National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Dapagliflozin, empagliflozin and sotagliflozin, in combination with insulin, for treating type 1 diabetes [ID1217]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca	Yes	Comment noted. No action required.
	Boehringer Ingelheim	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Sanofi	None.	Comment noted. No action required.
	UKCPA Diabetes & Endocrinology Group	yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	AstraZeneca	Yes	Comment noted. No action required.
	Boehringer Ingelheim	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Sanofi	None.	Comment noted. No action required.
	UKCPA Diabetes & Endocrinology Group	yes	Comment noted. No action required.
Timing Issues	AstraZeneca	AstraZeneca have filed and a licence is anticipated in [redacted]. We therefore propose that timings align with MA expectations. Based on publicly available information, [redacted]	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. To ensure timeliness, each technology will be appraised by the Single Technology Appraisal (STA) process. No action required.

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	Boehringer Ingelheim	[redacted] We believe clarity is needed on how NICE will address any potential timing difference of Marketing Authorisation between the technologies in this MTA: 1. Will the appraisal be postponed until the latest Marketing Authorisation is granted? 2. If the final licence indication is different, how will this be accounted in the MTA process?	Comments noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. To ensure timeliness, each technology will be appraised by the Single Technology Appraisal (STA) process. No action required.
	Royal College of Pathologists	Routine	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. No action required.
	Sanofi	CHMP opinion for sotagliflozin is expected [redacted] and Marketing Authorisation is expected in [redacted]. Sanofi will endeavour to keep NICE informed of any regulatory updates should they arise that would impact the appraisal scope or timelines. Sanofi are otherwise supportive of the current	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the

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		assessment schedule to enable access for patients as soon as possible following Marketing Authorisation.	marketing authorisation for a technology is granted. To ensure timeliness, each technology will be appraised by the Single Technology Appraisal (STA) process. No action required.
	UKCPA Diabetes & Endocrinology Group	urgent	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when the marketing authorisation for a technology is granted. No action required.
Additional comments on the draft remit	Sanofi	None.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	Thank you for including the statement around weight gain and hypoglycaemia as concerns with insulin, as requested in our previously submitted consultation form in October 2017. Further to this, we believe it would be worth highlighting that a significant proportion of patients treated with insulin are not meeting glycaemic targets, as well as other patient-relevant outcomes, to highlight the unmet need in the Type 1 diabetic population. For example, the NDA reported that only 30% of T1D patients achieved the target of HbA1c ≤58mmol (7.5%) in 2016-17	Comments noted. The background section has been amended.
	Boehringer Ingelheim	Yes	Comment noted. No action required.
	Royal College of Pathologists	No change suggested	Comment noted. No action required.
	Sanofi	None.	Comment noted. No action required.
	UKCPA Diabetes & Endocrinology Group	In the background section (line 4) the wording 'over years' might need reconsidering. The course to complications in diabetes is something that varies greatly in individuals i.e. in some it is decades and in some it might be months depending on the complication. You might consider using 'over the course of the disease' or similar to avoid this. In the background section (line 7) we would like to add in 'insulin' to treatment to be specific that it is the insulin that adds weight and one of the reasons why adjunctive medications with weight loss potential are being explored. We also felt a sentence or two could be added at this point to	Comments noted. The background section has been amended. The clinical effectiveness of SGLT-2 inhibitors will be considered in this appraisal and therefore, it is not appropriate to

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		better explain the other reasons for this TA. That in addition to improving glycaemic control in this population current evidence demonstrated a reduction in the total daily insulin dose, weight, and blood pressure when an SGLT2 inhibitor is used as adjunct therapy to insulin.	include in the background section.
The technology/ intervention	AstraZeneca	For the text*: "Dapagliflozin, empagliflozin, and sotagliflozin are being studied in combination with insulin in placebo controlled trials"* Propose to change to: *"Dapagliflozin, empagliflozin, and sotagliflozin are being studied in placebo controlled trials, in combination with adjustable insulin (multiple daily injections and subcutaneous insulin infusion)"*	Comment noted. At the scoping workshop, the clinical experts stated that they would not expect substantial differences for people treated with different insulin regimes. Therefore, no amendment has been made to this wording.
	Boehringer Ingelheim	Yes	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Sanofi	The text currently states: "Inhibition of SGLT-1 predominately reduces glucose absorption within the gut." We propose the following wording is more accurate and line with regulatory description: "Inhibition of SGLT-1 blocks transportation of glucose and galactose in the gut and reduces postprandial glucose".	Comments noted. This section provides a simple explanation of the actions of SGLT-1 inhibitors. No action required.

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	UKCPA Diabetes & Endocrinology Group	yes	Comment noted. No action required.
Population	AstraZeneca	Yes, the population is appropriate. [redacted]	Comment noted. No action required.
	Boehringer Ingelheim	Boehringer Ingelheim believes that "*inadequately controlled*" should be clearly defined in the scope. In addition, clarity is needed for the definition of insulin monotherapy. It should be clarified that whether insulin monotherapy includes all insulin analogues. Treatment regime should also be clarified (e.g. multiple dose insulin injection [MDI] regime and continuous subcutaneous insulin infusion [CSII]).	Comment noted. At the scoping workshop, there was no consensus on the definition of 'inadequately controlled', and it was stated that it was unlikely that it would be clearly defined in the marketing authorisations of the technologies. Therefore, the scope has been left broad. At the scoping workshop, the clinical experts stated that they would not expect substantial differences for people treated with

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			different insulin regimes. Therefore, no changes to the scope required.
	Royal College of Pathologists	These treatments might also be considered in people with type 1 diabetes and obesity (even if glycaemic control is on target).	Comment noted. The clinical trials for dapagliflozin, empagliflozin and sotagliflozin are for people with type 1 diabetes whose blood sugar levels are not controlled on insulin therapy. No action required.
	Sanofi	The population is stated as “Adults with type 1 diabetes that is inadequately controlled on insulin monotherapy”. Sanofi would welcome further clarification from NICE on the definition of “inadequately controlled”. Current NICE guidelines (NG17) suggest a target HbA1c of 6.5% (48 mmol/mol) or lower for adults with type 1 diabetes (T1D). We propose that “uncontrolled” in this context may be defined as HbA1c >6.5%.	Comment noted. At the scoping workshop, there was no consensus on the definition of ‘inadequately controlled’, and it was stated that it was unlikely that it would be clearly defined in the marketing authorisations of the technologies.

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		We also request further clarification on the definition of “insulin monotherapy”. We are concerned that this may be interpreted as basal insulin only whereas we believe the appropriate population may be on any insulin regimen i.e. multiple dose injection (MDI).	Therefore, the scope has been left broad. At the scoping workshop, the clinical experts stated that they would not expect substantial differences for people treated with different insulin regimes. Therefore, no changes to the scope required.
	UKCPA Diabetes & Endocrinology Group	The group felt this could be expanded upon to be clear about what is being looked at. The group felt that ‘Inadequately controlled ‘is quite vague and it might help to specify if this is just high HbA1c or is it that plus other factors including variability in blood glucose, regular hypos and DKAs etc	Comment noted. At the scoping workshop, there was no consensus on the definition of ‘inadequately controlled’, and it was stated that it was unlikely that it would be clearly defined in the marketing authorisations of the technologies. Therefore, the scope has been left broad.
Comparators	AstraZeneca	Yes – insulin is appropriate as this is the only treatment licensed and available on the NHS in T1D currently.	Comment noted. At the scoping workshop, the

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		Given the current evidence, metformin is not considered an appropriate comparator. Primarily, metformin is not licenced in the UK for the treatment of patients with T1D. In addition, a UK clinical specialist in Type 1 diabetes informed AstraZeneca that metformin has historically been used in a small proportion of patients on a trial basis with variable clinical outcomes. However, since the results of the REMOVAL study[1] were published in 2017, use of metformin in T1DM has further declined as this trial did not support the use of metformin to improve glycaemic control in adult patients with type 1 diabetes. [1] *Petrie JL et al. LAN DIAB ENDO 2017*	clinical experts stated that metformin is used in a small proportion of patients in clinical practice. Insulin in combination with metformin has therefore been included in the scope.
	Boehringer Ingelheim	Boehringer Ingelheim considers the comparators are appropriate. However, clarity is needed for the definition of insulin monotherapy as well as the treatment regime to be included.	Comment noted. At the scoping workshop, the clinical experts stated that they would not expect substantial differences for people treated with different insulin regimes. Therefore, no changes to the scope required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
	Sanofi	In the proposed comparators it is stated that: “The interventions will also be compared with each other”.	Comments noted. Each of the technologies will now be considered in separate appraisals and

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		In line with the approach preferred in the NICE Methods Guide, the established comparator is insulin therapy alone. At the time of assessment the other interventions in this MTA will not be established as standard of care. Due to the pre-authorisation status of all three interventions, all relevant data may not be publically available to enable a comparison. We therefore propose to include all interventions and comparators in the systematic review and conduct a network meta-analysis where feasible. However, insufficient data may preclude a full analysis. As this is a MTA, the Assessment Group may be in a better position to undertake this aspect of the assessment.	the other SGLT-2 inhibitors will be included "subject to ongoing NICE appraisal" as comparators where appropriate.
	UKCPA Diabetes & Endocrinology Group	Canagliflozin is not included in this MTA process. We are aware of the trial (Efficacy and Safety of Canagliflozin, a Sodium Glucose Cotransporter 2 Inhibitor, as Add-On to Insulin in Patients With Type 1 Diabetes[1]) which demonstrates efficacy in this population and so should potentially be considered as a comparator. We are aware that this trial along with the trials for sotagliflozin and dapagliflozin demonstrated increased rates of DKA. Given that this appears to be a class effect we do not believe it should be excluded for this reason. We are also aware that a small increase in lower limb amputations in patients taking canagliflozin was shown in two clinical trials, CANVAS and CANVAS-R. If this is the reason for exclusion we feel that this should be made clear. In the MTA process for monotherapy in treating type 2 diabetes (TA390) and combination therapy for treating type 2 diabetes (TA288, TA315, TA336), all three SGLT2 inhibitors (dapagliflozin, canagliflozin, and empagliflozin) have been considered together. There is no clear reason for exclusion and we	Comments noted. Canagliflozin was not mentioned as current practice in the NHS for treating type 1 diabetes and therefore has not been considered as a comparator in the scope.

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		feel that this should be added if it is felt that canagliflozin should specifically not be used to treat type 1 diabetes. 1. R.R. Henry, P. Thakkar, C. Tong, D. Polidori and M. Alba. Diabetes Care 2015 Dec; 38(12): 2258-2265. https://doi.org/10.2337/dc15-1730 The group felt it would like to see the comparators broken down into the following if possible: Insulin pump therapy +/- metformin Insulin basal/bolus regimen +/- metformin Insulin any other regimen +/- metformin As well as looking overall at insulin therapy +/- metformin It is possible that different insulin regimens may shift the cost/effectiveness of adding adjunctive therapies e.g. someone who is very well controlled on a basal bolus regimen might not benefit as greatly from adjunctive therapy as someone less well controlled on a mixed insulin regimen. It would be interesting to see if there was a difference overall if the evidence is there. We appreciate that NICE must work to the confines of where evidence exists.	At the scoping workshop, the clinical experts stated that they would not expect substantial differences for people treated with different insulin regimes. Therefore, no changes to the scope required.
Outcomes	AstraZeneca	We suggest adding total daily insulin dose back into the scope (we note that this was originally included and has been subsequently removed). We also suggest to include change in weight; these are both patient-relevant outcomes.	Comments noted. These outcomes have been added to the scope.

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	Boehringer Ingelheim	Boehringer Ingelheim broadly agrees with the outcomes selected within the draft scope, and would like to add the following comments: 1. It should be noted that mortality and complication of diabetes (including CV, renal and eye) can only be modelled by modification of risk factors such as glycaemic control, blood pressure and lipids. Trial duration is likely too short for any meaningful differences to be captured. 2. In addition to BMI, change of body weight should be included as an outcome measure. **3.** "total insulin dose" was included in the previous draft scope and relevant for this patient populations. This should be added as an outcomes measure.	Comments noted. These outcomes have been added to the scope.
	Royal College of Pathologists	Suggest add lower limb amputations to this.	Comment noted. This outcome has been added to the scope.
	Sanofi	The outcomes listed capture most of the relevant endpoints for T1D. While HbA1c is used as a primary outcome to assess glycaemic control and as a surrogate for risk of developing complications, it has limitations. It does not capture short-term variations in blood glucose or exposure to hypoglycaemia and hyperglycaemia; it also does not capture the impact of blood glucose variations on individuals' quality of life. As a result, a number of other endpoints are emerging as being clinically relevant to the management of T1D. These include glycaemic time-in-range (TIR) and reduction in post-prandial glucose[1]. TIR captures fluctuations in glucose levels and not just more acute instances of hypo- or hyperglycaemia. Post-prandial blood glucose plays an important role in glycaemic control and glycaemic variability on a day-to-day basis and therefore provides additional	Comments noted. 'Blood glucose variability' has been added to the scope.

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		information not captured by HbA1c. Post-prandial hyperglycaemia may be an important consideration for improving glycaemic control and diabetes self-management, and ultimately reduce the risk of diabetes-related complications. In addition to the outcomes listed, Sanofi will also present clinical data on the following outcomes: • HbA1c/glycaemic control (including post-prandial glucose and fasting plasma glucose) • Glycaemic time-in-range	
	UKCPA Diabetes & Endocrinology Group	We would list the outcomes as follows (new additions in italics): Mortality *Microvascular complications – neuropathy (nerve), retinopathy (eye), nephropathy (kidney)* *Macrovascular complications - coronary artery disease, peripheral arterial disease, and stroke* *Appropriate management of risk factors for macrovascular complications (e.g. blood pressure, lipids)* HbA1c/*Blood glucose variability* *Reduction in total daily insulin dose* Frequency and severity of hypos BMI and *waist circumference* All reported adverse effects of treatment Health related QALY We thought it was important to make the distinction between both macrovascular and microvascular complications given that these medications may have different mechanisms to improving outcomes in these two distinct areas. Some of which are not fully understood at this time.	Comment noted. The suggested outcomes have been added to the scope.

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		We added lipids to appropriate management of risk factors as we felt that these medications have the potential to aid lipid management but also dyslipidaemia is listed as a side effect in the summary of product characteristics for these medications, a clearer understanding of this as an outcome will aid clinical decision making. A reduction in dose of insulin has been shown in three clinical trials, for dapagliflozin (DEPICT-1), empagliflozin (EASE-1) and sotagliflozin (InTandem1, InTandem2, InTandem3) which is why we suggest including this. We added in waist circumference in addition to BMI as a second predictor for obesity related issues e.g. fatty liver and insulin resistance in addition to CV risk. We would recommend time in target glucose range as a marker for glycaemic variability in addition to HbA1c as there is evidence to show that glycaemic variability can be a significant issue for this population. The group again wants to acknowledge that they appreciate that NICE must work within the confines of the evidence that is there and appreciates that the evidence may not be available to report on all of the above outcomes.	
Economic analysis	AstraZeneca	Given the nature of the disease, we propose a lifetime horizon	Comment noted. No action required.
	Boehringer Ingelheim	Boehringer Ingelheim considers the draft scope is appropriate.	Comment noted. No action required.
	Royal College of Pathologists	Sufficient time should be allowed for diabetes complications to manifest.	Comment noted. No action required.

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	Sanofi	None.	Comment noted. No action required.
	UKCPA Diabetes & Endocrinology Group	No comments here	Comment noted. No action required.
Equality and Diversity	AstraZeneca	No equality issues have been identified	Comment noted. No action required.
	Boehringer Ingelheim	Boehringer Ingelheim does not have any concern on equality with the draft remit and draft scope of this proposed appraisal.	Comment noted. No action required.
	Sanofi	None.	Comment noted. No action required.
	UKCPA Diabetes & Endocrinology Group	The group did not see anything of concern	Comment noted. No action required.
Innovation	AstraZeneca	**Innovation** Yes – we consider the technology to be innovative. Currently there are no adjunct therapies approved for the treatment of patients with uncontrolled Type 1 diabetes. The intensification of insulin dose necessary to achieve glycaemic targets is often associated with adverse events (AE)s such as hypoglycaemia and weight gain, limiting the potential to achieve and maintain a target glycaemic profile. Further, many patients are not adequately controlled on insulin and there is therefore a high unmet need in this population.	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its

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		Dapagliflozin will be: • The first adjunct treatment available for patients with uncontrolled T1D treated with insulin • The first oral treatment for T1D, demonstrating a significant reduction in HbA1c versus placebo, with no increase in the incidence of hypoglycaemia **Health related benefits not captured in the QALY:** • Societal impact of sickness / working days lost • Family / caregiver days required to support patients • Fear of hypoglycaemic events: attainment of glycaemic targets, weight gain resulting from "defensive snacking", and impact on driving **Data for submission:** The submission will be based on clinical data from DEPICT 1: a multicenter, randomised, double-blind, placebo-controlled, phase 3 study (24 week and 52 week data), and DEPICT 2: a multicenter, randomised, double-blind, placebo-controlled, phase 3 study (24 week [redacted])	product in its submission. No action required.
	Boehringer Ingelheim	SGLT-2 inhibitors will potentially be the first licensed oral treatment class for type 1 diabetes that can help patients to achieve better glycaemic control with fewer overall adverse events compared to insulin monotherapy.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.

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	Royal College of Pathologists	***Safety and efficacy of sodium-glucose cotransporter 2 (SGLT2) inhibitors in type 1 diabetes: A systematic review and meta-analysis,*** *El Masri, Dana et al. Diabetes Research and Clinical Practice , Volume 137 , 83 – 92.*	Comments noted. No action required.
	Sanofi	While insulin treatment has dramatically improved outcomes for patients with T1D, most still fail to achieve glycaemic targets and experience periods of hyper- and hypo-glycaemia with marked daily fluctuations in blood glucose. Weight gain associated with insulin, severe hypoglycaemia, recurrent hypoglycaemia, hypoglycaemia unawareness, and poor post-prandial glycaemic control also remain a significant challenge. There have been no advances in licenced pharmaceutical interventions in the UK for T1D since the introduction of insulin analogues. Sotagliflozin, empagliflozin and dapagliflozin present a break-through in the management of the disease by offering an insulin independent mechanism to support insulin in controlling blood glucose levels in patients with this chronic disease. Sotagliflozin will be the first dual SGLT-1 and SGLT-2 inhibitor to be licenced in diabetes which act on reducing glucose levels in the GI tract (where it reduces post-prandial glucose and elevates GI hormones such as GLP-1 and PYY which have been associated with metabolic benefits) and prevents glucose reabsorption in the kidneys (increasing glucose excretion in the urine). Along with reductions in established endpoints such as HbA1c, body weight and systolic blood pressure, sotagliflozin studies have also shown that it reduces the variability of glucose levels and increases TIR in adults with T1D compared with insulin alone. TIR is becoming recognised as a more appropriate measure of glycaemic control compared with HbA1c	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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		alone and the benefits of sotagliflozin in this outcome may present an important improvement in the management of T1D and patient wellbeing[1].	
	UKCPA Diabetes & Endocrinology Group	Yes. The use of effective oral adjunctive agents to insulin will potentially aid glucose management and improve microvascular and macrovascular outcomes in patients with type 1 diabetes is innovative and has the potential to revolutionise the way we manage this disease.	Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
Other considerations	AstraZeneca	N/A	Comment noted. No action required.
	Boehringer Ingelheim	No additional comment.	Comment noted. No action required.
	Royal College of Pathologists	None	Comment noted. No action required.
	Sanofi	None.	Comment noted. No action required.
Questions for consultation	AstraZeneca	All consultation questions are covered in the above. We would like to reiterate that [redacted]	Comments noted. No action required.

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	Boehringer Ingelheim	In the case that there is significant time difference of marketing Authorisation, clarity is needed on how the MTA timing and process will be affected.	Comments noted. To ensure timeliness of NICE guidance, each technology will be appraised by the Single Technology Appraisal (STA) process. No action required.
	Sanofi	**Is the population defined appropriately?** **Sanofi**: Partially. Sanofi would welcome further clarification from NICE on the definition of "inadequately controlled". Current NICE guidelines (NG17) suggest a target HbA1c of 6.5% (48 mmol/mol) or lower for adults with T1D. We propose that "uncontrolled" in this context may be defined as HbA1c >6.5%. We also request further clarification on the definition of "insulin monotherapy". We are concerned that this may be interpreted as basal insulin only whereas we believe the appropriate population may be on any insulin regimen i.e. MDI. **Have all relevant comparators for dapagliflozin, empagliflozin and sotagliflozin, in combination with insulin, been included in the scope?** **Sanofi**: Partially. In the proposed comparators it is stated that: "The interventions will also be compared with each other".	Comments noted. Please see responses to this comment in the population section above.

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		In line with the approach preferred in the NICE Methods Guide, the established comparator is insulin therapy alone. At the time of assessment the other interventions in this MTA will not be established as standard of care. Due to the pre-authorisation status of all three interventions, all relevant data may not be publically available to enable a comparison. We therefore propose to include all interventions and comparators in the systematic review and conduct a network meta-analysis where feasible. However, insufficient data may preclude a full analysis. As this is a MTA, the Assessment Group may be in a better position to undertake this aspect of the assessment. **Are the outcomes listed appropriate?** **Sanofi**: Partially. The outcomes listed capture most of the relevant endpoints for T1D. While HbA1c is used as a primary outcome to assess glycaemic control and as a surrogate for risk of developing complications, it has limitations. It does not capture short-term variations in blood glucose or exposure to hypoglycaemia and hyperglycaemia; it also does not capture the impact of blood glucose variations on individuals' quality of life. As a result, a number of other endpoints are emerging as being clinically relevant to the management of T1D. These include glycaemic time-in-range (TIR) and reduction in post-prandial glucose[1]. TIR captures fluctuations in glucose levels and not just more acute instances of hypo- or hyperglycaemia. Post-prandial blood glucose plays an important role in glycaemic control and glycaemic variability on a day-to-day basis and therefore provides additional information not captured by HbA1c. Post-prandial hyperglycaemia may be an important consideration for improving glycaemic control and diabetes	Comment noted. Each of the technologies will now be considered in separate appraisals and the other SGLT-2 inhibitors will be included "subject to ongoing NICE appraisal" as comparators where appropriate. Blood glucose variability' has been added to the scope.

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		self-management, and ultimately reduce the risk of diabetes-related complications. In addition to the outcomes listed, Sanofi will also present clinical data on the following: • HbA1c/glycaemic control (including post-prandial glucose and fasting plasma glucose) • Glycaemic time-in-range **Are there any subgroups of people in whom dapagliflozin, empagliflozin and sotagliflozin are expected to be more clinically effective and cost effective or other groups that should be examined separately?** **Sanofi**: We anticipate that sotagliflozin will provide benefits, and could be used, in all adult patients with T1D who are uncontrolled on insulin therapy. NICE clinical guidelines (NG17) identifies subgroups such as those with BMI ≥25kg/m^2 , experiencing repeated or disabling hypoglycaemia, and experiencing erratic and unpredictable blood glucose. We anticipate sotagliflozin may demonstrate increased cost-effectiveness compared with insulin alone in these groups. However, we are not seeking restriction to these subgroups. We are also investigating further subgroups of people within the trials who may have increased benefit from treatment with sotagliflozin.	At the scoping workshop, it was confirmed that there were no subgroups that should be included in the scope. No action required.

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		Where do you consider dapagliflozin, empagliflozin and sotagliflozin will fit into the existing NICE pathway, Type 1 diabetes in adults? **Sanofi**: We believe the interventions may fit into the current pathway following insulin optimisation as an adjunct to insulin. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which dapagliflozin, empagliflozin and sotagliflozin will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Sanofi**: No. **Do you consider dapagliflozin, empagliflozin and sotagliflozin to be innovative in their potential to make a significant and substantial impact on health-related benefits and how it might improve the way**	No action required. No action required.

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		that current need is met (is this a 'step-change' in the management of the condition)? **Sanofi**: Yes. While insulin treatment has dramatically improved outcomes for patients with T1D, most still fail to achieve glycaemic targets and experience periods of hyper- and hypo-glycaemia with marked daily fluctuations in blood glucose. Weight gain associated with insulin, severe hypoglycaemia, recurrent hypoglycaemia, hypoglycaemia unawareness, and poor post-prandial glycaemic control also remain a significant challenge. There have been no advances in licenced pharmaceutical interventions in the UK for T1D since the introduction of insulin analogues. Sotagliflozin, empagliflozin and dapagliflozin present a break-through in the management of the disease by offering an insulin independent mechanism to support insulin in controlling blood glucose levels in patients with this chronic disease. Sotagliflozin will be the first dual SGLT-1 and SGLT-2 inhibitor to be licenced in diabetes which act on reducing glucose levels in the GI tract (where it reduces post-prandial glucose and elevates GI hormones such as GLP-1 and PYY which have been associated with metabolic benefits) and prevents glucose reabsorption in the kidneys (increasing glucose excretion in the urine). Along with reductions in established endpoints such as HbA1c, body weight and systolic blood pressure, sotagliflozin studies have also shown that it reduces the variability of glucose levels and increases TIR in adults with T1D compared with insulin alone. TIR is becoming recognised as a more appropriate measure of glycaemic control compared with HbA1c	Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.

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		alone and the benefits of sotagliflozin in this outcome may present an important improvement in the management of T1D and patient wellbeing[1]. **Do you consider that the use of dapagliflozin, empagliflozin and sotagliflozin can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Sanofi**: Yes. We believe the substantial benefits of improving TIR are unlikely to be accounted for in a validated economic model. TIR is a metric which can be observed via continuous glucose monitoring in conjunction with HbA1c however currently validated models do not allow for glycaemic control outcomes beyond HbA1c. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** **Sanofi**: Data from the inTandem RCT program will be made available to demonstrate the TIR benefit of sotagliflozin. The recent publication by Beck et al. 2017[1] supports the finding that TIR plays a significant role in determining glycaemic control. We are investigating if data exists that may robustly estimate the utility gains of increased TIR however it is evident from clinical practice that TIR is positively associated with quality of life. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.**	No action required. No action required.

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		Sanofi: We do not believe so. **NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at https://www.nice.org.uk/process/pmg19/chapter/introduction).** **Sanofi**: Please see above comments in "Timing issues" and "Comparators". We believe the MTA process is appropriate. **Reference** 1. Beck R.W. et al. 2017. The fallacy of average: how using HbA1c alone to assess glycaemic control can be misleading. Diabetes Care. Vol 40	No action required. To ensure timeliness of NICE guidance, each technology will be appraised by the Single Technology Appraisal (STA) process.
	UKCPA Diabetes & Endocrinology Group	**Are there any subgroups of people in whom dapagliflozin, empagliflozin and sotagliflozin are expected to be more clinically effective and cost effective or other groups that should be examined separately?** This group of medications could be considered for those with pre-existing macrovascular complications and/or risk factors for macrovascular complications if it was felt that the benefits seen in the CVOTs in the type 2 population could also be applicable here. Considering the evidence on weight benefit of this class of agents however, it would be appropriate for use in those who are overweight or obese with	At the scoping workshop, it was confirmed that there were no subgroups that

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		suboptimal glycaemic control, with or without metformin treatment, whereby minimising weight gain can improve weight-related comorbidities in this population. **Where do you consider dapagliflozin, empagliflozin and sotagliflozin will fit into the existing NICE pathway, Type 1 diabetes in adults?** Referring to the NICE guidance on type 1 diabetes in adults (NG17), we consider the SGLT2 inhibitors to be used as an adjunct therapy to optimise insulin therapy. The place of therapy would be the same as with the use of metformin as an adjunct to insulin therapy when appropriate i.e. to consider adding SGLT2s to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m^2 (23 kg/m^2 for people from South Asian and related minority ethnic groups) or above wants to improve their blood glucose control while minimising their effective insulin dose. This also fits with ensuring patients with type 1 diabetes have parity with patients with type 2 diabetes. Where it is recommended that combination of these drugs with insulin with or without other antidiabetic drugs is recommended as a treatment for type 2 diabetes (NG28).	should be included in the scope. No action required. Comment noted. No action required.
Additional comments on the draft scope	AstraZeneca	N/A	Comment noted. No action required.
	Sanofi	None.	Comment noted. No action required.