



eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

Relative effectiveness assessment of pharmaceutical technologies

**SOTAGLIFLOZIN IS AS AN ADJUNCT TO INSULIN THERAPY TO IMPROVE
GLYCAEMIC CONTROL IN ADULTS WITH TYPE 1 DIABETES MELLITUS
WITH A BODY MASS INDEX (BMI) ≥ 27 KG/M², WHO HAVE FAILED TO
ACHIEVE ADEQUATE GLYCAEMIC CONTROL DESPITE OPTIMAL INSULIN
THERAPY**

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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TABLE OF CONTENTS

DOCUMENT HISTORY AND CONTRIBUTORS	2
TABLE OF CONTENTS.....	4
LIST OF ABBREVIATIONS.....	6
EXECUTIVE SUMMARY OF THE ASSESSMENT OF SOTAGLIFLOZIN.....	9
<i>INTRODUCTION.....</i>	9
<i>OBJECTIVE AND SCOPE.....</i>	9
<i>METHODS.....</i>	9
<i>RESULTS.....</i>	11
<i>DISCUSSION.....</i>	12
<i>CONCLUSIONS.....</i>	13
1 BACKGROUND.....	19
1.1 <i>OVERVIEW OF THE DISEASE OR HEALTH CONDITION.....</i>	19
1.2 <i>CURRENT CLINICAL PRACTICE.....</i>	20
1.3 <i>FEATURES OF THE INTERVENTION.....</i>	21
2 OBJECTIVE AND SCOPE	25
2.1 <i>OBJECTIVE.....</i>	25
2.2 <i>SCOPE.....</i>	25
3 METHODS	29
3.1 <i>INFORMATION RETRIEVAL.....</i>	29
3.2 <i>DATA EXTRACTION.....</i>	30
3.3 <i>RISK OF BIAS ASSESSMENT.....</i>	30
3.4 <i>ANALYSES OF SUBMITTED DATA.....</i>	30
3.5 <i>PATIENT INVOLVEMENT.....</i>	36
4 RESULTS.....	38
4.1 <i>INFORMATION RETRIEVAL.....</i>	38
4.2 <i>STUDIES INCLUDED IN THE ASSESSMENT.....</i>	38
4.3 <i>EXCLUDED STUDIES.....</i>	39
4.4 <i>CHARACTERISTICS OF INCLUDED STUDIES.....</i>	40
4.5 <i>OUTCOMES INCLUDED.....</i>	46
4.6 <i>RISK OF BIAS.....</i>	49
4.7 <i>EXTERNAL VALIDITY.....</i>	51
4.8 <i>RESULTS ON CLINICAL EFFECTIVENESS AND SAFETY.....</i>	52
4.9 <i>SUBGROUP EFFECTS.....</i>	55
4.10 <i>INDIRECT COMPARISON.....</i>	56
5 PATIENT INVOLVEMENT.....	61
6 DISCUSSION.....	62
6.1 <i>MAIN CLINICAL EFFECTS.....</i>	62
6.2 <i>CERTAINTY OF EVIDENCE FOR DIRECT COMPARISONS.....</i>	62
6.3 <i>OTHER OUTCOMES.....</i>	63
6.4 <i>RELEVANCE OF OUTCOMES.....</i>	63
6.5 <i>COMPARATORS.....</i>	64
6.6 <i>THE RELEVANCE OF TREATMENT EFFECTS IN COST EFFECTIVENESS MODELLING.....</i>	64
7 CONCLUSIONS.....	65
8 REFERENCES.....	66
APPENDIX 1: GUIDELINES FOR DIAGNOSIS AND MANAGEMENT.....	69

APPENDIX 2: EVIDENCE GAPS 73
APPENDIX 3: GRADE EVIDENCE PROFILE..... 74

LIST OF TABLES AND FIGURES

Tables

Table 0.1. Summary of relative outcomes for mITT population ES1 pool BMI ≥ 27 kg/m².....12
 Table 0.2. Summary of findings of sotagliflozin (mITT population, patients with baseline BMI ≥ 27 kg/m²).....14
 Table 0.3. GRADE Summary of findings for comparisons in the NMA. Note that most studies include multiple doses, however we focus here on the highest dose in each study. Therefore, the same dose for Empagliflozin is not used for each endpoint.....18
 Table 1.1. Features of the intervention23
 Table 1.2: Administration and dosing of the technology24
 Table 2.1. Scope of the assessment26
 Table 3.1. Summary of information retrieval and study selection29
 Table 3.2. Patient characteristics of the included studies. Source: applicant submission.....32
 Table 3.3. List of outcomes for the NMA. Source: applicant submission32
 Table 3.4. Definition of hypoglycaemia reported across studies.....32
 Table 3.5. Summary of outcomes included in each trial at each timepoint. Source: applicant submission.....34
 Table 3.6. Outcomes specified in the project plan for which an NMA could have been performed from a technical point of view but were not included as part of the submission.....36
 Table 4.1. Study pool – list of relevant studies used for the assessment39
 Table 4.2. Excluded studies.....39
 Table 4.3. Characteristics of the included studies42
 Table 4.4. Characterisation of the interventions and comparators.....45
 Table 4.5. Baseline characteristics of ES1 pool BMI ≥ 27 kg/m² (from mITT population)45
 Table 4.6. Outcomes for mITT population ES1 and SAF-1 pool BMI ≥ 27 kg/m²47
 Table 4.7. Risk of bias in randomised studies49
 Table 4.8. Most frequent adverse events (safety population, patients with baseline BMI ≥ 27 kg/m²).....55
 Table 4.9. Ranking of treatments from most to least favourable.....56
 Table A1. Overview of guidelines used for this assessment.....69
 Overview of guidelines relevant to the diagnosis and management of patients with T1D69
 Table A2. Recommendations for research73
 Table A3. GRADE evidence profile. Sotagliflozin (200 mg) versus placebo, both as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D with BMI ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy (BMI ≥ 27 kg/m² subgroup).74
 Table A4. GRADE evidence profile. Sotagliflozin (400 mg) versus placebo, both as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D with BMI ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy (BMI ≥ 27 kg/m² subgroup).78
 Table A5. GRADE evidence profile. Sotagliflozin (400 mg) versus placebo, both as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy (mITT population).84
 Table A6. GRADE evidence profile for NMA90

Figures

Figure 3.1. Master evidence network for the NMA. Source: applicant submission.31
 Figure 4.1. Forest plot for HbA1c% CFB at 24 \pm 2 weeks. Source: applicant submission57
 Figure 4.2. Network diagram for proportion of patients with any hypoglycaemia at 24 \pm 2 weeks. Source: applicant submission.58
 Figure 4.3. Forest plot for proportion of patients with any hypoglycaemia at 24 weeks. Source: applicant submission.....58
 Figure 4.4. Network diagram for proportion of patients with severe hypoglycaemia at 24 \pm 2 weeks. Source: applicant submission.59
 Figure 4.5: Forest plot for proportion of patients with severe hypoglycaemia at 24 weeks. Source: applicant submission.....59
 Figure 4.6. Network diagram for proportion of patients with positively adjudicated/definite DKA at 24 \pm 2 weeks. Source: applicant submission.60
 Figure 4.7. Forest plot for positively adjudicated/definite DKA at 24 weeks. Source: applicant submission. ...60

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced Therapy Medicinal Products
BG	Blood Glucose
BHB	B-HydroxyButyrate
BMI	Body Mass Index
CI	Confidence Interval
CFB	Capillary Finger-stick Blood
CFB	Change From Baseline
CGM	Continuous Glucose Monitoring
CHMP	Committee for Medicinal Products for Human use
CrI	Credible Interval
CSII	Continuous Subcutaneous Insulin Infusion
CSR	Clinical Study Report
CTR	Clinical Trials Register
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DDG	Deutsche Diabetes Gesellschaft
DDS2	Diabetes Distress Screening Scale
DIC	Deviance Information Criterion
DKA	Diabetic KetoAcidosis
DPP	DiPeptidyl Peptidase
DTSQ	Diabetes Treatment Satisfaction Questionnaire
eGFR	Estimated Glomerular Filtration Rate
EAIR	Exposure-Adjusted Incidence Rate
EASD	European Society for the Study of Diabetes
EFF	Efficacy
EMA	European Medicines Agency
ES	Evidence Summary
ESC	European Society of Cardiology
EQ-5D-5L	EuroQol Questionnaire 5 Dimensions 5 Level
EQ-VAS	EuroQol Visual Analog Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE	Fixed Effects
FEM	Fixed Effects Model
FPG	Fasting Plasma Glucose
GLP-1	Glucagon Like Peptide-1

GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HbA1c	Glycated Haemoglobin
HDL-C	High Density Lipoprotein
HR	Hazard Ratio
HR-QoL	Health-related Quality of Life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
ICD	International Classification of Diseases
IDF	International Diabetes Federation
IDMC	Independent Data Monitoring Committee
IRR	Incidence Rate Ratio
IRT	Item Response Theory
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITC	Indirect Treatment Comparison
IU	International Unit
IVRS	Interactive Voice Response Survey
LDL-C	Low Density Lipoprotein
LSM	Least Squares Mean
MAH	Market Authorisation Holder
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MDII	Multiple Daily Insulin Injections
MeSH	Medical Subject Headings
mITT	Modified Intention to Treat
NA	Not Applicable
NE	Not Established
NMA	Network Meta-Analysis
NR	Not Reported
NICE	National Institute for Health and Care Evidence
DSU	Decision Support Unit
TSD	Technical Support Document
OC	Observed Cases
OR	Odds Ratio
PICO(S)	Population Intervention Comparator Outcome (Setting)
PP	Per Protocol
PPG	Postprandial Plasma Glucose
PT	Preferred Term
QoL	Quality of Life
RCT	Randomised Controlled Trial
RE	Random Effects
REA	Relative Effectiveness Assessment

REM	Random Effects Model
RR	Relative Risk
SAE	Serious Adverse Event
SAF	Safety
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGLT1	Sodium-glucose co-transporter 1
SGLT2	Sodium-glucose co-transporter 2
SH	Severe Hypoglycaemia
SLR	Systematic Literature Review
SMBG	Self-Monitoring Blood Glucose
SMD	Standardised Mean Difference
SOC	System Organ Class
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SR	Systematic Review
SUCRA	Surface Under the Cumulative Ranking
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
WHO	World Health Organization
USD	US Dollar
VAS	Visual Analog Scale
WP4	Work Package 4

EXECUTIVE SUMMARY OF THE ASSESSMENT OF SOTAGLIFLOZIN

Introduction

Type 1 diabetes mellitus (T1D) is a complex autoimmune disease characterised by rapidly progressive pancreatic β -cell destruction leading to insulin deficiency and consequently lifelong exogenous insulin dependence. The underlying aetiology of T1D is poorly understood, but various genetic and environmental factors are known to result in the progressive loss of β -cell mass and/or function. This ultimately manifests clinically as hyperglycaemia in both T1D and type 2 diabetes mellitus (T2D).

Patients with T1D have hyperglycaemia, metabolic imbalance, and typically exhibit one or more of the following clinical features: glycosuria leading to polyuria, ketosis, rapid weight loss, age of onset <50 years, and a personal and/or family history of autoimmune disease.

Insulin replacement therapy is the cornerstone of T1D treatment. Insulin is administered subcutaneously either as multiple daily insulin injections (MDII) or by continuous subcutaneous insulin infusion (CSII) using an insulin pump. Regular blood glucose monitoring is a prerequisite for insulin replacement therapy. Due to continuous basal insulin substitution, CSII represents a more physiological approach than MDII so may minimise the risk of hypoglycaemic events.

According to national and European evidence-based clinical guidelines, T1D should be treated with life-long intensive insulin replacement therapy (multiple insulin injections each day using insulin pens or continuous administration using a personal insulin pump) accompanied by patient monitoring of blood glucose levels.

Sotagliflozin (Zynquista[®]) is a small molecule dual inhibitor of sodium-glucose co-transporter 1 and 2 (SGLT1 and SGLT2). Sotagliflozin reduces blood glucose levels via two mechanisms: (i) by inhibiting SGLT1 in the small intestine to reduce glucose absorption, and (ii) by inhibiting SGLT1 and SGLT2 in the kidneys to reduce and delay glucose reabsorption from the urine. Sotagliflozin is administered as an oral tablet. Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy.

Objective and scope

Objective

The *rationale* for this assessment is to collaboratively produce structured (rapid) core HTA information on pharmaceutical technologies. The *aim* is to apply these collaborative assessments in the national or regional context. This rapid assessment addresses the research question of whether sotagliflozin (Zynquista[®]) as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy, is more effective and/or safe than optimised insulin monotherapy alone and to assess the relative effectiveness/safety of sotagliflozin compared to SGLT2 inhibitors.

Project scope

The project scope can be found in [Table 2.1](#).

Methods

Literature search and assessment approach

The market authorisation holder (MAH; Sanofi) conducted and provided a systematic literature review of the evidence, which was then critically appraised by authors of this assessment. The following electronic databases were searched for literature by the MAH: MEDLINE, EMBASE, the Cochrane database (Cochrane Library interface), clinicaltrials.gov, the World Health Organization

(WHO; International Clinical Trials Registry Platform metaregistry), and European (EU Clinical Trials Register) trial registries. The final database search was performed on October 5th 2018. The search protocol was included as part of the submission file. Overall, the authors considered that the reporting of the search followed EUnetHTA guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) statement. The search was conducted approximately five months before the start of the assessment. Therefore, the authors updated the search as indicated in the project plan on March 25th 2019 and found no additional relevant study data.

Risk of bias assessment was conducted at both the study and outcome levels for randomised controlled trials (RCTs) by the assessment's authors. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was applied by the authors to rate the quality of evidence [1]. The outcomes included in the direct comparison are listed in Table 0.1. (1).

Indirect treatment comparison

The MAH performed network meta-analysis (NMA) to compare sotagliflozin to empagliflozin and dapagliflozin. This NMA was conducted on the entire population rather than the BMI ≥ 27 kg/m² subgroup due to a lack of subgroup information in a number of the comparator trials. The NMA was conducted in a Bayesian framework using WinBUGS statistical software. NMAs were carried out at 24 \pm 2 weeks and 52 weeks. Given that more studies reported results at 24 \pm 2 weeks, the NMAs in this report focus on outcomes at 24 \pm 2. The authoring team note that the NMA was only conducted on a subset of outcomes.

Subgroup analysis and other effect modifiers

Subgroup analyses examining potential effect modifiers presented in the submission dossier were evaluated. Indirect comparison methods were applied and, if applicable, the justification in the event of deviations from the required approaches was evaluated.

Patient involvement

EUnetHTA conducted an open call asking general questions to elicit patients' views on living with diabetes, the important outcomes considered in this assessment, and expectations of the assessed drug. Questions were based on the HTAi questionnaire template.

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. The call generated answers from two organisations: [Diabetes UK](#) and [La Federación Española de Diabetes \(FEDE\)](#), Spain.

The patient organisations emphasised the importance of how, and to what extent, a new treatment affects various aspects of the quality of life (QoL) of a patient with diabetes. Challenges to the T1D patient such as the inability to maintain blood glucose levels within an acceptable range and failure to achieve target HbA1c levels were also discussed, as was the need for new and effective treatments. The problems and challenges (e.g., limited experience of ketone self-monitoring) to keeping side-effects, particularly hypoglycaemia and diabetic ketoacidosis (DKA), under control were also discussed as important aspects of a new therapy.

The following outcomes defined in the project plan were deemed to particularly reflect input from the patient organisations:

- Proportion of patients with HbA1c <53 mmol/mol (7%)
- Health-related quality of life
- Hypoglycaemia
- Diabetic ketoacidosis

These outcomes are directly reflected by endpoints of the inTandem1-3 trials, which are evaluated in this assessment. For health-related QoL, the specific measures were the Diabetes Distress Score (DDS2) and the Diabetes Treatment Satisfaction Score (DTSQ), which were used in the inTandem1-2 trials. Generic QoL measurements were also included in the material submitted by the MAH.

Results

Fourteen studies reported across 35 publications were retrieved in the systematic literature review (SLR). Of the 14 studies included in the complete SLR, seven evaluated metformin, three evaluated sotagliflozin, and two studies each evaluated dapagliflozin and empagliflozin. Six studies (inTandem1, inTandem2, DEPICT-1, DEPICT-2, EASE-2, and EASE-3) were included in the main assessment. The inTandem3 study was excluded from the main assessment since this study did not incorporate an insulin titration period before randomisation. However, inTandem3 was included in the NMA.

In the assessment, outcomes for a pool of patients from the modified intention-to-treat (mITT) population of inTandem1-2 with BMI ≥ 27 kg/m² were evaluated (the ES1 pool). The ES1 pool data from inTandem1-2 thus represented data from randomised placebo-controlled clinical trials where the efficacy and safety of sotagliflozin add-on to insulin was compared to placebo add-on to insulin. Together with inTandem3, inTandem1-2 were included in the market authorisation application for sotagliflozin. For indirect comparison by NMA of sotagliflozin versus dapagliflozin and sotagliflozin versus empagliflozin, the randomised placebo-controlled clinical trials DEPICT-1 and 2 (dapagliflozin versus placebo) and EASE-2 and 3 (empagliflozin versus placebo) were also included.

The ES1 pool contained 916 patients (46% used CSII, 49% female, mean age 45 years) randomised to placebo (298 patients), sotagliflozin 200 mg (305 patients), and sotagliflozin 400 mg (313 patients). Baseline mean body weight was 94 kg, mean BMI 32.16 kg/m², mean systolic blood pressure (SBP) 124.2 mmHg, and mean HbA1c 7.66%.

Treatment with sotagliflozin significantly reduced several crucial or important outcomes including HbA1c, symptomatic documented hypoglycaemia, glucose variability, body weight, and SBP compared to placebo ([Table 0.1](#) and [Table 0.2](#)). In addition, the proportion of patients with a net benefit from treatment (defined as the proportion of patients achieving an HbA1c < 53 mmol/mol ($< 7\%$) without experiencing severe hypoglycaemia or DKA) increased compared to placebo, along with the number of patients experiencing increased treatment satisfaction and less diabetes distress. Sotagliflozin increased the incidence of DKA: after one year of treatment with sotagliflozin, there was a significant increase in the incidence of DKA in patients in the inTandem1-2 trials with a BMI ≥ 27 kg/m².

Overall, the evidence for the effects of sotagliflozin versus placebo, as an add-on to optimised insulin therapy, was based on two RCTs. A substantial number of patients seemed to be excluded from the analyses provided by the MAH for outcomes that included a change from baseline, and the numbers fell below the mITT populations presented in the CONSORT flow diagrams of the trials. Since the BMI subgroup was extracted from these study bases, the authors assumed that any bias arising from this also applied to the BMI subgroup analyses. When queried by the authors, the MAH responded that either the value at baseline or the value at follow-up was unavailable for these patients. However, they did not provide an explanation why these values were missing and, therefore, the risk of bias has been set to high for change from baseline outcomes in the sotagliflozin studies and similarly for dapagliflozin trials. The approved indication for sotagliflozin includes a subgroup (BMI ≥ 27 kg/m²) from the original mITT populations, so this assessment was primarily based on the subgroup data. The authors concluded that the risk of bias for the subgroup data should not be downgraded further since the baseline characteristics were similar between the sotagliflozin and placebo groups and a pre-specified subgroup analysis of BMI < 25 kg/m² versus ≥ 25 kg/m², which was stratified at randomisation, showed similar patterns for relative effects. Furthermore, the effect estimates were similar to the BMI ≥ 27 kg/m² analyses in the mITT analyses.

The certainty of evidence varied between outcome measures and ranged from high (DKA), to moderate (net benefit), to low (e.g., severe hypoglycaemia, and symptomatic documented hypoglycaemia) and very low (health-related QoL) ([Table 0.2](#)).

Table 0.1. Summary of relative outcomes for mITT population ES1 pool BMI ≥ 27 kg/m²

Outcome	Timepoint	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
		LSM (95% CI), p-value	LSM (95% CI), p-value
HbA1c	52 weeks	-0.24 (-0.35 to -0.13), <0.001	-0.38 (-0.49 to -0.27), <0.001
Net benefit (mITT pool)	52 weeks	9.2 (4.30 to 14.15), <0.001	12.8 (7.75 to 17.83), <0.001
DTSQ	24 weeks	2.6 (1.9 to 3.3), <0.001	2.6 (1.9 to 3.3), <0.001
DDS2	24 weeks	-0.6 (-0.9 to -0.3), <0.001	-0.7 (-0.9 to -0.4), <0.001
Time in range	24 weeks	8.171 (2.296 to 14.046), 0.007	15.051 (9.403 to 20.699), <0.001
Body weight	52 weeks	-3.01 (-3.71 to -2.31), <0.001	-4.46 (-5.15 to -3.76), <0.001
SBP	52 weeks	-2.1 (-3.9 to -0.4), 0.018	-3.6 (-5.3 to -1.9), <0.001
Hypoglycaemia (≤ 55 mg/dL, ≤ 3.0 mmol/L)	52 weeks	-4.25 (-6.93 to -1.57), 0.0019	-3.42 (-6.14 to -0.7), 0.0138
EAIR of severe hypoglycaemia (positively adjudicated)	52 weeks	The risk diff of event rates: -34.52 (-76.78 to 7.74) The relative risk of event rates: 0.57 (0.28 to 1.14)	The risk diff of event rates: -39.98 (-81.04 to 1.09) The relative risk of event rates: 0.51 (0.24 to 1.02)
EAIR of DKA (positively adjudicated)	52 weeks	The risk diff of event rates: 24.94 (3.83 to 46.05) The relative risk of event rates: 7.77 (1.24 to 173.82)	The risk diff of event rates: 33.95 (10.57 to 57.34) The relative risk of event rates: 10.22 (1.74 to 221.94)

Abbreviations: DDS2=diabetes distress score; diff=difference; DKA=diabetic ketoacidosis; DTSQ=diabetes treatment satisfaction score; EAIR=exposure-adjusted incidence rate; LSM=least squares mean; SBP=systolic blood pressure

Although the inTandem3 study was excluded from the main body of the assessment to present the results representing the most homogeneous population (effects following an insulin titration period), pooling of the relative effects from inTandem3 with inTandem1-2 (ES2 pool) did not produce heterogeneity nor did it negatively alter the certainty of the evidence.

Indirect Treatment Comparison

The studies included in the NMA were at high risk of bias for several outcomes and included the mITT populations (also for sotagliflozin), since the BMI subgroup data were unavailable for the comparators dapagliflozin and empagliflozin. The NMA results contained quite a lot of uncertainty, making it difficult to draw conclusions about the benefit of sotagliflozin relative to dapagliflozin and empagliflozin (Table 0.3). However, it is of note that neither dose of sotagliflozin was ranked first for any of the outcomes included in the NMA.

Importantly, only random effects (RE) models were presented in the submission file. The authors expressed the need to have both RE models and fixed effects (FE) models for the purpose of this assessment, as well as a full set of available outcomes for the NMA. This information is considered of crucial importance for the analysis of the NMA and the overall assessment. Despite the author's request, these data were not provided by the MAH. As such, the authors consider the submission to be incomplete.

Discussion

For T1D patients with BMI ≥ 27 kg/m², add-on treatment with sotagliflozin to optimised insulin therapy significantly reduces HbA1c, body weight, blood pressure, and occurrence of hypoglycaemia and increases DKA occurrences compared to placebo. Sotagliflozin also increases the proportion of patients achieving a target HbA1c <7% without experiencing hypoglycaemia or DKA relative to placebo. Sotagliflozin improves glucose variability, relieves diabetes distress, and improves diabetes treatment satisfaction. Patients treated with sotagliflozin also on average use lower insulin doses.

The statistically significant treatment effect observed for HbA1c (0.24-0.38% for 200-400 mg) after one year approaches the limit commonly used as a non-inferiority margin for T2D in clinical trials (0.3-0.4% according to US Food and Drug Administration (FDA) and 0.3% according to the European Medicines Agency (EMA)).

Different adverse events were reported with sotagliflozin treatment. However, the frequency of hypoglycaemic events and DKA episodes reported in patients treated with the drug are of particular importance. Clinical trial evidence indicates that patients treated with sotagliflozin are at significantly decreased risk of hypoglycaemia but at significantly increased risk of DKA. Since the risk of hypoglycaemia is a source of anxiety for diabetic patients, reducing hypoglycaemic risk would be expected to have a positive effect on QoL. However, this is balanced against the increased frequency of DKA as a direct and serious complication of the treatment. Even though DKA risk might be even higher in clinical practice, sotagliflozin has been approved for restricted medical prescription only and patients will be required to perform ketone self-monitoring. This will help to reduce the problem of DKA, but the actual risk of DKA in real-world clinical practice is hard to predict.

Conclusions

For patients with BMI ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite optimal insulin therapy¹, add-on with 200 mg sotagliflozin resulted in placebo-adjusted changes in HbA1c of -0.24% [CI: -0.35 to -0.13] and 400 mg sotagliflozin resulted in placebo-adjusted changes in HbA1c of -0.38% [CI: -0.49 to -0.27] after one year of treatment compared to placebo. Both sotagliflozin doses also significantly improve the cardiovascular risk factors systolic blood pressure (SBP) (-3.6 mm Hg [CI: -5.3 to -1.9] for sotagliflozin 400 mg and -2.1 [-3.9 to 0.4] for sotagliflozin 200 mg) and body weight. However, the statistically significant treatment effect observed for HbA1c at both doses contains the commonly used non-inferiority margin for T2D in clinical trials (0.3-0.4% according to the FDA and 0.3% according to the EMA).

With respect to adverse events, there was a 43% and 49% lower risk of incidence of severe hypoglycaemia with 200 mg and 400 mg sotagliflozin, respectively, but the difference did not reach statistical significance. After one year with 200 mg and 400 mg sotagliflozin, the relative risk of incidence (EAIR) was 0.57 [CI: 0.28 to 1.14] and 0.51 [CI: 0.24 to 1.02], respectively. However, the corresponding risk of DKA was significantly increased with an incidence rate ratio with 200 mg and 400 mg of 7.8 [CI: 1.2 to 174] and 10.2 (1.7 to 222), respectively.

The increased risk of DKA occurrence is considerable but should be reduced by restricted medical prescription, patient and caregiver education, and patient self-monitoring of ketones. The extent of the problem with sotagliflozin and DKA in real clinical practice is difficult to assess and predict.

The NMA results contained quite a lot of uncertainty, making it difficult to draw conclusions about the benefit of sotagliflozin relative to dapagliflozin and empagliflozin. However, it is of note that neither dose of sotagliflozin was ranked in first position for any of the outcomes included in the NMA.

¹ Outcomes referred to in the conclusion section are derived from pooled one-year data from inTandem1-2 for patients of the mITT pools with BMI ≥ 27 kg/m². This corresponds to the population of the approved indication for sotagliflozin and is the main population examined in this REA.

Table 0.2. Summary of findings of sotagliflozin (mITT population, patients with baseline BMI ≥ 27 kg/m²)

Outcome	Anticipated absolute effects (95% CI or SD)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with sotagliflozin				
Diabetes-related micro/macrovascular complications (assessed by: HbA1c (%) , mean difference from baseline), 52 wks	-0.00 (0.042)	200 mg/day: -0.24 (0.041)	200 mg/day: 0.24 percentage points lower (0.13 to 0.35 lower)	200 mg/day: 603 (2 RCTs)	⊕⊕○○ LOW	Crucial outcome
		400 mg/day: -0.38 (0.040)	400 mg/day: 0.38 percentage points lower (0.27 to 0.49 lower)	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	
Diabetes-related micro/macrovascular complications (assessed by: proportion with HbA1c <7% , mean difference from baseline)	No data submitted for the BMI subgroup Proportion with HbA1c <7% for the mITT population (sotagliflozin 400 mg versus placebo): 31.6% versus 18.3% OR 2.09 (1.56 to 2.79) (moderate certainty of evidence)					Crucial outcome
Diabetes-related micro/macrovascular complications and short-term complications (assessed by: net benefit (%) : proportional difference in HbA1c < 7.0%, no severe hypoglycaemia, no diabetic ketoacidosis), 24 wks	19.1%	200 mg/day: 29.8%	200 mg/day: OR 1.80 (1.23 to 2.63)	200 mg/day: 603 (2 RCTs)	⊕⊕⊕○ MODERATE	Crucial outcome
		400 mg/day: 41.9%	400 mg/day: inTandem1: OR 3.62 (2.26 to 5.80) inTandem2; OR 2.45 (1.36 to 4.41)	400 mg/day: 611 (2 RCTs)	⊕⊕⊕○ MODERATE	
Mortality (%) (number of deaths/total), 52 wks	0.7%	200 mg/day: 0%	200 mg/day: NR	200 mg/day: 603 (2 RCTs)	⊕⊕○○ LOW	Crucial outcome
		400 mg/day: 0%	400 mg/day: NR	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	
Health-related QoL² (assessed by: treatment satisfaction with Diabetes Treatment Satisfaction Score [range 0-	-0.3 (0.27)	200 mg/day: 2.3 (0.26)	200 mg/day: 2.6 points higher (1.9 to 3.3 higher)	200 mg/day: 603 (2 RCTs)	⊕○○○ VERY LOW	Crucial outcome

² Is a multi-dimensional including physical, psychological, functional, and social domains related to a person's perception of quality of life affected by health status.

PTJA04 - Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy

Outcome	Anticipated absolute effects (95% CI or SD)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with sotagliflozin				
36 points, higher is better, mean difference from baseline), 24 wks		400 mg/day: 2.2 (0.26)	400 mg/day: 2.6 points higher (1.9 to 3.3 higher)	400 mg/day: 611 (2 RCTs)	⊕○○○ VERY LOW	
Health-related QoL (assessed by: EQ-5D-5L ³ generic health status score [higher is better], and EQ-VAS [scale 0-100, higher is better], mean difference from baseline)	No data submitted for the BMI subgroup QoL measures for mITT population (sotagliflozin 400 mg versus placebo): EQ-5D-5L: 0.01 points higher (0.0 lower to 0.02 higher) (low certainty of evidence) EQ-VAS: 1.7 points higher (0.11 to 3.2 higher) (moderate certainty of evidence)					Crucial outcome
Symptomatic documented hypoglycaemia with documented SMBG ≤ 55 mg/dL (assessed by: event rate, n events per person per year), 52 wks	18.0 events per person-year (15.9 to 20.1)	200 mg: 13.8 events per person-year (12.1 to 15.4)	200 mg: 4.3 events per person-year lower (1.6 to 6.9 lower)	200 mg/day: 603 (2 RCTs)	⊕⊕○○ LOW	Crucial outcome
		400 mg: 14.6 events per person-year (12.9 to 16.6)	400 mg: 3.4 events per person-year lower (0.7 to 6.1 lower)	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	
Severe hypoglycaemia (assessed by: positive adjudication by blinded review committee (n events per 1000 person-years adjusted to patient's exposure), 52 wks)	81.0 events per 1000 person-years (47.2 to 115)	200 mg: 46.5 events per 1000 person-years (21.2 to 71.8)	200 mg: IRR: 0.57 (0.28 to 1.14)	200 mg/day: 603 (2 RCTs)	⊕⊕○○ LOW	Crucial outcome
		400 mg: 41.1 events per 1000 person-years (17.8 to 64.3)	400 mg: IRR: 0.51 (0.24 to 1.02)	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	
Adverse events leading to discontinuation of study treatment (n)	4.4%	200 mg; 4.4%	200 mg: NR	200 mg/day: 603 (2 RCTs)	⊕⊕○○	Crucial outcome

³ EQ-5D is a validated generic instrument to collect health-related quality of life (HRQoL) alongside clinical data. It is practical and quick to use and may be applied in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ VAS. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale. This can be used as a quantitative measure of health outcome that reflects the patient's own judgement. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

PTJA04 - Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy

Outcome	Anticipated absolute effects (95% CI or SD)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with sotagliflozin				
events/total), 52 wks					LOW	
		400 mg: 4.2%	400 mg: NR	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	
Severe adverse events (assessed by: severe treatment-related adverse events [n events/total]), 52 wks	2.7%	200 mg: 3.0%	200 mg: NR	200 mg/day: 603 (2 RCTs)	⊕⊕○○ LOW	Crucial outcome
		400 mg; 4.5%	400 mg: NR	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	
Diabetic ketoacidosis (assessed by: positive adjudication by blinded review committee [n events per 1000 person-years adjusted to patient's exposure]), 52 wks	3.68 events per 1000 person-years (0.0 to 10.9)	200 mg: 28.6 events per 1000 person-years (8.8 to 48.5)	200 mg: IRR: 7.8 (1.2 to 174)	200 mg/day: 603 (2 RCTs)	⊕⊕⊕⊕ HIGH	Crucial outcome
		400 mg: 37.6 events per 1000 person-years (15.4 to 59.9)	400 mg: IRR 10.2 (1.7 to 222)	400 mg/day: 611 (2 RCTs)	⊕⊕⊕⊕ HIGH	
Diabetes related micro/macrovascular complications (assessed by: time in range : percent time spent in target range [3.9 -10.0 mmol/L [≥ 70 to ≤ 180 mg/dL], per 24 h, mean difference in % in the CGM substudy), 24 wks	-1.9 (2.3) percentage points	200 mg: 6.2 (2.2) percentage points higher	200 mg: 8.2 percent points higher (2.3 to 14.0 higher)	200 mg/day: 117 (2 RCTs)	⊕○○○ VERY LOW	Important outcome
		400 mg: 13.1 (2.0) percentage points higher	400 mg: 15.1 percent points higher (9.4 to 20.7 higher)	400 mg/day: 123 (2 RCTs)	⊕○○○ VERY LOW	
Total insulin dosage (assessed by: mean difference in IU/day from baseline), 24 wks	-0.39 (0.91) IU/day	200 mg: 3.8 (0.9) IU/day lower	200 mg: 3.4 IU/day lower (1.0 to 5.8 lower)	200 mg: 603 (2 RCTs)	⊕○○○ VERY LOW	Important outcome
		400 mg: 7.0 (0.9) IU/day lower	400 mg: 6.6 IU/day lower (4.3 to 9.0 lower)	400 mg: 611 (2 RCTs)	⊕○○○ VERY LOW	
Cardiovascular risk factors (assessed by: mean difference from baseline in systolic blood pressure [mm Hg],	0.4 (0.7) mm Hg higher	200 mg: 1.7 (0.7) mm Hg lower	200 mg: 2.4 mm Hg lower (5.8 lower to 1.1 higher)	200 mg: 200 (2 RCTs)	⊕○○○ VERY LOW	Important outcome

PTJA04 - Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy

Outcome	Anticipated absolute effects (95% CI or SD)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with sotagliflozin				
regardless of SBP at baseline [for absolute effects, 52 wks] and among patients with SBP of ≥ 130 mm Hg at baseline [for relative effects, 24 wks]		400 mg: for anticipated absolute effects 3.2 (0.7) mm Hg lower	400 mg: 2.5 mm Hg lower (5.8 lower to 0.8 higher)	400 mg: 207 (2 RCTs)	⊕○○○ VERY LOW	
Cardiovascular risk factors (assessed by: mean difference from baseline in body weight [kg]), 52 wks	0.9 (0.3) kg higher	200 mg: 2.2 (0.3) kg lower	200 mg: 3.0 kg lower (2.3 to 3.7 lower)	200 mg/day: 603 (2 RCTs)	⊕⊕○○ LOW	Important outcome
		400 mg: 3.6 (0.2) kg lower	400 mg: 4.5 kg lower (3.8 to 5.2 lower)	400 mg/day: 611 (2 RCTs)	⊕⊕○○ LOW	

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Abbreviations: CGM=continuous glucose monitoring; EQ-5D-5L=EuroQol Questionnaire 5 Dimensions 5 Level; EQ-VAS=EuroQol Visual Analog Scale; IRR=incidence rate ratio; NR=not reported; OR=odds ratio; QoL=quality of life; RCT=randomised controlled trial; SBP=systolic blood pressure

Table 0.3. GRADE Summary of findings for comparisons in the NMA. Note that most studies include multiple doses, however we focus here on the highest dose in each study. Therefore, the same dose for Empagliflozin is not used for each endpoint.

Outcome	Arm1	Arm2	Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
Type 1 diabetes related micro/macrovacular complications (assessed by: glycaemic control (HbA1c percent change from baseline [24 weeks])	Sotagliflozin 400 mg	Placebo	-0.42 (-0.48, -0.36)	2223 (3)	⊕⊕○○ low	Crucial outcome
	Dapagliflozin 10 mg	Placebo	-0.43 (-0.53, -0.33)	990 (2)	⊕⊕○○ low	Crucial outcome
	Empagliflozin 25 mg	Placebo	-0.53 (-0.62, -0.44)	967 (2)	⊕⊕⊕○ moderate	Crucial outcome
Any hypoglycaemia (proportion of patients [24 weeks])	Sotagliflozin 400 mg	Placebo	1.23 (0.78, 1.91)	2453 (3)	⊕⊕⊕○ moderate	Crucial outcome
	Dapagliflozin 10 mg	Placebo	0.98 (0.71, 1.34)	1098 (2)	⊕⊕⊕○ moderate	Crucial outcome
	Empagliflozin 25 mg	Placebo	1.01 (0.7, 1.46)	486 (1)	⊕⊕⊕○ moderate	Crucial outcome
Severe hypoglycaemia (assessed by: positive adjudication by blinded review committee (proportion of patients [24 weeks])	Sotagliflozin 400 mg	Placebo	0.9 (0.59, 1.38)	2453 (3)	⊕⊕⊕○ moderate	Crucial outcome
	Dapagliflozin 10 mg	Placebo	0.99 (0.63, 1.56)	1098 (2)	⊕⊕⊕○ moderate	Crucial outcome
	Empagliflozin 2.5 mg	Placebo	0.49 (0.12, 2)	482 (1)	⊕⊕○○ low	Crucial outcome
Diabetic ketoacidosis (assessed by: positively adjudication* by blinded review committee (proportion of patients [24 weeks])	Sotagliflozin 400 mg	Placebo	6.52 (2.52, 16.88)	2453 (3)	⊕⊕⊕⊕ high	Crucial outcome
	Dapagliflozin 10 mg	Placebo	3.19 (0.36, 28.10)	1098 (2)	⊕⊕⊕○ moderate	Crucial outcome
	Empagliflozin 2.5 mg	Placebo	0.66 (0.11, 4.01)	482 (1)	⊕⊕○○ low	Crucial outcome

* Defined as “definite + probably DKA” in the inTandem studies, as “definite” in the DEPICT studies and as confirmed adjudicated in the EASE studies.

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Abbreviations: NMA=network meta-analysis

1 BACKGROUND

1.1 Overview of the disease or health condition

Pathoetiology

Type 1 diabetes mellitus (T1D) is a complex autoimmune disease characterised by rapidly progressive pancreatic β -cell destruction that leads to insulin deficiency and consequently lifelong exogenous insulin dependence. The underlying aetiology is poorly understood, but diabetes is known to be multifactorial, with various genetic and environmental factors resulting in the progressive loss of insulin-producing pancreatic β -cell mass and/or function that manifests clinically as hyperglycaemia in both T1D and type 2 diabetes mellitus (T2D). More specifically, T1D is caused by autoimmune β -cell destruction that usually leads to absolute insulin deficiency and T2D is caused by the progressive loss of β -cell insulin secretion, frequently on a background of insulin resistance. Without insulin replacement, the absolute insulin deficiency seen in T1D is fatal (2-4).

T1D is typically first diagnosed before 30 years of age so was historically referred to as “juvenile-onset” diabetes. However, the conventional view that T2D only occurs in adults and T1D only in children is no longer appropriate, since both can and do occur at any age.

T1D is an autoimmune disease and lifestyle risk factors for developing the disease have been identified, environmental factors may trigger disease development in individuals who are genetically susceptible (5, 6). During the development of T1D, the insulin-producing β -cells are gradually destroyed by autoreactive antibodies, eventually leading to loss of insulin secretory function. After autoimmunity is triggered, the disease progresses through three identifiable stages: a first non-symptomatic stage with normal blood glucose levels, a second pre-symptomatic stage with impaired fasting blood glucose levels or impaired glucose tolerance, and a third symptomatic stage with hyperglycaemia and the clinical symptoms of diabetes (2, 5, 7).

Once the disease has developed, its complications can be reduced and delayed through a healthy diet and regular physical activity. The complications of diabetes include hyperglycaemia and metabolic imbalance, and people with untreated T1D exhibit one or more of the following features: glycosuria leading to polyuria, ketosis, rapid weight loss, and age of onset <50 years. Type 1 diabetic patients may also report having a personal and/or family history of autoimmune disease (8).

Complications

Insulin deficiency leads to uncontrolled blood glucose levels and life-threatening hyperglycaemia. Chronic hyperglycaemia damages blood vessels, leading to long-term complications which are usually grouped into microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular disorders (cardiovascular disease). These complications account for most of the increased morbidity and mortality associated with T1D (9).

In spite of progress made in insulin therapy, up to 70% of T1D patients are uncontrolled with optimal insulin therapy and have uncontrolled fluctuations (9). The burden of diabetes involves its acute metabolic complications: diabetic ketoacidosis (DKA), which is due to relative insulin deficiency, and diabetic coma, which is caused by treatment-induced hypoglycaemia (10). Both of these conditions can be deadly.

Diabetes and its complications have substantial consequences for society, with economic losses to health systems through direct medical costs and wider indirect losses through lost work and wages. Major cost drivers include hospital and outpatient care, but the rise in prescriptions of insulin analogues is also a contributing factor. In 2017, approximately 425 million adults were estimated to be living with diabetes worldwide, with almost 50 million of these cases being attributed to T1D (11). In total, diabetes was estimated to cost at least 727 billion US dollars (USD) in health expenditure in 2017.

To date, T1D treatment has been limited to insulin replacement with close monitoring of blood glucose levels. Despite substantial innovations in insulin delivery techniques, no new therapies have been developed.

Prevalence

The prevalence of T1D is approximately 0.5% but varies between countries according to statistics provided by the MAH. For instance, the prevalence of T1D is 0.25% in Italy (12), 0.55% in Sweden (13), and 0.69% in The Netherlands (14).

1.2 Current clinical practice

Insulin therapies

The current clinical management of T1D focuses on glycaemic control, usually through glucose self-monitoring, together with diet, exercise, and intensive insulin therapy. This approach is supported by active management of other cardiovascular risk factors such as hypertension and high circulating lipids.

Insulin replacement therapy is the cornerstone of T1D management. Insulin is administered subcutaneously and may be given as multiple daily insulin injections (MDII) or by continuous subcutaneous insulin infusion (CSII) using an insulin pump. Regular blood glucose monitoring is a prerequisite for insulin replacement therapy. Due to providing continuous basal insulin substitution, CSII can better mimic normal insulin physiology than MDII, so may better minimise the risk of hypoglycaemic events.

Different types of insulin are available including different forms of long-acting (basal) insulin and rapid-acting (bolus) insulin. Intensified insulin therapy typically involves the up-titration of the insulin dose, at least three insulin injections per day, and blood glucose monitoring by self-testing. The recommended standard treatment for people with T1D is a long-acting (basal) insulin combined with a short-acting (bolus) insulin at meal times according to the basal-bolus principle (7, 8, 15-17). For individuals using a CSII system, a single, rapid-acting insulin is used.

European and national guidelines

According to national (7, 8, 15-19) and European (3) evidence-based clinical guidelines, T1D should be treated by life-long intensive insulin replacement therapy (multiple insulin injections per day using insulin pens or continuous administration using a personal insulin pump) accompanied by patient monitoring of blood glucose levels.

The treatment goal is to keep blood glucose levels, as assessed over time by HbA1c levels, as close as possible to the normal range in order to prevent or delay complications. A general target in European guidelines is an HbA1c $\leq 7.0\%$ (≤ 53 mmol/mol) (3, 20), but it is standard recommended practice that HbA1c targets and treatment intensification should be individualised to take the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation, and history of hypoglycaemia into account. Therefore, the recommended targets vary between $\leq 6.5\%$ and $< 8.5\%$ (≤ 48 - 69 mmol/mol) based on individual patient needs.

Nevertheless, routines are basically the same throughout Europe, with small differences with respect to recommended individual treatment targets and use of technology for certain patient groups (see [Appendix 1](#)).

Add-on therapies to insulin

There are currently no licenced add-on therapies to insulin (at the European level) for patients with T1D, but many pharmaceuticals licensed for T2D have been studied in patients with T1D including metformin, thiazolidinediones, SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. In France, metformin is licensed for T1D ([STAGID, metformin embonate](#)), where it is mostly used in obese patients with uncontrolled hyperglycaemia. According to UK and Irish guidelines, adding metformin as an off-label adjunct to insulin therapy can be considered if an adult with T1D and a BMI ≥ 25 kg/m² (≥ 23 kg/m² for people from South Asia and related ethnic groups) wants to improve their blood glucose control while minimising their effective insulin dose (8). According to Polish guidelines, adding SGLT2 inhibitors to insulin therapy may improve glycaemic control and weight reduction in T1D (21).

Furthermore, in March 2019, dapagliflozin received marketing authorisation from the EMA for the treatment of type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

Size of the target population

Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy. According to data submitted by the MAH and based on diabetes prevalence in seven European countries (France, Germany, Italy, Ireland, Spain, Sweden, The Netherlands, and UK; approximately 70% of the total EU population), approximately 759,000 patients with T1D have failed to achieve adequate glycaemic control (70% of all adult patients with T1D) despite optimal insulin therapy. The MAH further estimates that 20-40% of T1D patients have a BMI ≥ 27 kg/m² in Europe. Therefore, 152,000-304,000 patients are estimated to belong to the sotagliflozin target population. This number is limited in clinical practice by additional factors such as patient willingness to perform ketone self-monitoring, acceptance of risk of DKA, or contraindications.

Another estimate can be made based on national registry data. In Sweden, for instance, 73% of patients with T1D have an HbA1c > 52 mmol/mol, and different (off-label) add-on treatments to insulin are given to approximately 4.5% of T1D patients, mostly those who are overweight (mean BMI 29.6) (22). The Swedish data suggest that ~110,000 patients in the EU belong to the sotagliflozin target population (approximately 410 million people in the EU are > 17 years of age, approximately 0.6% of these have T1D according to IDF data (11), and 4.5% of these are given oral adjunct therapy to insulin as estimated by Swedish registry data). These numbers will probably increase with the introduction of a licenced therapy.

1.3 Features of the intervention

The features of the intervention are summarised in [Table 1.1](#) and [Table 1.2](#).

Sotagliflozin

Sotagliflozin is an orally delivered small molecule dual inhibitor of sodium-glucose co-transporter 1 and 2 (SGLT1 and SGLT2) that reduces blood glucose levels via two mechanisms: inhibition of SGLT1 in the small intestine reduces glucose absorption, and inhibition of SGLT1 and SGLT2 in the kidneys reduces glucose reabsorption from the urine (23, 24).

Comparators

Sotagliflozin (200 mg and 400 mg) add-on to optimised insulin therapy is compared with:

- placebo add-on to optimised insulin therapy (direct comparison);
- empagliflozin and dapagliflozin add-on to optimised insulin therapy (indirect comparison).

Dapagliflozin (Forxiga®)

Dapagliflozin is indicated in adults for the treatment of insufficiently controlled:

- T2D as an adjunct to diet and exercise to improve glycaemic control
 - as monotherapy when metformin is considered inappropriate due to intolerance;
 - in addition to other medicinal products for the treatment of T2D.

Dapagliflozin 5 mg is also indicated for:

- T1D as an adjunct to insulin in patients with BMI ≥ 27 kg/m² when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy.

Empagliflozin (Jardiance®)

Empagliflozin is indicated for the treatment of adults with insufficiently controlled T2D as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance;
- in addition to other medicinal products for the treatment of diabetes.

Optimised insulin therapy

Insulin therapy is titrated over time (six weeks in the inTandem trials, but longer periods are common in practice) to achieve an individualised target HbA1c (usually below 7%, 53 mmol/mol) and without causing symptomatic hypoglycaemia. Different insulin regimens can be used for optimisation, e.g., MDII and CSII.

SGLT2 inhibitors

SGLT2 inhibitors reduce blood glucose by inhibiting SGLT2 in the kidneys, which reduces glucose reabsorption from the urine (25). Four SGLT2 inhibitors are approved in the EU for the treatment of T2D: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. As indicated above, this assessment includes an indirect comparison of sotagliflozin and the two SGLT2 inhibitors dapagliflozin (5 mg) and empagliflozin, for which there are published results from phase III clinical trials involving T1D patients. EMA adopted market authorisation for dapagliflozin (5 mg) for a new indication including T1D on in March 2019. Other treatments for diabetes (e.g., metformin and GLP1) are not included in this assessment, since these treatments do not have an approved indication for T1D. In addition, canagliflozin was excluded from the assessment because there are no ongoing phase III trials for canagliflozin regarding the indication for T1D.

Table 1.1. Features of the intervention

Non-proprietary name	Sotagliflozin	Dapagliflozin	Empagliflozin
Proprietary name	Zynquista®	Forxiga®	Jardiance®
Registered EMA indication	Sotagliflozin for adult patients with T1D and with a BMI ≥ 27 kg/m ² who have inadequate glucose control using optimised insulin or insulin analogues.	Dapagliflozin is indicated in adults for the treatment of insufficiently controlled: <ul style="list-style-type: none"> • T2D as an adjunct to diet and exercise to improve glycaemic control - as monotherapy when metformin is considered inappropriate due to intolerance; - in addition to other medicinal products for the treatment of type 2 diabetes. <p><i>Dapagliflozin 5 mg is also indicated for:</i></p> <ul style="list-style-type: none"> • T1D as an adjunct to insulin in patients with BMI ≥ 27 kg/m² when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy. 	Empagliflozin is indicated for the treatment of adults with insufficiently controlled T2D as an adjunct to diet and exercise: <ul style="list-style-type: none"> • as monotherapy when metformin is considered inappropriate due to intolerance; • in addition to other medicinal products for the treatment of diabetes.
Prospective Marketing authorisation holder	Sanofi	Astra Zeneca	Boehringer Ingelheim
Contraindications	Hypersensitivity to the active substance or to any of the excipients.	Hypersensitivity to the active substance or to any of the excipients.	Hypersensitivity to the active substance or to any of the excipients.
Drug class	SGLT1 and SGLT2 inhibitor	SGLT2 inhibitor	SGLT2 inhibitor
Active substance(s)	Sotagliflozin	Dapagliflozin	Empagliflozin
Pharmaceutical formulation(s)	Film-coated tablet	Film-coated tablet	Film-coated tablet
ATC code	A10BK06	A10BK01	A10BX12
Monitoring required	Self-monitoring of blood glucose required.	Self-monitoring of blood glucose required.	Self-monitoring of blood glucose required.
Orphan Designation	No	No	No
ATMP	No	No	No

Abbreviations: ATC=anatomical therapeutic chemical; ATMP=advanced therapy medicinal product; SGLT=sodium-glucose co-transporter

Table 1.2: Administration and dosing of the technology

	Sotagliflozin	Dapagliflozin	Empagliflozin
Method of administration	Oral use The tablets should be taken once daily before the first meal of the day.	Oral use The tablets can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.	Oral use The tablets can be taken with or without food, swallowed whole with water. If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.
Doses	Sotagliflozin 200 mg: 10, 20, 30, 60, 90, 100, 180 film-coated tablets, and a multipack of 200 film-coated tablets (2 packs of 100 film-coated tablets) in blisters.	Dapagliflozin 10 mg: 14, 28 or 98 tablets in calendar blisters; 30 or 90 tablets in blisters. Dapagliflozin 5 mg: 14, 28 or 98 tablets in calendar blisters; 30 or 90 tablets in blisters.	Empagliflozin 10 mg and 25 mg: 7, 10, 14, 28, 30, 60, 70, 90, and 100 tablets in blisters.
Dosing frequency	The recommended dose according to the SPC for patients with T1D is 200 mg once daily before the first meal of the day. After at least three months, if additional glycaemic control is needed, in patients tolerating sotagliflozin 200 mg, the dose may be increased to 400 mg once daily.”	The recommended dose according to the SPC for patients with T2D is 10 mg daily. For patients with severe hepatic impairment, the recommended starting dose is 5 mg daily. The recommended dose according to the SPC for patients with T1D is 5 mg daily.	The recommended dose according to the SPC for patients with T2D is 10 mg daily. For patients with severe hepatic impairment, the recommended starting dose is 5 mg daily.
Standard length of a course of treatment	As long as required by the prescribing healthcare professional.	As long as required by the prescribing healthcare professional.	As long as required by the prescribing healthcare professional.
Dose adjustments	No dose adjustment is recommended.	No dose adjustment is recommended.	No dose adjustment is recommended.

Abbreviations: SPC=summary of product characteristics

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Joint Relative Effectiveness Assessment (REA) is to compare the clinical effectiveness and safety of sotagliflozin in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on EUnetHTA Partner requirements) are defined in the project scope below.

The assessment was based on a dossier submitted by the MAH Sanofi.

The scope of the assessment deviates from the scope described in the project plan as follows:

- Canagliflozin was excluded from the assessment because there are no ongoing or published phase III trials for canagliflozin regarding the indication for T1D;
- Divergences regarding study selection were solved through discussion and not a third reviewer as suggested by the project plan.

2.1 Objective

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

- This (rapid) relative assessment addresses the research question of whether sotagliflozin (Zynquista®) as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy, is more effective and/or safer than optimised insulin monotherapy alone, and to assess the relative effectiveness/safety of sotagliflozin compared to any SGLT2 inhibitor in this setting.

2.2 Scope

The scope of the assessment is presented in [Table 2.1](#) below.

Table 2.1. Scope of the assessment

Description	Project Scope
<p>Population</p>	<ul style="list-style-type: none"> • Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy.^{1,2} • T1D • ICD-10: E10.xx • MeSH terms: Diabetes Mellitus, Type 1 <p>¹ Inadequate blood glucose control as defined in the clinical trials should be compared to definitions in European guidelines and also with possible differences from different national guidelines highlighted. According to European guidelines, inadequate blood glucose control can be defined as an individualised target not met (in general >7% (53 mmol/mol) for HbA1c if not prevented by symptomatic hypoglycaemia) after an insulin titration period.</p> <p>² The insulin regimen used in the clinical trials (e.g., number of injections, type of insulin, number of international units per kg/day, use of continuous subcutaneous delivery (CSII) versus multiple daily injections (MDII; basal/bolus versus mixed insulin)) should be compared with European and relevant national guidelines with possible deviations highlighted.</p> <p>Subgroup analysis with respect to insulin regimen (add-on to MDII and add-on to CSII with type of CSII defined (which includes stand-alone or in conjunction with continuous glucose monitoring or flash glucose monitoring)).</p>
<p>Intervention</p>	<p>Sotagliflozin (200 mg or 400 mg daily) administered orally as an add-on to optimised insulin therapy.</p> <p>Sotagliflozin is a small molecule dual inhibitor of SGLT1 and SGLT2 that improves glycaemic and metabolic control.</p>
<p>Comparison</p>	<p>Sotagliflozin (200 mg or 400 mg) versus placebo.</p> <p>Sotagliflozin (200 mg or 400 mg) versus any SGLT2 inhibitor.</p> <p>Rationale: Comparators are chosen according to those listed in the evidence-based clinical guidelines [ESC 2013; NICE 2016; Royal College of Physicians 2008; Scottish Intercollegiate Guidelines Network, 2018; World Health Organization 2011], the recommendations from the relevant HTAs, and the EUnetHTA guidelines [2].</p>
<p>Outcomes</p>	<p>EFF and SAF domain</p> <p>Crucial endpoints:</p> <ul style="list-style-type: none"> • Microvascular/macrovascular complications if available, and if not (EFF): <ul style="list-style-type: none"> ▪ Surrogate endpoint HbA1c, measured over at least 26 weeks (EMA guideline 2012/2018): <ul style="list-style-type: none"> ▪ Absolute change from baseline ▪ Proportion of patients with HbA1c <53 mmol/mol (7%)* ▪ Proportion of patients with HbA1c <70 mmol/mol

	<ul style="list-style-type: none"> ▪ Net benefit (HbA1c <53 mmol/mol (<7%) and no episode of severe hypoglycaemia or diabetic ketoacidosis) <ul style="list-style-type: none"> • Mortality (EFF and SAF) • Health-related QoL (EFF)* <ul style="list-style-type: none"> ▪ Diabetes treatment satisfaction score change from baseline ▪ Disease-specific health-related QoL measurements ▪ EQ5D for generic health status • Hypoglycaemia (incidence and number, by severity [level 1, 2, 3])* (SAF) • Severe adverse events (incidence and number) (SAF) • Adverse events leading to discontinuation (incidence and number) (SAF) • DKA (incidence and number; definition and validation of DKA explained) (SAF) <p>Important endpoints:</p> <ul style="list-style-type: none"> • Change from baseline in body weight (EFF) • Change in cardiovascular risk factors (e.g., serum lipids and blood pressure) (EFF) • Change from baseline in fasting plasma glucose (EFF) • Change from baseline in postprandial plasma glucose (EFF) • Time in range (EFF) • Insulin change from baseline (basal, bolus, total dose (IU)/day) (EFF) • Most frequent adverse events <p>* Outcomes related to issues particularly emphasised by patient organisations.</p> <p>Classification of hypoglycaemia (26):</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center;">Level</th> <th style="text-align: center;">Glycaemic criteria</th> <th style="text-align: center;">Description</th> </tr> </thead> <tbody> <tr> <td>Hypoglycaemia alert value (level 1)</td> <td>≤ 70 mg/dL (3.9 mmol/L)</td> <td>Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy</td> </tr> <tr> <td>Clinically significant hypoglycaemia (level 2)</td> <td>< 54 mg/dL (3.0 mmol/L)</td> <td>Sufficiently low to indicate serious, clinically important hypoglycaemia</td> </tr> <tr> <td>Severe hypoglycaemia (level 3)</td> <td>No specific glucose threshold</td> <td>Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery</td> </tr> </tbody> </table> <p>Rationale: Outcomes are selected based on outcome availability defined by the study design of the relevant studies and on the recommendations from the relevant HTAs, clinical guidelines, and the EUnetHTA Guidelines on Clinical and Surrogate Endpoints and Safety. The result of the patient survey for this assessment will also be taken into account in the selection of relevant outcomes. In addition to appropriate statistical analysis, the clinical relevance of minor changes in outcome measures should be considered (e.g., the EMA has defined when a change in HbA1c is clinically relevant from a non-inferiority perspective). Outcomes should generally be clinically relevant and</p>	Level	Glycaemic criteria	Description	Hypoglycaemia alert value (level 1)	≤ 70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy	Clinically significant hypoglycaemia (level 2)	< 54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycaemia	Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
Level	Glycaemic criteria	Description											
Hypoglycaemia alert value (level 1)	≤ 70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy											
Clinically significant hypoglycaemia (level 2)	< 54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycaemia											
Severe hypoglycaemia (level 3)	No specific glucose threshold	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery											

	<p>applicable in suitable cost-effectiveness modelling, particularly for the ones for which treatment benefits are claimed. Outcomes should also be coupled and discussed in relation to treatment goals in available guidelines and an association/correlation between a surrogate outcome and a patient-relevant outcome measure should be discussed/described.</p>
<p>Study design</p>	<p>EFF domain:</p> <p>If suitable evidence syntheses (systematic reviews [SRs]/HTA reports) are available:</p> <ul style="list-style-type: none"> • evidence syntheses (SRs/HTA reports); and • primary studies (as described in next bullet) published after the last search date of the latest SR/HTA document. <p>If suitable evidence syntheses (SRs/HTA reports) are NOT available:</p> <ul style="list-style-type: none"> • randomised controlled trials. <p>SAF domain:</p> <p>If suitable evidence syntheses (SRs/HTA reports) are available:</p> <ul style="list-style-type: none"> • evidence syntheses (SRs/HTA reports); and • primary studies (as described in next bullet) published after the last search date of the latest SR/HTA document. <p>If suitable evidence syntheses (SRs/HTA reports) are NOT available:</p> <ul style="list-style-type: none"> • Randomised controlled trials; • Non-randomised controlled trials; • Observational studies. <p>Only English language studies will be included.</p>

3 METHODS

The assessment is based on the data and analyses included in the submission dossier prepared by the MAH. The completeness of data and analyses in the submission dossier was verified during the assessment. Furthermore, the data analysis and synthesis methods applied by the MAH were checked against the requirements of the submission dossier and applicable EUnetHTA Guidelines and evaluated with respect to scientific validity.

3.1 Information retrieval

The evidence base with regard to the drug under assessment provided by the MAH was reviewed by the authoring team ([Table 3.1](#)). Search strategies were checked for appropriateness, and the results of information retrieval included in the MAH's submission dossier were checked for completeness against a search of study registries and against the studies included in the regulatory assessment report. Further supplementary searches were conducted to check for possible incompleteness of the study pool.

Table 3.1. Summary of information retrieval and study selection

Elements	Details
List of studies submitted by MAH	inTandem 1 (NCT02384941) inTandem 2 (NCT02421510) inTandem 3 (NCT02531035) DEPICT-1 (NCT02268214) DEPICT-2 (NCT02460978) EASE-2 (NCT02414958) EASE-3 (NCT02580591)
Databases and trial registries searched	MEDLINE (PubMed), EMBASE (search via Ovid), the Cochrane Library (Wiley), clinicaltrials.gov, WHO (International Clinical Trials Registry Platform) and European Union Clinical Trials Register (EU CTR)
Search date	3 rd October 2017; first search 5 th October 2018; updated search 25 th March 2019, updated search
Keywords	T1D, sotagliflozin, SGLT1/2, SGLT2, dapagliflozin, empagliflozin, canagliflozin, metformin, pramlintide
Inclusion criteria	RCTs for sotagliflozin, SGLT2 inhibitors
Exclusion criteria	RCTs for other interventions than specified in the PICO(S) (metformin, pramlintide), study duration <16 weeks
Date restrictions	1 st January 1980 to 3 rd October 2017; first search 1 st August 2017 to 5 th October 2018; updated search
Other search limits or restrictions	Not applicable

The study pool of the assessment was compiled on the basis of the following information:

Company sources in the submission dossier:

- study list from MAH on sotagliflozin and SGLT2 inhibitors (last search on 5th October 2018);
- bibliographical databases (last search on 5th October 2018);
- trials registries (last search on 5th October 2018).

Check of completeness of the study pool:

- trial registries (last search on 5th October 2018).

Further supplementary searches were conducted to check for possible incompleteness of the study pool:

- search in MEDLINE (PubMed), EMBASE (search via Ovid), the Cochrane Library (Wiley), clinicaltrials.gov, WHO (International Clinical Trials Registry Platform), and European Union Clinical Trials Register (EU CTR) for studies on sotagliflozin and SGLT2 inhibitors (last search on 25th March 2019) (see complete search strategy section of the project plan).

The check identified no additional relevant studies.

For full details of the search strategy, we refer to the [appendix on the search strategy](#).

3.2 Data extraction

The assessment of clinical effectiveness (EFF) and safety (SAF) is based on the data presented in the material submitted by the MAH.

3.3 Risk of bias assessment

The quality rating tool developed by the Cochrane Collaboration (revised version 2.0; October 2018) (27) was used to assess the risk of bias in randomised trials. Risk of bias at the study level was assessed for six different domains:

- Method used to generate the sequence of randomisation (random sequence generation);
- Method used to mask the sequence of allocation to treatment (allocation concealment);
- Measures used to ensure the 'blindness' of the study with respect to treatment assignment (blinding of participants, medical personnel, and outcome assessors);
- Completeness of the data for each outcome considered (incomplete outcome data);
- Selective description of the results (selective outcome reporting);
- Other sources of bias (e.g., bias due to the early interruption of the study because of the benefits without an appropriate stopping rule, use of a non-validated measurement instrument, incorrect statistical analysis).

For each domain, two independent assessors judged the risk of bias ('low risk', 'some concerns', 'high risk', or 'unclear') on the basis of the information retrieved from the full text publications, the protocols, and the submission dossier. Discrepancies were discussed and aligned. The results of the risk of bias assessment are at both the study and the outcome level (split by self-reported outcomes and outcome assessor-reported outcomes).

3.4 Analyses of submitted data

The information in the submission dossier on the study design, methods, populations, endpoints, and results was evaluated. The results of this evaluation are presented and were used to identify relevant analyses and considered for the conclusions of the assessment report.

Subgroup analysis and other effect modifiers

During the assessment, the subgroup analyses examining potential effect modifiers presented in the submission dossier and the corresponding methods applied were evaluated.

Indirect comparisons

Network meta-analysis (NMA) was performed to compare sotagliflozin to empagliflozin and dapagliflozin. The full network diagram is shown in [Figure 3.1](#). This NMA was conducted on the entire population rather than the BMI ≥ 27 kg/m² subgroup due to a lack of information about this subgroup in a number of the comparator trials. Details of the subset of outcomes included in the NMA are listed in [Table 3.3](#).

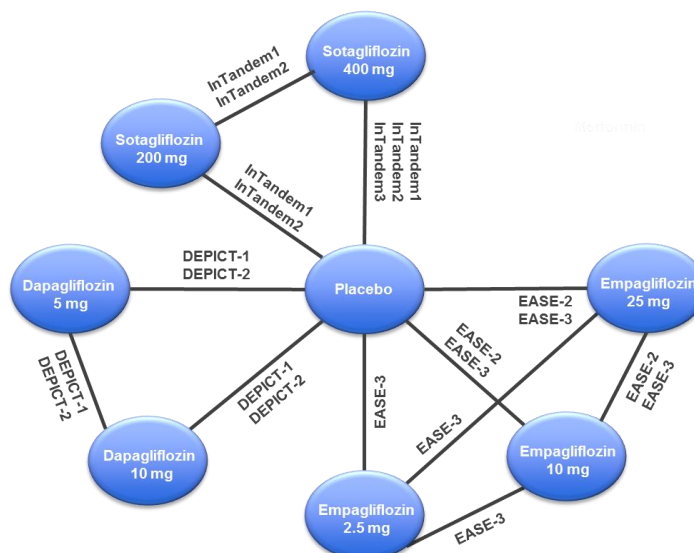


Figure 3.1. Master evidence network for the NMA. Source: applicant submission.

The NMA was conducted within a generalised linear model framework. The likelihood was modelled as normal, binomial, or Poisson for continuous, binary, or event-rate outcomes, respectively. For continuous outcomes, the link function was the identity function; for binary outcomes, the link function was the logit function; and for event rate outcomes, the link function was the log function.

The MAH highlighted that the NMA results should be interpreted with caution due to the presence of heterogeneity (degree of dissimilarity) between studies. The authors agreed that it is important to be mindful of heterogeneity when performing any NMA. However, based on the information presented by the MAH on this particular NMA, the authors believed that it was appropriate to perform an NMA for this network. The MAH also tested the results of the NMA for inconsistency (28) by evaluating the difference between the results of the direct and indirect comparisons in a closed loop. However, some of the closed loops had more than two arms from the same study, so no inconsistency should be expected from these loops.

The MAH provided the patient characteristics of the included studies ([Table 3.2](#)). The MAH stated that the contributing trials were similar in terms of mean age, gender distribution, mean blood pressure, disease duration, and BMI but varied in terms of mean HbA1c and MDII/CSII usage at baseline. However, no formal assessment of heterogeneity was included in the submission dossier. The authors therefore cannot conclude that these trials are substantially different in terms of HbA1c and MDII/CSII usage at baseline.

Table 3.2. Patient characteristics of the included studies. Source: applicant submission

Study name	Sample size	Mean age (years)	Female (%)	Mean BMI (kg/m ²)	Mean diabetes duration (years)	MDII (%) / CSII (%)	Mean SBP/DBP (mmHg)	BMI as inclusion criteria	Mean HbA1c at screening (%)	Mean HbA1c at baseline (%)
inTandem 1	793	46.1	51.7	29.7	24.4	40.4/59.6	120.1/76.1	NR	8.2	7.6
inTandem 2	782	41.2	48.1	27.8	18.4	74.3/25.7	123.1/76.6	NR	8.4	7.8
inTandem 3	1402	42.8	50.3	28.2	20.1	60.4/39.6	121.0/76.5	≥ 18.5	8.4	8.2
DE-PICT-1	778	42.5	52.1	28.3	20.3	63.0/37.0	NR	≥ 18.5	8.8	8.5
DE-PICT-2	813	42.7	56.0	27.6	19.3	66.1/33.9	NR	≥ 18.5	8.8	8.4
EASE-2	723	45.2	53.3	29.2	22.6	59.3/40.7	124.6/76.2	≥ 18.5	8.6	8.1
EASE-3	961	43.1	51.2	28.2	21.1	66.2/33.8	123.5/75.6	≥ 18.5	8.7	8.2

Abbreviations: BMI=body mass index; CSII=continuous subcutaneous insulin infusion; HbA1c=haemoglobin A1c; MDII=multiple daily insulin injections; NR=not reported; SBP=systolic blood pressure; DBP=diastolic blood pressure

Table 3.3. List of outcomes for the NMA. Source: applicant submission

Type of outcome	Outcome	Type of data or distribution	Information needed	Output statistics of NMA
Efficacy	HbA1c %, CFB	Continuous	Evaluable N, Mean/median and SD/SE/CI/p value	Mean difference (95% CrI)
Safety	Severe hypoglycaemia Any hypoglycaemia Diabetic ketoacidosis	Binomial	Evaluable N (safety set) with outcome (n)	Odds ratio (95% CrI)

Abbreviations: CFB=change from baseline; CI=confidence intervals; CrI=credible intervals; HbA1c=glycated haemoglobin A1c; NMA=network meta-analysis; SE=standard error; SD=standard deviation

The definition of hypoglycaemia reported across these studies is presented in [Table 3.4](#).

Table 3.4. Definition of hypoglycaemia reported across studies

Study name	Definition
inTandem1	Hypoglycaemic events (≤ 70 mg/dL): Investigator-reported and/or positively adjudicated hypoglycaemic events
inTandem2	
inTandem3	
DEPICT-1	Hypoglycaemic events (≤ 70 mg/dL): as defined by American Diabetic Association
DEPICT-2	
EASE-3	Sum of non-serious + serious hypoglycaemic events NOTE: The publication of EASE trials did not provide the proportion of patients with any hypoglycaemic event. Instead, investigator-reported symptomatic hypoglycaemic events with blood glucose < 54 mg/dL and/or severe hypoglycaemic events was provided. However, in the clinicaltrial.gov, the proportion of patients with serious and non-serious hypoglycaemia was reported. Hence, the proportion was assumed to be the sum of serious and non-serious AE.

An adjustment was made to the likelihood to correct for multi-arm trials as recommended in the NICE Decision Support Unit (28). The relative treatment effect between two interventions was expressed as mean differences with 95% credible intervals (CrIs) for continuous outcomes and as odds ratios with 95% CrIs for binary outcomes. With small trials with zero cells, the models were numerically unstable, so a value of “1” was added to the denominator and “0.5” to the numerator (28). A study could be removed from the analysis if it contained 0 events in all its arms.

The actual estimation was undertaken using Markov chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS 14. Code for the NMA was based on that recommended by the NICE Decision Support Unit (28). Vague prior distributions were used in all analyses for the treatment effects of interest as recommended in NICE Technical Support Document 2 (28).

The MAH analysed their data using a random effects (RE) model in the submission file. When conducting an NMA, the investigator must choose between a fixed effects (FE) model or a RE model. FE models assume that differences across trials do not impact treatment effects and that variation in the outcomes reported are due to differences between patients within a trial. RE models assume that variations in reported outcomes are due both to differences between patients within a trial and differences across trials. The authors are concerned about the MAH’s decision to present RE models only, without presenting the results from the FE models or presenting additional information on how this decision was made.

All chains were run for 200,000 iterations after burn-in (20,000) to obtain satisfactory convergence of the posterior distributions. Three MCMC chains were simulated starting from different initial values of selected unknown parameters. A thinning parameter ($thin \geq 10$) was set to ensure independence between simulations. Convergence was assessed by visualising the chain histories of relevant parameters against the iteration number, overlapping histories, and also Brooks-Gelman-Rubin (BGR) statistics. Auto-correlation plots were used to assess correlations between simulations. The accuracy of the posterior estimates was assessed by the Monte Carlo error; <5% of the sample standard deviation for each parameter of interest was deemed acceptable. The authors noted that the iteration number was larger than the burn-in. Upon request from the authors, the MAH provided the BGR statistics (31, 32), which confirmed that the chains had converged.

The MAH chose to only present results for HbA1c, hypoglycaemia, and DKA in the submission file. However, the authors believe that other outcomes are relevant to this assessment, and therefore, consider this submission to be incomplete without these additional outcomes in the NMA. For the crucial safety outcomes, only the NMAs for the proportion of patients experiencing an event are presented in this report. Additional NMAs examining the number of patients experiencing an event are excluded due to the similarity between the outcomes, as this outcome was reported in fewer trials so the NMAs would not be as informative. NMAs were carried out at 24 \pm 2 and 52 weeks. Given that more studies reported results at 24 \pm 2 weeks, the NMAs in this report focus on outcomes at 24 \pm 2 weeks. [Table 3.5](#) shows all reported outcomes in each trial at each time point.

Table 3.5. Summary of outcomes included in each trial at each timepoint. Source: applicant submission

Outcomes	inTandem1	inTandem2	inTandem3	DEPICT-1	DEPICT-2	EASE-2	EASE-3
Efficacy outcomes							
CFB HbA1c (%)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk
Net benefit (proportion of patients with HbA1c <7.0% and no episode of SH and episode of DKA)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	x	x
Proportion of patients at HbA1c target (<7%)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	52±2 wk	24±2 wk	x	x
CFB in time in range (%)	24±2 wk	24±2 wk	x	24±2 wk	24±2 wk	24±2 wk 52 wk	24±2 wk
CFB DDS2	24±2 wk 52 wk	24±2 wk 52 wk	x	x	x	x	x
CFB in DTSQ	24±2 wk	24±2 wk	x	x	x	x	x
CFB in EQ-5D-5L index score	52 wk	52 wk	x	x	x	x	x
CFB EQ-5D-5L VAS	52 wk	52 wk	x	x	x	x	x
Absolute CFB body weight (kg)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	x	24±2 wk 52 wk	24±2 wk
Percent CFB body weight	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	x	x
Absolute CFB in SBP (mm Hg)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	24±2 wk 52 wk	24±2 wk
Absolute CFB in DBP (mm Hg)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	24±2 wk 52 wk	24±2 wk
Absolute CFB in SBP in the subset of patients with SBP ≥ 130 mmHg at baseline (mmHg)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	52±2 wk ^s	x	x	x
Absolute CFB in FPG (mg/dL)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	52±2 wk (mmol/L)	x	24±2 wk 52 wk	24±2 wk
Absolute CFB in PPG (mg/dL)	24±2 wk	24±2 wk	x	x	x	x	x
Absolute CFB daily bolus insulin dose (IU/day)	24±2 wk	24±2 wk	24±2 wk	24±2 wk (% change)	x	24±2 wk 52 wk (IU/kg)	24±2 wk (IU/kg)
Absolute CFB daily basal insulin dose (IU/day)	24±2 wk	24±2 wk	24±2 wk	24±2 wk (% change)	x	24±2 wk 52 wk (IU/kg)	24±2 wk (IU/kg)
Absolute CFB total daily insulin dose (IU/day)	24±2 wk	24±2 wk	24±2 wk	24±2 wk	x	24±2 wk 52 wk (IU/kg)	24±2 wk (IU/kg)
Percent CFB total daily insulin dose (IU/day)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	24±2 wk (IU/kg)	24±2 wk (IU/kg)

Outcomes	inTandem1	inTandem2	inTandem3	DEPICT-1	DEPICT-2	EASE-2	EASE-3
Safety outcomes							
Total number of adverse events	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (52 wk)	24±2 wk
Total number of serious adverse events	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (52 wk)	24±2 wk
Total number of severe drug-related adverse events	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	x	x
Total number of adverse events leading to death	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk [§] 52 wk [§]	24±2 wk [§]	P (52 wk [§])	24±2 wk [§]
Total number of adverse events leading to study drug discontinuation	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (52 wk)	24±2 wk
Proportion of patients with any hypoglycaemia (≤ 70 mg/dL)	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	52 wk	24± 2 wk
Proportion of patients with documented blood glucose ≤ 55 mg/dL	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	P (24±2 wk 52 wk) [#]	24±2 wk [#]
Proportion of patients with SH*	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (24±2 wk 52 wk)	24±2 wk
Proportion of patients with DKA [^]	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (24±2 wk 52 wk)	24±2 wk
Event rate of any hypoglycaemia	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	x	x
Event rate of SH*	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (24±2 wk 52 wk)	24±2 wk
Event rate of DKA [^]	52 wk	52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	P (24±2 wk 52 wk)	24±2 wk
Most frequent adverse events	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x [°]	x [°]	x [°]	x [°]
CFB serum lipid LDL-C	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	x	x
CFB serum lipid HDL-C	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	x	x	x	x
Composite outcomes							
Proportion of patients with HbA1c reduction $\geq 0.5\%$ without severe hypoglycaemia	24±2 wk 52 wk	24±2 wk 52 wk	24±2 wk	24±2 wk 52 wk	24±2 wk	x	x

Not included in analysis; included in analysis

P: EASE-3 data from baseline to week 26 are presented for empagliflozin 2.5 mg from EASE-3, and pooled EASE-2 and EASE-3 data from baseline to week 52 are presented for empagliflozin 10 mg and empagliflozin 25 mg.

§ Seated SBP in patients with hypertension at baseline

* Positively adjudicated or as defined by the American Diabetic Association

Patient-reported symptomatic hypoglycaemic events with blood glucose, 54 mg/dL (totality of all reported events by patients)

° Not all adverse events (reported by $\geq 2\%$ / $\geq 5\%$ of patients) were presented by MedDRA SOC and PT

§ Reported as all-cause mortality, not adverse events leading to death

^ Positively adjudicated or definite

Abbreviations: CFB=change from baseline; DBP=diastolic blood pressure; DDS2=2-item Diabetes Distress Screening Scale; DKA=diabetic ketoacidosis; DTSQ=Diabetes Treatment Satisfaction Questionnaire; EQ-5D-5L=EuroQol Questionnaire 5 dimensions 5 level; FPG=fasting plasma glucose; HbA1c=glycated haemoglobin A1c; HDL-C=high-density lipoprotein; LDL-C=low-density lipoprotein; PPG=postprandial plasma glucose; PT=preferred term; SBP=systolic blood pressure; SH=severe hypoglycaemia; SOC=system organ class; VAS=visual analogue scale; wk: week

[Table 3.6](#) provides details of outcomes specified in the project plan for which an NMA could have been performed from a technical point of view but were not included as part of the submission either in the main document or the appendix. The MAH did not provide an explanation for why these outcomes were not analysed, which the authors believe is a limitation of the submission. Additional crucial and important endpoints detailed in the project plan were not feasible as these endpoints were not recorded in the EASE or DEPICT trials. We do not report the composite outcome of “proportion of patients with HbA1c reduction $\geq 0.5\%$ without severe hypoglycaemia”, as this was not included in the project plan.

Table 3.6. Outcomes specified in the project plan for which an NMA could have been performed from a technical point of view but were not included as part of the submission

Excluded outcome	Specified importance
Proportion of patients at HbA1c target (<7%)	Crucial
CFB in time in range	Crucial
Total number of adverse events	Crucial
Total number of serious adverse events	Crucial
Total number of adverse events leading to death	Crucial
Total number of adverse events leading to study drug discontinuation	Crucial
Proportion of patients with documented blood glucose ≤ 55 mg/dL	Crucial
Absolute CFB body weight (kg)	Important
Percent CFB body weight	Important
Absolute CFB in SBP (mmHg)	Important
Absolute CFB in DBP (mmHg)	Important
Absolute CFB in SBP in the subset of patients with SBP ≥ 130 mmHg at baseline (m Hg)	Important
Absolute CFB in FPG (mg/dL)	Important
Absolute CFB daily bolus insulin dose (IU/day)	Important
Absolute CFB daily basal insulin dose (IU/day)	Important
Absolute CFB total daily insulin dose (IU/day)	Important
Percent CFB total daily insulin dose (IU/day)	Important

Abbreviations: CFB=change from baseline; DBP=diastolic blood pressure; FPG=fasting plasma glucose; NMA=network meta-analysis; SBP=systolic blood pressure

Certainty of the evidence

For rating the quality of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was applied (1).

3.5 Patient involvement

For this Joint Assessment, an open call for patient input was published on the EUnetHTA website. This open call specifically asked patient organisations to answer the questions, as they are in a position to collect and present patients’ and caregivers’ views and experiences by engaging with a wide range of patients and their carers.

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

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

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. In the PICO(S) table ([Table 2.1](#)), the outcomes related to issues particularly emphasised by patient organisations are marked with asterisks (*).

4 RESULTS

4.1 Information retrieval

The MAH provided a systematic literature review of the evidence, which was critically assessed by the authors of this assessment. The following electronic databases were included in the MAH literature search: MEDLINE, EMBASE, Cochrane database (Cochrane Library interface), clinicaltrials.gov, WHO (International Clinical Trials Registry Platform metaregistry), and European (EU Clinical Trials Register) registries. The final search was performed on October 5th 2018. The search protocol was included as part of the submission file. Overall, the authors considered that the search followed EUnetHTA guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) statement. The search was conducted approximately five months before the start of the assessment. Therefore, the authors updated the search as indicated in the project plan on the 25th March 2019 and found no additional relevant study data.

4.2 Studies included in the assessment

The pivotal studies described in the dossier are three randomised placebo-controlled clinical trials (inTandem1-3) in which the efficacy and safety of sotagliflozin add-on to insulin were compared to the efficacy and safety of placebo add-on to insulin.

The licensed population represents a subgroup of the mITT population in the registration trials considered to have an improved risk-benefit profile, the *ES1 pool* (derived from inTandem1 and inTandem2). Efficacy and safety analyses for this subgroup of patients with a BMI ≥ 27 kg/m² at baseline were available for the main parameters (HbA1c, net benefit⁴, weight, SBP, safety) and for the residual group with baseline BMI < 27 kg/m². SAF-1 pool (52-week phase III studies): the primary safety pool used to describe common AEs and to assess potential risks associated with 200 mg and 400 mg sotagliflozin administration. The SAF-1 pool corresponds to efficacy ES1 pool.

Since there was no direct comparison available between sotagliflozin and the other comparators, the submitted material also provided indirect comparisons on the mITT population in the form of NMAs between sotagliflozin and dapagliflozin (DEPICT-1-2 trials), between sotagliflozin and empagliflozin (EASE-2-3 trials), and between different doses of sotagliflozin (lacking in the inTandem studies). In addition, canagliflozin was excluded from the assessment because there are no ongoing or published phase III trials for canagliflozin with respect to the indication including T1D. Indirect comparisons were performed with respect to the outcomes HbA1c, hypoglycaemia, and DKA. In the indirect comparison (NMA), data from the following studies were included:

- inTandem1 (sotagliflozin vs. placebo)
- inTandem2 (sotagliflozin vs. placebo)
- inTandem3 (sotagliflozin vs. placebo)
- DEPICT-1 (dapagliflozin vs. placebo)
- DEPICT-2 (dapagliflozin vs. placebo)
- EASE-2 (empagliflozin vs. placebo)
- EASE-3 (empagliflozin vs. placebo)

The studies listed in [Table 4.1](#) were included in the assessment.

Meta-analysis of pooled individual patient data for the BMI ≥ 27 kg/m² subgroup from the inTandem1-2 trials (ES1 pool) provided results for both safety (SAF) and efficacy (EFF) outcomes and these results are presented in the main body of this report. In addition, heterogeneity between studies (at the study level) was assessed in the GRADE assessment, and pooled direct meta-analyses estimates (meta-analyses at the study level) are provided in the footnotes as applicable.

For completeness, the GRADE assessment was also performed for the ES2 pool for the BMI ≥ 27 kg/m² subgroup (individual patient data from inTandem1-2 pooled with inTandem3) and for the

⁴ A composite consisting of the proportion of patients with HbA1c $< 7.0\%$ who had no episode of severe hypoglycaemia and no episode of diabetic ketoacidosis (DKA) at week 24

mITT populations (ES1 and ES2 pool; 400 mg sotagliflozin), including meta-analyses of pooled individual patient data and pooled direct meta-analyses estimates in the footnotes. Due to their size, the GRADE evidence profiles (sotagliflozin 200 mg and 400 mg versus placebo) for the BMI ≥ 27 kg/m² subgroup are presented in [Table A3](#) and [Table A4](#) in [Appendix 3](#). The GRADE evidence profile for the mITT population (sotagliflozin 400 mg versus placebo) is presented in [Table A5](#) in [Appendix 3](#), including meta-analyses of pooled individual patient data, and the pooled direct meta-analyses estimates in the footnotes are also presented in [Appendix 3](#). The GRADE evidence profiles for dapagliflozin and empagliflozin are presented for the mITT population in [Appendix 3](#). Note that most studies include multiple doses, however we focus here on the highest dose in each study. Therefore the same dose for each treatment is not used for each endpoint.

Table 4.1. Study pool – list of relevant studies used for the assessment

Study reference/ID	Study category			
	Study included in marketing authorisation (yes/no)	Study included in assessment (yes/no)	Sponsored or third-party study ^a	Available documentation
inTandem 1 NCT02384941	Yes	Yes	Sponsored (Lexicon Pharmaceuticals)	Buse et al. (33)
inTandem 2 NCT02421510	Yes	Yes	Sponsored (Lexicon Pharmaceuticals)	Danne et al. (24)
inTandem 3 NCT02531035	Yes	No	Sponsored (Lexicon Pharmaceuticals)	Garg et al. (23)
DEPICT-1 NCT02268214	No	Yes	Sponsored	Dandona et al. (34)
DEPICT-2 NCT02460978	No	Yes	Sponsored	Mathieu et al. (35)
EASE-2 NCT02414958	No	Yes	Sponsored	Rosenstock et al. (36)
EASE-3 NCT02580591	No	Yes	Sponsored	Rosenstock et al. (36)

^a Study sponsored by the MAH or in which the MAH participated financially in some other way

4.3 Excluded studies

The core document presents studies from the ES1 pool (inTandem1-2).

[Table 4.2](#) lists the studies that were included in the submission dossier provided by the MAH but were excluded for further consideration for the direct comparison. However, inTandem3 is included in the indirect comparison.

Table 4.2. Excluded studies

Study reference/ID	Reason for non-consideration of the study
inTandem3	inTandem3 was excluded from the main body of the assessment, mainly because the study design did not include insulin optimization before randomization. The absolute difference in change of HbA1c from baseline may be different between inTandem3 versus inTandem1-2 in the separate groups (intervention and placebo) due to the differences in insulin optimization methods (larger changes in inTandem3 because HbA1c was higher at baseline).

	<p>In addition, inTandem3 had a shorter follow-up (24 weeks instead of 52 weeks), which is only valid for HbA1c according to the project plan and therefore does not include any other outcome measures (e.g., DKA).</p> <p>For completeness and the purposes of discussion, however, effect estimates and the quality of evidence are presented in the GRADE evidence profiles for the pooled inTandem1-3 studies (only relevant for sotagliflozin 400 mg, since the inTandem3 study only assessed the 400 mg dose) next to the pooled data from the relevant inTandem1-2 studies.</p>
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4.4 Characteristics of included studies

[Table 4.3](#) and [Table 4.4](#) describe the studies used for the assessment.

Description of individual studies

inTandem1 and inTandem2

These were phase III, double-blind, randomised, international multicentre studies of sotagliflozin (200 or 400 mg daily) as an add-on to insulin versus placebo as an add-on to insulin. Insulin therapy was optimised six weeks prior to randomisation and continued throughout the studies. The studies consisted of two double-blind periods: a 24-week treatment period (the primary endpoint assessment) followed by a 28-week double-blind extension. The studies included men and women ≥ 18 years of age with inadequately controlled T1D using either MDII or CSII for insulin delivery and with HbA1c 7.0-11.0% at screening. Patients with B-hydroxybutyrate (BHB) levels >0.6 mmol/L at screening were excluded. The primary endpoint was change in HbA1c capillary finger-stick blood (CFB) from baseline to week 24. The first secondary endpoint was net benefit. Other secondary outcomes included change from baseline to week 24 in body weight, bolus insulin dose, fasting plasma glucose (FPG), and scores on the Diabetes Treatment Satisfaction Questionnaire Status (DTSQ) and Diabetes Distress Screening Scale (DDS2). 793 and 782 patients were included in the trials in a 1:1:1 randomisation to either sotagliflozin 200 mg, sotagliflozin 400 mg, or placebo. The ES1 pool included 916 patients with BMI ≥ 27 kg/m² from the 52-week studies.

inTandem3

This was a phase III, double-blind, randomised, international multicentre study of sotagliflozin as an add-on to insulin versus placebo as an add-on to insulin. After a two-week, single-blind run-in period during which all patients received placebo, eligible patients were randomly assigned in a 1:1 ratio to receive either sotagliflozin 400 mg or placebo for 24 weeks. Insulin optimisation was not performed before randomization and, after randomisation, results of laboratory tests for HbA1c, FPG and urinary glucose levels were masked to trial staff. Insulin doses were optimized to FPG and PPG targets based on SMBG monitoring. Men and women aged ≥ 18 years who had had T1D for over one year were eligible for participation if they had been treated with insulin at a stable basal dose for at least two weeks before the screening visit, had an HbA1c of 7.0-11.0%, and a BMI ≥ 18.5 kg/m². All patients were required to perform blood glucose self-monitoring. Key exclusion criteria were severe hypoglycaemia or DKA during the previous month, two or more episodes of DKA during the previous six months, and an estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m² of body surface. The primary endpoint was net benefit. Secondary endpoints were change from baseline to week 24 in HbA1c CFB, body weight, SBP (at week 16), and bolus insulin dose. 1405 patients were included in the trial in a 1:1 randomisation to either sotagliflozin 400 mg or placebo.

This study was excluded from the assessment for the reasons stated in [Table 4.2](#) but is detailed here for completeness.

DEPICT-1 and DEPICT-2

These were phase III, double-blind, randomised, international multicentre studies of dapagliflozin (5 or 10 mg daily) as an add-on to insulin versus placebo as an add-on to insulin in inadequately controlled patients. The primary endpoint was change in HbA1c from baseline to week 24 and secondary endpoints included daily insulin dose, body weight, blood glucose level (continuous glucose

monitoring; CGM), blood glucose amplitude excursion, time in range, and subjects with HbA1c change $\geq 0.5\%$ without severe hypoglycaemia (SH).

EASE-2

This study was a phase III, double-blind, randomised, international multicentre study of empagliflozin (10 or 25 mg daily) as an add-on to insulin versus placebo as an add-on to insulin in 730 patients. The primary endpoint was change in HbA1c from baseline to week 26. Secondary endpoints included symptomatic hypoglycaemia, changes in body weight, time in range, glucose variability, changes in insulin dose, SBP, and DBP.

EASE-3

This study was a phase III, double-blind, randomised, international multicentre study of empagliflozin (2.5, 10, or 25 mg daily) as an add-on to insulin versus placebo as an add-on to insulin in 977 patients. The primary endpoint was change in HbA1c from baseline to week 26. Secondary endpoints included symptomatic hypoglycaemia, changes in body weight, changes in insulin dose, SBP, and DBP.

Table 4.3. Characteristics of the included studies

Study reference/ID	Study design	Patient population	Sotagliflozin (number of randomised patients)	Intervention (number of randomised patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
Direct comparison: sotagliflozin vs. placebo						
Buse et al. (33) (inTandem 1) NCT02384941	Phase III, double-blind, placebo-controlled, randomised, multicentre international (North America)	Inadequately controlled T1D. HbA1c $\geq 7.0\%$ and $\leq 11.0\%$.	Sotagliflozin add-on to insulin 200 mg (N=263) 400 mg (N=262) Subpopulation BMI ≥ 27 kg/m ² : 200 mg (N=170) 400 mg (N=175)	Placebo add-on to insulin (N=268) Subpopulation BMI ≥ 27 : Placebo add-on to insulin (N=174)	Study duration: 24-week treatment period followed by a 28-week extension. 30 days safety follow-up.	Primary endpoint: HbA1c CFB change from baseline to week 24. Secondary endpoints (in hierarchical order), CFB at week 24: Net benefit*, body weight, bolus insulin dose, FPG, DTSQ score, and DDS2 score. Other endpoints: SBP and DBP at week 12.
Danne et al. [24] (inTandem 2) Danne et al. (24) (inTandem 2) NCT02421510	Phase III, double-blind, placebo-controlled, randomised, multicentre international (Europe, Israel)	Inadequately controlled T1D. HbA1c $\geq 7.0\%$ and $\leq 11.0\%$.	Sotagliflozin add-on to insulin 200 mg (N=261) 400 mg (N=263) Subpopulation BMI ≥ 27 kg/m ² : 200 mg (N=135) 400 mg (N=138)	Placebo add-on to insulin (N=258) Subpopulation BMI ≥ 27 : Placebo add-on to insulin: (N=124)	Study duration: 24-week treatment period followed by a 28-week extension. 30 days safety follow-up.	Primary endpoint: HbA1c CFB change from baseline at week 24 Secondary endpoints (in hierarchical order), CFB at week 24: Net benefit*, body weight, bolus insulin dose, FPG, DTSQ score, and DDS2 score. Other endpoints: SBP at week 12.

Study reference/ID	Study design	Patient population	Sotagliflozin (number of randomised patients)	Intervention (number of randomised patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
Garg et al. (23) (inTandem 3) NCT02531035	Phase III, double-blind, placebo-controlled, randomised, multicentre, global	Inadequately controlled T1D. HbA1c $\geq 7.0\%$ and $\leq 11.0\%$.	Sotagliflozin add-on to insulin 400 mg (N=700) Subpopulation BMI ≥ 27 kg/m ² : 400 mg (N=379)	Placebo add-on to insulin (N=705) Subpopulation BMI ≥ 27 kg/m ² : Placebo add-on to insulin (N=370)	24-week treatment period. 30 days safety follow-up.	Primary endpoint: Net benefit* at week 24 Secondary endpoints (in hierarchical order): HbA1c CFB at week 24, body weight at week 24, SBP at week 16, and bolus insulin dose at week 24. Other endpoints: FPG CFB at week 24.
Additional studies used in indirect comparison: sotagliflozin vs. dapagliflozin						
Dandona et al. (34) (DEPICT-1) NCT02268214	Phase III, double-blind, placebo-controlled, randomised, multicentre international	Inadequately controlled T1D. HbA1c $\geq 7.5\%$ and $\leq 11.0\%$.	Dapagliflozin add-on to insulin 5 mg (N=277) 10 mg (N=296)	Placebo add-on to insulin (N=260)	24-week treatment period.	Primary endpoint: Change in HbA1c from baseline at week 24. Secondary endpoints: Change in total insulin dose from baseline at week 24, Change in body weight from baseline at week 24, Change in 24-hour mean CGM glucose from baseline at week 24, Change in 24-hour CGM amplitude of glycaemic excursion from baseline at week 24, Time in range from baseline at week 24, Subjects with HbA1C reduction from baseline to week 24 $\geq 0.5\%$ and without SH events.
Mathieu et al. (35) (DEPICT-2) NCT02460978	Phase III, double-blind, placebo-controlled, randomised, multicentre international	Inadequately controlled T1D. HbA1c $\geq 7.5\%$ and $\leq 11.0\%$ at	Dapagliflozin add-on to insulin 5 mg (N=271) 10 mg (N=270)	Placebo add-on to insulin (N=272)	24-week treatment period.	Primary endpoint: Change in HbA1c from baseline at week 24. Secondary endpoints:

Study reference/ID	Study design	Patient population	Sotagliflozin (number of randomised patients)	Intervention (number of randomised patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
						Change in total insulin dose from baseline at week 24, Change in body weight from baseline at week 24, Change in 24-hour mean CGM glucose from baseline at week 24, Change in 24-hour CGM amplitude of glycaemic excursion from baseline at week 24. Time in range from baseline at week 24. Subjects with HbA1c reduction from baseline to week 24 $\geq 0.5\%$ and without SH events.
Additional studies used in indirect comparison: sotagliflozin vs. empagliflozin						
Rosenstock et al. (EASE-2) NCT02414958	Phase III, double-blind, randomised, multicentre international	Inadequately controlled T1D. HbA1c $\geq 7.5\%$ and $\leq 10.0\%$ at randomisation.	Empagliflozin add-on to insulin 10 mg (N=243) 25 mg (N=244)	Placebo add-on to insulin (N=243)	26-week treatment period.	Primary endpoint: Change from baseline in HbA1c at week 26. Secondary endpoints: Symptomatic hypoglycaemia, body weight, time in range, glucose variability, daily insulin dose, SBP, DBP.
Rosenstock et al. (EASE-3) NCT02580591	Phase III, double-blind, randomised, multicentre international	Inadequately controlled T1D. HbA1c $\geq 7.5\%$ and $\leq 10.0\%$ at randomisation.	Empagliflozin add-on to insulin 2,5 mg (N=242) 10 mg (N=248) 25 mg (N=245)	Placebo add-on to insulin (N=242)	26-week treatment period.	Primary endpoint: Change from baseline in HbA1c at week 26. Secondary endpoint: Symptomatic hypoglycaemia, body weight, daily insulin dose, SBP, DBP.

Abbreviations: BMI=body mass index; CFB=capillary finger-stick blood; CGM=continuous glucose monitoring; DBP=diastolic blood pressure; DDS2=2-item Diabetes Distress Screening Scale; DTSQ(s)=Diabetes Treatment Satisfaction Questionnaire (status); FPG=fasting plasma glucose; HbA1c=glycated haemoglobin A1C; SBP=systolic blood pressure; SH=severe hypoglycaemia; T1D=type 1 diabetes.

*Net benefit = a composite consisting of the proportion of patients with HbA1c $< 7.0\%$ who had no episode of severe hypoglycaemia and no episode of diabetic ketoacidosis (DKA) at week 24.

Table 4.4. Characterisation of the interventions and comparators

Study reference / ID	Sotagliflozin	Placebo	Treatment characteristics e.g. pre-treatment, treatment during the run-in phase, concomitant/prohibited medications as required
inTandem1 and inTandem2	Sotagliflozin 200 mg once daily or Sotagliflozin 400 mg once daily	Placebo once daily	6-week insulin optimisation before randomisation. Bolus insulin was reduced by 30% for the first meal after the first dose of study medication. Thereafter and throughout the 52-week study, investigators adjusted insulin doses according to self-monitoring blood glucose (SMBG) results, and the independent data monitoring committee (IDMC) evaluated the doses to week 24. HbA1c and FPG results were masked to study staff from the start of the six-week lead-in through week 24 (after week 12, HbA1c values $>11\%$ were unmasked to allow appropriate intervention). After week 24, HbA1c and FPG values were unmasked to investigators. From baseline to week 12, antihypertensive treatment was not adjusted unless required for patient safety.

[Table 4.5](#) shows the baseline characteristics of the patients in the studies included (ES1 pool BMI ≥ 27 kg/m²).

Table 4.5. Baseline characteristics of ES1 pool BMI ≥ 27 kg/m² (from mITT population)

Characteristics	Placebo (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
ES1 pool BMI ≥ 27 kg/m ² (from mITT)	N=298	N=305	N=313
Age in years, mean (SD)	43.3 (12.62)	45.9 (12.72)	45.5 (11.98)
Female sex, N (%)	143 (48.0)	148 (48.5)	159 (50.8)
Race ¹ white, N (%)	283 (95.0)	280 (91.8)	293 (93.6)
Duration of diabetes (years), N (%)			
<20	138 (46.3)	134 (43.9)	154 (49.2)
≥ 20 to <40	133 (44.6)	140 (45.9)	129 (41.2)
≥ 40	27 (9.1)	31 (10.2)	30 (9.6)
Body weight in kg, mean (SD)	94.20 (15.29)	94.68 (15.41)	93.66 (16.15)
BMI (kg/m ²), mean (SD)	32.03 (4.24)	32.49 (4.36)	31.96 (4.04)
Insulin delivery method ² , CSII, N (%)	138 (46.3)	140 (45.9)	147 (47.0)
Total daily insulin dose (IU/day), N, mean (SD)	N=298, 77.89 (41.52)	N=305, 76.08 (41.32)	N=313, 72.15 (37.22)
Bolus insulin dose (IU/day), mean (SD)	38.97 (27.11)	36.82 (23.91)	35.76 (24.53)

Characteristics	Placebo (N=298)	Sotagliflozin 200 mg (N=305)	Sotagliflozin 400 mg (N=313)
ES1 pool BMI ≥ 27 kg/m ² (from mITT)	N=298	N=305	N=313
Basal insulin dose (IU/day), mean (SD)	38.92 (19.41)	39.26(23.12)	36.35 (18.11)
HbA1c (%), mean (SD)	7.62 (0.76)	7.72 (0.75)	7.63 (0.75)
Baseline FPG (mg/dL), mean (SD)	157.33 (66.25)	163.46 (72.32)	156.33 (67.56)
SBP (mmHg), mean (SD)	124.3 (14.24)	124.6 (15.15)	123.6 (14.42)
SBP ≥ 130 mmHg ³ , n (%)	99 (33.2)	101 (33.1)	108 (34.5)
DBP (mm Hg), mean (SD)	78.0 (8.21)	79.1 (9.53)	77.8 (8.14)
2-hour PPG ⁴ (mg/dL), N, mean (SD)	N=58, 224.67 (81.38)	N=59, 213.68 (96.95)	N=65, 208.92 (82.84)
DTSQ score, mean (SD)	N=298, 28.7 (5.74)	N=305, 28.4 (5.15)	N=313, 28.8 (4.89)
DDS2 score, mean (SD)	N=298, 5.1 (2.25)	N=305, 5.4 (2.03)	N=313, 5.1 (2.14)
Time in range (≥ 70 to ≤ 180 mg/dL), (%)	N=58, 50.683 (14.55)	N=59, 52.155 (52.46)	N=65, 50.317 (50.80)

Abbreviations: BMI=body mass index; CSII=continuous subcutaneous insulin infusion; DBP=diastolic blood pressure; DDS=Diabetes Distress Screening Scale; DTSQ=Diabetes Treatment Satisfaction Questionnaire; FPG=fasting plasma glucose; PPG=postprandial glucose; SBP=systolic blood pressure; SD=standard deviation.

1: Only the most frequent category was presented

2: Only the category CSII was presented, all other patients were in category non-CSII

3: Only the category SBP ≥ 130 mm Hg was presented

4: 2hr-PPG was evaluated only in the CGM population in studies inTandem1 and inTandem2

4.5 Outcomes included

To assess clinical effectiveness, endpoints derived from pooled inTandem1-2 trial data for the specific subgroup with BMI ≥ 27 kg/m² were used, i.e., the ES1 pool subgroup corresponding to the approved indication. Of the three pivotal inTandem trials, inTandem1-2 were the most homogenous, and pooled data from these studies were thus deemed most relevant for assessment. Furthermore, 52-week endpoints were considered most relevant as this provided the most relevant estimate of the long-term effect of the continuous use of a possibly lifelong add-on therapy in patients with T1D.

Since the final approved indication of sotagliflozin only included patients with BMI ≥ 27 kg/m², the MAH performed additional post-hoc analysis of outcomes for this subgroup since this was not part of the initial RCTs. The results of this analysis included the main endpoints of relevance for this assessment, which are presented in this assessment report. Outcomes for the mITT population for the ES1 pool at both 24 and 52 weeks are presented in [Table 4.6](#).

Table 4.6. Outcomes for mITT population ES1 and SAF-1 pool BMI ≥ 27 kg/m²

Outcome	Timepoint	Sotagliflozin 200 mg N, LS Mean (SE)	Sotagliflozin 400 mg N, LS Mean (SE)	Insulin alone (placebo) N, LS Mean (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
					LSM (95% CI), p-value	LSM (95% CI), p-value
HbA1c	24 weeks	N=305, -0.43 (0.034)	N=313, -0.50 (0.034)	N=298, -0.04 (0.034)	-0.39 (-0.48 to -0.30), <0.001	-0.45 (-0.54 to -0.36), <0.001
	52 weeks	N=305, -0.24 (0.041)	N=313, -0.38 (0.040)	N=298, -0.00 (0.042)	-0.24 (-0.35 to -0.13), <0.001	-0.38 (-0.49 to -0.27), <0.001
Net benefit (mITT pool)	24 weeks	N=170/524 (32.4%)	N=199/525 (37.9)	N=97/526 (18.4)	14.0 (8.80 to 19.20), <0.001	19.5 (14.15 to 24.77), <0.001
	52 weeks	N=136/524 (26.0)	N=155/525 (29.5)	N=88/526 (16.7)	9.2 (4.30 to 14.15), <0.001	12.8 (7.75 to 17.83), <0.001
HbA1c < 7% (mITT pool)	24 weeks	N=184/524 (35.1)	N=212/525 (40.4)	N=100/526 (19.0)	-	-
	52 weeks	N=150/524 (28.6)	N=166/525 (31.6)	N=96/526 (18.3)	-	-
Serum lipids – LDL-C (mITT pool)	24 weeks	N=482, 4.1 (22.23)*	N=487, 5.5 (23.59)*	N=479, 3.0 (22.79)*	-	-
	52 weeks	N=390, 5.0 (21.60)*	N=380, 6.1 (25.06)*	N=375, 3.3 (24.50)*	-	-
DTSQ	24 weeks	N=305, 2.3 (0.26)	N=313, 2.2 (0.26)	N=298, -0.3 (0.27)	2.6 (1.9 to 3.3), <0.001	2.6 (1.9 to 3.3), <0.001
	52 weeks	-	-	-	-	-
DDS2	24 weeks	N=305; -0.5 (0.10)	N=313, -0.5 (0.10)	N=298, 0.1 (0.10)	-0.6 (-0.9 to -0.3), <0.001	-0.7 (-0.9 to -0.4), <0.001
	52 weeks	-	-	-	-	-
Time in range**	24 weeks	N=59, 6.254 (2.20)	N=65, 13.133 (2.0244)	N=58, -1.917 (2.25)	8.171 (2.296 to 14.046), 0.007	15.051 (9.403 to 20.699), <0.001
	52 weeks	-	-	-	-	-
FPG	24 weeks	N=305, -9.3 (3.33)	N=313, -18.6 (3.28)	N=298, 6.4 (3.36)	-15.7 (-24.7 to -6.7), <0.001	-25.0 (-33.9 to -16.1), <0.001
	52 weeks	-	-	-	-	-
PPG**	24 weeks	N=45, -36.8 (11.72)	N=57, -39.5 (10.72)	N=46, -17.7 (11.05)	-19.0 (-48.1 to 10.1), 0.20	-21.7 (-49.3 to 5.8), 0.12
	52 weeks	-	-	-	-	-
Body weight	24 weeks	N=305, -1.93 (0.20)	N=313, -2.98 (0.19)	N=298, 0.34 (0.20)	-2.27 (-2.81 to -1.74), <0.001	-3.32 (-3.85 to -2.79), <0.001
	52 weeks	N=305, -2.16 (0.25)	N=313, -3.61 (0.25)	N=298, 0.85 (0.26)	-3.01 (-3.71 to -2.31), <0.001	-4.46 (-5.15 to -3.76), <0.001
SBP	24 weeks	N=305, -2.9 (0.64)	N=313, -4.0 (0.64)	N=298, -1.6 (0.65)	-1.3 (-3.0 to 0.4), 0.13	-2.5 (-4.2 to -0.8), 0.005
	52 weeks	N=305, -1.7 (0.66)	N=313, -3.2 (0.65)	N=298, 0.4 (0.67)	-2.1 (-3.9 to -0.4), 0.018	-3.6 (-5.3 to -1.9), <0.001
SBP (in patients with SBP ≥ 130 mmHg at baseline)	24 weeks	N=101, -10.0 (1.29)	N=108, -10.1 (1.24)	N=99, -7.6 (1.29)	-2.4 (-5.8 to 1.1), 0.18	-2.5 (-5.8 to 0.8), 0.14
	52 weeks	-	-	-	-	-
Bolus insulin	24 weeks	N=305, -3.89 (0.72)	N=313, -5.91 (0.71)	N=298, -1.86 (0.72)	-2.02 (-3.92 to -0.12), 0.037	-4.05 (-5.93 to -2.17), <0.001
	52 weeks	-	-	-	-	-
Basal insulin	24 weeks	N=305, -0.14 (0.45)	N=313, -1.14 (0.45)	N=298, 1.57 (0.46)	-1.72 (-2.93 to -0.50), 0.006	-2.71 (-3.92 to -1.51), <0.001
	52 weeks	-	-	-	-	-

Outcome	Timepoint	Sotagliflozin 200 mg N, LS Mean (SE)	Sotagliflozin 400 mg N, LS Mean (SE)	Insulin alone (placebo) N, LS Mean (SE)	Sotagliflozin 200 mg vs. insulin alone (placebo)	Sotagliflozin 400 mg vs. insulin alone (placebo)
					LSM (95% CI), p-value	LSM (95% CI), p-value
Total insulin	24 weeks	N=305, -3.82 (0.90)	N=313, -7.01 (0.88)	N=298, -0.39 (0.91)	-3.43 (-5.82 to -1.04), 0.005	-6.62 (-8.99 to -4.25), <0.001
	52 weeks	-	-	-	-	-
Hypoglycaemia (≤55 mg/dL, ≤3.0 mmol/L)	24 weeks	-	-	-	-	-
	52 weeks	N, events per subject per year and Event rate (95% CI) N=305, 13.41 13.75 (12.12 to 15.37)	N, events per subject per year and Event rate (95% CI) N=313, 14.45 14.57 (12.88 to 16.6)	N, events per subject per year and Event rate (95% CI) N=298, 17.87 17.99 (15.86 to 20.13)	-4.25 (-6.93 to -1.57), 0.0019	-3.42 (-6.14 to -0.7), 0.0138
EAIR of severe hypoglycaemia (Positively adjudicated)	24 weeks	-	-	-	-	-
	52 weeks	N, events per subject per year and Event rate (95% CI) N=305, 13 (4.3) 46.51 (21.23 to 71.80)	N, events per subject per year and Event rate (95% CI) N=313, 12 (3.8) 41.06 (17.83 to 64.29)	N, events per subject per year and Event rate (95% CI) N=298, 22 (7.4) 81.03 (47.17 to 114.90)	The risk diff of event rates: -34.52 (-76.78 to 7.74) The relative risk of event rates: 0.57 (0.28 to 1.14)	The risk diff of event rates: -39.98 (-81.04 to 1.09) The relative risk of event rates: 0.51 (0.24 to 1.02)
EAIR of DKA (positively adjudicated)	24 weeks	-	-	-	-	-
	52 weeks	N, events per subject per year and Event rate (95% CI) N=305, 8 (2.6) 28.62 (8.79 to 48.46)	N, events per subject per year and Event rate (95% CI) N=313, 11 (3.5) 37.64 (15.39 to 59.88)	N, events per subject per year and Event rate (95% CI) N=298, 1 (0.3) 3.68 (0.00 to 10.90)	The risk diff of event rates: 24.94 (3.83 to 46.05) The relative risk of event rates: 7.77 (1.24 to 173.82)	The risk diff of event rates: 33.95 (10.57 to 57.34) The relative risk of event rates: 10.22 (1.74 to 221.94)

*Standard deviation, ** Data is based on CGM sub study.

Abbreviations: DBP=diastolic blood pressure; DDS=Diabetes Distress Screening Scale; DKA=diabetic ketoacidosis; DTSQ=Diabetes Treatment Satisfaction Questionnaire; EAIR=exposure-adjusted incidence rate; FPG=fasting plasma glucose; PPG=postprandial glucose; SBP=systolic blood pressure; SE=standard error

4.6 Risk of bias

[Table 4.7](#) describes the risk of bias at the study level stratified by two main outcome groups (outcomes relating to a change from baseline versus other outcomes). Risk of bias at the outcome level (split by self-reported [subjective] outcomes and assessor-reported [objective] outcomes) is included in [Table A3](#) and [Table A4](#).

Table 4.7. Risk of bias in randomised studies

Study reference/ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)*	Blinding of outcome assessment (detection bias)**	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other potential sources of bias	Risk of bias – study level
<i>Change from baseline (CFB) HbA1c</i>									
Garg 2017 (23) (inTandem3)	L ¹	L ¹	L ²	U ³	L ⁴	H ⁵	L ⁷	L ¹²	H
Buse 2018 (33) (inTandem2)	L ¹	L ¹	L ²	U ³	L ⁴	H ⁵	L ⁷	L ¹²	H
Danne 2018 (24) (inTandem1)	L ¹	L ¹	L ²	U ³	L ⁴	H ⁵	L ⁷	L ¹²	H
Dandona 2017 / 2018 (34) (DEPICT-1)	L ⁶	L ⁶	L ²	U ³	L ⁴	H ⁵	L ⁷	L ¹²	H
Mathieu 2018 (35) (DEPICT-2)	L ⁸	L ⁸	L ²	U ³	L ⁴	H ⁵	L	L ¹²	H
Rosenstock 2018 (36) (EASE trials)	L ⁹	L ⁹	L ²	U ^{3,10}	L ⁴	L ⁵	L	L ¹²	L
<i>Other outcome measures</i>									
Garg 2017 (23) (inTandem3)	L ¹	L ¹	L ²	U ³	L ⁴	L ⁵	L ⁷	L ¹²	L
Buse 2018 (33) (inTandem2)	L ¹	L ¹	L ²	U ³	L ⁴	L ⁵	L ⁷	L ¹²	L
Danne 2018 (24) (inTandem1)	L ¹	L ¹	L ²	U ³	L ⁴	L ⁵	L ⁷	L ¹²	L
Dandona 2017 / 2018 (34) (DEPICT-1)	L ⁶	L ⁶	L ²	U ³	L ⁴	L ⁵	L ⁷	L ¹²	L
Mathieu 2018 (35) (DEPICT-2)	L ⁸	L ⁸	L ²	U ³	L ⁴	L ⁵	L	L ¹²	L
Rosenstock 2018 (36) (EASE trials)	L ⁹	L ⁹	L ²	U ^{3,10}	L ⁴	L ¹¹	L	L ¹²	L
Footnotes: H: high risk; L: low risk; U: unclear risk; NA: not applicable									

* For self-reported outcomes including quality of life (e.g. DTSQ/EQ-5D), symptomatic documented hypoglycaemia

** For outcome assessor reported outcomes

1. For the InTandem trials, an interactive voice/web response system (IXRS) system was used to generate the random sequence and for allocation concealment.(37-39)

2. Blinding of trial staff and participants took place (during the first 24 weeks and also during the 24-28-week extension periods if applicable). Sotagliflozin and SGLT2 inhibitors are associated with specific side-effects (glycosuria effect), which may have compromised blinding. However, there was no evidence for a deviation from the intended intervention arising because of the experimental context (no relevant differences between study groups in loss-to-follow-up for reasons other than adverse events). Therefore, there was a low risk of bias in this domain.

3. Sotagliflozin and SGLT2 inhibitors are associated with specific side-effects (glycosuria effect), which may have compromised blinding of the participants. The outcome assessment of self-reported outcomes including DTSQ or symptomatic hypoglycaemia may have therefore been influenced, but not to a large extent since the incidence of polyuria was low in the studies. Therefore, there are some limited concerns about bias for these outcome measures.

4. In the sotagliflozin studies (inTandem1-3), an independent clinical endpoint committee, whose members were unaware of the treatment assignments, adjudicated events of special interest including severe hypoglycaemia, diabetic ketoacidosis, major adverse cardiovascular events, drug-induced liver injury, and death. An independent data and safety monitoring committee reviewed adverse events. Furthermore, in the Garg 2017 study (23), glycated haemoglobin and fasting plasma and urinary glucose (relevant because of the glycosuria effect of sotagliflozin) levels were masked to trial staff after randomisation. From week 16 until the end of the trial, investigators were informed about glycated haemoglobin levels higher than 11.0% so that necessary changes could be implemented.

In the Buse 2018 / Danne 2018 studies (24, 33), an independent insulin dose monitoring committee (IDMC) comprising diabetologists and certified diabetes educators blindly reviewed insulin titration decisions from the start of insulin optimisation (six weeks before baseline) through week 24 to determine whether insulin adjustments were consistent with self-monitoring of blood glucose (SMBG) patterns.

In the dapagliflozin studies (DEPICT-1/2), an independent blinded DKA adjudication committee adjudicated all potential DKA events. An external data monitoring committee periodically assessed all data for hypoglycaemia, DKA, laboratory measurements, and safety findings.

In the empagliflozin studies (EASE-2/3), adjudication of cardiovascular events, severe hypoglycaemia, DKA, and hepatic events was performed by masked, independent clinical event committees. Trial progress and safety were assessed by an unmasked and independent data monitoring committee. However, during the insulin intensification pre-treatment phase and throughout the entire duration of randomised treatment, investigators were unblinded to glycaemic markers (e.g., fasting plasma glucose, HbA1c, etc.), and could freely adjust the insulin regimen according to their clinical discretion and based on local guidelines to achieve the best standard of care.

5. A substantial number of patients were excluded from analysis in the mITT for HbA1c mean change from baseline (CFB) analyses. When queried by the authors, the MAH responded that either the value at baseline or the value at follow-up was unavailable for all patients but did not provide an explanation for these missings. This is also the case for dapagliflozin trials. In cases of missing data, imputation methods were used, but these results have not been published (at least in the paper/supplementary file). The non-responder imputation was used to assign a failure status to all binary endpoints with missing data at week 24 and, for continuous variables, mixed model repeated measures statistics were generated to summarise treatment effects under an assumption of missing at random; the latter was checked by performing sensitivity analyses based on multiple imputation methods. Notwithstanding the analyses that were performed, uncertainty remained with regards to the relatively high number of missings. Since the BMI subgroup was extracted from these study bases, the authors assumed that bias arising from this also applied to the BMI subgroup analyses. The risk of bias has therefore been set to high for sotagliflozin studies for all outcomes that include a change from baseline and similarly for dapagliflozin studies for these outcomes in the NMA. For all other outcomes (i.e., not depicting a change from baseline) and for change from baseline analyses in the empagliflozin study, there is almost no missing data and therefore the risk of bias has been set to low.

6. Random sequence generation and allocation concealment by an interactive voice response system. 55 patients were randomly assigned before discovery of an error with the IVRS used for randomisation (incorrectly and non-randomly allocated to only dapagliflozin treatment groups). These patients have not been included in the efficacy analysis set. Therefore, a low risk of bias was assigned.

7. The sensitivity analyses for robustness of effects by missing data analyses have not been published (appendices not retrievable). However, we incorporated this limitation under attrition bias.

8. Random sequence generation and allocation concealment by an interactive voice/web response system.

9. The randomisation of patients to the treatment groups was performed via IRT. The randomisation list was generated using a validated system, which involves a pseudorandom number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment was both reproducible and non-predictable.

10. Includes patient-reported symptomatic hypoglycaemic events (besides investigator reported).

11. The primary efficacy analysis included on-treatment data only as observed cases (OC) in the full analysis set (FAS), including all treated patients with baseline and on-treatment HbA1c measurements. This analysis is not according to the

mITT principle. However, an mITT (including all treated patients with baseline and post-randomisation HbA1c measurements (93-96-95% of the randomised participants)) analysis was in line with the FAS analysis (results reported in supplementary file of the publication). No imputation of missing data was performed. However, the proportion of missing data was low and similar between intervention and control groups. Therefore, we consider this a low risk of bias in this domain.

12. The BMI group of ≥ 27 kg/m², for which sotagliflozin received market authorisation, is a post-hoc subgroup analysis from the mITT populations of the RCTs. This subgroup arises from RCTs with a low risk of bias. We decided not to further downgrade for risk of bias because of the post-hoc subgroup analysis, since baseline variables of this subgroup were similar between the intervention and placebo groups and a pre-specified subgroup analysis by BMI ≥ 25 kg/m² versus < 25 kg/m², which was stratified for at randomisation in inTandem3, showed similar patterns for relative effects. Although every study was industry sponsored, we did not consider this a high risk of bias.

4.7 External validity

The external validity of the included trials was assessed using EUnetHTA guidelines on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals considering the following elements: population, intervention, comparator, outcomes, and setting (PICO(S)) [37].

All PICO(S) elements generally have validity in clinical practice; most importantly, the population is identifiable in practice and the outcomes are of real importance to patients. Patient organisations particularly emphasised hypoglycaemia, QoL, and HbA1c-target achievement (captured by the net benefit outcome) as relevant outcomes. Furthermore, despite the absence of hard endpoints for cardiovascular complications, HbA1c is an established surrogate measure that correlates with diabetic complications. Some specific comments on external validity for some elements of the PICO(S) are as follows:

Population

The population was largely clinically relevant but possibly included some patients that would not receive add-on therapy to insulin in a real clinical context, e.g., patients with HbA1c < 53 mmol/mol ($< 7.0\%$) at randomisation. However, most included patients were relevant, and additional post-hoc analysis focused on the relevant subgroup.

Intervention

The intervention probably reflected the doses used in clinical practice. Since the use of sotagliflozin is associated with a dose-dependent occurrence of DKA, there is a possibility that the lower dose will be mostly used in clinical practice.

Comparators

The comparators of the included RCTs (inTandem1-3) were relevant considering that no other approved add-on to insulin therapy was available at the time of study design or when the study was conducted. The indirect comparison with SGLT2 inhibitors covered alternative and similar treatments that might be used in clinical practice and might be approved for the same indication in the future.

Outcomes

For comparison with placebo, endpoints were reported at 24 weeks (inTandem1-3) and a follow-up at 52 weeks (inTandem1-2). Endpoints for one year of treatment were considered most relevant, as this gave the most relevant estimate of the long-term effect of the continuous use of a possibly lifelong add-on therapy in patients with T1D. The 24-week time was also valuable for estimating possible time-dependence in effectiveness. Therefore, endpoints derived from pooled trial data with 52-week time points (inTandem1-2) had the highest external validity and were mainly considered in the assessment.

Although a 52-week follow-up would have been preferable for the NMA, since three out of eight studies (inTandem-3, DEPICT-2, EASE-3) were only of 24 \pm 2 week duration, an NMA assessing this time point is likely to be more informative. The NMA compared the mITT group, which includes patients outside the licensed indication.

Setting

Since sotagliflozin is approved for restricted medical prescription and also requires ketone self-monitoring, its use in clinical practice will probably be well monitored and to some extent be used in a controlled context more similar to the clinical trial setting than normal. This might also result in better control of side-effects. From this point of view, the external validity of the study results was strengthened.

4.8 Results on clinical effectiveness and safety

Clinical effectiveness, direct comparison

Crucial surrogate endpoints for type 1 diabetes-related micro/macrovacular complications

HbA1c and net benefit

Sotagliflozin add-on to insulin significantly decreased HbA1c relative to placebo at 24 weeks. Based on pooled data from inTandem1-2 (BMI ≥ 27 kg/m²), the change in HbA1c at 24 weeks was -0.39% for 200 mg and -0.45% for 400 mg sotagliflozin. The effect appeared to be slightly attenuated, but not diminished, after one year (-0.24% for 200 mg and -0.38% for 400 mg sotagliflozin; low certainty of evidence, [Table A3](#) and [Table A4](#)). The effect was largely consistent throughout different subgroups.

The proportion of patients experiencing a net benefit (achievement of HbA1c $< 7\%$ without DKA or SH) was increased at 24 weeks with sotagliflozin compared to placebo: 14% for 200 mg and 19.5% for 400 mg sotagliflozin based on analysis of pooled data from all patients in inTandem1-2 (mITT, also including patients with BMI < 27 kg/m²; analysis of the subgroup with BMI ≥ 27 kg/m² in inTandem1-2 was not provided by the MAH). At 52 weeks, these numbers slightly decreased to 9.2% for 200 mg and to 12.8% for 400 mg sotagliflozin. The main contributing factor to the net benefit was the proportion of patients improving their HbA1c levels with sotagliflozin: 35% of patients taking 200 mg and 40% of patients taking 400 mg sotagliflozin reached an HbA1c $< 7\%$ compared to 19% for placebo at 24 weeks (mITT, also including patients with BMI < 27 kg/m²; analysis of the subgroup with BMI ≥ 27 kg/m² in inTandem1-2 was not provided by the MAH). After one year, the corresponding proportions were 29%, 32%, and 18%. The certainty of evidence was moderate for this outcome measure ([Table A3](#) and [Table A4](#)).

Important endpoints

Plasma glucose variability

Analysis of pooled data from inTandem1-2 (BMI ≥ 27 and patients included in CGM sub-study) showed that time in range (70-180 mg/dL) at 24 weeks significantly increased by 8.2% and 15.1% with 200 mg and 400 mg sotagliflozin, respectively, compared to placebo. This roughly corresponded to 1.4 and 3 hours/day. The certainty of evidence was very low ([Table A3](#) and [Table A4](#)).

Other important endpoints with relevance to cardiovascular complications: SBP and body weight

Among patients with SBP ≥ 130 mm Hg at baseline, sotagliflozin 200 mg and 400 mg decreased SBP at 24 weeks in the ES1 pool, albeit not significantly (-2.4 mm Hg [$p=0.18$] and -2.5 mm Hg [$p=0.14$] respectively; very low certainty of evidence). In the ES2 pool, sotagliflozin 400 mg Hg showed a substantially lower SBP after 24 weeks (-2.6 mm Hg; $p=0.021$; low certainty of evidence).

In patients regardless of their SBP at baseline, pooled data from inTandem1-2 (BMI ≥ 27 kg/m²) showed that 400 mg sotagliflozin significantly decreased SBP by 2.5 mm Hg at 24 weeks and by 3.6 mm Hg after one year compared to placebo. The effect of the lower 200 mg dose was statistically significant at 52 weeks (1.3 mm Hg at 24 weeks, and 2.1 mm Hg at 52 weeks; very low certainty of evidence, see [Table A3](#) and [Table A4](#)). Notably, for the whole mITT population of inTandem1-2, the effect on SBP was significant for both doses.

Patients treated with sotagliflozin significantly reduced their body weight by ~2-4 kg with a tendency towards dose- and treatment duration-dependency. Based on analysis of pooled data from inTandem1-2 (BMI ≥ 27 kg/m²), sotagliflozin resulted in weight loss of 2.3 kg and 3.3 kg at 24 weeks for 200 mg and 400 mg doses, respectively, compared to placebo. After one year, the corresponding weight losses were 3.0 kg and 4.5 kg (low certainty of evidence, [Table A3](#) and [Table A4](#)).

Health-related QoL outcomes

Sotagliflozin significantly improved patient-reported outcomes (Diabetes Distress Scale 2 (DDS2) and Diabetes Treatment Satisfaction Questionnaire (DTSQ)) compared to placebo as indicated by analysis of pooled data from inTandem1-2 (BMI ≥ 27 kg/m²). Diabetes distress was relieved by sotagliflozin at 24 weeks as indicated by a reduced DDS2 score by 0.6 units for 200 mg and by 0.7 units for 400 mg compared to placebo. After one year, the corresponding values were 0.3 and 0.4, respectively, when also including patients with a BMI <27 kg/m² (for the mITT population, one-year data for patients with BMI ≥ 27 kg/m² not reported by the MAH). Sotagliflozin also improved treatment satisfaction at 24 weeks compared to placebo as indicated by the DTSQ score increasing by 2.6 units for both 200 mg and 400 mg (very low certainty of evidence, [Table A3](#) and [Table A4](#)). In the mITT population (data not provided for patients with BMI ≥ 27 kg/m²), no change was observed for the general EQ5D index score (low certainty of evidence, [Table A5](#)), but the EQ-VAS score significantly increased compared to placebo (moderate certainty of evidence, [Table A5](#)).

Other endpoints

Insulin dose changes

Insulin dosing generally significantly decreased at 24 weeks with sotagliflozin (total insulin dose as well as bolus and basal). Pooled analysis of inTandem1-2 (BMI ≥ 27 kg/m²) showed that sotagliflozin decreased total insulin dose by 3.4 IU/day with 200 mg and by 6.6 IU/day with 400 mg compared to placebo after 24 weeks (very low certainty of evidence, [Table A3](#) and [Table A4](#)). Corresponding placebo-controlled changes for bolus insulin were -2 IU/day and -4 IU/day and for basal insulin -1.7 IU/day and -2.7 IU/day.

Safety, direct comparison

As for clinical effectiveness, safety outcome assessment was mainly based on pooled data from inTandem1-2 for patients with BMI ≥ 27 kg/m² (unless otherwise stated). The safety profile was as expected for an SGLT2 inhibitor, including reduction in hypoglycaemia and increases DKA. Additionally, SGLT1 inhibition by sotagliflozin can lead to diarrhoea.

Two patients (0.7%) experienced AE leading to death, both in the placebo group.

Most frequent adverse events

The most frequently reported AEs by system organ class included genital mycotic infections and diarrhoea ([Table 4.8](#)):

- Mycotic infections in men: six patients (3.8%) in the sotagliflozin 200 mg group, seven patients (4.5%) in the sotagliflozin 400 mg group, and one patient (0.6%) in the placebo group;
- Mycotic infections in females: 32 patients (21.6%) in the sotagliflozin 200 mg group, 28 patients (17.6%) in the sotagliflozin 400 mg group, and nine patients (6.3%) in the placebo group;
- Diarrhoea: 16 patients (5.2%) in the sotagliflozin 200 mg group, 27 patients (8.6%) in the sotagliflozin 400 mg group, and 20 patients (6.7%) in the placebo group.

Treatment-related severe adverse events

Up to week 52, severe drug-related AEs occurred more frequently in sotagliflozin-treated patients in the SAF-1 pool than in the insulin alone (placebo) group (low certainty of evidence, [Table A3](#) and [Table A4](#)). Eight patients (2.7%) in the insulin alone (placebo) group, nine patients (3.0%) in the sotagliflozin 200 mg group, and 14 patients (4.5%) in the sotagliflozin 400 mg group reported at least one severe drug-related AE.

Adverse events leading to discontinuation of the study treatment

Up to week 52, 13 patients (4.3%) in the sotagliflozin 200 mg group, 13 patients (4.2%) in the sotagliflozin 400 mg group, and 13 patients (4.4%) in the placebo group reported AEs leading to study drug discontinuation ([Table 4.8](#)) (low certainty of evidence, [Table A3](#) and [Table A4](#)).

Hypoglycaemia

Sotagliflozin reduced the occurrence of documented hypoglycaemia (BG ≤ 55 mg/dL by SMBG) and positively adjudicated severe hypoglycaemia. Over one year of treatment, sotagliflozin significantly reduced event rates for symptomatic documented hypoglycaemia (SMBG ≤ 55 mg/dl) compared to placebo. Compared to placebo, patients in inTandem1-2 with a BMI ≥ 27 kg/m² had 4.25 fewer events per year for 200 mg and 3.4 fewer events per year for 400 mg sotagliflozin (low certainty of evidence, [Table A3](#) and [Table A4](#)). Sotagliflozin 200 mg and 400 mg resulted in 34.5 and 40 fewer events of positively adjudicated severe hypoglycaemia per 1000 subject years (EAIR), respectively (low certainty of evidence, [Table A3](#) and [Table A4](#)).

Diabetic ketoacidosis

Sotagliflozin increased the incidence of DKA. After one year of treatment with sotagliflozin, there was a significant increase in DKA incidence in patients with a BMI ≥ 27 kg/m² in the inTandem1-2 trials. Compared to placebo, sotagliflozin 200 mg resulted in 25 more events of positively adjudicated DKA per 1000 subject years, and sotagliflozin 400 mg was associated with 34 more events per 1000 subject years (high certainty of evidence, [Table A3](#) and [Table A4](#)).

Table 4.8. Most frequent adverse events (safety population, patients with baseline BMI ≥ 27 kg/m²)

System organ/class/adverse events	Frequency (very common, common, uncommon, rare, very rare, not known)	SAF-1 pool				
		All grades				
		Sotagliflozin 200 mg N, n (%) EAIR per 1000 subject years (95% CI)	Sotagliflozin 400 mg N, n (%) EAIR per 1000 subject years (95% CI)	Insulin alone (placebo) N, n (%) EAIR per 1,000 subject-years (95% CI)	Sotagliflozin 200 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)	Sotagliflozin 400 mg vs. insulin alone (placebo) Risk difference of EAIR (95% CI) Relative risk of EAIR (95% CI)
Genital mycotic infections (male)	Common	N=157, 6 (3.8) 41.05 (8.20 to 73.89)	N=154, 7 (4.5) 47.74 (12.37 to 83.10)	N=155, 1 (0.6) 6.89 (0.00 to 20.39)	34.16 (-1.35 to 69.67) 5.96 (0.88 to 138.01)	40.85 (2.99 to 78.70) 6.93 (1.07 to 157.36)
Genital mycotic infection (female)	Very common	N=148, 32 (21.6) 240.02 (156.86 to 323.19)	N=159, 28 (17.6) 192.26 (121.05 to 263.48)	N=143, 9 (6.3) 71.25 (24.70 to 117.80)	168.78 (73.47 to 264.08) 3.37 (1.65 to 7.46)	121.01 (35.94 to 206.09) 2.70 (1.30 to 6.04)
Diarrhoea	Common	N=305, 16 (5.2) 57.25 (29.20 to 85.30)	N=313, 27 (8.6) 92.38 (57.53 to 127.23)	N=298, 20 (6.7) 73.67 (41.38 to 105.95)	-16.42 (-59.19 to 26.35) 0.78 (0.40 to 1.51)	18.71 (-28.79 to 66.22) 1.25 (0.70 to 2.27)
Total serious adverse events n (%)		N=305, 28 (9.2)	N=313, 31 (9.9)	N=298, 22 (7.4)		
Total deaths n (%)		N=305, 0	N=313, 0	N=298, 2 (0.7)		
Discontinuation due to AE (%)		N=305, 13 (4.3)	N=313, 13 (4.2)	N=298, 13 (4.4)		

Abbreviations: AE=adverse event; EAIR=exposure adjusted incidence rate; RR=relative risk; RD=risk difference

4.9 Subgroup effects

Analysis of pooled data from inTandem1-2 (whole mITT population) indicated that the outcomes were largely consistent across different subgroups (insulin delivery method CSII or MDII; BMI <25 or ≥ 25 kg/m²; week 2 HbA1c $\leq 8.5\%$ or $>8.5\%$; baseline eGFR <60, ≥ 60 to <90 or ≥ 90 mL/min).

Since the final approved indication of sotagliflozin only included patients with BMI ≥ 27 kg/m², the MAH also performed additional post-hoc analysis of outcomes for this subgroup. The results of this analysis provided the main endpoints of relevance for this assessment and are mainly presented throughout this assessment report. Although the analysis revealed no major differences with respect to the outcomes for the whole mITT population, the trend for some outcomes was towards a better effect, and a possible tendency towards a more pronounced effect for the higher dose (400 mg) was observed in some cases ([Table 4.5](#)).

Again, because the final approval for sotagliflozin was restricted to patients with BMI ≥ 27 kg/m², the MAH conducted post-hoc subgroup analysis for all endpoints with respect to modification by BMI (< 27 kg/m² or ≥ 27 kg/m²). As this is a comparison with a population outside the approved indication of the technology, the authors considered this analysis to be out of scope of the current assessment. For completeness, however, there were significant treatment interactions according to BMI for HbA1c, body weight, and the DTSQ ([Table A7](#)).

4.10 Indirect comparison

The results of the indirect comparison are presented in [Figure 4.1](#), [Figure 4.3](#), and [Figure 4.5](#). Credible intervals from most outcomes were quite wide, with few comparisons showing statistical significance of one treatment versus another, which is often the case when assessing indirect comparisons due to the additional uncertainty. Treatment rankings are shown in [Table 4.9](#). Treatments are ranked in descending order from the most favourable to the least favourable based on the point estimates of the forest plots. The positions of the two sotagliflozin doses are highlighted in bold for each outcome.

Table 4.9. Ranking of treatments from most to least favourable

	Greatest reduction of HbA1c % CFB	Lower proportion of patients experiencing any hypoglycaemia	Lower proportion of patients experiencing severe hypoglycaemia	Lower proportion of patients experiencing DKA
1	Empagliflozin 25 mg	Dapagliflozin 5 mg/ Empagliflozin 2.5 mg	Empagliflozin 2.5 mg	Empagliflozin 2.5 mg
2	Empagliflozin 10 mg	Dapagliflozin 5 mg/ Empagliflozin 2.5 mg	Sotagliflozin 200 mg	Placebo
3	Dapagliflozin 10 mg/ Sotagliflozin 400mg	Dapagliflozin 10 mg	Sotagliflozin 400 mg	Dapagliflozin 10 mg
4	Dapagliflozin 10 mg/ Sotagliflozin 400mg	Placebo	Dapagliflozin 5 mg	Dapagliflozin 5 mg
5	Sotagliflozin 200mg / Dapagliflozin 5 mg	Empagliflozin 25 mg	Dapagliflozin 10 mg	Sotagliflozin 200 mg
6	Sotagliflozin 200mg / Dapagliflozin 5 mg	Sotagliflozin 200 mg	Placebo	Sotagliflozin 400 mg
7	Empagliflozin 2.5 mg	Sotagliflozin 400 mg		
8	Placebo	Empagliflozin 10 mg		

Abbreviations: CFB=change from baseline; DKA=diabetic ketoacidosis. Note: this table should be read in conjunction with the forest plots in figures 4.3, 4.7, 4.9, and 4.11 for a complete picture. In circumstances where two interventions have the same point estimate in the forest plot, this is treated as a tie.

Sensitivity analyses

The MAH stated that they performed sensitivity analyses by excluding certain trials. However, these were not included in the submission dossier.

Crucial efficacy outcomes

Change in HbA1c (%) from baseline to week 24

This outcome contains all the studies in the full master network and so this is not repeated here. The results are summarised in [Figure 4.1](#).

Both sotagliflozin 200 mg and 400 mg were significantly better than placebo. Although non-significant, the point estimates indicated that sotagliflozin 400 mg was superior to dapagliflozin 5 mg and empagliflozin 2.5 mg, but inferior to empagliflozin 10 mg and 25 mg. The point estimates also indicated that sotagliflozin 200 mg was superior to empagliflozin 2.5 mg, but inferior to dapagliflozin 10 mg and empagliflozin 10 mg and 25 mg.

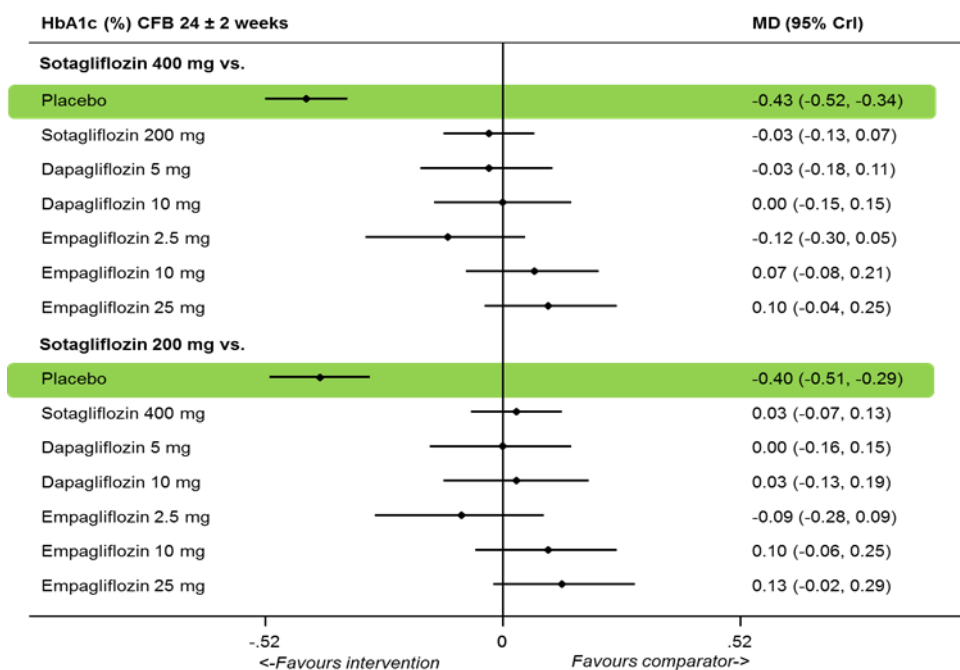


Figure 4.1. Forest plot for HbA1c% CFB at 24±2 weeks.

Source: applicant submission

Crucial safety outcomes

Any hypoglycaemia (proportion of patients)

The network and results are summarised in [Figure 4.2](#) and [Figure 4.3](#).

All results spanned 1 (line of no effect). Although non-significant, the point estimates implied that both sotagliflozin 400 mg and 200 mg were more favourable than empagliflozin 10 mg but less favourable than all other doses of dapagliflozin and empagliflozin. We also note that the point estimates for the three doses of empagliflozin were not in consecutive order, which may indicate that more precision is required.

PTJA04 - Sotagliflozin is indicated as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a Body Mass Index (BMI) ≥ 27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin therapy

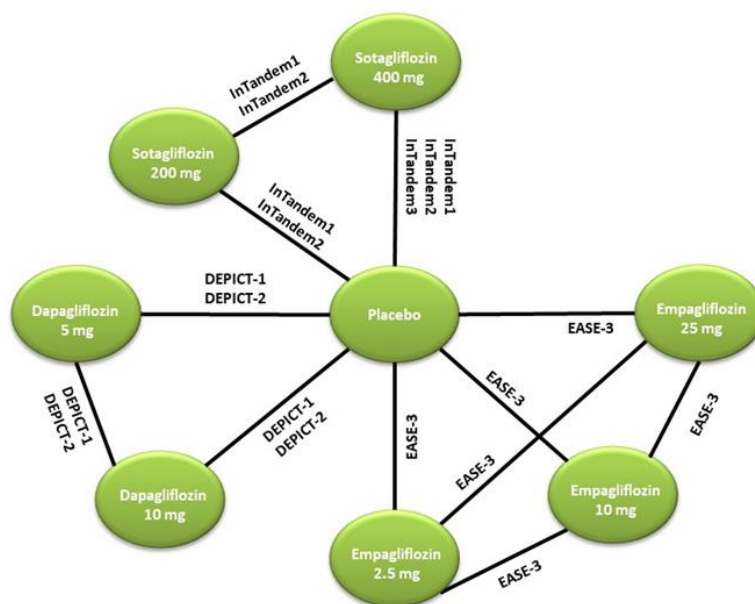


Figure 4.2. Network diagram for proportion of patients with any hypoglycaemia at 24 ± 2 weeks.

Source: applicant submission.

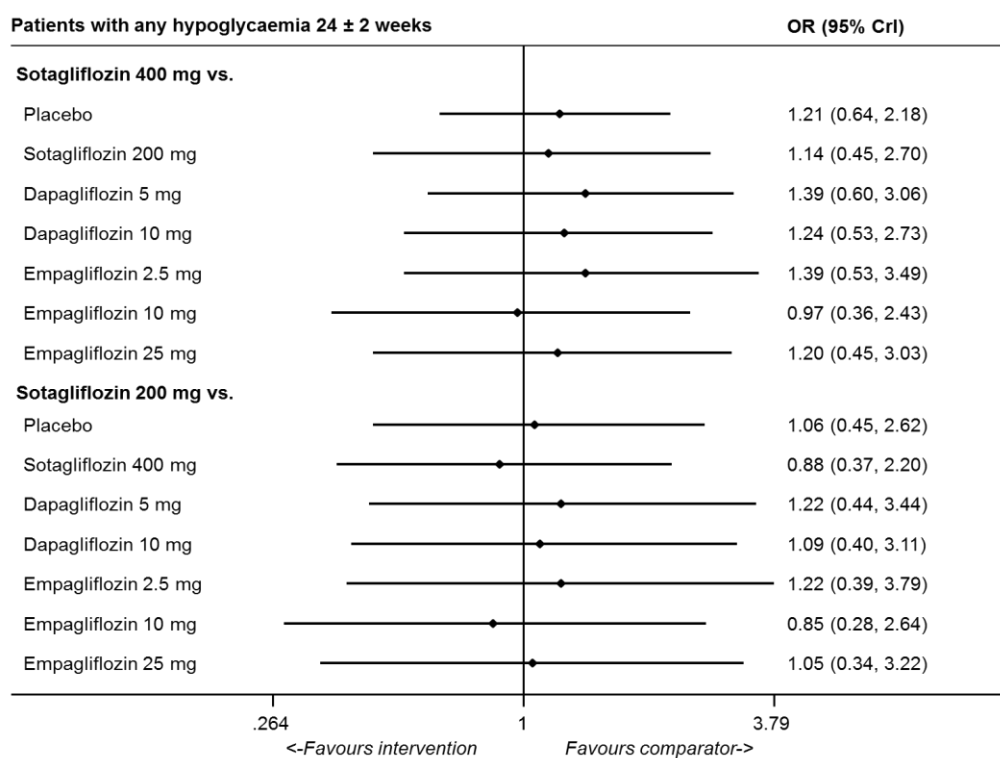


Figure 4.3. Forest plot for proportion of patients with any hypoglycaemia at 24 weeks.

Source: applicant submission.

Positively adjudicated severe hypoglycaemia (proportion of patients)

The network and results are summarised in [Figure 4.4](#), and [Figure 4.5](#).

The results of all models spanned 1 (line of no effect). Although non-significant, the point estimates of most comparisons were close to no effect, with the exception of a more favourable point estimate of empagliflozin 2.5 mg over both doses of sotagliflozin.

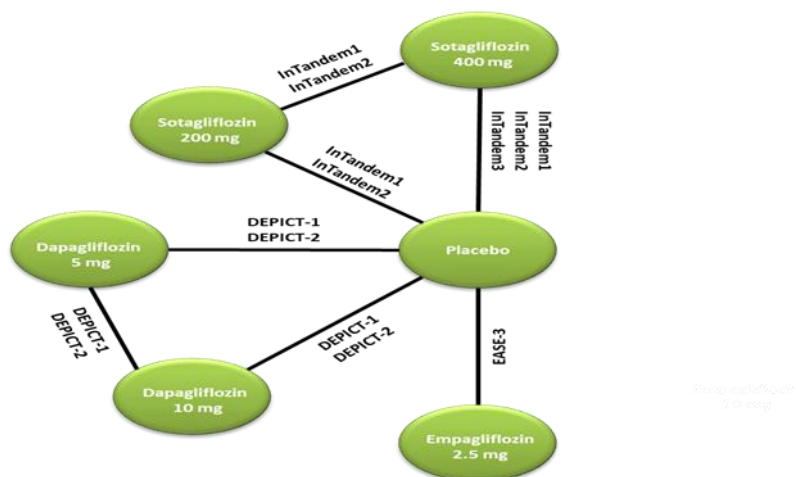


Figure 4.4. Network diagram for proportion of patients with severe hypoglycaemia at 24 ± 2 weeks.

Source: applicant submission.

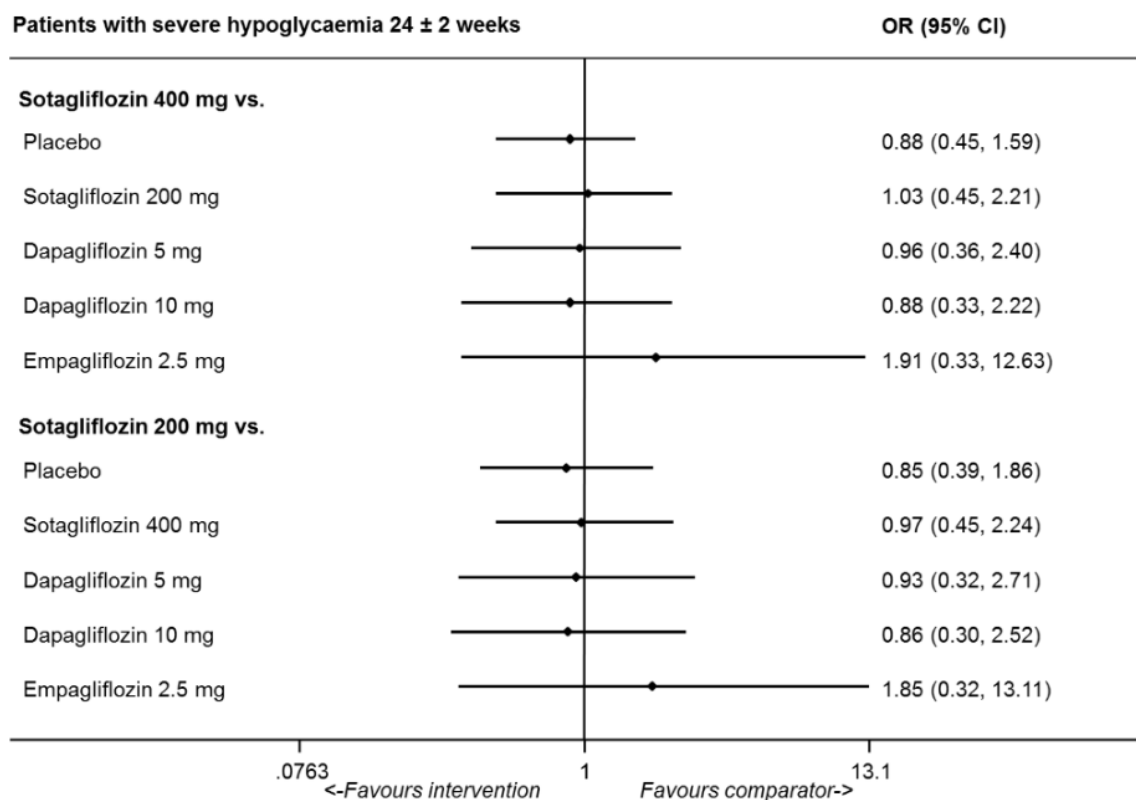


Figure 4.5: Forest plot for proportion of patients with severe hypoglycaemia at 24 weeks.

Source: applicant submission.

Positively adjudicated/definite DKA (proportion of patients)

The network and results are summarised in [Figure 4.6](#) and [Figure 4.7](#).

Placebo showed a significantly lower proportion of patients who experienced at least one DKA than sotagliflozin 400 mg. However, there was no significant difference for placebo versus sotagliflozin 200 mg.

Although non-significant, the point estimates indicated that all studied doses of dapagliflozin and empagliflozin showed a lower proportion of patients who experienced at least one DKA than both doses of sotagliflozin.

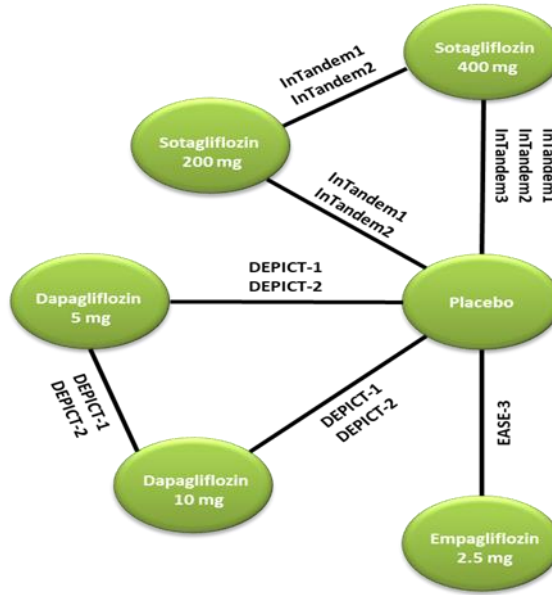


Figure 4.6. Network diagram for proportion of patients with positively adjudicated/definite DKA at 24 ± 2 weeks.

Source: applicant submission.

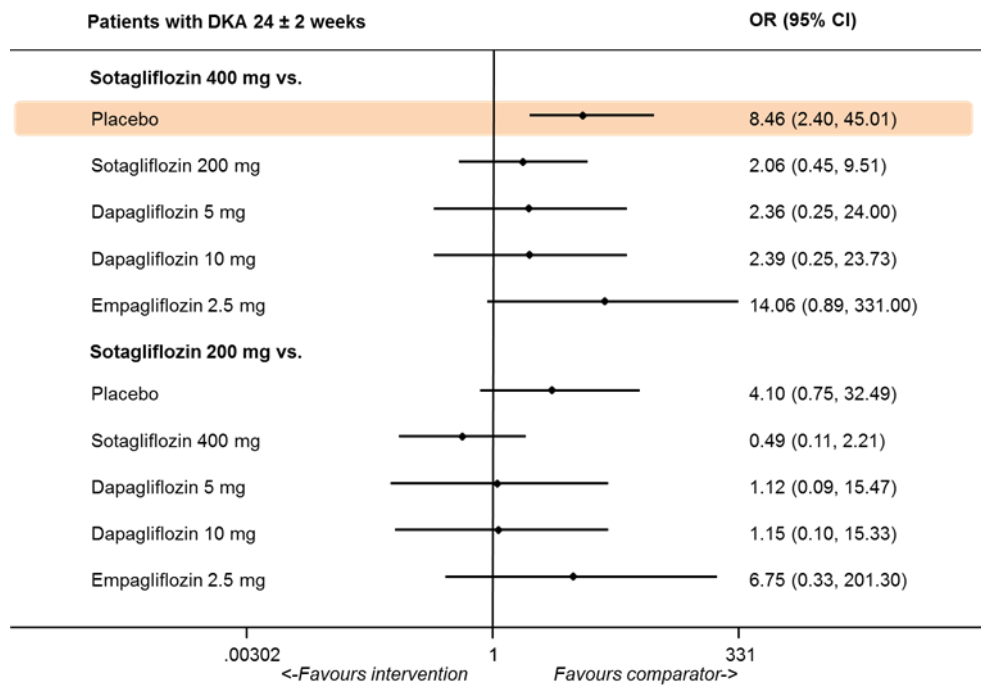


Figure 4.7. Forest plot for positively adjudicated/definite DKA at 24 weeks.

Source: applicant submission.

5 PATIENT INVOLVEMENT

The information gathered from the open call was used to inform the scope of this assessment, in particular the outcomes to be considered. The call generated answers from two organisations, Diabetes UK and La Federación Española de Diabetes (FEDE, Spain).

The patient organisations emphasised the importance of how, and to what extent, a new treatment affects various aspects of the quality of life of a diabetic patient. Challenges to the T1D patient, such as the inability to maintain blood glucose levels within an acceptable range and failure to achieve target HbA1c levels, were also discussed, as was the need for new and effective treatments. The problems and challenges (e.g., limited experience of ketone self-monitoring) associated with keeping side-effects, particularly hypoglycaemia and DKA, under control were also discussed as important aspects of a new therapy.

The following outcomes defined in the project plan were deemed to particularly reflect the input from the patient organisations:

- Proportion of patients with HbA1c <53 mmol/mol (7%)
- Health-related QoL
- Hypoglycaemia
- Diabetic ketoacidosis

These outcomes are directly reflected in the endpoints of the inTandem1-2 trials, which are evaluated in this assessment. For health-related QoL, the specific measures were the Diabetes Distress Score (DDS2) and the Diabetes Treatment Satisfaction Score (DTSQ), which were part of the inTandem1-2 trials. Generic QoL measurements (EQ-5D) were additionally included in material submitted by the MAH (for the whole mITT population only).

6 DISCUSSION

This assessment used outcomes derived from pooled one-year data from the inTandem1-2 trials (ES1 pool) to evaluate the relative clinical effectiveness of sotagliflozin versus placebo. inTandem1-2 had identical designs, included insulin dose adjustments similar to clinical practice, and provided data for one year of treatment. In contrast, inTandem3 lacked proper insulin optimisation and only provided data for 24 weeks of treatment and was therefore omitted from this evaluation. Furthermore, since the indication for sotagliflozin only includes patients with BMI ≥ 27 kg/m², this subgroup of the entire mITT population of inTandem1-2 was considered most relevant for assessment.

6.1 Main clinical effects

For T1D patients with BMI ≥ 27 kg/m², treatment with sotagliflozin add-on to optimised insulin therapy significantly reduced HbA1c, body weight, and blood pressure compared to placebo, as well as reducing the occurrence of documented symptomatic hypoglycaemia and increasing the occurrence of DKA. The proportion of patients achieving a target HbA1c $< 7\%$ without experiencing severe hypoglycaemia or DKA and weight gain also increased relative to placebo. In addition, sotagliflozin improved glucose variability, relieved diabetes distress, and improved diabetes treatment satisfaction. Patients treated with sotagliflozin also on average used lower insulin doses.

The statistically significant treatment effect observed for HbA1c (-0.24% to -0.38%) after one year approached the limit commonly used as a non-inferiority margin in clinical trials ($0.3-0.4\%$ according to the FDA and 0.3% according to the EMA [40, 41]).

Different adverse events were reported with sotagliflozin treatment. However, of particular importance was the frequency of hypoglycaemic events and DKA episodes reported in patients treated with the drug. Clinical trial evidence indicates that patients treated with sotagliflozin are at a significantly decreased risk of symptomatic documented hypoglycaemia but a significantly increased risk of DKA. Since the risk of hypoglycaemia is a source of anxiety for diabetic patients, this would be expected to have a positive effect on QoL. However, this is balanced against the increased frequency of DKA as a direct and serious complication of the treatment. Even though the risk of DKA might be even higher in clinical practice, sotagliflozin will be approved for restricted medical prescription only and patients will be required to perform ketone self-monitoring, identify at-risk situations to allow for early diagnosis of ketonaemia or ketonuria, and learn how to manage potential ketosis and maintenance for insulin therapy. Of note is that the EMA expert view was split on the acceptability of DKA risks. A majority of experts considered that the risk might be manageable with the preventive measures mentioned above to help mitigate DKA risk. However, the risk in real-world clinical practice is hard to predict since clinical trials usually provide better conditions for patient control. Hence, there is no guarantee that these methods for patient follow-up will decrease DKA episodes in real-world practice.

6.2 Certainty of evidence for direct comparisons

The certainty of evidence, as assessed by GRADE, is indicated for each outcome measure in the GRADE evidence profiles for sotagliflozin versus placebo for the BMI ≥ 27 kg/m² subgroup ([Table A3](#) and [Table A4](#)) and for the mITT population (400 mg dose) ([Table A5](#)). The explanations for certainty of evidence decisions for each outcome measure are also included. Here we only discuss the certainty of evidence for the crucial outcome measures emphasised by patient organisations. For efficacy, these are the proportion of patients with HbA1c < 53 mmol/mol (7%) and health-related QoL. For safety, these are hypoglycaemia and DKA.

The MAH did not submit evidence on the proportion of patients with HbA1c < 53 mmol/mol (7%) for the BMI ≥ 27 kg/m² subgroup. However, the net benefit analysis (proportion with HbA1c < 53 mmol/mol ($< 7\%$), no severe hypoglycaemia, no DKA) was primarily driven by the proportion of patients with HbA1c < 53 mmol/mol ($< 7\%$). Since HbA1c (with general treatment goal of < 53 mmol/mol ($< 7\%$)) is a surrogate outcome measure for prevention of diabetes-related micro/macrovacular complications, the evidence for an effect of sotagliflozin on this hard outcome measure is of moderate certainty (downgraded one level for indirectness). The inTandem1 and 2 studies showed consistent results within the ES1 pool (inTandem1-2) and the ES2 pool when inTandem3 was included.

This indicates that differences in baseline HbA1c (due to a lack of insulin optimisation in the inTandem3 trial) did not modify the relative treatment effect of sotagliflozin on the HbA1c outcome. Furthermore, the results and certainty of evidence were consistent with the mITT population ([Table A5](#)). Within the mITT population, the certainty of evidence for the proportion of patients with HbA1c <53 mmol/mol ($<7\%$) was moderate due to downgrading for indirectness (surrogate outcome measure).

Several instruments were used to assess health-related QoL including the DTSQ (and EQ-5D, EQ-VAS, only submitted for the mITT population). The certainty of evidence for an effect of sotagliflozin on health-related QoL in the BMI ≥ 27 kg/m² subgroup was very low. Treatment satisfaction, as assessed by DTSQ, does not assess QoL itself, and a higher DTSQ score does not necessarily translate into increased QoL [42]. Therefore, the certainty of evidence for an effect on QoL in the BMI subgroup was downgraded by two levels for indirectness. Furthermore, there was a high risk of bias. The effect on DTSQ was consistent between the ES1 and ES2 pools and between the BMI subgroup and the mITT population. In the mITT population, the certainty for an effect on QoL through EQ-5D-5L was low due to imprecision and a risk of bias, since the patient numbers assessed did not represent the mITT population; a significant number of patients were excluded from analyses for this outcome measure.

The certainty of evidence for an effect of sotagliflozin on symptomatic documented hypoglycaemia (≤ 55 mg/dL) in the BMI ≥ 27 kg/m² was low because of a high risk of bias and since inconsistency in effects between the studies could not be assessed by a direct meta-analysis, as the MAH did not submit this data. The same was true for severe hypoglycaemia. For this outcome measure, certainty of evidence was low due to unknown inconsistency and imprecision. Although inconsistency between studies could not be assessed formally, the effects between the ES1 and ES2 pools differed to a slight extent (smaller effect in the ES2 pool). In the mITT population, the certainty of evidence for an effect of sotagliflozin 400 mg on symptomatic documented hypoglycaemia (≤ 55 mg/dL) was high for both the ES1 and ES2 pools (relative effects the same). The certainty of evidence for an effect on severe hypoglycaemia was high in the ES1 mITT pool, but there existed moderate certainty in no effect of sotagliflozin on severe hypoglycaemia in the ES2 mITT pool because of imprecision.

The certainty of evidence for an effect of sotagliflozin on DKA was high in the BMI ≥ 27 kg/m² subgroup and also in the mITT population. Within the BMI ≥ 27 kg/m² subgroup, the effect and certainty of the evidence was consistent between the ES1 and ES2 pools. Furthermore, although not statistically assessed, the relative rate ratio for DKA seemed to be reduced in the BMI ≥ 27 kg/m² subgroup compared to the total mITT population.

6.3 Other outcomes

Treatment with sotagliflozin reduces the need for insulin, as reflected in reduced doses of insulin seen in the trials. A lower dose of insulin might be particularly advantageous for overweight patients, since higher insulin doses are associated with increased body weight (as well as an increased risk of hypoglycaemia). On the other hand, the positive effect of weight loss coupled with a lowered insulin dose might be counterbalanced by the increased risk of DKA normally associated with lower insulin dose (even though this is not explicitly evidenced by the study outcomes). The increased risk of DKA might to some extent be less of a problem for overweight patients because they generally use higher absolute doses of insulin.

6.4 Relevance of outcomes

The studies included in the assessment were not designed to evaluate long-term cardiovascular complications. Therefore, crucial endpoints were of a surrogate nature, which is accounted for in assessing the certainty of the evidence by GRADE. The scientific evidence of benefit of lowering HbA1c in T1D is solid and known to reduce microvascular complications in particular, and an association with cardiovascular complications has also been observed (46, 47). Similarly, the evidence of benefit of lowering other known cardiovascular risk factors such as blood pressure, body weight, and plasma lipids is also robust. These benefits are particularly important for overweight patients.

Outcomes related to plasma glucose levels (PPG, FPG, and plasma glucose variability) are of immediate relevance for patients, as they serve as primary sources of information for disease control

and insulin dosing. Even though there is some suggestion that these outcomes are directly coupled to diabetic complications [45], their benefit is mainly explained by the fact that keeping these values under control will translate into HbA1c reductions. These outcomes are therefore of putative value for patient QoL but, as surrogate probes for diabetic long-term complications, they are inferior to HbA1c.

6.5 Comparators

At the time the studies were conducted, there were no approved add-on therapies to insulin for T1D patients. The pivotal studies (inTandem1-3) compared sotagliflozin as an add-on to insulin with placebo as an add-on to insulin. However, in the intervening period, phase III trials investigating the efficacy of the SGLT2 inhibitors dapagliflozin and empagliflozin in T1D have been conducted. Empagliflozin are currently not licensed for the treatment of T1D patients. However, depending on the clinical trial outcomes, empagliflozin may obtain marketing authorisations for T1D patients in the future. Of note, 5 March 2019, dapagliflozin received marketing authorisation from the EMA for the treatment of type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m², when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy

[46]. It is therefore considered prudent to include dapagliflozin and empagliflozin as relevant comparators to sotagliflozin. Since empagliflozin has not yet been approved for T1D patients and dapagliflozin recently was approved for T1D patients, these drugs are not yet included in the national guidelines of any EU member country.

Comparison with SGLT2 inhibitors

Indirect comparisons between sotagliflozin and the SGLT2 inhibitors dapagliflozin and empagliflozin were performed for percentage change from baseline in HbA1C, hypoglycaemic events, and DKA. The NMA results contained quite a lot of uncertainty, making it difficult to draw conclusions about the benefit of sotagliflozin relative to dapagliflozin and empagliflozin. However, it is of note that neither dose of sotagliflozin was ranked in first position for any of the outcomes that were included in the NMA. Only random effects (RE) models were presented in the submission file. In general, RE models have wider credible intervals (Cris) than the alternative fixed effects (FE) models. The authors requested that FE models were included in the submission in addition to RE models, but this request was declined by the MAH. Given that neither dose of sotagliflozin was ranked in the first position for any of the outcomes, the authors are concerned that the results for sotagliflozin may be statistically significantly worse than empagliflozin or dapagliflozin if an FE model were to be used.

In addition, the MAH provided no reasoning as to why certain outcomes were included in the NMA and others were not. The authors requested that additional crucial and important outcomes be included in the submission, but this request was denied by the MAH. As such, the authors consider the submission to be incomplete.

6.6 The relevance of treatment effects in cost effectiveness modelling

Treatment effects typically used as input parameters in health economic modelling of the cost effectiveness of diabetes drugs are outcomes for HbA1c, cardiovascular risk factors, AEs, and generic QoL measurements. Thus, from this perspective, the most important of the reported outcomes for sotagliflozin include effects on HbA1c, blood pressure, plasma lipid levels, body weight (more commonly BMI), frequency of hypoglycaemia and DKA events of different severity, and QoL measures. Other reported outcomes such as time in range, plasma glucose, and insulin doses are not normally directly used as input parameters in health economic modelling in diabetes but can be indirectly accounted for by their effects on patient QoL. Since modelling aims to assess long-term effects, outcomes reported after one year of treatment are most relevant for this purpose. Furthermore, in cost-effective modelling for diabetes, effects are generally extrapolated over a lifetime perspective. This can lead to difficulties in accounting for a waning effect.

7 CONCLUSIONS

Adult patients with T1D and BMI ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite optimal insulin therapy⁵, add-on with 200 mg and 400 mg sotagliflozin resulted in placebo-adjusted changes in HbA1c by -0.24% [CI: -0.35 to -0.13] and -0.38 % [CI: -0.49 to -0.27], respectively, after one year of treatment compared to placebo (low certainty of evidence). Health-related QoL as assessed by the DDS2 and DTSQ showed significant placebo-controlled improvements (DDS: -0.6 and -0.7 units for 200 mg and 400 mg; DTSQ: 2.6 points higher for both doses). The certainty of evidence for an effect on health-related QoL was very low.

Both sotagliflozin doses also significantly reduce the cardiovascular risk factors systolic blood pressure (SBP) (low certainty of evidence) and body weight (low certainty of evidence). The change in SBP for sotagliflozin 400mg is -3.6 mm Hg [CI: -5.3 to -1.9] at 52 weeks, the 200 mg dose also improves SBP statistically significant, -2.1 mm Hg [CI: -3.9 to 0.4].”For body weight, the mean change after one year was -3.0 kg [CI: -3.7 to -2.3] with 200 mg and -4.5 kg [CI: -5.2 to -3.8] with 400 mg sotagliflozin.

With respect to AEs, a non-significant 50% lower risk of incidence of severe hypoglycaemia was observed. After one year with 200 mg and 400 mg sotagliflozin, the relative risk of incidence rate was 0.57 [CI: 0.28 to 1.14] and 0.51 [CI: 0.24 to 1.02], respectively (low certainty of evidence). In addition, the placebo-controlled rate of symptomatic documented hypoglycaemia (≥ 55 mg/mL) was significantly lower for both doses (low certainty of evidence). On the other hand, the corresponding risk of DKA was significantly increased; the incidence rate ratios with 200 mg and 400 mg were 7.8 [CI: 1.2 to 174] and 10.2 (1.7 to 222), respectively, but the confidence intervals are very wide and, therefore, should be interpreted with caution. The increased risk of DKA occurrence is considerable but is meant to be reduced by restricted medical prescription, patient and caregiver education, and patient self-monitoring of ketones. The extent of the problem with sotagliflozin and DKA in real clinical practice is difficult to assess.

The results of the NMA contained quite a lot of uncertainty, making it difficult to draw conclusions about the benefit of sotagliflozin relative to dapagliflozin and empagliflozin. However, it is of note that neither dose of sotagliflozin was ranked in first position for any of the outcomes included in the NMA.

⁵ Outcomes referred to in the conclusion section are derived from pooled one-year data from inTandem1-2 for patients of the mITT pools with BMI ≥ 27 kg/m². This corresponds to the population of the approved indication for sotagliflozin and is the main population of this REA.

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APPENDIX 1: GUIDELINES FOR DIAGNOSIS AND MANAGEMENT

Table A1. Overview of guidelines used for this assessment

Overview of guidelines relevant to the diagnosis and management of patients with T1D

Country	Institution (Year)	Title and reference	Development class*	Recommendations (level of evidence/recommendation)
<i>International guidelines</i>				
Europe	European Society of Cardiology (ESC) (2013 [corrigendum 2014])	Diabetes, Pre-Diabetes and Cardiovascular Diseases developed with the EASD ESC Clinical Practice Guidelines ^a [3]	S2k	An HbA1c target of 7.0% (53 mmol/mol) to reduce microvascular disease is a generally accepted level. (...) Consensus indicates that an HbA1c of $\leq 7.0\%$ should be targeted, but with acknowledgement of the need to pay attention to the individual requirements of the patient. (...). <i>(no level of evidence/recommendation provided)</i> More stringent targets (e.g. HbA1c 6.0 – 6.5% (42 – 48 mmol/mol)) might be considered in selected patients with short disease duration, long life expectancy and no significant CVD, if it can be achieved without hypoglycaemia or other adverse effects. (...) It follows that it is important to individualise treatment targets. <i>(no level of evidence/recommendation provided)</i>
Europe	European Association for the Study of Diabetes (EASD) (2016)	2016 European Guidelines on CVD Prevention in Clinical Practice ^b [47]	S2k	A target HbA1c for the reduction in risk of CVD and microvascular complications in diabetes mellitus of $<7.0\%$ (<53 mmol/mol) is recommended for the majority of non-pregnant adults with either T1D or T2D. <i>(I, A)</i> For patients with a long duration of diabetes mellitus, the elderly, frail, or those with existing CVD, a relaxing of the HbA1c targets (i.e. less stringent) should be considered. <i>(IIa, B)</i>
World	International Diabetes Federation (IDF) International Society for Pediatric and Adolescent Diabetes (ISPAD) (2011)	The Global IDF/ISPAD Guidelines for Diabetes in Childhood and Adolescence ^c [48]	S2k	The target HbA1c for all age-groups is recommended to be less than 7.5% (58 mmol/mol). <i>(no level of evidence/recommendation provided)</i> Targets for all age-groups include the requirement for minimal levels of SH and absence of hypoglycaemia unawareness. When SH occurs or when hypoglycaemia unawareness is present, glycaemic targets must be increased until hypoglycaemia awareness is restored and SH no longer occurs. <i>(no level of evidence/recommendation provided)</i>

Country	Institution (Year)	Title and reference	Development class*	Recommendations (level of evidence/recommendation)
<i>National Guidelines</i>				
France	Haute Autorité de Santé (2007)	GUIDE - AFFECTION DE LONGUE DURÉE: Diabète de type 1 de l'adulte (19)	S2k	The target is to maintain HbA1c <7.5% (glycaemic equilibrium) while considering hypoglycaemia risk. <i>(no level of evidence/recommendation provided)</i> To be modulated according to patient and situation. <i>(no level of evidence/recommendation provided)</i>
Germany	Deutsche Diabetes Gesellschaft (2018)	S3-Leitlinie Therapie des Typ-1-Diabetes, 2nd ed. 4/2018 [49]	S3	Individualised targets for glycaemic control. (A) HbA1c $\leq 7.5\%$ for adults as long as there occur no problematic hypoglycaemias. (B) In adults with low intrinsic hypoglycaemia risk, HbA1c $\leq 6.5\%$ can be targeted. (O) If therapeutic safety cannot be assured (SH, extensive comorbidities, advanced vascular complications) less stringent HbA1c targets (<8.5%). (B)
Italy	Associazione Medici Diabetologi Società Italiana di Diabetologia (2016)	Standard italiani per la cura del diabete mellito 2016 [50]	S2k	HbA1c <7.0% in patients to prevent macrovascular complications. (III, B) HbA1c <6.5% possible in newly diagnosed patients or <10 years since diagnosis. (III, C) less stringent targets (HbA1c <8.0%) in long-time patients, with CV disease, history of Poor glycaemic control, or other comorbidities. (VI, B) risk of hypoglycaemia needs to be considered. (III, B)
Netherlands	Federatie Medisch Specialisten Richtlijndatabase Diabetes Mellitus (2014)	Diabetes Mellitus [51]	S2k – S3	Aim for the treatment goal is to prevent or delay micro- and macrovascular complications as much as possible, to a good glycaemic regulation, based on an HbA1c within the per patient (doctor and patient) agreed target value. <i>(no level of evidence/recommendation provided)</i>

Country	Institution (Year)	Title and reference	Development class*	Recommendations (level of evidence/recommendation)
Netherlands	Nederlandse Diabetes Federatie (2015)	Zorgstandaard diabetes-type-1 [51]	n.a.	General target: HbA1c <53 mmol/mol (7.0%) HbA1c >69 mmol/mol is considered poorly regulated glycaemia with increased risk of microvascular complications. <i>(no level of evidence/recommendation provided)</i>
Poland	Polskie Towarzystwo Diabetologiczne (2019)	2019 Guidelines of the management of diabetic patients (21)	n.a.	The goal of diabetes type 1 management is to achieve good metabolic control with blood glucose levels as close to normal values as possible and HbA1c $\leq 6.5\%$ unless associated with episodes of hypoglycemia or reduced patient quality of life. In other cases, the therapeutic goal should be HbA1c $\leq 7.0\%$. The recommended treatment approach is intensive insulin therapy using multiple subcutaneous insulin doses or continuous subcutaneous insulin infusion (CSII) using a personal insulin pump. (A) •A key element of therapy for diabetes type 1 is the patient's ability to modify insulin doses based on carbohydrate meal content, baseline blood glucose level, and planned physical activity. Knowledge of the effect of protein and fat on blood glucose level is also important for optimization of insulin dosage. (E) In patients with diabetes type 1, use of insulin analogs is preferred due to a lower risk of hypoglycemia and better quality of life. (A)
Spain	Guías de práctica clínica en el SNS. Ministerio de sanidad, servicios sociales e igualdad (2012 [expired])	Guías de práctica clínica sobre Diabetes Mellitus tipo 1 (16)	S2k – S3	HbA1c <7% in the absence of hypoglycaemia to reduce risk of CV death and all cause death. (1+, A) Treatment targets should be individualised according to patient's risks and benefits. Less ambitious targets in patients with hypoglycaemia, no hypoglycaemia awareness, limited life expectancy or comorbidities, and small children. (A)
Sweden	Socialstyrelsen	National Guidelines for Diabetes Care - Support for governance and management	n.a.	T1D and T2D Diabetes: Target for HbA1c of under 52 mmol/mol (<6.9%). However, the relationship between risk and benefit of a course of intensive treatment is different for different

Country	Institution (Year)	Title and reference	Development class*	Recommendations (level of evidence/recommendation)
	National Board of Health and Welfare (2015)	(15)		people in both T1D and T2D. An upper target value for HbA1c can be 70 mmol/mol as values around and above this seriously increase the risk of diabetic complications. The treatment decision is always based on the individual patient's situation and should be made on the basis of an individual assessment of the benefit and potential risks of the treatment. <i>(no level of evidence/recommendation provided)</i>
	Socialstyrelsen (2018)	Nationella riktlinjer för diabetesvård	n.a.	(see above)
UK	The National Institute for Health and Care Excellence (NICE) (2015 [update July 2016])	Type 1 diabetes in adults: diagnosis and management [8]	S3	Support adults with T1D to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. Agree an individualised HbA1c target with each adult with T1D, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia Ensure that aiming for an HbA1c target is not accompanied by problematic hypoglycaemia in adults with T1D. <i>(no level of evidence/recommendation provided)</i>
Ireland	An Roinn Sláinte Department of Health (2018)	Adult type 1 diabetes mellitus. National Clinical Guideline No. 17 [52]	Guideline draws on NICE guidance 2015	Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia. <i>(no level of evidence/recommendation provided)</i>
* according to AWMF criteria: S1 Expert group recommendation; S2k Consensus-based; S2e Evidence-based; S3 Evidence- and consensus-based (AWMF Guidance Manual and Rules for Guideline Development, 1st Edition 2012. English version. Available at: http://www.awmf.org/leitlinien/awmf-regelwerk.html)				

Abbreviations: CVD = cardiovascular disease; EASD = European Association for the Study of Diabetes; ESC = European Society of Cardiology; HbA1c = haemoglobin A1c; IDF = International Diabetes Federation; T1D = type1 diabetes; T2D = type 2 diabetes.

APPENDIX 2: EVIDENCE GAPS

Table A2. Recommendations for research

Research question:	
Rationale:	
Evidence	<i>The NMA was only reported for a subset of outcomes. The authors requested that the NMA was performed for all crucial and important endpoints. However, the MAH declined this request. Table 3.6 details the endpoints for which this comparison is technically possible.</i>
Population	
Intervention	
Comparator	
Outcome(s)	<i>DKA risk in clinical practice Time-in-range and its effect on quality of life; effect on long-term diabetes related micro/macrovascular complications.</i>
Time stamp	
Burden of disease	
Study design	

APPENDIX 3: GRADE EVIDENCE PROFILE

Table A3. GRADE evidence profile. Sotagliflozin (200 mg) versus placebo, both as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D with BMI ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy (BMI ≥ 27 kg/m² subgroup).

ES1 pool (SAF1) presented for 52 weeks if applicable (pooled individual patient-data presented, with aggregated meta-analyses on study level in footnotes)

Certainty assessment							Number of patients		Effect ^{aa}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (200 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Type 1 diabetes related micro/macrovacular complications (assessed by: Glycaemic control (HbA1c [%] mean difference from baseline)												
ES1 (n=2) (52 wks)	RCTs	serious ^a	not serious ^b	serious ^c	not serious ^d	not found	305	298	NA	0.24 percentage points lower (0.13 to 0.53 lower)	⊕⊕○○ LOW	CRUCIAL
Type 1 diabetes related micro/macrovacular complications (assessed by: Glycaemic control (HbA1c < 7.0%, difference in proportion from baseline)												
No data has been submitted												CRUCIAL
Type 1 diabetes related micro/macrovacular complications (assessed by: Net Benefit (HbA1c < 7.0%, no severe hypoglycaemia, no diabetic ketoacidosis)												
ES1 (n=2) (24 wks)	RCTs	not serious	not serious ^e	serious ^f	not serious ^g	not found	91/305 (29.8%)	57/298 (19.1%)	OR 1.80 (1.23 to 2.63)	NR	⊕⊕⊕○ MODERATE	CRUCIAL
Mortality (assessed by: Number of deaths)												
SAF1 (n=2) (52 wks)	RCTs	not serious	not serious	not serious	very serious ^h	not found	0/305 (0%)	2/298 (0.7%)	NR	NR	⊕⊕○○ LOW	CRUCIAL
Health-related quality of life (assessed by: treatment satisfaction with Diabetes Treatment Satisfaction Score [range 0-36, higher is better, mean difference from baseline])												
ES1 (n=2) (24 wks)	RCTs	serious ^{la}	not serious ⁱ	very serious ^k	not serious ^l	not found	305	298	NA	2.6 points higher (1.9 to 3.3 higher)	⊕○○○ VERY LOW	CRUCIAL
Health-related quality of life (assessed by: EQ-5D-5L generic health status score [higher is better], and EQ-VAS [scale 0-100, higher is better], mean difference from baseline)												

Certainty assessment							Number of patients		Effect ^{aa}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (200 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
No data has been submitted											CRUCIAL	
Symptomatic documented hypoglycaemia with documented SMBG ≤ 55 mg/dL (assessed by: Event rate, n events per person per year)												
ES1 (n=2) (52 wks)	RCTs	serious ^a	serious ^m	not serious	not serious ⁿ	not found	NR/305	NR/298	NR	4.3 events per person-years lower (1.6 to 6.9 lower)	⊕⊕○○ LOW	CRUCIAL
Severe hypoglycaemia (assessed by: positive adjudication by blinded review committee [n events per 1000 person-years adjusted to patient's exposure])												
ES1 (n=2) (52 wks)	RCTs	not serious	serious ^m	not serious	serious ^o	not found	305	298	IRR: 0.57 (0.28 to 1.14)	34.5 events per 1000 person-years lower (76.8 lower to 7.7 higher)	⊕⊕○○ LOW	CRUCIAL
Adverse events leading to discontinuation of study treatment (n events/total)												
SAF1 (n=2) (52 wks)	RCTs	not serious	not serious	not serious	very serious ^p	not found	13/305 (4.4%)	13/298 (4.4%)	NR	NR	⊕⊕○○ LOW	CRUCIAL
Severe adverse events (assessed by: severe treatment-related adverse events [n events/total])												
SAF1 (n=2) (52 wks)	RCTs	not serious	not serious	not serious	very serious ^q	not found	9/305 (3.0%)	8/298 (2.7%)	NR	NR	⊕⊕○○ LOW	CRUCIAL
Diabetic ketoacidosis (assessed by: positively adjudication by blinded review committee [event rate per 1000 person-years adjusted to patient's exposure])												
SAF1 (n=2) (52 wks)	RCTs	not serious	not serious	not serious	not serious ^r	not found	305	298	IRR: 7.8 (1.24 to 174)	24.9 events per 1000 person-years higher (3.8 to 46.1 higher)	⊕⊕⊕⊕ HIGH	CRUCIAL
Time in range (assessed by: percent time spent in target range [3.9-10.0 mmol/L ≥ 70 to ≤ 180 mg/dL], per 24 h, mean difference in % in the CGM sub study)												
ES1 (n=2) (24 wks)	RCTs	serious ^{s,a}	serious ^t	very serious ^u	not serious	not found	59	58	NA	8.2 percent points higher (2.3 to 14.0 higher)	⊕○○○ VERY LOW	IMPORTANT

Certainty assessment							Number of patients		Effect ^{aa}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (200 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		

Total insulin dosage (assessed by: mean difference in IU/day from baseline)

ES1 (n=2) (24 wks)	RCTs	serious ^a	not serious	very serious ^v	not serious	not found	305	298	NA	3.4 IU/day lower (1.0 to 5.8 lower)	⊕○○○ VERY LOW	IMPORTANT
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Cardiovascular risk factors (assessed by: mean difference from baseline in systolic blood pressure [mm Hg], among patients with SBP of ≥ 130 mm Hg at baseline)

ES1 (n=2) (24 wks)	RCTs	serious ^{wa}	not serious ^x	serious ^y	serious ^z	not found	101	99	NA	2.4 mm Hg lower (5.8 lower to 1.1 higher)	⊕○○○ VERY LOW	IMPORTANT
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Cardiovascular risk factors (assessed by: mean difference from baseline in body weight [kg] [52 weeks])

ES1 (n=2) (52 wks)	RCTs	serious ^a	not serious	serious ^y	not serious	not found	305	298	NA	3.0 kg lower (2.3 to 3.7 lower)	⊕⊕○○ LOW	IMPORTANT
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Abbreviations:

CI: confidence interval; NA: not applicable; NR: not reported in submission file; NE: not established due to missing information; IRR: incidence rate ratio; OR: odds ratio

Explanations

- The BMI group of ≥ 27 kg/m², for which sotagliflozin has received market authorisation, is a post-hoc sub group analysis from the mITT populations of the RCTs. We have decided not to further downgrade for risk of bias because of the post-hoc sub group analysis, since baseline variables of this sub group were similar between the intervention and placebo groups, and a pre-specified sub group-analysis by BMI ≥ 25 kg/m² vs < 25 kg/m², for which was stratified for at randomisation in the inTandem3 study, did show similar patterns for relative effects. However, in the individual patient-data pooling of the data, there is uncertainty about the patient-numbers included (inconsistent in comparison to the mITT numbers in the CONSORT flow-diagram). Therefore, certainty of evidence has been downgraded by one level for risk of bias.
- The heterogeneity of the pooled estimate from the inTandem1 and 2 trials (I^2 is 0% ($p=0.72$)).
- HbA1c is a surrogate outcome measure for type 1 diabetes related long-term micro/macrovacular complications.
- In order to address the vulnerability of confidence intervals as a criterion for adequate precision, the optimal information size (OIS) can be considered as a necessary criterion. The OIS is applied as a rule according to the following: If the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial, consider rating down for imprecision. The inTandem2 trial states that with a detected treatment difference of at least 0.4% and a SD of this difference of 1.0%, an alpha of 0.05 and beta of 0.10, 250 patients per treatment group were required. With more than 250 patients included per treatment group, the OIS criterion has been met.
- The heterogeneity of the pooled estimate from the inTandem1-3 trials (I^2 is 0% ($p=0.45$)).
- This endpoint was driven by the category HbA1c $< 7\%$. HbA1c is a surrogate outcome measure for type 1 diabetes related long-term complications.
- There is no evidence for imprecision.
- As there are few events and the confidence interval of both the absolute and relative effect estimates includes appreciable benefit and harm, the quality of evidence is rated down by two levels for imprecision.
- Due to the specific side effects of sotagliflozin, blinding of participants may have been compromised and may have influenced this patient-reported outcome. However, polyuria was infrequent, and the influence of the side effect pattern should not have been that great that it severely influenced the patient-reported outcomes.

- j. The heterogeneity of the pooled estimate from the inTandem1 and 2 trials, including sotagliflozin 200 mg was (I^2 0% ($p=0.57$)).
- k. Although the improvement in treatment satisfaction assessed with DTSQ is expected to improve patient's QOL, it should be stressed that DTSQ does not assess QOL itself. Indeed, as QOL of patients with diabetes has been shown to be lower, a higher DTSQ score does not necessarily translate into higher QOL [42].
- l. As the CI is statistically significant, we do not downgrade for imprecision.
- m. The relative rates for symptomatic documented hypoglycaemia [≥ 55 ml/dl] were similar and significantly lower for sotagliflozin 200 mg groups than in placebo groups in the individual inTandem1 and 2 studies (inTandem1: RR 0.80 [95%CI: 0.67-0.96]; inTandem2: RR 0.76 [95%CI: 0.62-0.92]) for the mITT population. Also, in the mITT population, the proportion with ≥ 1 severe hypoglycaemia in the placebo groups were 9.7% and 5% and 200 mg sotagliflozin group 6.5% and 5% in inTandem1 and 2 studies, respectively. However, assessment of inconsistency has not been provided by a direct meta-analysis for the BMI subgroup by the MAH. Since this is unknown, the certainty of the evidence has been downgraded by one level for inconsistency
- n. There is no evidence for imprecision.
- o. Retrospective calculation of study power reveals that the power of the pooled analysis for this outcome is 0.29 (with a detected treatment difference of 34.5 events per 1000 person-years, and standard deviation of 298 [derived from 95%CI event rate in placebo group, and sample size of approximately 300 patients per group]). Therefore, the OIS criterion has not been met and certainty of evidence was downgraded by one level.
- p. As there are few events and the confidence interval of both the absolute and relative effect estimates includes appreciable benefit and harm the quality of evidence is rated down by two levels for imprecision.
- q. As there are few events and the confidence interval of the relative effect estimates includes appreciable benefit and harm (RR 1.10, 95% CI: 0.43-2.81, as calculated by the authors), the quality of evidence is rated down by two levels for imprecision.
- r. Retrospective calculation of study power reveals that the power of the pooled analysis for this outcome was 1.00 (with a detected treatment difference of 24.9 events per 1000 person-years, and standard deviation of 48 [derived from 95%CI event rate in placebo group, and sample size of 300 patients per group]). In addition, with a detected treatment difference of 24.9 and a SD of this difference of 48, an alpha of 0.05 and a beta of 0.10, 78 patients per treatment group were required. With approximately 300 patients per treatment group, the OIS criterion has been met.
- s. The adjunct of sotagliflozin to insulin, delivered by MDII or by CSII by an insulin pump (the latter is the CGM sub study), was accounted for in the studies by using CSII as a stratification factor at randomisation. CGM was blinded.
- t. Direct meta-analyses of the inTandem1 and 2 studies show that there is substantial heterogeneity (I^2 : 64%; $p=0.09$). inTandem1 shows a non-significant effect and inTandem2 a significant effect.
- u. Time in range is a surrogate outcome measure for type 1 diabetes related long-term microvascular complications (as is suggested by the MAH in the submission file: "the DCCT trial suggests that for participants with a similar time-in-range of around 52%, a 10% improvement may reduce the frequency of retinopathy by 20% from 10% to 8%, and the frequency of microalbuminuria by nearly 60% from 7% to 3%"). Whether this is independent from HbA1c, however, is not known and therefore the quality of the evidence is rated down by two levels for indirectness.
- v. Insulin dose, or a decrease therein, has not been validated as a surrogate outcome measure for patient-relevant outcome measures (e.g. micro/macrovascular complications, or quality of life). Therefore, the quality of the evidence is rated down by two levels for indirectness.
- w. Pre-specified endpoint.
- x. The heterogeneity of the pooled estimate from the inTandem1-3 trials, including both sotagliflozin 200 mg and 400 mg (dosages pooled since a dose effect was not present), was (I^2 35% ($p=0.19$)) and acceptable. Random effects model results presented. The patient numbers therefore represent the pooled 200/400 mg arms from the trials.
- y. Surrogate outcome measures for cardiovascular disease.
- z. Retrospective calculation of study power shows that the power of the pooled analysis is 0.26 (with a detected treatment difference of 2.4, and standard deviation of 12.8 [derived from the SE of 1.29 in the placebo group and sample size of 100 patients per group]). The OIS criterion has not been met.
- aa. Body weight is a surrogate outcome measure for cardiovascular disease.
- bb. Effect estimates presented in GRADE table are estimates from the pooled individual patient-data analyses, as submitted by the MAH for this assessment. They are in line with the estimates that are derived from aggregated meta-analyses on study level, if reported:
 - a. HbA1c: ES1: -0.25 [-0.14;-0.36]
 - b. Net benefit: not reported in submission file
 - c. DTSQ: 2.62 [1.92-3.31] in random effects model
 - d. Symptomatic/severe hypoglycaemia: not reported in submission file
 - e. DKA: not reported in submission file
 - f. Time in range: 8.5 [-1.9; 18.9]
 - g. Total insulin dose: ES1: -3.5 [-1.5; -5.9]
 - h. Systolic blood pressure: -2.1 [-0.4;-3.9]
 - i. Body weight: -3.0 [-2.3;-3.7]

Table A4. GRADE evidence profile. Sotagliflozin (400 mg) versus placebo, both as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D with BMI ≥ 27 kg/m² who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy (BMI ≥ 27 kg/m² subgroup).

- ES1 pool (SAF1) presented for 52 weeks if applicable (pooled individual patient-data presented, with aggregated meta-analyses on study level in footnotes)
- ES2 pool (SAF3) presented (for 24 weeks, for completeness and for providing information on quality of evidence when inTandem3 is included to ES1 pool)

Certainty assessment							Number of patients		Effect ^{bb}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Type 1 diabetes related micro/macrovacular complications (assessed by: Glycaemic control (HbA1c [%] mean difference from baseline)												
ES1 (52 wks)	RCTs	serious ^a	not serious ^b	serious ^c	not serious ^d	not found	313	298	NA	0.38 percentage points lower (0.27 to 0.49 lower)	⊕⊕○○ LOW	CRUCIAL
ES2 (24 wks)	RCTs	serious ^a	not serious ^b	serious ^c	not serious ^d	not found	692	668	NA	0.50 percentage points lower (0.43 to 0.57 lower)	⊕⊕○○ LOW	
Type 1 diabetes related micro/macrovacular complications (assessed by: Glycaemic control (HbA1c < 7.0%, difference in proportion from baseline)												
No data has been submitted											CRUCIAL	
Type 1 diabetes related micro/macrovacular complications (assessed by: Net Benefit (HbA1c < 7.0%, no severe hypoglycaemia, no diabetic ketoacidosis)												
inTandem1 (24 wks)	RCTs	not serious ^a	not serious ^e	serious ^f	not serious ^g	not found	85/175 (48.6%)	36/174 (20.7%)	OR 3.62 (2.26 to 5.80)	27.9 percentage points higher (18.3 to 37.4 higher)	⊕⊕⊕○ MODERATE	CRUCIAL
inTandem2 (24 wks)							46/138 (33.3%)	21/124 (16.9%)	OR 2.45 (1.36 to 4.41)	16.4 percentage points higher (6.1 to 26.7)	⊕⊕⊕○ MODERATE	
ES2 (24 wks)							240/692 (34.7%)	106/668 (15.9%)	OR 2.87 (2.21 to 3.73)	18.8 percentage points higher (14.3 to 23.3 higher)	⊕⊕⊕○ MODERATE	

Certainty assessment							Number of patients		Effect ^{bb}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		

Mortality (assessed by: number of deaths)

SAF1 (52 wks)	RCTs	not serious	not serious	not serious	very serious ^h	not found	0/313 (0%)	2/298 (0.7%)	NR	NR	⊕⊕○○ LOW	CRUCIAL
SAF3 (24 wks)	RCTs	not serious	not serious	not serious	NE	not found	NR/692	NR/668	NR	NR	NE	

Health-related quality of life (assessed by: treatment satisfaction with Diabetes Treatment Satisfaction Score [range 0-36, higher is better, mean difference from baseline])

ES1 (24 wks)	RCTs	serious ^{la}	not serious ^j	very serious ^k	not serious ^l	not found	313	298	OR 2.51 (1.54 to 3.49)	2.6 points higher (1.9 to 3.3 higher)	⊕○○○ VERY LOW	CRUCIAL
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Health-related quality of life (assessed by: EQ-5D-5L generic health status score [higher is better], and EQ-VAS [scale 0-100, higher is better], mean difference from baseline)

No data has been submitted											CRUCIAL
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Symptomatic documented hypoglycaemia with documented SMBG ≤ 55 mg/dL (assessed by: Event rate, n events per person per year)

ES1 (52 wks)	RCTs	serious ^a	serious ^m	not serious	not serious ^o	not found	NR/313	NR/298	NR	3.4 events per person-years lower (0.7 to 6.1 lower)	⊕⊕○○ LOW	CRUCIAL
ES2 (24 wks)	RCTs	serious ^a	serious ^m	not serious ⁿ	not serious ^o	not found	NR/692	NR/668	NR	2.5 events per person-years lower (0.9 to 4.1 lower)	⊕⊕○○ LOW	

Severe hypoglycaemia (assessed by: positive adjudication by blinded review committee [n events per 1000 person-years adjusted to patient's exposure])

Certainty assessment							Number of patients		Effect ^{bb}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
ES1 (52 wks)	RCTs	not serious	serious ^m	not serious	serious ^p	not found	12/313	22/298	IRR: 0.51 (0.24 to 1.02)	40.0 events per 1000 person-years lower (81.0 lower to 1.1 higher)	⊕⊕○○ LOW	CRUCIAL
ES2 (24 wks)	RCTs	not serious	serious ^m	not serious ⁿ	serious ^p	not found	21/692	32/668	IRR: 0.63 (0.36 to 1.08)	27.6 events per 1000 person-years lower (59.8 lower to 4.7 higher)	⊕⊕○○ LOW	

Adverse events leading to discontinuation of study treatment (n events/total)

SAF1 (52 wks)	RCTs	not serious	not serious	not serious	very serious ^q	not found	13/313 (4.2%)	13/298 (4.4%)	NR	NR	⊕⊕○○ LOW	CRUCIAL
SAF3 (24 wks)	RCTs	not serious	not serious	not serious	NE	not found	NR/692	NR/668	NR	NR	NE	

Severe adverse events (assessed by: severe treatment-related adverse events [n events/total])

SAF1 (52 wks)	RCTs	not serious	not serious	not serious	very serious ^r	not found	14/313 (4.5%)	8/298 (2.7%)	NR	NR	⊕⊕○○ LOW	CRUCIAL
SAF3 (24 wks)	RCTs	not serious	not serious	not serious	NE	not found	NR/692	NR/668	NR	NR	NE	

Diabetic ketoacidosis (assessed by: positively adjudication by blinded review committee [event rate per 1000 person-years adjusted to patient's exposure])

Certainty assessment							Number of patients		Effect ^{bb}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
SAF1 (52 wks)	RCTs	not serious	not serious	not serious	not serious ^s	not found	11/313	1/298	IRR: 10.2 (1.74 to 221.9)	34.0 events per 1000 person-years higher (10.6 to 57.3 higher)	⊕⊕⊕⊕ HIGH	CRUCIAL
SAF3 (up to 52 wks)	RCTs	not serious	not serious	not serious	not serious ^s	not found	20/738	2/716	IRR: 9.54 (2.59 to 60.5)	38.4 events per 1000 person-years higher (18.6 to 58.2 higher)	⊕⊕⊕⊕ HIGH	

Time in range (assessed by: percent time spent in target range [3.9-10.0 mmol/L ≥ 70 to ≤ 180 mg/dL], per 24 h, mean difference in % in the CGM sub study [24 weeks])

ES1 (24 wks)	RCTs	serious ^{la}	not serious ^u	very serious ^v	not serious	not found	65	58	NA	15.1 percent points higher (9.4 to 20.7 higher)	⊕○○○ VERY LOW	IMPORTANT
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Total insulin dosage (assessed by: mean difference in IU/day from baseline)

ES1 (24 wks)	RCTs	serious ^a	not serious	very serious ^w	not serious	not found	313	298	NA	6.6 IU/day lower (4.3 to 9.0 lower)	⊕○○○ VERY LOW	IMPORTANT
ES2 (24 wks)	RCTs	serious ^a	not serious	very serious ^w	not serious	not found	692	668	NA	6.6 IU/day lower (5.0 to 8.2 lower)	⊕○○○ VERY LOW	

Cardiovascular risk factors (assessed by: mean difference from baseline in systolic blood pressure [mm Hg], among patients with SBP of ≥ 130 mm Hg at baseline)

ES1 (24 wks)	RCTs	serious ^{xa}	not serious ^y	serious ^z	serious ^{aa}	not found	108	99	NA	2.5 mm Hg lower (5.8 lower to 0.8 higher)	⊕○○○ VERY LOW	IMPORTANT
ES2 (24 wks)	RCTs	serious ^{xa}	not serious ^y	serious ^z	not serious	not found	241	231	NA	2.6 mm Hg lower (0.4 to 4.7 lower)	⊕⊕○○ LOW	

Cardiovascular risk factors (assessed by: mean difference from baseline in body weight [kg] [52 weeks])

Certainty assessment							Number of patients		Effect ^{bb}		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
ES1 (52 wks)	RCTs	serious ^a	not serious	serious ^z	not serious	not found	313	298	NA	4.5 kg lower (3.8 to 5.2 lower)	⊕⊕○○ LOW	IMPORTANT
ES2 (24 wks)	RCTs	serious ^a	not serious	serious ^z	not serious	not found	692	668	NA	3.4 kg lower (3.0 to 3.7 lower)	⊕⊕○○ LOW	

Abbreviations:

CI: Confidence interval; NA: not applicable; NR: not reported in submission file; NE: not established due to missing information; IRR: incidence rate ratio; OR: odds ratio

Explanations

- a. The BMI group of ≥ 27 kg/m², for which sotagliflozin has received market authorisation, is a post-hoc sub group analysis from the mITT populations of the RCTs. We have decided not to further downgrade for risk of bias because of the post-hoc sub group analysis, since baseline variables of this sub group were similar between the intervention and placebo groups, and a pre-specified sub group-analysis by BMI ≥ 25 kg/m² vs <25 kg/m², for which was stratified for at randomisation in the inTandem3 study, did show similar patterns for relative effects. However, in the individual patient-data pooling of the data, there is uncertainty about the patient numbers included for outcomes that depict a change from baseline (inconsistent in comparison to the mITT numbers in the CONSORT flow-diagram). Therefore, certainty of evidence has been downgraded by one level for risk of bias.
- b. The heterogeneity of the pooled estimate from the inTandem and 2 trials (I^2) is 0% ($p=0.72$), and of the pooled inTandem1-3 trials is 0% ($p=0.42$).
- c. HbA1c is a surrogate outcome measure for type 1 diabetes related long-term micro/macrovascular complications. In the ES2 pool, the inTandem3 study did not apply insulin optimisation and had a higher baseline HbA1c level than the inTandem1 and 2 studies. However, it was decided not to downgrade for an extra level for indirectness since pooling of the relative effects of the inTandem3 study with the inTandem1 and 2 studies did not result in heterogeneity. Therefore, there are similar relative effects and there is no evidence of effect-modification of the relative effects by differences in study design with regard to insulin optimisation and therefore different HbA1c levels at baseline.
- d. In order to address the vulnerability of confidence intervals as a criterion for adequate precision, the optimal information size (OIS) can be considered as a necessary criterion. The OIS is applied as a rule according to the following: If the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial, consider rating down for imprecision. The inTandem2 trial states that with a detected treatment difference of at least 0.4% and a SD of this difference of 1.0%, an alpha of 0.05 and beta of 0.10, 250 patients per treatment group were required. With more than 250 patients included per treatment group, the Optimal Information Size (OIS) criterion has been met.
- e. The heterogeneity of the pooled estimate from the inTandem1-3 trials (I^2) is 0% ($p=0.50$).
- f. This endpoint was driven by the category HbA1c $<7\%$. HbA1c is a surrogate outcome measure for type 1 diabetes related long-term complications. In the ES2 pool it was decided not to downgrade for an extra level for indirectness since pooling of the relative effects of the inTandem3 study with the inTandem1 and 2 studies did not result in heterogeneity. Therefore, there are similar relative effects and there is no evidence of effect-modification of the relative effects by differences in study design with regard to insulin optimisation and therefore different HbA1c levels at baseline.
- g. There is no evidence for imprecision.
- h. As there are few events and the confidence interval of the relative effect estimates includes appreciable benefit and harm (RR 0.19, 95% CI: 0.01-3.98, as calculated by the authors) the quality of evidence is rated down by two levels for imprecision.
- i. Due to the specific side effects of sotagliflozin, blinding of participants may have been compromised and may have influenced this patient-reported outcome. However, polyuria was infrequent, and the influence of the side effect pattern should not have been that great that it severely influenced the patient-reported outcomes.
- j. The heterogeneity of the pooled estimate from the inTandem1 and 2 trials, including both sotagliflozin 200 mg and 400 mg (dosages pooled since a dose effect was not present) is (I^2) 0% ($p=0.50$).
- k. Although the improvement in treatment satisfaction assessed with DTSQ is expected to improve patient's QOL, it should be stressed that DTSQ does not assess QOL itself. Indeed, as QOL of patients with diabetes has been shown to be lower, a higher DTSQ score does not necessarily translate into higher QOL (45).
- l. There is no evidence for imprecision.
- m. Assessment of inconsistency has not been provided by a direct meta-analysis for the BMI subgroup by the MAH. Since this is unknown, the certainty of the evidence has been downgraded by one level for inconsistency.

- n. It was decided not to downgrade for an extra level for indirectness since pooling of the relative effects of the inTandem3 study with the inTandem1 and 2 study did result in a similar effect. Therefore, there are similar relative effects and there is no evidence of effect-modification of the relative effects by differences in study design with regard to insulin optimisation and therefore different HbA1c levels at baseline.
- o. There is no evidence for imprecision.
- p. SAF1: Retrospective calculation of study power reveals that the power of the pooled analysis for this outcome is 0.37 (with a detected treatment difference of 39.9 events per 1000 person-years, an SD of 298 [derived from the 95%CI of the effect in the placebo group and sample size of 300 patients per treatment]).
SAF3: Retrospective calculation of study power reveals that the power of the pooled analysis for this outcome is 0.33 (with a detected treatment difference of 27.6 events per 1000 person-years, an SD of 337 [derived from the 95%CI of the effect in the placebo group and sample size of 680 patients per treatment]). Therefore, in both study populations the OIS criterion has not been met.
- q. As there are few events and the confidence interval of the relative effect estimates includes appreciable benefit and harm (RR 0.95, 95% CI: 0.45-2.02, as calculated by the authors), the quality of evidence is rated down by two levels for imprecision.
- r. As there are few events and the confidence interval of the relative effect estimates includes appreciable benefit and harm (RR 1.67, 95% CI: 0.71-3.91, as calculated by the authors), the quality of evidence is rated down by two levels for imprecision.
- s. SAF1: Retrospective calculation of study power reveals that the power of the pooled analysis for this outcome was 1.00 (with a detected treatment difference of 34.0 events per 1000 person-years, and standard deviation of 48 [derived from 95%CI event rate in placebo group, and sample size of 300 patients per group]). In addition, with a detected treatment difference of 34.0 and a SD of this difference of 48, an alpha of 0.05 and a beta of 0.10, 78 patients per treatment group were required.
SAF3: Retrospective calculation of study power reveals that the power of the pooled analysis for this outcome was 1.00 (with a detected treatment difference of 38.4 events per 1000 person-years, and standard deviation of 74 [derived from 95%CI event rate in placebo group, and sample size of 725 patients per group]). In addition, with a detected treatment difference of 38.4 and a SD of this difference of 74, an alpha of 0.05 and a beta of 0.10, 79 patients per treatment group were required. Therefore, in both study populations, the OIS criterion has been met.
- t. The adjunct of sotagliflozin to insulin, delivered by MDII or by CSII by an insulin pump (the latter is the CGM sub study), was accounted for in the studies by using CSII as a stratification factor at randomisation. CGM was blinded.
- u. Direct meta-analyses of the inTandem1 and 2 studies show that there is some heterogeneity (I^2 : 46%; $p=0.17$). However, both effects point in the same direction. Random effects model results are presented.
- v. Time in range is a surrogate outcome measure for type 1 diabetes related long-term microvascular complications (as is suggested by the MAH in the submission file: “the DCCT trial suggests that for participants with a similar time-in-range of around 52%, a 10% improvement may reduce the frequency of retinopathy by 20% from 10% to 8%, and the frequency of microalbuminuria by nearly 60% from 7% to 3%”). Whether this is independent from HbA1c and therefore an independent surrogate outcome measure, however, is now known and therefore the quality of the evidence is rated down by two levels for indirectness.
- w. Insulin dose, or a decrease therein, has not been validated as a surrogate outcome measure for patient-relevant outcome measures (e.g. micro/macrovascular complications, or quality of life). Therefore, the quality of the evidence is rated down by two levels for indirectness.
- x. Pre-specified endpoint.
- y. The heterogeneity of the pooled estimate from the inTandem1-3 trials was (I^2) 0% ($p=0.96$) and acceptable.
- z. Surrogate outcome measures for cardiovascular disease.
- aa. Retrospective calculation of study power shows that the power of the pooled analysis is 0.28 (with a detected treatment difference of 2.5, and standard deviation of 12.8 [derived from the SE of 1.29 in the placebo group] and sample size of 100 patients per group).
- bb. Effect estimates presented in GRADE table are estimates from the pooled individual patient-data analyses, as submitted by the MAH for this assessment. They are in line with the estimates that are derived from aggregated meta-analyses on study level, if available:
 - a. HbA1c: ES1: -0.38 [-0.27;-0.49] and ES2: -0.49 [-0.42;-0.56]
 - b. Net benefit: not reported in submission file
 - c. DTSQ: 2.51 [1.54-3.49] in random effects model
 - d. Symptomatic/severe hypoglycaemia: not reported in submission file
 - e. DKA: not reported in submission file
 - f. Time in range: 15.1 [7.2 - 23.1]
 - g. Total insulin dose: ES1: not reported in submission file. ES2: -6.5 [-4.9;-8.2]
 - h. Systolic blood pressure: ES1: not reported in submission file. ES2: -2.4 [-0.2;-4.5]
 - i. Body weight: ES1: not reported in submission file. ES2: -3.4 [-3.0;-3.7]

Table A5. GRADE evidence profile. Sotagliflozin (400 mg) versus placebo, both as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy (mITT population).

- ES1 pool presented for 52 weeks if applicable (pooled individual patient-data presented, with aggregated meta-analyses on study level in footnotes)
- ES2 pool presented (only for 24 weeks) in order to provide information on quality of evidence when inTandem3 is included

Certainty assessment							Number of patients		Effect ^z		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
Type 1 diabetes related micro/macrovacular complications (assessed by: Glycaemic control (HbA1c [%] mean difference from baseline)												
ES1 (52 wks)	RCTs	serious ^a	not serious ^b	serious ^c	not serious ^d	not found	525	526	NA	0.32 percentage points lower (0.23 to 0.41 lower)	⊕⊕○○ LOW	CRUCIAL
ES2 (24 wks)	RCTs	serious ^a	not serious ^b	serious ^c	not serious ^d	not found	1224	1227	NA	0.43 percentage points lower (0.37 to 0.48 lower)	⊕⊕○○ LOW	
Type 1 diabetes related micro/macrovacular complications (assessed by: Glycaemic control (HbA1c < 7.0%, difference in proportion from baseline)												
ES1 (52 wks)	RCTs	not serious	not serious	serious ^c	not serious	not found	166/525 (31.6%)	96/526 (18.3%)	OR 2.09 (1.56 to 2.79)	NR	⊕⊕⊕○ MODERATE	CRUCIAL
ES2 (24 wks)	RCTs	not serious	not serious	serious ^c	not serious	not found	419/1224 (34.2%)	211/1227 (17.2%)	OR 2.54 (2.10 to 3.08)	NR	⊕⊕⊕○ MODERATE	
Type 1 diabetes related micro/macrovacular complications (assessed by: Net Benefit (HbA1c < 7.0%, no severe hypoglycaemia, no diabetic ketoacidosis)												
ES1 (52 wks)	RCTs	not serious	not serious ^e	serious ^f	not serious	not found	155/525 (19.5%)	88/526 (16.7%)	OR 2.10 (1.56 to 2.82)	12.8 percentage points higher (7.8 to 17.8 higher)	⊕⊕⊕○ MODERATE	CRUCIAL
ES2 (24 wks)	RCTs	not serious	not serious ^e	serious ^f	not serious	not found	399/1224 (32.6%)	204/1229 (16.6%)	OR 2.45 (2.02 to 2.98)	16.0 percentage points higher (12.7 to 19.4 higher)	⊕⊕⊕○ MODERATE	

Certainty assessment							Number of patients		Effect ^z		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		

Mortality (assessed by: number of deaths)

SAF1 (52 wks)	RCTs	not serious	not serious	not serious	very serious ^g	not found	0/525 (0%)	3/526 (0.6%)	OR 0.25 (0.03 to 2.23)	NR	⊕⊕○○ LOW	
SAF2 (24 wks)	RCTs	not serious	not serious	not serious	very serious ^g	not found	1/1224 (0.1%)	3/1229 (0.2%)	OR 0.56 (0.09 to 3.46)	NR	⊕⊕○○ LOW	

Health-related quality of life (assessed by: treatment satisfaction with Diabetes Treatment Satisfaction Score [range 0-36, higher is better, mean difference from baseline])

ES1 (24 wks)	RCTs	serious ^h	not serious ⁱ	very serious ^j	not serious ^k	not found	473	465	NR	2.1 points higher (1.6 to 2.7 higher)	⊕○○○ VERY LOW	CRUCIAL
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Health-related quality of life (assessed by: EQ-5D-5L generic health status score [higher is better], and EQ-VAS [scale 0-100, higher is better], mean difference from baseline)

ES1 (52 wks)	RCTs	serious ^l	not serious	not serious	serious ^l	not found	498	483	NR	EQ-5D-5L: 0.01 points higher (0.01 lower to 0.02 higher)	⊕⊕○○ LOW	CRUCIAL
ES1 (52 wks)	RCTs	serious ^l	not serious	not serious	not serious	not found	498	483	NR	EQ-VAS: 1.7 points higher (0.11 to 3.2 higher)	⊕⊕⊕○ MODERATE	

Symptomatic documented hypoglycaemia with documented SMBG ≤ 55 mg/dL (assessed by: Event rate, n events per person per year)

ES1 (52 wks)	RCTs	serious ^a	not serious ^m	not serious	not serious ⁿ	not found	525	526	IRR 0.82 (0.72 to 0.94)	NR	⊕⊕⊕○ MODERATE	CRUCIAL
ES2 (24 wks)	RCTs	serious ^a	not serious ^m	not serious	not serious ⁿ	not found	1224	1229	IRR 0.83 (0.75 to 0.91)	NR	⊕⊕⊕○ MODERATE	

Severe hypoglycaemia (assessed by: positive adjudication by blinded review committee [n events per 1000 person-years adjusted to patient's exposure])

Certainty assessment							Number of patients		Effect ^z		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
ES1 (52 wks)	RCTs	not serious	not serious	not serious	not serious ^o	not found	525	526	IRR: 0.59 (0.35 to 0.98)	34 events per 1000 person-years lower (1.6 to 66.5 lower)	⊕⊕⊕⊕ HIGH	CRUCIAL
ES2 (24 wks)	RCTs	not serious	not serious	not serious	serious ^o	not found	1224	1229	IRR: 0.94 (0.60 to 1.14)	5 events per 1000 person-years lower (38.1 lower to 28.1 higher)	⊕⊕⊕○ MODERATE	

Adverse events leading to discontinuation of study treatment (n events/total)

SAF1 (52 wks)	RCTs	not serious	not serious	not serious	not serious ^p	not found	35/525 (6.7%)	20/526 (3.8%)	OR 1.81 (1.03 to 3.18)	NR	⊕⊕⊕⊕ HIGH	CRUCIAL
SAF3 (24 wks)	RCTs	not serious	not serious	not serious	not serious ^p	not found	69/1224 (5.6%)	29/1229 (2.4%)	OR 2.48 (1.59 to 3.85)	NR	⊕⊕⊕⊕ HIGH	

Severe adverse events (assessed by: severe treatment-related adverse events [n events/total])

SAF1 (52 wks)	RCTs	not serious	not serious	not serious	serious ^q	not found	22/525 (4.2%)	11/526 (2.1%)	OR 2.05 (0.98 to 4.29)	NR	⊕⊕⊕○ MODERATE	CRUCIAL
SAF3 (24 wks)	RCTs	not serious	not serious	not serious	not serious	not found	29/1224 (2.4%)	14/1229 (1.1%)	OR 2.11 (1.11 to 4.02)	NR	⊕⊕⊕⊕ HIGH	

Diabetic ketoacidosis (assessed by: positively adjudication by blinded review committee [event rate per 1000 person-years adjusted to patient's exposure])

Certainty assessment							Number of patients		Effect ^z		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
SAF1 (52 wks)	RCTs	not serious	not serious	not serious	not serious	not found	525	526	IRR: 19.9 (3.67 to 416)	39.8 events per 1000 person-years higher (21.0 to 58.6 higher)	⊕⊕⊕⊕ HIGH	CRUCIAL
SAF3 (up to 52 wks)	RCTs	not serious	not serious	not serious	not serious	not found	1224	1229	IRR: 8.32 (3.19 to 27.56)	54.8 events per 1000 person-years higher (32.3 to 77.2 higher)	⊕⊕⊕⊕ HIGH	

Time in range (assessed by: percent time spent in target range [3.9-10.0 mmol/L ≥ 70 to ≤ 180 mg/dL], per 24 h, mean difference in % in the CGM sub study [24 weeks])

ES1 (24 wks)	RCTs	serious ^{ar}	not serious ^s	very serious ^t	not serious	not found	65	58	NA	15.1 percent points higher (9.4 to 20.7 higher)	⊕○○○ VERY LOW	IMPORTANT
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Total insulin dosage (assessed by: mean difference in IU/day from baseline)

ES1 (24 wks)	RCTs	serious ^a	not serious	very serious ^u	not serious	not found	313	298	NA	6.6 IU/day lower (4.3 to 9.0 lower)	⊕○○○ VERY LOW	IMPORTANT
ES2 (24 wks)	RCTs	serious ^a	not serious	very serious ^u	not serious	not found	692	668	NA	6.6 IU/day lower (5.0 to 8.2 lower)	⊕○○○ VERY LOW	

Cardiovascular risk factors (assessed by: mean difference from baseline in systolic blood pressure [mm Hg], among patients with SBP of ≥ 130 mm Hg at baseline)

ES1 (24 wks)	RCTs	serious ^{va}	not serious ^w	serious ^x	serious ^y	not found	108	99	NA	2.5 mm Hg lower (5.8 lower to 0.8 higher)	⊕○○○ VERY LOW	IMPORTANT
ES2 (24 wks)	RCTs	serious ^{va}	not serious ^w	serious ^x	not serious	not found	241	231	NA	2.6 mm Hg lower (0.4 to 4.7 lower)	⊕⊕○○ LOW	

Cardiovascular risk factors (assessed by: mean difference from baseline in body weight [kg] [52 weeks])

Certainty assessment							Number of patients		Effect ^z		Certainty	Importance
N studies	Study design	Risk of bias	Inconsistence	Indirectness	Imprecision	Other factors	Sotagliflozin (400 mg)	placebo	Relative (95% CI)	Absolute (95% CI)		
ES1 (52 wks)	RCTs	serious ^a	not serious	serious ^x	not serious	not found	313	298	NA	4.5 kg lower (3.8 to 5.2 lower)	⊕⊕○○ LOW	IMPORTANT
ES2 (24 wks)	RCTs	serious ^a	not serious	serious ^x	not serious	not found	692	668	NA	3.4 kg lower (3.0 to 3.7 lower)	⊕⊕○○ LOW	

Abbreviations:

CI: Confidence interval; NA: not applicable; NR: not reported in submission file; NE: not established due to missing information; IRR: incidence rate ratio; OR: odds ratio

Explanations

- All studies used a modified mITT approach but this did not result in exclusion of an unacceptable number of participants from the studies (according to the CONSORT flow-diagrams). In the individual patient-data pooling of the data, however, there is uncertainty about the patient numbers included (inconsistent in comparison to the mITT numbers in the CONSORT flow-diagram). Therefore, certainty of evidence has been downgraded by one level for risk of bias.
- The heterogeneity of the pooled estimate from the inTandem1 and 2 trials (I^2) is 0% ($p=0.91$), and of the pooled inTandem1-3 trials is 20% ($p=0.29$).
- HbA1c is a surrogate outcome measure for type 1 diabetes related long-term micro/macrovacular complications. In the ES2 pool, the inTandem3 study did not apply insulin optimisation and had a higher baseline HbA1c level than the inTandem1 and 2 studies. However, it was decided not to downgrade for an extra level for indirectness since pooling of the relative effects of the inTandem3 study with the inTandem1 and 2 studies did not result in heterogeneity. Therefore, there are similar relative effects and there is no evidence of effect-modification of the relative effects by differences in study design with regard to insulin optimisation and therefore different HbA1c levels at baseline.
- In order to address the vulnerability of confidence intervals as a criterion for adequate precision, the optimal information size (OIS) can be considered as a second, necessary criterion. The OIS is applied as a rule according to the following: If the total number of patients included in a systematic review is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial, consider rating down for imprecision. The inTandem2 trial states that with a detected treatment difference of at least 0,4% and a SD of this difference of 1.0%, an alpha of 0.05 and beta of 0.10, 250 patients per treatment group were required. With more than 250 patients included per treatment group, the Optimal Information Size (OIS) criterion has been met.
- The heterogeneity of the pooled estimate from the inTandem1-2 trials (I^2) is 0% ($p=0.85$) and from the inTandem1-3 trials is 0% ($p=0.58$).
- This endpoint was driven by the category HbA1c <7%. HbA1c is a surrogate outcome measure for type 1 diabetes related long-term complications. It was decided not to downgrade for an extra level for indirectness for the ES2 pool since pooling of the relative effects of the inTandem3 study with the inTandem1 and 2 study did not result in heterogeneity. Therefore, there are similar relative effects and there is no evidence of effect-modification of the relative effects by differences in study design with regard to insulin optimisation and therefore different HbA1c levels at baseline.
- As there are few events and the confidence interval of both the absolute and relative effect estimates includes appreciable benefit and harm the quality of evidence is rated down by two levels for imprecision.
- Due to the specific side effects of sotagliflozin, blinding of participants may have been compromised and may have influenced this patient-reported outcome. However, polyuria was infrequent, and the influence of the side effect pattern should not have been that great that it severely influenced the patient-reported outcomes. The patient numbers assessed do not represent the mITT population, and a significant number have been excluded from analyses.
- The heterogeneity of the pooled estimate from the inTandem1 and 2 trials, including sotagliflozin 400 mg is (I^2) 55% ($p=0.14$). However, effects point in the same direction.
- Although the improvement in treatment satisfaction assessed with DTSQ is expected to improve patient's QOL, it should be stressed that DTSQ does not assess QOL itself. Indeed, as QOL of patients with diabetes has been shown to be lower, a higher DTSQ score does not necessarily translate into higher QOL [42].
- There is no evidence for imprecision. There is no evidence for imprecision.
- The confidence interval spans no effect.
- The heterogeneity of the pooled estimate from the inTandem 1 and 2 trials (I^2) is 0% ($p=0.38$). The I^2 of the pooled estimate from inTandem1-3 trials is 8.4% ($p=0.34$)

- n. The OIS criterion has been met.
- o. ES1: There is no evidence for imprecision.
 - a. ES2: Retrospective power calculation reveals a power of 0.05 for the detected treatment difference of 5 events per 1000 person-years, and with alpha 0.05, an SD of 425 (calculated from the 95% CI of the effect in the placebo group), and 1225 participants in each treatment group.
- p. There is no evidence for imprecision.
- q. The confidence interval spans no effect.
- r. The adjunct of sotagliflozin to insulin, delivered by MDII or by CSII by an insulin pump (the latter is the CGM sub study), was accounted for in the studies by using CSII as a stratification factor at randomisation. CGM was blinded.
- s. Direct meta-analyses of the inTandem1 and 2 studies show that there is some heterogeneity (I^2 : 46%; p -0.173). However, both effects point in the same direction. Random effects model results are presented.
- t. Time in range is a surrogate outcome measure for type 1 diabetes related long-term microvascular complications (as is suggested by the MAH in the submission file: “the DCCT trial suggests that for participants with a similar time-in-range of around 52%, a 10% improvement may reduce the frequency of retinopathy by 20% from 10% to 8%, and the frequency of microalbuminuria by nearly 60% from 7% to 3%”). Whether this is independent from HbA1c, however, is not known and therefore the quality of the evidence is rated down by two levels for indirectness.
- u. Insulin dose, or a decrease therein, has not been validated as a surrogate outcome measure for patient-relevant outcome measures (e.g. micro/macrovascular complications, or quality of life). Therefore, the quality of the evidence is rated down by two levels for indirectness.
- v. Pre-specified endpoint.
- w. The heterogeneity of the pooled estimate from the inTandem1-3 trials, including both sotagliflozin 200 mg and 400 mg (dosages pooled since a dose effect was not present) was (I^2) 35% (p =0.19) and acceptable. Random effects model results presented. The patient numbers therefore represent the pooled 200/400 mg arms from the trials.
- x. Surrogate outcome measures for cardiovascular disease.
- y. The confidence interval spans no effect.
- z. Effect estimates presented in GRADE table are estimates from the pooled individual patient-data analyses, as submitted by the MAH for this assessment. They are in line with the estimates that are derived from aggregated meta-analyses on study level, if available:
 - a. HbA1c: ES1: -0.38 [-0.27; -0.49] and ES2: -0.49 [-0.42;-0.56]
 - b. Net benefit: not reported in submission file
 - c. DTSQ: 2.51 [1.54-3.49] in random effects model
 - d. Symptomatic/severe hypoglycaemia: not reported in submission file
 - e. DKA: not reported in submission file
 - f. Time in range: 15.1 [7.2 - 23.1]
 - g. Total insulin dose: ES1: not reported in submission file. ES2: -6.5 [-4.9;-8.2]
 - h. Systolic blood pressure: ES1: not reported in submission file. ES2: -2.4 [-0.2;-4.5]
 - i. Body weight: ES1: not reported in submission file. ES2: -3.4 [-3.0;-3.7]

Table A6. GRADE evidence profile for NMA

GRADE for treatments and studies included in the indirect treatment comparison (ITC). All treatments are considered as an adjunct to optimised insulin therapy, for providing improved glycaemic control in adults with T1D who have failed to achieve adequate glycaemic control despite individually optimised insulin therapy. As this GRADE assessment is based on the ITC the population of interest is the full study population and outcomes are measured at 24 weeks. Most studies include multiple doses, however we focus here on the highest dose in each study. As separate meta-analyses were not reported for each comparison, the results for each direct comparison from the NMA (RE model) are reported here. Therefore, these figures may differ slightly from the numbers in the table above. Note that also similar outcomes may have been assessed differently in the NMA, for example percentage change from baseline is provided in the NMA, whereas absolute change from baseline was assessed in the GRADE table above.

				Certainty assessment					Number of patients		Effect		Certainty	Importance
N studies	Study design	Arm1	Arm2	Risk of bias	Inconsistency	Indirectness	Imprecision ⁿ	Other factors	Intervention	Placebo	Relative (95% CrI)	Absolute (95% CrI)		

Type 1 diabetes related micro/macrovascular complications (assessed by: Glycaemic control (HbA1c percent change from baseline [24 weeks])

3	RCTs	Sotagliflozin 400mg	Placebo	serious ^a	not serious ^d	Serious ^m	not serious ^o	not found	1110	1113	NA	-0.42 (-0.48, -0.36)	⊕⊕○○	CRUCIAL
													low	
2	RCTs	Dapagliflozin 10 mg	Placebo	serious ^a	not serious ^e	Serious ^m	not serious ^p	not found	496	494	NA	-0.43 (-0.53, -0.33)	⊕⊕○○	CRUCIAL
													low	
2	RCTs	Empagliflozin 25mg	Placebo	not serious ^b	not serious ^f	Serious ^m	not serious ^q	not found	486	481	NA	-0.53 (-0.62, -0.44)	⊕⊕⊕○	CRUCIAL
													moderate	

Any hypoglycaemia (proportion of patients [24 weeks])														
3	RCTs	Sotagliflozin 400mg	Placebo	not serious ^c	not serious ^g	not serious	Serious ^f	not found	1187/1224	1184/1229	OR=	NA	⊕⊕⊕○	CRUCIAL
											1.23 (0.78, 1.91)		moderate	
2	RCTs	Dapagliflozin 10 mg	Placebo	not serious ^c	not serious ^h	not serious	Serious ^f	not found	466/566	441/532	OR=	NA	⊕⊕⊕○	CRUCIAL
											0.98 (0.71, 1.34)		moderate	
1	RCTs	Empagliflozin 25 mg	Placebo	not serious ^c	NA	not serious	Serious ^f	not found	151/245	148/241	OR=	NA	⊕⊕⊕○	CRUCIAL
											1.01 (0.7, 1.46)		moderate	

Severe hypoglycaemia (assessed by: positive adjudication by blinded review committee (proportion of patients [24 weeks]))

3	RCTs	Sotagliflozin 400mg	Placebo	not serious ^c	not serious ⁱ	not serious	Serious ^f	not found	39/1224	42/1229	OR= 0.9 (0.59, 1.38)	NA	⊕⊕⊕○	CRUCIAL
													moderate	
2	RCTs	Dapagliflozin 10 mg	Placebo	not serious ^c	not serious ^j	not serious	Serious ^f	not found	42/566	42/532	OR= 0.99 (0.63, 1.56)	NA	⊕⊕⊕○	CRUCIAL
													moderate	
1	RCTs	Empagliflozin 2.5 mg	Placebo	not serious ^c	NA	not serious	Very Serious ^s	not found	3/241	6/241	OR= 0.49 (0.12, 2)	NA	⊕⊕○○	CRUCIAL
													low	

Diabetic ketoacidosis (assessed by: positively adjudication* by blinded review committee (proportion of patients [24 weeks]))

3	RCTs	Sotagliflozin 400mg	Placebo	not serious ^c	not serious ^k	not serious	Not serious ^t	not found	33/1224	4/1229	OR= 6.52 (2.52, 16.88)	NA	⊕⊕⊕⊕	CRUCIAL
												high		
2	RCTs	Dapagliflozin 10 mg	Placebo	not serious ^c	not serious ^l	not serious	Serious ^u	not found	11/566	3/532	OR= 3.19 (0.36, 28.10)	NA	⊕⊕⊕○	CRUCIAL
												moderate		
1	RCTs	Empagliflozin 2.5 mg	Placebo	not serious ^c	NA	not serious	Very Serious ^s	not found	2/241	3/241	OR= 0.66 (0.11, 4.01)	NA	⊕⊕○○	CRUCIAL
													low	

CrI: Credible interval (from result of Bayesian NMA); **NA:** not applicable; **OR;** odds ratio

Explanations

- Outcomes examining change from baseline were subject to larger attrition for sotagliflozin and dapagliflozin. Therefore, we down-rate these outcomes for risk of bias.
- EASE trials had lower attrition for change from baseline than the inTandem or DEPICT trials.
- Binary outcomes showed a low risk of bias for the majority of domains.
- The heterogeneity of the pooled estimate (I^2) from the inTandem1&2&3 trials for CFB in HbA1c is 6.3% ($p=0.344$).
- The heterogeneity of the pooled estimate from the DEPICT1&2 trials for CFB in HbA1c is 0% ($p=0.344$).
- The heterogeneity of the pooled estimate from the EASE2&3 trials for CFB in HbA1c is 0% ($p=1$).
- The heterogeneity of the pooled estimate (I^2) from the inTandem1&2&3 trials for any hypoglycaemia is 0% ($p=0.538$).
- The heterogeneity of the pooled estimate from the DEPICT1&2 trials for any hypoglycaemia is 0% ($p=0.938$).
- The heterogeneity of the pooled estimate (I^2) from the inTandem1&2&3 trials for severe hypoglycaemia is 0% ($p=0.376$).
- The heterogeneity of the pooled estimate from the DEPICT1&2 trials for severe hypoglycaemia is 0% ($p=0.593$).
- The heterogeneity of the pooled estimate (I^2) from the inTandem1&2&3 trials for DKA is 0% ($p=0.717$).
- The heterogeneity of the pooled estimate from the DEPICT1&2 trials for DKA is 50.1% ($p=0.157$), which is considered moderately high. However, relative effects are in the same direction so we therefore rate as not serious. For DEPICT1 the proportion with DKA was 1.69% (Dapagliflozin 10mg) vs 1.15% and for DEPICT2 the proportion with DKA was 2.22% (Dapagliflozin 10mg) vs 0%.
- HbA1c is a surrogate outcome measure for type 1 diabetes related long-term micro/macrovacular complications.
- For continuous outcomes (% CFB HbA1c), the difference is obtained from the results of the NMA, the SD is taken from the largest SD for one of the arms in the trial. For binomial outcomes proportions are taken as the average over the individual trials. Alpha=0.05, beta=0.2.
- Pooled numbers are greater than the required OIS (57) for % CFB HbA1c in the inTandem &2&3 trials in for each treatment group and the CrI did not span no effect.
- Pooled numbers are greater than the required OIS (58) for % CFB HbA1c in the DEPICT1&2 trials in for each treatment group and the CrI did not span no effect.
- Pooled numbers are greater than the required OIS (34) for % CFB HbA1c in the EASE2&3 trials in for each treatment group and the CrI did not span no effect.
- Pooled numbers are less than the required OIS (>2,000) in for each treatment group and the CrI spans no effect.
- The CrI spans no effect. In addition, the total number of events is very small so we downgrade by 2 levels.
- Pooled numbers are greater than the required OIS (414) for proportion DKA in the inTandem1&2&3 trials in for each treatment group and the CrI did not span no effect.
- Pooled numbers are less than the required OIS (1,061) for proportion DKA in the DEPICT1&2 trials in for each treatment group and the CrI spans no effect.