NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Canagliflozin in combination therapy for treating type 2 diabetes

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Association of British Clinical Diabetologists (endorsed by the Royal College of Physicians)	The Association of British Clinical Diabetologists (ABCD) has no further comments to make on this report and is satisfied with the evidence presented to allow use of canagliflozin as dual therapy, triple therapy and in combination with insulin in the treatment of diabetes.	Comment noted.
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.
Janssen	Janssen believes that the ACD is a fair, balanced and thorough review of the original submission, the analyses conducted by the Evidence Review Group (ERG) and other supporting evidence. The recommendations for the use of canagliflozin in Type 2 diabetes mellitus (T2DM), as described in Section 1 of the ACD, are fully supported by the evidence. Janssen supports the recommendations, and we have no comments on Section 1 of the document. There are, however, two points within Section 4 that we would respectfully request that the NICE Committee considers:	Comment noted.
Janssen	<u>Sections 4.3 and 4.7: Evidence for canagliflozin compared to sulfonylurea in dual therapy with metformin</u> Janssen understands the committee's view that sulfonylureas are not considered to be a relevant comparator to canagliflozin in dual therapy. We appreciate that this view is consistent with current clinical guidelines in the UK. Whilst we are content to accept the committee's view on this matter, Janssen does believe that it would be useful for NICE to include some commentary on the clinical and cost-effectiveness of canagliflozin versus sulfonylureas in section 4 for broader context. Whilst it was not considered directly relevant to the decision-making process, we do believe that	Comment noted. Because sulfonylureas were not considered to be a comparator for canagliflozin, the Committee did not find it necessary to comment on the comparison. No change to the FAD required.

Consultee	Comment	Response
	the results of a direct, head to head comparison of canagliflozin against a standard of care agent in the UK should at least be referenced and reported in the FAD.	
Janssen	Section 4.10: Use of canagliflozin in combination with metformin and pioglitazone Janssen agrees that pioglitazone is no longer routinely initiated in clinical practice However, there is a historical patient population that still receives pioglitazone and can thus be assumed to tolerate it. Janssen believes that the clinical evidence shows, that for patients who are failing on a regimen of metformin (MET) and pioglitazone (PIO), the addition of canagliflozin offers an effective treatment option. We therefore request that, within Section 4.10, the clinical and cost-effectiveness of canagliflozin in combination with MET plus PIO, as a treatment option for patients currently tolerating PIO who need added glycaemic control is discussed in more detail. DIA3012 demonstrated that this combination can provide HbA_{1c} reduction, weight loss and BP reductions (Figures 18, 21 and 24 of the original Janssen submission), similar to the reductions seen with canagliflozin in other combinations. From a clinical perspective, fluid retention and risk of oedema with PIO (1) may be balanced by the diuretic effect of canagliflozin (2), thus making this a clinically useful combination and perhaps explaining to some degree the good efficacy seen in DIA3012, as presented in the original submission.	Comment noted. The Committee has given further consideration to this point and has now recommended canagliflozin in combination with metformin and a thiazolidinedione as a treatment option for people with type 2 diabetes (see sections 1.2, 4.10 and 4.23 of the FAD).
Janssen	Section 4.17: 104 week data for canagliflozin Two year data is presented in Figures 7, 9, 11 and 14 of the original manufacturer's submission to NICE. It is therefore requested that the following sentence is amended from: *"The manufacturer clarified that although there were 4-year data for the DPP-4*	Comment noted. This has been amended in the FAD.

Consultee	Comment	Response
	inhibitors and GLP-1 analogues, only 52-week data were available for canagliflozin." To the following: *"The manufacturer clarified that although there were 4-year data for the DPP-4 inhibitors and GLP-1 analogues, only 104-week data were available for canagliflozin."*	
Janssen	<u>Sections 3.32 and 3.33: incremental cost and QALY data not previously provided</u> The ICERs provided in Janssen's answers to the ERG Clarification Questions did not provide the incremental costs and QALYs for the comparisons described, and this was flagged in the ACD report in four instances as "costs and QALYs not provided". For completeness, these increments are given below, with the original sentence followed by the suggested revision with increments added.	Comment noted.
Janssen	<u>Section 3.32</u> Please consider replacing the sentence: *"The ICER provided by the manufacturer at the clarification stage for the comparison with dapagliflozin was £2993 per QALY gained (incremental costs and QALYs not provided)."* With: *"The ICER provided by the manufacturer at the clarification stage for the comparison with dapagliflozin was £2993 per QALY gained (incremental costs £33; incremental QALYs 0.011)."* Please consider replacing the sentence: *Canagliflozin 100 mg continued to be less effective and less costly than a GLP-1 analogue after correcting the BMI data (incremental costs and QALYs not provided).* With:	Comment noted. The incremental costs and QALYs have been added to the FAD.

Consultee	Comment	Response
	"Canagliflozin 100 mg continued to be less effective and less costly than a GLP-1 analogue after correcting the BMI data (incremental costs -£2,414; incremental QALYs -0.034)."	
Janssen	<u>Section 3.33</u> Please consider replacing the sentence: *"The ICER provided at the clarification stage for the comparison with dapagliflozin was £21,626 per QALY gained (incremental costs and QALYs not provided)."* With: *"The ICER provided at the clarification stage for the comparison with dapagliflozin was £21,626 per QALY gained (incremental costs £616; incremental QALYs 0.029)."* Please consider replacing the sentence: *"Canagliflozin 300 mg continued to be less effective and less costly than a GLP-1 analogue after correcting the BMI data (incremental costs and QALYs not provided)."* With: *"Canagliflozin 300 mg continued to be less effective and less costly than a GLP-1 analogue after correcting the BMI data (incremental costs -£1,879; incremental QALYs -0.018)."*	Comment noted. The incremental costs and QALYs have been added to the FAD.
Royal College of Nursing	This is to inform you that there are no comments to submit on behalf of the Royal College of Nursing to inform on the ACD of the above appraisal. Thank you for the opportunity to review this document.	Comment noted.

Comments received from clinical specialists and patient experts

There were no comments from clinical specialists or patient experts.

Comments received from commentators

Commentator	Comment	Response
AstraZeneca	Section 1: Appraisal Committee's preliminary recommendations 1. SGLT2-inhibitors are not effective in renally impaired patients. NICE should specify that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60). 2. There is insufficient consideration as to how the two doses of canagliflozin will be used by health care professionals. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance. 3. The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling. 4. Due to lack of stability, the model itself needs to be validated against an established model. Further information for each of these points is below:	Comments noted. A response to each point is given in the rows below.
AstraZeneca	1. Approximately 30% of type 2 diabetes patients have an eGFR < 60 ml/min/1.73 m^2 (Middleton, 2006) representing a clinically important sub-group. For these patients, the efficacy of canagliflozin in reducing HbA_{1C} is nearly 50% lower (at both doses) than for patients with normal or mild renal function and there are specific safety concerns linked to hypotension and volume depletion for the 300mg dose. This is reflected in the license whereby canagliflozin should not be initiated in	Comment noted. NICE can only produce guidance on a technology within its licensed indication. The information in section 4.2 of the summary of product characteristics that relates to the use of canagliflozin in patients with renal impairment was reproduced in section 2.2 of the ACD and is included in the FAD. No change to the FAD required.

Commentator	Comment	Response
	patients with an eGFR < 60 ml/min/1.73 m^2 and monitoring is required to ensure that patients whose eGFR falls below 60ml/min/1.73 m^2 only receive the 100 mg dose. Furthermore, the level of efficacy (-0.47% reduction in HbA_{1C} from a pooled analysis of regulatory RCTs, Woo 2013) for the 100 mg dose in patients with an eGFR < 60 ml/min/1.73 m^2 is less than the NICE CG87 criteria of 0.5% HbA_{1C} reduction for continued OAD treatment. Such patients would receive a greater clinical benefit and lower risk of adverse events from an alternative class of treatment, such as DPP4 inhibitors. Based on the evidence available, we therefore strongly request that NICE specifically states a restriction that canagliflozin should not be used in patients with eGFR <60. A bullet point making this restriction explicit should be added to the recommendations.	
AstraZeneca	2. We are concerned that the preliminary recommendations do not fully consider the consequences of the SPC dose titration requirements for canagliflozin. As the two doses have a different cost and a different risk-benefit profile, we consider that the proportion of patients likely to use each dose should be considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. There is IMS real-world data from the U.S., where canagliflozin was launched in April 2013, demonstrating that approximately 50% of usage is at the 300mg dose (IMS NPA data 5th April 2013-27th December 2013). We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.	Comment noted. See sections 4.12 and 4.19 of the FAD.
AstraZeneca	3. The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling: • A specific modelling scenario only including renally impaired patients does	Comments noted. The cost-effectiveness estimates for canagliflozin were based on the trial populations, which did not include patients with severe renal impairment. The Committee did not receive any feedback from

Commentator	Comment	Response
	not seem to be available, although it is unlikely that canagliflozin will be cost-effective in these patients due to significantly lower efficacy compared with patients with normal to mild renal function. We ask that this clinically important sub-group of patients is explored in a specific modelling scenario, which if cost-effectiveness is not demonstrated, would support a specific restriction that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60). • The model prescribes that patients discontinuing canagliflozin due to a drop in eGFR are switched to insulin rather than the more clinically appropriate and licensed DPP4 inhibitors. The higher efficacy of insulin compared with DPP4 inhibitors may result in more favourable ICERs for canagliflozin and does not reflect clinical practice whereby patients and physicians aim to delay insulin use for as long as possible. We ask that a scenario where renally impaired patients are switched to DPP4 inhibitors is run. • The lipid profile of dapagliflozin and canagliflozin differs considerably yet the same lipid profiles for both drugs have been applied in the model. We request that these differences in lipid profiles are taken into account in the economic modelling.	professional groups or clinical specialists that the treatment pathway in the model was not plausible. No changes to the FAD required. The lipid profiles used in the modelling have been discussed in section 4.17 of the FAD.
AstraZeneca	4. We are concerned about the lack of stability of the ICERs generated using the ECHO model. We consider the very wide range of ICERs generated for the same drug comparisons to demonstrate a high level of uncertainty in the cost-effectiveness analyses. Therefore, we request that the results from the ECHO economic model are validated using an alternative validated diabetes model such as the NICE-recommended, type 2 diabetes CORE model.	Comment noted. The Committee heard that the wide range of ICERs for the same comparisons was primarily because of the ratio was strongly affected by small changes to the incremental differences on costs and QALYs as a result of the increments themselves being very small. This has been clarified in section 4.14 of the FAD. The ECHO-T2DM model has been validated against other models, including CORE. This has also been clarified in section 4.14 of the FAD.
AstraZeneca	<u>Section 2: Technology</u> Canagliflozin has different selectivity compared to other SGLT2 inhibitors and as this	Comment noted. The technology section provides a brief and accurate overview of canagliflozin's mechanism of action. Because this is a STA and

Commentator	Comment	Response
	may have implications on efficacy and safety, this should be specifically described in section 2. Further information on this is as follows: We believe that canagliflozin should be described as a selective SGLT-2 inhibitor with a low potency for SGLT-1 inhibition. It should be clarified that canagliflozin is not highly selective relative to other SGLT inhibitors. This may have implications when treating patients with canagliflozin regarding efficacy, but more importantly regarding the safety and adverse event profile of canagliflozin compared with other more selective SGLT2 inhibitors, such as dapagliflozin and empagliflozin. There is data showing the additional contribution of SGLT-1 to the efficacy of canagliflozin above its effects on the kidney (i.e. SGLT-2 inhibition alone), especially via inhibition of SGLT-1 via the gut (Polidori, 2013). However, this additional SGLT-1 inhibition may also have implications in terms of a higher risk of hypoglycaemia with canagliflozin compared to hypoglycaemia rates observed with the other SGLTs. As glucose excretion by the urine is also accompanied by fluid loss (osmotic), the diuresis may also lead to episodes of hypovolaemia, and dehydration. Thus, the EPAR for canagliflozin concludes that "some conditions exist in which a starting dose of 100 mg should be used for safety reasons since drop in blood pressure and volume depletion or its sequelae could be more pronounced upon onset of treatment. Therefore, a starting dose of 100 mg is recommended for all patients as a precautionary measure and to simplify posology" (EPAR, section 2.6.2).	not a MTA the comparator technologies mode of action are not described or compared to the technology being appraised. No change to the FAD required.
AstraZeneca	<u>Section 3 – the manufacturer's submission</u> 1. SGLT2s are not effective in renally impaired patients. NICE should specify	Comments noted. A response to each point is given in the rows below.

Commentator	Comment	Response
	that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60). 2. There is insufficient consideration as to how the two doses of canagliflozin will be used by health care professionals. As the two doses have a different cost and a different risk-benefit profile, the proportion of patients likely to use each dose should be fully considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance. 3. The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling. 4. Due to lack of stability, the model itself needs to be validated against an established model. 5. The higher odds ratio of hypoglycaemia for canagliflozin compared to dapagliflozin is unlikely to reflect differences in trial outcome definitions and may relate to the different mechanism of actions of these drugs. We request clarification on how this has been approached in the economic modelling. 6. There are limitations of the RCT evidence supporting canagliflozin's preliminary recommendations, which should be highlighted further in the ACD. Further information on this is as follows:	
AstraZeneca	**1. SGLT2s are not effective in renally impaired patients. NICE should specify that canagliflozin should not be used in patients with moderate renal impairment (eGFR <60).**	Comment noted. NICE can only produce guidance of a technology within its licensed indication. The information in section 4.2 of the summary of product characteristics that relates to the use of canagliflozin in patients with renal impairment was

Commentator	Comment	Response
	Approximately 30% of type 2 diabetes patients have an eGFR < 60 ml/min/1.73 m^2 (Middleton, 2006) representing a clinically important sub-group. For these patients, the efficacy of canagliflozin in reducing HbA_{1C} is nearly 50% lower at both doses than for patients with normal or mild renal function (see figure below) and there are specific safety concerns linked to hypotension and volume depletion for the 300mg dose. This is reflected in the license, which specifies criteria for the use of canagliflozin in renally impaired patients. Canagliflozin should not be initiated in patients with an eGFR < 60 ml/min/1.73 m^2; patients receiving canagliflozin whose eGFR persistently falls below 60 should be down-titrated from 300 to 100 mg dose or maintained at 100 mg dose. Canagliflozin should be discontinued when eGFR is persistently below 45. Furthermore, although the 100 mg dose is licensed for patients with an eGFR ≥ 45 and <60, there is evidence from a pooled analysis of canagliflozin regulatory RCTs that patients receiving 100mg canagliflozin mg with an eGFR ≥ 45 and <60 receive limited benefit with a mean HbA1C reduction from baseline of 0.47 % (Woo, 2013). For patients with eGRF in a lower range (≥ 30 and < 50), the mean reduction in HbA1C from baseline was 0.27% in a 52-week randomised controlled trial (Nieto, 2013). This level of efficacy does not meet the criteria of a maintained benefit of HbA1C reduction of 0.5% at 6 months for continued treatment of type 2 diabetes specified in NICE Clinical Guideline 87 for Type 2 diabetes [1]. It is therefore highly likely that for this sub-group of patients, canagliflozin will not be an efficacious option in dual, triple or add onto insulin indications and is therefore unlikely to be cost-effective. Such patients are likely to receive a greater clinical benefit and lower risk of adverse events from an alternative class of treatment, such as a DPP4-inhibitor. For example, saxagliptin at a dose of 2.5mg in patients with moderate to severe renal impairment shows sustained reductions of -0.73% at 1 year (Nowicki 2011).	reproduced in section 2.2 of the ACD and is included in the FAD. No change to the FAD required.

Commentator	Comment	Response
	Furthermore, there is prospective cardiovascular safety evidence for patients with moderate and severe renal impairment treated with saxagliptin from the large cardiovascular outcome trial SAVOR. We therefore strongly request that NICE recognises the limitations of canagliflozin in patients with renal impairment and specifically states a restriction that canagliflozin should not be used in patients with an eGFR <60. A bullet point making this restriction explicit should be added to the recommendations.	
AstraZeneca	2. **There is insufficient consideration as to how the two doses of canagliflozin will be used by health care professionals. As the two doses have a different cost and a different risk-benefit profile, the proportion of patients likely to use each dose should be fully considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.** Manufacturer's cost-effectiveness results: Section 3.41 (sensitivity analyses): There is IMS data from real-world use of canagliflozin in the US, where canagliflozin was launched in April 2013, regarding dose titration and the percentage of patients receiving the 100 and 300 mg doses, which has not been considered when forming these preliminary recommendations. This data shows that approximately 50% of real-world usage is at the 300mg dose (IMS NPA data 5th April 2013-27th December 2013 [unequalised]). The percentage of patients, which were up-titrated to the 300mg dose is unclear from the current modelling scenario of dose titration and the current scenario is based on clinical specialist opinion rather than real-world data.	Comment noted. See sections 4.12 and 4.19 of the FAD.

Commentator	Comment	Response
	Even in the STA report (the submission by the manufacturer page 14) the manufacturers recognise that “it is likely that a higher proportion of patients receiving canagliflozin 100mg as part of a triple therapy or as an add-on to insulin therapy would require tighter glycaemic control and would therefore be switched to canagliflozin 300mg”. As such, the estimate of 50% usage at 300mg does not seem unreasonable. As the two doses have a different cost and a different risk-benefit profile, we consider that the proportion of patients likely to use each dose should be fully considered within the assessment of clinical and cost effectiveness and budget impact of canagliflozin. We recommend that further economic modelling scenarios whereby 50% of patients receive each dose are carried out to inform the final guidance.	
AstraZeneca	3. **The canagliflozin economic model inputs regarding moderately renally impaired patients and differences in lipid profiles between dapagliflozin and canagliflozin are inaccurate and require re-modelling.** a. The economic modelling approach to renally impaired patients is not entirely clear, but seems to take a less conservative approach to favour canagliflozin: • A specific modelling scenario only including renally impaired patients does not seem to be available. As stated above in point 1, it is unlikely that canagliflozin will be cost-effective in these patients due to significantly lower efficacy and increased rates of adverse events related to hypoglycaemia, dehydration or hypovolaemia for the 300mg dose compared with patients with normal to mild renal function. We ask that this clinically important sub-group of patients is explored in a specific modelling scenario, which if cost-effectiveness is not demonstrated, would support a specific restriction that canagliflozin should not be used in patients with	Comments noted. NICE can only produce guidance on a technology within its licensed indication. The information in section 4.2 of the summary of product characteristics that relates to the use of canagliflozin in patients with renal impairment was reproduced in section 2.2 of the ACD and is included in the FAD. The Committee did not receive any feedback from professional groups or clinical specialists that the treatment pathway in the model was not plausible. No changes to the FAD required.

Commentator	Comment	Response
	moderate renal impairment (eGFR <60). • The model prescribes that patients discontinuing canagliflozin due to a drop in eGFR are switched to insulin rather than to the more clinically appropriate and licensed DPP4 inhibitors. The higher efficacy of insulin compared with DPP4 inhibitors may result in more favourable ICERs for canagliflozin and does not reflect clinical practice whereby patients and physicians aim to delay insulin use for as long as possible. There is ample evidence of patient and physician reluctance to initiate insulin (Khunti 2013). We ask that a scenario where renally impaired patients are switched to DPP4 inhibitors is run; both in the modelling for all patients and in the specific sub-group analysis for renal patients. • The base case modelling seems to include a clinically appropriate stopping rule for canagliflozin treatment when eGFR drops below 60 ml/min/1.73m2, yet this is not reflected in the preliminary recommendations. We strongly request that NICE specifically states a restriction that canagliflozin should not be used in patients with eGFR <60. A bullet point making this restriction explicit should be added to the recommendations.	
AstraZeneca	b. We are concerned that the same lipid profiles for canagliflozin and dapagliflozin have been applied in the model (see table 56, page 102 in the evaluation report). It should be noted that the lipid profile of dapagliflozin and canagliflozin differs considerably. The pooled analyses from the entire dapagliflozin and canagliflozin trial programmes show the much increased levels of LDL-C seen across the canagliflozin program, with rises of 9.3% for canagliflozin 300 mg (see figure 1 below, FDA January 2013) compared to a rise of 2.7% with dapagliflozin 10 mg (see figure 2 below, Hardy 2013). The increase in LDL-C observed with canagliflozin	Comments noted. The Committee heard from the ERG that it had found that assuming different lipid profiles for canagliflozin and dapagliflozin had little impact on the ICER. This is explained in section 4.17 of the FAD.

Commentator	Comment	Response
	300mg dose was particularly high in certain indications: up to 13.3% from baseline (Vercruysse, EASD 2013) as add on to metformin and SU or 14.2% from baseline (Langslet EASD 2013) as add on to metformin. This increase in LDL-C was worrying enough for the independent monitoring committee of CANVAS, the canagliflozin cardiovascular safety outcome study, to partially unblind the results and to terminate enrolment in the preplanned extension of the study (FDA Canagliflozin medical review, 2013). In the interim analysis of CANVAS, a numeric imbalance in major adverse cardiac events (MACE) in the early treatment period of CANVAS between canagliflozin and non-canagliflozin treatment arms was observed (FDA Canagliflozin summary review, 2013). Additionally, a pooled analysis of canagliflozin RCTs showed a HR exceeding 1.0 for fatal/non-fatal stroke for canagliflozin compared to non-canagliflozin treatment arms (figure provided but not reproduced). Neither were such large increases in LDL-C nor imbalances in MACE events noted in the overall dapagliflozin programme (figure provided by not reproduced). Therefore, we request that these differences in lipid profiles are taken into account when modelling the effects of canagliflozin.	
AstraZeneca	**1. Due to lack of stability, the model itself needs to be validated against an established model, such as the NICE-recommended CORE model.** a. We are concerned about the lack of stability of the ICERs generated using the ECHO model. We consider the very wide range of ICERs generated for the same drug comparisons to demonstrate a high level of uncertainty in the cost-effectiveness analyses. The ERG's exploratory analyses described in section 3.49 of the ACD demonstrated cases where small differences in incremental QALYs could drive a large variation in the ICER compared with the	Comment noted. The Committee heard that the wide range of ICERs for the same comparisons was primarily because of the ratio was strongly affected by small changes to the incremental differences on costs and QALYs as a result of the increments themselves being very small. This has been clarified in section 4.14 of the FAD.

Commentator	Comment	Response
	manufacturer's ICER. For example, the ERG exploratory analyses showed an ICER of £100,719 per QALY gained for canagliflozin 100mg versus dapagliflozin in dual therapy compared to an ICER of £8,674 per QALY gained for this comparison from the manufacturer analyses presented in section 3.32. This is a very wide difference in results, which generates concern about the stability of the ECHO model.	The ECHO-T2DM model has been validated against other models, including CORE. This has also been clarified in section 4.14 of the FAD.
AstraZeneca	b. In other NICE appraisals of type 2 diabetes treatments (liraglutide: TA203, exenatide: TA248, dapagliflozin:TA288), the CORE model was requested to validate the results presented from manufacturer models. For consistency in assessing the cost-effectiveness of canagliflozin, we therefore request that the CORE model is also used for this appraisal.	Comment noted. The ECHO-T2DM model has been validated against other models, including CORE. This has also been clarified in section 4.14 of the FAD. The NICE methods guide does not require manufacturers to use the same model as previous appraisals when submitting evidence for a single technology appraisal.
AstraZeneca	c. The ECHO model seems particularly sensitive to changes in HbA1C including HbA1C drift over time with the consequence that the ECHO model may not be as sensitive to other differences between drugs, such as adverse events, as the CORE model. For example, the model does not seem to be sensitive to the difference in hypoglycaemia rate (OR of 3.43-3.65) between dapagliflozin and canagliflozin.	Comment noted. The roles of HbA_{1c} and hypoglycaemia in the manufacturer's model are discussed in sections 4.17 and 4.18 of the FAD. The uncertainty associated with the cost-effectiveness estimates generated using the manufacturer's model is discussed in section 4.20.
AstraZeneca	d. The differential HbA1C reduction between the two doses of canagliflozin is limited at a range of 0.09% (insulin sub-study DIA3008) to 0.21% (study DIA3002), yet the monthly cost of the 300 mg dose is £10.79 greater than the cost of the 100 mg dose of canagliflozin. This does not seem to be reflected in the outcomes of the economic modelling where canagliflozin 300mg seems to be more cost-effective than canagliflozin 100mg. As such, this may be a further example of the lack of stability of	Comment noted. The cost-effectiveness estimates depend on a host of factors, not just HbA_{1c}, and the incremental QALYs over a lifetime are small for the different treatments. The Committee heard that the wide range of ICERs for the same comparisons was primarily because of the ratio was strongly affected

Commentator	Comment	Response
	the model analyses.	by small changes to the incremental differences on costs and QALYs as a result of the increments themselves being very small. This has been clarified in section 4.14 of the FAD.
AstraZeneca	5. The higher odds ratio of hypoglycaemia for canagliflozin compared to dapagliflozin is unlikely to reflect differences in trial outcome definitions and may relate to the different mechanism of actions of these drugs. We request clarification in the ACD on how this has been approached in the economic modelling. The manufacturers of canagliflozin explain that the higher odds of hypoglycaemia in a canagliflozin patient versus dapagliflozin (OR of 3.43-3.65) are due to differences in the definition of hypoglycaemia outcomes in the trials. The table below shows the definitions used. As can be seen, total hypoglycaemia reported in the dapagliflozin trials (i.e. considering the event rate for all three outcomes below) is more encompassing than the definition in the canagliflozin trials, where documentation of blood levels was also required, unless a major neurological symptom occurred. The dapagliflozin trials included the “other” category to capture those events where a blood test may not have been available, even in less major cases. However, the threshold was set at a lower level for major hypoglycaemic events, but given that any major symptoms of hypoglycaemia would also contribute to a major event, this lower threshold is unlikely to have changed the results much. Thus, given the narrower definition used in the canagliflozin trial, the differences in hypoglycaemia rates are likely to be even higher. The increased odds ratio of hypoglycaemia with canagliflozin versus dapagliflozin may be explained by the different mechanism of actions of these drugs. Canagliflozin is not as selective for the SGLT-2 transporter versus SGLT-1	Comment noted. The manufacturer included only a small disutility for hypoglycaemic events in the model (ranging from -0.0036 to -0.0118, see MS Table 38). From the Tornado plots given for the manufacturer’s deterministic sensitivity analysis it does not appear these greatly influence ICERs (though it has been noted that the manufacturer did not include DSA for canagliflozin versus dapagliflozin). This has been discussed in section 4.17 of the FAD.

<table>
<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>transporter as dapagliflozin or empagliflozin. This may have implications in terms of risk of hypoglycaemia (Nagata, 2013). This is because 90% of glucose reabsorption occurs via SGLT-2 transporters in the kidney and the rest by SGLT-1 transporters. Highly selective inhibition of only SGLT-2 (i.e. with dapagliflozin and empagliflozin) means that some glucose is able to be reabsorbed by the SGLT-1 transporter, thereby reducing the risk of hypoglycaemia. Concurrent SGLT-1 inhibition with canagliflozin would potentially remove this “built-in” safeguard and may explain the higher odds ratios of hypoglycaemia seen with canagliflozin in the NMA.

It is unclear whether this significant OR with cost consequences has been taken into account in the modelling. We therefore request clarification on how this has been approached in the economic modelling.
<table>
<tr><th>Dapagliflozin trials</th><th>Canagliflozin trials</th></tr>
<tr><td>Major episodes of hypoglycaemia: symptomatic episodes requiring external (3rd party) assistance due to severe impairment in consciousness or behaviour with a capillary or plasma glucose value below 3.0 mmol/L(54 mg/dl) and prompt recovery after glucagon administration.</td><td>Documented hypoglycaemic episodes, including biochemically documented episodes (concurrent fingerstick glucose or plasma glucose ≤3·9 mmol/L with or without symptoms) and severe episodes (those needing assistance of another individual or resulting in seizure or loss of consciousness).</td></tr>
<tr><td>Minor episodes of hypoglycaemia – defined as either a symptomatic episode with a capillary or plasma glucose measurement below 3.5 mmol/L (63 mg/dl) regardless of need for external assistance or an asymptomatic capillary or plasmaglucose measurement below 3.5 mmol/L (63 mg/dl), that does not qualify as a major episode.</td><td></td></tr>
<tr><td>Other hypoglycaemia – defined as events suggestive of hypoglycaemia with symptoms that the subject experienced as hypoglycaemia and no confirmative measurement.</td><td></td></tr>
</table></td><td></td></tr>
<tr><td>AstraZeneca</td><td>2. There are limitations of the RCT evidence supporting canagliflozin’s</td><td>Comments noted. It was acknowledged in the ACD</td></tr>
</table>

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	preliminary recommendations, which should be highlighted further in the ACD. • The manufacturer's submission Section 3.2 of the ACD: The canagliflozin trials did not include a dose titration regimen and rather assessed the two doses separately; thus the trial data does not reflect how canagliflozin will be used in real-world practice. We recommend that further real world practice based economic modelling scenarios are carried out to inform the final guidance, as described above. • ERG's comments on the manufacturer's clinical-effectiveness evidence section 3.25: We note the ERG's comment regarding the manufacturer's clinical-effectiveness section that the per-protocol analyses did not show superiority for canagliflozin 300mg in the two dual therapy trials unlike the modified intention to treat analyses. This is an unusual sequence of analysis as in non-inferiority trials, typically the initial analysis would be conducted in the PP population and only then conducted in the ITT population once a significant result was demonstrated in the PP population. We ask for consideration of why these results differ by analysis and whether this is driven by unequal discontinuations across the treatment arms. • The manufacturer's submission Section 3.2 of the ACD : The add onto insulin data for canagliflozin is limited to a sub-group analysis of the CANVAS study including patients with a history or at high risk of CV disease. Whilst we appreciate that most diabetes patients requiring insulin will have CV risk factors, there will be a spectrum of risk in these patients. As such, the CANVAS study is unlikely to be generalisable to patients with lower CV risk. Additionally, only 18-week data is currently available for this	that there was uncertainty around dose escalation in England because of a lack of clinical evidence and experience with the drug. Given this uncertainty, the Committee chose to consider the 100 mg and 300 mg doses separately (see section 4.12 of the FAD). Comment noted. The Committee concluded that, taken as a whole, the results of the clinical trials and network meta-analyses, canagliflozin as part of dual therapy in combination with metformin appeared to provide broadly comparable glycaemic control to the other antidiabetic drugs (see section 4.7 of the FAD). As described in the ACD, the Committee heard from the clinical specialists that the DIA3008 insulin sub-study could be considered generalisable to the patient population in England (see section 4.6 of the FAD).

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	population.	
AstraZeneca	Section 4 Consideration of the evidence 1. **Due to lack of stability, the model itself needs to be validated against an established model, such as the NICE-recommended CORE model.** We are concerned about the lack of stability of the ICERs generated using the ECHO model. We consider the very wide range of ICERs generated for the same drug comparisons to demonstrate a high level of uncertainty in the cost-effectiveness analyses. In other NICE appraisals of type 2 diabetes treatments, the CORE model was requested to validate the results presented from manufacturer models. For consistency in assessing the cost-effectiveness of canagliflozin, we therefore request that the CORE model is also used for this appraisal. Please see section 3 for further detail concerning the rationale for this request.	Comment noted. The Committee heard that the wide range of ICERs for the same comparisons was primarily because of the ratio was strongly affected by small changes to the incremental differences on costs and QALYs as a result of the increments themselves being very small. This has been clarified in section 4.14 of the FAD. The ECHO-T2DM model has been validated against other models, including CORE. This has also been clarified in section 4.14 of the FAD.
AstraZeneca	2. **Whilst we appreciate that dapagliflozin was not considered a comparator to canagliflozin in triple therapy, as to date it has not been recommended in triple therapy by NICE TA 288, we clarify that a triple therapy RCT for dapagliflozin (in combination with metformin plus a sulphonylurea) is now available.** This RCT demonstrates: • A clinically relevant decrease in HbA1c of -0.86% with dapagliflozin vs. -0.17% for placebo (p value for difference <0.0001) at 24 weeks • Significant weight loss of -2.65 kg with dapagliflozin vs -0.58 kg for placebo (p <0.0001) at 24 weeks (Matthei, 2013)	Comment noted.
Eli Lilly	Thank you for the opportunity to review and respond to the Appraisal Consultation Document (ACD) for canagliflozin in combination therapy for treating type 2	Comment noted.

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	diabetes. Eli Lilly supports the development of new technologies which provide individual treatment choices and a patient-centred approach to diabetes management. With regard to the specific questions posed in the ACD, we have no comments to make.	
Merck Sharp and Dohme	General comment on the ACD: The clinical effectiveness data that has been considered in the technology appraisal for canagliflozin versus the sulphonylurea comparator has relied on glimepiride data. However, in England and Wales, gliclazide is the most commonly used sulphonylurea.	Comment noted. The manufacturer used clinical effectiveness data for glimepiride because this was the sulfonylurea used in the canagliflozin clinical trial programme. However, costs for gliclazide were used in the manufacturer's economic model because it is the most widely prescribed sulfonylurea in England. No change to the FAD requested or required.
Merck Sharp and Dohme	Section 2.4 – the expected annual cost of canagliflozin 100mg and 300mg The expected annual cost of canagliflozin 100mg and 300mg reported in the ACD of £477.36 and £608.83, respectively, appear to be incorrectly calculated if the cost of a 30-tablet pack is £39.20 and £49.99 for canagliflozin 100mg and 300mg, respectively. The annual expected cost of canagliflozin 100mg, based on a 30-tablet pack cost of £39.20 is £476.93 (assuming there are 365 days per year). The annual expected cost of canagliflozin 300mg, based on a 30-tablet pack cost of £49.99 is £608.21 (assuming there are 365 days per year).	Comment noted. These expected annual costs were taken from the manufacturer's submission. They have been updated in the FAD.
Merck Sharp and Dohme	Section 3.13 – Dual therapy with a metformin background In this section, the results from the manufacturer's network meta-analysis for HbA_{1c} change at 52 weeks are reported for dual therapy with a metformin background. The source of the data is not clear in this section. For clarification, we would recommend	Comment noted. This has been clarified in section 3.13 of the FAD.

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	that the initial text is updated to state that this is sourced from the manufacturer's network meta-analysis (bold text added): "The manufacturer presented differences in HbA1c change for canagliflozin 100mg and 300mg compared with the different comparators as dual therapy with a metformin background **from the network meta-analysis they conducted**"	
Merck Sharp and Dohme	<u>General comment on the manufacturer's network meta-analysis</u> Sections 3.13 to 3.23 present the results from the manufacturer's network meta-analyses and include interpretations of the results. When interpreting the results, the mean results and any numerical differences should be considered alongside the 95% credible intervals – however, this has not been done consistently in sections 3.13 to 3.23 of the ACD. Ideally, the mean results with the 95% confidence intervals should be presented for every drug and dose included in each network meta-analysis for each endpoint in each indication without any interpretation to reflect the limitation of network meta-analyses. It should be noted that network meta-analyses need to be interpreted with caution, however, should an interpretation be included, then the 95% credible intervals must be reported throughout and considered as part of the interpretation. The following comments below outline our recommended changes.	Comment noted.
Merck Sharp and Dohme	<u>Section 3.13 – Dual therapy with a metformin background</u> The text in this section states that "canagliflozin 100mg produced a greater reduction in HbA_{1c} than sitagliptin 100mg (-0.01% [-0.48 to 0.44]) and dapagliflozin 10mg (-0.14% [-0.81 to 0.47])". This conclusion is incorrect as the 95% credible intervals for both drugs cross the line of no effect. The interpretation stated for the network meta-analysis results for canagliflozin 100mg versus liraglutide 1.2mg,	Comment noted. It has been clarified in section 3.13 of the FAD that these are numerically greater reductions.

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	canagliflozin 300mg, pioglitazone 30mg, exenatide 10µg or glimepiride is not appropriately phrased in this section, as these results only show non-inferiority. As such, the text should be updated to either: • Report the mean results and 95% credible intervals for each drug and dose with no interpretation • Or, updated to the following: "canagliflozin 100mg produced a **non-inferior** reduction in HbA_{1c} versus sitagliptin 100mg (-0.01% [-0.48 to 0.44]), dapagliflozin 10mg (-0.14% [-0.81 to 0.47]), liraglutide 1.2 mg (0.40% [-0.33 to 1.11]), canagliflozin 300 mg (0.13% [-0.25 to 0.52]), pioglitazone 30 mg (0.11% [-0.44 to 0.84]), exenatide 10 micrograms (0.02% [-0.65 to 0.55]) or glimepiride (0.00% [-0.45 to 0.46])." and remove the text referring to "greater reduction". The text in this section also states that "canagliflozin 300mg produced a greater reduction in HbA1c than pioglitazone 30mg (-0.02% [-0.57 to 0.72]), exenatide 10µg (-0.11% [-0.78 to 0.42]), glimepiride (-0.13% [-0.58 to 0.33]), canagliflozin 100 mg (−0.13% [−0.52 to 0.25]), sitagliptin 100 mg (−0.14% [−0.61 to 0.31]) and dapagliflozin 10 mg (−0.27% [−0.94 to 0.34])". This conclusion is incorrect as the 95% credible intervals for both drugs crosses the line of no effect. The interpretation from the network meta-analysis for canagliflozin 300mg compared with liraglutide 1.2mg is also inappropriately phrased in this section. As such, the text should be updated to either: • Report the mean results and 95% credible intervals for each drug and dose with no interpretation • Or, updated the text to the following: "canagliflozin 300mg produced a **non-inferior r**eduction in HbA_{1c} versus pioglitazone 30 mg (-0.02% [-0.57 to 0.72]), exenatide 10 micrograms (-0.11% [-0.78 to 0.42]), glimepiride (-0.13% [-0.58 to	

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	0.33]), canagliflozin 100 mg (−0.13% [−0.52 to 0.25]), sitagliptin 100 mg (−0.14% [−0.61 to 0.31]), dapagliflozin 10 mg (−0.27% [−0.94 to 0.34]) and liraglutide 1.2 mg (0.27% [−0.46 to 0.98]" and remove the text referring to "greater reduction"	
Merck Sharp and Dohme	Section 3.14, 3.15 and 3.16 – Dual therapy with a metformin background No 95% credible intervals have been reported for the network meta-analysis results for change in weight, systolic blood pressure or hypoglycaemia risk, and therefore it is not possible to verify if the conclusions such as "greater weight reduction" are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals and the conclusions reflecting the 95% credible intervals and whether they demonstrate statistically significant or non-inferior differences. In section 3.14, the results have been interpreted as "at least similar" – this is an inappropriate way to interpret the results. Any differences seen should be interpreted as whether they are statistically significant or non-inferior. In section 3.14, the phrase "gave a lesser weight reduction" should be corrected to state "gave a smaller weight reduction".	Comments noted. The FAD has been amended accordingly.
Merck Sharp and Dohme	Section 3.17 – Triple therapy with a metformin plus sulphonylurea background No 95% credible intervals have been reported for the network meta-analysis results for change in HbA1c, weight, systolic blood pressure or hypoglycaemia risk, and therefore it is not possible to verify if the conclusions such as "greater weight reduction" are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals. Should an interpretation be included, the conclusions need to reflect the 95% credible intervals and state whether they are statistically significant or non-inferior differences. The current interpretations included in this section, such as "produced a similar reduction" or "slightly greater"	Comments noted. The FAD has been amended accordingly.

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	should be removed, as these statements are subjective and do not take into consideration the 95% credible intervals.	
Merck Sharp and Dohme	Section 3.18 – Triple therapy with a metformin plus thiazolidinedione background No 95% credible intervals have been reported for the network meta-analysis results for change in HbA1c, weight, systolic blood pressure or hypoglycaemia risk, and therefore it is not possible to verify if the conclusions are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals. Should an interpretation be included, the conclusions need to reflect the 95% credible intervals and state whether they are statistically significant or non-inferior differences. The current interpretations included in this section, such as "smaller reduction" should be removed, as these statements are subjective and do not take into consideration the 95% credible intervals.	Comments noted. The FAD has been amended accordingly.
Merck Sharp and Dohme	Section 3.19 and 3.20 – add-on to insulin with or without an antihyperglycaemic background No 95% credible intervals have been reported for the network meta-analysis results for change in HbA_{1c}, weight or systolic blood pressure, and therefore it is not possible to verify if the conclusions such as "the reduction in HbA_{1c} at 26 weeks with canagliflozin 100 mg and 300 mg was greater than sitagliptin 100 mg" are appropriate. The mean results for each drug and dose must be reported along with the 95% credible intervals and the conclusions reflecting the 95% credible intervals and whether they demonstrate statistically significant or non-inferior differences. The current interpretations included in this section, such as "greater reduction" should be removed unless this can be substantiated by statistically significant differences.	Comments noted. The FAD has been amended accordingly.
Merck Sharp and Dohme	Section 3.22 and 3.23 – adverse events	Comments noted. The reporting of the data is

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	This section reports numerical differences for adverse events observed between different therapy groups. However, there are no p-values reported and it is unclear if any statistical analysis was conducted. If the conclusions in this section are purely based on numerical differences, no subjective interpretation stating if the percentages are numerically higher or lower should be included. For example, the text: • "The incidence of adverse events leading to discontinuation in the broad dataset was higher in the canagliflozin 300 mg group (7.3%) than the canagliflozin 100 mg (5.6%) and non-canagliflozin (5.0%) groups" should be updated to state the findings removing any interpretation: "The incidence of adverse events leading to discontinuation rate in the broad dataset was 7.3%, 5.6% and 5.0% in the canagliflozin 300 mg, canagliflozin 100 mg and non-canagliflozin groups, respectively". • "The incidence of adverse events considered related to the study drug by the investigator was slightly higher in the canagliflozin 100 mg and 300 mg groups (33.6% and 29.4% respectively) than the non-canagliflozin group (21.8%)" should be updated to state the findings removing any interpretation: "The incidence of adverse events considered related to the study drug by the investigator was 33.6%, 29.4% and 21.8% in the canagliflozin 100 mg, 300 mg and non-canagliflozin groups, respectively" • "the incidence of genital mycotic infection adverse events in women was higher in those receiving canagliflozin 100 mg (14.7%) and canagliflozin 300 mg (13.9%) than in those taking placebo (3.1%)" should be updated to state the findings removing any interpretation "the incidence of genital mycotic infection adverse events in women was 14.7%, 13.9% and 3.1% in those receiving canagliflozin 100	accurate. No claims are made regarding any statistical significance. No change to the FAD required.

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	mg, canagliflozin 300 mg (13.9%) and placebo, respectively”	
Merck Sharp and Dohme	Section 3.25 – comparative clinical-effectiveness data at 26-weeks and 52-weeks The ACD states that the ERG identified the following uncertainty: “It was not convinced by the manufacturer’s justification for network meta-analysis for triple therapy assessing effects at 26 weeks, rather than at 52 weeks.” Given the long-term time horizon of the model and the uncertainty noted by the clinical specialists on the long-term efficacy and safety data of the newer treatment options (section 4.3), the NICE Appraisal Committee need to consider the cost-effectiveness results based on the 52-week data in addition to the analysis using 26-week data, as part of their deliberations even if these includes data for fewer comparators.	Comment noted. The Committee’s considerations in the treatment duration in the meta-analyses can be found in section 4.5 of the FAD.
Merck Sharp and Dohme	Section 3.30 – cost-effectiveness data and the use of annual ‘drift’ values The ACD states: “The manufacturer explained that diabetes treatments have an initial effect followed by annual ‘drift’, where the effect lessens over time. Biomarker values after the first cycle were estimated using annual drift values for each treatment. Based on published values, HbA_{1c} drift was assumed to be 0.14% for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 analogues, 0.07% for thiazolidinediones, 0.24% for sulfonylureas and 0.15% for insulin.” The manufacturer has sourced HbA_{1c} drift values from the ADOPT study, which analysed metformin, TZD and SU and demonstrated different drift values for each therapy. The manufacturer assumed that the HbA_{1c} drift values for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 were the same as metformin. However, the deterministic sensitivity analyses demonstrated that the HbA_{1c} drift values was	Comment noted. The manufacturer provided clarification on this point, which was considered by the Committee and is described in section 4.18 of the FAD.

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	the key driver of the cost-utility model (section 3.39, ACD) and therefore it is important to adequately understand the implications of this assumption. It seems likely that the HbA_{1c} drift values for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1 would vary between different treatments and exploratory analyses looking at different scenarios are required.	
Merck Sharp and Dohme	<u>Section 4.12 – clinical and cost-effectiveness of canagliflozin dose escalation strategy</u> The recommended starting dose for canagliflozin is 100mg. The summary of product characteristics states that the dosage can be increased to 300mg if tighter glycaemic control is needed. However, there is no clinical trial evidence for canagliflozin based on dose escalation from 100mg to 300mg. In section 4.12, the ACD states that "The committee concluded that there was uncertainty about the precise clinical effectiveness of canagliflozin when escalating the dose in clinical practice". The expected annual cost of canagliflozin 300mg (£608.83, stated in section 2.4) is significantly higher than 100mg (£477.26, , stated in section 2.4), costing £131.57 more per patient than canagliflozin 100mg. Given the lack of clinical trial data for the dose escalation and the significant drug acquisition cost difference between the two canagliflozin doses, the cost-effectiveness of the dose escalation strategy for canagliflozin is unknown – therefore the NICE Committee cannot conclude with sufficient confidence that a dose escalation strategy is more cost-effective than canagliflozin 100mg.	Comment noted. The Committee did not form any conclusion about the cost effectiveness of dose escalation because it considered the manufacturer's scenario analysis for dose escalation to be highly uncertain because of the lack of evidence informing it (see sections 4.12 and 4.19 of the FAD). Consequently, it considered the cost effectiveness of the two doses separately (see section 4.19 of the FAD).
Merck Sharp and Dohme	<u>Section 4.13 – Adverse events associated with canagliflozin</u> The ACD confirms that the Committee has considered the clinical specialist perspective on the rate of genital infections and management of these occurrences	Comments noted. NICE strives to involve patients in its work wherever possible but no submissions were received from patient organisations or patient experts for this appraisal and no patient expert

<table>
<tr><th>Commentator</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>with canagliflozin. However, it does not appear that the committee has considered the perspective of patients. The most common adverse events for canagliflozin are genital infections. Genital infections increase the risk of patients requiring GP visits, prescriptions and potentially hospital visits and many patients will fear the risk associated with such infections. The Committee should consider the patient perspective on the risk of GIs associated with canagliflozin and consider this as part of their deliberations. Furthermore, evidence associated with canagliflozin related to bone fractures does not to appear to have been considered. The EPAR included the following table on incidence of bone fractures (all and low trauma)
<table>
<tr><th></th><th>Non-CANA</th><th>CANA 100mg</th><th>CANA 300mg</th></tr>
<tr><td>Total no. of subjects with adverse events n(%)</td><td>47 (1.4)</td><td>58 (1.9)</td><td>54 (1.8)</td></tr>
<tr><td>Low Trauma</td><td>31 (1.0)</td><td>41 (1.3)</td><td>39 (1.3)</td></tr>
</table>
The EPAR states “The Kaplan-Meier plot indicates a questionable increase in low-trauma fractures with CANA (both doses). The difference became obvious very early in treatment (after around 6 weeks). Thus, it remains unclear whether this effect could be caused by CANA. Usually bone changes (e.g. noticeable decrease in bone density) need more time to develop. On the other hand, the increase in fractures (if true) may be due to increased falls related to CANA-induced dizziness or hypotension”. The committee should consider this adverse event when assessing the adverse event profile of canagliflozin.</td><td>attended the Committee meeting, meaning that the Committee was limited in the evidence it had for consideration. The patient perspective was represented by the lay lead team member at the first Committee meeting. No change to the FAD required.

The Committee has reviewed the evidence for the associated of canagliflozin with bone fractures and its considerations are included in section 4.13 of the FAD.</td></tr>
<tr><td>Novo Nordisk</td><td>Section 4.5: Network of evidence
In the insulin failure network there are differences in concomitant medication across the network; concomitant medication is expected to have a considerable impact on</td><td>Comments noted. The Committee’s consideration of the clinical evidence for canagliflozin as an add-on treatment to insulin has been expanded and is</td></tr>
</table>

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	treatment effects. If the concomitant medications are not the same this may make the indirect comparison biased. No discussion provided around the differences in trial design (treat-to-target insulin vs. static insulin doses) or baseline characteristics (weight and HbA1c). One study included insulin-naïve patients. The networks presented in the canagliflozin and dapagliflozin manufacturer submissions (MS) are different. The canagliflozin network is much larger and the individual studies appear heterogeneous.	described in section 4.11 of the FAD. There was no discussion around treating to target and static insulin doses because this was not part of the manufacturer's submission. Differences in network meta-analyses provided in two submissions by different manufacturers could be expected; however, the main issue is that the Committee found the meta-analyses conducted for this appraisal to be acceptable. No change to the FAD required.
Novo Nordisk	<u>Section 4.16, 4.17: Cost-effectiveness analysis</u> The majority of assumptions were reasonable; however, the assumption behind HbA1c drift (one of the largest drivers of the model) is unclear. There is an underlying assumption that canagliflozin, dapagliflozin, DPP-4s and GLP-1ra all have equal HbA1c drift but it appears to have been modelled independently for each product, therefore breaking this assumption and potentially introducing additional uncertainty to the results. The baseline characteristics for the canagliflozin on insulin background were of patients at high risk for cardiovascular disease (CVD); it is unknown to what extent this will impact the results however it may bias in favour of interventions which affect CVD risk factors including systolic blood pressure (SBP) and lipid (e.g. canagliflozin). More detailed information on assumptions around the modelling is described in the appendices of the MA. Unfortunately, Novo Nordisk did not have access to these	Comment noted. Clinical advice to the ERG was that the HbA1c drift assumptions used in the cost effectiveness analysis were based on robust studies and were appropriate. (ERG report p105; see also section 4.18 of FAD). Each treatment comparison was conducted on a pairwise basis. The manufacturer's analyses included second order uncertainty which does introduce variability into the comparison of the different treatments for all parameters. However, the ERG conducted additional analyses which did not include second order uncertainty and do not therefore break the assumption of equal HbA_{1c} drift for canagliflozin, dapagliflozin, DPP-4 inhibitors and GLP-1-a (ERG

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	documents since they are not distributed as part of the evaluation report. It would be beneficial for the consultees and commentators to have access to this information as part of the review process to contribute to the development their informed response.	report section 4.3). No change to the FAD required. The manufacturer's main submission is expected to contain the information that is key to the Committee's decision-making, with only supplementary information in the appendices. Appendices to a manufacturer's submission do not form part of Committee's papers (they are supplied on request), which is why they are not included in the evaluation report.
Novo Nordisk	Section 3.38: Uncertainty An incomplete deterministic sensitivity analysis (DSA) was submitted and therefore uncertainty was not fully explored. Upper and lower bounds used in the DSA were poorly described and tornado diagrams excluded dominated or dominant results. The probabilistic sensitivity analysis (PSA) was poorly documented and the extent to which uncertainty was explored is unclear. Multiple cost-effectiveness acceptability curves (CEAC) and the cost-effectiveness acceptability frontiers (CEAF) were absent from the MS (the model was restricted to pair-wise analysis only) which is not in line with the NICE reference case.	Comment noted. The Committee's consideration of uncertainty was explored by the manufacturer is now explicitly detailed in section 4.20 of the FAD.
Novo Nordisk	Section 4.21: External validation The results in the dapagliflozin and canagliflozin MS conflict when the respective SGLT-2s are compared with DPP-4s in combination with insulin. This increases the uncertainty of the results in the canagliflozin MS. MS Dapagliflozin: Dapagliflozin is cost-effective compared with sitagliptin.	Comment noted. The submissions for the two drugs contained two different models developed by different manufacturers. Both models generated small differences in QALYs compared with DPP-4 inhibitors. Because of this, even minor changes to

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	MS Canagliflozin: Dapagliflozin is dominated by canagliflozin. To be consistent with the dapagliflozin MS, canagliflozin should be cost-effective compared with sitagliptin, which it is not.	QALY gains in the model can have a great impact on the ICERs. No change to the FAD required.
Novo Nordisk	The committee rejected the analysis against GLP-1 in combination with insulin (out of scope) and Canagliflozin 100 mg is recommended with insulin background despite being dominated by DPP-4s and GLP-1ra. From Novo Nordisk's point of view the combination of GLP-1ra with insulin is a relevant comparator in the add-on to insulin indication and it should be considered to inform the final recommendation on the grounds that is a commonly used option in clinical practice.	Comment noted. As described in section 4.21 of the ACD, the Committee noted that the NICE scope specified the comparators for the add-on to insulin indication were oral agents, and so disregarded the cost-effectiveness estimates for a GLP-1 analogue. No change to the FAD required.

Comments received from members of the public

There were no comments from members of the public.