SBP, proteinuria, and BMI.

Macular oedema (MO) is included in PRIME with three levels of severity: no MO; MO; and, blindness. The rate of onset was derived from data from the WESDR study, and risks were adjusted according to patient's retinopathy status and HbA_{1c} level. Risks of progression or regression were

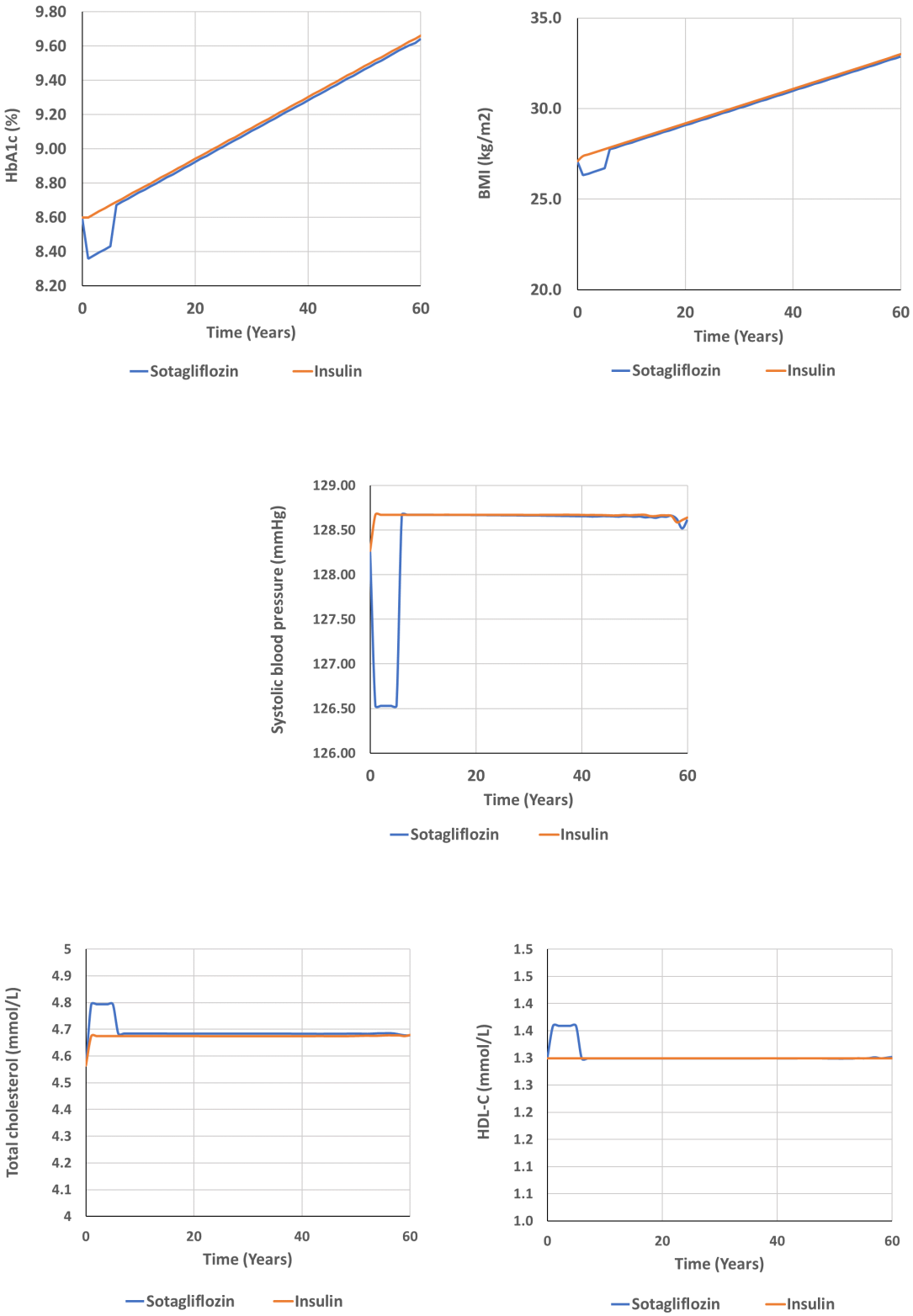
treatment dependent, with rates of recovery determined by Ford *et al.* 2013.[54] Data for non-response to treatment were also considered and taken from RESTORE trial.[55] Non-response to treatment leading to the risk of progression was informed by data from the WESDR study.

Hypoglycaemia was included in PRIME as severe and non-severe, and the risk of each was adjusted according to levels of HbA_{1c}. Non-severe hypoglycaemia (NSH) was informed by a range of phase III/IV insulin studies, while SH was informed by data from the DCCT study. The latter was also used to inform the risk of hospitalisation, and subsequently, the risk of death.[56]

The risk of ketoacidosis was estimated from a Swedish study,[57] which indicated a rate of 1,585 events per 100,000 patient-years. This risk was adjusted using EuroDiab data according to duration of diabetes and HbA_{1c} level.[58]

Progressions of the key parameters informing the treatment effectiveness for PRIME are given in Figure 24.

Figure 24. Phsyiological parameter progression for the PRIME model base case



5.4.5.4 ERG critique

The ERG considers the company's estimates of treatment effects at year 1 to be appropriate given the availability of data. The company updated their original base case to use the pooled analysis of the inTandem1 and inTandem2 trials from the subgroup of patients with a BMI ≥ 27 kg/m^2 as this was more in line with the company's likely marketing authorisation. Although this broke randomisation in the trials, the ERG considered this more appropriate than the company's original base case, which was based on the intention-to-treat analysis of only the inTandem2 trial, as it was closer to the population expected to be eligible to receive the drug in the UK. The ERG noted no key differences in baseline characteristics in this subpopulation, and this is discussed further in Section 4.2.2.

The ERG considered the applicability of the data with regard to clinical practice in the UK and, based on clinical expert opinion, considered an even more applicable subgroup would be those who had baseline HbA_{1c} > 8.5% and who receive insulin by MDI as opposed to insulin pumps. However, the subgroup with both of these characteristics reduced the numbers to a level that was not suitable to analyse and, therefore, the company provided the results of each characteristic separately to assess the potential impact.

Based on the pooled analysis of the inTandem1 and inTandem2 trials using the subgroup of patients with a BMI ≥ 27 kg/m^2, the subgroup with MDI insulin delivery had a lesser reduction in HbA_{1c} of 0.19% compared to those who received insulin pumps whose reduction was 0.29%. This may, therefore, suggest that the combined group may overestimate the benefits in terms of HbA_{1c}. However, the impact on HbA_{1c} for the subgroup with baseline HbA_{1c} > 8.5%, showed a greater benefit than its complement, with reductions of 0.31 and 0.21, respectively. This, conversely to the subgroup analysis relating to MDI use, suggests a potential underestimation of the HbA_{1c} benefits of sotagliflozin treatment by using the combined population.

The effects of these two characteristics in the subgroups discussed are in opposing directions and thus will cancel out to some extent, suggesting the combined population may be reflective of the expected outcomes. However, this is not necessarily the case for other outcomes. This is discussed further in Section 4.3, but no common trend was shown in the results making it difficult to assess the overall impact of these subgroups on the outcomes. The ERG considers that, given the limitations of the available data, the population in the company's base case analysis is likely to be the most appropriate data and most reflective of the population expected to receive given the available analyses.

Although the ERG considered these treatment effect estimates from the trial to be reasonable, the ERG was concerned with the assumptions made with regard to the progression of the physiological parameters over time. The company changed all of the key progressions after clarification without providing a rationale for why such a different approach was taken. The ERG is concerned about the

appropriateness of the new approach, given that it is very different to the original submission and results in very different values over time.

The company's original analysis was partly based on type 2 diabetes progression models, which may not be unreasonable as the impact of the physiological parameters on the risk of complications is potentially unrelated to the type of diabetes. The updates that the company made to the progressions after clarification were based on data from type 1 diabetes patients; however, the company made the assumption that the progressions were linear over time. This could be too simplified and may not reflect the true progressions of the physiological parameters over time. Therefore, the more complex models based on the type 2 UKPDS progression models may in fact be more plausible.

As the company's updated base case analysis removes any treatment benefit after 5 years, i.e., the physiological parameter values are equal for both treatment groups after 5 years, the lack of complexity will not impact the results after 5 years. Therefore, the key impacts on the results are the benefits modelled by the company within the initial 5-year period. A greater concern, therefore, is the assumption that benefits are maintained for as long as 5 years. The company's model is based on treatment effects measured for just 1 year, meaning that the extra 4 years of benefit is uncertain and is potentially overestimated.

The ERG notes that the progression data used for HbA_{1c} and BMI in the company's updated base case analysis are based on more recent data from the EDIC study rather than the older DCCT data. These data may reflect the insulin group better given that more recent clinical practice may have improved resulting in better control of HbA_{1c}. However, these data do not necessarily reflect the progression in the sotagliflozin group after the first year of treatment. The data from the EDIC study are not based on the use of sotagliflozin and, therefore, cannot be assumed to reflect the associated treatment effects. It is possible that the treatment benefits provided by sotagliflozin treatment may reduce more quickly than that observed in the EDIC study, i.e., there could be a rebound towards the insulin group sooner than when the trend observed in the EDIC study comes into effect. The ERG considers the impact of a potentially more rapid return to the baseline values in a scenario analysis in Section 6.

As discussed in Section 3.2, another consideration raised by the ERG's clinical experts, is that the treatment benefits of sotagliflozin may not actually reduce after the initial benefits are observed but instead, the patients' compliance with the general management of their condition, such as maintaining a healthy diet, may reduce leading to an "overall" reduction in benefit of treatment. This potentially means that the treatment benefits are counteracted by a potential negative impact on other aspects of treatment for maintenance of these physiological parameters. A further point to consider is that a clinician may be reluctant to withdraw treatment even if a patient's HbA_{1c} or BMI has returned to their baseline value or deteriorated further, as the reduction in effect may not be a result of treatment

waning, and withdrawal of treatment could cause further deterioration of these parameters. This is discussed further in Section 3.2.

The ERG was also concerned that the company had potentially inflated the benefit of sotagliflozin by allowing the HbA_{1c} for the insulin group to increase from 8.6% to 8.7%. The company stated that this was to allow the treatment effect for the insulin group to be applied. However, the ERG considers a more appropriate and accurate approach would be to apply the constant baseline value of 8.6% in the insulin group and apply the treatment-group difference in HbA_{1c} at year 1 to the sotagliflozin group and apply the progression estimates to that group alone. The ERG explored the impact of this and the results are given in Section 6.

In terms of the PRIME model, the ERG considers there to be a potential benefit in comparison to the CDM in that the risk data are taken from only T1D data. However, this was based on a wide variety of studies, largely from Sweden, which may not be applicable to the UK. A key difference noted by the ERG is that the heart failure risks were based on patients with an HbA_{1c} level of less than 6.5%.

The ERG is concerned that there are key differences in the outputs of the CDM and PRIME models in that the incidences of complications over the time horizon of the model are not aligned. Firstly, it is not clear on what basis these cumulative incidences are measured in the PRIME model. The values are all less than one suggesting that they may be on a per-patient basis; however, this suggests excessively high incidences occur, for instance, the incidence of 0.471 per patient for MI (or 471 per thousand patients) compared to the CDM's output of 18 per thousand patients.

There also appears to be large differences in some of the relative differences between complications. For instance, in the CDM the incidence of stroke for insulin is approximately 4.93 per thousand, while ESRD is 11.46 per thousand. In PRIME, however, the equivalent values are 0.200 and 0.003, respectively. Regardless of the units of measurement, the strong reversal of the weighting suggests that at least one of the models is producing implausible results or that there are aspects that are not fully captured. The cumulative incidences produced by the models are given in Figure 25 and Figure 26 for the PRIME and CDM models, respectively.

Figure 25. Incidences of complciations in PRIME using company's preferred assumptions as per the CDM base case (reproduced from the PRIME model)

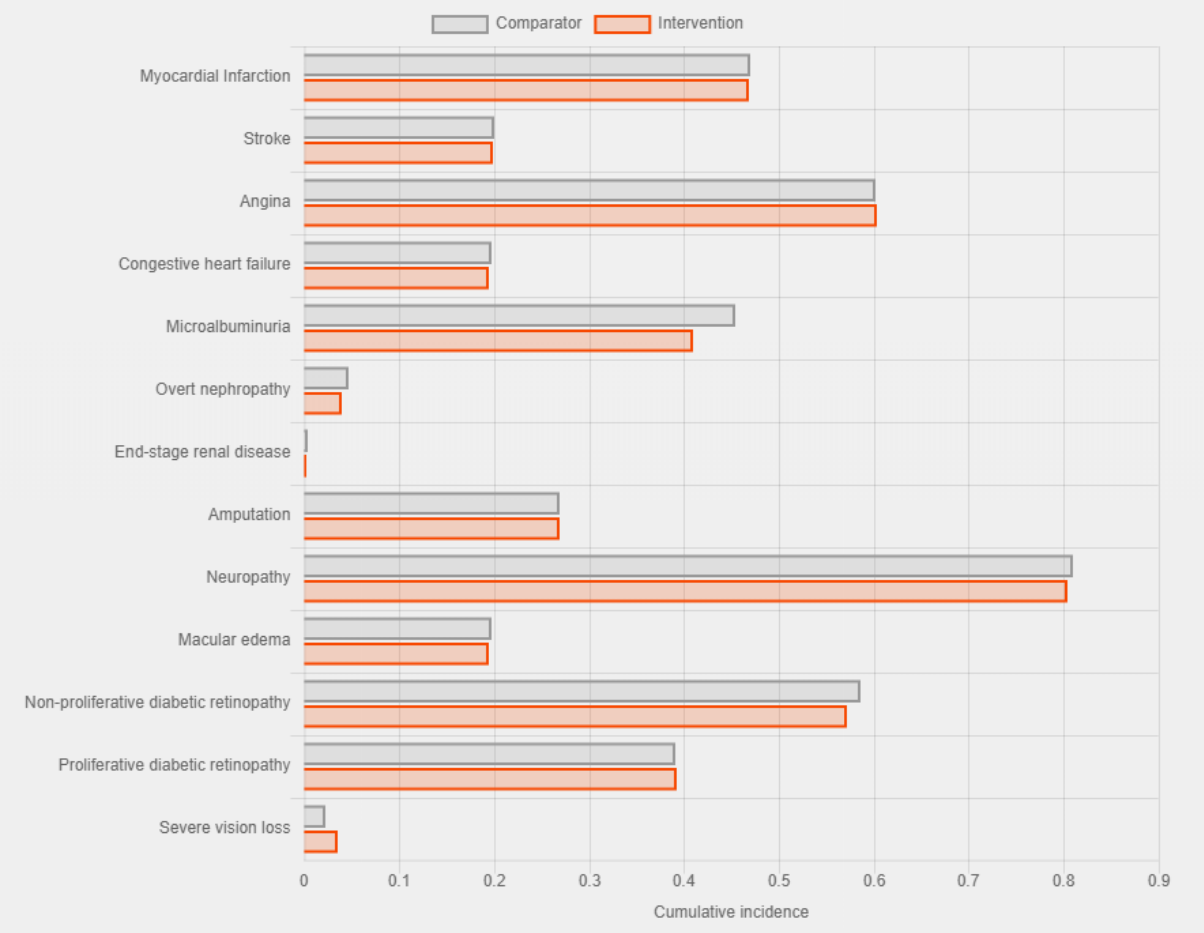
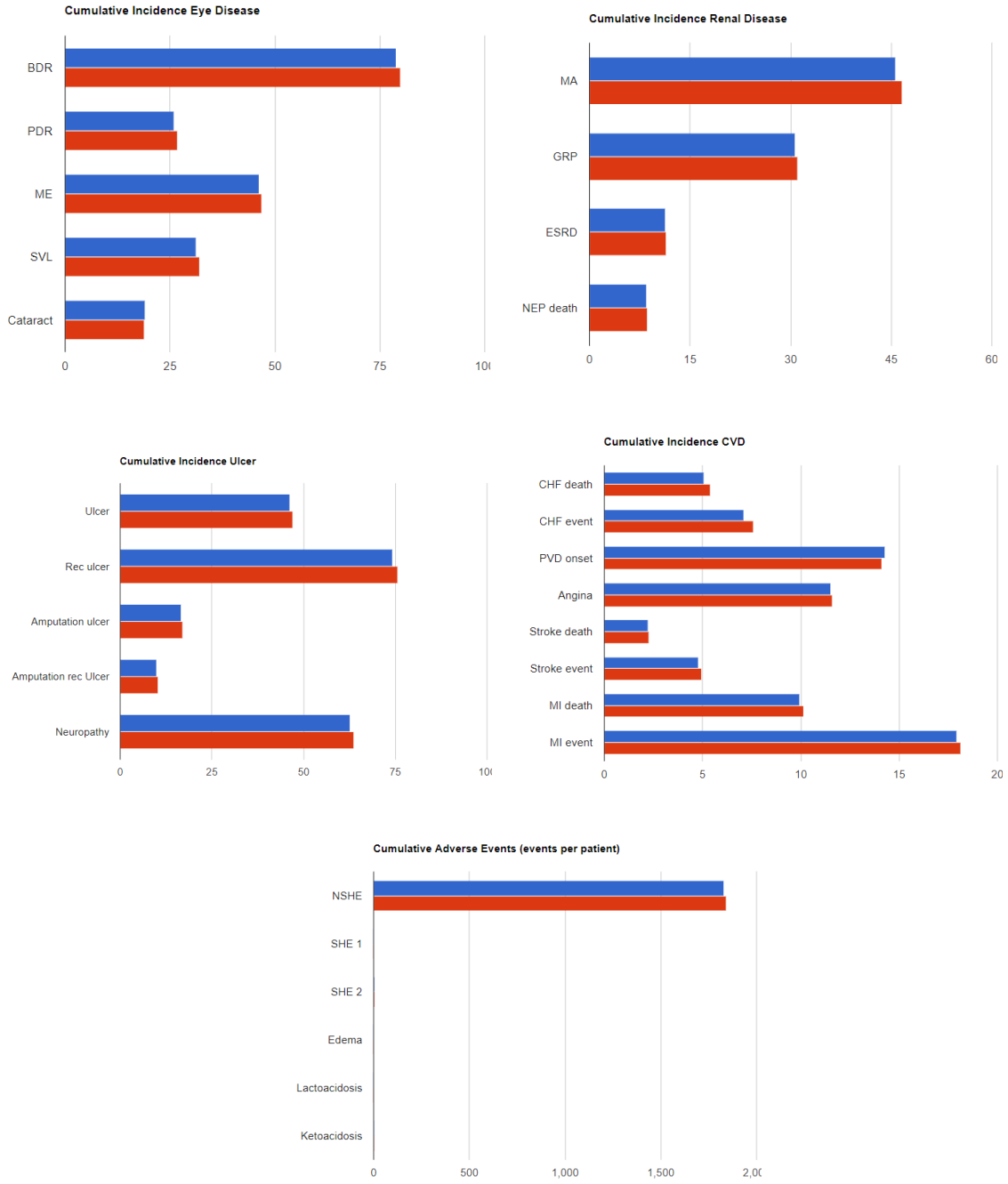


Figure 26. Incidences of complications in the company's base case (reproduced from the CDM)



The potential lack of consistent plausibility between the two models is also evident when assessing the overall outputs of the two models. Although overall the expected life-years and QALYs produced by the company's base case, and the PRIME model with the equivalent assumptions applied, are similar the total costs are quite different. The CDM base case produces total costs of around £79,000 for each group, whereas the equivalent PRIME analysis estimates only £52,000 to £54,000 for insulin alone and sotagliflozin, respectively. This may indicate that either the PRIME model is missing some key aspects, or that the CDM is overestimating, or overvaluing, certain aspects.

The key difference in costs appears to be in the costs relating to eye treatment and ulcer/amputation/neuropathy costs. The breakdown in costs for the PRIME model and CDM are given in Table 28 and Table 29, respectively. Given that the costs applied are equivalent across the models, this indicates a potentially key difference in how treatment effects impact the model and ultimately affect the cost-effectiveness.

Table 28. PRIME costs breakdown

Cost category	Total costs	
	Sotagliflozin	Insulin alone
Treatment	£35,951	£33,895
Cardiovascular	£6,204	£6,310
Renal	£105	£0
Ocular complications	£3,188	£3,286
Neuropathy and amputation	£4,223	£4,256
Adverse events	£4,505	£4,564

Table 29. CDM cost breakdown

Cost category	Total costs	
	Sotagliflozin	Insulin alone
Treatment	£31,655	£29,794
Cardiovascular	£3,220	£3,269
Renal	£4,993	£5,093
Ocular complications	£13,718	£14,521
Ulcer, neuropathy and amputation	£18,725	£19,387
Severe hypoglycaemia	£4,469	£4,626
Ketoacidosis	£227	£110

The ERG also noted that the progressions applied for HbA_{1c} and BMI were not the same as applied in the CDM but instead were in line with those recommended in the ScHARR report that the company requested. However, the ERG considers the progressions are not likely to have a major impact on the cost effectiveness results as they are assumed to be equivalent after 5 years. The focus should, therefore, be on the initial 5-year period. As stated previously for the CDM, the ERG considers that the treatment effects being extended for 5-years may be an overestimation, particularly for HbA_{1c}.

A final point regarding the treatment effectiveness applied in the CDM is that the adjustments applied to CVD risks are based on a composite risk of CVD rather than having complication specific adjustments based on changes in HbA_{1c}. The ERG considers that this may be too simplified but also that it may not be able to be improved because of a lack of more granular data. The ERG also considers that the CDM generally applies risk data from the same sources, i.e., largely from the EDIC study, which may be more reliable than the variety of different sources used in PRIME.

Overall, the ERG considers the evidence used to estimate treatment effectiveness in their base case analysis using the CDM to be reasonable. The key uncertainties relate to the duration for which the benefits are assumed to apply. The plots for HbA_{1c} appear to show a trend towards the insulin group sooner than the company's assumption of 5 years. The ERG considers 2 years to be more likely. However, this may not apply to all effects, which may last for the duration of treatment.

Given the difference in outputs of PRIME compared to the CDM, the ERG suggests that caution should be taken when interpreting the results and clinical expert opinion should be sought to validate the plausibility of the predicted complication incidences further. If the insulin-only group produces complication incidences that are plausible from the view of an expert clinicain, and the treatment effects applied for the sotagliflozin group are plausible too, then the results may potentially be considered reliable and fit for decision making.

5.4.6 Adverse events

The company considered the impact of adverse events (AEs) that were Grade 3 to 5 according to the Common Terminology Criteria for Adverse Events (CTCAE). The company based the incidence of AEs on the pooled analysis of inTandem1 and inTandem2, taking into account the statistical significance between the two treatment groups. Following these criteria, the company included number of severe and non-severe hypoglycaemic and DKA events. The rates of AEs applied in the company's base case analysis for the pooled inTandem1 and inTandem2 with BMI $\geq$ 27kg/m^2 compared to the original inTandem2 are given in Table 30.

Table 30. Adverse event rates per 100 patient years in company's analyses (adapted from Table 88 of the company's clarification response document)

Adverse event	inTandem2 only (whole population)		Pooled inTandem1 & inTandem2 (BMI≥27kg/m^2)	
	Placebo	Sotagliflozin 200 mg	Placebo	Sotagliflozin 200 mg
Non−Severe Hypoglycaemic events (/100 patient years)	6,715	5,595	6,040	5,280
Severe Hypoglycaemic events (/100 patient years)	8.0	8.0	11.4	8.9
Diabetes Ketoacidosis (/100 patient years)	1.26	5.86	0.4	3.2

Abbreviations: CDM, CORE Diabetes Model, ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

5.4.6.1 ERG critique

The ERG considers the company's inclusion of AEs to be reasonable and considers those included to be the key treatment-related AEs that can have an important impact on costs, utilities as well as the risk of mortality. The impact of the latter is discussed in Section 5.4.7, while the impact on costs and utilities of these AEs is discussed in Sections 5.4.9 and 5.4.8, respectively.

However, the ERG is concerned that the values produced in the output of the model for the company's base case analysis do not reflect those that are stated as inputs. The company's output shows zero events occur in both treatment groups at year 1, and 0.04 events per patient at year 2 – the latter being equivalent to 2 per 100 patient-years (averaged over the first 2 years), rather than the 3.2 as observed in the trials (at 52 weeks).

5.4.7 Mortality

The company's model considers all-cause mortality based on the UK Office for National Statistics data for 2015–2017. The model also has specific mortality rates for a number of the complication sub-models. These are: MI, CHF, stroke, neuropathy, ulcer/amputation, hypoglycaemia, ketoacidosis and lactic acidosis.

The probability of death from MI was specified by sex using the default values in the CDM, with values of 0.393 and 0.364 for males and females, respectively. Death from stroke had equivalent values for males and females with a value of 0.124 following the first stroke and a probability of 0.422 for recurrent strokes. The probability of death from a major hypoglycaemic event was given as 0.003 while death from ketoacidosis had a probability of 0.05. These values are much lower than the values used in the company's original analysis, which were 0.05 and 0.027, respectively.

The probabilities of mortality for severe hypoglycaemia and diabetic ketoacidosis (DKA) were also changed to much lower values based on Wolowacz *et al.* 2014.

5.4.7.1 ERG critique

The ERG considers the company's approach to estimating mortality to be reasonable and notes that the uncertainty regarding this aspect is similar to the estimation of all treatment effects. The estimation of the risk of death is similar to the estimation of the risks of complications and is reliant on short term trial data as well as the reliability of the risk equations that determine the risk of complications that can lead to death. The added uncertainty is in the probabilities applied to those with the complications. However, the ERG considers the approach to be generally reasonable, with the key concern relating to the assumptions of treatment effect duration, as discussed in Section 5.4.5.

5.4.8 Health-related quality of life

During the inTandem1 and inTandem2 trials, patients completed the EQ-5D-3L questionnaire at trial baseline and week 52; and at baseline and week 24 in the inTandem 3 trial. A description of the EQ-5D data collected in the inTandem2 trial, provided by the company at the clarification stage, is provided in Table 31. The company did not provide summary statistics for the EQ-5D data collected in inTandem1 or inTandem3.

Table 31 EQ−5D index scores collected from patients with baseline BMI ≥27 kg/m^2 in the inTandem2 trial (adapted from Table 92 of the company's clarification responses)

Statistic	Placebo (N=124)	Sotagliflozin 200 mg (N=135)	Sotagliflozin 400 mg (N=138)
Baseline			
N (%)	122 (98.4)	131 (97.0)	137 (99.3%)
Mean (SD)	0.85 (0.153)	0.84 (0.165)	0.83 (0.171)
Week 52			
N (%)	117 (94.4)	125 (92.6)	134 (97.1%)
Mean (SD)	0.85 (0.146)	0.83 (0.161)	0.83 (0.167)
Change from baseline at Week 52			
LSM (SE)	−0.02 (0.013)	−0.02 (0.012)	−0.01 (0.012)
95% CI for change from baseline	(−0.04, 0.01)	(−0.04, 0.01)	(−0.04, 0.01)
p value	0.2083	0.2042	0.2470
Summary of treatment comparison			
LSM (SE) from placebo	-	0.00 (0.016)	0.00 (0.016)
95% CI for difference	-	(−0.03, 0.03)	(−0.03, 0.03)
p value	-	0.9806	0.8938

Abbreviations: BMI, body mass index; CI, confidence interval; LSM, least square mean; mITT, modified intent-to-treat; SD, standard deviation; SE, standard error

The company did not consider the utility data collected in the inTandem trials as the trials assessed the impact of treatment over a short period and did not capture the impacts on HRQoL due to long-term complications. For this reason, utility data for the economic analysis was taken from published sources.

In both the original CS and addendum to that submission supplied to the ERG at the clarification stage, the company stated that utility data were taken from Peasgood *et al.* 2016 wherever possible. The Peasgood study estimated the utilities and disutilities associated with T1D using data from a UK research programme on the Dose Adjustment For Normal Eating (DAFNE) education programme.[59] When utility data were not reported in Peasgood, *et al.* 2016, the company also stated that data from Beaudet *et al.* 2014 and Currie *et al.* 2006, both undertaken in patients with T2D, were used to inform the economic analysis.[60, 61]

The resulting health state utility values (permanent health impacts) and disutility values (one-off health impacts) reported in the CS and applied in the CDM, are provided in Table 32. Unlike the CDM, PRIME applies disutilities in subsequent years for events that have permanent health impacts. For completeness, the ERG has also added the disutility values included in PRIME to Table 32. However, when the ERG checked the utility inputs in the revised analyses provided at the clarification stage, the ERG found that the company employed utility values in PRIME, "*Based on ScHARR settings review in November 2018*". No rationale for this decision was given to the ERG. Nonetheless, those inputs are also provided in Table 32. The ERG has not been able to identify references for all

health state utility inputs taken from the ScHARR 2018 review given that the ERG only has access to the more recent ScHARR 2019 review. The ERG believes that both reviews by ScHARR have been prepared for the company's internal use and are therefore not publicly available. However, one study recommended in the ScHARR 2019 review, and used in the company's revised analysis, included Alva *et al*. 2004.[62] The Alva study used EQ-5D-3L data collected between 1997 and 2007 in patient with T2D in the UK Prospective Diabetes Study.

Table 32. Summary of utility data for the economic analysis

CDM health state (PRIME)	Inputs reported in the CS used to inform the original analysis (CDM and PRIME) and revised analysis (CDM)			ScHARR 2018 review used to inform the revised analysis (PRIME)	
	CDM input	PRIME input	Reference	PRIME input	Reference
T1D without complication	0.839	0.839	Peasgood *et al.* 2016	0.839	Peasgood *et al.* 2016
MI event	−0.024	-0.024	Peasgood *et al.* 2016 [a]	-0.065	Alva *et al.* 2014
Post-MI	0.815	-0.024	Peasgood *et al.* 2016 [a]	-0.065	Alva *et al.* 2014
Angina	0.749	-0.09	Beaudet *et al.* 2014	-0.028	-
Chronic (congestive) heart failure	0.743	-0.096	Currie *et al.* 2006	-0.101	-
Stroke event	−0.033	-0.033	Peasgood *et al.* 2016 [a]	-0.165	Alva *et al.* 2014
Post-stroke	0.806	-0.033	Estimation	-0.165	Alva *et al.* 2014
Peripheral vascular disease	0.778	NA	Beaudet *et al.* 2014	NA	-
Microalbuminuria	0.000	0.000	Assumption	0.000	-
Gross renal proteinuria (overt nephropathy)	0.791	-0.048	Beaudet *et al.* 2014	-0.028	-
Haemodialysis	0.604	-0.235	Beaudet *et al.* 2014	-0.140	-
Peritoneal dialysis	0.581	-0.258	Beaudet et al. 2014	-0.140	-
Renal transplant	0.829	-0.010	Peasgood *et al.* 2016 [a]	-0.086	-
BDR (moderate)	0.810	-0.029	Peasgood *et al.* 2016 [a]	-0.054	Peasgood *et al.* 2016 [b]
BDR wrongly treated (severe)	0.810	-0.029	Peasgood *et al.* 2016 [a]	-0.054	Peasgood *et al.* 2016 [b]
PDR laser treated (laser NR)	0.769	-0.070	Peasgood *et al.* 2016 [a]	-0.029	Peasgood *et al.* 2016 [a]
PDR no laser (laser NR)	0.769	-0.070	Peasgood *et al.* 2016 [a]	-0.029	Peasgood *et al.* 2016 [a]
Macular oedema	0.799	-0.040	Beaudet *et al.* 2014	0.000	-
Severe vision loss	0.780	-0.059	Peasgood *et al.* 2016 [a]	-0.208	-
Cataract	0.823	NA	Beaudet *et al.* 2014	NA	-
Neuropathy	0.603	-0.236	Peasgood *et al.* 2016 [a]	-0.050	Peasgood *et al.* 2016 [b]
Healed ulcer	0.839	NA	Assumption	NA	-
Active ulcer	0.715	NA	Peasgood *et al.* 2016 [a]	NA	-
Amputation, year of event	−0.117	-0.117	Peasgood *et al.* 2016 [a]	-0.117	Peasgood *et al.* 2016 [a]
Post-amputation	0.722	-0.117	Estimation	-0.117	-
NSHE daytime	0.000	0.000	Assumption	-0.004	-
NSHE nocturnal	0.000	0.000	Assumption	-0.008	-

SHE during daytime (time NR)	−0.002	-0.002	Peasgood *et al.* 2016 [a]	-0.047	-
SHE nocturnal (time NR)	−0.002	-0.002	Peasgood *et al.* 2016 [a]	-0.047	-
Ketoacidosis event	−0.009	-0.009	Peasgood *et al.* 2016 [a]	-0.012	Peasgood *et al.* 2016 [b]
Oedema (macular oedema)	−0.010	-0.040	Beaudet *et al.* 2014	0.000	-
Post-oedema	0.829	-0.040	Beaudet *et al.* 2014	0.000	-
Depression not treated	0.587	NA	Peasgood *et al.* 2016 [a]	NA	-
Depression treated	0.839	NA	Peasgood *et al.* 2016 [a]	NA	-
Disutility associated with 1 unit increase in BMI >25 kg/m^2	−0.003	-0.003	Peasgood *et al.* 2016 [a]	-0.003	Peasgood *et al.* 2016 [a]

Abbreviations: BDR, background diabetic retinopathy; BMI, body mass index; MI, myocardial infarction; NA, not applicable; NR, not reported; NSHE, non-severe hypoglycaemic event; PDR, proliferative diabetic retinopathy; SE, standard error; SHE; severe hypoglycaemic event; T1D, type 1 diabetes

a random-effects model

b fixed-effects model

5.4.8.1 ERG critique

The key source of utility data (Peasgood *et al*. 2016) measured changes in HRQoL directly from patients with T1D in the UK, using a generic preference-based measure (EQ-5D), following the key components of the NICE reference case.[59, 63] Even so, the ERG would like to comment on: the utility data collected in the inTandem trials; the utility data collected in patients with T2D; the BMI disutility; the ScHARR 2018 review; and, the approach used to estimate QALYs. Each of these points is described in turn below.

5.4.8.1.1 inTandem trial data

In the CS, the company did not make a comparison between the EQ-5D utility data collected in the inTandem trials and the utility data identified in the SLR. However, when additional EQ-5D data from the inTandem2 trial were provided by the company at the clarification stage, the ERG was satisfied that the mean utilities in the inTandem2 trial (ranging from 0.83 to 0.85 across treatment arms at baseline and week-52) were similar to the mean utility for T1D without complications obtained from Peasgood *et al.* 2016 (0.839). The ERG also agrees that the utility data from inTandem2 trial is unable to inform any long-term complications of T1D.[7]

5.4.8.1.2 Utility data collected in patients with T2D

The ERG also considers the utility data obtained from Beaudet *et al.* 2014 and Currie *et al.* 2006 in patients with T2D to be useful in the absence of utility data in patients with T1D.[60,61] This approach is consistent with the economic analysis in the NICE guidance for T1D in adults (NG17) and employed NICE's preferred measure of HRQoL (EQ-5D).[8, 63] Clinical experts also advised the ERG that the utilities for complications informed by Beaudet *et al.* 2014 and Currie *et al.* 2006 would have the same impact in patients with T1D or T2D.

However, as part of the clarification process, the ERG highlighted potential discrepancies in how disutility values were estimated from Beaudet *et al.* 2014.[60] Unfortunately, the company's response did not resolve matters, as shown in Table 33. In short, the ERG considers that the utility values should be corrected to those reported in Beaudet *et al.* 2014 that were reiterated by the company at the clarification stage. The ERG also considers that the utility post-oedema should return to baseline (0.839), to reflect the assumption in NG17. Nonetheless, the impact of these corrections was negligible when the ERG explored a scenario in PRIME. As described in Section 5.5, the ERG is unable to run simulations in the CDM, but the impact is expected to be similar given the small number of patients entering the concerned health states in both models.

Table 33 Discrepancies in utility values obtained from Beaudet *et al.* 2014

Health state	CDM and Table 3.10 in the CS	PRIME	Company's response to clarification, Table 91	Table 3 in Beaudet *et al.* 2014
Haemodialysis	0.604 (0.839-0.235)	-0.235	-0.164	-0.164
Peritoneal dialysis	0.581 (0.839-0.258)	-0.258	NA	-0.204
Oedema (macular oedema)	−0.010	-0.04	-0.04	-0.04
Post-oedema	0.829	-0.04	*"event based – return to previous utility"*	NR
Abbreviations: CDM, Core Diabetes Model; CS, company submission; NA, not applicable; NR, not reported				

5.4.8.1.3 BMI

In Peasgood *et al.* 2016, the disutility per 1 unit increase above 25kg/m² varied from -0.0052 in the fixed-effects model to -0.0028 in the random-effects model and the company choose the smaller estimate from the random-effects model in each of their analyses.[59] However, the ERG notes that the disutility for a 1 unit increase above 25kg/m² in Beaudet *et al.* 2014 (-0.006) was similar to the fixed-effects estimate in the Peasgood *et al*. 2016, and as noted in the following sub-section, fixed-effect estimates were preferred in the Peasgood study.[59, 60] For these reasons, the ERG requested the company at the clarification stage to explore a scenario using a disutility of -0.006 for a 1 unit increase in BMI above 25kg/m².

The impact of using a larger disutility was noteworthy and the company reported that the ICER decreased from £10,012 to £8,659 in the CDM. However, the simulated cohort in the company's scenario was informed by the pooled analysis population (inTandem1 and inTandem2 in patients with BMI >27 kg/m²) rather than the NDA (the company's base case assumption). The ERG was also unable to run an analysis using the NDA to inform the simulated cohort for the reasons outlined in Section 5.5. However, the ERG has run the requested scenario in PRIME keeping all other preferred assumptions from the CDM base case (including the NDA cohort). This resulted in a decrease in the ICER in PRIME from £18,117 to £15,086. Overall, these scenarios demonstrate that BMI is an important measure of the impact of treatment on patients and a key driver in the models.

5.4.8.1.4 ScHARR review

As outlined in Section 5.4.8, the company employed utility inputs from a ScHARR 2018 review in PRIME at the clarification stage. However, the company only provided the ERG with the ScHARR 2019 review and, therefore, the ERG cannot validate the utility data employed by the company. Moreover, the ERG questions why the company choose the 2018 review instead of the updated 2019 review to inform their revised analyses and why the company did not apply the results from either ScHARR review in the CDM. Even so, it is clear that either ScHARR review employs more utility inputs from Peasgood *et al*. 2016 that were estimated from the fixed-effects model rather than the random-effects model (to account for the fact that the authors of the paper had more confidence in the fixed-effects estimates).[7]

To explore the impact of using the company's inputs reported in the CS, the ScHARR 2018 review and the ScHARR 2019 review, the ERG ran simulations in PRIME (keeping all other preferred assumptions from the CDM base case). The ERG was unable to run simulations in the CDM for the reasons outlined in Section 5.5. As shown in Table 34, the source of utility data had a large impact on the ICER. The ERG notes that one of the key drivers responsible for these differences includes the disutility associated with SH. This is because placebo is associated with a higher rate of SH events than sotagliflozin (see Section 5.4.2 and therefore, the source associated with the highest SH disutility (i.e. the ScHARR 2018 review) produces the lowest ICER in favour of sotagliflozin. However, it is important to reiterate that the ERG cannot adequately assess the company's approach using the ScHARR 2018 review given the currently available information.

Table 34. Impact of utility data in PRIME

Scenario	Disutility for a 1 unit increase in BMI >25 kg/m^2	Disutility for SH	QALY estimation	ICER
Inputs reported in the CS	-0.0028[a]	-0.002	Additive	£18,117
ScHARR 2018	-0.0028	-0.047	Additive	£8,834
ScHARR 2019	-0.0028	-0.002	Additive	£25,745
ScHARR 2019	-0.0052[b]	-0.002	Additive	£21,204

Abbreviations: BMI, body mass index; CS, company submission; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ScHARR, School of Health and Related Research; SH, severe hypoglycaemia

a Corrected by the ERG from 0 to -0.0028 in the model

b -0.0028 reported in ScHARR 2019, but -0.0052 follows the preferred estimation methods in ScHARR 2019

Overall, the ERG's preferred utility inputs are based on the recommendations in the ScHARR 2019 review (Table 35) for the following key reasons:

1. The review includes inputs from Beaudet *et al.* 2014 that address the discrepancies seen in the CS (see Section 5.4.8.1.2);[60]

2. The review includes inputs from Peasgood *et al.* 2016 estimated from the fixed-effects model (the authors preferred model), where avalaible;[59]

3. The review includes inputs from Alva *et al.* 2014 which uses EQ-5D data collected in the UKPDS cohort for stroke and MI in place of the random-effect estimates from Peasgood *et al.* 2016. [59, 62]

Table 35. Summary of utility data obtained from the ScHARR 2019 review

CDM health state (PRIME)	ScHARR 2019 review	
	Input	Reference
T1D without complication	0.8390	Peasgood *et al.* 2016
MI event	-0.0650	Alva *et al.* 2014
Post-MI	-0.0570	Alva *et al.* 2014
Angina	-0.0900	Clarke *et al.* 2002
Chronic (congestive) heart failure	-0.0960	Currie *et al.* 2006
Stroke event	-0.1650	Alva *et al.* 2014
Post-stroke	-0.1650	Alva *et al.* 2014
Peripheral vascular disease	NA	-
Microalbuminuria	-0.0170	Coffey *et al.* 2002
Gross renal proteinuria (overt nephropathy)	-0.0277	Peasgood *et al.* 2016 [a]
Haemodialysis	-0.1640	Beaudet *et al.* 2014
Peritoneal dialysis	-0.2040	Beaudet *et al.* 2014
Renal transplant	-0.0097	Peasgood *et al.* 2016 [a]
BDR (moderate)	-0.0544	Peasgood *et al.* 2016 [b]
BDR wrongly treated (severe)	-0.0544	Peasgood *et al.* 2016 [b]
PDR laser treated (laser NR)	-0.0288	Peasgood *et al.* 2016 [a]
PDR no laser (laser NR)	-0.0288	Peasgood *et al.* 2016 [a]
Macular oedema	0.0000	-
Severe vision loss	-0.2080	Coffey *et al.* 2002
Cataract	NA	-
Neuropathy	-0.0550	Coffey *et al.* 2002
Healed ulcer	NA	-
Active ulcer	NA	-
Amputation, year of event	-0.1172	Peasgood *et al.* 2016 [a]
Post-amputation	-0.1172	Peasgood *et al.* 2016 [a]
NSHE daytime	0.0000	-
NSHE nocturnal	0.0000	-
SHE during daytime (time NR)	-0.0020	Peasgood *et al.* 2016 [b]
SHE nocturnal (time NR)	-0.0020	Peasgood *et al.* 2016 [b]
Ketoacidosis event	-0.0091	Peasgood *et al.* 2016 [b]
Oedema (macular oedema)	0.0000	-
Post-oedema	NA	-
Depression not treated	NA	-
Depression treated	NA	-

Disutility associated with 1 unit increase in BMI	-0.0052[c]	Peasgood *et al.* 2016 [b]

Abbreviations: BDR, background diabetic retinopathy; BMI, body mass index; MI, myocardial infarction; NA, not applicable; NR, not reported; NSHE, non-severe hypoglycaemic event; PDR, proliferative diabetic retinopathy; SE, standard error; SHE; severe hypoglycaemic event; T1D, type 1 diabetes

a random-effects model

b fixed-effects model

c -0.0028 reported in the ScHARR 2019 review, but -0.0052 follows the authors preferred estimation methods

5.4.8.1.5 QALY estimation

As part of the clarification process, the ERG also highlighted potential discrepancies in how QALYs were estimated in the CDM and PRIME models. On page 107 in the CS it states, "*A multiplicative approach was used to estimate QALY in the base case with an additive approach used as a sensitivity analysis*." However, on page 131 in the CS it states that, "*Both models [PRIME and CORE] used an additive approach to estimate QALY*".

In response to the ERG's clarification questions, the company explained that the minimum QALY approach was taken in the CDM, while an additive QALY approach was taken in PRIME (in the absence of a minimum approach). A summary of the different approaches is provided by the ERG in Box 1. When the company provided the results using a multiplicative approach in the CDM, the ICER decreased from £10,012 to £9,371. However, the simulated cohort in the company's scenario was informed by the pooled analysis population (inTandem1 and inTandem2 in patients with BMI >27 kg/m, rather than the NDA (the company's base case assumption). The ERG was also unable to run an analysis using the NDA to inform the simulated cohort for the reasons outlined in Section 5.5.

The company was also unable to provide results using a multiplicative approach in PRIME as this, "*has not yet been rigorously tested*". However, given that the multiplicative approach is included as an option in PRIME, and therefore, validated by the developers (Ossian Health Economics and Communications GmbH), the ERG explored a scenario using the multiplicative approach. The impact of this was large and increased the ICER from £18,117 to £22,359 (keeping all other preferred assumptions from the CDM base case, including the NDA cohort). The ERG also found similar increases in the ICER when a multiplicative approach was applied to utility data from the ScHARR 2018 review and ScHARR 2019 review.

Overall, the ERG's preference is to use the multiplicative approach, and this is supported by the NICE decision support unit technical support document 12, which suggests that the multiplicative approach should be adopted when multiple evidence sources are used to obtain utility values.[64]

Box 1. Definition of QALY estimations

Minimum approach: if a patient experiences multiple events, the lowest health state utility value is applied

Multiplicative approach: if a patient experiences multiple events, the health state utility values associated with each event are multiplied to derive an overall utility score

Additive approach: if a patient experiences multiple events, the health state utility values associated with each event are added to derive an overall utility score

Finally, the ERG notes that the company did not include age related utility decrements in their economic analysis to accurately estimate the total QALYs accrued for each treatment. However, the ERG acknowledges that this is a limitation of the existing CDM and PRIME models, rather than an omission by the company.

5.4.9 Resources and costs

Costs are described in the following subsections for treatment-associated costs, complication costs and management costs. All costs from sources published before 2017 were inflated to 2017 prices using the Personal Social Services (PSS) pay and prices index included in the Personal Social Service Research Unit (PSSRU).[65]

5.4.9.1 Treatment-associated costs

Sotagliflozin

The dosing schedule modelled by the company for sotagliflozin was 200 mg once daily, in line with the draft SmPC provided in Appendix C of the CS. However, the CHMP positive opinion covers the 200 mg and 400 mg doses so the ERG requested that cost-effectiveness analyses be provided for both during the clarification phase.[3]

Sotagliflozin is administered orally, and according to the company does not incur administration costs. Acquisition costs obtained from the company are summarised in Table 36. It is currently anticipated by the company that the 400 mg tablet will be made available in [redacted]. However, until the 400 mg tablet is made available, the company considered the cost of taking two 200 mg tablets a day.

As described in Section 3.2, the company assumed that potentially 10% of patients may require dose escalation to the 400 mg dose. Following this, the company applied a 110% price increase to the acquisition cost of the 200 mg tablet for the scenario based on the 400 mg dose. The results of this scenario are provided in Section 5.5.3.

Table 36. Sotagliflozin acquisition costs

Drug	Pack price	Pack size	Daily dose	Annual cost
Sotagliflozin 200 mg	£39.20	30 tablets	200 mg	£477.30

Treatment with sotagliflozin was continued for 5 years in the economic analysis, at which point patients continued with insulin alone (as modelled in the placebo arm). The company's base case analysis also assumed 100% persistence with treatment. However, the draft SmPC states that treatment with sotagliflozin should be continued until the patient is no longer receiving benefit or until unacceptable side-effects. The ERG's critique regarding the duration of sotagliflozin is given in detail in Section 5.4.9.3.1.

Insulin-related resources

In the addendum to the CS provided at the clarification stage, the company stated that the mean daily basal and bolus insulin doses were taken from the pooled analysis population (inTandem1 and inTandem2), instead of inTandem2. However, only doses received in the inTandem2 trial were reported (Table 37). Those doses were conservatively assumed to be constant over time, despite the 52-week outcomes showing slightly lower insulin usage in the sotagliflozin group.

Table 37 Mean daily basal and bolus insulin doses (reproduced from Table 31 of the CS addendum and Table 3.11 in the original CS)

Delivery method	Insulin type	Placebo (IU/day)	Sotagliflozin 200 mg (IU/day)
CSII	Bolus	30.850	28.610
	Basal	28.380	27.850
MDI	Bolus	32.510	32.000
	Basal	30.240	29.650

Abbreviations: CSII, Continuous subcutaneous insulin infusion; MDI, multiple daily injection

The cost of insulin regimens (cartridges and pre-filled pens) were taken from the BNF (Table L.5 of the Appendix) and market share data were taken from IQVIA Longitudinal Patient Database (LPD) data (Tables L.6 and L.7 of the Appendix for MDI and CSII, respectively).[66, 67] This led to annual drug costs of £509 and £469 for MDI and CSII, respectively.

Needle costs for MDI were calculated as a weighted average based on the prices of the ten most commonly used needles (Prescription Cost Analysis, England data) (Table L.8 of the Appendix).[68] Then, using the frequency of insulin therapies reported in NICE guideline for T1D in adults (NG17), the annual needle cost associated with MDI was estimated to be £151.13.[8]

Insulin pump costs (£624) and consumables (£1,813) for CSII were estimated from NICE NG17.[8] Then, adding the annual drug costs of CSII (£469) the total annual pump cost considered by the company is £2,906.

In the addendum to the CS provided at the clarification stage, the company noted the high proportion of CSII users seen in the pooled analysis population (inTandem1 and inTandem2) of 46.4%. Therefore, the company maintained the proportion seen in the inTandem2 trial where 74.3% of the

overall population were on MDI and 25.7% were on CSII and applied the same proportions to each treatment arm. Following this, the annual weighted cost of MDI (including the cost of drugs and needles) was £490 (£660*0.743) and the annual weighted cost of CSII (including the cost of drugs, consumables and the pump) was £747 (£2,906*0.257).

Self-monitoring blood ketone

Based on recommendations from NHS sick day guidelines[69, 70] that patients with a high risk of ketones require 20 strips a year and newly diagnosed patients require ten strips a year, the company assumed patients on sotagliflozin in combination with insulin required 20 strips a year and patients receiving placebo in combination with insulin required ten strips a year.

Then, using the prices of the four most commonly used blood ketone strips (Prescription Cost Analysis, England data) (Table L.11 of the Appendix) annual costs of £40.03 and £20.02 were applied to sotagliflozin in combination with insulin and placebo in combination with insulin, respectively.[68] The company also performed a sensitivity analysis that assumed 100 blood ketone test strips for sotagliflozin-treated patients.

Self-monitoring of blood glucose (SMBG)

The company assumed that test strips and lancets would be required four times per day based on NG17.[8] Then, using the prices of the 10 most commonly used strips and lancets (Prescription Cost Analysis, England data) (Tables L.10 and L.11 of the Appendix for strips and lancets, respectively) the annual cost of SMBG per patient, regardless of treatment arm, was estimated to be £437.80.[68]

Total treatment-associated costs

The total annual treatment costs per patient in each treatment arm are summarised in Table 38.

Table 38. Annual treatment costs per patient (adapted from Table 3.14 of the CS and Table 34 of the CS addendum)

Intervention	Drug costs (excluding insulin)	MDI costs (inc. needles)	Pump costs (inc. CSII)	SMBG costs	Self-monitoring blood ketone costs	Total annual cost
Sotagliflozin 200 mg in combination with insulin	£477.30	£490.21	£746.79	£437.90	£40.03	£2,192.23
Placebo in combination with insulin	£0.00	£490.21	£746.79	£437.90	£20.02	£1,694.92*

Abbreviations: CSII, continuous subcutaneous insulin infusion; MDI; multiple daily injection; SMBG, self-monitoring of blood glucose
*erroneously summed to £1,732.48 in the CS

5.4.9.2 Complication and management costs

All SH events reported in the inTandem2 trial required medical assistance and all hypoglycaemia not requiring medical assistance were assumed to be non-severe. The cost of SH (requiring medical assistance) was estimated from NHS Reference Costs 2016-17 using a weighted average of the admissions for diabetes with hypoglycaemic disorder with CC score 5 to 8+ (Table L.13 of the Appendix).[71] This led to a cost of £2,320.03 per SH event (requiring medical assistance). As for non-SH, no costs were incurred.

The company assumed SH could be used as a proxy for DKA. Following this, the cost of DKA was estimated from NHS Reference Costs 2016-17 using a weighted average of the admissions for diabetes with hyperglycaemic disorder with CC score 1 to 8+ (Table L.12 of the Appendix).[71] This led to a cost of £1,556.22 per DKA event.

In summary, event costs were based on NHS Reference Costs 2016-17, NG17 (inflated to 2017 prices), or the default values in the CDM.[8, 71] In addition to SH and DKA, complications costs comprised of: cardiovascular complications; renal complications; eye disease; neuropathy; foot ulcers; and, amputations. Management costs comprised of: statins; aspirin; angiotensin-converting-enzyme inhibitor (ACEi); and, screening for: eyes; microalbuminuria; gross renal proteinuria; feet; and, depression. All complication and management costs applied in the company's economic analysis are given in Table 3.15 of the CS.

5.4.9.3 ERG critique

The company obtained resource use estimates and unit costs from reliable UK sources including: NG17, NHS Prescription Cost Analysis data, IQVIA LPD real-world data, NHS Reference Costs 2016-17, and the BNF.[8, 66-68, 71] However, when the ERG checked the inputs in the revised analyses provided at the clarification stage, the ERG found that the company used alternative costs in PRIME. No sources of cost data or rationale for this change were provided to the ERG and given that the company did not mention those alternative inputs in the addendum to the CS, the ERG has focussed its critique on the cost inputs used to inform the original and revised CDM.

The ERG also had major concerns related to the duration of sotagliflozin, the cost associated with SH and the insulin delivery method, these concerns are explained in Sections 5.4.9.3.1, 5.4.9.3.2 and 5.4.9.3.3, respectively.

One other minor concern of the ERG's was the potential omission of treatment-specific (healthcare professional) monitoring costs, as this was not touched upon in the CS. However, in response to the ERG's clarification questions the company stated that, "*Even though a regular medical follow-up of the patient can be considered, its incremental value would equally affect all interventional arms.*" On

a similar note, the company did not cost the 6-week insulin optimisation phase between screening and baseline that the patients in the inTandem1 and inTandem2 trials received. However, the ERG considers this to be a reasonable omission given that its clinical experts stated that insulin optimisation before treatment initiation is unlikely to occur in UK practice.

5.4.9.3.1 Duration of sotagliflozin

The company assumed that patients would remain on sotagliflozin for 5 years before switching to insulin therapy, while the draft SmPC states that sotagliflozin should be continued until the patient is no longer receiving benefit or until unacceptable side-effects.

Clinical experts advised the ERG that sotagliflozin would be stopped in the event of unacceptable side-effects. However, they anticipated that patients are likely to be kept on treatment indefinitely after an initial benefit is achieved because it will be difficult to isolate continued drug effects from changes in patient-related factors (e.g. diet, exercise, management of insulin). Moreover, if sotagliflozin was stopped there would be concerns as to whether a patient's condition would deteriorate. To explore this issue, the ERG requested the company provide scenario analyses assuming sotagliflozin is received for a patient's lifetime, one assuming treatment effects rebound to placebo after 5 years (i.e. the base case) and a second after 2 years to reflect the duration of the inTandem trials. However, the company stated that these scenarios were, "*not appropriate to model as not in line with either the anticipated decisions of physicians given the risk/benefit profile of this class of medicines, effective use of NHS resources in line with the NHS Long-Term Plan, nor in line with the market authorisation which supports safe clinical decision making for this medicine*." As such, the ERG is concerned that the company has misunderstood the issue posed as the company has responded assuming it concerned a lack of effectiveness of sotagliflozin. Whereas, it is more a reflection of the ERG's clinical experts' view that reduced patient compliance with other aspects of their treatment would return them to baseline.

As explained in Section 5.4.5, some treatment effects were permanently maintained even after treatment discontinuation which the ERG considers to be inconsistent with the assumption that patients only remain on sotagliflozin for 5 years. Furthermore, it is unclear why it is assumed that patients remain on sotagliflozin for 5 years and then discontinue. For completeness, the ERG considered performing the requested scenario analyses assuming sotagliflozin is received for a patient's lifetime. However, when the ERG checked the revised analyses provided at the clarification stage, the ERG found that the company had already performed those scenarios in the CDM. However, the simulated cohort in those scenarios was informed by the pooled analysis population (inTandem1 and inTandem2 in patients with BMI >27 kg/m^2) rather than the NDA (the company's base case

assumption). Nonetheless, Table 39 presents the results of those analyses and it is clear sotagliflozin is no longer a cost-effective option when sotagliflozin is received indefinitely.

Clinical experts advising the ERG considered that if sotagliflozin was discontinued when a patient was no longer receiving benefit, it may only be continued for 2 years based on the declining 24- and 52-week trends in HbA_{1c} in the inTandem trials.[32, 33] To explore this issue, the ERG asked the company to provide scenario analyses assuming sotagliflozin is continued for 2 years and 5 years and treatment effects rebound to placebo after 2 years. The ERG also requested another scenario where sotagliflozin treatment effects wanes after 1 year and rebound to placebo after 2 years of treatment.

In response to the ERG's clarification questions, the company explained that assuming the treatment effect for sotagliflozin wanes after 1 year and returns to placebo after 2 years is equivalent to the scenario where treatment effects rebound to placebo at 2 years. However, in PRIME, the company treated these as separate scenarios: in the former scenario, treatment effects switch to placebo at 1 year and rebound to placebo at 2 years; and, in the latter scenario, treatment effects switch to placebo at 2 years. Furthermore, the company only provided results in the CDM using the pooled analysis population (inTandem1 and inTandem2 in patients with BMI >27 kg/m²) to inform the simulated cohort. The company did not provide scenario analyses requested by the ERG in the CDM using the NDA to inform the simulated cohort (the company's base case assumption) and the ERG was also unable to run analyses in the CDM for the reasons outlined in Section 5.5. However, the ERG has run the requested scenarios in PRIME keeping all other preferred assumptions from the CDM base case (including the NDA cohort).

Finally, the company's base case analysis assumed 100% persistence with treatment. The ERG would consider this to be a reasonable assumption given that dropout at 24 and 52 weeks was balanced across groups and unlikely to impact relative treatment effects (see Section 4.2.1). However, there may be decreased rates in subsequent years, particularly if clinicians stop treatment if sotagliflozin is considered to be no longer improving or maintaining glycaemic control. For these reasons, the ERG would recommend using decreased rates in subsequent years to the inTandem trials informed by other trial data. Due to time constraints the ERG was unable to address this issue; however, given the low drop-out rates in the inTandem trial period, the ERG considers this unlikely to have a large impact on the ICER.

Table 39. Results of scenario analyses varying the duration of sotagliflozin treatment

Duration of sotagliflozin	Sotagliflozin treatment effects rebound to placebo after	ICER, CDM (provided by the company using the pooled analysis population to inform the simulated cohort)	ICER, PRIME (ran by the ERG using the NDA to inform the simulated cohort)
2 years	wanes after 1 year and rebounds after 2 years	NA (£25,638)	£17,854

2 years	2 years	£25,638	£13,000
5 years	2 years	£26,463	£15,452
5 years	5 years	£10,012	£18,117
Lifetime	2 years	£297,768	£137,943
Lifetime	5 years	£124,481	£76,532
Abbreviations: CDM, Core Diabetes Model; ICER, incremental cost-effectiveness ratio; NDA, National Diabetes Audit; NA, not available			

5.4.9.3.2 Cost to treat SH

In the inTandem2 trial SH was defined as, "*any hypoglycaemic event that required assistance from another person or during which the patient lost consciousness or had a seizure*". The company then assumed that all SH events required medical assistance and the ERG has two concerns with this. Firstly, the cost to treat SH in the company's analysis (£2,320) was approximately seven times higher than that employed by NG17 (taken from Hammer *et al.* 2009) to treat "major hypoglycaemic events" (£333 in 2014 prices).[71,1] Secondly, the ERG disagrees with the company that "assistance from another person" translates into medical assistance. This view was also reiterated by the ERG's clinical experts who advised the ERG that around 50% of SH events would require medical assistance. The base case analysis in the Hammer *et al.* 2009 study also assumed 50% of events were treated by a family member or friend (group 1), 25% required emergency treatment from a paramedic or a medical practitioner without requiring treatment in a hospital (group 2), and 25% were treated in a hospital (group 3).[1] To address these concerns, the ERG asked the company at the clarification stage to provide scenarios that combine alternative proportions of SH events that require medical assistance (100% and 50%) with the following cost sources:

1. NHS Reference Costs 2016-17[71] using a weighted average of the admissions for diabetes with hypoglycaemic disorder with complication and comorbidity (CC) score 5 to 8+ (the base case assumption);

2. NHS Reference Costs 2016-17[71] using a weighted average of the admissions for diabetes with hypoglycaemic disorder with CC score 0 to 8+;

3. Hammer *et al.* 2009[1] (inflated to 2017 prices).

The scenarios provided by the company are given in Table 40. However, the company only provided results in the CDM using the pooled analysis population (inTandem1 and inTandem2 in patients with BMI >27 kg/m²) to inform the simulated cohort. The company did not provide scenario analyses requested by the ERG in the CDM using the NDA to inform the simulated cohort (the company's base case assumption) and the ERG was also unable to run analyses in the CDM for the reasons outlined in Section 5.5. However, the ERG has run the requested scenarios based on Hammer *et al.* 2009 in

PRIME keeping all other preferred assumptions from the CDM base case (including the NDA cohort).[1]

Compared to the base case results, the ERG's preferred scenario that comprised of lower hospitalisation rates (50%) and lower treatment costs (Hammer *et al.* 2009[1]) had a noteworthy increase on the ICER. The ERG also notes that the cost to treat SH without medical assistance in Hammer *et al*. 2009 (£32 estimated from group 1) was included in the PRIME Diabetes Model, but not the CDM. For completeness, the ERG would have preferred the company to use groups 1 and 2 in Hammer *et al.* 2009 (i.e. events treated by a family member or friend, and events that required emergency treatment from a paramedic or a medical practitioner without requiring treatment) to inform the cost of managing the proportion of SH events that did not require hospitalisation. Nonetheless, the ERG considers the company's approach to use the lower cost estimate to be conservative.

Table 40. Results of scenario analyses in the revised population (BMI >27 kg/m²) using alternative SH costs and hosptalisation proportions (sotagliflozin 200 mg in combinaiton with insulin vesus insulin alone)

Cost source	Cost of SH	Proportion hospitalised	ICER, CDM (provided by the company using the pooled analysis population to inform the simulated cohort)	ICER, PRIME (ran by the ERG using the NDA to inform the simulated cohort)
NHS reference costs with CC scores 5 to 8 [71]	£2,320	100%	£10,012	£18,117
Hammer *et al.* 2009[1]	£999	100%	£11,386	£18,230
Hammer *et al.* 2009[1]	£999	50%	£11,905	£18,797
NHS reference costs with CC scores 0 to 8[71]	£2,121	100%	£10,219	NA
NHS reference costs with CC scores 0 to 8[71]	£2,121	50%	£11,322	NA

*Company base case
Abbreviations: CC, complications and comorbidities; CDM, Core Diabetes Model; ICER, incremental cost-effectiveness ratio; NA, not available; SH, severe hypoglycaemia

5.4.9.3.3 Insulin delivery method

In the revised analyses provided to the ERG at the clarification stage, the ERG could not match the total annual treatment costs per patient in the CDM (£1,694.91 and £2,400.82 for placebo and sotagliflozin, respectively) with the PRIME model (£1,963.41 and £2,400.82 for placebo and sotagliflozin, respectively) or the costs reported in addendum to the CS (£1,694.91 and £2,192.23, respectively). The ERG was also unable to investigate this discrepancy because the models do not break down the total annual treatment cost into its separate components (i.e. drug costs, MDI costs, pump costs, SMBG costs, self-monitoring blood ketone costs).

Moreover, the company assumed that 25.7% of patients receive insulin via CSII based on the proportion in the overall inTandem2 population. The ERG has two conflicting issues with this assumption. On the one hand, the proportion should ideally come from the same population from which effectiveness data were derived (i.e. the pooled analysis population including inTandem1 and inTandem2 in patients with BMI >27 kg/m²). On the other hand, the proportion of CSII seen in inTandem1 (59.6%), inTandem2 (25.7%) and the pooled analysis (46.7%) is much higher than the UK (15% in England and Wales according to the NDA Insulin Pump Report).[9] Given that the same proportion is used to calculate the total annual cost of sotagliflozin treatment and total annual cost of placebo treatment, reducing the proportion of CSII users would only reduce the total cost of each treatment (because CSII is more expensive than MDI) without impacting the incremental results. As explained previously in Sections 3.1 and 5.4.2 the ERG requested the company to provide cost-effectiveness results for MDI users, but due to limited patients numbers, this was not feasible.

5.5 Results included in company's submission

In response to the ERG's clarification questions, the company submitted revised results which incorporated the changes shown in Table 41.

Table 41. Changes to the base case analysis in the CDM (reproduced from Table 21 of the company's addendum)

Variable	Revised company base case (likely marketing authorisation)	Company base case (original submission)
Population	NDA	NDA
Time horizon	60 years	60 years
Cycle length	1 year	1 year
Efficacy outcomes	inTandem1 and 2 (pooled) sub-population with BMI ≥27kg/m²	inTandem2 (ITT population)
HbA_{1c} progression	0.012% per year*	0.045% per year
BMI progression	0.094 kg/m² per year*	0.2375 kg/m² per year
eGFR progression	−1.227 (mL/min/1,73 m^2) per year*	0 (mL/min/1,73 m^2) per year
SBP progression	0.118 mmHg per year*	UKPDS risk equation
DBP progression	−0.588 mmHg*	0
Total Chol progression	−0.588 (mg/dL) per year*	Framingham risk equation
HDL-C progression	1.059 (mg/dL) per year*	Framingham risk equation
LDL-C progression	−1.412 (mg/dL) per year*	Framingham risk equation
Triglycerides progression	−1.176 (mg/dL) per year*	Framingham risk equation
Probability of. Mortality-severe hypoglycaemia	0.003% (Wolowacz *et al* 2015) per year[72]	5% (Ben-Ami H *et al* 1999)[73]
Probability of mortality-DKA	0.05% (Wolowacz *et al* 2015) per year[72]	2.7% (MacIsaac RJ *et al.* 2002)[74]
Duration of sotagliflozin treatment	5 (base case) or 2 (SA) years treatment effect and then rebound for a convergence between treatment arms. Cost of optimised insulin treatment as rescue treatment for the rest of the time horizon. No treatment effects assumptions for rescue treatment but a constant rate of AEs. Rescue treatment as substitution in the base case, and as addition in other SAs (up to 2, 5 years and lifetime).	

*Estimated based on 8.5 years of data (2004 to 2012/13) and using the EDIC intensive insulin arm
Abbreviations: AEs, adverse events; BMI, body mass index; DCCT, Diabetes Control and Complications Trial; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ITT, intention -to-treat; NDA, National Diabetes Audit; SA, sensitivity analysis; SBP, systolic blood pressure; UKPDS, United Kingdom Prospective Diabetes Study.

The company's primary analysis comprised a comparison of sotagliflozin 200 mg in combination with insulin versus insulin alone. For this comparison, the company presented base case results deterministically (bootstraps with 1st order sampling) as well as probabilistically (bootstraps with 2nd order sampling). The company also carried out deterministic sensitivity analysis to test the robustness of model results to changes in model parameters and assumptions.

However, the ERG considers it important to highlight the fact that it has not been able to replicate any of the company's analyses in the CDM because of an error related to treatment costs. In short, the error, "*Simulation can not run. The Intervention treatment has no cost defined in the treatment cost set group*" was posed to the ERG whenever a new simulation was run in the CDM. This error also occurred prior to any additions to the data made by the ERG. To address this issue, the ERG contacted the developers, but they did not respond at the time of writing this report.

In the original submission, the company also presented a comparison with metformin in combination with insulin. However, on the advice of clinical experts, the ERG does not consider metformin a relevant comparator for sotagliflozin and made this clear to the company at the clarification stage. As a result, the company excluded the results of this comparison in the addendum to the CS.

5.5.1 Base case results

The company performed an analysis with 1st order sampling in the CDM using 1,000 patients and 1,000 iterations. According to the company's analysis, sotagliflozin 200 mg in combination with insulin generates 0.108 incremental quality-adjusted life years (QALYs) and £209 incremental costs over a patient's lifetime compared with insulin. This translates into an incremental cost-effectiveness ratio (ICER) of £1,934 per QALY gained.

Table 42. Company's base case results (sotagliflozin 200 mg in combination with insulin versus insulin alone) (adapted from Table 37 of the company's addendum)

Treatment	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£78,731	17.194	8.695	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£78,940	17.223	8.803	£209	0.029	0.108	£1,934

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

In the original submission, the company used the PRIME model to run a simulation that was designed to reproduce the base case analysis undertaken in the CDM. However, in the addendum to the CS, the

company only presented base case results estimated in the CDM. The ERG also considers it important to note that all scenario analyses performed in the PRIME model provided to the ERG after clarification were informed by a simulation on the pooled analysis cohort (in place of the NDA) and alternative cost and utility inputs to the CDM, without justification. As mentioned throughout this report, the ERG has run additional analyses in the PRIME model to reflect the inputs reported in the CS. The results of the PRIME model using the company's preferred assumptions (including a correction) are given in Table 43.

Table 43. Results of company's revised base-case analysis in PRIME corrected by the ERG

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Analysis using the preferred assumptions from the CDM base case (addendum inputs) excluding BMI correction					
Placebo	£52,458	11.767	-	-	-
Sotagliflozin	£54,176	11.846	£1,718	0.078	£21,982
Analysis using the preferred assumptions from the CDM base case (addendum inputs) including BMI correction (from 0 to -0.0028)					
Placebo	£52,458	11.598	-	-	-
Sotagliflozin	£54,176	11.693	£1,718	0.095	£18,117
Abbreviations: BMI, body mass index; CDM, Core Diabetes Model; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NDA, National Diabetes Audit; PLA, placebo; QALYs, quality-adjusted life years; SOTA, sotagliflozin					

5.5.2 Probabilistic sensitivity analysis

The company performed an analysis with 2nd order sampling in the CDM using 10,000 patients and 1,000 iterations. According to the CDM user guide, when standard deviations (SDs) surrounding input parameters are included, 2nd order sampling results in the selection of patient characteristics and treatment effects from distributions surrounding the means (usually normally distributed).[75] However, it is unclear if alternative distributions were chosen by the company.

During the clarification stage, the company added that utility estimates were varied based on the standard errors (SEs) reported in Peasgood *et al.* 2016, and not SDs as specified in the CDM user guide.[59] When SEs were not reported in the Peasgood study, the SEs at baseline (i.e. SE corresponding to T1D without complication [0.231]) were considered. Furthermore, the distribution of costs was calculated using 20% of the mean value, rather than the variation reported in the source.

According to the revised PSA, the mean ICER was £2,434. The north-east quadrant of the cost-effectiveness plane contained 61% of PSA simulations, and the probability that sotagliflozin 200 mg in combination with insulin was cost-effective at a threshold of £20,000 per QALY was 89%. The ERG has not provided the scatterplots and cost-effectiveness acceptability curves presented in the addendum to the CS on the basis that the comparator in those figures is labelled with metformin.

The ERG has not been able to run PSA in the CDM because of the error related to treatment costs noted previously in Section 5.5.

5.5.3 Deterministic sensitivity analysis

The company carried out sensitivity analyses in the CDM exploring the impact of applying:

- A 2-year treatment effect with 2-year costs;
- No BMI disutility;
- Utility values collected in patients with T2D (replacing the utility associated with T1D without complications from Peasgood *et al*. 2016[59] [0.839] with the utility associated with T2D without complications from Beaudet *et al.* 2014[60] [0.785]);
- 100 blood ketone monitoring strips per year for sotagliflozin treated patients;
- Acquisition cost of sotagliflozin 200 mg increased by 10% (in order to provide cost-effectiveness results for the 400 mg dose, a 110% price increase is applied to reflect potentially 10% of patients who may require dose escalation from the 200 mg dose to the 400 mg dose);
- A simulated cohort using baseline characteristics from the pooled analysis population (inTandem1 and inTandem with BMI≥27 kg/m²).

The company also presented two analyses that varied parameters (discount rates, management costs, complication costs and utilities) in the 'Economics' sheet of the CDM by +20% and by -20%. In the CS, the company implied that this was undertaken as one-way sensitivity analysis. However, the company did not present the results of varying each parameter individually. Instead, the company reported the combined effect of varying all inputs in the 'Economics' sheet: one using +20% and another using -20%. Due to time constraints and the ERG's inability to run simulations in the CDM, the ERG has not been able to determine the most sensitive parameters in the company's analysis.

The results of the company's deterministic sensitivity analysis are provided in Table 44. The simulated cohort in each deterministic sensitivity analysis was based on the NDA, except for the analysis that explored cohort characteristics using the pooled analysis population (inTandem1 and inTandem2 with BMI≥27 kg/m²). Overall, all sensitivity analyses resulted in an ICER below the cost-effectiveness threshold of £20,000 per QALY.

Table 44. Results of sensitivity anlaysis (sotagliflozin 200 mg in combination with insulin versus insulin alone) (adapted from Table 41 of the company's addendum)

Analysis	Costs			QALYs			ICER
	Sotagliflozin	Placebo	Inc.	Sotagliflozin	Placebo	Inc.	
Base case	£78,940	£78,731	£209	8,803	8,695	0.108	£1,934
2-year treatment effect with 2-year costs	£78,913	£78,735	£178	8.733	8.695	0.038	£4,654
T2D utility values	£78,940	£78,731	£209	8.612	8.495	0.116	£1,796
No BMI disutility	£78,940	£78,731	£209	8.970	8.869	0.101	£2,073
Blood ketone monitoring 100 strips per year	£79,524	£78,731	£793	8.803	8.695	0.108	£7,347
Price of sotagliflozin +10%	£79,114	£78,731	£383	8.803	8.695	0.108	£3,548
Economics +20%	£88,397	£88,519	-£122	8.802	8.694	0.108	Dominant
Economics–20%	£69,483	£68,944	£539	8.802	8.694	0.108	£4,997
Simulated cohort (pooled inTandem1 and inTandem2 with BMI≥27 kg/m²)	£72,126	£71,511	£615	10.490	10.428	0.061	£10,012

Abbreviations: BMI, body mass index; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; T2D, type 2 diabetes

5.5.4 Model validation

The company's base case analysis was based on an online model that has been used extensively in economic analyses for both T1D and T2D. In particular, the model was used to help inform economic evaluations for NG17. The model is also thoroughly tested within the Mount Hood Diabetes Challenge Network. Thus, the ERG considers the model to be well validated and the functioning of the model is likely to be sound.

The ERG notes that given the "black box" nature of the model makes it difficult for the ERG to provide a fully independent critique and validation of the model structure. However, the results can be compared against existing published economic evaluation results to demonstrate plausibility of model outputs.

The ERG considered the economic analyses performed as part of NG17 and note that an evaluation of different types of insulin was undertaken using the CDM. The ERG considers that these results could be expected to approximately represent the insulin-only group for this appraisal. The results in NG17 (See Appendix N of NG17)[8] show that, as expected, the breakdown of costs by complication is more closely aligned to the company's base case analysis than the PRIME analyses, as it is based on the same model. However, the total costs are around £40,000 to £45,000, which is more closely aligned to the outputs of PRIME. This may shed some uncertainty on the plausibility of the current results.

To determine the preferred model requires clinical validation of the plausibility of model outputs such as the incidence rates for each complication. As far as the ERG can ascertain, this validation process was performed by the guideline development group – consisting of a number of expert clinicians – as part of the model development process in NG17. Therefore, despite the difference in total costs, the CDM is potentially more likely to give plausible results given that the breakdown in costs per complication in the company's analysis is more aligned with the results from NG17 than the PRIME model. The overall discounted costs and QALYs from the NG17 analyses are given in Table 45.

Table 45. Results in NG17

Insulin	Costs	QALYs
Degludec once	£45,029	12.29
NPH four	£44,534	12.00
Detemir twice	£41,586	12.41
Glargine once	£41,577	12.35
Detemir once	£41,484	12.33
NPH twice	£41,277	12.28
NPH once	£40,416	12.25

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

Two issues related to PRIME are summarised here, together with the combined impact of the corrections on the final incremental cost-effectiveness ratio (ICER). The ERG made the following corrections:

1. All analyses performed in the PRIME model provided to the ERG after clarification were informed by a simulation on the pooled analysis cohort (in place of the NDA) and alternative cost and utility inputs to the CDM, without justification. To reflect the revised base case assumptions applied in the CDM (and reported in the addendum to the CS), the ERG corrected the data sources in the model

2. The company did not apply the disutility associated with a 1 unit increase in BMI > 25 kg/m^2 in PRIME and therefore the ERG amended the input in the model from 0 to -0.0028.

Results are provided in Table 46 including those changes.

Table 46. Results of company's revised base-case analysis in PRIME corrected by the ERG

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	PRIME data notes
Analysis using the preferred assumptions from the CDM base case (addendum inputs) excluding BMI correction						Cohort: SOTA NDA CDM Treatments: PLA NICE A1c vs. SOTA200 NICE A1a Cost: CDM cost set Utility: SOTA CDM Country: SOTA (UK) NICE response
Placebo	£52,458	11.767	-	-	-	
Sotagliflozin	£54,176	11.846	£1,718	0.078	£21,982	
Analysis using the preferred assumptions from the CDM base case (addendum inputs) including BMI correction (from 0 to -0.0028)						Cohort: SOTA NDA CDM Treatments: PLA NICE A1c vs. SOTA200 NICE A1a Cost: CDM cost set Utility: ERG SOTA CDM copy with BMI disutility Country: SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£54,176	11.693	£1,718	0.095	£18,117	

Abbreviations: BMI, body mass index; CDM, Core Diabetes Model; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NDA, National Diabetes Audit; PLA, placebo; QALYs, quality-adjusted life years; SOTA, sotagliflozin

6.2 ERG scenario analysis

Throughout Section 5 the ERG has described several scenarios that warrant further exploration in addition to the company's sensitivity analyses to ascertain the impact of these changes on the ICER. The scenarios that the ERG have produced are applied to the revised company base case in PRIME and are as follows:

1. A simulated cohort informed by the pooled analysis population (see Section 5.4.2);

2. Alternative utility values from the Beaudet et al. 2014 study including all other utility inputs reported in the CS (see Section 5.4.8.1.2);

3. Alternative utility values from a ScHARR 2019 review (see Section 5.4.8.1.4);

4. Multiplicative QALY estimation approaches (see Section 5.4.8.1.5);

5. Alternative durations of sotagliflozin treatment (see Section 5.4.9.3.1);

6. Alternative costs to manage SH from Hammer et al. 2009 (see Section 5.4.9.3.2).

Table 47. ERG scenarios in the PRIME model

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Notes
Analysis using the preferred assumptions from the CDM base case (addendum inputs) including BMI correction						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£54,176	11.693	£1,718	0.095	£18,117	
QALY estimation: multiplicative						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility copy multiplicative Country SOTA (UK) NICE response
Placebo	£52,458	12.043	-	-	-	
Sotagliflozin	£54,176	12.120	£1,718	0.077	£22,359	
Simulated cohort informed by the pooled analysis population						Cohort SOTA NICE A1a Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£48,924	10.557	-	-	-	
Sotagliflozin	£50,569	10.656	£1,645	0.099	£16,539	
Alternative Beaudet *et al.* 2014 disutility values (QALY estimation: additive)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA CDM copy (corrected Beaudet 2014) additive Country SOTA (UK) NICE response
Placebo	£52,458	11.624	-	-	-	
Sotagliflozin	£54,176	11.718	£1,718	0.094	£18,241	

Alternative Beaudet *et al.* 2014 disutility values (QALY estimation: multiplicative)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA CDM copy (corrected Beaudet 2014) multiplicative Country SOTA (UK) NICE response
Placebo	£52,458	12.059	-	-	-	
Sotagliflozin	£54,176	12.136	£1,718	0.076	£22,470	
ScHARR 2018 utility values (QALY estimation: additive)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility SOTA ScHARR aligned Peasgood BMI Country SOTA (UK) NICE response
Placebo	£52,458	8.498	-	-	-	
Sotagliflozin	£54,176	8.693	£1,718	0.194	£8,834	
ScHARR 2018 utility values (QALY estimation: multiplicative)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA ScHARR aligned Peasgood BMI multiplicative Country SOTA (UK) NICE response
Placebo	£52,458	9.746	-	-	-	
Sotagliflozin	£54,176	9.895	£1,718	0.149	£11,515	
ScHARR 2019 utility values (QALY estimation: additive)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA ScHARR 2019 review additive Country SOTA (UK) NICE response
Placebo	£52,458	12.342	-	-	-	
Sotagliflozin	£54,176	12.423	£1,718	0.081	£21,204	
ScHARR 2019 utility values (QALY estimation: multiplicative)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA ScHARR 2019 review multiplicative Country SOTA (UK) NICE response
Placebo	£52,458	12.610	-	-	-	
Sotagliflozin	£54,176	12.677	£1,718	0.067	£25,472	
1-year waning effects to 2-year placebo effects and 2-year costs						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a 2 year wane Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£53,202	11.640	£745	0.042	£17,854	

2-year effects and 2-year costs						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a 2 years Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£53,155	11.652	£697	0.054	£13,000	
2-year effects and 5-year costs						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a effects 2 years costs 5 years Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£53,481	11.665	£1,023	0.066	£15,452	
Lifetime costs						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. ERG SOTA200 NICE A1a lifetime costs, rebound 5 years Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£59,715	11.693	£7,257	0.095	£76,532	
2-year effects and lifetime costs						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. ERG SOTA200 NICE A1a 2 year effects lifetime costs Cost CDM cost set Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£52,458	11.598	-	-	-	
Sotagliflozin	£59,855	11.652	£7,397	0.054	£137,943	
Cost of SH (Hammer *et al.* 2009 & 100% hospitalised)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost ERG CDM cost set (Hammer et al. 2009 & 100% hospitalised) copy Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£54,435	11.598	-	-	-	
Sotagliflozin	£56,164	11.693	£1,729	0.095	£18,230	
Cost of SH (Hammer *et al.* 2009 & 50% hospitalised)						Cohort SOTA NDA CDM Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost ERG CDM cost set (Hammer et al. 2009 & 50% hospitalised) Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE
Placebo	£53,505	11.598	-	-	-	
Sotagliflozin	£55,288	11.693	£1,782	0.095	£18,797	

						response
Simulated cohort informed by the pooled analysis population plus ScHARR 2019 utility values (QALY estimation: additive)						Cohort SOTA NICE A1a Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA ScHARR 2019 review additive Country SOTA (UK) NICE response
Placebo	£48,924	11.318	-	-	-	
Sotagliflozin	£50,569	11.406	£1,645	0.089	£18,585	
Simulated cohort informed by the pooled analysis population plus ScHARR 2019 utility values (QALY estimation: multiplicative)						Cohort SOTA NICE A1a Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost CDM cost set Utility ERG SOTA ScHARR 2019 review multiplicative Country SOTA (UK) NICE response
Placebo	£48,924	11.684	-	-	-	
Sotagliflozin	£50,569	11.758	£1,645	0.074	£22,187	
Simulated cohort informed by the pooled analysis population plus cost of SH (Hammer *et al.* 2009 & 50% hospitalised)						Cohort SOTA NICE A1a Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost ERG CDM cost set (Hammer et al. 2009 & 50% hospitalised) Utility ERG SOTA CDM copy with BMI disutility Country SOTA (UK) NICE response
Placebo	£49,922	10.557	-	-	-	
Sotagliflozin	£51,627	10.656	£1,705	0.099	£17,147	
Simulated cohort informed by the pooled analysis population plus cost of SH (Hammer *et al.* 2009 & 50% hospitalised) plus ScHARR 2019 utility values (QALY estimation: multiplicative)						Cohort SOTA NICE A1a Treatments PLA NICE A1c vs. SOTA200 NICE A1a Cost ERG CDM cost set (Hammer et al. 2009 & 50% hospitalised) Utility ERG SOTA ScHARR 2019 review multiplicative Country SOTA (UK) NICE response
Placebo	£49,922	11.684	-	-	-	
Sotagliflozin	£51,627	11.758	£1,705	0.074	£23,003	
Abbreviations: BMI, body mass index; CDM, Core Diabetes Model; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NDA, National Diabetes Audit; PLA, placebo; QALYs, quality-adjusted life years; SOTA, sotagliflozin						

6.3 ERG base case ICER

Although the ERG was not able run analyses using the CDM, the ERG has outlined its preferred assumptions in Section 6.3.1. The ERG has provided analyses using the PRIME model in Section 6.3.2. However, there were some restrictions in what the ERG was able to adapt in PRIME, so the ERG's preferred base case could not be fully implemented. An analysis similar to the ERG's preferred assumptions is given in Section 6.3.2.

6.3.1 ERG's preferred assumptions

- Simulated cohort informed by the pooled trial analysis population as per the treatment effects;
- Treatment effects for HbA_{1c} to return to the placebo group effects at 2 years;
- Treatment duration to remain at 5 years with all other treatment effects maintained for this duration;
- Using Hammer *et al.* 2009 to inform costs for SH and assuming 50% are hospitalised; and,
- Multiplicative utilities based on the ScHARR 2019 review.

6.3.2 PRIME preferred base case

As noted previously, the ERG could not fully implement their preferred assumptions in PRIME because of apparent restrictions in modifying treatment effect durations. A similar analysis is outline below with the results given in Table 48.

- Simulated cohort informed by the pooled trial analysis population as per the treatment effects;
- Treatment effects for HbA_{1c} to return to the placebo group effects at 3 years;
- Treatment effects for the other physiological parameters, and treatment costs, maintained for a further year;
- Using Hammer *et al.* 2009 to inform costs for SH and assuming 50% are hospitalised; and,
- Multiplicative utilities based on the ScHARR 2019 review.

Table 48. ERG preferred analysis in PRIME given the model restrictions†

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Placebo	£49,922	11.684	-	-	-
Sotagliflozin	£50,908	11.739	£986	0.054	£18,134

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

† The restrictions prevented the ERG from applying treatment effect durations separately for each of the physiological parameters. It was only possible by duplicating and editing one of the company's files, but this had limited ability to specify the duration.

7 END OF LIFE

The company did not make a case for sotagliflozin to be considered as an end of life treatment, which the ERG considers appropriate.

8 OVERALL CONCLUSIONS

Evidence for sotagliflozin, in combination with insulin, for treating type 1 diabetes (T1D) is available from three high quality, phase III, head-to-head randomised controlled trials (RCTs): inTandem1 (North America), inTandem2 (Europe and Israel) and inTandem3 (global), which vary in their applicability to the UK by geography, management and delivery of insulin, and baseline glycaemic control. While inTandem3 is likely to most closely reflect baseline glycaemic control and insulin management in UK clinical practice, it but does not provide evidence for the 200 mg dose, and only provides 24-week follow-up data. Consequently, the ERG agrees with the company that pooled evidence from inTandem1 and inTandem2 is the most appropriate primary dataset to assess both doses of sotagliflozin over 52 weeks, and to retain statistical power when the population is limited to the subgroup of patients with BMI $\geq$ 27 kg/m^2 in line with the likely marketing authorisation.

The proposed marketing authorisation was confirmed after the scope was finalised and is narrower than the population defined in the NICE final scope, because the CHMP asked the company to identify a subgroup of patients for whom the benefits of sotagliflozin would outweigh the increased risk of DKA. Evidence provided by the company in line with the proposed marketing authorisation showed a range of statistically significant but modest benefits of sotagliflozin 200 mg and 400 mg over insulin alone after a year of follow up (HbA_{1c}, body weight, measures of cardiovascular risk, insulin dose, and measures of diabetes distress and treatment satisfaction). Sotagliflozin increases the rate of genital mycotic infections and, less commonly, volume depletion and DKA, but there have been no fatal cases of DKA across the clinical trial programme and the preference for MDI in the UK may mean patients are at a lower risk than in the trials.

There was inconsistency in the magnitude of absolute and relative treatment effects for various outcomes across the range of analyses submitted, and there does not appear to be a consistent pattern by dose or length of follow-up. Moreover, the trials provide limited evidence of the durability of initial treatment effects – which appear to wane between 24 and 52 weeks for HbA_{1c} and improve for BMI and body weight – and they were not designed to determine long-term cardiovascular benefits. The ERG's clinical experts expressed concern that treatment may be continued indefinitely if there are no clear criteria for judging when a patient is no longer receiving benefit.

The ERG considers there to be some evidence for larger or more sustained benefits of the 400 mg dose compared with 200 mg for some outcomes (e.g. HbA_{1c}, bolus insulin dose) and there were differences in the frequency of some adverse effects. The company state that the 400 mg tablet will not be available at launch in the UK, but a cost-effectiveness analysis was requested with assumptions to account for the lack of escalation from 200 mg in the trials. The ERG highlights that, should

sotagliflozin be approved for use in the NHS, escalation to 400 mg would be possible by taking two 200 mg tablets, which would double the acquisition cost until the 400 mg tablet is available. The ERG's clinical experts expressed concern that clinicians might default to the higher dose when it becomes available unless differences between the doses are clarified and criteria are provided to judge patient suitability for the higher dose.

The ERG's clinical experts expect the judgement of suitability for sotagliflozin in UK clinical practice to be more selective than the clinical trials to maximise clinical benefit and minimise the risk of rare but serious side effects (e.g. DKA, volume depletion). However, investigation of patient subgroups was limited because the trial population had already been restricted to patients with BMI $\geq$ 27 kg/m^2 in line with the proposed marketing authorisation. The ERG expects that the preferred patient group outlined by its clinical experts (i.e. BMI > 30 kg/m^2, eGFR >60, insulin via MDI, HbA_{1c} > 8.5%, high cardiovascular risk, carbohydrate intake > 80 mg/day and willing to monitor blood glucose and urine ketones) to see larger benefits and lower risks than shown in the primary analyses, but these patients represent a small subset of the T1D population for whom sotagliflozin is likely to be licensed.

The economic analyses are heavily reliant on assumptions around the duration of treatment effects, beyond the 52-week data observed in the trials. This makes the results highly uncertain. Differences in the outputs of the CORE Diabetes Model (CDM) and the PRIME Diabetes Model add uncertainty to the plausibility of the results. The ERG considers clinical expert validation of the complication incidences to be necessary in order to mitigate this uncertainty.

The ERG considers that extending the treatment effects to 5 years to be an overestimation for HbA_{1c}, which may, therefore, underestimate the ICER. The other physiological parameters do not show a strong trend during the trial period and, therefore, these effects are potentially maintained for the duration of treatment.

Treatment duration is another area of uncertainty that needs to be considered when assessing the results. The company assumes that treatment would be withdrawn after 5 years as the effectiveness is reduced. The ERG considers that clinicians may maintain treatment beyond this period as there is uncertainty as to whether a patient may have a reduction in effects after treatment is withdrawn.

Overall, the ERG considers the CDM is likely to be a robust model given the extensive model validation. However, caution should be taken when assessing the results due to the structural uncertainty indicated by the results of the PRIME model, as well as the uncertainty in the short term observed treatment effects.

8.1 Implications for research

The ERG highlights the following key evidence gaps for sotagliflozin:

- There is currently no evidence for the safety and efficacy of sotagliflozin 400 mg when patients escalate from 200 mg, or appropriate analyses to inform when to escalate dose and in which patients;

- The long-term glycaemic and cardiovascular benefits of sotagliflozin at either dose are unproven, and would require a large trial with longer follow-up than the inTandem trial programme, or long-term collection of real-world data through existing registries where sotagliflozin is already in use;

- Routine collection of adverse event data for sotagliflozin is required to assess the risk of DKA and other rare but serious adverse events in a real-world setting where patient adherence to blood glucose and ketone monitoring may be lower than in a trial setting.

9 REFERENCES

1. Hammer M, Lammert M, Mejias SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. J Med Econ. 2009;12(4):281-90.

2. National Institute for Health and Care Excellence. Single Technology Appraisal: Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376] Final scope2018 5 Mar 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10376/documents/final-scope.

3. European Medicines Agency. CHMP summary of positive opinion for Zynquista 2019 [18 Mar 2019]. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/zynquista.

4. Diabetes.co.uk. Type 1 Diabetes2019 18 Mar 2019. Available from: https://www.diabetes.co.uk/type1-diabetes.html.

5. Aronoff SL, Berkowitz K, Shreiner B, Want L. Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. Diabetes Spectrum 2004;17(3):183-90.

6. Baxter M, Hudson R, Mahon J, Bartlett C, Samyshkin Y, Alexiou D, et al. Estimating the impact of better management of glycaemic control in adults with Type 1 and Type 2 diabetes on the number of clinical complications and the associated financial benefit (supplementary information online). Diabet Med. 2016;33(11):1575-81.

7. Sanofi. Data on file: Clinical Practice Research Datalink (CPRD) Analysis to support economic modelling activities in a UK-specific context. 2019.

8. National institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management: NICE guideline [NG17]2016 Feb 2019. Available from: https://www.nice.org.uk/guidance/ng17.

9. NHS Digital. National Diabetes Insulin Pump Audit, 2016-2017: England and Wales2017 5 Mar 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/insulin-pump-report-2016-17.

10. Lawton J, Rankin D, Cooke D, Elliott J, Amiel S, Heller S, et al. Patients' experiences of adjusting insulin doses when implementing flexible intensive insulin therapy: a longitudinal, qualitative investigation. Diabetes Res Clin Pract. 2012;98(2):236-42.

11. Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. Diabetes Care. 2006;29(7):1486-90.

12. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. Diabetes Care. 2008;31(11):2198-202.

13. Kilpatrick ES, Rigby AS, Atkin SL. Mean blood glucose compared with HbA1c in the prediction of cardiovascular disease in patients with type 1 diabetes. Diabetologia. 2008;51(2):365-71.

14. Ceriello A. Postprandial hyperglycemia and diabetes complications: is it time to treat? Diabetes. 2005;54(1):1-7.

15. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, Group DER. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial--revisited. Diabetes. 2008;57(4):995-1001.

16. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353(25):2643-53.

17. Cryer PE. The barrier of hypoglycemia in diabetes. Diabetes. 2008;57(12):3169-76.

18. Gerich JE. Physiology of glucose homeostasis. Diab Obs Metab. 2000;2(6):345-50.

19. Nathan DM, Bayless M, Cleary P, Genuth S, Gubitosi-Klug R, Lachin JM, et al. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. Diabetes. 2013;62(12):3976-86.

20. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions Complications (DCCT/EDIC) Research Group. Risk Factors for Cardiovascular Disease in Type 1 Diabetes. Diabetes. 2016;65(5):1370-9.

21. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH, et al. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care. 2008;31(7):1360-6.

22. Bode BW, Garg SK. The emerging role of adjunctive noninsulin antihyperglycemic therapy in the management of type 1 diabetes. Endocr Pract. 2016;22(2):220-30.

23. Graveling AJ, Frier BM. The risks of nocturnal hypoglycaemia in insulin-treated diabetes. Diabetes Res Clin Pract. 2017;133:30-9.

24. Walker AJ, Majzner RG, Zhang L, Wanhainen K, Long AH, Nguyen SM, et al. Tumor Antigen and Receptor Densities Regulate Efficacy of a Chimeric Antigen Receptor Targeting Anaplastic Lymphoma Kinase. Molecular therapy : the journal of the American Society of Gene Therapy. 2017;25(9):2189-201.

25. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32(7):1335-43.

26. Aragona M, Giannarelli R, Del Prato S. Intensive insulin treatment and postprandial control in Type 1 diabetes. Acta Biomed. 2005;76 Suppl 3:26-30.

27. Suh S, Kim JH. Glycemic Variability: How Do We Measure It and Why Is It Important? Diabetes Metab J. 2015;39(4):273-82.

28. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management (NG17) London: National Institute for Health and Care Excellence; 2015 [cited 2019 February]. Available from: https://www.nice.org.uk/guidance/ng17.

29. National institute for Health and Care Excellence. Single Technology Appraisal: Dapagliflozin, in combination with insulin, for treating type 1 diabetes [ID1478] Final Scope2018 11 Mar 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10374/documents/final-scope.

30. NHS Digital. National Diabetes Audit 20182018 5 Mar 2019. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/.

31. Petrie JR, Chaturvedi N, Ford I, Hramiak I, Hughes AD, Jenkins AJ, et al. Metformin in adults with type 1 diabetes: Design and methods of REducing with MetfOrmin Vascular Adverse Lesions (REMOVAL): An international multicentre trial. Diabetes Obes Metab. 2017;19(4):509-16.

32. Buse JB, Garg SK, Rosenstock J, Bailey TS, Banks P, Bode BW, et al. Sotagliflozin in Combination With Optimized Insulin Therapy in Adults With Type 1 Diabetes: The North American inTandem1 Study. Diabetes Care. 2018;41(9):1970-80.

33. Danne T, Cariou B, Banks P, Brandle M, Brath H, Franek E, et al. HbA1c and Hypoglycemia Reductions at 24 and 52 Weeks With Sotagliflozin in Combination With Insulin in Adults With Type 1 Diabetes: The European inTandem2 Study. Diabetes Care. 2018;41(9):1981-90.

34. Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. N Engl J Med. 2017;377(24):2337-48.

35. ClinicalTrials.gov. Dose-ranging Study in Patients With Type 1 Diabetes Mellitus (inTandem4) 2016 [8 Apr 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02459899.

36. ClinicalTrials.gov. Efficacy and Safety of Sotagliflozin in Young Adult Patients With Type 1 Diabetes Mellitus and Elevated Hemoglobin A1C 2016 [8 Apr 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02383940.

37. Siddiqui O, Hung HM, O'Neill R. MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat. 2009;19(2):227-46.

38. Fisher L, Hessler D, Polonsky W, Strycker L, Masharani U, Peters A. Diabetes distress in adults with type 1 diabetes: Prevalence, incidence and change over time. J Diabetes Complications. 2016;30(6):1123-8.

39. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. Science (New York, NY). 2018;359(6382):1361-5.

40. Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009;169(14):1307-16.

41. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE Diabetes Model. Value Health. 2014;17(6):714-24.

42. Clarke PM, Gray AM, Briggs A, Farmer AJ, Fenn P, Stevens RJ, et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia. 2004;47(10):1747-59.

43. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Gudbjornsdottir S, Swedish National Diabetes R. A new model for 5-year risk of cardiovascular disease in Type 1 diabetes; from the Swedish National Diabetes Register (NDR). Diabet Med. 2011;28(10):1213-20.

44. Zgibor JC, Ruppert K, Orchard TJ, Soedamah-Muthu SS, Fuller J, Chaturvedi N, et al. Development of a coronary heart disease risk prediction model for type 1 diabetes: the Pittsburgh CHD in Type 1 Diabetes Risk Model. Diabetes Res Clin Pract. 2010;88(3):314-21.

45. Lung TW, Clarke PM, Hayes AJ, Stevens RJ, Farmer A. Simulating lifetime outcomes associated with complications for people with type 1 diabetes. Pharmacoeconomics. 2013;31(6):509-18.

46. Klein BE, Klein R, McBride PE, Cruickshanks KJ, Palta M, Knudtson MD, et al. Cardiovascular disease, mortality, and retinal microvascular characteristics in type 1 diabetes: Wisconsin epidemiologic study of diabetic retinopathy. Arch Intern Med. 2004;164(17):1917-24.

47. Gordin D, Waden J, Forsblom C, Thorn L, Rosengard-Barlund M, Tolonen N, et al. Pulse pressure predicts incident cardiovascular disease but not diabetic nephropathy in patients with type 1 diabetes (The FinnDiane Study). Diabetes Care. 2011;34(4):886-91.

48. Koivisto VA, Stevens LK, Mattock M, Ebeling P, Muggeo M, Stephenson J, et al. Cardiovascular disease and its risk factors in IDDM in Europe. EURODIAB IDDM Complications Study Group. Diabetes Care. 1996;19(7):689-97.

49. Lind M, Bounias I, Olsson M, Gudbjornsdottir S, Svensson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet. 2011;378(9786):140-6.

50. Tesfaye S, Chaturvedi N, Eaton SE, Ward JD, Manes C, Ionescu-Tirgoviste C, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med. 2005;352(4):341-50.

51. Jonasson JM, Ye W, Sparen P, Apelqvist J, Nyren O, Brismar K. Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. Diabetes Care. 2008;31(8):1536-40.

52. Sahakyan K, Klein BE, Lee KE, Myers CE, Klein R. The 25-year cumulative incidence of lower extremity amputations in people with type 1 diabetes. Diabetes Care. 2011;34(3):649-51.

53. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XXII the twenty-five-year progression of retinopathy in persons with type 1 diabetes. Ophthalmology. 2008;115(11):1859-68.

54. Ford JA, Lois N, Royle P, Clar C, Shyangdan D, Waugh N. Current treatments in diabetic macular oedema: systematic review and meta-analysis. BMJ Open. 2013;3(3).

55. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118(4):615-25.

56. Parsaik AK, Carter RE, Pattan V, Myers LA, Kumar H, Smith SA, et al. Population-based study of severe hypoglycemia requiring emergency medical service assistance reveals unique findings. J Diabetes Sci Technol. 2012;6(1):65-73.

57. Wang ZH, Kihl-Selstam E, Eriksson JW. Ketoacidosis occurs in both Type 1 and Type 2 diabetes--a population-based study from Northern Sweden. Diabet Med. 2008;25(7):867-70.

58. Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. Diabetologia. 1994;37(3):278-85.

59. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. Med Decis Making. 2016;36(8):1020-33.

60. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462-70.

61. Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Curr Med Res Opin. 2006;22(8):1523-34.

62. Alva M, Gray A, Mihaylova B, Clarke P. The effect of diabetes complications on health-related quality of life: the importance of longitudinal data to address patient heterogeneity. Health Econ. 2014;23(4):487-500.

63. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 [Feb 2019]. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.

64. Ara R, Wailoo AJ. NICE DSU Technical Support Document 12: The use of health state utility values in decision models2011. Available from: http://www.nicedsu.org.uk.

65. Curtis L, Burns A. Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury. 2017.

66. British National Formulary (BNF). BNF Online 2018 [Feb 2019]. Available from: https://www.bnf.org/.

67. Hatah E, Braund R, Tordoff J, Duffull SB. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol. 2013;77(1):102-15.

68. Pulman J, Buckley E. Assessing the efficacy of different upper limb hemiparesis interventions on improving health-related quality of life in stroke patients: a systematic review. Top Stroke Rehabil. 2013;20(2):171-88.

69. Anonymous. CAR T Cells Infiltrate Brain, Target Tumors. Cancer Discov. 2017;7(9):926.

70. NHS. North Central London Joint Formulary Committee. Guideline for blood glucose & ketone monitoring for adults with diabetes. 2018 [cited 2018 February]. Available from: https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/6_Blood_glucose_ketone_monitoring.pdf.

71. NHS Improvement. National schedule of reference costs 2016/2017 2016 [Feb 2019]. Available from: https://improvement.nhs.uk/resources/reference-costs/.

72. Wolowacz S, Pearson I, Shannon P, Chubb B, Gundgaard J, Davies M, et al. Development and validation of a cost-utility model for Type 1 diabetes mellitus. Diabet Med. 2015;32(8):1023-35.

73. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Glibenclamide-induced hypoglycemic coma in 51 older patients with type 2 diabetes mellitus. J Am Geriatr Soc. 1999;47(5):631-3.

74. MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C, Jerums G. Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. Intern Med J. 2002;32(8):379-85.

75. V. Foos, J. Palmer, D. Grant, A. Lloyd, M. Lamotte, P. McEwan. THE IMS CORE DIABETES MODEL USER GUIDE: A Guide to Preparing and Performing Analyses Using the IMS CORE Diabetes Model. 2012.

10 APPENDICES

10.1 Baseline characteristics

Table 49. Key baseline characteristics for the subset of each inTandem trial with BMI ≥ 27 kg/m^2

	inTandem1			inTandem2			inTandem3	
	SOTA 200mg	**SOTA 400mg**	**Insulin alone**	**SOTA 200mg**	**SOTA 400mg**	**Insulin alone**	**SOTA 400mg**	**Insulin alone**
N (% of ITT)	**N = 170 (64.6)**	**N= 175 (66.8)**	**N= 174 (64.9)**	**N = 135 (51.7)**	**N = 138 (52.5)**	**N = 124 (48.1)**	**N = 379 (54.2)**	**N = 370 (52.6)**
Age, years mean (SD)	47.0 (13.52)	46.6 (12.02)	44.7 (11.80)	44.4 (11.51)	43.9 (11.82)	41.2 (13.47)	44.9 (13.39)	44.7 (12.51)
Female sex, n (%)	85 (50.0)	91 (52.0)	82 (47.1)	63 (46.7)	68 (49.3)	61 (49.2)	181 (47.8)	188 (50.8)
White ethnicity, %	153 (90.0)	163 (93.1)	164 (94.3)	127 (94.2)	130 (94.2)	119 (96.0)	340 (89.7)	334 (90.3)
Duration of diabetes < 20 years ≥ 20 to 40 years ≥ 40 years	62 (36.5) 85 (50.0) 23 (13.5)	65 (37.1) 89 (50.9) 21 (12.0)	68 (39.1) 89 (51.1) 17 (9.8)	72 (53.3) 55 (40.7) 8 (5.9)	89 (64.5) 40 (29.0) 9 (6.5)	70 (56.5) 44 (35.5) 10 (8.1)	195 (51.5) 152 (40.1) 32 (8.4)	188 (50.8) 152 (41.1) 30 (8.1)
HbA_{1c}, % (SD)	7.69 (0.70)	7.57 (0.71)	7.54 (0.71)	7.75 (0.80)	7.72 (0.79)	7.73 (0.82)	8.19 (0.88)	8.21 (0.93)
FPG, mmol/L (SD)	160.32 (72.51)	146.82 (63.43)	156.02 (65.37)	167.41 (72.14)	168.39 (70.88)	159.15 (67.69)	162.98 (70.09)	162.97 (65.99)
Weight, kg (SD)	96.08 (15.36)	94.17 (15.65)	95.36 (15.82)	92.92 (15.34)	93.00 (16.48)	92.58 (14.44)	93.17 (14.40)	92.22 (15.08)
BMI, mg/kg2 (SD)	32.97 (4.45)	32.36 (4.20)	32.32 (4.21)	31.89 (4.19)	31.45 (3.80)	31.61 (4.27)	31.94 (3.96)	31.87 (4.18)
SBP, mmHg (SD)	122.1 (15.08)	121.8 (14.67)	122.5 (12.62)	127.6 (14.73)	125.9 (13.82)	126.8 (15.96)	125.2 (14.51)	124.5 (14.32)
DBP, mmHg (SD)	78.0 (9.37)	77.2 (8.15)	77.6 (8.09)	80.3 (9.61)	78.5 (8.09)	78.5 (8.39)	78.1 (8.49)	78.4 (8.93)
SBP ≥130 mm Hg, no. (%)	46 (27.1)	50 (28.6)	48 (27.6)	55 (40.7)	58 (42.0)	51 (41.1)	133 (35.1)	132 (35.7)
Total insulin dose, IU/day (SD)	78.34 (47.01)	73.38 (41.39)	79.41 (45.26)	73.23 (32.74)	70.58 (31.16)	75.76 (35.69)	66.46 (31.28)	68.25 (32.73)
Basal insulin dose, IU/day (SD)	41.77 (26.34)	38.29 (20.21)	40.73 (21.38)	36.09 (17.87)	33.90 (14.80)	36.37 (15.98)	34.26 (18.27)	34.41 (17.46)
Bolus insulin dose, IU/day (SD)	36.57 (26.57)	35.09 (25.73)	38.67 (28.00)	37.13 (20.17)	36.62 (22.29)	39.38 (25.93)	32.19 (19.25)	33.84 (21.48)
Insulin via pump, n (%)	103 (60.6)	112 (64.0)	104 (59.8)	37 (27.4)	35 (25.4)	34 (27.4)	156 (41.2)	156 (42.2)

Data are mean (SD) unless otherwise indicated. Where 3 decimal places were reported by the company, the ERG has limited to 2.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose, HbA_{1c}, glycated haemoglobin; ITT, intention-to-treat population; IU, international unit; n, number of patients; SBP, systolic blood pressure; SOTA, sotagliflozin; SD, standard deviation.

10.2 Concomitant medications in the phase III inTandem trials

Table 50. Summary of non-insulin concomitant medications used by >10% of patients in the inTandem phase III studies (randomised population with BMI ≥ 27 kg/m^2; adapted from clarification response appendix A, Tables 1–3)

WHO ATC Level 2 (Therapeutic Class)	inTandem1 n (%)	inTandem2 n (%)	inTandem3 n (%)
Lipid modifying agents	291 (56.1%)	154 (38.8%)	385 (51.4%)
Agents acting on the renin-angiotensin system	273 (52.6%)	167 (42.1%)	353 (47.1)
Vitamins	243 (46.8%)	65 (16.4%)	170 (22.7%)
Analgesics	173 (33.3%)	110 (27.7%)	172 (23.0%)
Antithrombotic agents	163 (31.4%)	76 (19.1%)	157 (21.0%)
Anti-inflammatory and antirheumatic products	162 (31.2%)	77 (19.4%)	118 (15.8%)
Thyroid therapy	148 (28.5%)	80 (20.2%)	164 (21.9%)
Antibacterials for systemic use	145 (27.9%)	100 (25.2%)	114 (15.2%)
Psychoanaleptics	133 (25.6%)	55 (13.9%)	136 (18.2%)
Antihistamines for systemic use	105 (20.2%)	31 (7.8%)	88 (11.7%)
Drugs for acid related disorders	95 (18.3%)	62 (15.6%)	111 (14.8%)
Cough and cold preparations	81 (15.6%)	38 (9.6%)	42 (5.6%)
Mineral supplements	80 (15.4%)	10 (2.5%)	58 (7.7%)
Diuretics	77 (14.8%)	61 (15.4%)	89 (11.9%)
Nasal preparations	75 (14.5%)	19 (4.8%)	39 (5.2%)
Sex hormones and modulators of the genital system	75 (14.5%)	57 (14.4%)	97 (13.0%)
Psycholeptics	66 (12.7%)	18 (4.5%)	60 (8.0%)
Drugs for obstructive airway diseases	58 (11.2%)	22 (5.5%)	63 (8.4%)
Calcium channel blockers	55 (10.6%)	45 (11.3%)	74 (9.9%)
Anti-anaemic preparations	52 (10.0%)	11 (2.8%)	38 (5.1%)
Beta blocking agents	41 (7.9%)	68 (17.1%)	97 (13.0%)

Notes: The denominator for percentages is the number of patients in the Randomized Population for each treatment group and concomitant Medications are defined as those taken between first dose and last dose of double-blind study treatment.
Abbreviations: n, number.

Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376]

ADDENDUM TO THE ERG REPORT

May 2019

This report was commissioned by the NIHR HTA Programme as project number 127657

BMJ Technology Assessment Group

1 INTRODUCTION

The Evidence Review Group (ERG) did not have full working access to the CORE Diabetes Model (CDM) in time to include results for the ERG's preferred base case analysis within the ERG report. This addendum, therefore, provides these results now that the ERG has the required access.

The key changes that the ERG made to the company's base case were:

1. Setting the cohort to the pooled trial population;
2. Applying Hammer *et al.* 2009[1] costs for severe hypoglycaemic events an assuming 50% of patients are hospitalised;
3. Reducing the HbA_{1c} treatment effect to just 1 year;
4. Utilities based on the 2019 ScHARR report (provided by the company at clarification); and,
5. Applying a multiplicative approach to utilities.

The ERG also conducted some scenarios around this base case with the following changes:

1. Using the National Diabetes Audit (NDA)[2] cohort;
2. Using the company's preferred utilities;
3. Assuming the HbA1c treatment effect lasts a further year; and
4. Using the minimum value approach for utilities.

The results of these analyses are given in Section 2 and a discussion of the results is given in Section 3.

2 RESULTS

The results of the ERG base case analysis, as described in Section 1, are given in Section 2.1. The mean results are outlined in Table 1 and a scatterplot, displaying the spread of the samples produced from the 1,000 simulations of the model, is given in Figure 1. The mean results of the scenario analyses described in Section 1, are given in Table 2 to Table 5 in Section 2.2. An assessment of the impact of diabetic ketoacidosis (DKA) on the model results is discussed in Section 2.3, with results of an additional scenario analysis to remove these events given in Table 6.

2.1 ERG's preferred base case

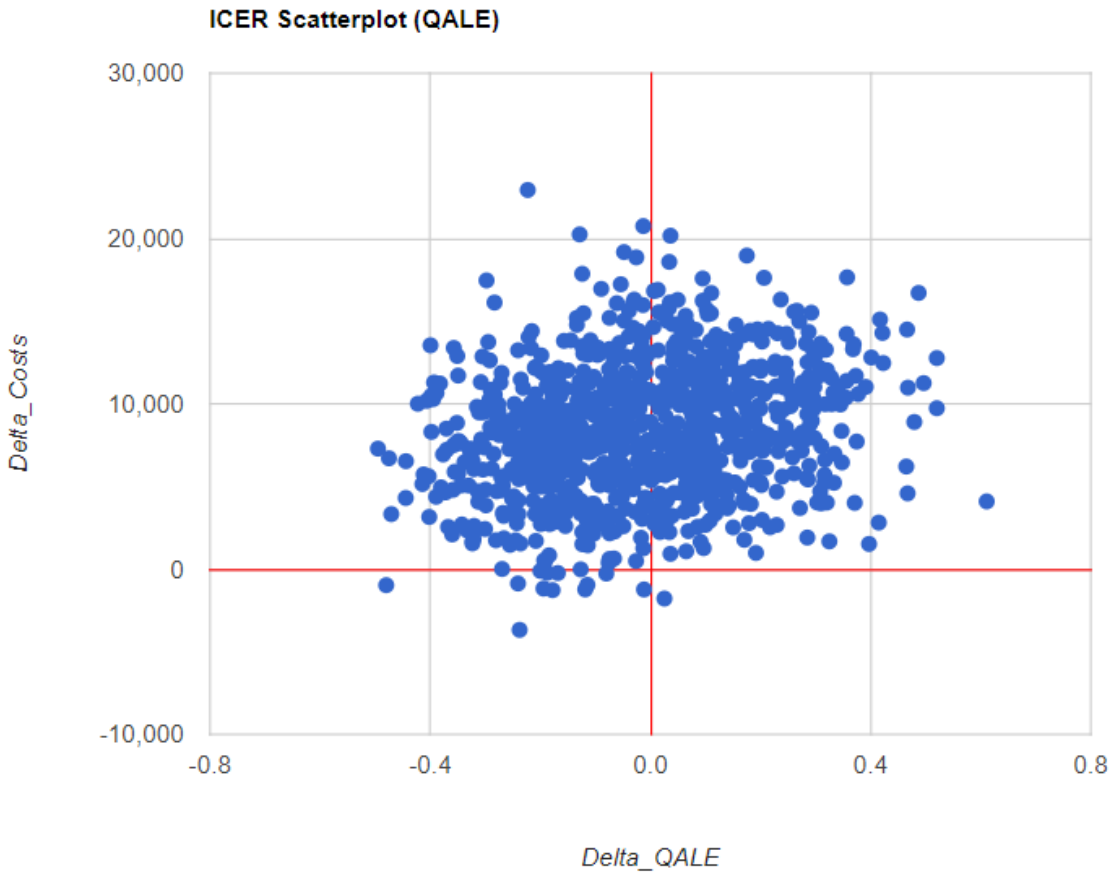
The results of the ERG's changes are presented, incorporating each change cumulatively, in Table 1. An incremental cost effectiveness ratio (ICER) for each individual change compared to the base case is also given.

Table 1. ERG base case ICER (CDM).

	Results per patient	**Insulin alone (1)**	**Sotagliflozin 200 mg in combination with insulin (2)**	**Incremental value (2-1)**
	Company's base case			
	Total costs	£78,731	£78,940	£209
	QALYs	8.695	8.803	0.108
	ICER	-		£1,934
(1)	**Setting the cohort to the pooled trial population (CQ B2)**			
	Total costs	£71,327	£72,277	£950
	QALYs	10.500	10.554	0.055
	ICER (compared with base case)	-		£17,327
	ICER with all changes incorporated (1)	-		£17,327
(2)	**Applying Hammer *et al.* 2009[1] costs for severe hypoglycaemic events an assuming 50% of patients are hospitalised**			
	Total costs	£75,101	£75,433	£332
	QALYs	8.695	8.803	0.108
	ICER (compared with base case)	-		£3,073
	ICER with all changes incorporated (1) + (2)	-		£19,497
(3)	**Reducing the HbA1c treatment effect to just 1 year**			
	Total costs	£78,735	£86,676	£7,942
	QALYs	8.695	8.736	0.041
	ICER (compared with base case)	-		£196,087
	ICER with all changes incorporated (1) + (2) + (3)	-		£1,011,447

(4)	**Utilities based on the 2019 ScHARR report (provided by the company at clarification)**			
	Total costs	£78,731	£78,940	£209
	QALYs	12.346	12.412	0.066
	ICER (compared with base case)	-		£3,148
	ICER with all changes incorporated (1) + (2) + (3) + (4)	-		Sotagliflozin dominated
(5)	**Applying a multiplicative approach to utilities**			
	Total costs	£78,731	£78,940	£209
	QALYs	9.179	9.300	0.121
	ICER (compared with base case)	-		£1,719
	ERG's preferred base case ICER with all changes incorporated (1) + (2) + (3) + (4) + (5)	-		Sotagliflozin dominated
Abbreviation used in the table: CQ, clarification question; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.				

Figure 1. Scatterplot showing 1,000 simulations of the model for the ERG's preferred base case analysis (CDM).



2.1.1 Comparison of CDM and PRIME results

The company's base case analysis resulted in a much lower ICER in the CDM compared to the equivalent analysis using PRIME, with ICERs of £1,934 and £18,117 per QALY, respectively. The scenario that changed the population to represent the pooled trial with a BMI of greater than or equal to 27kg/m^2, increased the ICER in the CDM to £17,327 per QALY. In PRIME, however, the equivalent change caused a reduction in the ICER to £16,539 per QALY. It's not clear to the ERG exactly why this is the case. Another change that impacts in opposing directions in the two models was the multiplicative application of utilities. In the CDM the ICER reduced to £1,719, whereas in PRIME the ICER increased to £22,359 per QALY. Due to the "black box" nature of the two models, it is difficult to determine exactly why the changes have such dissimilar effects on the results.

The other changes, including the application of the Hammer *et al.* 2009[1] costs for severe hypoglycaemic events while assuming 50% of patients will be hospitalised, and the application of utilities from the ScHARR 2019 report provided by the company at clarification, resulted in similar changes to the ICERs, although the ScHARR utilities caused a slightly greater reduction in QALYs in the CDM than in PRIME.

The ERG notes that comparable analyses could not be performed in CDM and PRIME with regard to the ERG's preferred application of HbA_{1c} treatment effects. The ERG, therefore, cannot fully assess any differential impact that this may have between the two models.

2.2 ERG scenario analyses

Table 2. Scenario 1: Using NDA cohort (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£75,105	29.78	12.78	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£83,169	29.81	12.81	£8,064	-0.032	0.027	£296,476

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 3. Scenario 2: Using the company's preferred utilities (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	11.13	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£76,048	30.56	11.14	£8,395	-0.074	0.006	£1,311,720

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 4. Scenario 3: HbA_{1c} treatment effect extended to 3 years (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	12.98	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£75,878	30.58	12.98	£8,224	-0.053	-0.005	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. a Undiscounted							

Table 5. Scenario 4: Minimum value approach for utilities (CDM).

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	12.40	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£76.048	30.56	12.38	£8,395	-0.074	-0.015	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. a Undiscounted							

2.3 Impact of diabetic ketoacidosis (DKA) events

Within the pooled subpopulation with a body mass index (BMI) ≥ 27 kg/m^2, 2.6%, 3.5% and 0.3% of patients receiving sotagliflozin 200 mg, sotagliflozin 400mg and insulin alone had at least one episode of DKA during 52 weeks of treatment. Based on these results, the DKA event rates per 100 patient years applied in the CDM were 3.2 for sotagliflozin 200 mg and 0.4 for insulin alone.

DKA events can have an important impact on costs, utilities as well as the risk of mortality. In the company's base case analysis and the ERG's preferred base case analysis, the cost to treat a DKA event (£1,556) was estimated from NHS Reference Costs 2016-17, the disutility (-0.0091) was estimated from Peasgood *et al.* 2016 and the risk of mortality (0.05% per year) was estimated from Wolowacz *et al*. 2015.[2-4]

To explore the impact of DKA events in the model, the ERG ran an analysis excluding DKA events. The impact of this was large and switched the incremental quality-adjusted life years (QALYs) from negative to positive in favour of sotagliflozin. As a result, sotagliflozin was no longer dominated by insulin. However, the ICER is still above the standard upper willingness-to-pay threshold of £30,000 per QALY used by NICE. The results of this analysis are given in Table 6.

Table 6. ERG base case ICER with and without DKA events (CDM).

Results per patient	Insulin alone (1)	Sotagliflozin 200 mg in combination with insulin (2)	Incremental value (2-1)
ERG's preferred base case			
Total costs	£67,653	£76,048	£8,395
QALYs	12.981	12.965	-0.016
ICER	-		Sotagliflozin dominated
ERG's preferred base case excluding DKA events			
Total costs	£67,464	£76,669	£9,204
QALYs	12.977	13.051	0.054
ICER	-		£171,401
Abbreviation used in the table: DKA, diabetic ketoacidosis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.			

3 TECHNICAL TEAM PREFERRED ANALYSIS

The NICE technical team for this appraisal specified their preferred base case analysis to be largely in line with the ERG's preferred analysis but with a change to the application of treatment discontinuation. The change applied the treatment discontinuation rates observed in the pooled inTandem trials for the first year followed by treatment discontinuation for all patients after 2 years. This is in contrast to the ERG's assumption that treatment is continued for 5 years for all patients, as clinical expert opinion sought by the ERG suggested that treatment may continue even after the treatment effect returns to the baseline values.

To apply appropriate costs with treatment discontinuation incorporated, the ERG reduced the cost of sotagliflozin by the proportion who discontinued in the first year. After this time, treatment costs in the sotagliflozin group were set equal to the insulin-only group. The proportion who discontinued was based on discontinuation due to treatment-emergent adverse events (TEAEs), as data on overall discontinuation was not available. The proportion who discontinued due to TEAEs in the sotagliflozin group of the pooled inTandem trial population used for the treatment effectiveness, was 4.3%. The results of this analysis are given in Table 7.

The ERG also conducted a scenario to test the sensitivity of the rates of DKA for the NICE preferred base case analysis by removing all DKA events from each treatment group. The results of this are provided in Table 8.

Table 7. NICE technical team preferred base case.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,653	30.63	12.98	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£68,085	30.56	12.97	£431	-0.047	-0.016	Dominated

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Table 8. NICE technical team preferred base case without DKA events.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£67,464	30.67	13.00	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£68,647	30.80	13.05	£1,182	0.056	0.054	£22,017

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4 DISCUSSION

The results of the ERG's preferred base case are very different to the company's preferred base case. The ERG's results show that sotagliflozin is dominated by insulin alone, in contrast to the company's ICER of £1,934 per quality-adjusted life-year QALY, which was well below the standard upper willingness-to-pay threshold of £30,000 per QALY used by NICE.

The reason for such contrasting results is that the overall QALY gain, even in the company's base case analysis, is not large, with an increase of 0.108. Although the ERG considers that this value is likely to be overestimated because of the potentially implausible extrapolations of treatment effects beyond the trial period, this is still a relatively modest benefit. This value represents the margin, in terms of QALYs, between the company's apparently cost-effective ICER of £1,934 per QALY and an infinite ICER, thus, demonstrating how sensitive the model results are to any changes that may reduce this QALY gain.

The ERG's preferred base case ICER, however, removes this benefit entirely and shows that insulin alone generates a greater QALY yield. The incremental value for sotagliflozin compared to insulin alone in the ERG's preferred base case was -0.016. The reason for this is that sotagliflozin has both positive and negative treatment effects that can impact on the QALYs gained. The key parameter driving the positive benefits for sotagliflozin is the improvement, at least in the short term, of HbA_{1c} levels. However, sotagliflozin treatment increases the risk of ketoacidosis, which can be fatal. Given the relatively modest difference in treatment effects with sotagliflozin or insulin, subtle differences in assumptions can flip the QALY difference to be either positive or negative.

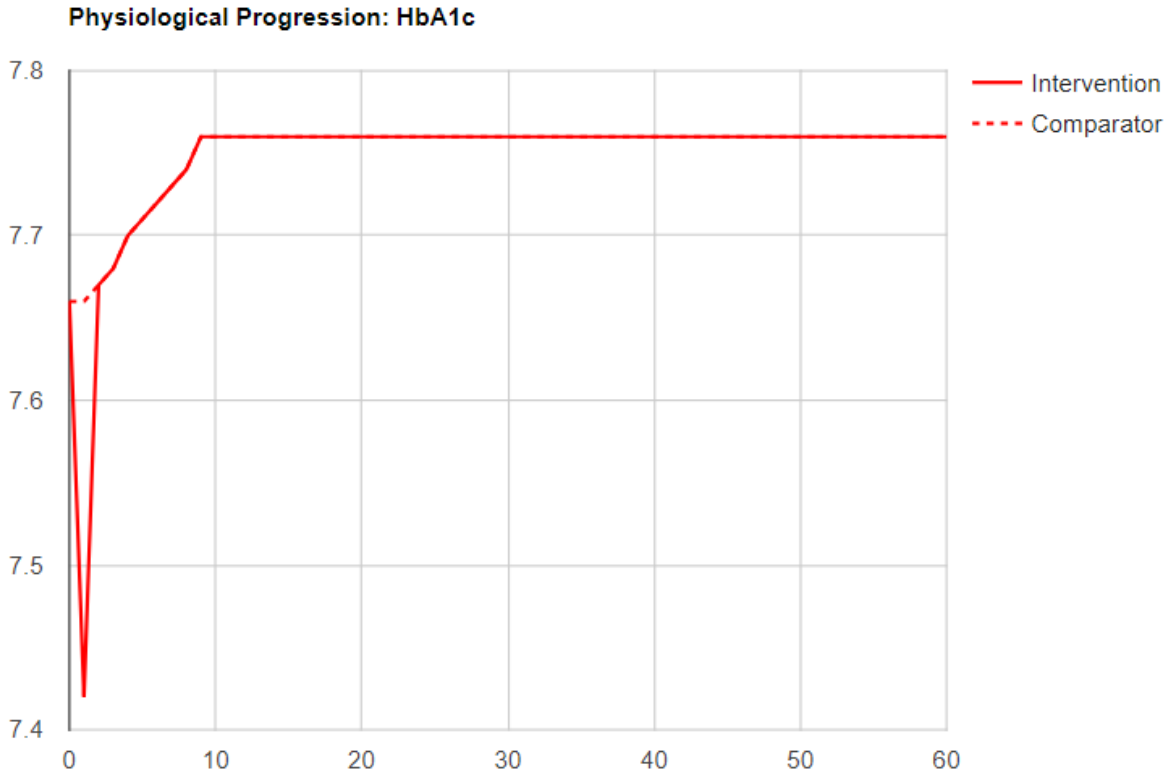
The ERG considers the company to have potentially overestimated the benefits in terms of HbA_{1c}, as the trial data appear to show a trend back towards the insulin alone group. If the observed trend continues beyond the trial period (1-year), then the treatment will be lost by approximately the end of the second year. The ERG, therefore, chose to reduce the duration of effect for HbA_{1c} in its preferred base case to return to the insulin alone group by the end of the second year. The ERG notes that the model has annual cycles and, therefore, it does not capture the initial decreasing and then increasing effect within the first and second years, respectively. It only takes the values at baseline, year 1 and year 2, from which point on the difference in treatment effect is kept constant at zero. This limitation may, therefore, not fully capture the treatment effect accurately. Other physiological parameters did not show a clear trend over the trial period, therefore, the ERG assumed that these effects were maintained for the duration of treatment as the company did in their preferred analysis (Appendix A).

The ERG notes a limitation in the results of its preferred base case analysis being that the body mass index (BMI) disutility based on the ScHARR 2019 report could not be implemented within the time

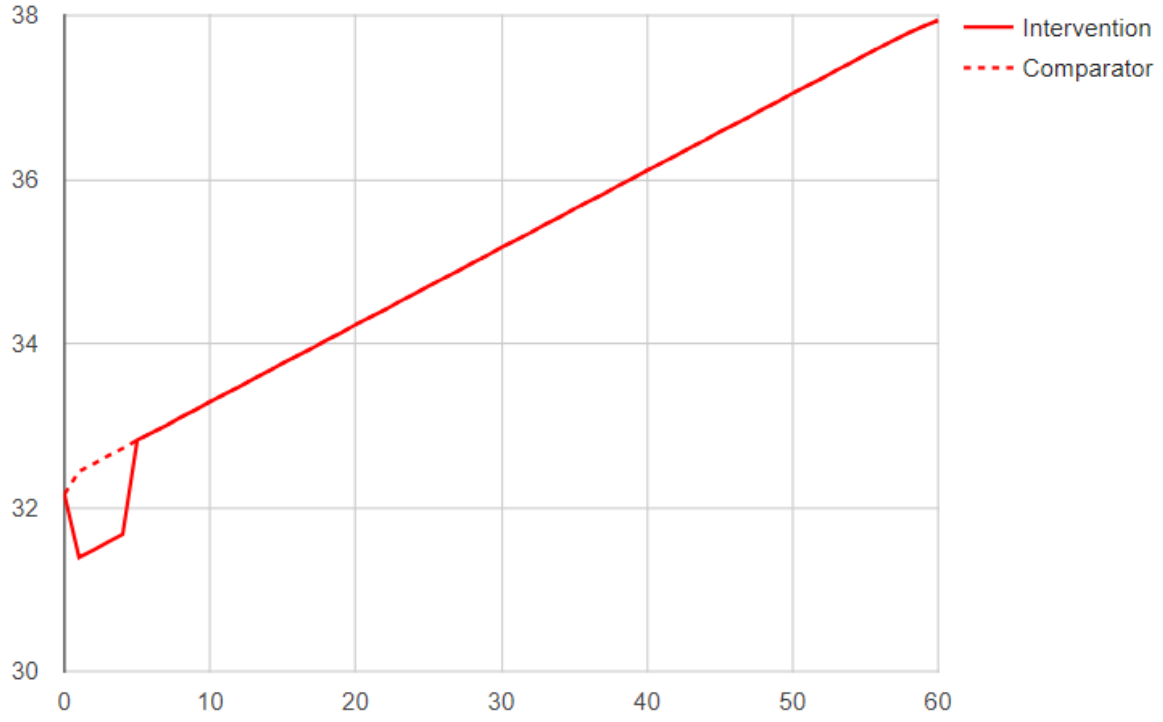
frame as it required manual input for each BMI value between 25 and 50 in increments of 0.1. However, as the disutility per unit change in BMI (-0.0052) compared to the company's value (-0.0028) was not greatly different, and the impact is only applied in the first 5 years, the ERG considers this unlikely to have an important impact on the results.

APPENDICES

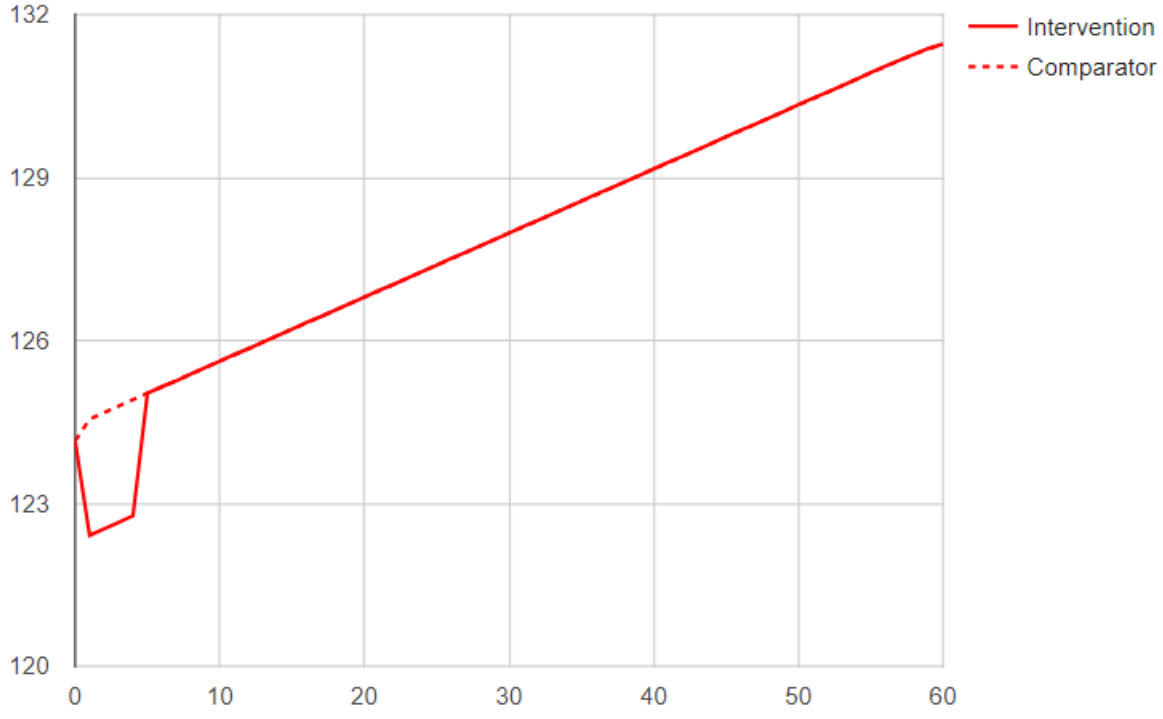
A. Progression graphs for physiological parameters in ERG's base case analysis



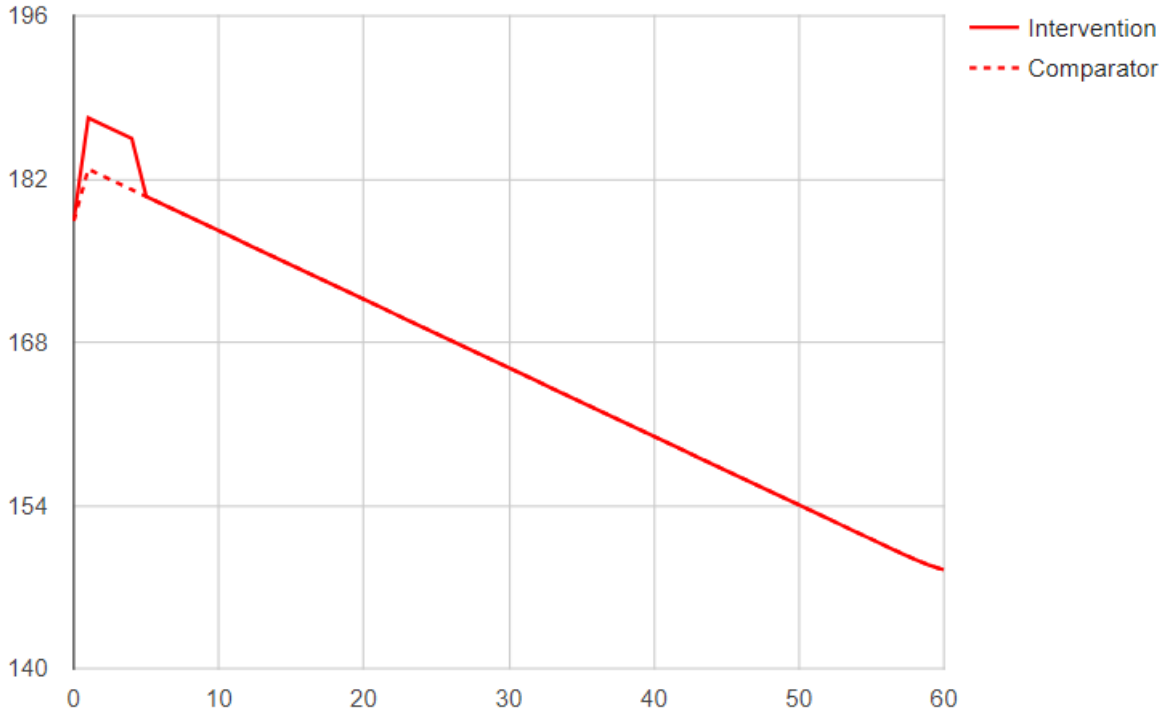
Physiological Progression: BMI



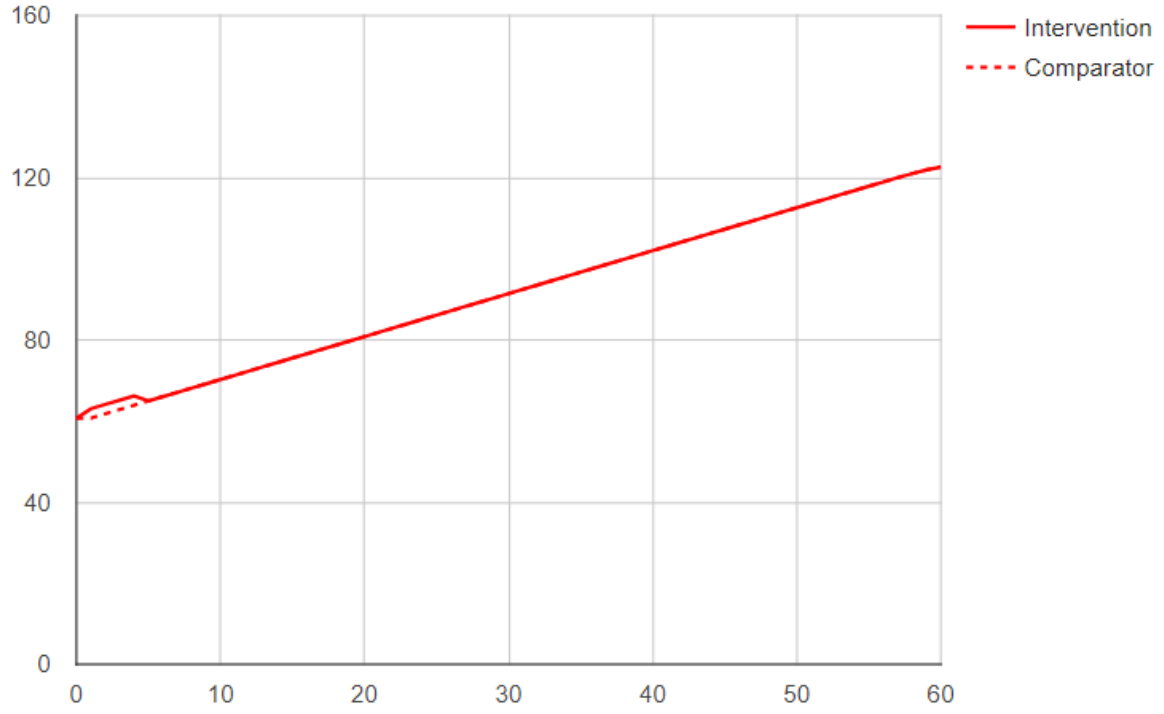
Physiological Progression: SBP



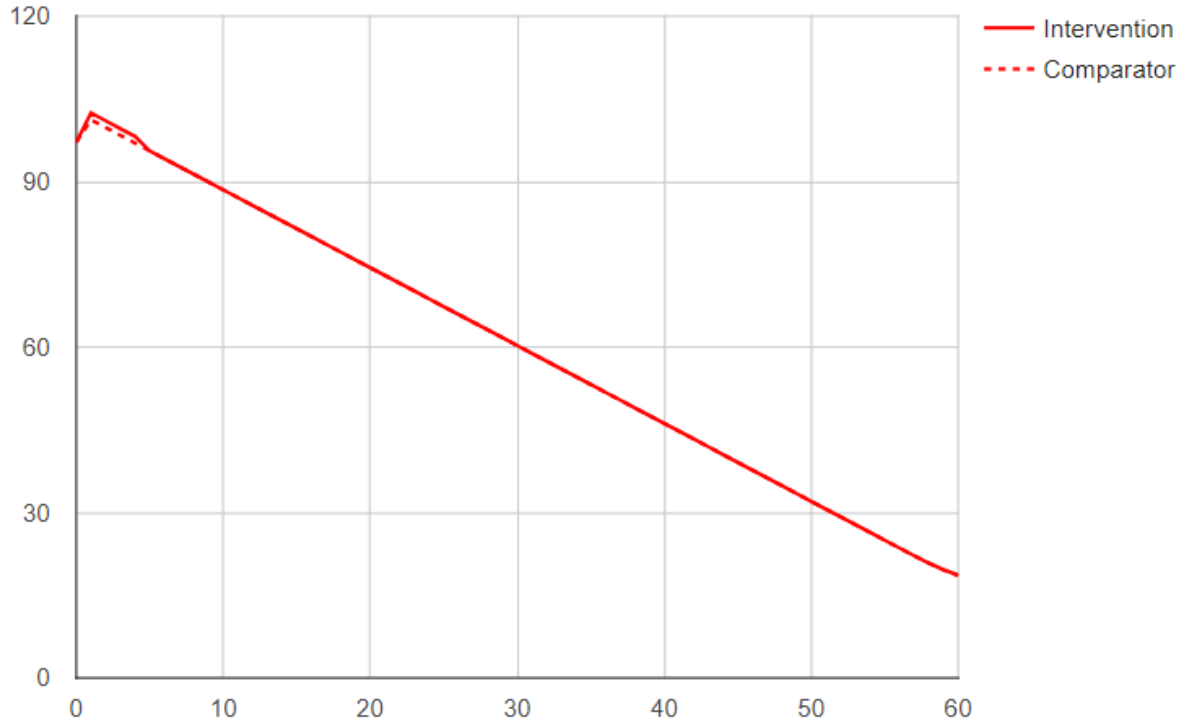
Physiological Progression: Total Cholesterol



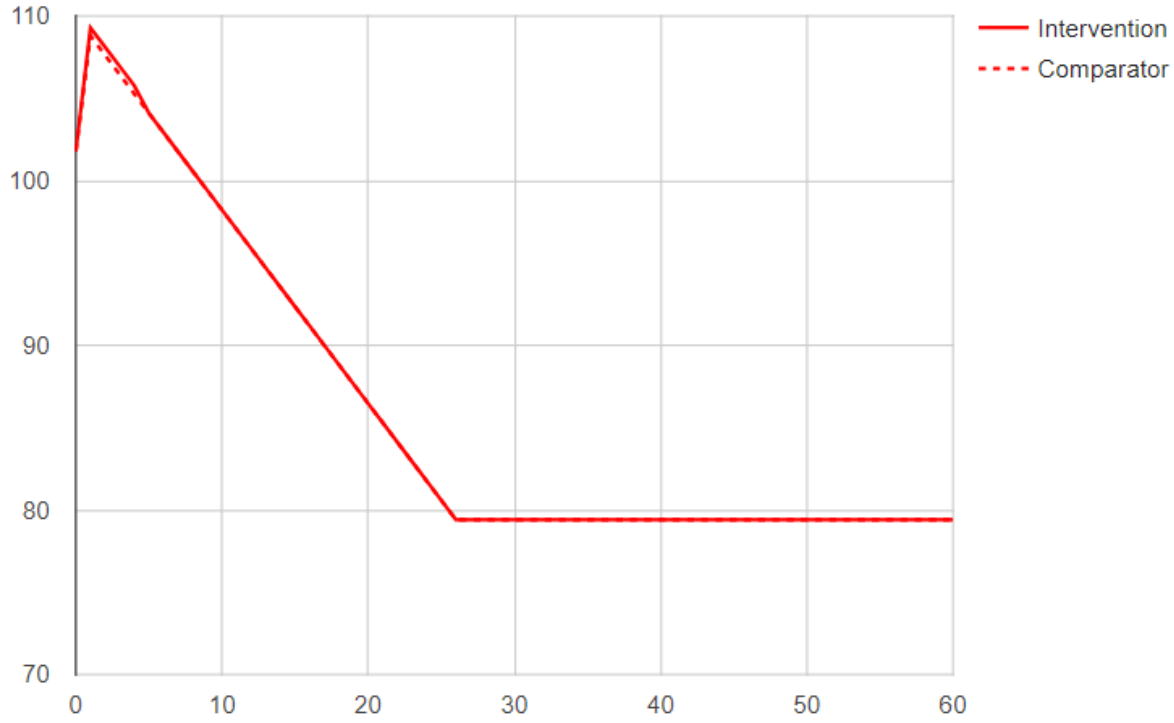
Physiological Progression: HDL

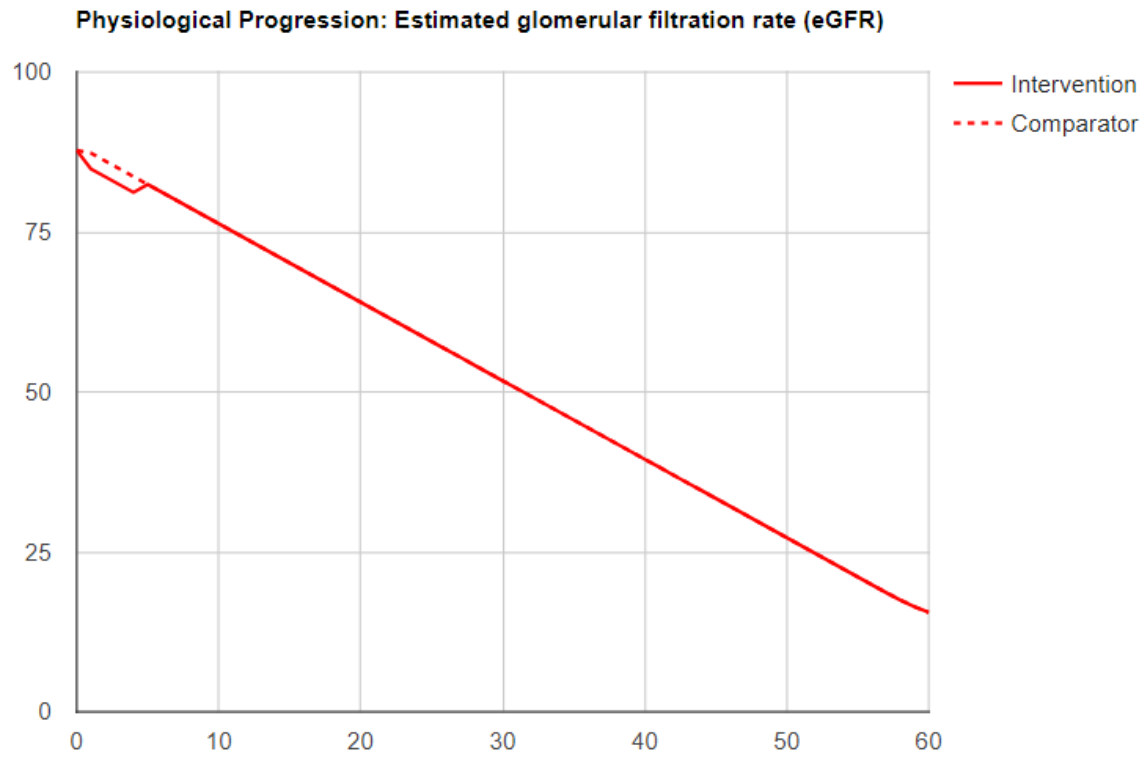


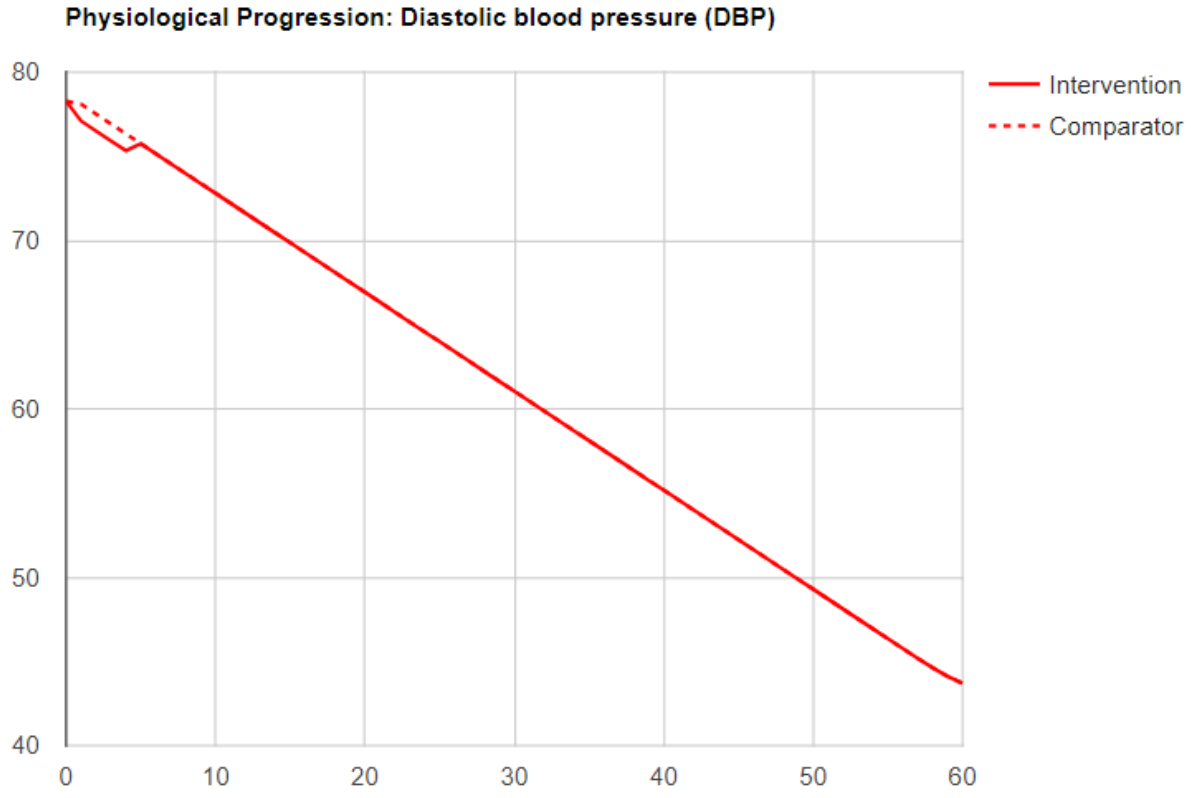
Physiological Progression: LDL



Physiological Progression: Triglyceride

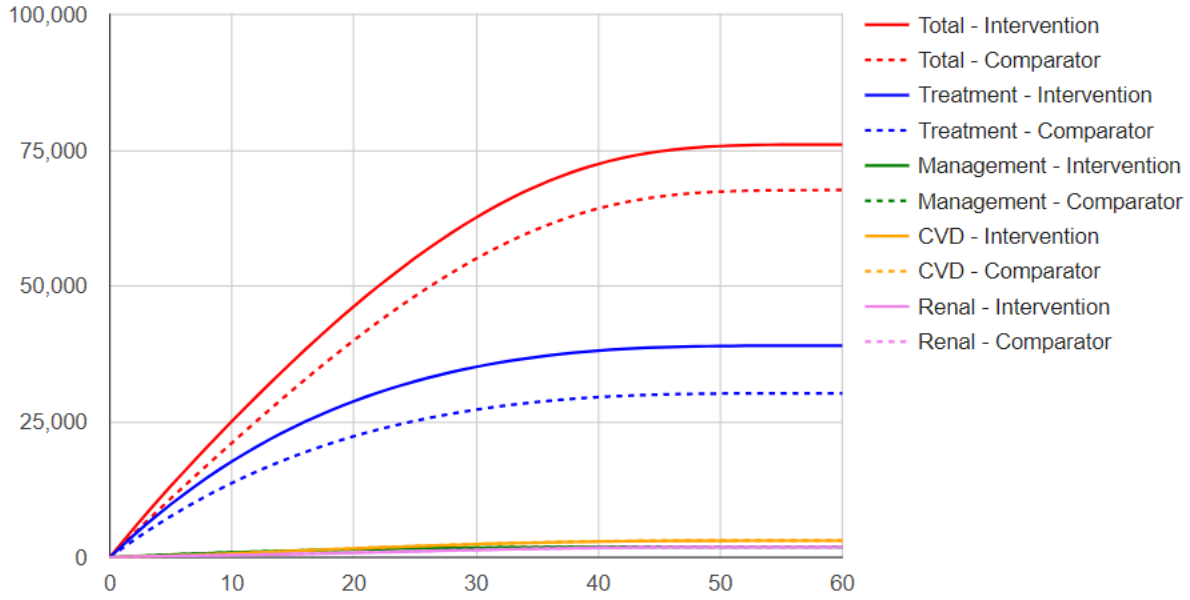




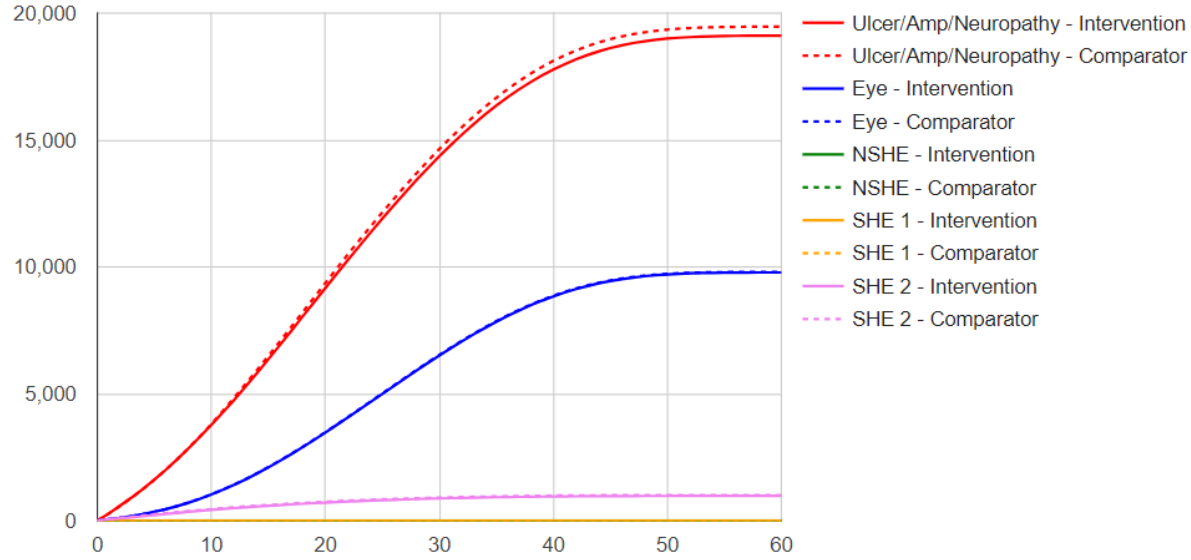


B. Breakdown of costs and event incidences graphs for the ERG's preferred base case analysis

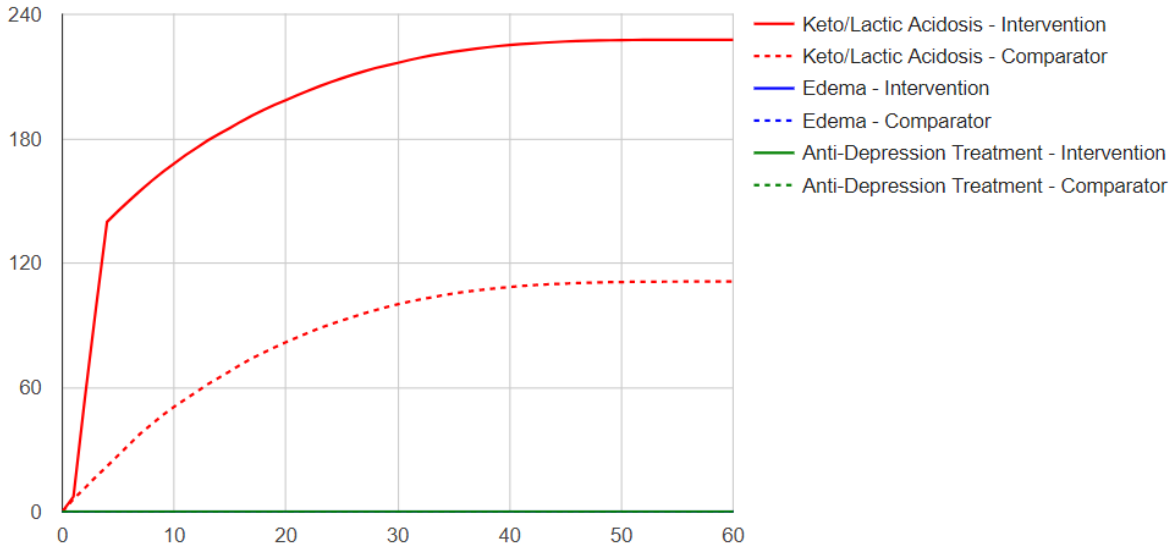
Breakdown of direct costs 1/3



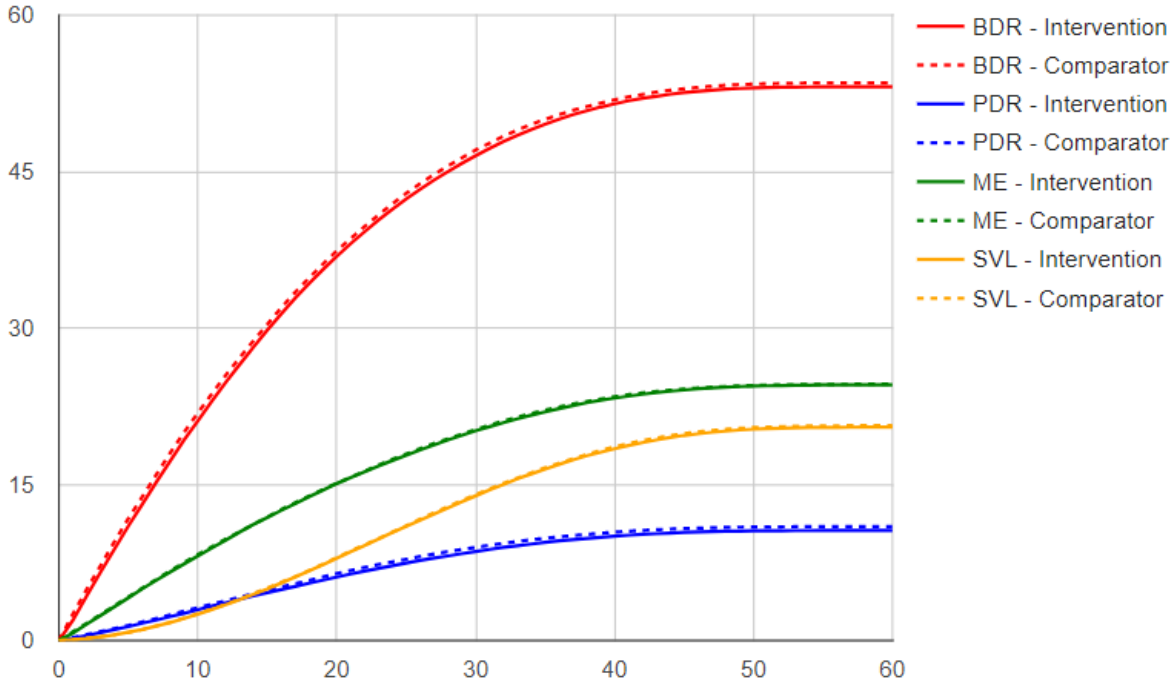
Breakdown of direct costs 2/3



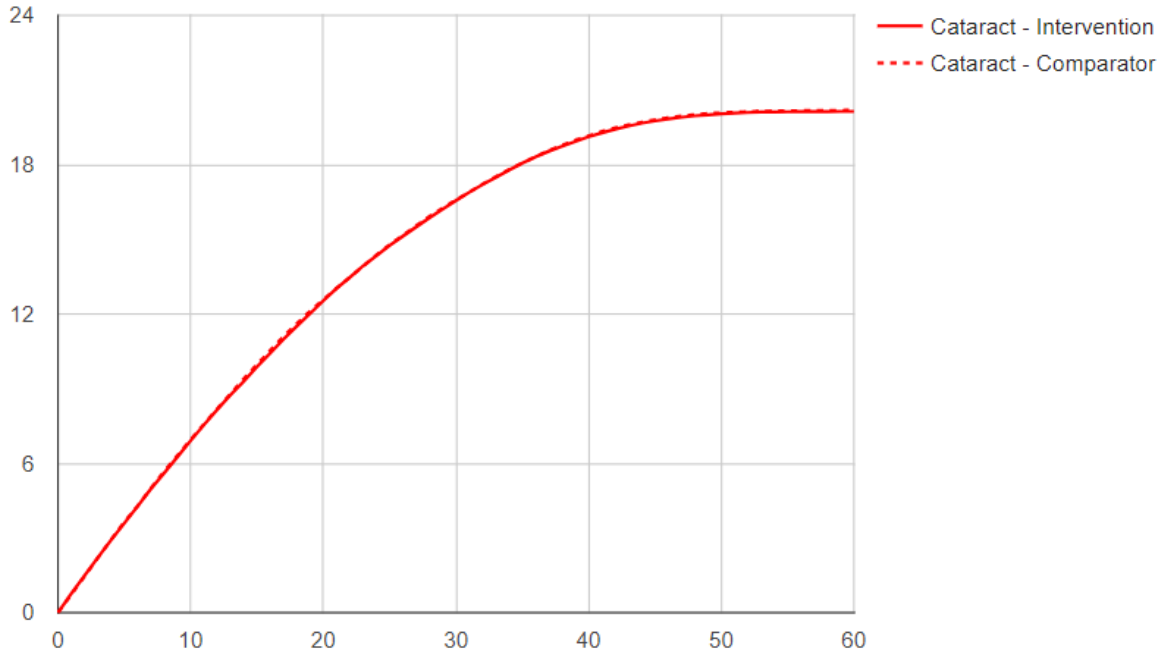
Breakdown of direct costs 3/3



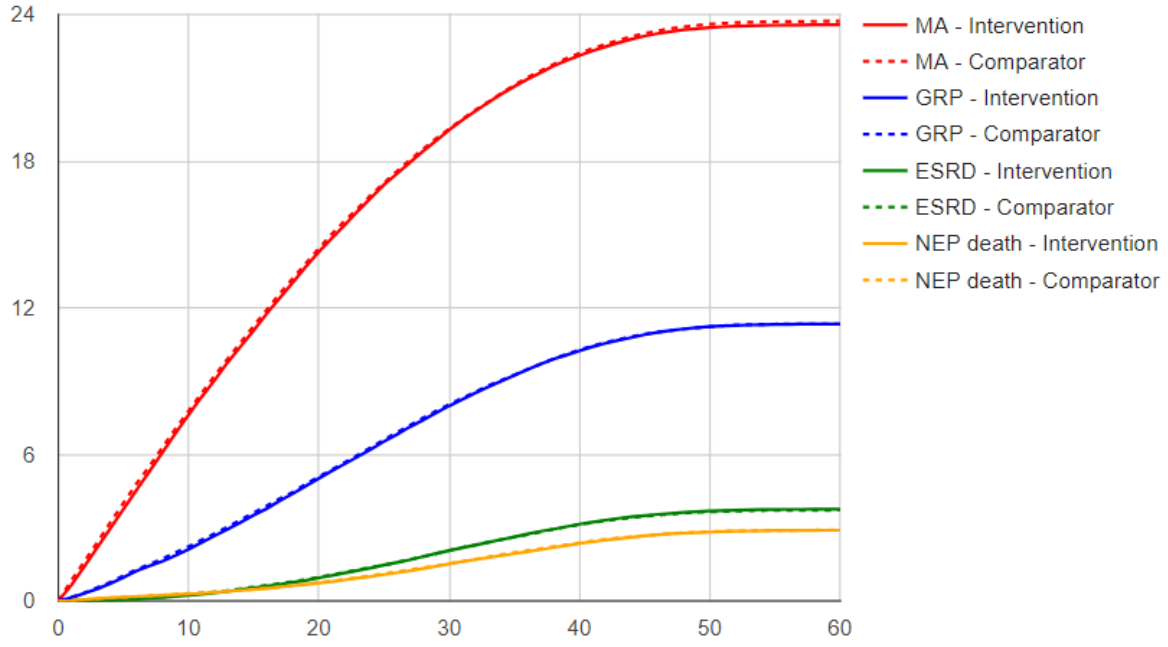
Cumulative Incidence Eye Disease 1/2



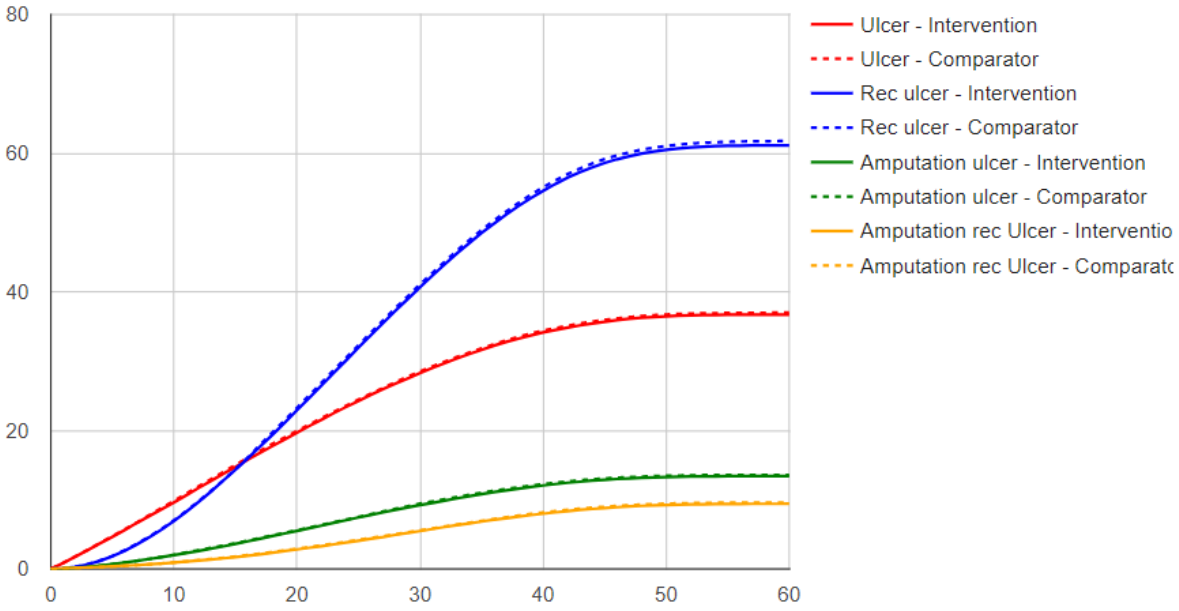
Cumulative Incidence Eye Disease 2/2



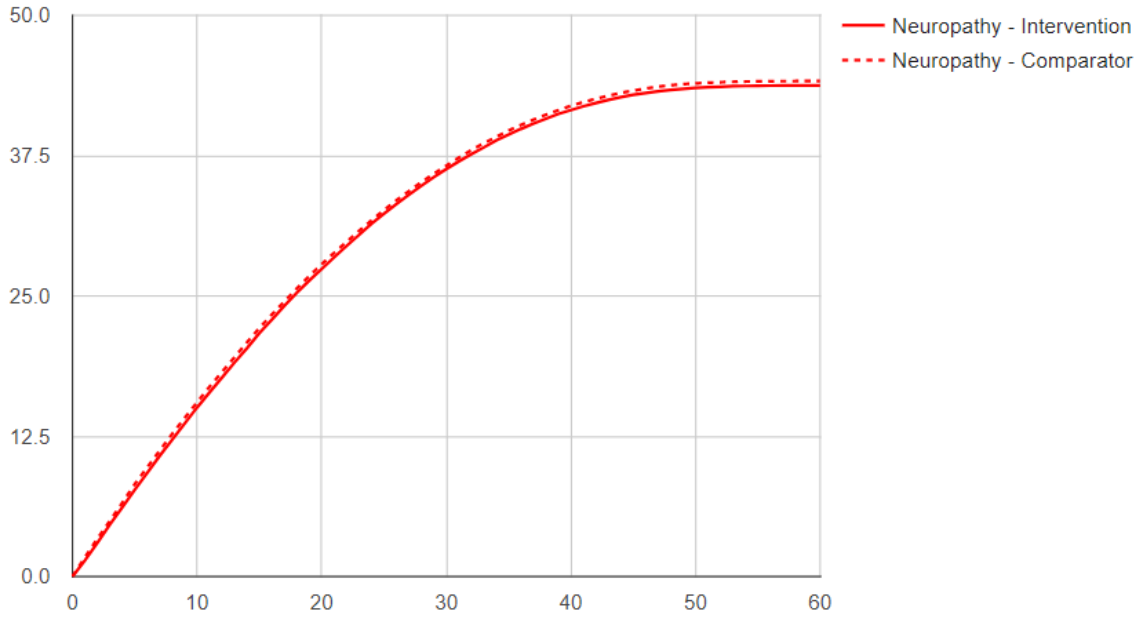
Cumulative Incidence Renal Disease



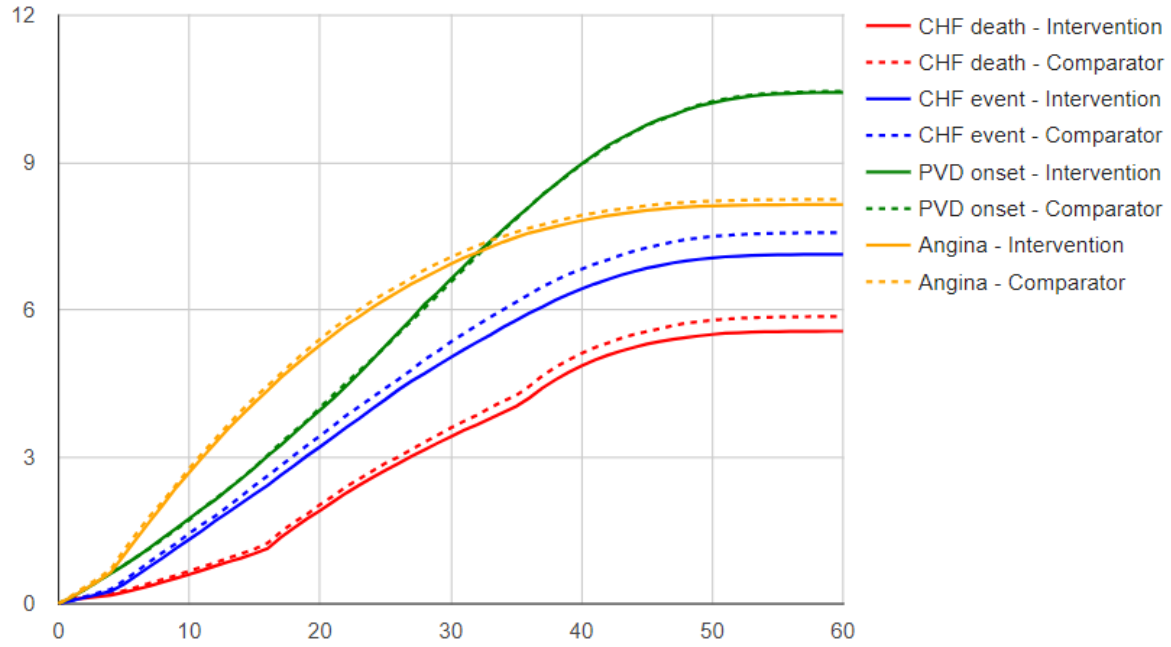
Cumulative Incidence Ulcer 1/2



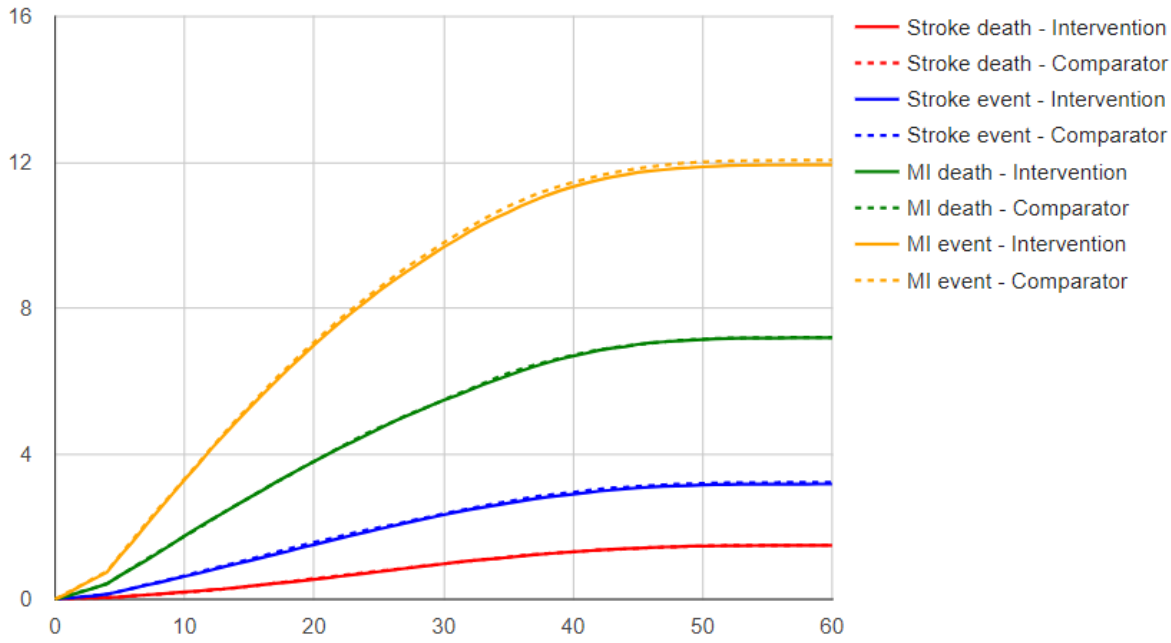
Cumulative Incidence Ulcer 2/2



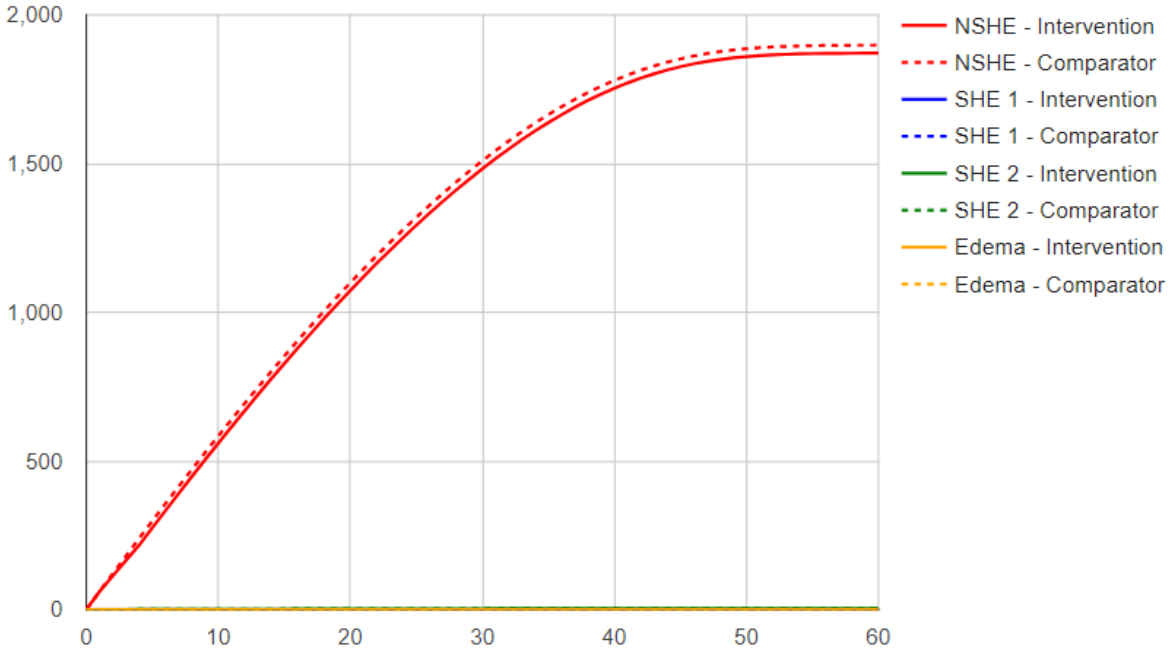
Cumulative Incidence CVD 1/2



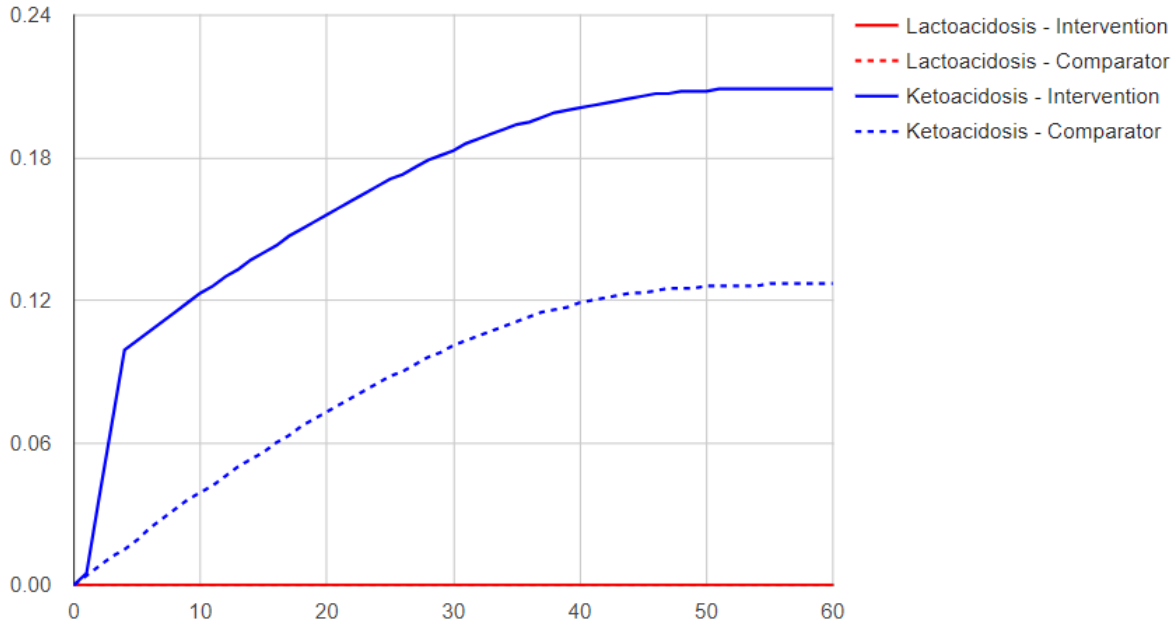
Cumulative Incidence CVD 2/2



Cumulative Adverse Events (events per patient) 1/2



Cumulative Adverse Events (events per patient) 2/2



REFERENCES

1. Hammer M, Lammert M, Mejias SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. *J Med Econ* 2009; **12**: 281-90.

2. NHS Improvement. National schedule of reference costs 2016/2017. 2016. Available from: https://improvement.nhs.uk/resources/reference-costs/. Date accessed: Feb 2019.

3. Peasgood T, Brennan A, Mansell P, Elliott J, Basarir H, Kruger J. The Impact of Diabetes-Related Complications on Preference-Based Measures of Health-Related Quality of Life in Adults with Type I Diabetes. *Med Decis Making* 2016; **36**: 1020-33.

4. Wolowacz S, Pearson I, Shannon P, Chubb B, Gundgaard J, Davies M, et al. Development and validation of a cost-utility model for Type 1 diabetes mellitus. *Diabet Med* 2015; **32**: 1023-35.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Sotagliflozin with insulin for treating type 1 diabetes [ID1376]

You are asked to check the ERG report from BMJ Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **the end of 9 May** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1: Clarifying role of PRIME in the context of the CDM model

Description of problem	Description of proposed amendment	Justification for amendment
Page 18. The company also provided an alternative set of analyses using the PRIME Diabetes Model as a validation exercise to test structural uncertainty. PRIME had a similar overall structure but included fewer complications (although some of the	We would request that NICE consider the inclusion of the following statement to improve the accuracy of description of PRIME model, particularly in comparison to CDM: Although the company intention in providing PRIME as validation model, it should be noted that both CDM and PRIME models were built by independent modelling teams	Much of the ERG report relates to discrepancies between the CDM and PRIME and gives the impression that because the model inputs are not the same the plausibility of the results are in question. By adding the proposed amendment, Sanofi

missing ones were not used in the CDM) and had different assumptions regarding progression of physiological parameters. Alternative sources of risk data were also used, based on T1D populations, many of which were based on Swedish registry data. *[add suggested text shown in the next column*]	with no direct communication between the groups permitted. While many of the model inputs were the same between the two models, there are differences in terms of utilities, complication costs and treatment costs (all of which can be referenced). A simulation has been performed in PRIME where CDM analysis was copied as much as possible (complication costs, treatment costs and utility values all matched) and this was made available to the ERG.	believes a more accurate picture is provided to the reader as to the reasons for the differences without compromising the result each model produces. Making the reader aware that a simulation has been performed to mirror CDM inputs as much as possible is very important as will address a number of concerns raised later in the report .

The following list of issues relate to the CDM model:

Issue 1: Reference source for CV risk equations

Description of problem	Description of proposed amendment	Justification for amendment
Page 17 - In the ERG's report is says "The risks of cardiovascular (CV) complications were informed largely by the United Kingdom Prospective Diabetes Study 68 (UKPDS 68) – a study based on type 2 diabetes (T2D) patients. This study provides a range of risk equations, derived from UKPDS data, that predict the risk of each of a number of CV complications based on various risk factors, such as	All analysis provided by Sanofi have consistently used CV risk equations derived from the EDIC T1DM study.	Accuracy and potential misunderstanding

HbA1c, BMI, lipids, and the presence of existing complications. The risks produced by these equations were weighted by composite CV risks estimated from the EDIC study data.		

Issue 2: HbA1c progression assumption is incorrect

Description of problem	Description of proposed amendment	Justification for amendment
Page 19 - An additional point regarding the effects in the company's base case is that they allow HbA1c to continue rising by 0.1% in the comparator group. This effectively increases the relative effect, thus, overestimating the treatment effect.	After applying the 1 year effects of the clinical trials, both arms continue to increase equally according to the EDIC evidence (natural progression) up to 8.7% after which point HbA1c stabilises. No special disadvantage was given to the placebo arm in comparison to the Sotagliflozin arm.	Accuracy and clarification of a potential misunderstanding.

Issue 3: Source for utilities

Description of problem	Description of proposed amendment	Justification for amendment
Page 20 - The ERG also had some key concerns relating to the application of utilities in the model. In Peasgood et al. 2016, the disutility per 1 unit increase above 25kg/m² varied from -0.0052 in the fixed-effects model to -0.0028 in the random-effects model and the company	The company chose the random-effects model in each of their analyses because it consistently reports all required values unlike the fixed effect model.	The company did not use the random effects model results because they were smaller, but because they consistently report all required values. In the Peasgood 2016 article, the report of fixed effects misses a total of 7 key values, so

chose the smaller estimate from the random-effects model in each of their analyses.		mixing the results of two different models was considered by Sanofi to ultimately produce a lack of consistency in the model inputs.

Issue 4: ScHARR review

Description of problem	Description of proposed amendment	Justification for amendment
Page 20 - The ERG questions why the company chose the 2018 review instead of the updated 2019 review to inform their revised analyses, and why the company did not apply the results from either ScHARR review in the CDM.	In the addendum base case analysis using the CDM, the 2019 SCHARR review was used to inform the HbA_{1c} progression. However instead of using the weighted average for HbA_{1c} progression between the intensive and conventional (0.018%) as recommended by the ScHARR review, the company used instead the value for the intensive arm only (0.012%) as this was considered to more closely represent current practice of diabetic patients.	To clarify there is only one ScHARR review conducted in 2018 but the report is dated 2019. The evidence from this review has been used to inform the revised base case, and was also used in the PRIME model (this is discussed further below under the PRIME section): 1. ScHARR review 2018/2019: Estimated values from 2004 – 2012/13 EDIC combining intensive and conventional insulin arms. 2. 2019 Sanofi update: Estimated values from 2004 – 2012/13 EDIC intensive insulin arm.

		SHARR recommends the use of mean yearly background progression observed in the 2004 – 2012/13 EDIC study for the combined intensive and conventional insulin treatment arms. The ScHARR report also provides mean yearly progression for progression observed in the 2004 – 2012/13 EDIC study for the each intensive and conventional insulin treatment arms separately. To increase the accuracy of this suggestion, in the addendum base case Sanofi used only the values derived from the intensive insulin arm (instead of the weighted average). This was done as the intensive insulin arm is considered to represent the current practice more closely.

Issue 5: Access to the model

Description of problem	Description of proposed amendment	Justification for amendment
Page 134 - However, the ERG considers it important to highlight the fact that it has not been able to replicate any of the	The following statement needs to be removed "To address this issue, the ERG contacted the developers,	In response to a request from the ERG about access to the updated analyses Sanofi replied by email on the 10-04-2019 with the following

<table>
<tr>
<td>company’s analyses in the CDM because of an error related to treatment costs. In short, the error, “Simulation can not run. The Intervention treatment has no cost defined in the treatment cost set group" was posed to the ERG whenever a new simulation was run in the CDM. This error also occurred prior to any additions to the data made by the ERG. To address this issue, the ERG contacted the developers, but they did not respond at the time of writing this report.”</td>
<td>but they did not respond at the time of writing this report.”</td>
<td>details.

<table>
<tr><th>Description</th><th>Name in the CDM</th></tr>
<tr><td>Link to enter the model</td><td>https://old.core-diabetes.com/Login.aspx</td></tr>
<tr><td>Folder with the simulation outcomes</td><td>Sotagliflozin_NICE_analyses</td></tr>
<tr><td>Group</td><td>Sotagliflozin 2019 NICE</td></tr>
</table>

Sanofi was not made aware that the ERG was subsequently unable to access the model.

Access details to Prime were also provided.</td>
</tr>
</table>

The following inaccuracies relate to the PRIME model

Issue 1 Selection of utility values used in the modelling analysis

Description of problem	Description of proposed amendment	Justification for amendment
Page 18 - Description by the ERG is misleading: When utility data were not reported in Peasgood, et al. 2016, the company also stated that data from Beaudet et al. 2014 and Currie et al. 2006, both undertaken in patients with T2D, were used to inform the economic analysis. However, when the ERG checked the utility inputs in the revised analyses provided at the clarification stage, the ERG found that the company employed utility values in PRIME, "Based on ScHARR settings review in November 2018".	The utilities used in the PRIME Diabetes Model were based primarily on the Peasgood et al. (2016) publication. Where this was not the most appropriate data source, as reviewed by ScHARR in 2019, alternative data sources were used selected to provide UK-specific values for diabetes patients, with EQ-5D data preferred over other instruments.	For the utilities used in the PRIME Diabetes Model analysis, we used Peasgood et al. (2016) preferentially (as did the ScHARR review) and our utilities are taken mainly from the sources listed and are aligned with the ScHARR 2019 review (as noted above, there is only one review, Sanofi apologies for any confusion caused). Justification was provided where this was not the case. We've provided a full table of utilities, sources and reasons for inclusion in previous technical reports duplicated below. The utilities used in the PRIME Diabetes Model analysis were selected to be the most appropriate for use in the T1D population in the UK by focusing on UK-specific data (first priority), in T1D patients (second priority), being internally consistent (third priority) and generated using a reliable instrument, ideally EQ-5D (fourth priority). Estimation of QALY between the CDM and PRIME Diabetes Model is analogous, with a minimal approach taken to health state utility estimation and an additive approach

		taken to event utilities. It can be explained as follows: In any given year of the simulation, each patient is assigned a state utility based on their medical history. For patients with no complications, this would be 0.839. Where a patient has a history of complications, the state utility is evaluated by adding the greatest disutility available from the patient's pre-existing conditions (e.g. for a patient with a history of angina (disutility −0.028) and history of stroke (disutility −0.165), the stroke disutility is greatest and would be added to state utility (0.839−0.165 = 0.674). For each event occurring in that year of the simulation, then the disutilities for each event that occurs are then added to return the utility score for that year (e.g. 0.674 + MI (−0.065) + non-severe hypo (−0.004) = 0.605). Multiplicative estimation of QALYs is also available in the PRIME Diabetes Model and can be used by the ERG team as part of their evaluation. [please see appendix 1]

Issue 2 Different treatment costs used in the CORE Diabetes Model and the PRIME Diabetes Model

Description of problem	Description of proposed amendment	Justification for amendment
Page 18 - Treatment costs: However, when the ERG checked the inputs in the revised analyses provided at the clarification stage, the ERG found that the company used alternative costs in the PRIME model without reference or justification.	The references and justification for the costs used in PRIME have since been provided to the ERG.	We would like to take this opportunity to apologise for not providing these details earlier. We have included the relevant inputs as an appendix to this document. (See Appendix 2) For the PRIME Diabetes Model analysis, treatment costs were estimated based on resource use data at 52 weeks from the inTandem-2 clinical trial and published costs for the UK setting. Annual costs were calculated as a weighted average of costs for patients on MDI and for those on insulin pump therapy, with the costs of ketoacidosis testing subsequently added on. The calculations were provided in the original submission and are duplicated below (for the sota 200 mg treatment group. These costs were used consistently at the time of submission and at the clarification stage with the PRIME Diabetes Model. One area of difference between the models was that the CDM cost estimate used weighted averages of basal insulin, bolus

		insulin, basal-bolus insulin, needle and lancet costs. This information was not available to the PRIME Diabetes Model team at the time of analysis and therefore representative unit costs for each item were used. Another issue is that insulin doses were based on 52-week data for the PRIME Diabetes Model treatment cost estimates and on 24-week data for the CORE Diabetes Model analysis. Annual CSII costs were taken from different sources with the PRIME Diabetes Model estimates taken from Riemsma et al. Health Technol Assess. 2016; 20(17): v-xxxi, 1-251 and Curtis and Burns, and the CORE Diabetes Model estimates based on "NICE 2015" Whilst these difference led to similar annual costs in the placebo arm, the estimates of costs in the sotagliflozin arms were higher with PRIME than with the CDM.

Issue 3 Suggestion of "model restrictions" preventing analysis

Description of problem	Description of proposed amendment	Justification for amendment
Page 21 - It was stated that:	The statement on restrictions should be removed as it is incorrect. We believe the preferred base case analysis could	The claim that there are restrictions in the PRIME Diabetes Model that precludes the

The ERG was unable to run analyses using the CDM as this returned an error message, and PRIME appeared to have restrictions in what the ERG could modify. Therefore, the ERG could not implement its preferred base case analysis in either model. The ERG's preferred assumptions are: to use the simulated population based on the pooled trial data that informed the treatment effectiveness; to apply SH costs based on Hammer et al. 2009 and assume 50% of patients are hospitalised; using multiplicative utilities based on values from the ScHARR 2019 review; and, apply treatment effects for HbA1c for just 2 years, while all other effects are maintained for the treatment duration of 5 years. The ERG was able to present a similar analysis but with the HbA1c effect removed at 3 years and other treatment effects removed after a further year, along with treatment costs. This resulted in an ICER of £18,134, a slight increase compared to the PRIME model results using the company's preferred assumptions.	be run using the PRIME Diabetes Model without difficulty.	NICE preferred analysis is incorrect. The preferred analysis as described by NICE could be run in PRIME, as far as we understand it, and indeed many of the features listed by NICE were included in the simulations run at the clarifications stage. It is possible to limit HbA1c effects at 2 years. It is also possible to limit other treatment effects at this time, or continue them on for 5 years. It is possible to apply sota costs for 2 years or 5 years too. This can all be done using the treatment sequencing functionality (and in many cases has been for the clarifications response). Multiplicative QALY estimation is available to the ERG team using the PRIME Diabetes Model (it has been available via the model interface since March 27).

Issue 4 Discrepancies in the cost sets used

Description of problem	Description of proposed amendment	Justification for amendment
Page 21 - The ERG noted some discrepancies in costs used in the updated PRIME model compared to the CDM based on the revised analyses provided at the clarification stage. No sources of cost data or rationale for the changes were provided to the ERG and given that the company did not mention the alternative inputs for the PRIME model in the addendum to the CS, the ERG focussed its critique on the cost inputs used to inform the original and revised CDM. However, the ERG would like further clarity on whether those changes were made in PRIME erroneously or not.	The text should be clarified to point out there were no errors in the PRIME Diabetes Model cost set and that the costs described were appropriately referenced.	In the PRIME Diabetes Model, the only cost data that differed at the time of the clarifications and the original submission were those costs the ERG requested to be changed (e.g. severe hypoglycaemia). There are differences in the costs used in the CORE Diabetes Model analysis and the PRIME Diabetes Model analysis as the two groups worked independently to perform the cost-effectiveness evaluations. No changes were introduced to the PRIME Diabetes Model cost set and all cost sources were referenced in the original submission and, wherever relevant, at the clarifications stage.

Appendix 1: Table of utilities, sources and reasons for inclusion in previous technical reports

Health state	Mean utility (variance)	Justification and reference
Type 1 diabetes with no complications	0.839 (SD 0.231)	Baseline EQ-5D index value from DAFNE study sample, UK type 1 diabetes population – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Cardiovascular complications		
Angina, year of onset	−0.028 (SE 0.022)	UK type 2 diabetes population (UKPDS), EQ-5D data for ischaemic heart disease (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Angina, subsequent years	−0.028 (SE 0.022)	UK type 2 diabetes population (UKPDS), EQ-5D data for ischaemic heart disease (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Congestive heart failure, year of onset	−0.101 (SE 0.032)	UK type 2 diabetes population (UKPDS), EQ-5D data (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Congestive heart failure, subsequent years	−0.101 (SE 0.032)	UK type 2 diabetes population (UKPDS), EQ-5D data (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Myocardial infarction, year of onset	−0.065 (SE 0.030)	UK type 2 diabetes population (UKPDS), EQ-5D data (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Myocardial infarction, subsequent years	−0.065 (SE 0.030)	UK type 2 diabetes population (UKPDS), EQ-5D data (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Stroke, year of onset	−0.165 (SE 0.035)	UK type 2 diabetes population (UKPDS), EQ-5D data (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014;

Health state	Mean utility (variance)	Justification and reference
		23(4): 487-500
Stroke, subsequent years	−0.165 (SE 0.035)	UK type 2 diabetes population (UKPDS), EQ-5D data (chosen due to low numbers of CVD events in Peasgood *et al.* type 1 diabetes population analysis) – Alva et al. Health Econ. 2014; 23(4): 487-500
Microvascular complications (not including renal and eye complications)		
Amputation, year of onset	−0.1172 (SE 0.055)	UK type 1 diabetes population, EQ-5D data (random effects model as no fixed effects model value was available) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Amputation, subsequent years	−0.1172 (SE 0.055)	UK type 1 diabetes population, EQ-5D data (random effects model as no fixed effects model value was available) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Neuropathy, year of onset	−0.0497 (SE 0.043)	UK type 1 diabetes population, EQ-5D data for painful neuropathy (fixed effects model) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Neuropathy, subsequent years	−0.0497 (SE 0.043)	UK type 1 diabetes population, EQ-5D data for painful neuropathy (fixed effects model) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Renal complications		
Microalbuminuria, year of onset	0	Assumed to have no impact on patients' quality of life in line with previous NICE evaluations
Microalbuminuria, subsequent years	0	Assumed to have no impact on patients' quality of life in line with previous NICE evaluations
Overt nephropathy, year of onset	−0.0277 (SE 0.032)	UK type 1 diabetes population, EQ-5D data for proteinuria (random effects model as no fixed effects model value was available) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Overt nephropathy,	−0.0277 (SE 0.032)	UK type 1 diabetes population, EQ-5D data for proteinuria (random effects model as no fixed

Health state	Mean utility (variance)	Justification and reference
subsequent years		effects model value was available) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Haemodialysis, year of onset	−0.14 (SE 0.016)	UK population, EQ-5D-5L data for patients with diabetes on the transplant waiting list (Li et al. Table 3, Model 4) (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis – Li et al. Value Health. 2017; 20(7): 976-84
Haemodialysis, subsequent years	−0.14 (SE 0.016)	UK population, EQ-5D-5L data for patients with diabetes on the transplant waiting list (Li et al. Table 3, Model 4) (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Li et al. Value Health. 2017; 20(7): 976-84
Peritoneal dialysis, year of onset	−0.14 (SE 0.016)	UK population, EQ-5D-5L data for patients with diabetes on the transplant waiting list (Li et al. Table 3, Model 4) (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Li et al. Value Health. 2017; 20(7): 976-84
Peritoneal dialysis, subsequent years	−0.14 (SE 0.016)	UK population, EQ-5D-5L data for patients with diabetes on the transplant waiting list (Li et al. Table 3, Model 4) (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Li et al. Value Health. 2017; 20(7): 976-84
Renal transplant, year of onset	−0.086 (SE 0.016)	UK population, EQ-5D-5L data for patients with diabetes and a transplant (Li et al. Table 3, Model 4) (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Li et al. Value Health. 2017; 20(7): 976-84
Renal transplant, subsequent years	−0.086 (SE 0.016)	UK population, EQ-5D-5L data for patients with diabetes and a transplant (Li et al. Table 3, Model 4) (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Li et al. Value Health. 2017; 20(7): 976-84
Eye complications		
Macular edema, year of onset	0	Assumed to have no additional impact on patients' quality of life beyond retinopathy disutilities

Health state	Mean utility (variance)	Justification and reference
Macular edema, subsequent years	0	Assumed to have no additional impact on patients' quality of life beyond retinopathy disutilities
Mild non-proliferative retinopathy, year of onset	−0.0544 (SE 0.023)	UK type 1 diabetes population, EQ-5D data for retinopathy (fixed effects model), assumed to be the same for all non-proliferative retinopathy health states – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Mild non-proliferative retinopathy, subsequent years	−0.0544 (SE 0.023)	UK type 1 diabetes population, EQ-5D data for retinopathy (fixed effects model), assumed to be the same for all non-proliferative retinopathy health states – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Moderate non-proliferative retinopathy, year of onset	−0.0544 (SE 0.023)	UK type 1 diabetes population, EQ-5D data for retinopathy (fixed effects model), assumed to be the same for all non-proliferative retinopathy health states – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Moderate non-proliferative retinopathy, subsequent years	−0.0544 (SE 0.023)	UK type 1 diabetes population, EQ-5D data for retinopathy (fixed effects model), assumed to be the same for all non-proliferative retinopathy health states – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Severe non-proliferative retinopathy, year of onset	−0.0544 (SE 0.023)	UK type 1 diabetes population, EQ-5D data for retinopathy (fixed effects model), assumed to be the same for all non-proliferative retinopathy health states – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Severe non-proliferative retinopathy, subsequent years	−0.0544 (SE 0.023)	UK type 1 diabetes population, EQ-5D data for retinopathy (fixed effects model), assumed to be the same for all non-proliferative retinopathy health states – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Proliferative retinopathy, year of onset	−0.0288 (SE 0.026)	UK type 1 diabetes population, EQ-5D data for proliferative retinopathy (random effects model as no fixed effects model value was available) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33

Health state	Mean utility (variance)	Justification and reference
Proliferative retinopathy, subsequent years	−0.0288 (SE 0.026)	UK type 1 diabetes population, EQ-5D data for proliferative retinopathy (random effects model as no fixed effects model value was available) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Severe vision loss, year of onset	−0.208 (SE 0.013)	Type 1 diabetes population, QWB-SA utility for blind in two eyes, considered representative and used in previously published analyses (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Coffey et al. Diabetes Care. 2002; 25(12): 2238-43
Severe vision loss, subsequent years	−0.208 (SE 0.013)	Type 1 diabetes population, QWB-SA utility for blind in two eyes, considered representative and used in previously published analyses (chosen due to low numbers of ESRD events in Peasgood *et al.* type 1 diabetes population analysis) – Coffey et al. Diabetes Care. 2002; 25(12): 2238-43
Adverse events		
Non-severe hypoglycaemia	−0.004 (95%CI 0.001 to 0.006)	Type 1 diabetes population, UK appropriate, TTO utility used in previously published analyses, chosen from a source providing values for all hypoglycaemia type and separate daytime/nocturnal disutilities – Evans et al. Health Qual Life Outcomes. 2013; 11: 90
Severe hypoglycaemia	−0.047 (95%CI 0.033 to 0.062)	Type 1 diabetes population, UK appropriate, TTO utility used in previously published analyses, chosen from a source providing values for all hypoglycaemia type and separate daytime/nocturnal disutilities for sensitivity analyses – Evans et al. Health Qual Life Outcomes. 2013; 11: 90
Ketoacidosis	−0.0119 (SE 0.011)	UK type 1 diabetes population, EQ-5D data for diabetic ketoacidosis (fixed effects model) – Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33
Other		
Each unit of BMI over	−0.0052 (SE 0.002)	UK type 1 diabetes population, EQ-5D data (fixed effects model) – Peasgood et al. Med Decis

Health state	Mean utility (variance)	Justification and reference
25 $kg.m^{-2}$		Making. 2016; 36(8): 1020-33 *Note: a revised value of −0.0028 was used in the clarifications response in line with the ERG request*

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DAFNE, Dose Adjustment for Normal Eating; NICE, National Institute for Health and Care Excellence; QWB-SA, quality of well being scale self administered; SD, standard deviation; SE, standard error; TTO, time trade-off, UK, United Kingdom; UKPDS, United Kingdom Prospective Diabetes Study. Note: Utilities derived from the fixed effects model described by Peasgood et al. were preferred to those of the random effects model where both were available as the authors noted that, "For all outcome measures, we find evidence of an individual time-invariant error term (based on modified Breusch-Pagan Lagrange multiplier tests, which adopt a null hypothesis that the variance of the unobserved, time-invariant individual effect is zero) and evidence of correlation of this individual error term with the other regressors, suggesting the superiority of a fixed-effects model (based on a Hausman test that compares the parameter estimates from the fixed- and random-effects approaches." (Peasgood et al. Med Decis Making. 2016; 36(8): 1020-33)

Appendix 2: Details of treatment costs used in PRIME

	Daily dose	Pack contents	Cost per pack (GBP)	Daily cost (GBP)	Annual cost (GBP)	Reference / comment

	Daily dose	Pack contents	Cost per pack (GBP)	Daily cost (GBP)	Annual cost (GBP)	Reference / comment
Sotagliflozin plus MDI						
Sotagliflozin	200 mg	30 x 200 mg	39.20	1.31	477.26	Not applicable
Basal insulin (at week 52)	28.63 IU	1,500 IU	37.77	0.72	263.31	inTandem-2 CSR, Table 14.2.10.4.1, page 1,459
Bolus insulin (at week 52)	29.46 IU	1,500 IU	28.30	0.56	203.01	inTandem-2 CSR, Table 14.2.4.4.1, page 1,071
Needles	4.0	100 needles	9.69	0.39	141.57	Assumed, one bolus and three basal injections daily
SMBG test strips	4.0	50 strips	6.99	0.56	204.25	Assumed SMBG 4 times daily
SMBG lancets	4.0	100 lancets	2.19	0.09	32.00	Assumed SMBG 4 times daily
Total					**1,321.39**	

	Daily dose	Pack contents	Cost per pack (GBP)	Daily cost (GBP)	Annual cost (GBP)	Reference / comment
Sotagliflozin plus CSII						
Sotagliflozin	200 mg	30 x 200 mg	39.20	1.31	477.26	Not applicable
Basal insulin (at week 52)*	27.94 IU	1,500 IU	28.30	0.53	192.54	inTandem-2 CSR, Table 14.2.10.4.1, page 1,449
Bolus insulin (at week 52)	24.76 IU	1,500 IU	28.30	0.47	170.62	inTandem-2 CSR, Table 14.2.4.4.1, page 1,061
CSII and consumables	N/A	Annual	2,262.31		2,262.31	All patients were using CSII
Percentage using CGM (weighted annual cost)	66.18%	Annual	3,213.43		2,126.54	inTandem-2 CSR, Table 14.2.32.8.1, page 1832
Percentage using SMBG (weighted annual cost)	33.82%		(same cost assumptions as above for MDI)		79.91	inTandem-2 CSR, Table 14.2.32.8.1, page 1832
Total					**5,309.17**	
Weighted average cost		**%**		**Annual cost**	**Product**	
Patients on MDI		73.95		1,321.39	977.12	inTandem-2 CSR, Table 11.2.1-1, page 151
Patients on CSII		26.05		5,309.17	1,383.23	inTandem-2 CSR, Table 11.2.1-1, page 151
Weighted average (no ketone testing)					**2,360.35**	

	Daily dose	Pack contents	Cost per pack (GBP)	Daily cost (GBP)	Annual cost (GBP)	Reference / comment
Ketone testing costs	**Tests per week**	**Pack contents**	**Cost per pack**	**Weekly cost**	**Annual cost**	
Ketone test strips	0.4	Cost per strip	2.00	0.77	40.03	Advisory Board assumption of 20 tests per year
Lancets (assumed same as SMBG lancets)	0.4	100 lancets	2.19	0.07	0.44	Advisory Board assumption of 20 tests per year
Total					**40.47**	
Weighted average annual cost (with ketone testing)					**2,400.82**	

Abbreviations: CSII, continuous subcutaneous insulin infusion; CSR, clinical study report; GBP, Pounds Sterling; MDI, multiple daily injections of insulin; SMBG, self-monitoring of blood glucose

* Costs of rapid-acting insulin were used as this row refers to non-prandial insulin infusion administered by an insulin pump.

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

22th July 2019.

Dear Jasdeep,

Re: Sotagliflozin in combination with insulin, for treating type 1 diabetes [ID1376]

Once again Sanofi welcomes the opportunity to respond to the technical consulation for the above appraisal and are pleased to provide the technical team and the ERG with further analyses as requested on the 17th July.

The questions are restated below along with our answers.

Technical team questions 1 & 2:

1. ***Please provide the following data cut from the inTandem 1 and inTandem 2 pooled population:**

    a. people with a BMI of greater than or equal to27 kg/m^2

    b. exclude people with low insulin requirements in line with the SPC (0.5 units per kg of body weight or less)

    c. only include people with a post-optimisation HbA1c of 7% or more

    This data needs to be in a format that allows it to be input into the economic model for all relevant inputs for example the treatment effectiveness, baseline characteristics, adverse events.

    Please also provide the data in a format in which the committee can consider the baseline characteristics of the population and compare these with previous data cuts.

2. ***Please provide the following data cut from the inTandem 1 and inTandem 2 pooled population:**

    a. people with a BMI of greater or equal to than 27 kg/m^2

    b. exclude people with low insulin requirements in line with the SPC (0.5 units per kg of body weight or less)

    c. only include people with a post-optimisation HbA1c of 8% or more

    This data needs to be in a format that allows it to be input into the economic model for all relevant inputs for example the treatment effectiveness, baseline characteristics, adverse events.

Please also provide the data in a format in which the committee can consider the baseline characteristics of the population and compare these with previous data cuts.

Sanofi response to Technical team questions 1 & 2:

We have updated the spreadsheet that we sent on the 17th of July to include the required data and uploaded to NICE Docs. These data are provided in Excel format following the way they are inputted into the model. This file also includes a comparative summary across the required populations in order to facilitate a comparison of baseline characteristics and treatment effects.

Technical team questions 3, 4 & 5.

The technical teams preferred base case assumptions:
note: these are the assumptions agreed on during the pre-meet with the lead team and the Chair. the technical team strongly advises providing these analyses for committee.

3. Analysis of the indicated population for sotagliflozin using pooled data **from inTandem 1 and inTandem 2**. The relevant clinical data (e.g. baseline characteristics, effectiveness data, adverse events, number of patients in this group). The population is defined as:
    a. people with a BMI of greater or equal to than 27 kg/m^2
    b. exclude people with low insulin requirements in line with the SPC (0.5 units per kg of body weight or less)
    c. only include people with a post-optimisation HbA1c of 7% or more
4. Use baseline characteristics from the pooled data for inTandem 1 and inTandem 2
5. **Stopping treatment**: 2 years on treatment

Sanofi response to Technical team questions 3, 4 & 5:

The basecase agreed on during the pre-meet with the lead team and the Chair was for the inTandem 2 population and not the pooled population. The pooled population was cited as a sensitivity analysis. In order to provide the results as quickly as we could we presented the preffered assumptions using the inTandem2 population. The pooled population required new post hoc data extraction from the clinical trial outcomes. We have now received the datacut and are pleased to include the results for the pooled population with the additional HbA_{1c} constrains at 7% and 8% below.

Please note that we believe question 4 above requesting the analysis to be provided on the pooled population is nested already in question 3 and so have not provided a separate analysis for it.

In line with our understanding of the likely requirements of the committee most of the simulations we submit here included the treatment stopping after 2yrs. It is important to note that this was not compatible with the stopping rules requested in item 6 below. Therefore we have developed a specific analysis trying to integrate this stopping rule.

Table 1. Incremental results for the pooled populations with HbA_{1c} at 7 and 8%

	Insulin alone (1)	Sotagliflozin 200 mg + Insulin (2)	Incremental value (2-1)
Pooled inTandem1 and inTandem 2 population with: • **BMI greater or equal to than 27 kg/m2** • **People with baseline optimised insulin dose of >0.5iu/kg excluded** • **People with post-optimisation HbA_{1c} of 7% or more** • **Treatment stopped at 2 years** **Also includes:** **- Treatment effects observed in the trials at 52 weeks to inform the 1st yr of simulation** **- Rebound to Placebo after year 1** **- ScHARR utility values completed by our submitted values when not reported by ScHARR** **- Multiplicative approach to QALYs** **- Adverse Events preferences applied (urogenital infections and hypoglycaemia)**			
Total Costs	£87,077.27	£87,695.07	£617.80
QALYs	13.366	13.399	0.033
		ICER	**£18,721**
Pooled inTandem1 and inTandem 2 population with: • **BMI greater or equal to than 27 kg/m2** • **People with baseline optimised insulin dose of >0.5iu/kg excluded** • **People with post-optimisation HbA_{1c} of 8% or more** • **Treatment stopped at 2 years** **Also includes:** **- Treatment effects observed in the trials at 52 weeks to inform the 1st yr of simulation** **- Rebound to Placebo after year 1** **- ScHARR utility values completed by our submitted values when not reported by ScHARR** **- Multiplicative approach to QALYs** **- Adverse Events preferences applied (urogenital infections and hypoglycaemia)**			
Total Costs	£89,540.14	£90,571.48	£1,031.34
QALYs	12.774	12.822	0.048
		ICER	**£21,486**

Technical team question 6.

6. **Duration of treatment effect, no continued benefit from treatment for any risk factors after 2 years**: Treatment duration should be based on the trial data. The treatment effect in year 1 should be based on the treatment effect from the trial data and the observed trial data from 6 to 12 months should be extrapolated to get the treatment effect for year 1 to year 2. Treatment effect should return to placebo when treatment stops.

Sanofi response to Technical team question 6

In order to accommodate this request as closely as we could given the constraints of the CDM we have had to slightly modify the way in which the analysis was done. We hope this is sufficient to accommodate the needs of the committee

The 1y effects observed in our trials are applied in the 1st year of the simulation.
It is important then to keep in mind that:

- The CDM uses yearly cycles, and
- The decrease in benefit on HbA1c observed in our trials between week 24 and week 52 does not return Sota arm to Pbo at year 2.

We have captured our approach in Table 2 below.

Table 2. Approach to capturing the extrapolation of treatment effect between 6 months and 1 year.

Year 1	Year 2	Year 3	Subsequent years
52-week effects from our trials	Decrease in HbA1c benefit applying an extrapolation of observations made in our trials between 6 and 12 months. Natural progression for all other parameters.	Treatment is stopped; all parameters return to the Placebo arm to remove any remaining benefit.	Natural progression for all parameters whatever the arm, all patients on insulin alone.

For the purpose of these additional simulations, only week 52 results were requested due to the time constraint. This is because an additional 2 sets of results (week 24 results for patients with a base line HbA1c ≥ 7% and for patients with a base line HbA1c ≥ 8%) are required. This would have delayed our simulations by 24 to 48 hours which would have prevented us from providing an answer to the deadline requested.

Further details of the analyses including graphical representations of the treatment effect are provided on the accompanying spreadsheet.

From a previous post hoc analysis both 24 and week 52 results in patients from the pool of inTandem1 and inTandem2, with a base line BMI ≥ 27 kg/m² were available. We have used these existing results to extrapolate 6 to 12 month data on the HbA_{1c} effect. We do not believe that this approximation will cause a substantive impact on the results.

The incremental results are provided overleaf.

Table 3. Incremental results for the pooled populations from inTandem 1 & 2 with HbA1c at 7 and 8% and treatment effect extrapolated between 6 months and 1 year.

	Insulin alone (1)	Sotagliflozin 200 mg + Insulin (2)	Incremental value (2-1)
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 7% or more • **Treatment extrapolation according to approach in Table 2**			
Total Costs	£91,826.71	£93,537.80	£1,711.09
QALYs	12.895	12.956	0.061
ICER			**£28,051**
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 8% or more • **Treatment extrapolation according to approach in Table 2**			
Total Costs	£94,271.90	£96,499.19	£2,227.29
QALYs	12.304	12.382	0.078
ICER			**£28,555**

Technical team question 7.

7. **Treatment discontinuation rate** based on extrapolation of trial data observation between 6 and 12 months, treatment stops if patients do not have an improvement in HbA1c of 0.3% or more.

Sanofi response to Technical team question 7

Treatment discontinuation in the CDM is based on an HbA1c threshold or time under treatment. For these technical reasons we are unable to mix the 2 conditions and we cannot discontinue a given proportion of the cohort.

Therefore, we are unable to apply a treatment discontinuation rate based on extrapolation of trial data observation between 6 and 12 months.

In order to accommodate the request for a stopping rule based on an improvement in HbA1c of 0.3% or more we have approached this request by switching patients to insulin alone in the model when they reach a specific HbA1c threshold defined as the average baseline HbA1c of the cohort decreased by 0.3%. It is important to note that this switch can happen after 2 years for some patients.

Results are provided in Table 4.

Table 4. Incremental results for the pooled populations from inTandem 1 & 2 with HbA1c at 7 and 8% and treatment effect extrapolated between 6 months and 1 year.

	Insulin alone (1)	Sotagliflozin 200 mg + Insulin (2)	Incremental value (2-1)
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 7% or more • **HbA_{1c} stopping rule applied**			
Total Costs	£91,826.71	£93,537.80	£1,711.09
QALYs	12.895	12.956	0.061
		ICER	**£28,051**
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 8% or more • **HbA_{1c} stopping rule applied**			
Total Costs	£94,271.85	£96,761.30	£2,489.45
QALYs	12.304	12.351	0.047
		ICER	**£52,967**

The analysis incorporating people with HbA1c greater than 7% provides identical results to that not including the stopping rule. This is because, by coincidence all patients stop at the same point in time. Full details are provided in the accompanying spreadsheet which includes the rates for progression and graphs to show how HbA1c evolves over time under these scenarios. (See Support_SA1 and SA2 worksheets).

Technical team question 8

8. Utilities based on the ScHARR review using a fixed effects approach.

Sanofi response to Technical team question 8

Not all requested utility values were provided by ScHARR. For the missing values, we informed the model with utility values previously used in our submission. These values can be identified easily in the Excel files uploaded to NICE Docs summarising all the data used in simulations.

Technical team question 9 & 10

9. Use the multiplicative approach to QALYs in line with NICE TSD 12: the use of health state utility values in decision models.
10. Adverse events:

a. Include impact of rare life threatening urogenital infections such as Fournier's gangrene following the MHRA warning issued for SGLT2 inhibitors in February 2019.
b. Hypoglycaemic events: 50% of severe hypoglycaemic events need medical attention, costs in line with the NICE clinical guideline

Sanofi response to Technical team questions 9 & 10

In order to provide the analyses requested on time the impact of rare life threatening urogenital infections such as Fournier's gangrene are included in all the simulations. We have shown in previous responses that the rarity of these infections means that the ICER is not substantively affected by their inclusion.

The request to include hypoglycaemic events is included in all simulations submitted in this wave.

We have simulated that half of severe hypoglycaemia events required medical assistance while the other half didn't. In the absence of specific cost for severe hypoglycaemia not requiring any medical assistance, half of the price of a severe hypoglycaemia requiring medical assistance was applied in the model.

Technical teams preferred scenarios and sensitivity analyses applied to the above base case population
note: these are the preferred scenario and sensitivity analysis agreed on during the pre-meet with the lead team and the Chair. The technical team strongly advises to consider providing these analyses for committee.

Technical team scenario 1

1. Population specified in the technical teams preferred base case (1) with HbA1c cut off of 8%

Sanofi response to Technical scenario 1

This request is included in all simulations submitted in this wave. The results are provided above.

Technical team scenario 2

2. **Duration of treatment and effect**: the technical team would like to see a variety of scenarios looking at the duration of treatment:

    a. 1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1
    b. 2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years
    c. 2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.

For each treatment duration outlined above (11.a.b.c) apply the following duration of treatment benefit:

    a. No continued benefit from treatment for any risk factors after treatment stops

b. No benefit of HbA1c improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.
c. No impact of HbA1c on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.

Sanofi response to Technical scenario 2

These requests have raised some technical requirements which are not possible to accommodate within the structure of the CDM.

The model runs on annual cycles and does not allow for treatment benefit to decline immediately at the end of a given year. The model 'wanes' treatment effect over the subsequent year so it is not possible to switch immediately from full benefit in year 1 to no or half benefit in year 2 followed by immediate cessation of benefit thereafter. It may be useful to consider the plots shown in the accompanying spreadsheet for each scenario for visualisation of how treatment effect changes over time.

This applies equally to all benefits being ceased or only some. For example it is not possible to cut cardiovascular risk immediately at the end of year 1 but to maintain other benefits for the full 2 years followed by immediate cessation of benefit. This is similarly the case for the analyses estimating the impact of weight.

Technical team scenario 3

3. Adverse events:

    a. Scenario using DKA mortality rate of 4%

Sanofi response to Technical scenario 3a

We consider this analysis to be an extreme case and highly unlikely to be observed in clinical practice. Given the time constraints we have carried out this sensitivity analysis only using the HbA1c ≥7% cohort. We hope this is acceptable to the committee.

Table 5. Incremental results for the pooled populations from inTandem 1 & 2 including DKA mortality rate of 4%

	Insulin alone (1)	**Sotagliflozin 200 mg + Insulin (2)**	**Incremental value (2-1)**
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 7% or more • **DKA mortality rate of 4%**			
Total Costs	£87,077.27	£87,635.65	£558.38

QALYs	13.366	13.378	0.012
		ICER	**£46,532**

b. Scenario using Severe Hypoglycaemic mortality rate of 4.45%

Sanofi response to Technical scenario 3a

Again, we believe this is an extreme case unlikely to be observed and given the time constraints we have carried out this sensitivity analysis only using the HbA1c ≥7% cohort. We hope this is acceptable to the committee.

Table 6. Incremental results for the pooled populations from inTandem 1 & 2 including Severe Hypoglycaemic mortality rate of 4.45%

	Insulin alone (1)	**Sotagliflozin 200 mg + Insulin (2)**	**Incremental value (2-1)**
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 7% or more • **Severe Hypoglycaemic mortality rate of 4.45%**			
Total Costs	£84,951.39	£86,109.73	£1,158.34
QALYs	13.144	13.187	0.043
		ICER	**£22,178**

We believe that if these extreme scenarios are to be considered then it is useful to incorporate both analysis. The results of this simulation are provided in

Table 7. Incremental results for the pooled populations from inTandem 1 & 2 including DKA mortality rate of 4% and Severe Hypoglycaemic mortality rate of 4.45%

	Insulin alone (1)	**Sotagliflozin 200 mg + Insulin (2)**	**Incremental value (2-1)**
Pooled inTandem1 and inTandem 2 population with: • BMI greater or equal to than 27 kg/m2 • People with baseline optimised insulin dose of >0.5iu/kg excluded • People with post-optimisation HbA_{1c} of 7% or more • **Severe Hypoglycaemic mortality rate of 4.45%** • **DKA mortality rate of 4%**			
Total Costs	£84,951.39	£86,109.73	£1,158.34
QALYs	13.144	13.187	0.043
		ICER	**£26,938**

Technical team scenario 4

4. Dose escalation:

    d. Explore sensitivity analysis on the proportion of people that require dose escalation
    e. Use data from the 400mg arm on effectiveness and adverse events to inform dose escalation

Sanofi response to Technical scenario 4

We have been unable to run these scenarios in time for this response. Furthermore due to technical constraints within the CDM it is not possible to switch patients from one treatment to another and to maintain the 2 year treatment duration for patients remaining on the 200mg dose. We have considered how to approximate meaningful analyses for the committee and will run the following:

- Implement the base case set of inputs from Table 1 with HbA1c at baseline ≥ 7%
- This will include patients starting on 400mg sotogliflozin AND attracting the treatment effects and adverse event profile associated with this dose.
- Provide a weighted average ICER between the 200mg basecase and the 400 mg scenario for 5%, 10%, 15% and 20% use of the 400mg dose.

These results will be available from the 24th July 2019. We realise that this is too late for this to be incorporated into the committee papers but will have these to hand and will be able to discuss them in committee if required.

We hope these additional analyses are useful to the committee.

Yours sincerely,

Jessamy Baird.

Director of patient Access, Sanofi UK and Ireland.

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

08th July 2019.

Dear Jasdeep,

Re: Sotagliflozin in combination with insulin, for treating type 1 diabetes [ID1376]

Sanofi welcomes the opportunity to respond to the technical consulation for the above appraisal and are pleased to provide the Committee with additional analyses for the basecase according to the preffered assumptions of the technical team. The cummulative impact on the ICER is presented in **Table 1** below for the following assumptions:

- **Scenario analysis 1**: Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and a HbA1c ≥ 7% and Total Basal insulin dose > 0.4units/kg/day
- **Scenario analysis 2:** Use the multiplicative approach to QALYs in line with NICE TSD 12
- **Scenario analysis 3:** Include impact of rare life-threatening urogenital infections
- **Scenario analysis 4:** Hypoglycaemic events: 50% of serious hypoglyceamic (SH) events need medical attention and costs in line with the NICE clinical guideline
- **Scenario analysis 5:** Scenario in which costs and benefits are cut at 2 years.

Note that this analysis excludes patients from the studies with insulin equal to or below 0.4 units/kg of bodyweight/day as discussed last week. We do not believe that it will make a substantive difference but will follow up with an equivalent analysis excluding pateints with 0.5 insulin equal to or below 0.5 units/kg of bodyweight/day.

Table 1. Cumulative impact of scenario analyses 1 to 5.

Analysis		ICER
SA1	Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and a HbA1c ≥ 7% and Total Basal ins dose > 0.4	£15,840
SA2 + SA1	Use the multiplicative approach to QALYs in line with NICE TSD 12	£13,753
SA3 + SA 1 + SA2	Include impact of rare life-threatening urogenital infections	£13,753
SA4 + SA1 + SA2 + SA3	Hypoglycaemic events: 50% of SH need medical attention and costs in line with the NICE clinical guideline	£13,753
SA5 + SA1 + SA2 + SA3 + SA4	Costs and benefits are cut at 2 years	**£24,696**

The cumulative impact of these scenarios results in an ICER of £24,696.

The incremental costs and QALYs for these analyses are provided in **Table 2** overleaf.

Table 2. Incremental costs and QALYs for scenario analyses 1 to 5.

		Insulin alone (1)	Sotagliflozin 200 mg + Insulin (2)	Incremental value (2-1)
Company Base Case				
	Total Costs	£ 78,731	£ 78,940	£ 209
	QALYs	8.695	8.803	0.108
	ICER			£ 1,934
SA 1	**Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and a HbA1c ≥ 7% and Total Bsl ins dose > 0.4**			
	Total Costs	£ 80,834.07	£ 82,055.32	£ 1,221.25
	QALYs	£13.09	£ 13.16	£ 0.08
	ICER (with all changes incorporated [SA 1])			**£ 15,840.00**
	ICER change (compared with Base Case)			£13,906.00
SA 2	**Use the multiplicative approach to QALYs in line with NICE TSD 12**			
	Total Costs	£ 80,834.07	£ 82,055.32	£ 1,221.25
	QALYs	£12.68	£ 12.77	£ 0.09
	ICER (with all changes incorporated [SA 1 + SA 2])			**£13,753.00**
	ICER change (compared with Base Case)			£11,819.00
SA 3	**Include impact of rare life-threatening urogenital infections**			
	Total Costs	£80,834.07	£82,055.32	£1,221.25
	QALYs	£12.68	£12.77	£ 0.09
	ICER (with all changes incorporated [SA 1 + SA 2 + SA 3])			**£13,753.00**
	ICER change (compared with Base Case)			£ 11,819.00
SA 4	**Hypoglycaemic events: 50% of SH need medical attention and costs in line with the NICE clinical guideline**			
	Total Costs	£80,834.07	£ 82,055.32	£1,221.25
	QALYs	£12.68	£12.77	£0.09
	ICER (with all changes incorporated [SA 1 + SA 2 + SA 3 + SA 4])			**£13,753.00**
	ICER change (compared with Base Case)			£ 11,819.00
SA 5	**2yrs scenario**			
	Total Costs	£ 80,833.12	£ 81,448.07	£ 614.95
	QALYs	£12.68	£12.71	£0.03
	ICER (with all changes incorporated [SA 1 + SA 2 + SA 3 + SA 4 + SA 5])			**£ 24,696.00**
	ICER change (compared with Base Case)			£ 22,762.00

We will continue to work on further analyses and provide these as soon as we can.

Yours sincerely,
Jessamy Baird.
Director of patient Access, Sanofi UK and Ireland.

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

10th July 2019.

Dear Jasdeep,

Re: Sotagliflozin in combination with insulin, for treating type 1 diabetes [ID1376]

Once again Sanofi welcomes the opportunity to respond to the technical consulation for the above appraisal and are pleased to provide the Committee with updated analyses for the basecase according to the preffered assumptions of the technical team. The cummulative impact on the ICER is presented in **Table 1** below for the following assumptions:

- **Scenario analysis 1**: Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and Total Basal insulin dose > 0.5units/kg/day (NOTE this does not include an HbA1c cut off. This is in line with the recommendation in the FAD for dapagliflozin)
- **Scenario analysis 2:** Use the multiplicative approach to QALYs in line with NICE TSD 12
- **Scenario analysis 3:** Include impact of rare life-threatening urogenital infections
- **Scenario analysis 4:** Hypoglycaemic events: 50% of serious hypoglyceamic (SH) events need medical attention and costs in line with the NICE clinical guideline
- **Scenario analysis 5:** Scenario in which costs and benefits are cut at 2 years.

Note that this analysis **excludes** patients from the studies with insulin equal to or below 0.5 units/kg of bodyweight/day and **does not** include an HbA_{1c} cut-off as an entry criterion. Analyses are for the 200mg group from inTandem2 only as requested.

Table 1. Cumulative impact of scenario analyses 1 to 5.

Analysis		ICER
SA1	Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and Total Basal ins dose > 0.5iu/kg	£10,227
SA2 + SA1	Use the multiplicative approach to QALYs in line with NICE TSD 12	£8,930
SA3 + SA 1 + SA2	Include impact of rare life-threatening urogenital infections	£8,930
SA4 + SA1 + SA2 + SA3	Hypoglycaemic events: 50% of SH need medical attention and costs in line with the NICE clinical guideline	£10,558
SA5 + SA1 + SA2 + SA3 + SA4	Costs and benefits are cut at 2 years	£23,267

The cumulative impact of these scenarios results in an ICER of £23,267.

The incremental costs and QALYs for these analyses are provided in **Table 2** overleaf.

Table 2. Incremental costs and QALYs for scenario analyses 1 to 5.

		Insulin alone (1)	Sotagliflozin 200 mg + Insulin (2)	Incremental value (2-1)
Company Base Case				
	Total Costs	£ 78,731	£ 78,940	£ 209
	QALYs	8.695	8.803	0.108
	ICER			£ 1,934
SA 1	**Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and Total Basal ins dose > 0.5iu/kg**			
	Total Costs	£78,939.17	£79,776.80	£837.63
	QALYs	13.09	13.16	0.08
	ICER (with all changes incorporated [SA 1])			**£ 10,277**
	ICER change (compared with Base Case)			£8,293
SA 2	**Use the multiplicative approach to QALYs in line with NICE TSD 12**			
	Total Costs	£78,939.17	£79,776.80	£837.63
	QALYs	13.21	13.31	0.09
	ICER (with all changes incorporated [SA 1 + SA 2])			**£8,930**
	ICER change (compared with Base Case)			£6,996
SA 3	**Include impact of rare life-threatening urogenital infections**			
	Total Costs	£78,939.17	£79,776.80	£837.63
	QALYs	13.21	13.31	0.09
	ICER (with all changes incorporated [SA 1 + SA 2 + SA 3])			**£8,930**
	ICER change (compared with Base Case)			£6,996
SA 4	**Hypoglycaemic events: 50% of SH need medical attention and costs in line with the NICE clinical guideline**			
	Total Costs	£77,832.83	£78,823.14	£990.31
	QALYs	13.21	13.31	0.09
	ICER (with all changes incorporated [SA 1 + SA 2 + SA 3 + SA 4])			**£10,558**
	ICER change (compared with Base Case)			£8,624
SA 5	**2yrs scenario**			
	Total Costs	£77,832.83	£78,516.88	£684.05
	QALYs	13.21	13.24	0.03
	ICER (with all changes incorporated [SA 1 + SA 2 + SA 3 + SA 4 + SA 5])			**£23,267**
	ICER change (compared with Base Case)			£21,333

The baseline patient characteristics for this population are provided in Appendix 1

We hope these additional analyses are useful to the committee.
Yours sincerely,
Jessamy Baird.
Director of patient Access, Sanofi UK and Ireland.

Appendix 1. CDM inputs. Baseline characteristics: inTandem2 200mg sotagliflozin patients with a BMI ≥ 27 kg/m² and Total Basal ins dose > 0.5iu/kg

PATIENT DEMOGRAPHICS	Mean	SD	SE
Start age	43.14	12.26	0.66
Duration of Diabetes	19.17	10.45	0.57
Prop. Male	0.556		

BASELINE RISK FACTORS	Mean	SD	SE
HbA1c	7.76	0.81	0.04
SBP	127.14	14.70	0.80
DBP	79.29	0.80	0.04
T-CHOL	188.96	36.26	1.97
HDL	58.63	15.34	0.83
LDL	106.11	31.79	1.72
Baseline triglycerides	119.07	72.61	3.94
BMI	31.58	3.92	0.21
eGFR	89.43	17.60	0.95
Haemoglobin	14.29	1.31	0.07
White Blood Cells	6.8		0.00
Heart rate	72		0.00
Waist-to-hip ratio	0.9		0.00
Urine albumin creatinine ratio	3.1		0.00
Serum creatinin	0.860	0.160	0.01
Serum albumin	4.32	0.24	0.01
Prop. smoker	0.01		
Cigarettes/day	2.00		
Alcohol consumption	9.00		

RACIAL CHARACTERISTICS	Mean
Prop. White	0.950
Prop. Black	0.003
Prop. Hispanic	0.009
Prop. Native American	0.009
Prop. Asian/Pacific Islander	0.012
Prop. Australian (south Europ.)	0.009
Prop. Australian (Aboriginal)	0.009

BASELINE CVD COMPLICATIONS	Mean
Prop. MI	0.018
Prop. Angina	0.009
Prop. PVD	0.009
Prop. stroke	0.003
Prop. HF	0.003
Prop. Atrial filbrillation	0.009

Prop. LVH	0.003

BASELINE RENAL COMPLICATIONS	Mean
Prop. MA	0.015
Prop. GRP	0.003
Prop. ESRD	0.003

BASELINE RETINOPATHY COMPLICATIONS	Mean
Prop. BDR	0.232
Prop. PDR	0.003
Prop. SVL	0.000

BASELINE MACULAR EDEMA	Mean
Prop. ME	0.006

BASELINE CATARACT	Mean
Prop. cataract	0.035

BASELINE FOOT ULCER COMPLICATIONS	Mean
Prop. uninfected ulcer	0.009
Prop. infected ulcer	0.000
Prop. healed ulcer	0.000
Prop. history of amputation	0.009

BASELINE NEUROPATHY	Mean
Prop. neuropathy	0.197

BASELINE DEPRESSION	Mean
Prop. depression	0.085

Appendix 2. CDM inputs. Safety: inTandem2 200mg sotagliflozin patients with a BMI ≥ 27 kg/m² and Total Basal ins dose > 0.5iu/kg

Variable	Placebo	Sotagliflozin 200mg	Sotagliflozin 400mg
Non severe documented symptomatic hypoglycaemia (plasma glucose <= 70 mg/dL [3.9 mmol/L]) (Core + Long-term Extension)			
Number of events	5600	5737	5621
Even rate per 100 patient years	56.3	55.1	48.9
Severe hypoglycaemia (Core + Long-term Extension)			
Number of events	8	3	4
Even rate per 100 patient years	7.692	2.632	3.279
DKA during the Overall (Core + Long-term Extension)			
Number of events	0	2	4

Even rate per 100 patient years	0	1.754	3.279
Fournier's gangrene (using the spot of Edema event in the model)			
Even rate per 100 patient years	0	0.001	0.001

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

12th July 2019.

Dear Jasdeep,

Re: Sotagliflozin in combination with insulin, for treating type 1 diabetes [ID1376]

Once again Sanofi welcomes the opportunity to respond to the technical consulation for the above appraisal and are pleased to provide the Committee with the following sensitivity analyses including the preffered assumptions of the technical team. As a reminder the preferred assumptions forming the 'technical team base case' are as follows:

- **Scenario analysis 1**: Clinical data from inTandem2 considering patients with a BMI ≥ 27 kg/m² and Total Basal insulin dose > 0.5units/kg/day
- **Scenario analysis 2:** Use the multiplicative approach to QALYs in line with NICE TSD 12
- **Scenario analysis 3:** Include impact of rare life-threatening urogenital infections
- **Scenario analysis 4:** Hypoglycaemic events: 50% of serious hypoglyceamic (SH) events need medical attention and costs in line with the NICE clinical guideline
- **Scenario analysis 5:** Scenario in which costs and benefits are cut at 2 years.

Working from the aggregated preferred assumptions we have undertaken the following sensitivity analyses:

Table 1. Summary of sensitivity analyses 5.1 to 5.6.

Analysis		ICER
SA 5.1	Preferred settings + effects up to 5yrs	£10,568
SA 5.2	Preferred scenario decreasing DKA rate by 5%	£22,760
SA 5.3	Preferred scenario increasing DKA rate by 5%	£19,451
SA 5.4	Preferred scenario decreasing DKA mortality rate by 5%	£23,267
SA 5.5	Preferred scenario increasing DKA mortality rate by 5%	£23,246
SA 5.6	Preferred scenario decreasing SH mortality rate by 5%	£23,267
SA 5.7	Preferred scenario decreasing SH mortality rate by 5%	£23,267

There is very little or no effect due to increasing or decreasing the DKA rate or mortality rates due to DKA or severe hypo (SH). This is because the DKA and SH rates observed in the population of interest were very low and varying these by 5% makes very little difference. (Table 2).

Table 2. DKA, DKA and SH rates observed in the population of interest

Scenario	DKA	DKA mortality	SH mortality
Base case	1.754	0.0500%	0.0030%
-5%	1.67	0.0475%	0.0029%
5%	1.84	0.0525%	0.0032%

The incremental costs and QALYs for these analyses are provided in **Table 3** below. Please note these are not cumulative.

Table 3. Incremental costs and QALYs for scenario analyses 5.1 to 5.6.

		Insulin alone (1)	Sotagliflozin 200 mg + Insulin (2)	Incremental value (2-1)
NICE/ERG Preferred Settings (equal to cumulative SA5)				
	Total Costs	£77,832.83	£78,516.88	£684.05
	QALYs	13.214	13.243	0.029
			ICER	**£23,246**
SA 5.1	**Preferred settings + effects up to 5yrs**			
	Total Costs	£77,832.83	£78,824.11	£991.28
	QALYs	13.214	13.307	0.093
			ICER	**£10,568**
			ICER change (compared with Base Case)	-£12,699
SA 5.2	**Preferred scenario decreasing DKA rate by 5%**			
	Total Costs	£77,832.83	£78,395.00	£562.17
	QALYs	13.214	13.238	0.02
			ICER	**£22,760**
			ICER change (compared with Base Case)	-£507
SA 5.3	**Preferred scenario increasing DKA rate by 5%**			
	Total Costs	£77,832.83	£78,488.32	£655.49
	QALYs	13.214	13.247	0.033
			ICER	**£19,451**
			ICER change (compared with Base Case)	£0
SA 5.4	**Preferred scenario decreasing DKA mortality rate by 5%**			
	Total Costs	£77,832.83	£78,516.88	£684.05
	QALYs	13.214	13.243	0.029
			ICER	**£23,267**
			ICER change (compared with Base Case)	£0
SA 5.5	**Preferred scenario increasing DKA mortality rate by 5%**			
	Total Costs	£77,832.83	£78,511.60	£678.77
	QALYs	13.214	13.243	0.029
			ICER	**£23,246**
			ICER change (compared with Base Case)	-£21
SA	**Preferred scenario decreasing SH mortality rate by 5%**			

5.6	*Total Costs*	£77,832.83	£78,516.88	£684.05
	QALYs	13.214	13.243	0.029
			ICER	**£23,267**
			ICER change (compared with Base Case)	£0
SA 5.7	**Preferred scenario increasing SH mortality rate by 5%**			
	Total Costs	£77,832.83	£78,516.88	£684.05
	QALYs	13.214	13.243	0.029
			ICER	**£23,267**
			ICER change (compared with Base Case)	£0

An additional question was asked by the technical team after providing the analyses on the 10/07/2019 which included the cumulative effect for the preferred assumptions (**Scenario analyses 1 to 5**):

NICE Question:

1. *I note that scenario 3 does not seem to impact on the incremental costs or QALYs and I assume this is because it is a rare adverse event that has very little impact overall. However, it would be useful for committee to have more information on how this scenario has been implemented in the model and the assumptions used. Please could you provide this? Additionally, please could you provide the ICERs for applying each individual scenario to the base case.*

Sanofi answer:

1. **Adverse event rates:** The MHRA warning states 6 Yellow Cards concerning Fournier's gangrene have been reported in a total estimated exposure to SGLT2 inhibitors of 548,565 patient's year in the UK. The estimated event rate per 100 patient years applied in the model was therefore estimated to be 0.001 (0.000010937*100) while patients remain on the Sotagliflozin arm.
   Given that the Core Diabetes Model doesn't have a dedicated place to capture this event, Fournier's gangrene was inputted into the model in the previously unused input for "Edema". Outcomes show 0 expected events given the low rate and the fact that the preferred settings consider a treatment rebound and discontinuation of Sotagliflozin at year 2."

2. We apologise that the ICERs for each individual scenario were not provided. To quickly provide the conservative scenario in which the cumulative ICER was calculated the CORE diabetes model was run with each scenario building on the last one. Hence, we have not simulated each scenario separately. If this is required, we can run the model again but we won't be able to send these results until early in the week commencing the 15th July.

We hope these additional analyses are useful to the committee.

Yours sincerely,

Jessamy Baird.

Director of patient Access, Sanofi UK and Ireland.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Sotagliflozin, in combination with insulin, for treating type 1 diabetes

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **27 June 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Michelle Lam**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**UK Clinical Pharmacy Association (UKCPA) Diabetes & Endocrinology Group**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: use of sotagliflozin in clinical practice	
1) In the appraisal of dapagliflozin for type 1 diabetes clinical experts explained that a period of optimised management would not be needed before starting treatment with dapagliflozin. Would this assumption also hold for sotagliflozin. If not, how long would insulin need to be trialled for? What would optimised management entail?	**The proposed place in therapy stated that optimised insulin should be in place before starting sotagliflozin. Optimised insulin therapy should entail the use of optimal doses of basal and mealtime insulin to achieve the glycaemic control closest to the individualised HbA1c and/or blood glucose targets without causing adverse effects, such as hypoglycaemia.**
2) What did optimised insulin manag in the inTandem trials entail? What proportion of patients in the trials had formal structured education, for example similar to Dose Adjustment For Normal Eating (DAFNE) used in the NHS?	**Prior to randomisation, participants underwent a 6-week insulin optimisation phase. Patients were not excluded from the trial if their HbA1c dropped by > 0.5% or to > 7.5% during the optimisation phase. Insulin optimisation refers to the adjustment of insulin to meet standard-of-care glycaemic targets starting 6 weeks prior to randomisation, which continued for the entire study. Optimised insulin was to maintain fasting or preprandial blood glucose between 4.4 and 7.2 mmol/L and 1- to 2-h postprandial glucose <10 mmol/L.**
3) In the appraisal of dapagliflozin for type 1 diabetes clinical experts noted that treatment effect might be greater in people who did not have a clinically significant improvement in HbA1c during the lead in phase of the trial. Would the expected treatment effect of sotagliflozin be different (higher or lower) for	**In real life clinical practice, we do not tend to see a 'lead-in' improvement so the treatment effect is likely to be higher when sotagliflozin is initiated.**

people who had a clinically significant reduction in HbA1c as a result of optimised management than people who saw little or no change?	
4) Who is likely to receive sotagliflozin in clinical practice?	**Those who are overweight/obese, in whom increasing insulin doses could lead to more weight gain and/or cause hypoglycaemia.**
5) Would patients with HbA1c lower than 7% be treated with sotagliflozin?	**According to NICE recommended HbA1c target of <6.5%, yes. However, not for those whose individualised target is >7%, e.g. the elderly frail patients, at risk of falls/severe hypoglycaemia.**
6) What is considered a clinically meaningful reduction in HbA1c with bolus insulin dose?	**HbA1c reduction of at least 1%**
Issue 2: generalisability of the inTandem trial population	
7) Who is likely to receive sotagliflozin in clinical practice?	**Same as question 4 above.**
8) Are the patients in the inTandem trials likely to reflect people seen in the NHS?	**Yes, the inclusion and exclusion criteria are reasonable and reflect patients seen in the NHS.**
Issue 3: prediction of complications associated with HbA1c levels	
9) Are results of the epidemiology of diabetes interventions and complications (EDIC) study generalisable to therapies such as sotagliflozin?	**It is true that SGLT2 inhibitors trial design and results do not match those of the EDIC and DCCT trial, and the EDIC and DCCT did not include the use of SGLT2 inhibitors. Also, the older insulins used in EDIC and DCCT do not match the insulin used in current clinical practice. However, these are the most robust data we currently have and the predictions based on these trial results seem reasonable.**
10) Are the assumptions in the company's economic model for predicting complications for changes reasonable (see table 1)?	**The economic model using the EDIC data is reasonable to predict the treatment impact of sotagliflozin. Given the EDIC trial is a relatively older study, our patient population is perhaps worse due to rising obesity leading to higher CVD risk and poorer glycaemic**

	control. The EDIC study may over-predict the impact of sotagliflozin because of the higher baseline risk in the current population. However, sotagliflozin has weight benefits that could reduce weight gain associated with insulin, which could lead to a more neutral prediction.
Issue 4: stopping treatment	
11) How would the stopping rule "consider discontinuing sotagliflozin if adequate insulination cannot be achieved on treatment" be applied in clinical practice? i) no improvement in glycaemic control? How would this be defined? ii) any other reason for stopping sotagliflozin in clinical practice (e.g. poor liver function)? iii) what proportion of patients are likely to stop sotagliflozin for any reason every year? Is the rate likely to be constant over time? Should the same probability of stopping treatment apply beyond year 1?	**If sotagliflozin is becoming a barrier to optimise insulin therapy, sotagliflozin should be stopped.** **i) If HbA1c reduction is less than 0.5% (5.5 mmol/mol), from SPCs, the average range of HbA1c reduction across the SGLT2s is 8-11 mmol/mol.** **ii) Dehydration leading to adverse effects, recurrent genitourinary infections that is intolerable to patient, acutely deteriorating renal function, DKA.** iii) **The rate is likely to be lower over time due to most side effects/adverse effects will arise during initial treatment period.**
12) Would people return to their baseline risk factor levels for all complications after stopping treatment?	**It has been demonstrated that there is a legacy effect with improved glycaemic control, such 'metabolic memory' leads to a reduction in microvascular complications in the future.**

	Hence, depending on the magnitude and duration of glycaemic improvement, people may have improved risk factors for complications after stopping treatment.
Issue 5: duration of treatment effect	
13) How long would you expect the treatment benefit of sotagliflozin to be maintained while on treatment? Would you expect treatment benefit to wane, if so after how long?	**Glycaemic control is expected to maintain or improve on treatment provided insulin therapy remains optimised and weight is maintained. Weight reduction due to reduced glucose reabsorption with sotagliflozin is dependent on plasma glucose concentration. Weight loss is also dose related. Hence, weight loss appears to be the greatest in the initial treatment period, when glycaemic control improves, a lower magnitude or a plateau of weight loss is expected (commonly within the first 6 months of starting treatment).**
Issue 6: baseline characteristics in the economic model	
14) Is it reasonable to apply the treatment effects from inTandem to the baseline characteristics from patients in the national diabetes audit?	**yes**
15) Do the baseline characteristics in the simulated cohort (table 3) reflect patients that would receive sotagliflozin in UK practice?	**Yes. BMI >27 and hba1c >8 sounds sensible**
Issue 7: – utility values	
16) Which approach is most appropriate for the estimation of QALYs, additive, multiplicative or minimum?	**The additive and multiplicative models assume a constant absolute or proportional effect, respectively, while the minimum model applies a disutility that can vary depending on the baseline utility modeled. The additive and multiplicative models have been shown to**

	produce similar results for individuals with both diabetes and thyroiditis. The multiplicative model produced accurate utilities for several comorbid conditions. Therefore, the multiplicative model appears to be the more appropriate approach in people with T1DM, in whom co-morbidities are common.
Issue 8: modelling adverse events	
17) Are all adverse events captured in the model?	**Yes**
18) Would the adverse event profile differ for sotagliflozin 400 mg dose compared with the 200 mg dose? If yes, how would it differ in terms of the frequency and type of adverse event.	**From trial data, the adverse event rates and severity are different between the two doses, e.g. DKA rates and hypoglycaemia rates.** **In inTandem 2, the rate of severe hypoglycaemia is higher in the sotagliflozin 200mg group (5%) than in the 400mg group (2.3%). Rate of DKA is lower in those receiving sotagliflozin 200 mg (6 patients, 2.3%) with one of whom used CSII, compared to those receiving sotagliflozin 400 mg (9 patients, 3.4%) with five of whom used CSII. 12 patients (4.6%) taking sotagliflozin 200 mg and 19 patients (7.2%) taking sotagliflozin 400 mg had GI side effects (diarrhoea).**
19) Is there a risk of Fournier's gangrene with sotagliflozin?	**Post-marketing cases of Fournier's gangrene have been reported in patients taking other SGLT2 inhibitors. Warnings about Fournier's gangrene will be added to the product information for all SGLT2 inhibitors. Hence, it is reasonable to assume this risk with sotagliflozin.**
20) what proportion of adverse events require	**It seems to be more reasonable to assume 50% of severe hypoglycaemic events need**

medical assistance? Do the costs from Hammer et al. or the NHS reference costs with CC scores 5 to 8 more appropriately reflect the cost of a severe hypoglycaemic event in clinical practice?	**medical assistance, rather than 100%. The NHS reference costs based on NICE NG 17 would more appropriately reflect this cost.**
21) In clinical practice, what proportion of patients eligible for sotagliflozin are experience experience diabetic ketoacidosis events currently, and what proportion would be expected to experience events on sotagliflozin?	**In an 8-week study in T1D patients, approximately 5% of patients treated with empagliflozin (2 of 42) were withdrawn from the study when they developed diabetic ketoacidosis.** **Ref: Cherney DZ, Perkins BA, Soleymanlou N, et al. . Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation . 2014;129:587–597.** **Ref: Perkins BA, Cherney DZ, Partridge H, et al. Sodium-glucose cotransporter 2 inhibition and glycemic control in type 1 diabetes: results of an 8-week open-label proof-of-concept trial. Diabetes Care . 2014;37:1480–1483.** **From the Food and Drug Administration Adverse Event Reporting System, between 2014 Q1 and 2016 Q3, found 2397 DKA reports with an SGLT2i. These included 680 DKA reports among 5694 individuals with reports for dapagliflozin (11.9%), 1362 DKA reports among 14,117 for canagliflozin (9.6%) and 355 DKA reports among 2719 for empagliflozin (13.1%). When searched specifically in type 1 DM patients, the number of DKA reports found for: Dapagliflozin was 85 (in 128 patients), Canagliflozin was 206 (in 297 patients), Empagliflozin was 26 (in 48 patients), Any SGLT2i was 317 (in 472 patients).** **Rate/1000 patients: Dapagliflozin 664.1, Canagliflozin 693.6, Empagliflozin 541.7, any SGLT2i 671.6.**

	This can give a prediction of real-life DKA rate of sotagliflozin. **Ref: SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA Adverse Event Reporting System. https://link.springer.com/article/10.1007/s00125-017-4301-8**
Issue 9: dose escalation	
22) The company estimated that *** people would be escalated to the 400 mg dose. Is this consistent with what is expected in clinical practice?	**Yes, doses should be escalated where possible for those who are not achieving glycaemic target on 200mg.**
23) The company have assumed that people with a BMI of 35 kg/m^2 or more will require dose escalation. Is this consistent with what is expected in clinical practice?	**Yes.**

Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376]

ERG CRITIQUE OF THE COMPANY'S RESPONSE TO TECHNICAL ENGAGEMENT

July 2019

This report was commissioned by the NIHR HTA Programme as project number 127657

BMJ Technology Assessment Group

1 SUMMARY OF ADDITIONAL ANALYSES CONDUCTED BY THE COMPANY

This report provides the ERG's critique of the company's response to the NICE Technical Team's latest set of preferred analyses that were requested of the company on 17 July 2019. The ERG provided an initial response by email to NICE regarding the company's previous analyses that were submitted by the company at various stages between 8 and 12 July. These analyses are largely superseded by the company's latest submission and, therefore, they will not be discussed further. This report will focus only on the analyses requested by NICE on 17 July.

One of the key differences in the updated set of analyses is the use of the pooled inTandem1 and inTandem2 trials to inform both the treatment effectiveness inputs and the baseline characteristics, as opposed to the company's earlier submission, which used only the inTandem2 trial. Although the inTandem2 trial included a European population with some UK patients, using this trial alone had limitations. The study had higher levels of the use of insulin pumps compared to the UK, and the sample size was smaller than the pooled trial analysis. The larger data set also allowed for more robust estimates when restricting by baseline HbA1c levels (post-optimisation) and insulin requirements. The NICE Technical Team's preferred base case is as follows:

1. Population for treatment effects and baseline characteristics:
    a. inTandem1 and inTandem2 pooled;
    b. BMI $\geq$ 27 kg/m^2;
    c. Insulin requirements $\geq$0.5 units per kg of body mass;
    d. Post-optimisation HbA1c $\geq$ 7%;
2. Treatment duration of 2 years;
3. Duration of 2 years for all treatment effects;
4. Utilities recommended by ScHARR 2019 report, based on fixed effects model;
5. Use multiplicative approach for utilities;
6. Include Fournier's gangrene in adverse events;
7. Apply costs of hypoglycaemic events from NICE guideline and assume 50% are hospitalised.

The NICE Technical Team also requested the following scenario analyses around this preferred base case. These are as follows:

1. Restrict the population further by increasing the post-optimisation HbA1c cut-off to 8%;
2. Range of alternatives for treatment duration and treatment effect durations:
    a. 1 year on treatment, 1 year of benefit;
    b. 2 years on treatment, 2 years of benefit;
    c. 2 years of treatment, half treatment effect in year 2.
3. For each of the scenarios 2a, 2b and 2c, applying the following additional criteria:
    a. No benefit oh HbA1c after 1 year but BMI effects are extrapolated beyond trial period;
    b. No impact of HbA1c on cardiovascular risk compared with placebo after 1 year but other benefits continue for the duration of treatment;
4. Increasing diabetic ketoacidosis mortality rate to 4%;
5. Increasing severe hypoglycaemia mortality rate to 4.45%;
6. Explore sensitivity analyses on proportion of patients who require dose escalation to 400mg, making use of the 400mg dose trial data to inform the effectiveness and adverse events rates for the proportion of patients assumed to escalate.

The ERG's assessment of the analyses submitted by the company in response to the NICE Technical Team's preferred analyses is given in Section 2.

2 ERG CRITIQUE OF THE NEW EVIDENCE

2.1 NICE Technical Team's base case population

The NICE Technical Team's preferred base case analysis based on the pooled trial data with the subgrouping criteria applied as per the description in Section 1, resulted in a sample size of 217 for the sotagliflozin group and 216 for the placebo group. These data were used to inform the baseline characteristics and treatment effectiveness in the NICE Technical Team's preferred base case. The company's base case used pooled data from the inTandem1 and inTandem2 trials (with only the BMI restriction applied) for treatment effectiveness but data from the National Diabetes Audit (NDA) for the baseline characteristics.

The ERG considers it important that the data used to estimate treatment effects are used to inform the baseline characteristics to which the effects are applied. If different sources are used, then the potential correlation between baseline values and the treatment effects is lost and potentially biases the results. However, the ERG notes that there is a limitation in the NICE Technical Team's and ERG's preferred approach in that the trial population may not be fully reflective of the UK population expected to receive sotagliflozin if a positive recommendation were to be granted. This is a limitation that cannot be fully tested as there is no evidence of treatment effects in this population. However, the ERG has performed some scenarios to test the impact of changing certain individual values for the baseline characteristics in the NICE Technical Team's preferred analysis to the values of the NDA cohort where there are important differences. The full results of these analyses are given in Section 3. A comparison of the baseline characteristics in this updated dataset compared to the data used to estimate treatment effects in the company's base case and the NDA cohort used for baseline characteristics is given in Table 1.

Table 1. Comparison of baseline characteristics

Baseline Values	Units/Range	NICE Technical Team's preferred cohort	Company's treatment effectiveness cohort	NDA cohort used to inform baseline characteristics in company's base case
Demographics				
Start age	Years	43.95	44.87	42.98
Duration of Diabetes	Years	21.42	22	17
Prop. Male	[0-1]	0.550	0.509	0.567
Risk Factors				
HbA1c	%-points	7.85	7.66	8.6
SBP	mmHg	124.35	124.15	128.27
DBP	mmHg	78.33	78.28	80
T-CHOL	mg/dL	178.73	178.41	176.5
HDL-C	mg/dL	58.08	60.67	50.25
LDL-C	mg/dL	98.82	97.15	109.75
Baseline triglycerides	mg/dL	108.02	101.79	81.5
BMI	kg/m2	32.24	32.16	27.09
eGFR	ml/min/1.73m2	88.86	87.77	77.5
Haemoglobin	gr/dl	14.33	14.22	14.5
White Blood Cells	10^6/ml	6.8	6.8	6.8
Heart rate	bpm	72	72	72
Waist-to-hip ratio	(1 unit)	0.9	0.9	0.9
Urine albumin creatinine ratio	mg/mmol	3.1	3.1	3.1
Serum creatinine	mg/dl	0.87	0.86	1.1
Serum albumin	g/dl	4.3	4.3	3.9
Proportion of smokers	[0-1]	0.01	0.01	0.22
Cigarettes/Day	Number/Day	2	11	12
Alcohol consumption	Oz/week	9	9	9

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T-CHOL, total cholesterol;

The notable differences between the NICE Technical Team's preferred cohort and the NDA cohort identified by the ERG are: duration of diabetes; baseline HbA1c; high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C); triglycerides; eGFR; serum creatinine; the proportion who are smokers; and, the number of cigarettes smoked per day. As the lipid parameters are all highly correlated, the ERG tested these together as one scenario. The ERG notes also that BMI is lower in the NDA cohort but given the BMI restrictions in the marketing authorisation, the NICE Technical Team's preferred cohort is more reflective than the NDA for this parameter.

2.2 Comparison of treatment effects

A comparison of the treatment effects for the NICE Technical Team's preferred data set and the data set used in the company's base case analysis is given in Table 2.

Table 2. Comparison of treatment effects

Treatment effects	Units/Range	NICE Technical Team's preferred cohort			Company's treatment effectiveness cohort		
		Sota.	Placebo	Difference	Sota.	Placebo	Difference
HbA1c	%-points	-0.31	-0.03	**-0.28**	-0.24	0	**-0.24**
SBP	mmHg	-1.38	0.8	**-2.18**	-1.74	0.4	**-2.14**
DBP	mmHg	-0.69	0.12	**-0.81**	-1.18	-0.18	**-1.00**
T-CHOL	mg/dL	9.27	4.82	**4.45**	8.84	4.44	**4.40**
HDL-C	mg/dL	2.9	0.33	**2.57**	2.36	0.04	**2.32**
LDL-C	mg/dL	1.55	0.25	**1.3**	5.29	4.07	**1.22**
Triglycerides	mg/dL	7.63	8.96	**-1.33**	7.5	7.01	**0.49**
BMI	kg/m2	-0.6	0.33	**-0.93**	-0.77	0.28	**-1.05**
eGFR	ml/min/1.73m^2	-3.02	-0.89	**-2.13**	-2.9	-0.43	**-2.47**

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Sota., sotagliflozin; T-CHOL, total cholesterol;

The ERG notes that the NICE Technical Team's preferred set of analyses results in a marginally greater treatment effect in terms of HbA1c but has a lesser effect on diastolic blood pressure (DBP). Another notable difference between the treatment effects estimated from the two data sets is that in the NICE Technical Team's preferred analysis, triglycerides have a lesser increase for sotagliflozin compared to placebo whereas in the company's analysis sotagliflozin increased triglycerides more than placebo. In addition, although the difference in effect between the two treatment groups is not too dissimilar, there were very different treatment effects for LDL-C between the two data sets.

2.3 Company's analyses

2.3.1 NICE Technical Team's base case

The company appear to have implemented the NICE Technical Team's preferred base case appropriately and the ERG has not identified any errors in their intended application of the analyses.

The ERG notes that the treatment costs in the model are slightly different to those applied for the company's base case analysis, and this difference has not been reported by the company. However, the difference in costs between the sotagliflozin group and the placebo group appears to be very similar, and the ERG considers the difference may relate to the differences in baseline insulin delivery methods in the updated data set.

2.3.2 Scenario with 8% HbA1c cut-off

The company provided a scenario in which the data set used for the NICE Technical Team's preferred analysis was restricted further with an 8% HbA1c cut-off. This reduced the sample size to 98 in the sotagliflozin group and 84 in the placebo group. In terms of baseline characteristics, there was a clear expected difference in the baseline HbA1c levels and some slight increases in lipids and a reduced proportion of males, but generally the values were very similar. A comparison of the baseline characteristics between the NICE Technical Team's preferred analysis and the scenario analysis is shown in Table 3.

Table 3. Comparison of baseline characteristics

Baseline Values	Units/Range	NICE Technical Team's preferred cohort	8% HbA1c cut-off
Patient demographics			
Start age	Years	43.95	44.33
Duration of Diabetes	Years	21.42	21
Prop. Male	[0-1]	0.550	0.502
Baseline risk factors			
HbA1c	%-points	7.85	8.43
SBP	mmHg	124.35	125.07
DBP	mmHg	78.33	78.96
T-CHOL	mg/dL	178.73	185.19
HDL-C	mg/dL	58.08	58.16
LDL-C	mg/dL	98.82	104.02
Baseline triglycerides	mg/dL	108.02	113.63
BMI	kg/m2	32.24	32.7
eGFR	ml/min/1.73m 2	88.86	89.83
Haemoglobin	gr/dl	14.33	14.2
White Blood Cells	10^6/ml	6.8	6.8
Heart rate	bpm	72	72
Waist-to-hip ratio	(1 unit)	0.9	0.9
Urine albumin creatinine ratio	mg/mmol	3.1	3.1
Serum creatinin	mg/dl	0.87	0.85
Serum albumin	g/dl	4.3	4.27
Proportion of smokers	[0-1]	0.01	0.01
Cigarettes/Day	Number/Day	2	2

Alcohol consumption	Oz/week	9	9

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T-CHOL, total cholesterol;

In terms of treatment effects, the difference in HbA1c change is reduced slightly in the data with the 8% cut-off applied. SBP shows a greater reduction in this scenario while DBP appears to be higher in the placebo group resulting in a slightly greater reduction rather than an increase.

Total cholesterol shows a large change with much closer values in the scenario analyses compared to a greater increase from baseline in the sotagliflozin group for the NICE Technical Team's preferred analysis. A more extreme change was shown in LDL-C in which the direction of effect reversed from a greater increase for sotagliflozin to a relative decrease in the scenario analysis. Other parameters showed some differences but less extreme. A comparison of the values is given in Table 4.

Table 4. Comparison of treatment effects

Treatment effects	Units/Range	NICE Technical Team's preferred cohort			Scenario with 8% HbA1c cut-off		
		Sota.	Placebo	Difference	Sota.	Placebo	Difference
HbA1c	%-points	-0.31	-0.03	**-0.28**	-0.41	-0.16	**-0.25**
SBP	mmHg	-1.38	0.8	**-2.18**	-1.62	1.06	**-2.68**
DBP	mmHg	-0.69	0.12	**-0.81**	-0.33	-0.35	**0.02**
T-CHOL	mg/dL	9.27	4.82	**4.45**	7.29	7.62	**-0.33**
HDL-C	mg/dL	2.9	0.33	**2.57**	2.26	-0.23	**2.49**
LDL-C	mg/dL	1.55	0.25	**1.3**	3.44	7.11	**-3.67**
Triglycerides	mg/dL	7.63	8.96	**-1.33**	7.4	9.76	**-2.36**
BMI	kg/m2	-0.6	0.33	**-0.93**	-0.46	0.25	**-0.71**
eGFR	ml/min/1.73m^2	-3.02	-0.89	**-2.13**	-3.70	-1.71	**-1.99**

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Sota., sotagliflozin; T-CHOL, total cholesterol;

2.3.3 Scenario with treatment effects in trial data from 6 to 12 months extrapolated to year 2

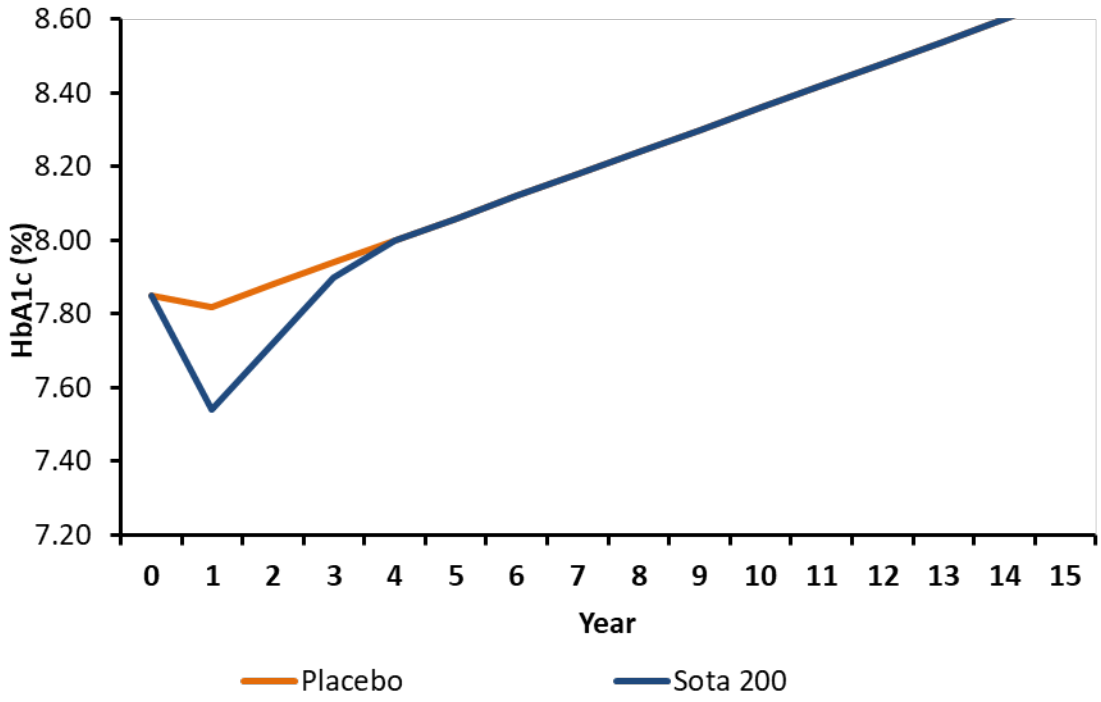
In response to NICE's request for this analysis the company stated that the treatment effect decrease between week 24 and week 52 in the trials does not return to placebo at year 2 and have provided an analysis to attempt to demonstrate this. Due to time constraints, the company were unable to request the 24-week data cuts for the NICE Technical Team's preferred data set in time to provide the relevant trends in HbA1c for this population. However, the company have used the 24- and 52-week data from the previous analysis of the pooled inTandem1 and inTandem2 trials with BMI≥27kg/m^2 and applied these trends to extrapolate the treatment effects in the NICE Technical Team's preferred analysis. The data used to estimate the trends is given in Table 5.

Table 5. Data used to estimate HbA1c trends

Time	Placebo	Sotagliflozin
24 weeks	7.61	7.27
52 weeks	7.67	7.45
Incremental	**0.06**	**0.18**

The company used the values of 0.06 and 0.18 for the insulin-only group and sotagliflozin group, respectively, and applied these at each yearly cycle to estimate the future HbA1c levels until the sotagliflozin value would become greater than the insulin-only group, at which point the sotagliflozin group value was capped by the insulin only group value. The resulting progressions are demonstrated in Figure 1.

Figure 1. HbA1c progressions in the scenario (extracted from company's supplementary excel file)



However, the ERG notes that the company have taken differences in HbA1c over a 6-month period and applied them directly as annual changes in the model. Therefore, the ERG considers the company's application of this scenario analysis to be flawed, and these differences should have been doubled to reflect extrapolated annual progressions rather than 6-monthly progressions.

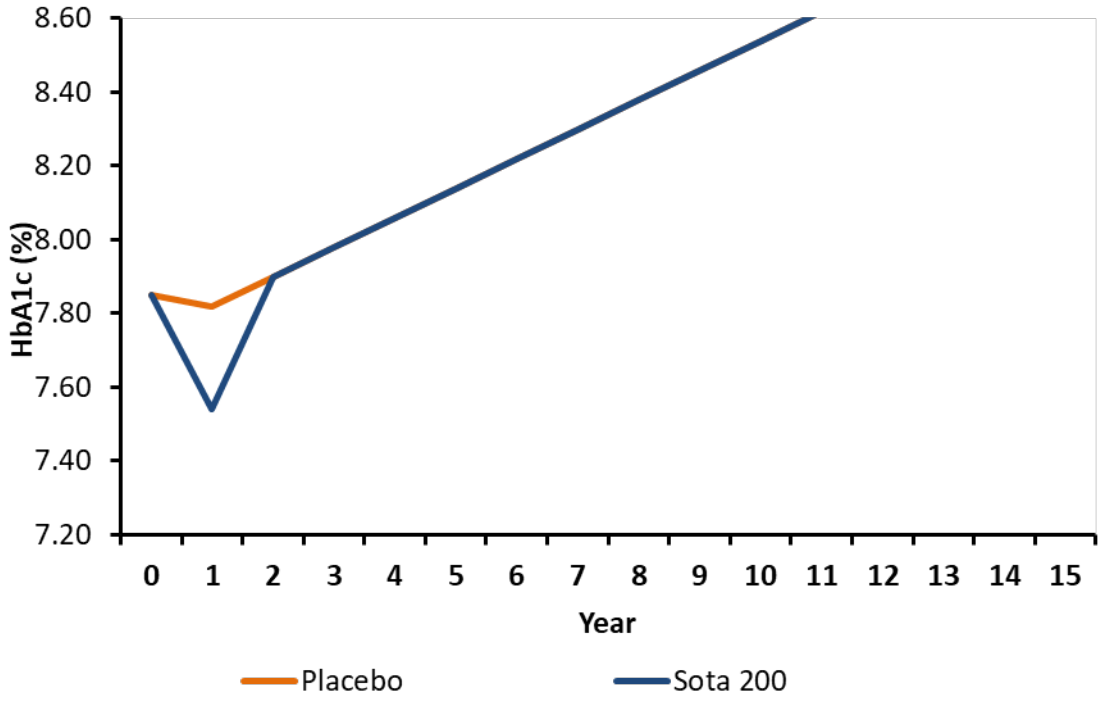
Further to this, the ERG in unsure of the data used in the company's analysis and this does not match the data that the ERG has reviewed previously, as shown in Table 9 on page 56 of the original ERG report. An extract of this data is given in Table 6.

Table 6. HbA1c (%) change from baseline analyses for the pooled inTandem1 and inTandem2 trials with BMI ≥ 27 kg/m2 subpopulation

Analysis	LSM change from baseline (%)	
	Sotagliflozin 200 mg	Insulin-only
24 weeks	−0.43	−0.04
52 weeks	−0.24	−0.00

These data show that the HbA1c levels increase by 0.19% in the sotagliflozin group and by 0.04% in the insulin-only group. This is equivalent to annual increases of 0.38% and 0.08%, respectively. Applying these increments to the year 1 HbA1c levels in the NICE Technical teams preferred analysis results in HbA1c levels of 8.20% and 7.62%, for the sotagliflozin group and the insulin-only group, respectively. Thus, in year 2 the HbA1c levels are expected to go well beyond that of the insulin only group under the assumptions of this extrapolation, and the treatment effect would be lost by year 2. This is shown graphically in Figure 2. The impact of this is similar to the NICE Technical Team's preferred analysis, as described in Section 1, so the ERG has not re-run this analysis in the model. Note that the ICERs, presented in Section 3, are greater than the NICE Technical Team's preferred base case because treatment duration was increased to 5 years to account for the extended benefits in the company's analysis.

Figure 2. ERG corrected HbA1c progressions for this scenario



2.3.4 Treatment discontinuation rate extrapolated from trial data between 6 and 12 months, and all discontinue if the improvement in HbA1c is not greater than 0.3%

Due to limitations in the CORE Diabetes Model (CDM), the company were unable to apply two different criteria for treatment discontinuation. Therefore, to partially address the question, the company applied a discontinuation rule in which patients would switch to the insulin-only group when they reach a certain HbA1c threshold. This threshold was defined as 0.3% less than the average baseline HbA1c of the cohort. The company noted that this rule meant that some patients would discontinue after 2 years.

However, the supplementary Excel inputs file provided by the company suggests that the company applied discontinuation for all patients in the model cycle when HbA1c is increased by at least 0.3% from the year-1 value. This is different to assuming a minimum reduction of 0.3% from the cohort average. Furthermore, the analyses implemented in the CDM do not appear to be applied correctly. The treatment durations applied are for 5 years for all patients and the treatment effects differ from those that the company applied in Section 2.3.3 despite the company's supplementary inputs Excel file stating that they are intended to be equivalent. These inputs indicate that the treatment effects should have been the same as those applied by the company in Section 2.3.3 but the treatment duration reduced to 3 years; the point at which the HbA1c level increased by at least 0.3% from the year-1 value. In addition, the results provided in the document do not match the results in the CDM simulation. Due to time constraints, the ERG is unable to re-run the appropriate analysis. As the ERG considers the results of this analysis unreliable, they are not presented.

2.3.5 Mortality rates scenarios

The company performed the scenarios requested by the NICE Technical Team relating to the mortality rates for diabetic ketoacidosis and severe hypoglycaemia and these appear to have been implemented correctly.

3 COMPANY'S SUBMITTED ANLAYSES

3.1 NICE Technical Team's preferred base case

The results of the NICE Technical Team's preferred base case, as described in Section 1, are given in Table 7, and the results of the scenario analyses using the data with the 8% HbA1c cut-off are given in Table 8.

Table 7. NICE Technical Team's preferred base case

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£87,077	30.67	13.37	-	-	-	-
Sotagliflozin	£87,695	30.75	13.40	£618	0.08	0.03	£18,665
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 8. NICE Technical Team's preferred base case with 8% HbA1c cut-off

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£89,540	29.15	12.77	-	-	-	-
Sotagliflozin	£90,571	29.25	12.82	£1,031	0.10	0.05	£21,309
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

3.2 Scenario for treatment effect extrapolation from trial data between 6 and 12 months

The results of this scenario using the 7% HbA1c cut-off and the 8% HbA1c cut-off are given in Table 9 and Table 10, respectively.

Table 9. Treatment effect extrapolation (7% HbA1c cut-off)

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£91,827	29.42	12.90	-	-	-	-
Sotagliflozin	£93,537	29.53	12.96	£1,711	0.11	0.06	£28,189
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 10. Treatment effect extrapolation (8% HbA1c cut-off)

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£94,271	27.88	12.30	-	-	-	-
Sotagliflozin	£96,499	28.06	12.38	£2,227	0.18	0.08	£28,628

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.

3.3 Scenario with HbA1c stopping rule applied

Company's analyses were not implemented correctly and thus the results have not been presented here.

3.4 Scenario with diabetic ketoacidosis mortality rate set to 4%

The scenario analysis with the mortality rate for diabetic ketoacidosis set to 4% was only performed on the dataset with the 7% HbA1c cut-off. The results are given in Table 11.

Table 11. Diabetic ketoacidosis mortality rate set to 4% (7% HbA1c cut-off)

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£87,077	30.67	13.37	-	-	-	-
Sotagliflozin	£87,636	30.70	13.38	£558	0.03	0.01	£47,725
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

3.5 Scenario with severe hypoglycaemia mortality rate set to 4.45%

The scenario analysis with the mortality rate for severe hypoglycaemia set to 4.45% was only performed on the dataset with the 7% HbA1c cut-off. The results are given in Table 12.

Table 12. Severe hypoglycaemia mortality rate set to 4.45% (7% HbA1c cut-off)

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£84,951	29.96	13.14	-	-	-	-
Sotagliflozin	£86,215	30.10	13.20	£1,264	0.14	0.06	£21,871
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

3.6 Scenario with diabetic ketoacidosis mortality rate set to 4% and severe hypoglycaemia mortality rate set to 4.45%

The scenario with the diabetic ketoacidosis mortality rate set to 4% and the severe hypoglycaemia mortality rate set to 4.45% was only performed on the dataset with the 7% HbA1c cut-off. The results are given in Table 13.

Table 13. Diabetic ketoacidosis mortality rate set to 4% and severe hypoglycaemia mortality rate set to 4.45% (7% HbA1c cut-off)

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£84,951	29.96	13.14	-	-	-	-

Sotagliflozin	£86,109	30.08	13.19	£1,158	0.12	0.04	£26,567
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

4 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG conducted a range of scenarios to test the impact that various baseline characteristics had on the results. This was done using the NICE Technical Team's preferred base case and changing single parameters to those from the NDA cohort. The results of each analyses are given in Table 14 to Table 21.

Table 14. Baseline duration of diabetes from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£86,649	30.33	13.29	-	-	-	-
Sotagliflozin	£87,014	30.44	13.34	£365	0.11	0.04	£8,357
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 15. Baseline HbA1c from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£95,939	29.04	12.60	-	-	-	-
Sotagliflozin	£96,210	29.07	12.63	£271	0.03	0.01	£10,815
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 16. Baseline lipids from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£86,605	30.50	13.30	-	-	-	-
Sotagliflozin	£87,599	30.55	13.32	£994	0.05	0.02	£42,308
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 17. Baseline eGFR from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£87,077	30.67	13.37	-	-	-	-
Sotagliflozin	£87,695	30.75	13.40	£618	0.08	0.03	£18,665
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 18. Baseline serum creatinine from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£87,077	30.67	13.37	-	-	-	-
Sotagliflozin	£87,695	30.75	13.40	£618	0.08	0.03	£18,665
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 19. Baseline proportion of smokers from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£86,857	30.60	13.34	-	-	-	-
Sotagliflozin	£87,777	30.66	13.37	£920	0.06	0.03	£31,948
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 20. Baseline number of cigarettes from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£87,121	30.68	13.37	-	-	-	-
Sotagliflozin	£87,713	30.75	13.40	£593	0.03	0.03	£18,237
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 21. Baseline proportion of smokers and the number of cigarettes from NDA

Treatment group	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Insulin-only	£86,772	30.59	13.34	-	-	-	-
Sotagliflozin	£87,777	30.67	13.37	£1,005	0.08	0.04	£30,104
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

5 DISCUSSION

The ERG would like to highlight that all the analyses presented show a relatively small gain in quality-adjusted life-years (QALYs) and this makes the results of the cost-effectiveness analysis unstable. Small changes in QALYs or costs can drastically change the overall incremental cost effectiveness ratio (ICER).

Further to this, the ERG would like to reiterate that the data applied are based on non-randomised subgroups of trial data which adds uncertainty to the treatment effects. As well as this, the treatment effects are being extrapolated beyond the 1 year of data available, and assumptions are required to determine how long patients remain on treatment. This added uncertainty in the inputs, combined with the instability of the outputs, brings potentially serious uncertainty to the conclusion of cost effectiveness.

This uncertainty is highlighted in scenarios such as those performed by the ERG to test the impact of the baseline characteristics. Changing just the values for lipids to those from the NDA cohort increases the ICER well above NICE's preferred upper threshold of £30,000 per QALY.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Sotagliflozin, in combination with insulin, for treating type 1 diabetes

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: July 2019

1. Summary of the technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale. Judgements that have been updated after engagement are highlighted in **bold** below.

1.1 In summary, the technical team considered the following:

Issue 1 **The population should be people with inadequate glycaemic control (HbA1c of 7% or more) and exclude people with low insulin requirement in line with the SPC for sotagliflozin.**

Issue 2 **Please note after technical engagement the issue 'generalisability of the inTandem trial population' was moved to 'outstanding uncertainties in the evidence base' see table 2.**

Issue 3 **The EDIC trial data is the best source of data available for the prediction of complications for type 1 diabetes, however the complications predicted using this data may not be translatable to sotagliflozin. Alternative scenarios for treatment benefit after the trial has ended should be considered.**

Issue 4 The probability of stopping sotagliflozin for any reason (for example, adverse events, not clinically effective) should be applied in year 1, decreasing in subsequent years.

Issue 5 There is a lack of evidence for the duration of treatment for sotagliflozin. **Treatment effect for HbA1c and weight may wane after the trial period. Different extrapolation of treatment benefit beyond the trial should be considered.**

Issue 6 The baseline characteristics in the company's economic model are taken from the national diabetes audit, for patients with an average starting BMI of 27 kg/m^2. Which does not fully reflect the marketing authorisation for sotagliflozin. **Baseline**

characteristics from the pooled inTandem trials seem most appropriate to be used in the economic model as it the same population that efficacy data is based on.

Issue 7 **Please note the issue 'utility values' was resolved during technical engagement, see table 3.**

Issue 8 **The rate of diabetic ketoacidosis events for sotagliflozin is uncertain but can have a large impact on the cost effectiveness. A range of diabetic ketoacidosis events should be explored in the economic model.**

Issue 9 **Please note after technical engagement the issue 'dose escalation' was moved to 'outstanding uncertainties in the evidence base' see table 2.**

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Patients who received the 400 mg dose in the inTandem trials did not escalate from the 200 mg dose contrary to dose escalation in the SPC and its intended use in clinical practice.
- In a scenario in the company's economic model the 400 mg dose was costed as 2 x 200 mg tablets. A single 400 mg dose of sotagliflozin is not expected to launch in the UK until [redacted]

1.3 The company did not provide a formal response to technical engagement to address the impact of the technical team's assumptions on the cost effectiveness. However, the company are due to provide additional analyses, which will be circulated ahead of the committee meeting and have not been incorporated in this document. An addendum to this report will be provided once results from analyses using the technical teams preferred assumptions is available.

1.4 The technology may be innovative (see table 3). However, it may not represent a step-change in the management of type 1 diabetes.

1.5 No equality issues were identified.

2. Key issues for consideration

Issue 1 – use of sotagliflozin in clinical practice

Questions for engagement	• In the appraisal of dapagliflozin for type 1 diabetes clinical experts explained that a period of optimised management would not be needed before starting treatment with dapagliflozin. Would this assumption also hold for sotagliflozin. If not, how long would insulin need to be trialled for? What would optimised management entail? • What did optimised insulin management in the inTandem trials entail? What proportion of patients in the trials had formal structured education, for example similar to Dose Adjustment For Normal Eating (DAFNE) used in the NHS? • In the appraisal of dapagliflozin for type 1 diabetes clinical experts noted that treatment effect might be greater in people who did not have a clinically significant improvement in HbA1c during the lead in phase of the trial. Would the expected treatment effect of sotagliflozin be different (higher or lower) for people who had a clinically significant reduction in HbA1c as a result of optimised management than people who saw little or no change? • Who is likely to receive sotagliflozin in clinical practice? • Would patients with HbA1c lower than 7% be treated with sotagliflozin? • What is considered a clinically meaningful reduction in HbA1c with bolus insulin dose?
Background/description of issue	The **company** positions sotagliflozin as an adjunct to insulin in people with type 1 diabetes when insulin does not provide adequate glycaemic control. The inTandem1 and inTandem2 trials included people who had glycated haemoglobin (HbA1c) levels that were between 7.0% and 11.0% at the time of sceening, however inadequately controlled HbA1c is defined as greater than 6.5% in the NICE guideline for type 1 diabetes in adults. The trials included a 6 week lead-in period in which insulin therapy was adjusted to achieve fasting self-monitored blood glucose between 4.4 and 7.2mmol/L and 2 hour peak postprandial self monitored blood glucose of less than 10mmol/L. When diabetes management was optimised HbA1c was less than 7% for 17% to 20% of patients (ERG report, section 4.5.1 p33). The **ERG** notes that optimisation prior to treatment initiation would not be practical in UK clinical

	practice. It is not clear whether someone who has a large reduction in HbA1c after 6 weeks of optimised management may continue to see improvements in glycaemic control beyond this point. The **technical team** notes that in clinical practice, measurements of HbA1c are not recommended less than every 3 months, optimisation before starting treatment would not be practical in UK clinical practice. In the appraisal of dapagliflozin for type 1 diabetes clinical experts explained that a period of optimised management would not be needed before starting treatment with dapagliflozin because it is expected that patients with type 1 diabetes will be on an optimised management plan routinely. Further, clinical experts also noted that treatment effect might be greater in people who did not have a clinically significant improvement in HbA1c during the lead in phase. The **company** originally provided an analysis of sotagliflozin in the intention to treat (ITT) population. In response to clarification questions, the company submitted post-hoc analysis based on the population in the positive CHMP opinion (patients who have a Body Mass Index higher than 27 kg/m2) based on pooled data from inTandem 1 and inTandem 2, (n=916). The **ERG's** clinical experts suggested that in clinical practice sotagliflozin may be further restricted to people who will derive greater treatment benefit (that is, used in people with a BMI greater than 30, estimated glomerular filtration rate of more than 60, receiving insulin by multiple daily injection, HbA1c of more than 8.5%, high cardiovascular risk, carbohydrate intake of more than 80 mg/day or willing to monitor blood glucose and urine ketones). The ERG were unable to assess this target population because the number of patients in this subgroup was too small.
Why this issue is important	If the lead-in period was too short and HbA1c levels were measured too early (less than 3 months), then the improvements observed in the early part of the trial could also be because of the effects of optimised management. Also, if in the NHS most people already have inadequate control despite 'optimised management', then few people would be expected to have a large reduction in HbA1c. If people who have large reductions in HbA1c during the optimisation period have a different response to sotaglioflozin than people with no or little change in HbA1c, then the treatment effect associated with sotagliflozin may not be generalisable to patients seen in the NHS. If the population likely to receive sotagliflozin is narrower than the positive CHMP opinion then the clinical efficacy of treatment in clinical practice is likely to differ with that seen in the trials.
Technical team preliminary	The 6-week, lead-in period is possibly too short to allow for stable HbA1c levels following optimised

judgement and rationale	management, which may affect the results. It is unclear whether people who have a large reduction in HbA1c as a result of therapy optimisation would have a different response to sotagliflozin than people who do not. The population likely to be seen in the NHS is narrower than the population outlined by the marketing authorisation. The clinical effectiveness of sotagliflozin for these people is therefore uncertain. In economic analyses looking at the population with inadequate glycaemic control (HbA1c more than 6.5%) at the start of treatment with sotagliflozin (after the lead in period) should be explored.
Summary of comments	**Comments received from company:** The company provided updated analyses which included clinical data from inTandem 2 for patients with a BMI of 27 kg/m² or more and a HbA1c of 7% or more and Total Basal insulin dose of more than 0.5 units/kg/day. This increased the company's base case ICER from £1,934 (based on baseline characteristics from the National Diabetes Audit and including all patients with a BMI of 27 kg/m^2 or more) to £10,277 per QALY gained. The company clarified verbally that the inTandem trials did not include any formal education such as DAFNE during the insulin optimisation period. The optimisation period was based on a protocol for insulin administration. **Comments received from a professional organisation:** A professional organisation stated that sotagliflozin is likely to be given to those who are overweight or obese, where increasing insulin doses could lead to more weight gain or cause hypoglycaemia. In clinical practice the organisation stated that it would not tend to see a 'lead-in' improvement in HbA1c, as seen in the inTandem trials. Therefore the treatment effect of sotagliflozin is likely to be higher in clinical practice than in the trials. In addition, it stated that the target for HbA1c levels in the NICE guidance is less than 6.5%. However some people will have individualised targets for HbA1c levels are more than 7%, for example for elderly patients at risk of falls or severe hypoglycaemia. A clinically meaningful reduction in HbA1c would be a reduction of at least 1%.

Technical team judgement after engagement	The SPC for sotagliflozin notes that sotagliflozin should not be initiated when patients are at a higher risk of diabetic ketoacidosis, such as people with low insulin needs. In the appraisal of dapagliflozin (ID1478) low insulin need was defined by clinical experts as 0.5 units of insulin per kilogram of body weight per day. The definition of 'low insulin need' is not expected to differ with sotagliflozin. Therefore, the updated population provided by the company for patients with a Total Basal insulin dose of more than 0.5 units/kg/day is in line with people who would receive sotagliflozin in the NHS. Although there are a range of different target levels for HbA1c in clinical practice, target levels are likely to be set at HbA1c of 7% or more in clinical practice. Therefore the technical team's preferred base case population includes people with a post-optimisation HbA1c level of 7% or more. The clinically meaningful reduction in HbA1c suggested by the professional organisation during technical engagement (1%) is higher than that suggested in the dapagliflozin appraisal ID1478 (0.3%). Clinical experts in the dapagliflozin appraisal explained that larger reductions in HbA1c are more difficult to reach at lower starting levels, so a clinically meaningful reduction in HbA1c depends on the starting level. For example, if the baseline level of HbA1c was no more than 8.5% then a reduction of 0.4% may be considered clinically meaningful. The committee concluded that a minimum, clinically meaningful reduction in HbA1c should consider variability baseline HbA1c levels and how long the reduction is sustained.

Issue 2 – generalisability of the inTandem trial population

Please note after technical engagement this issue was moved to 'outstanding uncertainties in the evidence base' see table 2.

Issue 3 – prediction of complications associated with HbA1c levels

Questions for engagement	• Are results of the epidemiology of diabetes interventions and complications (EDIC) study generalisable to therapies such as sotagliflozin? • Are the assumptions in the company's economic model for predicting complications for changes reasonable (see table 1)?
Background/description of issue	The **technical team** noted that the progression of HbA1c was not based on data for the use of sotagliflozin. This was also an issue in the appraisal of dapagliflozin, in combination with insulin, for treating type 1 diabetes (ID1478). The committee were concerned that the application of risk

equations in the trial population (DEPICT; a randomised placebo controlled phase III trial evaluating dapagliflozin as an add-on to insulin therapy in people with type 1 diabetes) to those in the population on which the risk equations were developed (Diabetes Control and Complications Trial [DCCT], a randomised trial evaluating the impact of intensive and conventional diabetes therapy on long term complications with an average follow up of 6.5 years; and EDIC an observational follow-up to the DCCT trial) may lead to unreliable extrapolations of the benefits of dapagliflozin in terms of avoided complications. The HbA1c improvement seen in DCCT/EDIC was substantially bigger (17 mmol/mol [2%] reduction) and sustained for substantially longer (over 10 years) than that seen in the DEPICT trials (0.34 percentage points reduction over 1 year relative to placebo)[1].

This also applies to the evidence for sotagliflozin. Pooled analyses of the inTandem trials showed that people with a BMI of 27 kg/m^2 or more had a reduction of 0.24% and 0.38% for sotagliflozin 200 mg and 400 mg respectively, compared with insulin alone over 1 year.

The **company** used more recent EDIC data to predict slower progression of HbA1c and BMI (0.012% in HbA1c and annual increase of 0.094 kg/m^2) in the economic model than the DCCT data. Both the EDIC data and the DCCT data are not based on the use of sotagliflozin. The assumptions made for reductions in HbA1c are given in table 1.
The **ERG** commented that the EDIC data reflects the insulin group better than the DCCT data because it is more recent. However, it cannot be assumed to reflect treatment effects of sotagliflozin. There is no other long-term data available to predict the progression of physiological parameters for sotagliflozin, therefore the possible impact on cost-effectiveness is unknown.

The **ERG** commented that the progression of physiological parameters over time may be over simplified in the company's model. More complex models based on the type 2 UKPDS progression models may be more plausible than the linear models used in the company's base case.

Table 1: summary of parameter values applied in the CORE diabetes model (ERG report page 95 table 26)

Parameter	Value

[1] Figures from the DEPICT trial have been updated here after technical engagement, because updated figures in the FAD for dapagliflozin ID1478.

<table>
<tr><td></td><td>
<table>
<tr><th colspan="2">Reduction in risk for 10% reduction in HbA_{1c}</th></tr>
<tr><td>Background diabetic retinopathy</td><td>50%</td></tr>
<tr><td>Proliferative diabetic retinopathy</td><td>50%</td></tr>
<tr><td>Macular oedema</td><td>50%</td></tr>
<tr><td>Microalbuminuria</td><td>50%</td></tr>
<tr><td>End-stage renal disease</td><td>0%</td></tr>
<tr><td>Neuropathy</td><td>45%</td></tr>
<tr><td>Myocardial infarction</td><td>20%</td></tr>
<tr><td>Heart failure</td><td>20%</td></tr>
<tr><td>Stroke</td><td>20%</td></tr>
<tr><td>Angina</td><td>20%</td></tr>
<tr><th colspan="2">Reduction in risk for 1% reduction in HbA_{1c}</th></tr>
<tr><td>Gross-proteinuria</td><td>20%</td></tr>
<tr><td>Cataract</td><td>0%</td></tr>
<tr><td>Haemodialysis mortality</td><td>12%</td></tr>
<tr><td>Peritoneal mortality</td><td>12%</td></tr>
<tr><td>Renal transplant mortality</td><td>0%</td></tr>
<tr><td>1^{st} ulcer</td><td>17%</td></tr>
</table>
</td></tr>
<tr><td>Why this issue is important</td><td>Smaller and shorter term HbA1c improvement seen in trials might not linearly extrapolate and be as great as the benefit associated with sustained lower HbA1c in terms of fewer complications seen in EDIC with sotagliflozin. The complications seen in the EDIC trial may not translate to sotagliflozin.</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>A scenario analysis in which there are no ongoing benefits associated with improved glycaemic control and body weight beyond the 52 week trial period could help to show an upper bound for the ICER.

Further, scenarios that do not assume a linear relationship between a percentage reduction in</td></tr>
</table>

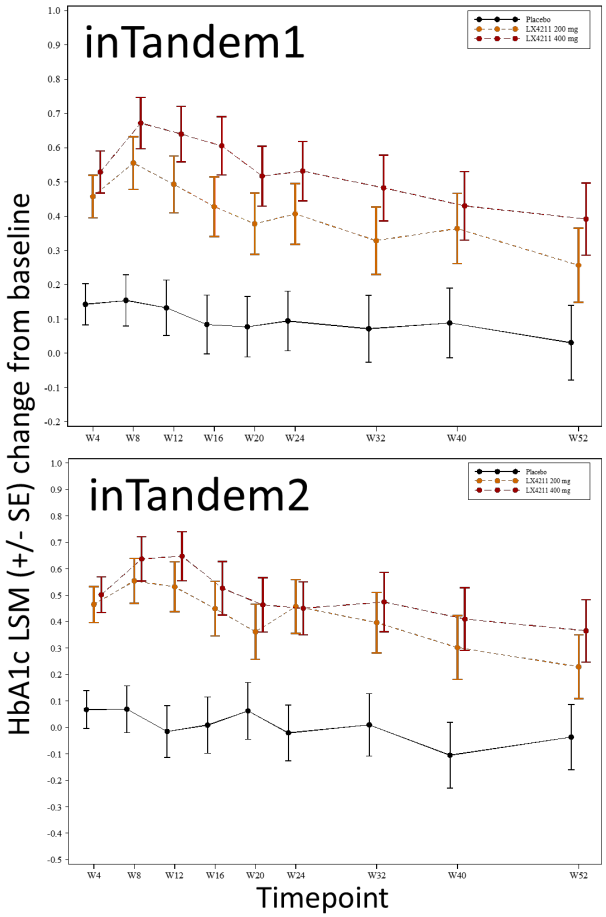
	HbA1c and the risk of long term complications could be useful.
Summary of comments	**Comments received from company:** No formal comments received in response to technical engagement. The company clarified verbally that the data used to predict complications was the best source of data available. **Comments received from professional organisation:** A professional organisation stated that the EDIC and DCCT trials are the most robust data available to inform the prediction of complications. However there are limitations: • The EDIC/DCCT trials are older than the inTandem trials, therefore the current population may have poorer glycaemic control because of rising obesity. • EDIC/DCCT did not include any SGLT2 inhibitors, the trial design for sotagliflozin is different to the EDIC/DCCT trials and the type of insulin used is also different. The impact of sotagliflozin may therefore be over-estimated using EDIC/DCCT because of the higher baseline risk in the current population. However, the weight benefits associated with sotagliflozin could cancel out the potential over-estimation.
Technical team judgement after engagement	The EDIC trial data used in the company's model is the best source of data available for the prediction of complications for type 1 diabetes. However, this is likely to overestimate the long term of reductions in HbAlc with sotagliflozin based on 1 year of trial data. The same issue applied to the appraisal for dapagliflozin, the company characterised this uncertainty by supplying an analysis that assumed HbA1c had no impact on cardiovascular risk. The company should provide analysis of more conservative long-term effects of reduced HbA1c.

Issue 4 – stopping treatment

Questions for engagement	• How would the stopping rule "consider discontinuing sotagliflozin if adequate insulination cannot be achieved on treatment" be applied in clinical practice?
	  ○ no improvement in glycaemic control? How would this be defined?
	  ○ any other reason for stopping sotagliflozin in clinical practice (e.g. poor liver function)?
	  ○ what proportion of patients are likely to stop sotagliflozin for any reason every year? Is the rate likely to be constant over time? Should the same probability of stopping treatment apply beyond year 1?

Background/description of issue	The SPC notes to consider discontinuing treatment if "adequate insulination cannot be achieved". The trial protocol specified that sotagliflozin may be stopped for the following: • A life-threatening or serious adverse event • Refusal of the study drug • Investigator decides that it is not medically acceptable for the patient to continue • Patient meets specific criteria for liver function abnormalities • Pregnancy The trial protocol also specified that if there is a serum creatinine increase of 30% or more above the baseline value, then consider assessing: volume status, diuretic dosage, discontinuing nonsteroidal anti-inflammatory drugs, and other testing as appropriate for example renal imaging techniques. The **company** assumed in its economic model that treatment with sotagliflozin continued up until 5 years, with 100% treatment persistence in both arms, because there was no clinical evidence on the effects of discontinuing sotagliflozin. The **ERG's** clinical experts advised that treatment with sotagliflozin may continue indefinitely if a patient is receiving benefit, otherwise they would expect treatment to continue up to 2 years based on trial data trends between week 24 and 52 in changes in HbA1c (see figure 1). The ERG acknowledged that treatment duration was highly uncertain and based on only 1 year of trial data, it preferred to assume a treatment duration of 5 years. **Figure 1: HbA_{1c} (%) change from baseline for the BMI of 27 kg/m^2 or greater subpopulation (ERG**

report figure 5 page 57)



The **technical team** note that the trial data available for sotagliflozin is up to 1 year, and that it is unlikely that treatment would continue if no benefit is seen for sotagliflozin. In the appraisal of dapagliflozin for type 1 diabetes the committee considered that it would be reasonable that dapagliflozin would be stopped if it did not result in improved glycaemic control and that the stopping rate in the

model should be based on stopping for any reason in the trial. Clinical experts noted that the rate of stopping treatment in subsequent years is likely to decrease because most adverse events occur in the first year. Therefore, analyses that include a stopping rate based on the probability of stopping for any reason from the inTandem trials in year 1 and decreased rates in subsequent years would be appropriate. Further, table 2 shows the primary reason that patients discontinued the trial in inTandem2.

Table 2 primary reason for discontinuation of study for inTandem1 and inTandem2 (inTandem1 CSR p150; inTandem2 CSR p145)

	inTandem1, n (%)			inTandem2, n (%)		
Primary reason for early discontinuation of study:	**Placebo**	**Sotagliflozin 200mg**	**Sotagliflozin 400mg**	**Placebo**	**Sotagliflozin 200mg**	**Sotagliflozin 400mg**
Adverse event	11 (4.1)	13 (4.9)	17 (6.5)	9 (3.5)	10 (3.8)	18 (6.8)
Death	0	0	0	1 (0.4)	0	0
Lost to follow-up	3 (1.1)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	0
Noncompliance with study drug	2 (0.7)	0	1 (0.4)	1 (0.4)	0	0
Other	4 (1.5)	0	1 (0.4)	4 (1.6)	2 (0.8)	3 (1.1)
Physician decision	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)	3 (1.1)
Pregnancy	0	0	1 (0.4)	1 (0.4)	1 (0.4)	0
Protocol deviation	3 (1.1)	0	0	1 (0.4)	2 (0.8)	0
Withdrawal by patient	26 (9.7)	19 (7.2)	20 (7.6)	14 (5.4)	18 (6.9)	12 (4.6)

Why this issue is important

The stopping rule has a considerable impact on the ICER, for example in the company's analyses using the pooled inTandem1 and inTandem2 cohort when treatment was received for 5 years the ICER was £10,012 per QALY gained for sotagliflozin plus insulin compared with insulin alone. When treatment

	was received for 2 years the ICER increased by more than £15,000 per QALY gained to £25,638 per QALY gained. This is partly because treatment effect is assumed to return to placebo when treatment stops.
Technical team preliminary judgement and rationale	The stopping rule should be in line with the available trial data. Therefore, scenario analyses on stopping treatment should include: • analyses that include a stopping rate for sotagliflozin based on the probability of stopping for any reason from the inTandem trials, and extrapolation of the data observed between months 6 and 12 of the inTandem trials (see technical teams preferred assumptions). It is not appropriate for treatment to continue beyond the loss of treatment effect. The ERG supplied an analysis to better reflect the technical team preferences: applying a reduced cost of sotagliflozin by the proportion who discontinued in the first year. After this, treatment costs in the sotagliflozin group were set equal to the insulin-only group. However, the proportion who discontinued was based on discontinuation due to treatment-emergent adverse events (TEAEs) because of limited data on overall discontinuation.
Summary of comments	**Comments received from company:** No formal comments received in response to technical engagement. The company clarified verbally that the CORE diabetes economic model does not have the ability to implement treatment discontinuation observed between 6 and 12 months or discontinuation of a proportion of patients at a certain time period. Therefore, it could not provide this analysis. **Comments received from professional organisation:** The professional organisation considered that no improvement in glycaemic control would be defined as a reduction less than 0.5% (5.5 mmol/mol) because, in the summary of product characteristics for SGLT2s the average range of reduction is 8 mmol/mol to 11 mmol/mol. Other reasons for stopping sotagliflozin might include dehydration leading to adverse effects, recurrent genitourinary infections, acutely deteriorating renal function, diabetic ketoacidosis. The rate of stopping sotagliflozin is likely to decrease over time because most side effects will occur during the initial treatment period.

Technical team judgement after engagement	The technical team's judgement (2 year treatment benefit) has not changed after technical engagement.

Issue 5 – duration of treatment effect

Questions for engagement	• How long would you expect the treatment benefit of sotagliflozin to be maintained while on treatment? Would you expect treatment benefit to wane, if so after how long? • Would people return to their baseline risk factor levels for all complications after stopping treatment?
Background/description of issue	The **ERG** clinical experts were concerned that absence of clear guidance for treatment with sotagliflozin could lead to indefinite continuation of treatment if an initial benefit is achieved, even when HbA1c has returned to the baseline level, because the patients condition could deteriorate and the longer-term weight and cardiovascular benefits of sotagliflozin are unknown. The **company** commented that applying costs after discontinuation of treatment benefit is not appropriate because it is not in line with practice given the risk/benefit profile of this class of medicines. The **technical team** note that the summary of product characteristics for sotagliflozin states consider to discontinuing treatment with sotagliflozin if, "adequate insulinisation cannot be achieved" and that treatment with sotagliflozin is unlikely to continue beyond treatment benefit.
Why this issue is important	The duration of treatment effect has a substantial impact on the ICER. The ERG explored 2 year, 5 year and lifetime treatment duration combined with between 2 and 5 year duration of treatment effect. The ICERs ranged from £13,000 per QALY gained (2 year treatment duration with 2 year treatment effect), to £137,943 per QALY gained (lifetime treatment duration with 2 year treatment effect).
Technical team preliminary judgement and rationale	A scenario that extrapolates the treatment effect observed between 6 and 12 months would be appropriate.
Summary of comments	**Comments received from company:** None.

	Comments received from professional organisation: A professional organisation commented that glycaemic control is expected to be maintained or improve on treatment. Weight loss is greatest in the initial trial period and a lower magnitude or plateau of weight loss is expected over time (commonly within the first 6 months of starting treatment). A 'legacy effect' has been shown for glycaemic control, for example it may lead to future reductions in microvascular complications. Therefore, some benefits of sotagliflozin may continue after stopping treatment, depending on the magnitude and duration of glycaemic improvement.
Technical team judgement after engagement	The duration of treatment effect is uncertain beyond the trial data period of 1 year, the technical team prefers analysis based on the trial data. That is, treatment effect for HbA1c and weight wanes after 1 year and returns to placebo at year 2.

Issue 6 – baseline characteristics in the economic model

Questions for engagement	• Is it reasonable to apply the treatment effects from inTandem to the baseline characteristics from patients in the national diabetes audit? • Do the baseline characteristics in the simulated cohort (table 3) reflect patients that would receive sotagliflozin in UK practice?
Background/description of issue	In order to reflect patients with type 1 diabetes in the UK the **company's** economic model uses baseline characteristics from a simulated population based primarily on the National Diabetes Audit (NDA) data, used in NICE Guideline for type 1 diabetes in adults: diagnosis and management NG17. The **ERG** explored the differences between the NDA and inTandem population for people with BMI more than 27 kg/m^2 (table 3) and highlighted that patients in the simulated cohort had a lower starting BMI of 27 kg/m^2 compared with patients in the inTandem pooled primary population 32 kg/m^2. The ERG disagrees with the company's base case and thinks that the baseline characteristics should be taken from inTandem 1 and inTandem 2. This is because the baseline characteristics should align with the population from which the treatment effects were derived (source: email correspondence between NICE and ERG).

Table 3: Pooled baseline characteristics for primary efficacy population (inTandem1 and inTandem2 BMI ≥27 kg/m^2) and simulated cohort (ERG report table 6 p49 to 50)

	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)	Insulin alone (N = 298)	Simulated cohort (used in economic model)
Age in years, Mean (SD)	45.9 (12.72)	45.5 (11.98)	43.3 (12.62)	42.98 (19.14)
Female sex, n (%)	148 (48.5)	159 (50.8)	143 (48.0)	(43.3)
Race white, n (%)	280 (91.8)	293 (93.6)	283 (95.0)	92.0
Duration of diabetes (years), n (%) <20	134 (43.9)	154 (49.2)	138 (46.3)	Mean 16.92 (SD 13.3)
≥20 to <40	140 (45.9)	129 (41.2)	133 (44.6)	
≥40	31 (10.2)	30 (9.6)	27 (9.1)	
BMI (kg/m^2), Mean (SD)	32.49 (4.363)	31.96 (4.049)	32.03 (4.240)	27.09 (5.77)
HbA1c (%), Mean (SD)	7.72 (0.747)	7.63 (0.747)	7.62 (0.760)	8.60 (4.00)
SBP (mm Hg), Mean (SD)	124.6 (15.15)	123.6 (14.42)	124.3 (14.24)	128.27 (16.07)
DBP (mm Hg), Mean (SD)	79.1 (9.53)	77.8 (8.14)	78.0 (8.21)	80.0 (0.00)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose, HbA_{1c}, glycated haemoglobin; ITT, intention-to-treat population; IU, international unit; n, number of patients; SBP, systolic blood pressure; SOTA, sotagliflozin; SD, standard deviation.

Why this issue is important	The baseline characteristics used in the economic model affect the rate of complications and therefore the cost-effectiveness.
Technical team preliminary	The technical team consider the NDA simulation cohort to broadly represent patients who could

judgement and rationale	receive sotagliflozin in clinical practice in the UK. However, the average starting BMI in the NDA (27 kg/m^2) is likely to be lower than those treated with sotagliflozin in the NHS, because sotagliflozin is indicated for people with a BMI of 27 kg/m^2 or greater. Therefore, it is most appropriate to use baseline characteristics from the inTandem trials.
Summary of comments	**Comments received from company:** The company provided a scenario analysis including the technical teams preferred assumptions for baseline characteristics. The scenario used clinical data from inTandem 2 for patients with a BMI of 27 kg/m² or more and a HbA1c of 7% or more and total basal insulin dose of more than 0.5 units/kg/day. Which increased the company's base case ICER from £1,934 per QALY gained to £10,227 per QALY gained. The same analysis with total basal insulin dose of more than 0.4 units/kg/day gave an ICER of £15,840 per QALY gained. However, please note that these analyses do not capture all of the technical team's preferences. **Comments received from professional organisation:** A professional organisation considered it reasonable to use baseline characteristics of patients from the national diabetes audit (used in the company's original base case) in the economic model. These characteristics (BMI of more than 27 kg/m^2 and HbA1c of more than 8%) reflect patients that would receive sotagliflozin in clinical practice.
Technical team judgement after engagement	The technical team consider it appropriate for the population in the economic model to match the population on which the efficacy data in the model is based. The baseline characteristics from the NDA are based on people with an average BMI of 27 kg/m^2, therefore it might not reflect baseline characteristics of people eligible for sotagliflozin (BMI more than 27 kg/m^2). Therefore the baseline characteristics from the pooled inTandem trials should be used in the economic model.

Issue 7 – utility values

Please note after technical engagement this issue was resolved, it has been moved to 'other issues for information' see table 3.

Issue 8 – modelling adverse events

Questions for engagement	• Are all adverse events captured in the model? • Would the adverse event profile differ for sotagliflozin 400 mg dose compared with the 200 mg dose? If yes, how would it differ in terms of the frequency and type of adverse event. • Is there a risk of Fournier's gangrene with sotagliflozin? • What proportion of adverse events require medical assistance? Do the costs from Hammer et al. or the NHS reference costs with CC scores 5 to 8 more appropriately reflect the cost of a severe hypoglycaemic event in clinical practice? • In clinical practice, what proportion of patients eligible for sotagliflozin experience diabetic ketoacidosis events currently, and what proportion would be expected to experience events on sotagliflozin?
Background/description of issue	The **ERG** note that the clinical efficacy of 400 mg sotagliflozin in the economic model was assumed to be the same as the 200 mg dose. However, it did not consider it reasonable to assume the same level and severity of adverse events as the 200 mg dose. Adverse events of special interest (diabetic ketoacidosis, genital mycotic infections and diarrhoea) in the pooled inTandem 1 and inTandem 2 trial data differed between the two doses. A higher proportion of patients in the 400 mg arm (3.5%) experienced DKA than patients in the 200 mg arm (2.6%) and diarrhoea was experienced for a higher proportion of patients in the 400 mg arm (8.6%) than the 200mg arm (5.2%). Further, a lower proportion of female patients experienced genital mycotic infections in the 400 mg arm (17.6%) than the 200 mg (21.6%) arm and a higher proportion of male patients experiences genital mycotic infections in the 400 mg arm (4.5%) than the 200mg arm (3.8%). The **technical team** note that during the appraisal of dapagliflozin for type 1 diabetes the committee concluded that the economic model should include disutility and risk of death from Fournier's gangrene, a life-threatening urogenital infection. This has not been included in the **company** or **ERG** model for sotagliflozin. Further, the committee also preferred to see ketone testing 3x higher in

	the dapagliflozin arm compared with insulin alone. The **company** assumed that all severe hypoglycaemic events needed medical assistance and the cost of treating an event was £2,320. The **ERG** were concerned that the cost of treating severe hypoglycaemia in the company's model was 7 times higher than that used in NICE clinical guideline for type 1 diabetes in adults: diagnosis and management. Further, the ERGs clinical experts estimated that around 50% of severe hypoglycaemic events require medical assistance. Therefore, the ERG preferred to use the same source for costs as the NICE clinical guideline (Hammer et al, 2009; £999 per event) and assumed that 50% of events require medical assistance. The ERG and Company's economic models assume that 8 times more patients experience diabetic ketoacidosis events for every 100 patient years in the sotagliflozin arm (3.2 events for every 100 patient years) compared with insulin alone (0.4 events per 100 patient years). Diabetic ketoacidosis events are a key driver of costs and disutility in the economic model, for example the ICER for sotagliflozin vs insulin varied from being dominated with a QALY loss of -0.016 (in the ERGs base case) to £171,401 per QALY gained and a QALY gain of 0.054 (in a scenario using the ERGs base case assuming no diabetic ketoacidosis events).
Why this issue is important	The draft SPC notes that the dose of sotagliflozin be escalated to 400mg in people who have been taking the 200mg dose for 3 months and require 'additional glycaemic control'. The company have estimated that 10% patients will be escalated to 400mg based on market insights, but have included the disutility and costs associated with the 200mg dose. Costs and disutilities for adverse events may be underestimated for sotagliflozin for the 400mg dose. The ERG comments that the 400mg dose is likely to have a different adverse effects profile to the 200mg dose. The severity and frequency of adverse events based on the number of people on the 400mg dose could be underestimated in the model. It is important that the model captures adverse events that could have a substantial impact on the cost or the quality of life of the patient. It is important that the costs and frequency of events in the economic model reflect clinical practice. Changes in this assumption do not impact greatly on the results of the model. The ERG carried out

	sensitivity analyses where it varied the source of the costs from Hammer et al. and the NHS reference cost and used different combinations for the proportion of people hospitalised (50% and 100%) the ICER ranged from £10,012 to £11,905.
Technical team preliminary judgement and rationale	• The inclusion of Fournier's gangrene in the model should be explored • The economic model should reflect the clinical expert opinion that 50% of severe hypoglycaemic events need medical attention and use costs in line with the NICE clinical guideline for type 1 diabetes in adults.
Summary of comments	**Comments received from company:** The company provided a scenario analysis including the technical teams preferred assumptions for the approach to modelling adverse events. It provided 2 scenarios: • Including the impact or rare life-threatening urogenital infections – no substantial effect on the ICER • Assuming 50% of severe hypoglycaemic events need medical attention and costs from the NICE clinical guideline for type 1 diabetes in adults – increased the ICER by £1,628 per QALY gained **Comments received from professional organisation:** The professional organisation stated that it is reasonable to assume a risk of Fournier's gangrene for sotagliflozin because there have been post marketing cases for people taking other SGLT2 inhibitors. It further stated that it is reasonable to assume that 50% of severe hypoglycaemic events need medical assistance and to use the NHS reference cost based on the NICE clinical guideline. The professional organisation noted that adverse event rates and severity differ between the 200mg and 400mg arms in the inTandem trial, for example the rate of DKA is lower for people having the 200mg dose (6 patients, 2.3%) than those receiving the 400mg dose (9 patients, 3.4%). It further highlighted that in an 8-week study in T1D patients (Cherney et al., 2014; Perkins et al., 2014), approximately 5% of patients treated with empagliflozin (2 of 42) were withdrawn from the study when they developed diabetic ketoacidosis. The professional organisation highlighted that data that could help to inform real world rates of diabetic ketoacidosis (DKA) events are available from the Food and Drug Administration Adverse

	Event Reporting System. Between 2014 and 2016 there were 2397 DKA reports with an SGLT2 inhibitor: • Dapagliflozin: 680 in 5,694 patients reported DKA events (12%) • Canagliflozin: 1,362 in 14,117 patients reported DKA events (10%) • Empagliflozin: 355 in 2,719 patients reported DKA events (13%) The occurrence was higher when searching specifically for type 1 diabetes: • Dapagliflozin: 85 in 128 patients reported DKA events (66%) • Canagliflozin: 206 in 297 patients reported DKA events (70%) • Empagliflozin: 26 in 48 patients reported DKA events (54%) • Any SGLT2i: 317 in 472 patients reported DKA events (67%)
Technical team judgement after engagement	The affect of diabetic ketoacidosis needs to be explored in the economic model with the range based on input from clinical experts. The technical team notes that DKA event rates received from the professional organisation in response to technical engagement are much higher than those observed in the trials and used in the economic model, however this patient population may be at higher risk of DKA than the population that sotagliflozin is indicated for: • Professional organisation response: 54% to 67% of patients with type 1 diabetes reported DKA on a SGLT2 inhibitor; FDA 2014 to 2016 • InTandem trials pooled data for patients with a BMI of 27 kg/m^2 or more: proportion of patients with at least 1 episode of DKA 2.6% sotagliflozin 200 mg, 3.5% sotagliflozin 400 mg, 0.3% insulin alone • Economic model: 3.2 events per 100 patient years sotagliflozin 200 mg and 400 mg, 0.4 events per 100 patient years placebo arm The company provided additional analyses which varied the rate of DKA and the rate of DKA mortality but the range used was considered to be too narrow. After technical engagement company was asked the provide scenario analysis which reflect DKA rate and mortality which are more applicable to clinical practice to be submitted before the committee meeting (to follow).

Issue 9 – dose escalation

Please note after technical engagement this issue was moved to 'outstanding uncertainties in the evidence base' see table 2.

3. Other issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions

Note: changes to the technical team preferred assumptions since technical engagement are written in bold in the table below. The impact on cost effectiveness of the technical team's preferred assumptions has not been estimated. Updated analyses will be provided by the company, critiqued by the ERG and circulated ahead of the committee meeting. An addendum to this report will be provided once results from analyses using the technical teams preferred assumptions is available.

Alteration	Technical team rationale
Company base case	**–**
1. Baseline characteristics from the pooled inTandem 1 and 2 trial population for patients with a BMI of 27 kg/m^2 or more, a **Total Basal insulin dose of more than 0.5 units/kg/day and HbA1c of 7% or more**.	See issue 6. The inTandem pooled population more closely reflects the indicated population than the NDA data, therefore baseline characteristics should be used from the pooled results of the inTandem trials.
2. Multiplicative approach to utilities.	See issue 7 and ERG report section 5.4.8.1.5. The multiplicative utility approach is the most appropriate as utilities in the economic model are taken from different sources.
3. **Include impact of rare life-threatening urogenital infections**	See issue 8. Comments received from a professional organisation during technical engagement agree that it is reasonable to assume a risk of Fournier's gangrene for sotagliflozin. Because there have been

Alteration	Technical team rationale
	post marketing cases for people taking other SGLT2 inhibitors.
4. Severe hypoglycaemia costs from Hammer et al 2009, assuming 50% are hospitalised	See issue 8 and ERG report section 5.4.9.3.2. The rate and cost of severe hypoglycaemia should reflect clinical expert opinion and existing NICE guidance on type 1 diabetes.
5. Treatment effects for HbA1c to return to the placebo group effects at 2 years	See issue 5 and ERG report section 5.4.5.4. Treatment duration should be in line with the available clinical evidence, the effect beyond 1 year is unknown and clinicians are unlikely to continue treatment when benefit ceases. Note: this analysis does not fully capture the technical team's preferences for stopping treatment (issue 4).
6. Utilities based on the ScHARR 2019 review	See issue 7 and ERG report section 5.4.8.1.5.
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Generalisability of the inTandem trial population (previously issue 2)	If patient characteristics differ (for example BMI, HbA1c and the use of insulin pumps) to patients in the NHS, some of these factors may have an influence on how well the treatment works. That may mean that the results of the trial may not be generalisable to the NHS.	It is difficult to comment on the generalisability of the trial data to the NHS as the marketing authorisation is for patients with a BMI of greater than 27 kg/m^2 and we do not have data for this population from the national diabetes audit.
Randomisation broken in analyses of the pooled population of inTandem 1 and inTandem 2	Sotagliflozin is indicated for people with a BMI of 27 kg/m^2 or more. However, BMI was not a stratification factor in the inTandem trials, so randomisation is broken. The indicated population is narrower than the population in the inTandem trials. It represents 58% of the total trial populations of inTandem 1 and inTandem 2 combined, patients in this subgroup were on average older, with higher systolic blood pressure and a longer prior duration of diabetes.	The ERG does not note any key imbalances between treatment groups, there is not likely to be an impact on cost effectiveness.
Dose escalation (previously issue 9)	The technical team notes that the SPC for sotagliflozin states that it can be escalated to 400mg in people who have been taking the 200mg dose for at least 3 months and require additional glycaemic control. There is no data on dose escalation in the clinical trials for sotagliflozin. Therefore, the efficacy and proportion of people who require the 400mg dose is unknown. The 400mg dose appears to have an effect	The proportion of people requiring dose escalation could not be estimated from the inTandem clinical trials because they did not allow for dose escalation. The impact on cost effectiveness is unknown.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	on some outcomes (HbA1c and bolus insulin dose) for example in the pooled analyses for inTandem 1 and 2 in people with BMI of 27 kg/m2 or more; mean change in HbA1c was -0.24 (-0.35 to -0.13 95% confidence interval) for sotagliflozin 200mg and -0.38 (-0.49 to -0.27 95% confidence interval).	
Uncertain whether 400 mg dose will be given as 2 x 200 mg tablets or a 400 mg tablet	The 400 mg tablet will not be available at launch in the UK, therefore the acquisition cost for people having the 400 mg dose during this time will be double that of the 200 mg tablet.	If the 400 mg dose of sotagliflozin is given as 2 x 200 mg tablets then this would increase the acquisition cost for sotagliflozin and therefore increase the ICER. [redacted] in scenarios that include dose escalation.
There is limited evidence for the durability of treatment effect for sotagliflozin	The inTandem trials provide limited evidence of the durability of the initial treatment effects of sotagliflozin, further they were not designed to show cardiovascular benefit.	The long-term effect of sotagliflozin on HbA1c, BMI and cardiovascular events is highly uncertain and the model is sensitive to changes in treatment effect.
Age related utility decrements not included in the economic models	The CDM and PRIME models do not allow for age related utility decrements to be included in the model.	This impacts on the accuracy of the QALY calculation. Hoverer, the ERG acknowledges that this is a limitation of the existing diabetes models.

Table 3: Other issues for information

Issue	Comments
Utility values	During technical engagement issue 7, utility values, was resolved. The multiplicative approach to QALYs is most appropriate because multiple evidence sources were used to obtain utility values. **Comments received from company:** The company provided a scenario analysis including the technical teams preferred assumptions (multiplicative approach) for the approach to utility values in line with the NICE technical support document 12. Applying this assumption to the scenario using clinical data from inTandem2 considering patients with a BMI of 27 kg/m² or more and a HbA1c of 7% or more and Total Basal insulin dose of more than 0.5 units/kg/day, decreased the ICER slightly by £1,347 per QALY gained. **Comments received from professional organisation:** The multiplicative model appears to be the more appropriate approach in people with T1DM, in whom co-morbidities are common (because it re-produces similar results for individuals with diabetes and thyroiditis). The multiplicative models assume constant proportional effects, while the minimum model applies a disutility that can vary depending on the baseline utility modelled.
Model validation	The economic models have not been validated using epidemiological data. The main source of data available is for type 1 diabetes is from the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study, these are used to develop risk equations that predict the relationship between changes in HbA1c levels (among other risk factors) and some long-term complications. These studies can therefore not be used to validate the model outputs. This issue was raised during the dapagliflozin appraisal and the committee concluded that this remained an outstanding uncertainty in the evidence base.
Comparators	Metformin was included in the scope as a relevant comparator. The company and ERG agree that metformin is not a relevant comparator to sotagliflozin. The ERG commented in its report that metformin is rarely used in the UK for type 1 diabetes, it is not licensed for this indication and it showed little benefit compared with placebo in the

Issue	Comments
	REMOVAL trial. It is appropriate to exclude metformin as a comparator.
Innovation	The company considers sotagliflozin to represent a breakthrough in the management of type 1 diabetes, as it is an adjunct to insulin with a different mechanism of action to insulin. Clinical experts commented that sotagliflozin may be considered innovative but may not represent a step change in practice.
Equality	The UKPCA highlighted that the number of minority ethnic groups included in the inTandem trials was small and that the average BMI was more than 28kg/m^2. This is not considered an equalities issues, however it may impact on the generalisability of the trial results to the general population. The committee will take this into account in its decision making.

Authors

Amanda Adler

Appraisal committee chair

Jessica Cronshaw

Technical lead

Eleanor Donegan

Technical adviser

Jasdeep Hayre

Associate director

With input from the lead team:

Nick Latimer

Lead team member

Nigel Westwood

Lead team member

Sarah Wild

Lead team member

Issue date: July 2019

Sotagliflozin ID1376: additional data request

Following the committee meeting for the appraisal of sotagliflozin ID1376, additional data is needed

1. ***Please provide the efficacy data and baseline characteristics at 24 weeks from the inTandem 1 and inTandem 2 pooled population:**

    a. people with a BMI of greater than or equal to 27 kg/m^2

    b. exclude people with low insulin requirements in line with the SPC (0.5 units per kg of body weight or less)

    c. only include people with a post-optimisation HbA1c of 7% or more

    This data needs to be in a format that allows it to be input into the economic model for all relevant inputs for example the treatment effectiveness, baseline characteristics, adverse events.

    Please also provide the data in a format in which the committee can consider the baseline characteristics of the population and compare these with previous data cuts.

Committee assumptions:
The committee would like to see analyses including the following assumptions. Please provide the following analyses:

1. Analysis of the indicated population for sotagliflozin using pooled data **from inTandem 1 and inTandem 2**. The relevant clinical data (e.g. baseline characteristics, effectiveness data, adverse events, number of patients in this group). The population is defined as previously submitted:

    a. people with a BMI of greater or equal to than 27 kg/m^2

    b. exclude people with low insulin requirements in line with the SPC (0.5 units per kg of body weight or less)

    c. only include people with a post-optimisation HbA1c of 7% or more

2. Do not assume a relationship between baseline characteristics and diabetes related complications, other than HbA1c.

3. **Stopping treatment**: 2 years on treatment, as previously submitted.

4. **Duration of treatment effect, no continued benefit from treatment for any risk factors after 2 years**: Treatment duration should be based on the trial data. The treatment effect in year 1 should be based on the treatment effect from the trial data and the observed trial data from 6 to 12 months should be extrapolated to get the treatment effect for year 1 to year 2. Treatment effect should return to placebo when treatment stops. Based on the technical teams preferred population as outlined in point 1.

5. **Treatment discontinuation rate** based on extrapolation of trial data observation between 6 and 12 months.

6. Apply a clinically plausible mortality rate that is less than for DKA and a hazard ratio for DKA that reflects the UK. (please see note about implementation)

7. Utilities based on the ScHARR review using a fixed effects approach, as previously submitted.

8. Use the multiplicative approach to QALYs in line with NICE TSD 12: the use of health state utility values in decision models, as previously submitted.

9. Adverse events, as previous submitted:

    a. Include:

        i. Impact of rare life threatening urogenital infections such as Fournier's gangrene (following the MHRA warning issued for SGLT2 inhibitors in February 2019).

        ii. Hypoglycaemic events: 50% of severe hypoglycaemic events need medical attention, costs in line with the NICE clinical guideline

Additional and sensitivity analyses applied to the above base case population
note: these are the preferred scenario and sensitivity analysis agreed on during the committee. Please provide the following analyses:

10. **Duration of treatment and effect**: the technical team would like to see a variety of scenarios looking at the duration of treatment:

    a. 1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1

    b. 2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years

    c. 2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.

For each treatment duration outlined above (11.a.b.c) apply the following duration of treatment benefit:

    a. No continued benefit from treatment for any risk factors after treatment stops

    b. No benefit of HbA1c improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.

    c. No impact of HbA1c on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.

11. Adverse events:

    a. Sensitivity analysis varying the DKA mortality rate from 0.16% to 2%

    b. Scenario using Severe Hypoglycaemic mortality rate of 4.45% (as previously submitted)

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

28th August 2019

Dear Jasdeep,

Re: Sotagliflozin in combination with insulin, for treating type 1 diabetes [ID1376] - Additional analyses feedback

Sanofi welcomes the opportunity to provide additional support to the NICE technical team and ERG for the above appraisal. Responses to the additional analyses feedback sent on Friday 23rd August 2019 are presented in Appendix 1.

Sanofi would welcome the opportunity to discuss this feedback, request and the response here within.

We hope these additional analyses are useful to the committee.

Yours sincerely,

Jessamy Baird.
Director of Patient Access, Sanofi UK and Ireland.

Appendix 1

1. **Explanation 'the CORE diabetes model structure does not facilitate part a) of the treatment duration and effect analysis and exploratory analysis of part a) showed no impact on the ICER.'**

   As previous documented the CORE diabetes model incorporates rules as part of its structural architecture. The rules as defined by the user are applied within the annual cycles of the model. However the rules must not conflict one another, in the case of analysis part a) (1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1) and would require patients at the end of year 1 to mirror those in the SoC arm. This would require simultaneous application of treatment effect at baseline and application of treatment waning within the first year, which is not possible within the model due to the annual model cycle.

a) Provide a list of the physiological parameters that are assumed to be modified by treatment with sotagliflozin in the model and how each is modelled each with respect to length and quality of life

Parameters modelled including HbA1c, BIM, SBP, DBP, total cholesterol. LDL, HDL and triglycerides, are modelled in line with the standard CDM algorithm. Sotagliflozin directly impacts HbA_{1c} only.

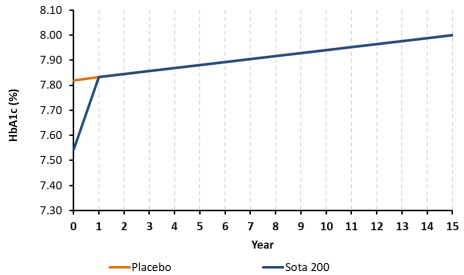
b) Provide graphs to show the impact of each physiological parameter on the treatment

Sotagliflozin directly impacts HbA_{1c} only, graphs for HbA_{1c} have been presented previously. Given the short time for this request further graphs could not be produced for each physiological parameter.

c) Provide any exploratory analyses that are carried out to support the explanation

Exploratory analyses for part a) are presented in Table 6 and further discussed below. To explore implementation of this scenario an analysis was run where the HbA_{1c} drop seen at 52 weeks in the trial was applied at time 0. Thus at the beginning of Year 1 patients in the sotagliflozin arm presented in the model with lower HbA_{1c} values compared with those in the SoC arm (7.54% vs. 7.82%).

As soon as the patients entered the model a treatment waning effect was applied over year 1 at a rate of +0.29%. This waning effect is higher than that observed within the pooled data between months 6 to 12 (+0.18%), and a more conservative approach to ensure the sotagliflozin arm mirrors SoC at the start of year 2.



d) p18 table 6 scenario 1a please provide interpretation of the result i.e. that there is no difference in benefit, but an increase in cost for sotagliflozin

This analysis produced an incremental cost of £480, but no incremental QALYs were reported. Therefore an ICER could not be presented. This is as a result of the limited time patients experience the benefits of the full treatment effect. This exploratory analysis assumes patients enter the model with the full treatment effect and with the waning effect applied on entry to the model until the end of year 1 where the sotagliflozin arm mirrors the SoC arm. Thus a limited effect is seen over the one-year treatment period, in the analysis time horizon.

e) **Please confirm whether Fournier's gangrene is included in the company's base case**
Yes, this is included

2. Analyses

a) Please include life years gained and incremental life years for each analysis

Sanofi feel the presentation of life years gained and incremental life years would not accurately capture the benefits of sotagliflozin for this chronic disease. Given the short treatment duration (2 years) and time horizon (60 years) the model is unlikely to present a significant life year gain.

b) On p11 please present the ICER for each change made to the post committee base case compared with the base case presented to committee

The case presented at committee was not representative of the Company's base case as updates to the analysis following technical engagement were not presented. The updates to the post-committee base case (Sanofi's final 'base case') were not made in a piecewise fashion due the time required to perform analyses within the CDM, all changes were made simultaneously.

3. Other

a) The analyses of DKA mortality rate (p22) seem to be counterintuitive. When DKA rate is increased from 0.16 to 1% the ICER increases, however when it is increased from 1% to 2% the ICER decreases. Please provide explanation for this inconsistency.

This inconsistency has been noted, Sanofi will check with the modelling team once they have returned from annual leave on Monday 9th September.

b) **Please provide any references and supplementary excel sheets with your response.**
Joint British Diabetes Societies Inpatient Care Group. The Management of Diabetic Ketoacidosis in Adults 2nd Ed, 2013.

National Institute for Health and Care Excellence,
10 Spring Gardens,
London,
SW1A 2BU,
United Kingdom.

20th August 2019

Dear Jasdeep,

Re: Sotagliflozin in combination with insulin, for treating type 1 diabetes [ID1376] - additional data request

Sanofi welcomes the opportunity to respond to the questions raised by the NICE committee members and the technical team for the above appraisal and are pleased to provide the Committee with the following the summary of preferred base case assumptions and sensitivity analyses. We present a base case that is aligned to the NICE technical team preferred assumptions.

A summary of the assumptions forming Sanofi's final 'base case' for consideration by the committee are presented below:

1. Analysis of the indicated population for sotagliflozin using pooled data from inTandem 1 and inTandem 2, defined as:
    a. people with a Body Mass Index (BMI) of greater or equal to than 27 kg/m^2
    b. exclude people with low insulin requirements in line with the Summary of Product Characteristics (SPC) (0.5 units per kg of body weight or less)
    c. only include people with a post-optimisation HbA_{1c} of 7% or more
2. The model incorporates relevant clinical data (e.g. baseline characteristics, effectiveness data, adverse events, number of patients in this group) from this pooled analysis.
3. Stopping treatment: 2 years on treatment
4. Duration of treatment effect, no continued benefit from treatment for any risk factors after 2 years: The treatment effect in year 1 is based on the treatment effect from the trial data. Treatment effect is waned in year 2 to rebound the sotagliflozin profile to mirror the Standard of care (SoC); defined as insulin, profile following treatment discontinuation at the end of year 2.
5. Utilities based on the ScHARR review using a fixed effects approach.
6. Multiplicative approach to (quality adjusted life years) QALYs in line with NICE TSD 12: the use of health state utility values in decision models.
7. Adverse events including diabetic ketoacidosis (DKA), Severe hypoglycaemia (SH) and non-SH updated with NICE technical teams' recommendations post appraisal committee.

This update of the analysis using the NICE preferred base case generates an Incremental Cost-Effectiveness Ratio (ICER) of £16,093/QALY, a reduction of £2,572 from the original base case submitted. The original NICE technical team base case scenario generated an ICER of £18,665/QALY. This updated base case estimate is lower due to a change in mortality rate associated with DKA to

0.7%, in line with feedback from clinical experts at the NICE committee meeting and a recent meta-analysis of UK evidence (JBDS 02, 2013)[1].

We feel the final updated company base case presented is representative of the target population when using the 52-week pooled population data, use of earlier data points such as at 24-weeks is not considered appropriate use of the ITT trial data.

For transparency a new folder has also been created in the model called "*Sotagliflozin NICE- ERG August 2019*", which can be viewed along with previous analyses undertaken by Sanofi during the submission process.

Sanofi would like to thank the NICE committee and technical team for their deliberations, support and input throughout this submission.

We hope these additional analyses are useful to the committee.

Yours sincerely,

Jessamy Baird.
Director of Patient Access, Sanofi UK and Ireland.

Attached:

1. *Appendix 1: Summary efficacy data and baseline characteristics at baseline, 24 weeks from the inTandem1 and inTandem2 pooled population.*
2. *Appendix 2: analysis of the NICE preferred base case assumption and sensitivity analysis.*
3. *Inputs_T1DM_CEA_CDM_09_August_2019: contains a summary of clinical and cost inputs* used in the economic model.

[1] *Joint British Diabetes Societies Inpatient Care Group. The Management of Diabetic Ketoacidosis in Adults 2nd Ed, 2013*

Appendix 1: Subpopulation characteristics and efficacy data

Table 1 overleaf presents a summary of the efficacy data and baseline characteristics at baseline, 24 weeks and 52 weeks from the inTandem1 and inTandem2 pooled population. Safety data for the population is presented in Table 2. Please also refer to the Microsoft Excel workbooks accompanying this response letter 'Sotagliflozin 24-week data' for details of key efficacy and safety data at baseline, 24-weeks and 52-weeks and 'Inputs_T1DM_CEA_CDM_09_August_2019' for a summary of clinical and cost inputs used during the analysis.

Table 1: Target subpopulation characteristics and efficacy data at baseline and 24-weeks (BMI >= 27 kg/m² & Week -2 HbA_{1c} > 7% & Baseline total daily insulin dose > 0.5 IU/kg/day)

Population characteristics	Baseline			Week 24			Change from baseline at Week 24			Summary of Treatment Comparison	
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Sotagliflozin 200 mg	Sotagliflozin 400 mg
	(N=216)	(N=217)	(N=222)	(N=216)	(N=217)	(N=222)	(N=216)	(N=217)	(N=222)	(N=217)	(N=222)
Change from Baseline in HbA1c (%)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	204 (94.4%)	202 (93.1%)	209 (94.1%)					
Mean (SD)	7.82 (0.669)	7.90 (0.687)	7.83 (0.693)	7.75 (0.856)	7.40 (0.723)	7.26 (0.694)					
LS Mean Difference (SE) from Placebo							-0.08 (0.041)	-0.48 (0.041)	-0.57 (0.040)	-0.39 (0.055)	-0.49 (0.055)
95% CIs for Change from baseline							(-0.16, -0.00)	(-0.56, -0.40)	(-0.65, -0.49)	(-0.50, -0.29)	(-0.60, -0.38)
p-value							0.043	<.001	<.001	<.001	<.001
Change from Baseline in Body weight (kg)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	205 (94.9%)	202 (93.1%)	208 (93.7%)					
Mean (SD)	95.28 (15.355)	95.03 (14.852)	94.46 (15.943)	95.72 (15.942)	92.99 (15.033)	91.85 (16.214)					
LS Mean Difference (SE) from Placebo							0.55 (0.226)	-1.78 (0.227)	-2.75 (0.223)	-2.33 (0.314)	-3.30 (0.311)
95% CIs for Change from baseline							(0.11, 0.99)	(-2.22, -1.33)	(-3.19, -2.31)	(-2.94, -1.71)	(-3.91, -2.69)
p-value							0.015	<.001	<.001	<.001	<.001
Change from Baseline in BMI											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	205 (94.9%)	202 (93.1%)	208 (93.7%)					
Mean (SD)	32.28 (4.355)	32.52 (4.222)	31.94 (3.868)	32.42 (4.628)	31.79 (4.324)	31.04 (3.954)					
LS Mean Difference (SE) from Placebo							0.17 (0.078)	-0.63 (0.078)	-0.93 (0.077)	-0.80 (0.108)	-1.10 (0.107)
95% CIs for Change from baseline							(0.02, 0.32)	(-0.78, -0.48)	(-1.08, -0.78)	(-1.01, -0.59)	(-1.31, -0.89)
p-value							0.029	<.001	<.001	<.001	<.001
Change from baseline in Mean Daily Basal Insulin Dose (IU/day)											

N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	203 (94.0%)	202 (93.1%)	209 (94.1%)					
Mean (SD)	41.95 (18.967)	43.14 (24.124)	38.86 (16.552)	43.75 (21.043)	43.21 (26.951)	38.31 (18.063)					
LS Mean Difference (SE) from Placebo							1.83 (0.543)	0.30 (0.545)	-0.69 (0.535)	-1.53 (0.746)	-2.52 (0.738)
95% CIs for Change from baseline							(0.76, 2.89)	(-0.77, 1.37)	(-1.74, 0.36)	(-2.99, -0.06)	(-3.97, -1.07)
p-value							<.001	0.578	0.2	0.041	<.001
Percent change from baseline in Mean Daily Basal Insulin Dose											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	203 (94.0%)	202 (93.1%)	209 (94.1%)					
Mean (SD)	41.95 (18.967)	43.14 (24.124)	38.86 (16.552)	43.75 (21.043)	43.21 (26.951)	38.31 (18.063)					
LS Mean Difference (SE) from Placebo							4.93 (1.550)	1.51 (1.548)	-2.63 (1.529)	-3.43 (2.097)	-7.57 (2.080)
95% CIs for Change from baseline							(1.89, 7.98)	(-1.53, 4.55)	(-5.63, 0.37)	(-7.54, 0.69)	(-11.65, -3.48)
p-value							0.002	0.33	0.086	0.103	<.001
Change from baseline in Mean Daily Bolus Insulin Dose (IU/day)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	203 (94.0%)	199 (91.7%)	208 (93.7%)					
Mean (SD)	42.25 (27.161)	40.76 (23.739)	39.23 (22.741)	39.64 (27.746)	35.19 (22.279)	32.54 (19.841)					
LS Mean Difference (SE) from Placebo							-2.43 (0.877)	-5.01 (0.881)	-7.40 (0.865)	-2.58 (1.200)	-4.97 (1.187)
95% CIs for Change from baseline							(-4.15, -0.71)	(-6.73, -3.28)	(-9.10, -5.70)	(-4.93, -0.22)	(-7.30, -2.64)
p-value							0.006	<.001	<.001	0.032	<.001
Percent change from baseline in Mean Daily Bolus Insulin Dose											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	203 (94.0%)	199 (91.7%)	208 (93.7%)					
Mean (SD)	42.25 (27.161)	40.76 (23.739)	39.23 (22.741)	39.64 (27.746)	35.19 (22.279)	32.54 (19.841)					
LS Mean Difference (SE) from Placebo							-4.01 (2.400)	-9.35 (2.410)	-14.31 (2.367)	-5.34 (3.290)	-10.30 (3.254)
95% CIs for Change from baseline							(-8.72, 0.71)	(-14.08, -4.61)	(-18.95, -9.66)	(-11.80, 1.12)	(-16.69, -3.91)
p-value							0.095	<.001	<.001	0.105	0.002
Change from baseline in Fasting Plasma Glucose (mg/dL)											

N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	205 (94.9%)	201 (92.6%)	207 (93.2%)					
Mean (SD)	161.39 (65.162	169.97 (78.465	162.88 (67.281	162.90 (69.557	149.47 (53.284	140.61 (51.195					
LS Mean Difference (SE) from Placebo							1.67 (3.986)	-12.61 (4.020)	-20.61 (3.966)	-14.28 (5.523)	-22.28 (5.475)
95% CIs for Change from baseline							(-6.16, 9.50)	(-20.50, -4.71)	(-28.40, -12.83)	(-25.12, -3.43)	(-33.04, -11.53)
p-value							0.675	0.002	<.001	0.01	<.001
Change from baseline in Systolic blood pressure (mmHg)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	205 (94.9%)	202 (93.1%)	209 (94.1%)					
Mean (SD)	124.81 (13.935	124.25 (15.170	123.98 (14.781	123.35 (13.104	121.35 (13.664	120.86 (13.136					
LS Mean Difference (SE) from Placebo							-1.18 (0.744)	-2.98 (0.745)	-3.25 (0.736)	-1.80 (1.016)	-2.07 (1.007)
95% CIs for Change from baseline							(-2.64, 0.28)	(-4.45, -1.52)	(-4.70, -1.81)	(-3.80, 0.19)	(-4.05, -0.09)
p-value							0.113	<.001	<.001	0.077	0.04
Change from baseline in Diastolic blood pressure (mmHg)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	205 (94.9%)	202 (93.1%)	209 (94.1%)					
Mean (SD)	78.22 (8.115)	78.88 (9.485)	77.90 (8.283)	77.53 (8.560)	77.50 (9.193)	77.39 (8.023)					
LS Mean Difference (SE) from Placebo							-0.56 (0.469)	-1.13 (0.471)	-0.55 (0.464)	-0.58 (0.642)	0.01 (0.636)
95% CIs for Change from baseline							(-1.48, 0.36)	(-2.06, -0.21)	(-1.46, 0.36)	(-1.84, 0.69)	(-1.24, 1.26)
p-value							0.234	0.016	0.236	0.371	0.989
Change from baseline in Total Cholesterol (mg/dL)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	205 (94.9%)	199 (91.7%)	212 (95.5%)					
Mean (SD)	180.11 (36.571	178.24 (41.156	177.86 (36.083	182.19 (35.787	183.22 (44.516	185.02 (39.120					
LS Mean Difference (SE) from Placebo							4.97 (1.949)	6.18 (1.965)	8.09 (1.919)	1.21 (2.629)	3.12 (2.592)
95% CIs for Change from baseline							(1.14, 8.80)	(2.32, 10.04)	(4.32, 11.85)	(-3.95, 6.37)	(-1.97, 8.21)
p-value							0.011	0.002	<.001	0.645	0.23
Change from baseline in Low-density lipoprotein (mg/dL)											

N (%)	215 (99.5%)	217 (100.0%)	222 (100.0%)	197 (91.2%)	198 (91.2%)	212 (95.5%)					
Mean (SD)	100.03 (32.058	97.62 (33.863)	98.83 (30.624)	102.30 (31.870	101.48 (36.665	103.55 (33.425					
LS Mean Difference (SE) from Placebo							4.15 (1.714)	4.29 (1.702)	5.44 (1.659)	0.14 (2.299)	1.29 (2.264)
95% CIs for Change from baseline							(0.79, 7.52)	(0.95, 7.63)	(2.19, 8.70)	(-4.37, 4.65)	(-3.16, 5.74)
p-value							0.016	0.012	0.001	0.951	0.569
Change from baseline in High-density lipoprotein (mg/dL)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	202 (93.5%)	198 (91.2%)	212 (95.5%)					
Mean (SD)	57.25 (15.909)	58.35 (15.707)	58.64 (14.195)	55.80 (16.209)	59.66 (15.335)	60.46 (15.436)					
LS Mean Difference (SE) from Placebo							-1.38 (0.607)	1.79 (0.611)	1.88 (0.595)	3.17 (0.823)	3.26 (0.811)
95% CIs for Change from baseline							(-2.57, -0.18)	(0.59, 2.99)	(0.72, 3.05)	(1.55, 4.79)	(1.67, 4.85)
p-value							0.024	0.003	0.002	<.001	<.001
Change from baseline in Triglycerides (mg/dL)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	204 (94.4%)	198 (91.2%)	212 (95.5%)					
Mean (SD)	110.66 (70.270	111.56 (61.251	102.00 (50.636	125.41 (95.280	110.86 (63.758	105.16 (54.149					
LS Mean Difference (SE) from Placebo							18.57 (4.222)	2.21 (4.275)	3.51 (4.152)	-16.36 (5.762)	-15.05 (5.678)
95% CIs for Change from baseline							(10.28, 26.86)	(-6.19, 10.60)	(-4.64, 11.66)	(-27.67, -5.04)	(-26.20, -3.90)
p-value							<.001	0.606	0.398	0.005	0.008
Change from baseline in eGFR (mL/min/1.73m^2)											
N (%)	216 (100.0%)	217 (100.0%)	222 (100.0%)	204 (94.4%)	199 (91.7%)	205 (92.3%)					
Mean (SD)	89.01 (18.786)	89.28 (19.666)	88.30 (18.228)	88.03 (18.096)	86.52 (17.955)	87.15 (18.538)					
LS Mean Difference (SE) from Placebo							-1.27 (0.729)	-2.18 (0.733)	-1.94 (0.724)	-0.91 (0.998)	-0.67 (0.990)
95% CIs for Change from baseline							(-2.70, 0.16)	(-3.62, -0.74)	(-3.36, -0.52)	(-2.87, 1.05)	(-2.61, 1.27)
p-value							0.082	0.003	0.008	0.361	0.498
Change from baseline in DDS2 score 1 (Feeling overwhelmed by the demands of living with diabetes)											

N (%)	212 (98.1%)	214 (98.6%)	220 (99.1%)	204 (94.4%)	202 (93.1%)	213 (95.9%)					
Mean (SD)	2.52 (1.150)	2.64 (1.197)	2.41 (1.223)	2.61 (1.225)	2.35 (1.213)	2.33 (1.039)					
LS Mean Difference (SE) from Placebo							0.11 (0.068)	-0.20 (0.068)	-0.14 (0.066)	-0.31 (0.092)	-0.24 (0.091)
95% CIs for Change from baseline							(-0.03, 0.24)	(-0.34, -0.07)	(-0.27, -0.01)	(-0.49, -0.13)	(-0.42, -0.06)
p-value							0.125	0.003	0.038	<.001	0.008
Change from baseline in DDS2 score 2 (Feeling that I am often failing with my diabetes routines)											
N (%)	212 (98.1%)	214 (98.6%)	220 (99.1%)	204 (94.4%)	202 (93.1%)	213 (95.9%)					
Mean (SD)	2.81 (1.312)	2.89 (1.133)	2.79 (1.221)	2.78 (1.326)	2.41 (1.144)	2.32 (1.070)					
LS Mean Difference (SE) from Placebo							0.04 (0.072)	-0.32 (0.072)	-0.42 (0.070)	-0.36 (0.096)	-0.45 (0.095)
95% CIs for Change from baseline							(-0.10, 0.18)	(-0.46, -0.18)	(-0.55, -0.28)	(-0.55, -0.17)	(-0.64, -0.27)
p-value							0.601	<.001	<.001	<.001	<.001
Change from baseline in DDS2 Total score											
N (%)	212 (98.1%)	214 (98.6%)	220 (99.1%)	204 (94.4%)	202 (93.1%)	213 (95.9%)					
Mean (SD)	5.33 (2.261)	5.53 (2.064)	5.20 (2.194)	5.39 (2.318)	4.76 (2.127)	4.65 (1.848)					
LS Mean Difference (SE) from Placebo							0.12 (0.120)	-0.54 (0.119)	-0.57 (0.116)	-0.66 (0.161)	-0.69 (0.159)
95% CIs for Change from baseline							(-0.11, 0.36)	(-0.78, -0.31)	(-0.80, -0.34)	(-0.98, -0.35)	(-1.00, -0.38)
p-value							0.305	<.001	<.001	<.001	<.001

Abbreviations: BMI, Body mass index; CI, Confidence interval; DDD2, Diabetes Distress Scale 2; dL, Decilitre; IU, International units; kg, Kilograms; LS, Least squared; m^2, Meters squared, mg, Milligrams, mmHg; Millimetres of mercury; N, Number of patients, SD, Standard deviation, SE, Standard error.

Table 2: Safety data from subpopulation of safety analysis; (BMI >= 27 kg/m² & Week -2 HbA_{1c} > 7% & Baseline total daily insulin dose > 0.5 IU/kg/day) during the core treatment period (randomisation to 24-weeks)

Adverse event	Placebo (N=216)	Sotagliflozin 200 mg (N=217)	Sotagliflozin 400 mg (N=222)
Treatment emergent Adjudicated DKA			
Total patient years of exposure	97.9	96.8	100.7
Treatment emergent Adjudicated DKA			
Number of patients with events, n (%)	0	0	5 (2.3%)
Number of patients with events per patient years	0	0	0.05
Number of events	0	0	5
Number of events per patient years	0	0	0.05
Severe hypoglycaemia			
Total patient years of exposure	97.9	96.8	100.7
Severe hypoglycaemia			
Number of patients with events, n (%)	12 (5.6%)	6 (2.8%)	6 (2.7%)
Number of patients with events per patient years	0.123	0.062	0.06
Number of events	13	12	6
Number of events per patient years	0.133	0.124	0.06
Non severe documented symptomatic hypoglycaemia (plasma glucose <= 70 mg/dL [3.9 mmol/L])			
Total patient years of exposure	97.9	96.8	100.7
Non severe documented symptomatic hypoglycaemia			
Number of patients with events, n (%)	192 (88.9%)	192 (88.5%)	199 (89.6%)
Number of patients with events per patient years	1.961	1.983	1.976
Number of events	5854	5528	5450
Number of events per patient years	59.8	57.11	54.12

Abbreviations: DKA, Diabetic ketoacidosis; dL, decilitre; IU, International units; kg, Kilograms, m^2, meters squared, mg, milligrams, n, number

Appendix 2: Committee Preferred Base Case

Table 3 presents a summary of the NICE technical team preferred base case results presented at committee and NICE preferred base case post committee/Sanofi final base case results. Please refer to the Microsoft Excel workbook accompanying this response letter 'Inputs_T1DM_CEA_CDM_09_August_2019' and the model folder "*Sotagliflozin NICE- ERG August 2019*", for a summary of clinical and cost inputs used during the analysis.

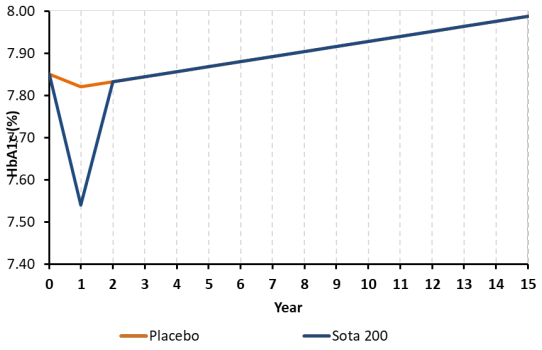
Table 3: Incremental costs and QALYs for Company and NICE 'preferred base case'

Outcome	Sotagliflozin 200 mg + Insulin	Insulin alone	Incremental value
NICE technical team preferred base case presented at committee			
Total Costs	£87,695	£87,077	£618
QALYs	13.40	13.37	0.03
ICER			**£18,665**
NICE preferred base case post committee/Sanofi final base case			
Total Costs	£85,434.51	£84,645.93	£788.58
QALYs	13.262	13.213	0.049
ICER			**£16,093.47**
Change in ICER from technical team base case presented to committee			*-£2,571.53*
Abbreviations: ICER, Incremental cost effectiveness ratio; mg, Milligrams; QALY, Quality-adjusted life year;			

A summary of the 'NICE preferred base case' and descriptions of how requested settings where incorporated into the CORE diabetes model if they varied from the Company base case are presented in Table 4. If a requested parameterisation could not be incorporated as defined an explanation is provided justifying deviation from the request.

Table 4: Summary of NICE preferred base case analysis

Description	Explanation

Analysis of the indicated population for sotagliflozin using pooled data from inTandem 1 and inTandem 2. The relevant clinical data (e.g. baseline characteristics, effectiveness data, adverse events, number of patients in this group). The population is defined as previously submitted: • people with a BMI of greater or equal to than 27 kg/m2 • exclude people with low insulin requirements in line with the SPC (0.5 units per kg of body weight or less) • only include people with a post-optimisation HbA_{1c} of 7% or more	Reflects the Company 'updated base case'.
Do not assume a relationship between baseline characteristics and diabetes related complications, other than HbA_{1c}.	This setting was applied within the CORE model in form of a clinical setting. Whereby adjustments to HbA_{1c} from other parameters such as SBP, race and metabolic memory effects were neutralized i.e. a value of 0 is used for risk adjustments and a value of 1 for multipliers and increased risks.
Stopping treatment: 2 years on treatment.	**Reflects the Company's 'updated base case'.** To ensure the sotagliflozin profile mirrors the SoC arm at the end of year 2 full treatment effect is applied for year 1 and a waning effect applied for the second year. As presented in the figure below: 

<table>
<tr>
<td>Duration of treatment effect, no continued benefit from treatment for any risk factors after 2 years: Treatment duration should be based on the trial data. The treatment effect in year 1 should be based on the treatment effect from the trial data and the observed trial data from 6 to 12 months should be extrapolated to get the treatment effect for year 1 to year 2. Treatment effect should return to placebo when treatment stops. Based on the technical teams preferred population as outlined in point 1.</td>
<td>Risk factors in the model depend on physiological parameters. By waning the treatment effects of sotagliflozin to mirror SoC risk factors for both arms adjust at the same level, therefore additional settings do not need to be applied.
If the observed treatment effect in months 6-12 is used and extrapolated from year 1 to 2, at the end of year 2 the sotagliflozin arm would not have waned sufficiently to equal the SoC arm at the beginning of year 3.
The model therefore applies a waning effect on HbA_{1c} of +0.29%. This waning effect is higher than that observed within the pooled data between months 6 to 12 (+0.18%). Therefore a more conservative approach was taken to ensure the sotagliflozin arm mirrors SoC at the start of year 3.

<table>
<tr><th>Full sotagliflozin Effect (HbA_{1c} %)</th><th>Month 6-12 progression (HbA_{1c} %)</th><th>Modelled wane effect (HbA_{1c} %)</th></tr>
<tr><td>-0.31%</td><td>+ 0.18 %
(7.4% to 7.58%)</td><td>+0.29%</td></tr>
</table>
</td>
</tr>
<tr>
<td>Treatment discontinuation rate based on extrapolation of trial data observation between 6 and 12 months.</td>
<td>The ‘updated base case’ assumes 2 years of treatment, with 1 year of full treatment effect waning to placebo over the second year.
It is not technically feasible to implement two simultaneous stopping conditions (waning and discontinuation) within the CORE model. This is due to the model restricting the number of stopping conditions.
The impact of discontinuation is likely to be limited, as can be seen from the table below discontinuation during the long-term extension period (24-weeks to 52-weeks) was at almost halve the rate compared to the core treatment period (initiation to 24 weeks) across all treatment arms.

<table>
<tr><th></th><th>Placebo n (%)</th><th>Sotagliflozin 200 mg n (%)</th><th>Sotagliflozin 400 mg n (%)</th></tr>
<tr><td>Number of Patients Who Received At Least One Dose of Study Drug During Core Treatment Period</td><td>216 (100.0)</td><td>217 (100.0)</td><td>222 (100.0)</td></tr>
<tr><td>Number of Patients Who Discontinued Study During Core Treatment Period</td><td>16 (7.4)</td><td>17 (7.8)</td><td>15 (6.8)</td></tr>
<tr><td>Number of Patients Who Completed Long-term Extension Period</td><td>192 (88.9)</td><td>190 (87.6)</td><td>200 (90.1)</td></tr>
<tr><td>Number of Patients Who Discontinued Study During Long-term Extension Period</td><td>8 (3.7)</td><td>10 (4.6)</td><td>7 (3.2)</td></tr>
<tr><td>Number of Patients Who Completed Study</td><td>192 (88.9)</td><td>190 (87.6)</td><td>200 (90.1)</td></tr>
<tr><td>Number of Patients Who Discontinued Study</td><td>24 (11.1)</td><td>27 (12.4)</td><td>22 (9.9)</td></tr>
</table>
Abbreviations: mg: Milligrams
</td>
</tr>
</table>

<table>
<tr><td>Apply a clinically plausible mortality rate that is less than for DKA and a hazard ratio for DKA that reflects the UK.</td><td>Sanofi have used a DKA mortality rate of 0.7%, this value was reported in JBDS guidelines on the management of DKA in adults (JBDS 02, 2013)[2]. We believe this a clinically plausible rate to include in the base case analysis and is in line with the clinical expert feedback. This value is subsequently converted to the mortality event rate per 100-patient years for use in the model.

We have maintained death from severe hypoglycaemia at 4% in line with the NICE technical team and ERG's assumptions.

Please note adverse events are considered with the CORE Diabetes model as event rate per 100-patient years.

<table>
<tr><th>Concept</th><th>Value</th><th>Reference</th></tr>
<tr><td>Death from severe hypoglycaemia</td><td>4%</td><td>Heller, 2008[3] & Wolowacz,2014[4]</td></tr>
<tr><td>Death from diabetic ketoacidosis</td><td>0.7%</td><td>Joint British Diabetes Societies Inpatient Care Group[5]</td></tr>
</table>
</td></tr>
<tr><td>Utilities based on the ScHARR review using a fixed effects approach.</td><td>Reflects the Company 'updated base case'.</td></tr>
<tr><td>Use the multiplicative approach to QALYs in line with NICE TSD 12: the use of health state utility values in decision models</td><td>Reflects the Company 'updated base case'.</td></tr>
<tr><td colspan="2">Adverse events</td></tr>
<tr><td>a) Impact of rare life threatening urogenital infections such as Fournier's gangrene (following the MHRA warning issued for SGLT2 inhibitors in February 2019).</td><td>Reflects the Company 'updated base case'.</td></tr>
<tr><td>b) Hypoglycaemic events: 50% of severe hypoglycaemic events need medical attention, costs in line with the NICE clinical guideline</td><td>Reflects the Company 'updated base case'.</td></tr>
</table>

2 Joint British Diabetes Societies Inpatient Care Group. The Management of Diabetic Ketoacidosis in Adults 2nd Ed, 2013
3 Heller S. Sudden death and hypoglycaemia. Diabetic Hypoglycaemia 2008 Sep; 1(2): 2-7.
4 Wolowacz S, Pearson 1 et al. Development and validation of a cost–utility model for Type 1 diabetes mellitus. DiabeticMedicine 2014

Sensitivity analysis

Sensitivity analysis undertaken on the NICE preferred base case include:

1. Duration of treatment and effect: the technical team would like to see a variety of scenarios looking at the duration of treatment:

    a. 1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1

    b. 2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years

    c. 2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.

2. For each treatment duration outlined above (1.a.b.c) apply the following duration of treatment benefit:

    a. No continued benefit from treatment for any risk factors after treatment stops

    b. No benefit of HbA_{1c} improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.

    c. No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.

3. Adverse events:

    a. Sensitivity analysis varying the Diabetic ketoacidosis (DKA) mortality rate from 0.16% to 2%

    b. Scenario using Severe Hypoglycaemic mortality rate of 4.45% (as previously submitted)

Summary ICER results from sensitivity analysis requested by the NICE committee in Table 5. Detailed explanations of the analysis undertaken and incremental cost and QALY results for each scenario are presented in Table 6, Table 7 and Table 8.

Table 5: Summary ICER results for sensitivity analysis

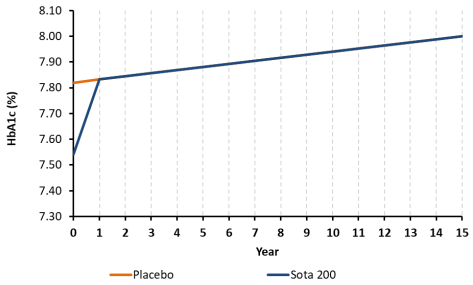
Analysis		ICER (£/QALY)	*ICER change* (vs. NICE base case)
Base case (NICE)		**£16,093.47**	
1. Duration of treatment and effect:			
a)	1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1	**-***	**-***
b)	2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years	Reflects the Company 'updated base case'.	
c)	2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.	Reflects the Company 'updated base case'.	
2. For each treatment duration outlined above (1.a.b.c) apply the following duration of treatment benefit:			
a) 1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1			
i.	No continued benefit from treatment for any risk factors after treatment stops	The CORE diabetes model's structure does not facilitate part a) of the treatment duration and effect analysis and exploratory analysis of part a) showed no impact on the ICER.	
ii.	No benefit of HbA_{1c} improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.		
iii.	No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.		
b) 2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years			
i.	No continued benefit from treatment for any risk factors after treatment stops	Reflects the Company 'updated base case'.	
ii.	No benefit of HbA_{1c} improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.	Subpopulation extrapolation of weight was not considered robust enough to be presented.	
iii.	No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.	Reflects the Company 'updated base case'.	
c) 2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.			
i.	No continued benefit from treatment for any risk factors after treatment stops	The CORE diabetes model's structure does not facilitate full implementation	
ii.	No benefit of HbA_{1c} improvement after the trial period (1 year). The only benefit that continues		

		after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.	of part c) of the treatment duration and effect analysis.	
	iii.	No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.		
3. Adverse events:				
DKA mortality rate: base case = 0.7%				
	i.	DKA mortality rate = 0.16%	**£14,842.55**	*-£1,250.92*
	ii.	DKA mortality rate = 1% (additional analysis)	**£17,670.64**	*-£1,577.17*
	iii.	DKA mortality rate = 2%	**£16,816.00**	*£722.53*
	Severe Hypoglycaemic mortality rate of 4.45%		**£15,937.22**	*£156.25*

*See Table 6 for explanation of analysis undertaken

Abbreviations: DKA, diabetic ketoacidosis; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.

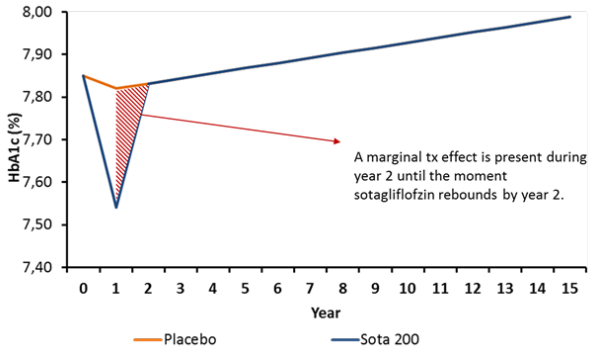
Table 6: Scenario 1 -Duration of treatment and effect sensitivity analysis justification

a) 1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1			
Notes: The annual cycle length of the CORE Diabetes model does not facilitate incorporation of this analysis. Treatment effect is applied for the first year but cannot be simultaneously removed in the first year. To explore implementation of this scenario further analysis was run where HbA_{1c} drop seen at 52 weeks in the trial was applied at time 0 and then the treatment effect was waned over year 1 to equal SoC at the end of 1 year. This meant that sotagliflozin patients started with a HbA_{1c} value of 7.54%.  			
	Sotagliflozin 200 mg + Insulin	**Insulin alone**	**Incremental value**
Total Costs	£84,959.37	£84,479.40	£479.97
QALYs	13.211	13.211	0
		ICER	-
		ICER change (compared with NICE base case)	-
b) 2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years			
Notes: This scenario reflects the 'updated base case'. To ensure no treatment effect or treatment legacy is continued beyond the end of year 2, a waning effect must be applied from the end of year 1 for the intervention is equal to SoC at the end of year 2.			
c) 2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.			
Notes: This scenario reflects the 'updated base case'. To ensure the SoC profile is matched at the end of year 2, and no treatment benefit or treatment legacy is continued beyond the end of year 2 the model must assume a waning factor applied to the treatment effect at a rate equal to that required to reduce any clinical benefit gained from treatment in year 1.			

Abbreviations: ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted-life years; mg, Milligrams; SoC, Standard of care (insulin).

Table 7: Scenario 2 - For each treatment duration outlined above (1.a.b.c) apply the following duration of treatment benefit sensitivity analysis justification

a) 1 year on treatment: Full benefit of treatment to year 1, treatment stops at year 1		
i.	No continued benefit from treatment for any risk factors after treatment stops	Notes: The CORE diabetes model structure does not facilitate part a) of the treatment duration and effect analysis and exploratory analysis of part a) showed no impact on the ICER.
ii.	No benefit of HbA_{1c} improvement after the	Notes: The CORE diabetes model structure does not facilitate part a) of the treatment duration and effect analysis and

	trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.	exploratory analysis of part a) showed no impact on the ICER. Also given the few data points available in the post-hoc analysis for this sub-population (3 data points), an extrapolation of weight was not considered robust enough to be presented.
iii.	No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.	Notes: The CORE diabetes model structure does not facilitate part a) of the treatment duration and effect analysis and exploratory analysis of part a) showed no impact on the ICER. Also risk factors in the CORE diabetes model are influenced by physiological parameters such as HbA_{1c}, BMI and SBP. The model assumes waning of treatment effect on these factors to mirror the SoC profile at the point of treatment discontinuation. Therefore, following discontinuation of treatment at the end of year 2, the profile is identical to that of SoC, thus it is assumed no continued benefit is present for any of the risk factors.
b)	**2 years on treatment: Full benefit of treatment up to 2 years, treatment stops at 2 years**	
i.	No continued benefit from treatment for any risk factors after treatment stops	Notes: This scenario reflects the 'updated base case'. Risk factors in the CORE diabetes model are influenced by physiological parameters such as HbA_{1c}, BMI and SBP. The model assumes waning of treatment effect on these factors to mirror the SoC profile. Therefore, following discontinuation the sotagliflozin and SoC profiles are identical, thus it is assumed no continued benefit is present for any of the risk factors.
ii.	No benefit of HbA_{1c} improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.	Notes: The annual cycle length of the CORE diabetes model treatment effects cannot be applied and removed at the same time. The figure below presents the marginal effect (red triangle) carried over during year 2 until the treatment effect rebounds to the SoC profile at the end of year 2.  Also given the few data points available in the post-hoc analysis for this sub-population (3 data points), an extrapolation of weight was not considered robust enough to be presented.

iii.	No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.	Notes: This scenario reflects the 'updated base case'. Risk factors in the CORE diabetes model are influenced by physiological parameters such as HbA_{1c}, BMI and SBP. The model assumes waning of treatment effect on these factors to mirror the SoC profile at the point of treatment discontinuation. Therefore, following discontinuation of treatment at the end of year 2, the profile is identical to that of SoC, thus it is assumed no continued benefit is present for any of the risk factors.
c)	**2 years on treatment: Full benefit of treatment up to year one, half of the treatment effect for year 2.**	
i.	No continued benefit from treatment for any risk factors after treatment stops	Notes: This scenario reflects the 'updated base case'. The CORE diabetes model structure does not facilitate full implementation of part c) of the treatment duration and effect analysis.
ii.	No benefit of HbA_{1c} improvement after the trial period (1 year). The only benefit that continues after treatment stops is for weight. Benefits for weight should be extrapolated in line with the trial data.	Notes: This scenario reflects the 'updated base case'. The CORE diabetes model's structure does not facilitate full implementation of part c) of the treatment duration and effect analysis.
iii.	No impact of HbA_{1c} on cardiovascular risk compared with placebo after the trial period, other benefits from treatment continue until treatment stops. When treatment stops no continued benefit for any risk factors.	Notes: This scenario reflects the 'updated base case'. The CORE diabetes model structure does not facilitate full implementation of part c) of the treatment duration and effect analysis.

Abbreviations: BMI, body mass index; ICER, Incremental cost-effectiveness ratio; SoC, Standard of care (insulin); SBP, Systolic blood pressure

Table 8: Scenario 3 – Adverse events sensitivity analysis justification

a) DKA mortality rate: base case = 0.7%			
i. DKA mortality rate = 0.16%	**Sotagliflozin 200 mg + Insulin**	**Insulin alone**	**Incremental value**
Total Costs	£85,402.90	£84,645.93	756.97
QALYs	13.264	13.213	0.052
		ICER	**£14,842.55**
		ICER change (compared with NICE base case)	*£1,250.92*
ii. DKA mortality rate = 1% (additional	**Sotagliflozin**	**Insulin alone**	**Incremental**

analysis)	200 mg + Insulin		value
Total Costs	£85,476.45	£84,645.93	£830.52
QALYs	13.26	13.213	0.047
		ICER	**£17,577.17**
		ICER change (compared with NICE base case)	*-£1,577.17*
iii. DKA mortality rate = 2%	**Sotagliflozin 200 mg + Insulin**	**Insulin alone**	**Incremental value**
Total Costs	£85,486.73	£84,645.93	£840.81
QALYs	13.263	13.213	0.05
		ICER	**£16,816.00**
		ICER change (compared with NICE base case)	*-£722.53*
b) Severe Hypoglycaemic mortality rate of 4.45%			
	Sotagliflozin 200 mg + Insulin	**Insulin alone**	**Incremental value**
Total Costs	£85,145.28	£84,284.67	£860.61
QALYs	13.241	13.187	0.054
		ICER	**£15,937.22**
		ICER change (compared with NICE base case)	*£156.25*

Abbreviations: DKA, diabetic ketoacidosis; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year.

Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376]

ERG Review of Analyses Post ACM1

This report was commissioned by the NIHR HTA Programme as project number 127657

BMJ Technology Assessment Group

1 INTRODUCTION

In the previous appraisal committee meeting, the company clarified that their previously preferred base case was the same as the NICE technical team's previously preferred base case, with an ICER of £18,665. However, since this meeting the NICE technical team requested some amendments to this base case, as well as some additional scenarios. In response to these requests, the company provided an updated version of their own preferred base case analysis along with a subset of the requested scenario analyses.

A comparison of the analyses requested by the NICE technical team and those provided by the company, is given in Section 2.

2 COMPARISON OF NICE TECHNICAL TEAM'S PREFERRED BASE CASE AND COMPANY'S ANALYSIS

The NICE technical team's latest request for additional analyses after the first ACM was largely in line with the previous preferred base case but with a few changes to certain inputs. The NICE request document provided to the Evidence Review Group (ERG) suggested a more plausible mortality rate associated with diabetic ketoacidosis (DKA) was required. The company applied a value of 0.7% as the probability of death following the onset of DKA and stated that this was based on clinical expert opinion in the committee meeting and is based on a recent meta-analysis.[1] Given the discussion from clinical experts at the ACM that the risk of mortality following DKA is less than 1%, and the company's reference for the value of 0.7%, the ERG considers this to be reasonable.

The NICE technical team requested an analysis with a value of 4.45% for the mortality risk associated with a severe hypoglycaemic event (SHE), which was previously provided by the company as a scenario analysis. The company applied a value of 4% in their preferred base case model, and although this difference is unlikely to make an important impact on the results, the ERG updated this value to 4.45% in a revised analysis presented in Section 3.

The NICE technical team requested that the company should not assume a relationship between baseline characteristics and diabetes related complications, with the exception of HbA1c. The ERG requested further clarity on their preferred assumptions in this regard as the baseline characteristics are an inherent part of the model, which will impact the baseline risk of complications for the population, and therefore there must be some relationship between the two. The NICE technical team clarified that the key issue they wanted to address was the assumption that sotagliflozin only has an effect on HbA1c but not on any other physiological parameter.

The company interpreted this differently and stated that they neutralised the effect that other parameters had on HbA1c, such as systolic blood pressure (SBP) and race. However, firstly, these model parameters were not impacting on HbA1c as the company states, but they were impacting the risk of certain complications that are dependent on such parameters as SBP levels at baseline or otherwise. The ERG does not consider these changes to be in line with the requests of the NICE technical team and furthermore the company's analyses do not make changes relating to any of the other parameters affecting the results of the model. Therefore, the ERG reinstated these adjustments for the analyses presented in Section 3. Note these adjustments were originally applied as defaults in the Core Diabetes Model (CDM).

Another key aspect that the company did not address is the request for extrapolations of the treatment effects using the 24- and 52-week data. Although the company provide the 24-week data to

supplement the previously submitted 52-week data, the company did not use this to provide extrapolated estimates for the second year in the model. Note that the company still uses the 52-week data in their analyses and not the 24-week data. The ERG used the supplied 24-week data to estimate extrapolated treatment effects for the second year and provided scenario analyses using these extrapolated effects. The results are given in Section 4.

The company submitted an updated base case incremental cost effectiveness ratio (ICER) of £16,093, although the ERG notes that this appears to be based on rounded costs and quality-adjusted life-years (QALYs) taken from the model and is not based on the ICER produced by the model. The correct ICER produced by the model is slightly lower at £15,963 per QALY. Note that all of the results reported by the company for their analyses appear to calculate the ICERs based on the rounded results and so are slightly inaccurate.

The ERG reran the company's updated base case but with the default adjustments for SBP and race, etc., reinstated, as well as applying the NICE technical team's preferred value of 4.45% for the SHE mortality risk (as opposed to the company's 4%). This increased the ICER to £19,046 per QALY. The ERG will consider this the company's corrected base case and will assess all scenario analyses relative to this.

As a validation exercise, the ERG also ran an analysis using the previous preferred base case that produced an ICER of £18,665 per QALY and altered the mortality risks for DKA and SHE to 0.7% and 4.45%, respectively. This increased the ICER to £19,370 per QALY. Each of these analyses uses the same apparent assumptions with regard to treatment effects and treatment duration, i.e. two years of treatment but only one year of effect for all physiological parameters. The only difference between these analyses appears to be the that the cohort for the former (£19,046 per QALY) has a slight alteration to the number of cigarettes that smokers consume per day. This was increased from 2 to 10 per day and the company referenced a study in their model inputs Excel file from which this value was taken. The ERG is unsure why this value is not based on the population of the trials from which treatment effects were estimated, as per all of the other baseline characteristics.

With the exception of this newly altered value, the baseline characteristics are taken from the pooled trial cohort used to inform the treatment effectiveness. However, as noted by the ERG previously, the value of 2 cigarettes per day in the previous submission appeared to be much lower than the value from the pooled trial data before it was subject to further sub-grouping by HbA1c levels and insulin requirements. The company's previously preferred cohort without these sub-grouping requirements applied had a value of 11 cigarettes per day. However, the impact on the results was shown to not be important, as is also shown with these updated analyses.

The company appears to have interpreted some of the NICE technical team's analyses inappropriately and have thus not provided analyses that could have been implemented. The company state that a one-year treatment effect could not be implemented as the effect, "cannot be simultaneously removed in the first year" after being applied in the first year. However, the treatment effect merely needs to be removed for the second year for a one-year effect to be applied, which is not a subsequent application and removal of the effect in the first year. The company attempted to demonstrate this by applying the effect at time zero (effectively having different baseline values in each treatment group) and then applies the removal of the effect for the first year. This is, therefore, zero effect for the first year (and onwards), hence why the QALY difference is zero. The ERG has conducted the appropriate analysis for a one-year treatment effect and have presented the results in Section 4.

Another analysis the company did not provide is the application of half the treatment effect in the second year. The company state that this is part of the updated base case; however, they also state that the two-year treatment effect is part of the updated base case, therefore, they cannot both be true. Note the company's preferred base case has only one year of effect applied. The ERG has conducted this analysis and has presented the results in Section 4. The company also stated that the requested analysis assuming the HbA1c has no impact on cardiovascular risk is part of the updated base case; however, this is also not the case, but the ERG has conducted this analysis and the results are presented in Section 4.2. For this analysis, the ERG changed the risk reductions for cardiovascular events (myocardial infarction, heart failure, stroke and angina) relating to a 10% lower HbA1c level compared to the comparator treatment, i.e. from 20% to zero.

The company appear to have presented erroneous results for the scenarios using alternative DKA mortality risks. In Table 8 of the company's response, the results reported for the DKA mortality risk of 1% are actually for the scenario using a value of 1%. The results of the 1% scenario do not appear to be included within the CDM analyses, although it would be plausible if the results presented for the 2% scenario in the company's response actually relate to the 1% scenario.

3 ERG ADDITIONAL ANALYSES

The ERG conducted a number of analyses to address some of the NICE technical team's preferences that were not addressed by the company. The key analyses are as follows:

1. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters;
2. Use of the 24- and 52-week data to extrapolate *only* the treatment effect for HbA1c to the second year with all other effects only applied for 1 year;
3. Only benefit applied is for HbA1c and uses the 24- and 52-week data to extrapolate the treatment effect to the second year;
4. Applying the HbA1c effect for the first year only, BMI is sustained for the time horizon and no other effects are applied;
5. Applying the HbA1c effect for the first year only, BMI is sustained for the time horizon and no other effects are applied, and treatment costs are only applied for the first year;
6. Applying half of the 52-week treatment effect as an estimate of the second-year effect for all physiological parameters;
7. Applying 52-week effects for the second year for all physiological parameters;
8. Applying 52-week effects for the first year only and assuming no benefit beyond this point, but with treatment costs only applied for the first year;
9. DKA mortality risk set to 0.16%;
10. DKA mortality risk set to 2%.
11. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters and cardiovascular event risk adjustments for HbA1c changes set to zero.
12. Use of the 24- and 52-week data to extrapolate *only* the treatment effect for HbA1c to the second year with all other effects only applied for 1 year, and cardiovascular event risk adjustments for HbA1c changes set to zero.
13. Only benefit applied is for HbA1c and uses the 24- and 52-week data to extrapolate the treatment effect to the second year, and cardiovascular event risk adjustments for HbA1c changes set to zero.

4 RESULTS

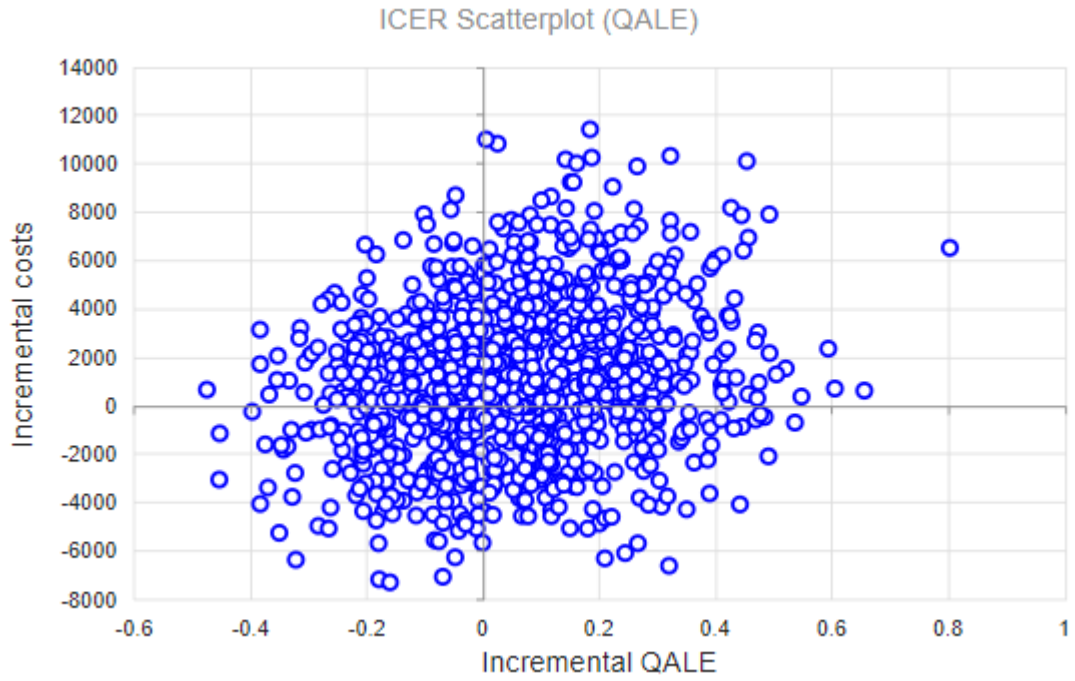
4.1 ERG's corrected company base case

Table 1. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£86,201	30.11	13.20	£1,162	0.16	0.06	£19,046

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Figure 1. Scatterplot showing 1,000 sampled pairs of incremental costs and QALYs



4.2 ERG's scenarios

Each of the following analyses, unless otherwise stated, is based on the NICE technical team's preferred base case assumptions, i.e. that treatment duration is two years and the risks of mortality for DKA and SHE are 0.7% and 4.45%, respectively.

4.2.1 Scenario 1

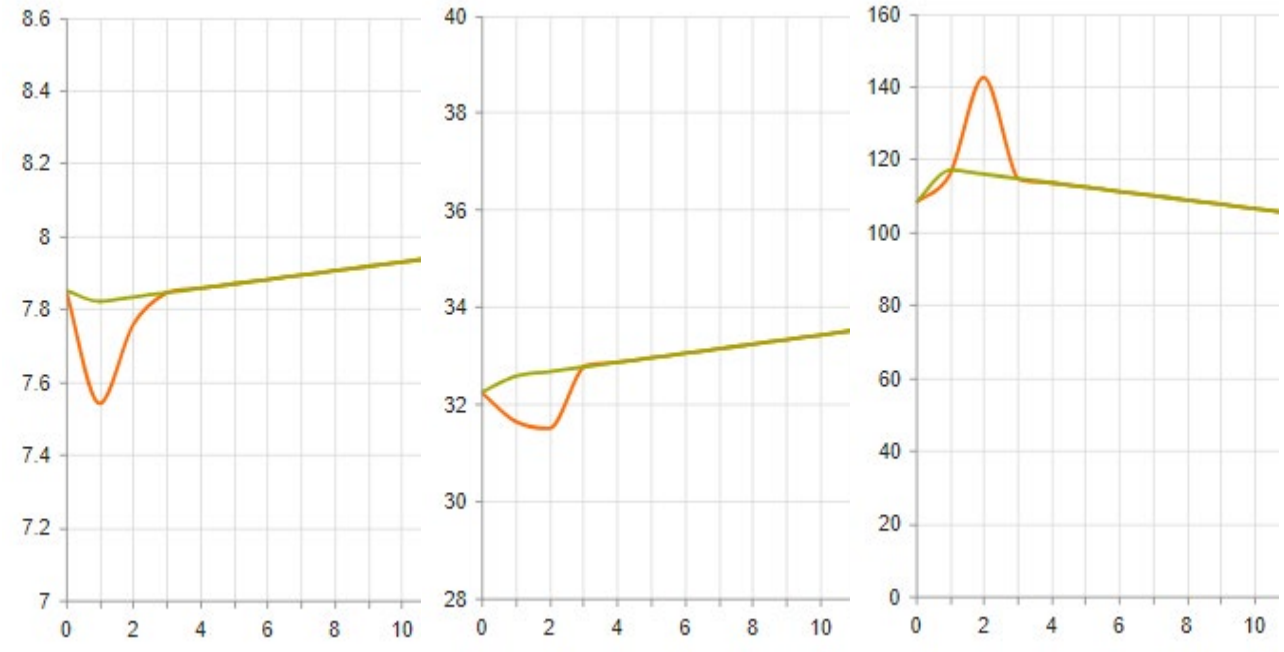
Table 2. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,919	30.11	13.20	£879	0.15	0.06	£15,163

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Note that because effects are applied compared to the placebo group, this scenario can result in potentially implausible extrapolations, and this appears to be the case at least for triglycerides, as can be seen on the right of Figure 1. This crossing of curves is a result of the placebo group showing a relatively large drop in triglycerides between 24 and 52 weeks, in contrast to sotagliflozin causing an increase over this period. As the model applies effects relative to placebo, this effectively results in a large relative increase for sotagliflozin in comparison to placebo. However, in reality, as none of the submitted evidence has shown the sotagliflozin group to have greater triglyceride levels than the placebo group, a more plausible extrapolation may be for the sotagliflozin value to assymptote to the placebo group value. Due to time constraints, the ERG could not explore this further; however, the scenario that applies half of the 52-week effect, shown in 4.2.7, avoids this potentially implausible extrapolation.

Figure 2. Progression of HbA1c (%), BMI (kg/m^2) and triglycerides (mg/dl), respectively, for



the first 10 years of model.

Key: Sotagliflozin – Orange; Placebo – Green.

4.2.2 Scenario 2

Table 3. Use of the 24- and 52-week data to extrapolate only the treatment effect for HbA1c to the second year with all other effects only applied for one year

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£86,202	30.18	13.22	£1,163	0.22	0.08	£14,205

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.3 Scenario 3

Table 4. Only benefit applied is for HbA1c and uses the 24- and 52-week data to extrapolate the treatment effect to the second year

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,941	30.04	13.18	£902	0.08	0.04	£25,115

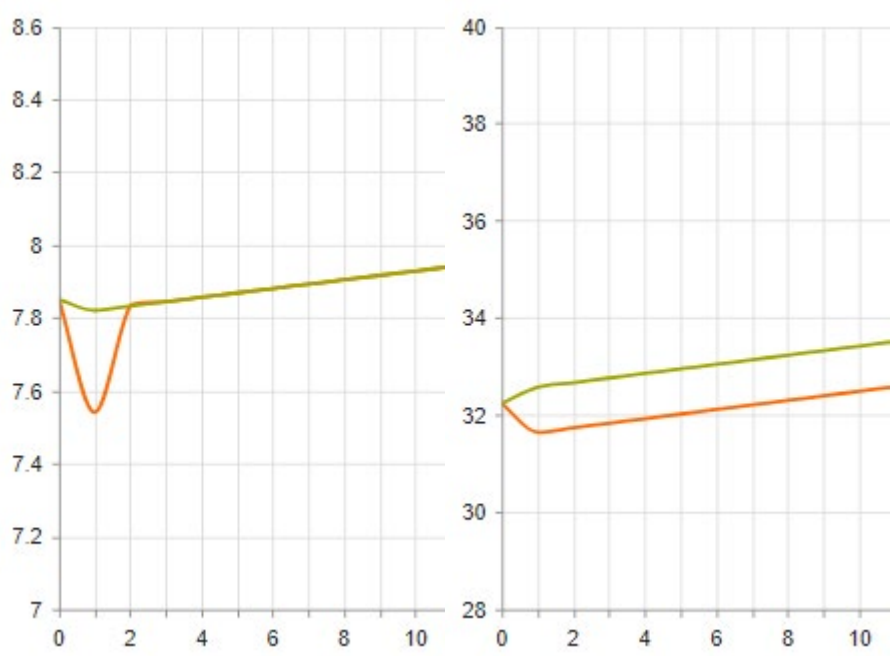
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.4 Scenario 4

Table 5. Applying the HbA1c effect for the first year only, BMI is sustained for the time horizon and no other effects are applied

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£86,201	30.11	13.25	£1,162	0.16	0.11	£10,992
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. a Undiscounted							

Figure 3. Progression of HbA1c (%) and BMI (kg/m^2), respectively, for the first 10 years of model.



Key: Sotagliflozin – Orange; Placebo – Green.

4.2.5 Scenario 5

Table 6. Applying the HbA1c effect for the first year only, BMI is sustained for the time horizon and no other effects are applied, and treatment costs are only applied for the first year

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,740	30.11	13.25	£700	0.16	0.11	£6,626
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. a Undiscounted							

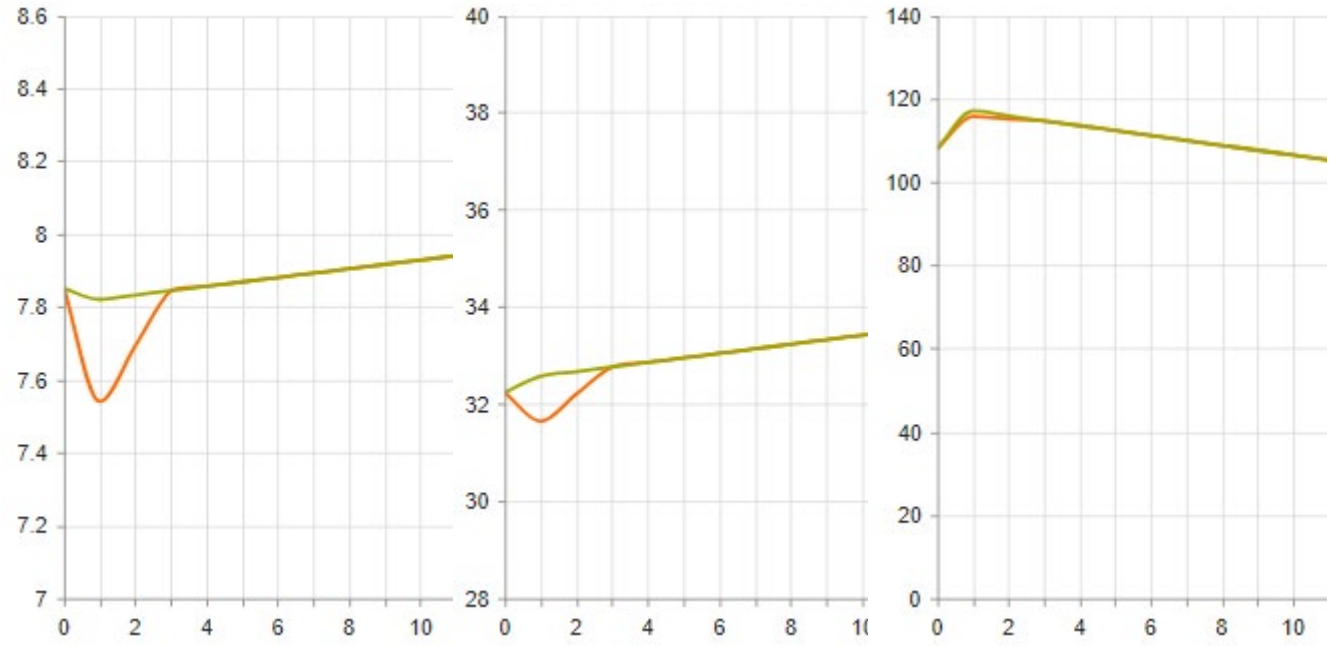
4.2.6 Scenario 6

Table 7. Applying half of the 52-week treatment effect as an estimate of the second-year effect for all physiological parameters

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,810	30.11	13.20	£771	0.15	0.06	£13,129

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Figure 4. Progression of HbA1c (%), BMI (kg/m^2) and triglycerides (mg/dl), respectively, for the first 10 years of model.



Key: Sotagliflozin – Orange; Placebo – Green.

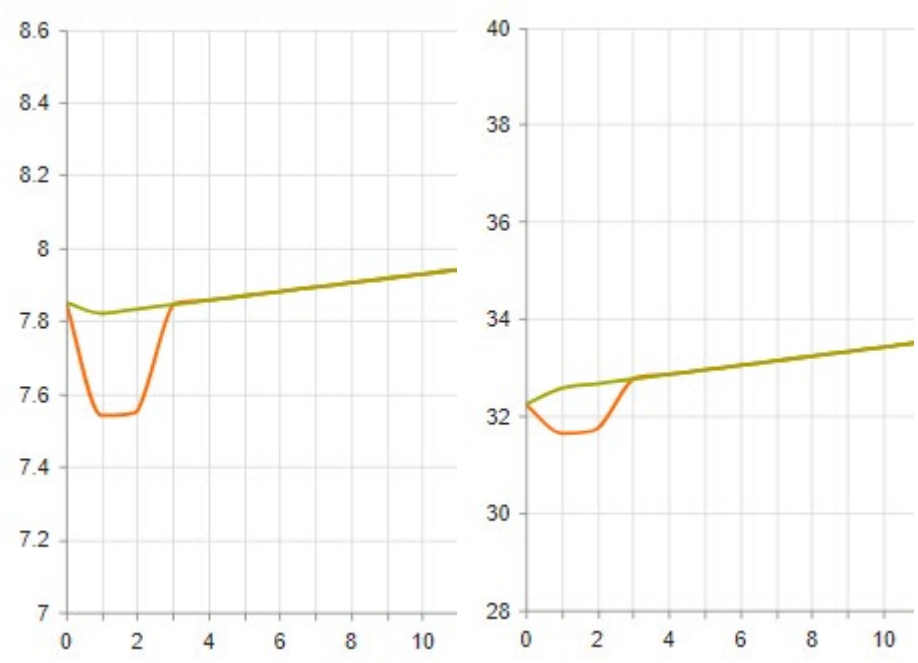
4.2.7 Scenario 7

Table 8. Applying 52-week effects for the second year for all physiological parameters

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,741	30.14	13.22	£702	0.19	0.08	£8,921

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

Figure 5. Progression of HbA1c (%) and BMI (kg/m^2), respectively, for the first 10 years of model.



Key: Sotagliflozin – Orange; Placebo – Green.

4.2.8 Scenario 8

Table 9. Applying 52-week effects for the first year only and assuming no benefit beyond this point, but with treatment costs only applied for the first year

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,740	30.11	13.20	£700	0.16	0.06	£11,482

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.9 Scenario 9

Table 10. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters and DKA mortality risk set to 0.16%

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,912	30.11	13.20	£873	0.16	0.06	£14,293

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.10 Scenario 10

Table 11. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters, and DKA mortality risk set to 2%

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.96	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,920	30.10	13.20	£881	0.15	0.05	£16,415

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.11 Scenario 11

Table 12. Use of the 24- and 52-week data to extrapolate the treatment effects to the second year for all physiological parameters, and cardiovascular event risk adjustments for HbA1c changes set to zero.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.99	13.14	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,824	30.06	13.18	£818	0.06	0.03	£26,136

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.12 Scenario 12

Table 13. Use of the 24- and 52-week data to extrapolate only the treatment effect for HbA1c to the second year with all other effects only applied for 1 year, and cardiovascular event risk adjustments for HbA1c changes set to zero.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,039	29.99	13.15	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,824	30.08	13.19	£970	0.09	0.04	£24,064

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

4.2.13 Scenario 13

Table 14. Only benefit applied is for HbA1c and uses the 24- and 52-week data to extrapolate the treatment effect to the second year, and cardiovascular event risk adjustments for HbA1c changes set to zero.

Treatment	Total costs	Total LYG[a]	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER
Insulin alone	£85,006	29.99	13.15	-	-	-	-
Sotagliflozin 200 mg in combination with insulin	£85,965	30.00	13.19	£970	0.01	0.00	£252,166

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.
a Undiscounted

DISCUSSION

Although the results of all the scenario analyses fall under a willingness-to-pay threshold of £30,000 per QALY, the ERG would like to highlight the instability in the results. This is caused by a relatively small QALY gain, meaning that only a small change to the total costs or total QALYs can have a large impact on the ICER.

The ERG also urges caution when considering the plausibility of some of the scenarios, in particular the scenario in which treatment effects are extrapolated for the second year. Some of the extrapolations may be implausible, although the only parameter that stood out was the triglycerides as stated in Section 4.2. The ERG considers it reasonable to opt for a move conservative approach and assume the only extrapolated benefit applied is for HbA1c. The evidence for this appears to show a clearer trend back towards the placebo group within (approximately) the first two years.

Further to this, the combination of assuming that the only benefit of sotagliflozin is HbA1c and that HbA1c does not have an impact on cardiovascular events, shows great instability in the ICER as the QALY gain becomes close to zero. This demonstrates the uncertainty in the results and shows that caution should be taken when interpreting them.

REFERENCES

1. Lin SF, Lin JD, Huang YY. Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. Chang Gung Med J. 2005;28(1):24-30.