Sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1376]

STA REPORT

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Title: Sotagliflozin, in combination with insulin, for treating type 1 diabetes

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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
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All authors read and commented on draft versions of the ERG report.

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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 $\geq$ 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/m²;[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]

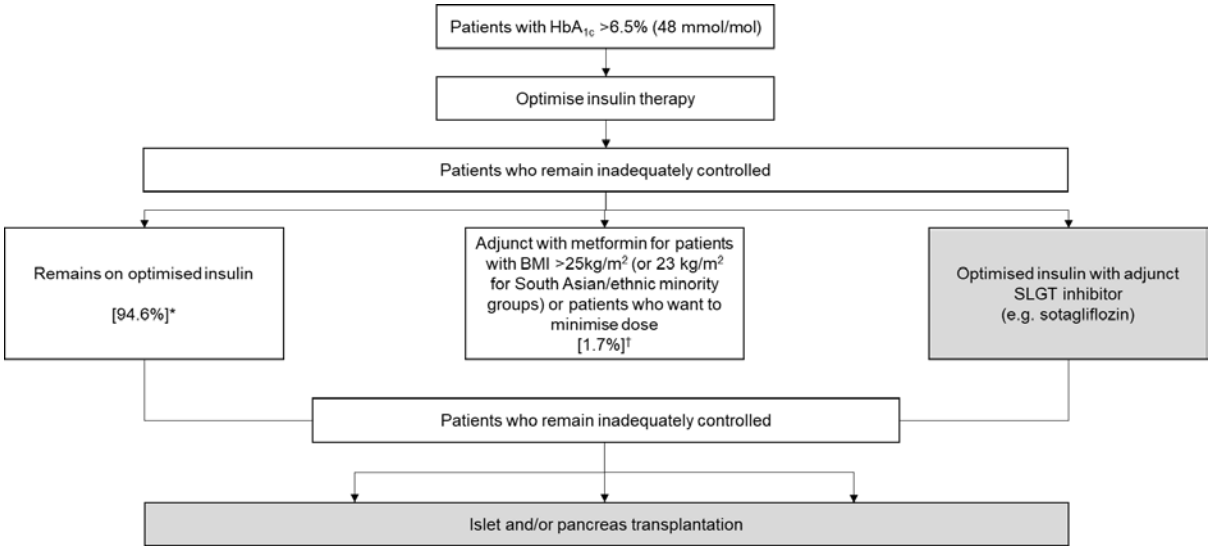
2.2 Critique of company's overview of current service provision

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 ≥ 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 ≤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

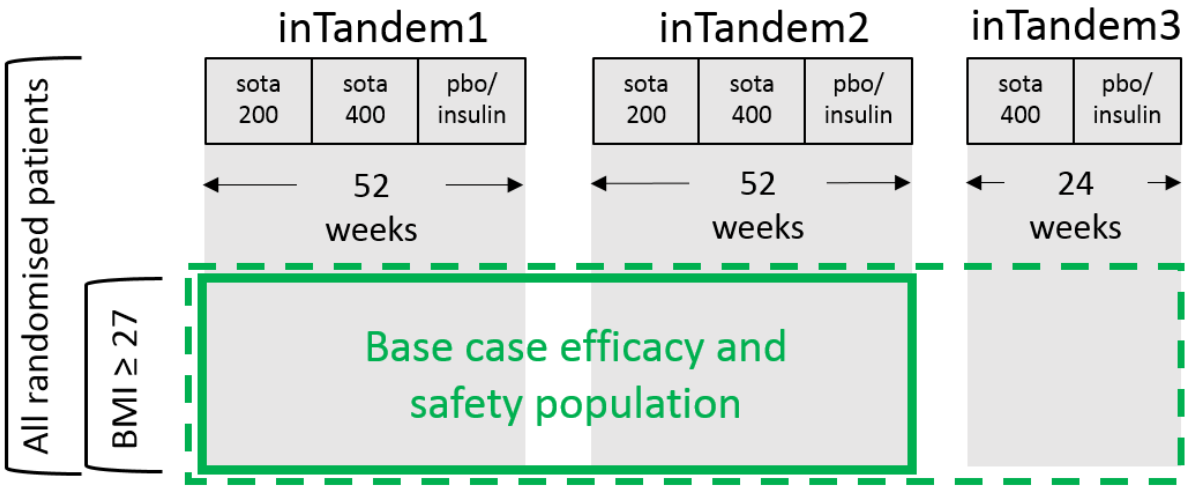
The company presented results from twin RCTs as evidence of clinical effectiveness: one trial was conducted in North America (inTandem1) and one in Europe and Israel (inTandem2) but the trials were

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 $\geq$ 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.

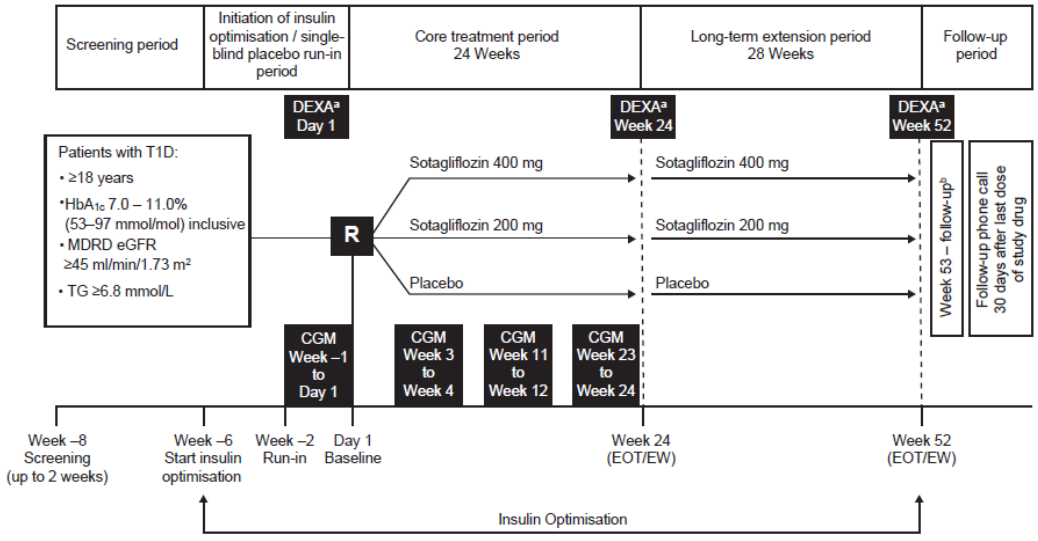
4.2.1 Trial conduct

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 $\geq$ 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 $\geq$ 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 ($HbA_{1c} \leq$ 8.5%, > 8.5%). Randomisation was not stratified by BMI, and so randomisation does not hold for the subset of patients with BMI $\geq$ 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.

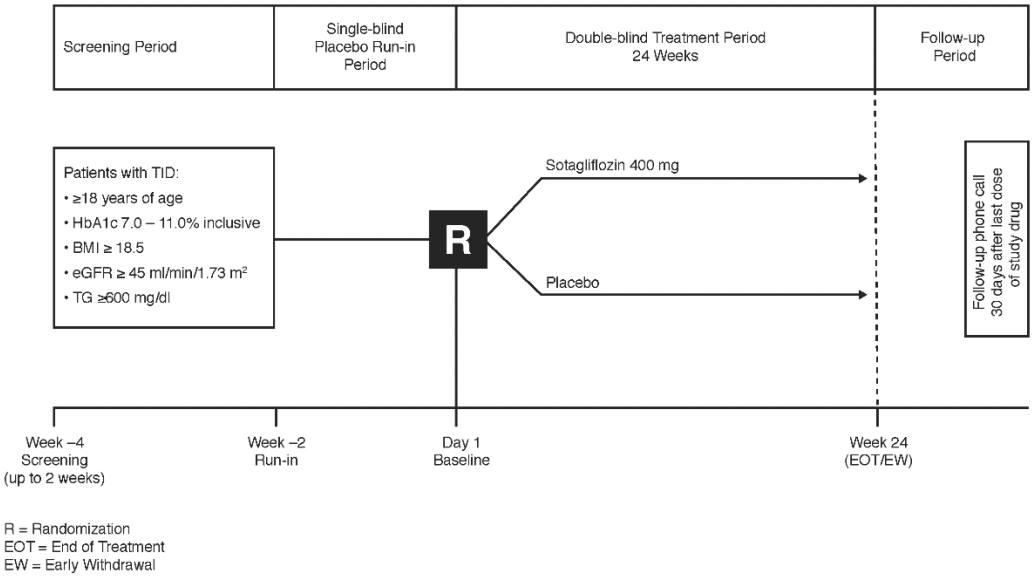
The trials included two sub-studies that included patients recruited at selected sites. The continuous glucose monitoring (CGM) sub-study included approximately 18% of participants across inTandem1 and inTandem2 (n = 288; CS Appendices, Figure G.1 and G.2) and used blinded monitoring over four 1-week 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 $\geq$ 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, $\geq$ 25 kg/m^2), insulin delivery method (MDI, CSII) and screening HbA_{1c} ($\leq$ 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 $\geq$ 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 $\geq$ 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

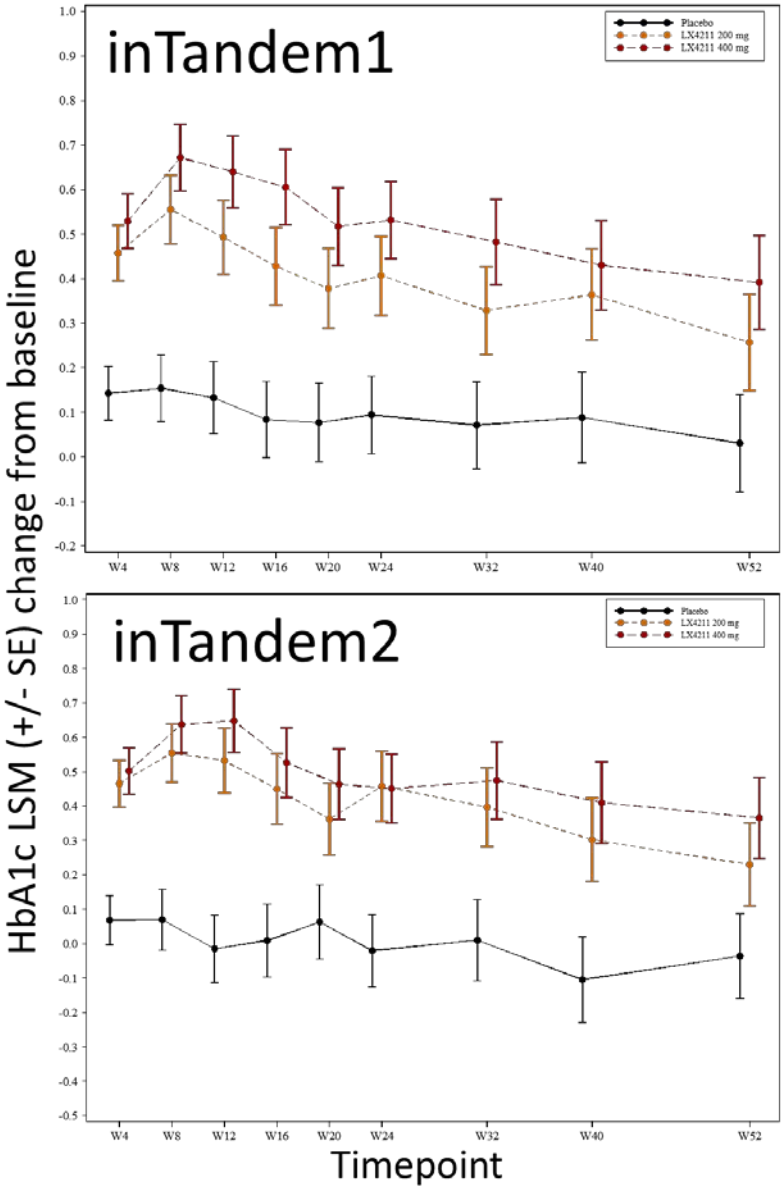
Analysis	LSM change from baseline (SE)			LSM difference between groups (95% CI)	
	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
Primary efficacy population – inTandem1 and inTandem2 pooled					
24 weeks	−0.43 (0.03)	−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.

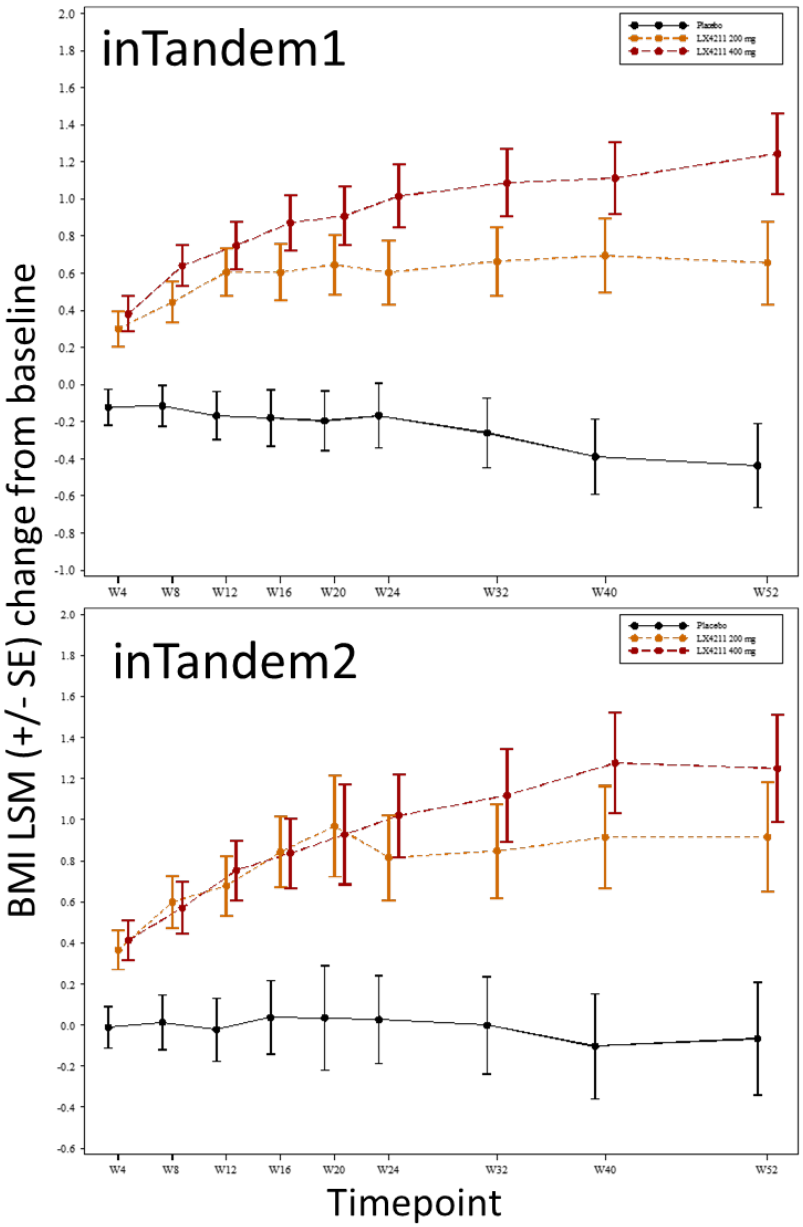
Table 11. BMI change from baseline (BMI ≥ 27 kg/m^2 subpopulation)

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 (4.3%)	279 (91.5%)	13 (4.2%)	292 (93.3%)	24 (8.1%)	276 (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)

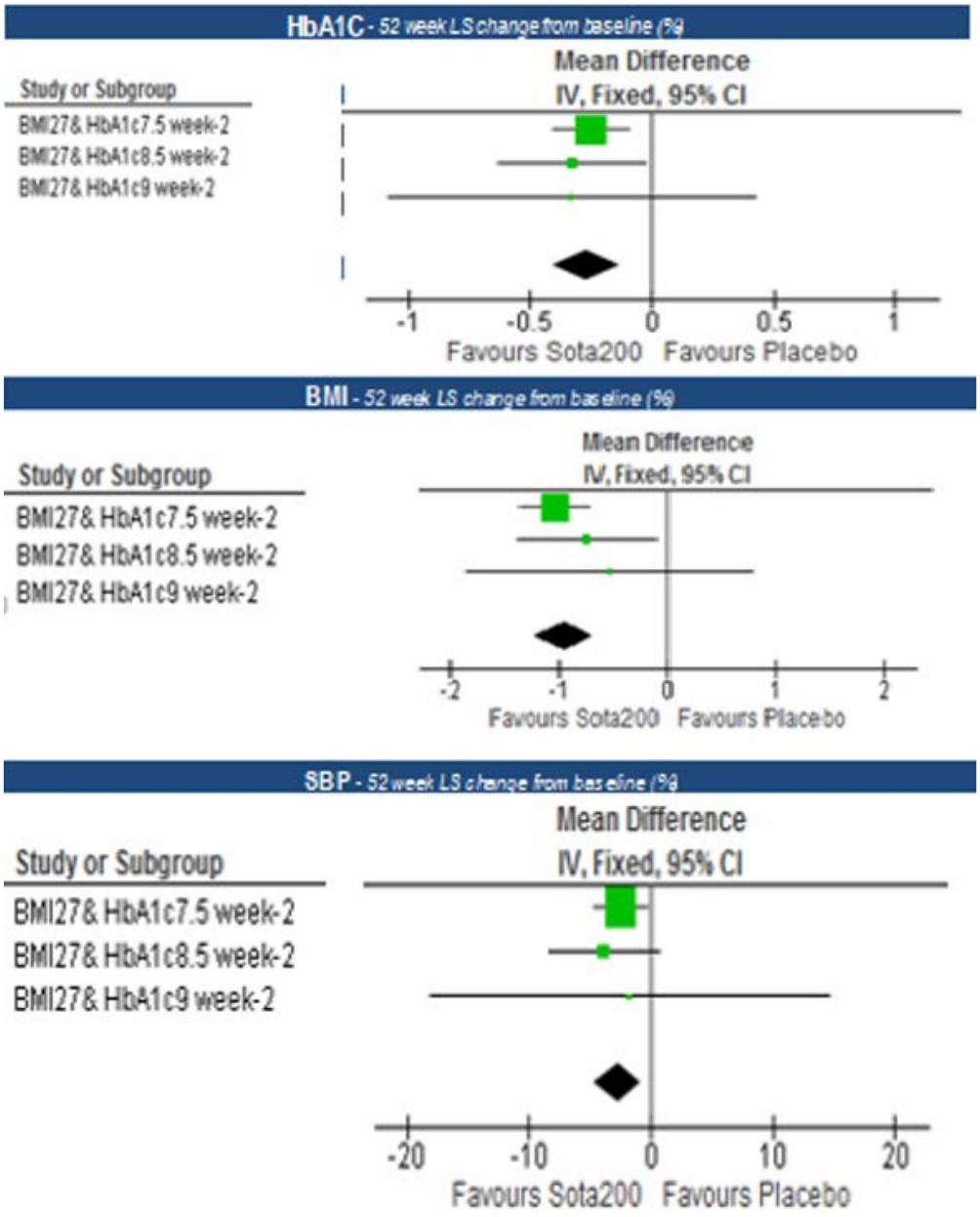
Subgroup	N	LSM change from baseline (95% CI)			LSM difference between groups (95% CI)	
		Sota 200 mg	Sota 400 mg	Insulin alone	Sotagliflozin 200 mg vs insulin alone	Sotagliflozin 400 mg vs insulin alone
24 weeks						
CSII	613	−0.41 (0.042)	−0.45 (0.042)	−0.02 (0.042)	**−0.39 (−0.49 to −0.28) <0.001**	**−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.

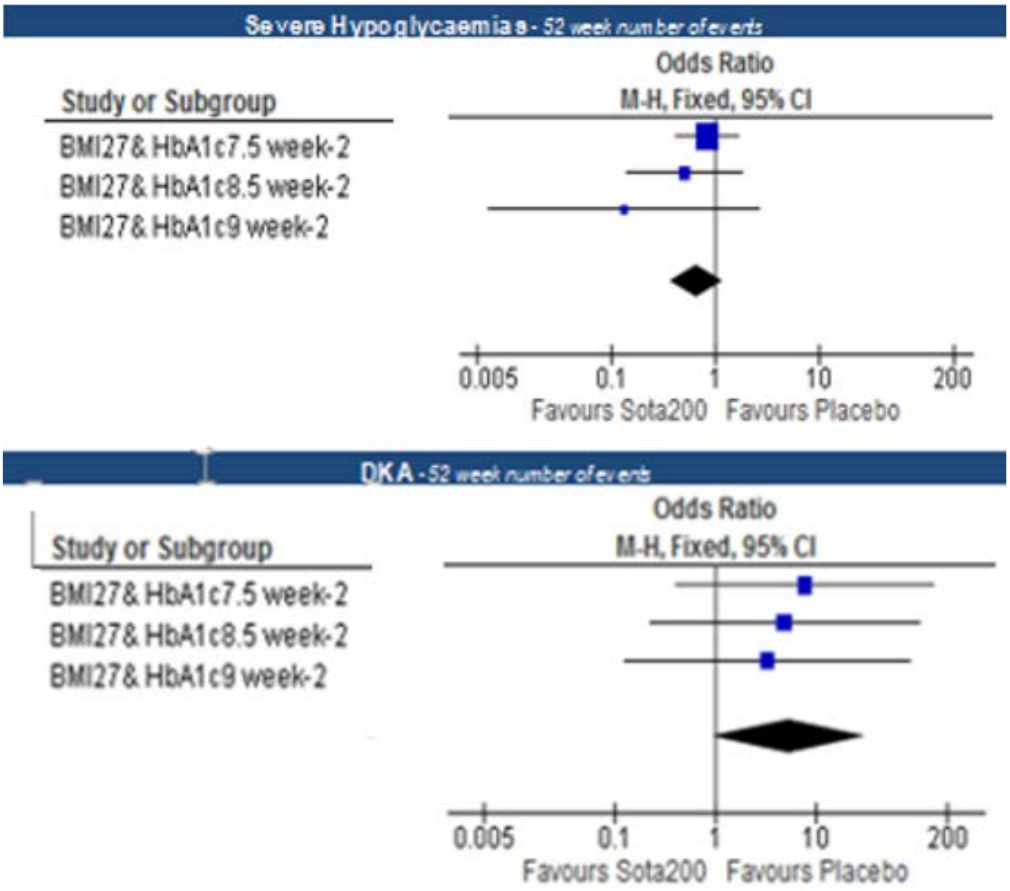
Subgroup analyses using the full trial populations or the BMI ≥ 27 kg/m^2 subpopulation were not conducted for any other outcome, but the company submitted forest plots to show correlation between 52-week HbA_{1c}, BMI, SBP, SH and DKA at different HbA_{1c} cut-offs (7%, 8.5% and 9%) within the BMI subpopulation. 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)

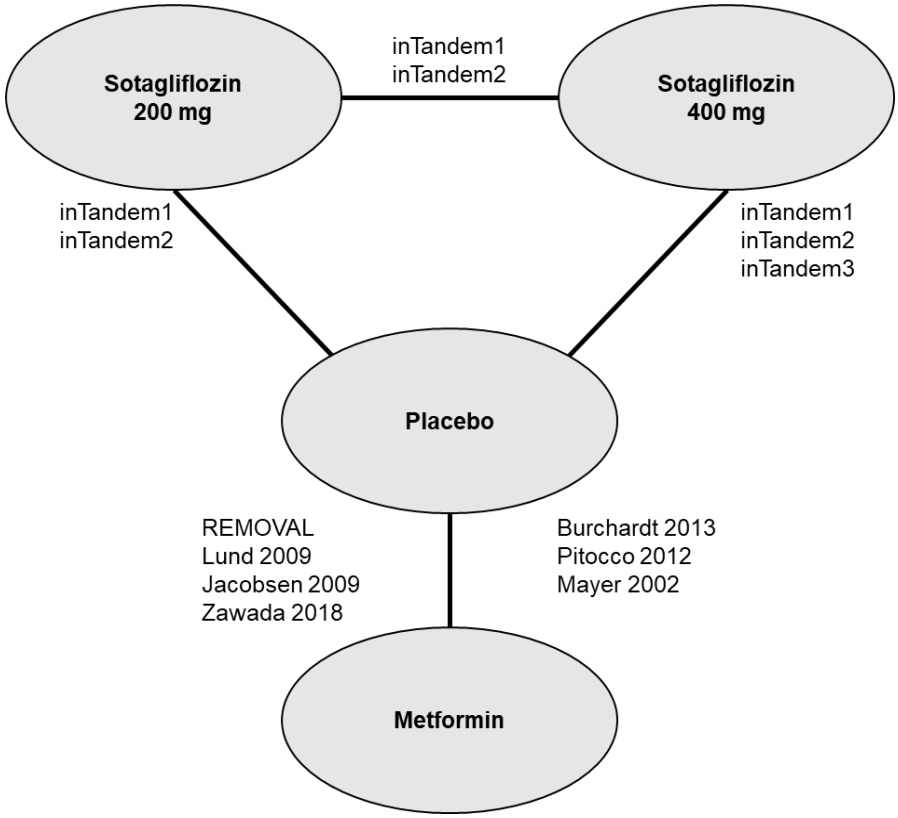


Abbreviations: BMI, body mass index; CI, confidence interval; DKA, diabetic ketoacidosis; HbA_{1c}, glycated haemoglobin; M-H, Mantel–Haenszel; SH, severe hypoglycaemia.

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 and outcomes	Yes – 60 years.
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

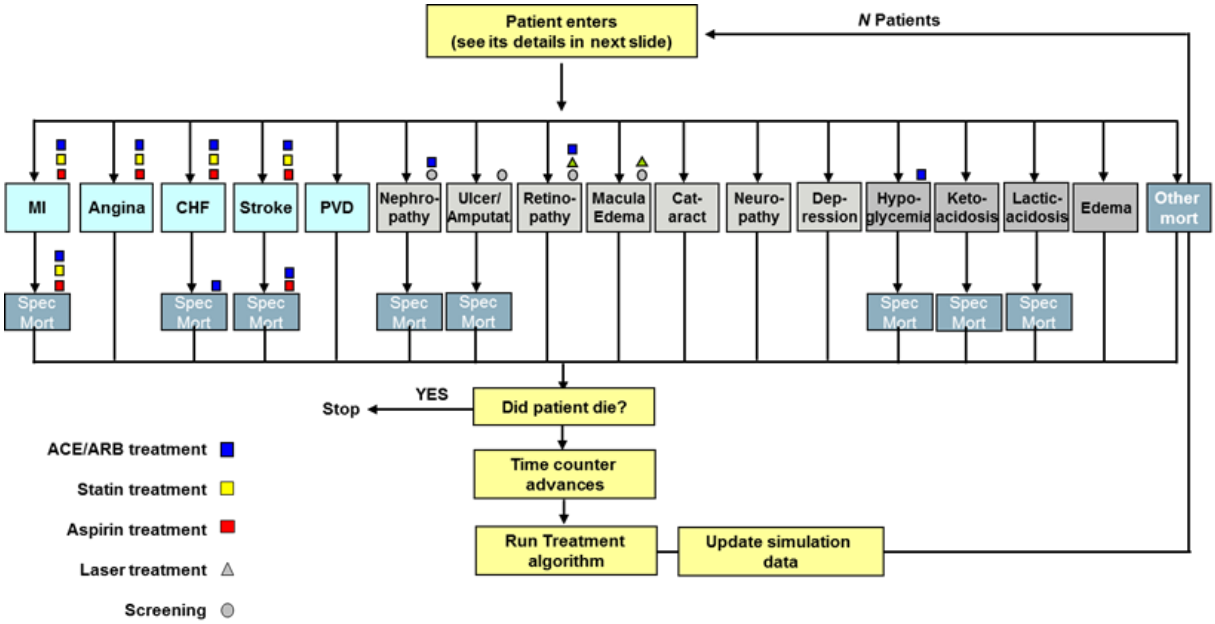
The company's base case analysis was performed using version 9 of the CDM. This model is a non-product-specific web-based platform allowing economic evaluations of a variety of different interventions for both T1D and T2D. It has been used extensively for economic evaluations of therapies for T1D, including 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)

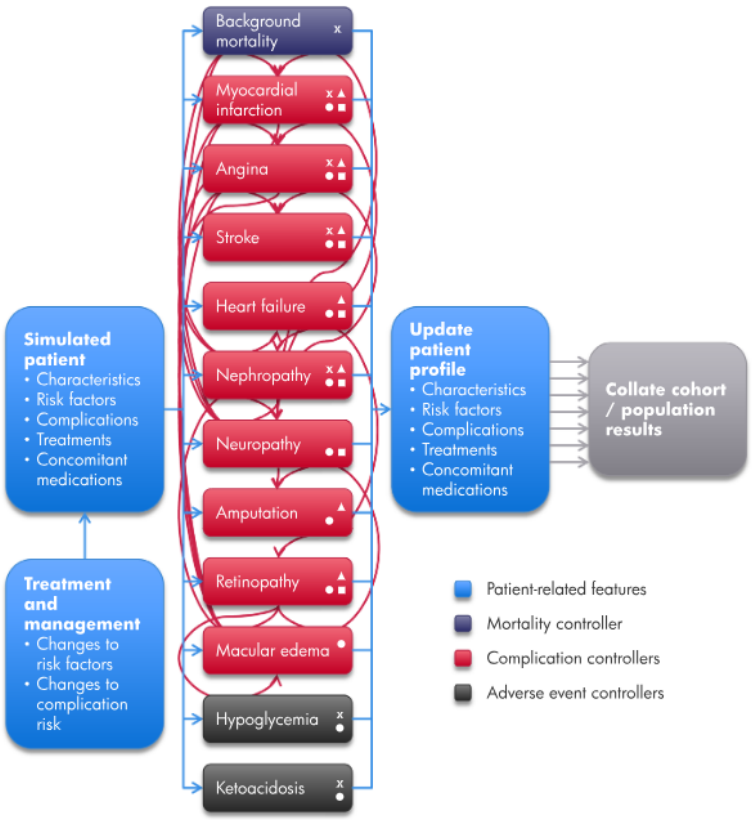


Fig. 1 – Schematic diagram of the PRIME Diabetes Model. Interactions between complication controllers are indicated by red arrows. X, risk of mortality is associated with this complication controller; ▲, SBP is a direct risk factor; ●, HbA_{1c} is a direct risk factor; ■, BMI is a direct risk factor. 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.

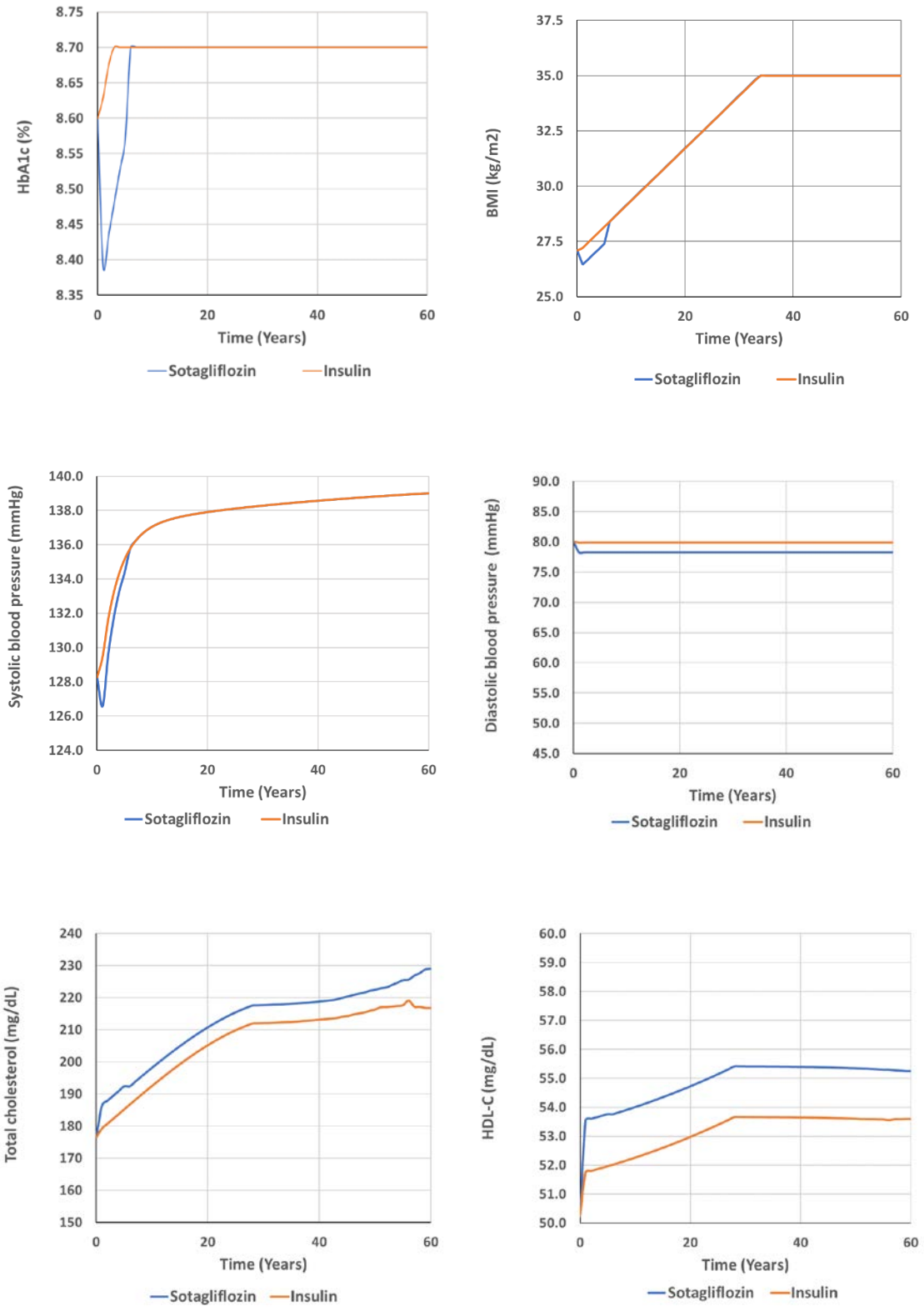
For HbA_{1c}, the company considered a slight increase of 0.1% above the baseline to be a plausible cap, as this allowed the treatment effect for the insulin group (0.03%) to be applied in the first year. The company assumed that the HbA_{1c} treatment effect for sotagliflozin was removed after 5 years 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.

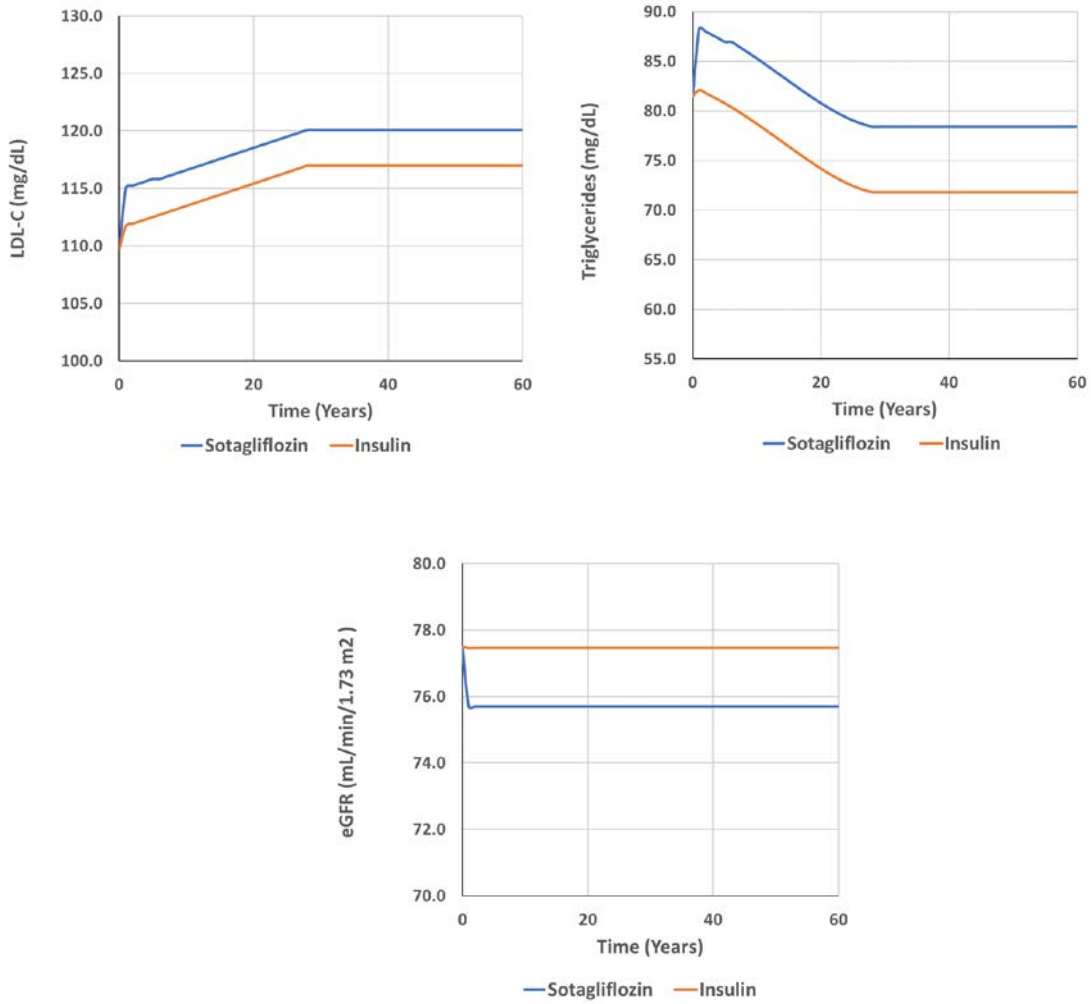
SBP progression following on from the treatment effects applied in the first year, was initially estimated using the United Kingdom Prospective Diabetes Study 68 (UKPDS 68) risk equation option within the CDM.[42] The treatment effect was maintained for the duration of treatment with sotagliflozin (5 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%
1st 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 1st 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

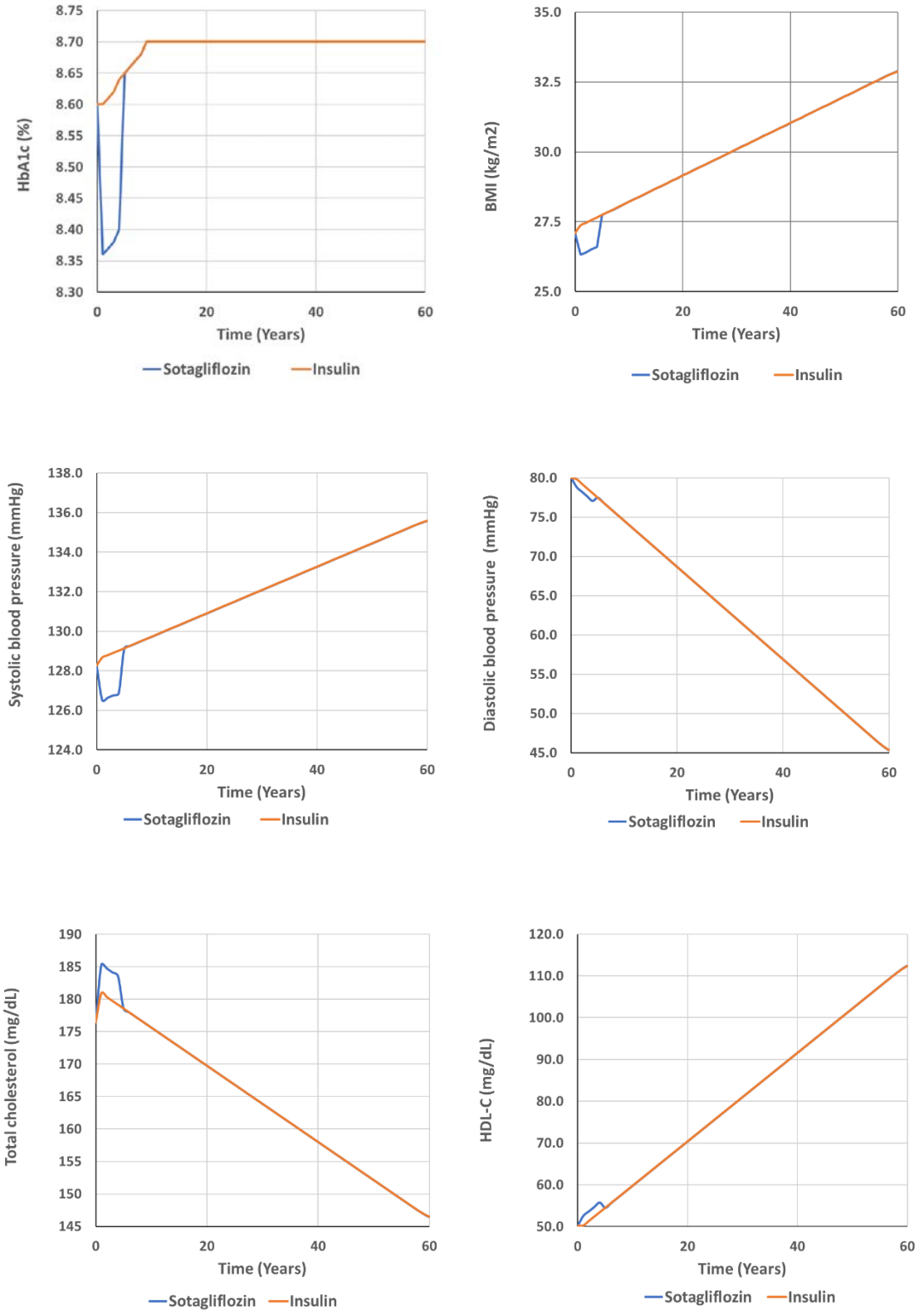
5.4.5.2 Post-clarification

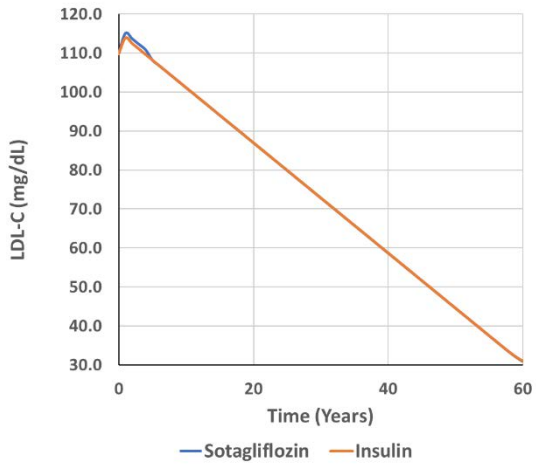
In response to clarification questions, the company provided an updated base case analysis. This analysis was still based on the CDM but used different sources of data to inform the treatment effects and the progression of physiological parameters over time.

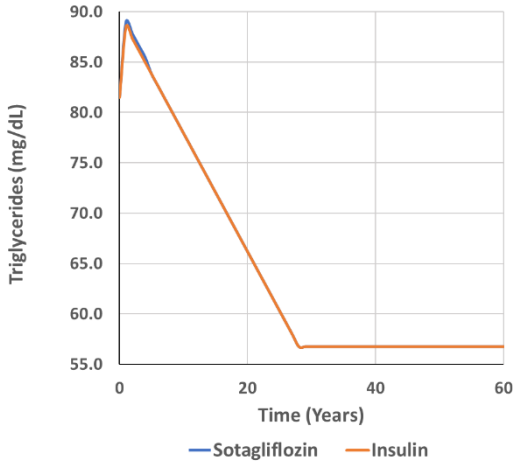
The company updated the efficacy outcomes to those based on the pooled inTandem1 and inTandem2 trials for patients who have a BMI $\geq 27 kg/m^2$. This analysis was more aligned with the likely marketing authorisation. The company also chose to change the progressions over time for all the key physiological parameters, based on alternative sources of data.

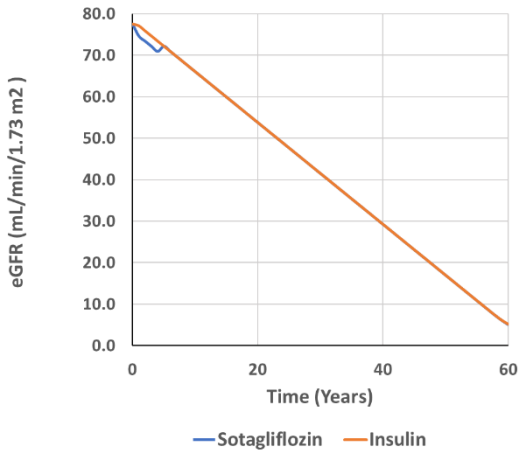
The company's updated base case analysis is now based on linear trends estimated from the outcomes of the EDIC study. The EDIC study provides more recent data than the DCCT and shows a slower progression of HbA_{1c} with an annual increase of 0.012%. The progression of BMI was also shown to be greatly 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

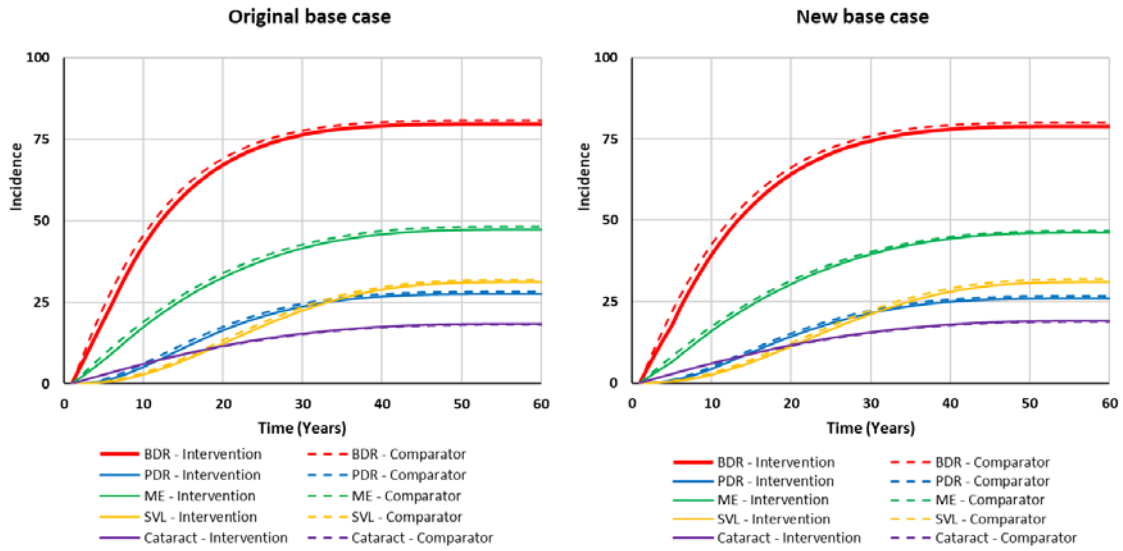


Figure 15. Renal disease incidence

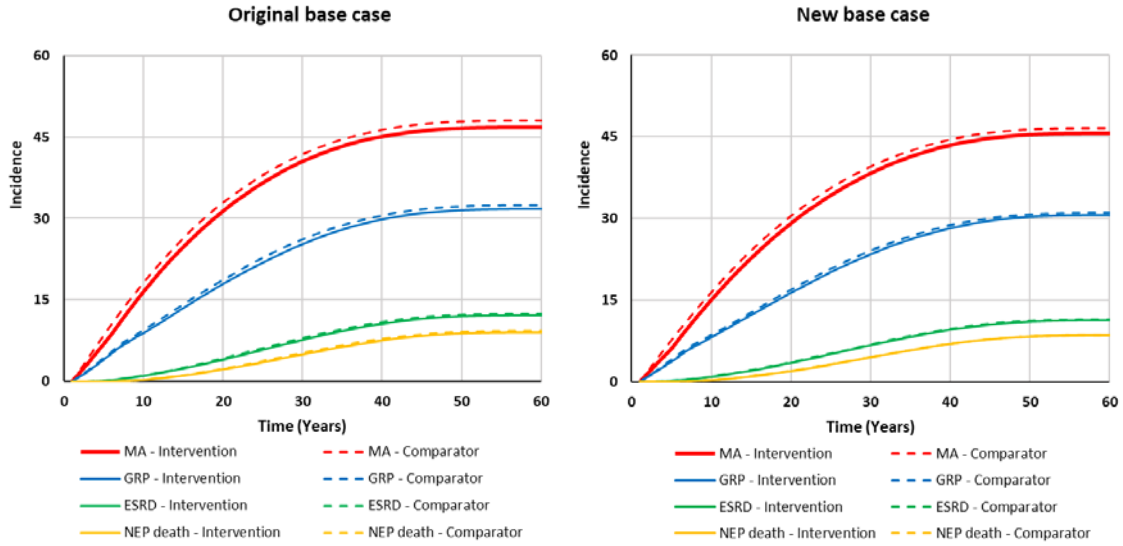


Figure 16. Ulcer incidence

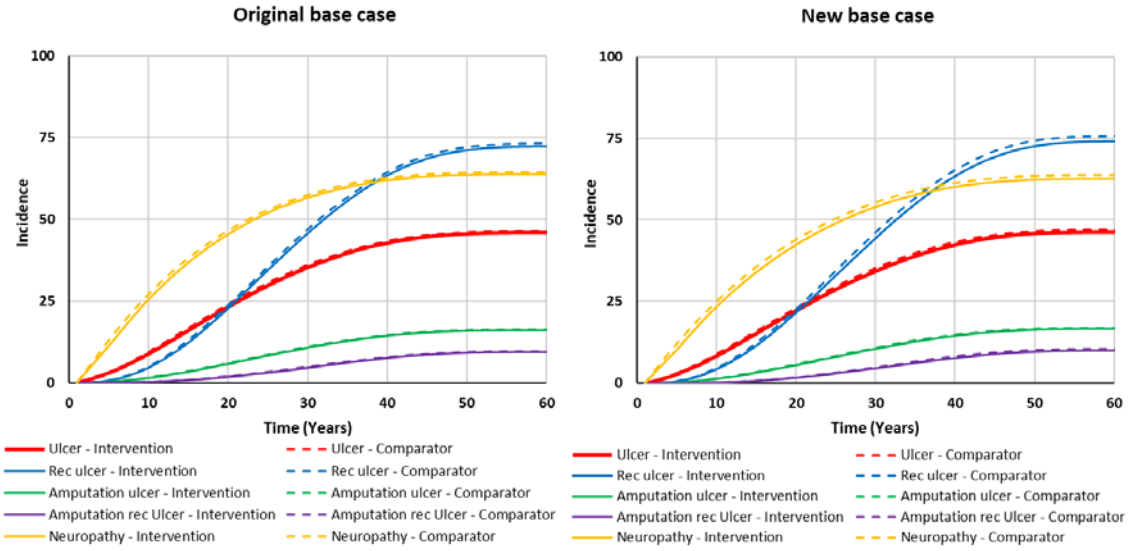


Figure 17. CVD disease incidence (1 of 2)

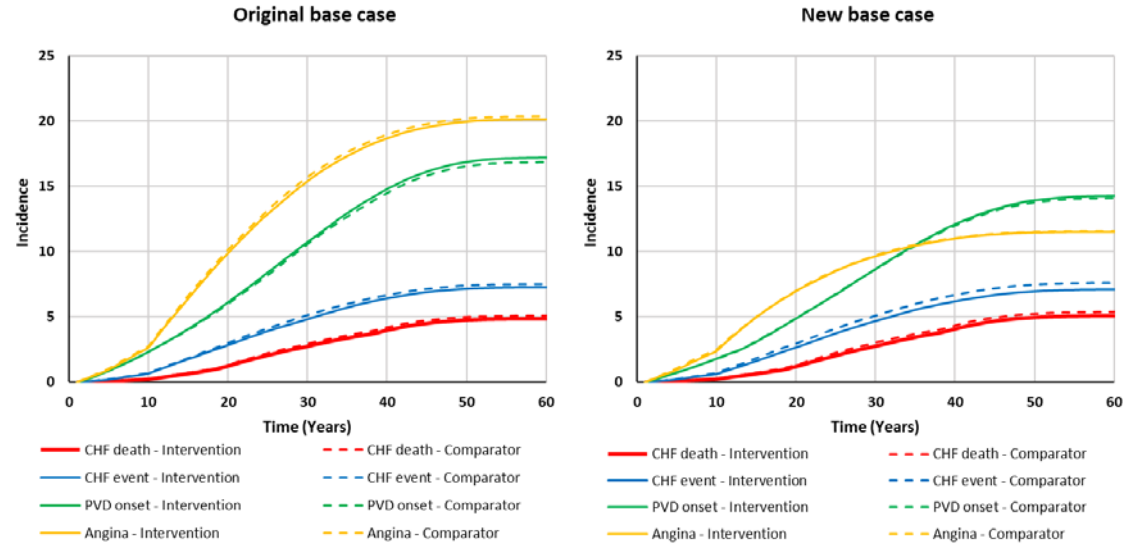


Figure 18. CVD incidence (2 of 2)

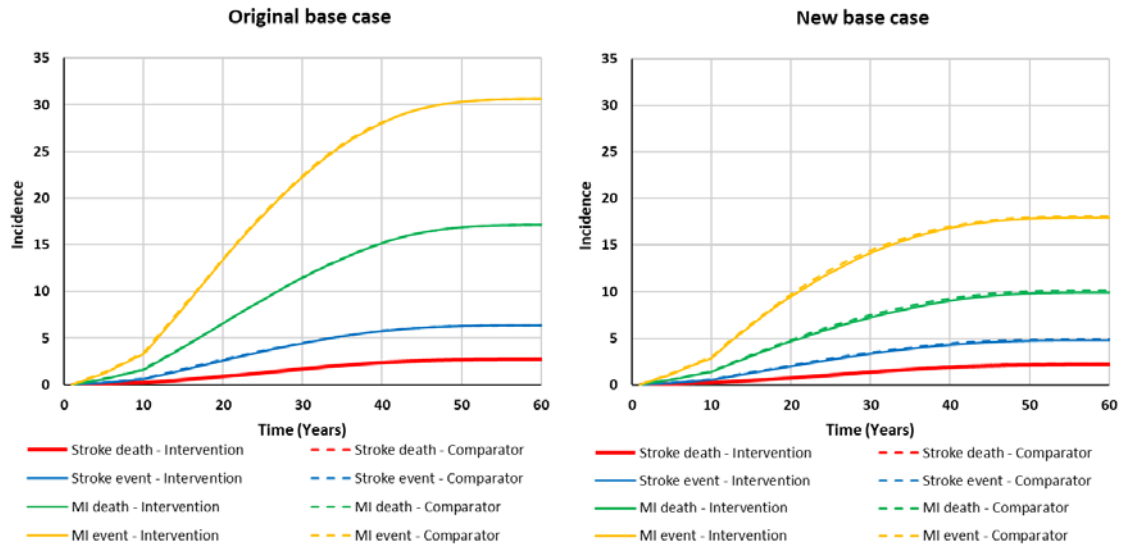


Figure 19. AE incidence (1 of 2)

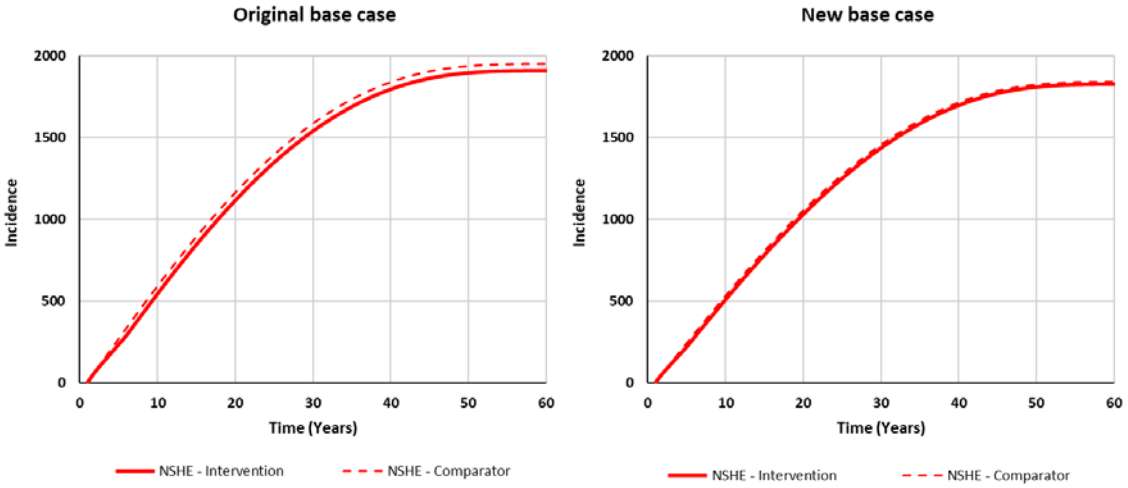


Figure 20. AE incidence (2 of 2)

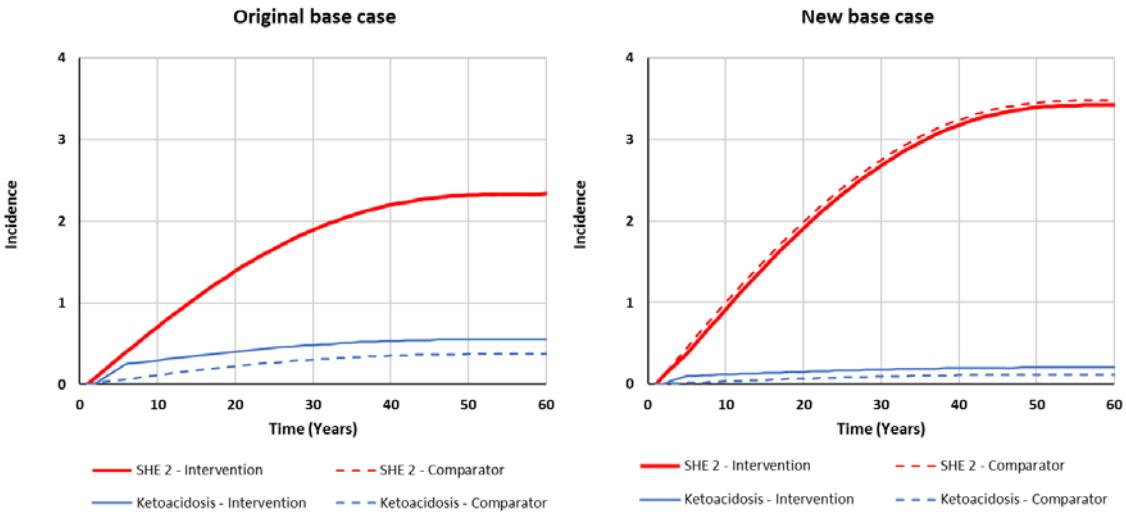


Figure 21. Cost breakdown (1 of 3)

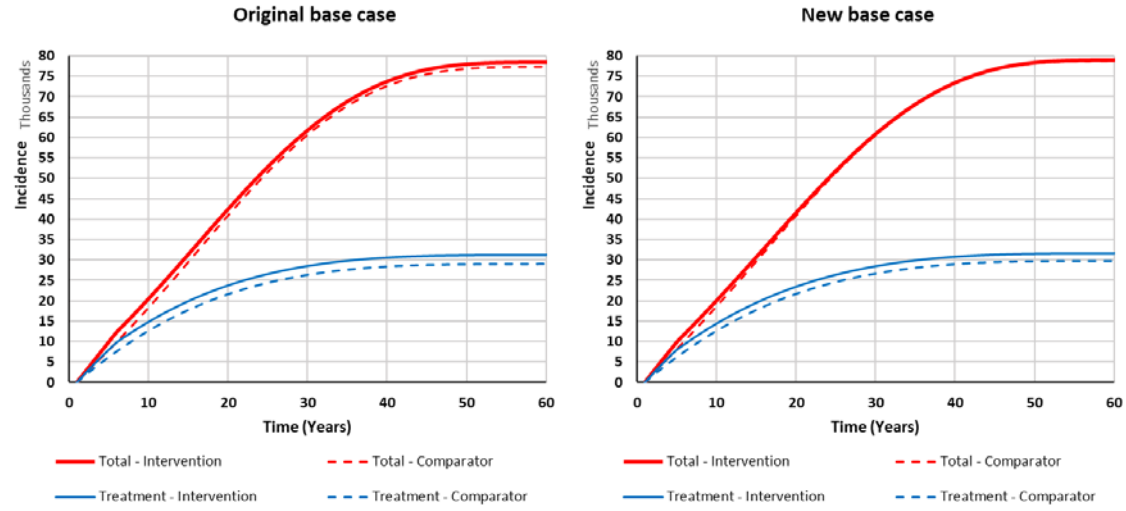


Figure 22. Cost breakdown (2 of 3)

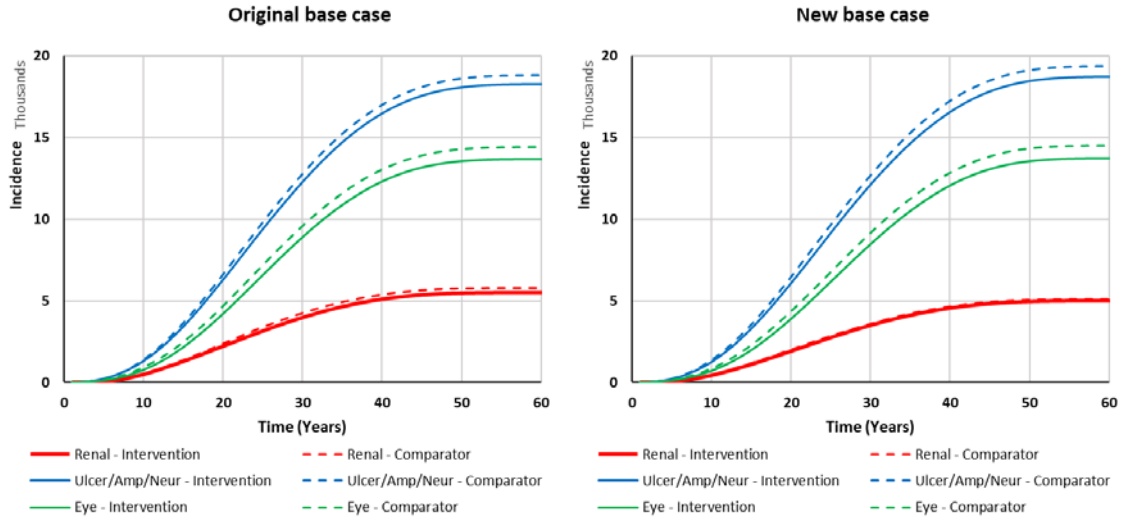
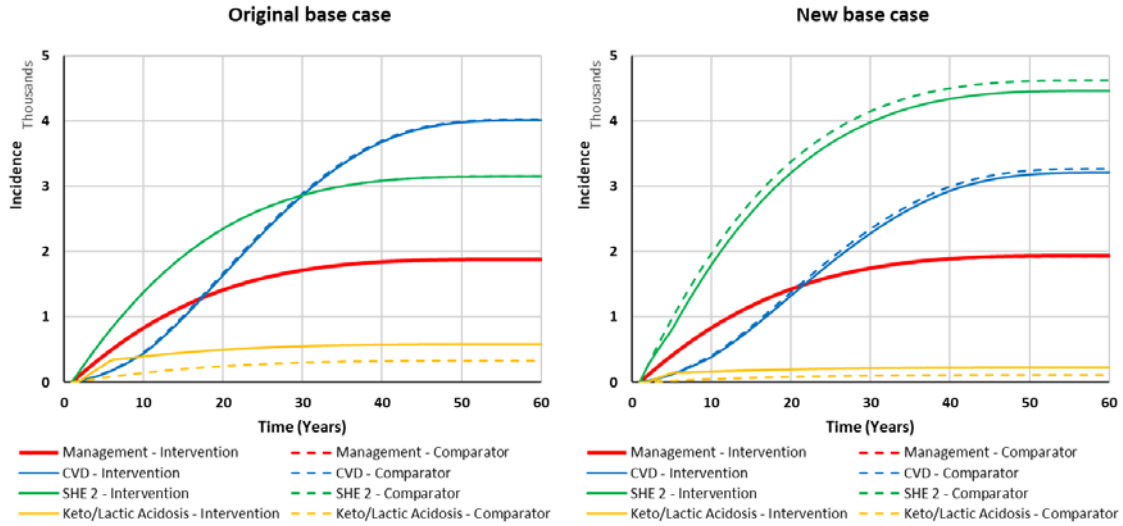


Figure 23. Cost breakdown (3 of 3)



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

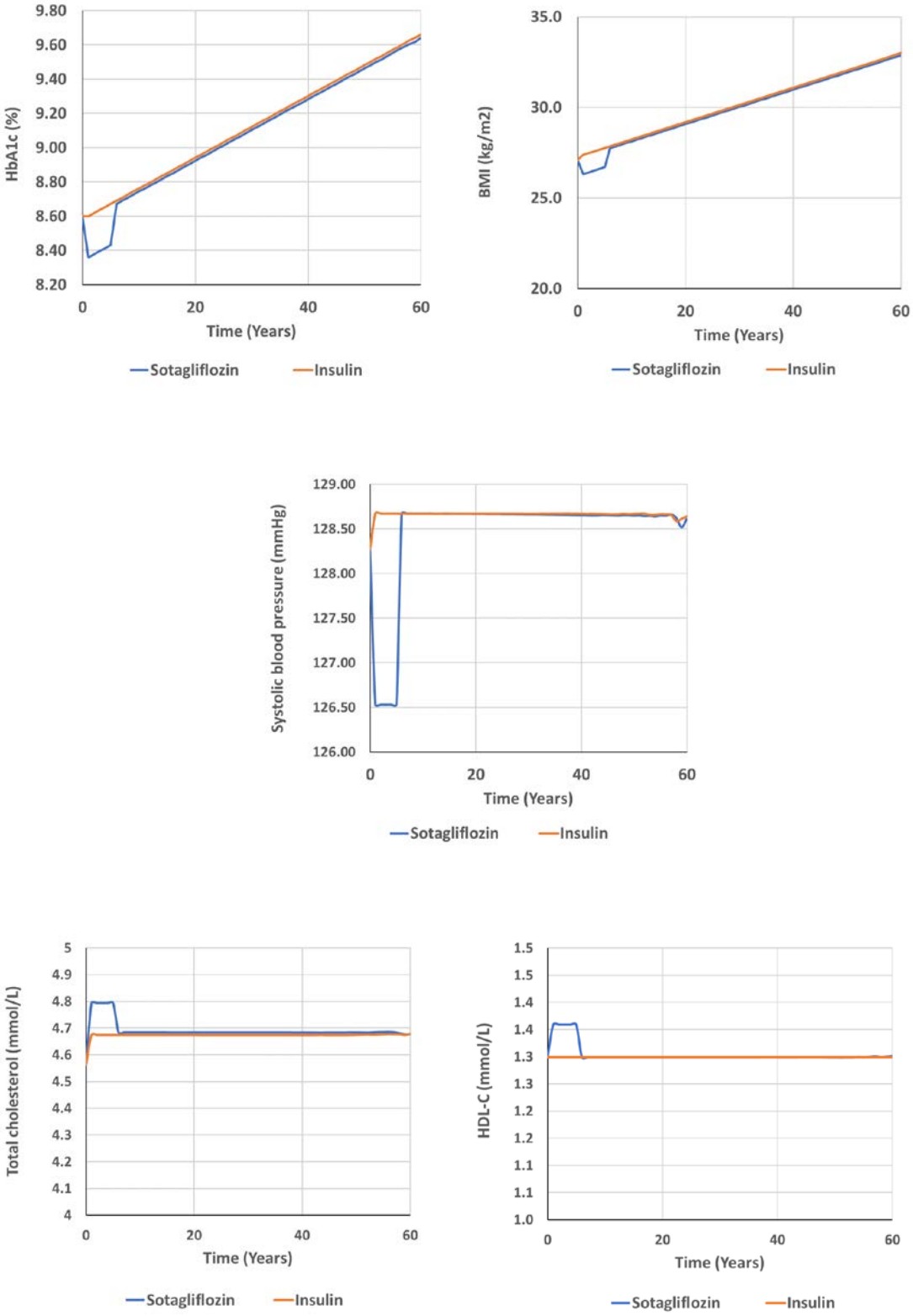
dependent, with rates of recovery determined by Ford *et al.* 2013.[54] Data for non-response to treatment were also considered and taken from RESTORE trial.[55] Non-response to treatment leading to the risk of progression was informed by data from the WESDR study.

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)

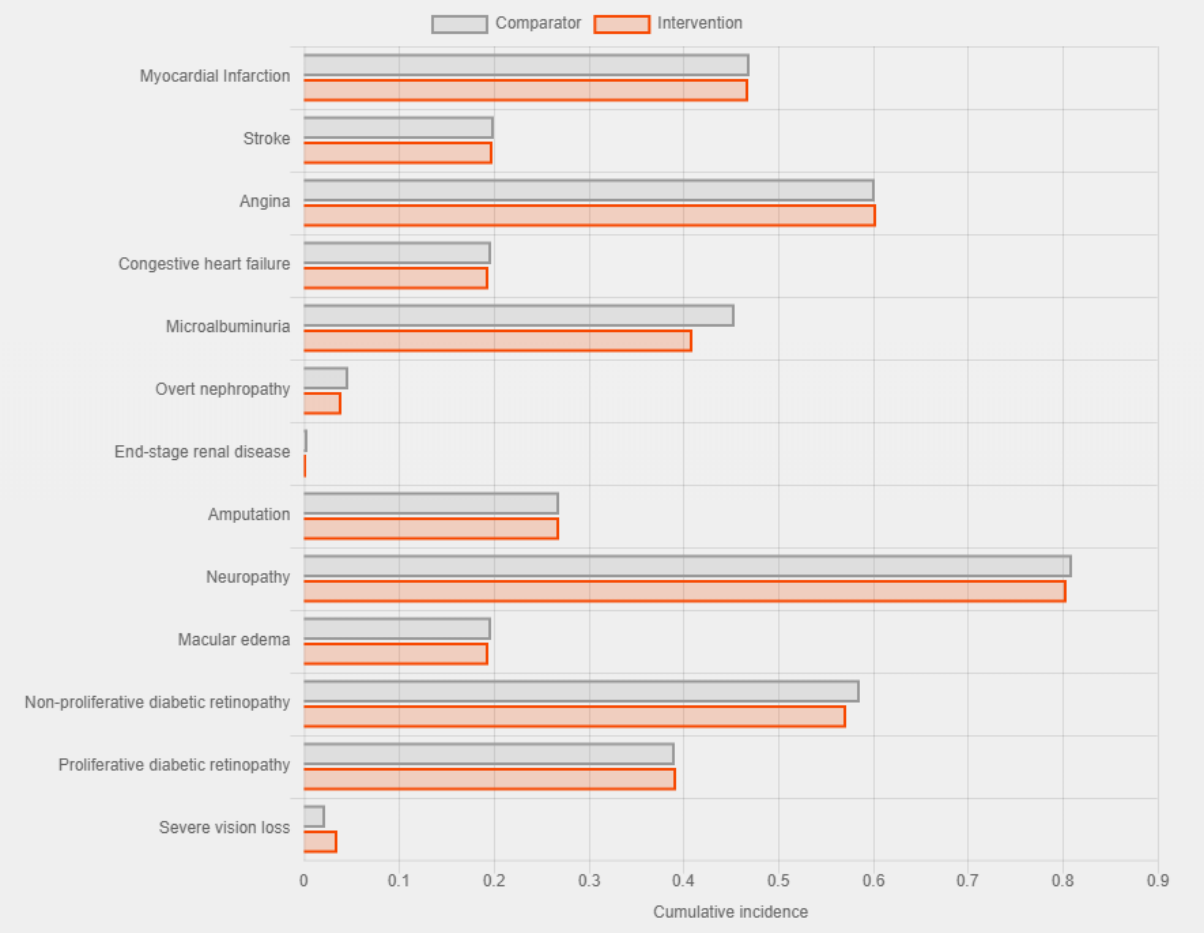
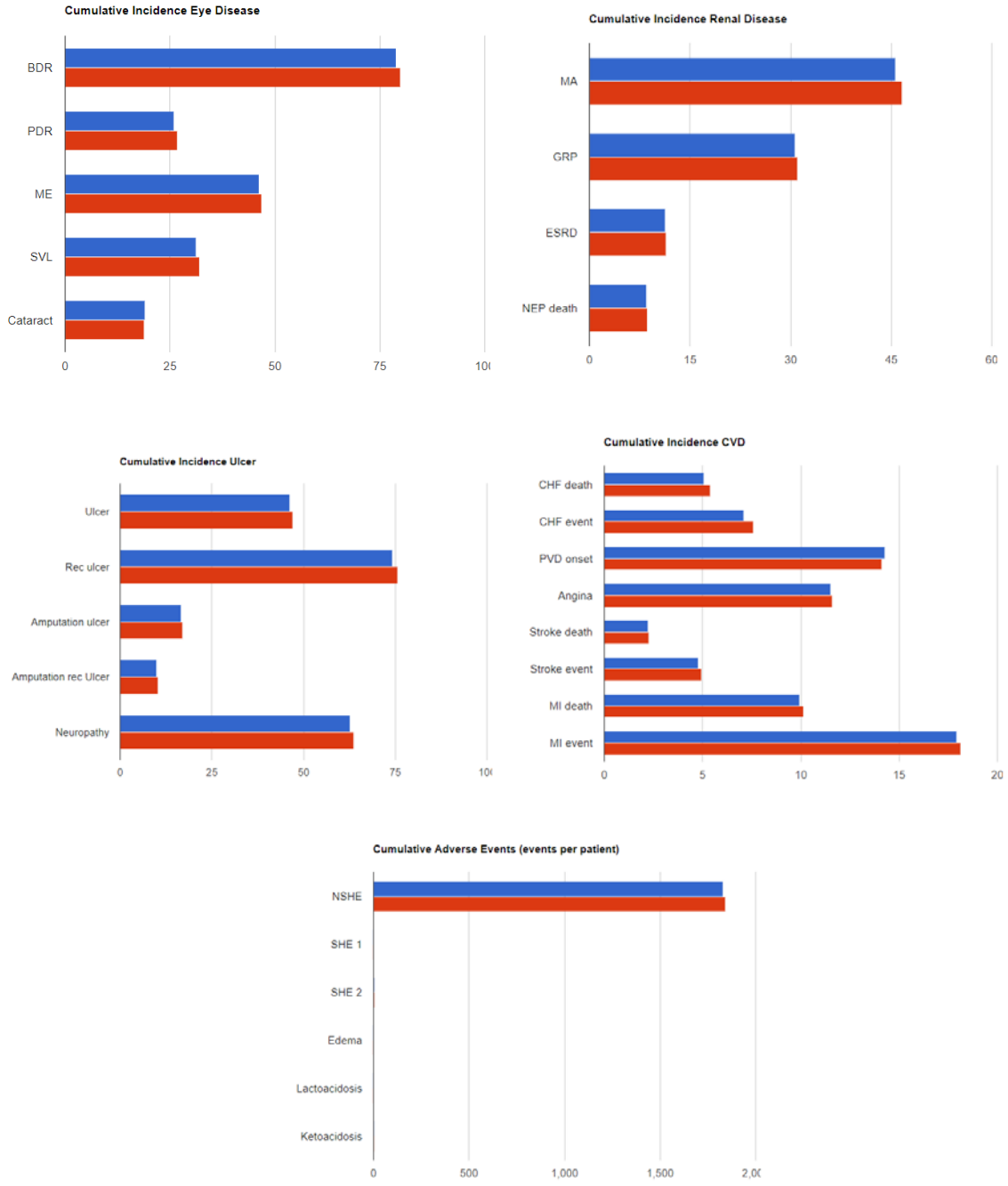


Figure 26. Incidences of complications in the company's base case (reproduced from the CDM)



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
Placebo	£53,505	11.598	-	-	-	
Sotagliflozin	£55,288	11.693	£1,782	0.095	£18,797	

						Country SOTA (UK) NICE 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.

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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.