NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Canagliflozin, dapagliflozin and empagliflozin as monotherapies 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 companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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.

Comments received from consultees

Commentator	Comment [sic]	Response
AstraZeneca	AstraZeneca thank NICE for the opportunity to respond to the appraisal consultation document (ACD). • We believe the ACD is a fair and robust reflection of the available evidence, the assessment group (AG) report and the Committee meeting, and support NICE's recommendation for the positioning of Sodium-glucose co-transporter-2 (SGLT2s) in monotherapy: *where a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed, and a sulfonylurea or pioglitazone is not appropriate.* • Given the evidence base in monotherapy and challenges discussed during the process, AstraZeneca also agree with the Committee that the clinical and cost evidence submitted did not support any differences between SGLT2s. • We wish to highlight that cost-effectiveness results for SGLT2s reported in the ACD (company results pages 20-22, and AG results pages 30-32) include the anomalous study Kaku et. al. 2014 which had different baseline characteristics to other included studies. Sensitivity analyses demonstrated this study had a significant negative effect on the results for dapagliflozin; we therefore request NICE clarify that the ICERs presented include this study and therefore may not be truly reflective of the cost-effectiveness of dapagliflozin.	Thank you for your comments. The evidence section is intended to provide a brief overview of the available clinical and cost effectiveness evidence. The considerations section of the FAD notes that results for dapagliflozin in the network meta-analyses were sensitive to the inclusion of trial that had different baseline characteristics to the others, and when this was removed, results were similar to the other SGLT-2 inhibitors. Please see FAD section 4.6.

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AstraZeneca	**AG comment in report P. 6 Section 3.6:** …an eGFR of less than 60 ml/min/1.73 m2) because its efficacy depends on renal function. Reduced efficacy at lower eGFR is common for the class. Please alter the text to: "because the efficacy of SGLT2s depends on renal function", or include text on eGFR restriction for each flozin	Thank you for your comments. This section has now been updated. Please see FAD section 2.
AstraZeneca	**AG comment in report P.19:** The costs in the AstraZeneca model were higher than those assumed by the AG; the AG was not sure why there was a discrepancy. **AG comment in report P. 25:** the company had used the same source for the costs of complications of diabetes (blindness and amputation; UKPDS84) as the AG, but that the AG had derived lower values. Please note data from the UKPDS84 (cost year 2012) were used but were inflated to 2014 using the hospital & Community health services (HCHS) index.	Thank you for your comments. In response to this comment, the Assessment Group stated it is "still not clear why there are the discrepancies between the Astrazeneca unit costs and the AG unit costs derived from the UKPDS84". Please see the Assessment Group responses to the comments received on the ACD.
AstraZeneca	**AG comment in report P. 25:** inpatient and outpatient costs appeared to be completely omitted if the patient did not experience a complication. It stated that if this was the case, it would be a serious omission.... AstraZeneca note that the difference in life years between the treatment arm and the control arm is minor meaning that patients in the treatment arm live at most 0.004 years longer; the impact therefore seems negligible.	Thank you for your comments. In response to this comment, the Assessment Group stated "The AG remains of the opinion that the Astrazeneca method somewhat exaggerates the cost impact of developing complications and so is a serious omission in terms of model structure". Please see the Assessment Group responses to the comments received on the ACD.
AstraZeneca	**AG comment in report P.36:** However, it heard from the AG and AstraZeneca (the company for	Thank you for your comments.

Commentator	Comment [sic]	Response
	dapagliflozin) that the results for dapagliflozin were sensitive to the inclusion of a trial by Kaku et al. (2014), and when this was removed, results were similar to the other SGLT-2 inhibitors AstraZeneca agree with this statement. We note that the reason for the removal of this trial was due to the differences in baseline characteristics versus all other SGLT2 studies including: 1. Lower baseline HbA1c; 7.5% vs. 7.9%-8.3% 2. Lower eGFR; 67.1 mL/min1.73m2 vs. all studies >86 mL/min1.73m2	
AstraZeneca	**AG comment in report P.38**: BMI-2 scenario (in which weight gains were maintained and weight losses rebounded to natural history after 1 year) best reflected the treatment effect on weight loss. AstraZeneca agree this is the most appropriate scenario listed; however we note that data have demonstrated SGLT2s in monotherapy maintain weight over two years (Ferrannini et al. 2010). As such, rebounding after two years would be considered better aligned to clinical data.	Thank you for your comments.
Boehringer Ingelheim	Boehringer Ingelheim agrees with the Appraisal Committee's preliminary recommendation as stated in section 1.1 and 1.2.	Thank you for your comments.
Boehringer Ingelheim	**Section 4.3 Page 8** Where stating "The reductions for empagliflozin were also greater than those for sitagliptin (statistical significance was not presented).": In the publication by Roden et al (2013), Figure 2 (changes in HbA1c and FPG) details the differences and statistical significance values of the adjusted mean change from baseline in HbA1c for empagliflozin 10 mg and 25 mg compared to sitagliptin. The difference in adjusted mean change from baseline in HbA1c	Thank you for your comments. This section has now been updated. Please see FAD section 3.7.

Commentator	Comment [sic]	Response
	for empagliflozin 10 mg compared to sitagliptin is 0.00% (p= 0.96) and -0.12% (p= 0.106) for empagliflozin 25 mg compared to sitagliptin.	
Boehringer Ingelheim	**Section 4.4 Page 9** Where stating "Compared with placebo, all SGLT-2 inhibitors reduced systolic blood pressure, however no results were statistically significant.": In the publication by Roden et al (2013), Figure 4 (Changes in blood pressure in the full analysis set) illustrates the adjusted mean change from baseline in systolic blood pressure (SBP) and associated p-values. The difference in adjusted mean change from baseline in SBP for empagliflozin 10 mg compared to placebo is -2.6 mmHg (p= 0.023) and -3.4 mmHg (p= 0.003) for empagliflozin 25 mg compared to placebo. Therefore, the results for empagliflozin 10 mg and 25 mg compared to placebo were statistically significant in reducing SBP.	Thank you for your comments. This section has now been reworded to state "Compared with placebo, all SGLT-2 inhibitors reduced systolic blood pressure". Please see FAD section 3.8.
Boehringer Ingelheim	**Section 4.47 Page 27** Where stating "The company did not present any sensitivity or scenario analyses for model B.": Boehringer Ingelheim provided 4 economic models (model A and model B, each carried out at 24 and 52 weeks). This was deemed extensive enough to capture any areas of uncertainty. As the two models validate each other in their direction of results it was not deemed necessary to present the sensitivity analysis. Nevertheless, one-way sensitivity analyses were carried out on both model A and model B, showing that the results are most sensitive to the incidence of hypoglycaemic events (empagliflozin 10mg and empagliflozin 25 mg and the comparator), likely due to the wide 95% confidence intervals. Weight loss and	Thank you for your comments. This information has been added to the FAD. Please see FAD section 3.49.

Commentator	Comment [sic]	Response
	the incidence of UTIs also have a considerable impact on the ICER. Other variables, including cost and utility decrements associated with AEs had a comparably minimal impact on the ICER results.	
Boehringer Ingelheim	**Section 4.48 Page 27** Where stating "The AG also stated that it was concerned about why the reported UKPDS costs of model B were around half of those of model A, whereas the QALY values of model A and B were similar. It stated that the reason for the discrepancy was unclear.": It is known with the UKPDS Outcomes Model 1 (OM1) that running 40 years together (as was done for model A) versus running the model 1 year at a time (as was done for model B), results in the costs being underestimated for the latter. Usually, they are underestimated by about half. This has already been acknowledged as an issue by the Oxford team of developers. The reason model B was ran for 1 year at a time, was to be able to account for treatment switches and weight changes on a yearly basis, since these are not directly modelled for in the UKPDS model. This workaround method was validated with the developers, who have improved the issue in the newly developed UKPDS Outcomes Model 2 (OM2). Overall, the costs are underestimated for all treatment groups in model B compared to model A. Therefore, the resulting incremental cost-effectiveness ratios (ICERs) are still reflective of the relative differences between treatments for both models.	Thank you for your comments. This text has now been removed from the FAD.
Boehringer Ingelheim	**Section 4.65 Page 38** Boehringer Ingelheim agrees with the Committee's opinion that "weight loss does affect quality of life". Boehringer Ingelheim also agrees that "the evidence [shows] that SGLT-2 inhibitors do have a significant effect on weight loss, and that the AG's BMI-2 scenario (in which weight gains were maintained and weight losses rebounded to natural history after 1 year) best reflected the treatment effect on weight loss." Nevertheless, it remains a valid point that the very small QALY differences between treatments make the	Thank you for your comments.

Commentator	Comment [sic]	Response
	ICERs unstable.	
Janssen	Janssen welcomes the opportunity to comment on the preliminary recommendation made by the Appraisal Committee detailed in the Appraisal Consultation Document (ACD). Janssen is pleased to see the Appraisal Committee's preliminary decision that canagliflozin, dapagliflozin and empagliflozin as monotherapies should be recommended as options for treating type 2 diabetes in adults when diet and exercise alone do not provide adequate glycaemic control in patients and for whom metformin is contraindicated or not tolerated, if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed. Janssen is disappointed, however, to see that the recommendation for the use of these products is restricted to cases in which sulphonylurea and pioglitazone are not appropriate. Janssen is committed to working with NICE in order to address the Committee's key uncertainties as outlined in the ACD, which are hopefully addressed within the context of answering the questions posed by the Committee as part of this consultation process: • Has all of the relevant evidence been taken into account? • Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? Additionally, in Appendix 1 on page 14 of this document, Janssen has provided the median values and ranges for HbA1c, weight and blood pressure changes as requested by the Committee at first Appraisal Committee Meeting, on 25th November 2015.	Thank you for your comments.
Janssen	**1. Janssen believes the evidence base considered in this appraisal process does not support the provisional recommendations made for guidance to the NHS**	Thank you for your comments. When using its preferred model (AG model) and its preferred assumptions

Commentator	Comment [sic]	Response
	Considering all of the evidence presented by all stakeholders in this appraisal review process and specifically in the original Janssen submission, Janssen does not believe that the recommendation made in sections 1.1 and 4.68 that restricts the use of SGLT2 inhibitors to only if: "a sulfonylurea or pioglitazone is not appropriate" is suitable, which is further supported by the recently published NICE clinical guidelines for the management of type 2 diabetes (NG28).(1) Restricting the use of SGLT2 inhibitors to only be considered after both sulphonylurea and pioglitazone does not allow the guidance for individualised care proposed in NG28 and by the ACD (see section 4.58, page 34) to be supported. Recent publications further highlight the importance of individualising care and support the opinion that not all patients will be suitable for treatment with pioglitazone and/ or sulphonylurea; e.g. due to predisposition of hypoglycaemia, chronic heart failure or weight gain.(2, 3) Restricting the use of just one class of anti-hyperglycaemic agents (AHAs) at monotherapy, may lead to confusion and subsequent lack of individualisation of care at a stage in therapy when it is arguably one of the most important opportunities for tight glycaemic control to increase the chance of improved long-term outcomes for an individual with T2DM. Furthermore, the recommendation appears to contradict itself, as DPP4 inhibitors are not subject to these same restrictions. Clinicians do not have to consider whether a sulphonylurea or pioglitazone is first appropriate before prescribing a DPP-4 inhibitor as monotherapy. Moreover, the analyses presented by both the manufacturers and the AG in this appraisal process consistently demonstrate the cost-effectiveness of all SGLT2 inhibitors, and in particular canagliflozin, compared to DPP4 inhibitors. Furthermore, supporting the confusing nature of this recommendation for clinicians when making a decision about individualising care. Canagliflozin is effective in lowering HbA1c and has the added benefits of blood pressure (BP) lowering and weight loss, which helps to minimise the risk of long-term complications associated with the progression of T2DM. Canagliflozin has also shown consistent dose dependant response across all treatment lines and can be administered in combination with pioglitazone, sulphonylureas and insulin when patients need to progress from canagliflozin monotherapy to dual therapy, giving patients and clinicians a wide array of treatment options from which to	about the effect of treatment on BMI (scenario BMI-2), the ICERs for SGLT-2 inhibitors were: over £52,400 per QALY gained compared with pioglitazone, over £71,000 per QALY gained when compared with sulfonylureas, and were less than £29,300 per QALY gained compared with DPP4 inhibitors. In summary, at ICERs of £20,000 to £30,000 per QALY gained, the SGLT-2 inhibitors were cost effective compared with DPP-4 inhibitors, but not cost effective compared with pioglitazone and sulfonylureas. Therefore the Committee concluded that canagliflozin, dapagliflozin and empagliflozin as monotherapy were a cost-effective use of NHS resources, but only when pioglitazone or sulfonylureas were not appropriate treatment options. Please see FAD section 4.11 to 4.13.

Commentator	Comment [sic]	Response
	choose the most suitable regimen. Two pivotal studies provide the clinical evidence for canagliflozin monotherapy. Both studies showed a significant reduction in HbA1c versus placebo from a mean baseline HbA1c of 8%.(4, 5) A dose-dependent reduction in HbA1c with canagliflozin was demonstrated in CANTATA-M (LS mean change from placebo at 26 weeks) of -0.91% with the 100 mg dose and -1.16% with the 300 mg dose;(5) this clinical benefit was maintained out to 52 weeks.(6) Clinically relevant reductions in systolic blood pressure (SBP) (-3.7 mmHg with the 100 mg and -5.4 mmHg with the 300 mg in CANTATA-M, and -5.2 mmHg with the 100 mg in the Japanese study) and body weight (2.2-3.3% loss) were seen in both clinical trials,(4, 5) and maintained out to 52 weeks with both the of doses of canagliflozin.(6, 7) The Janssen network meta-analysis (NMA) reports that: • Canagliflozin 300 mg was ranked highest in terms of mean change from baseline in HbA1c and canagliflozin 100 mg was third highest after glipizide (data from 40 studies); • Canagliflozin 300 mg was the second most effective agent in achieving HbA1c <6.5%, behind pioglitazone (22 studies), and the most effective agent in lowering fasting plasma glucose (FPG) (36 studies); • Canagliflozin 300 mg and 100 mg were ranked first and second for weight loss (19 studies), reduction in BMI (six studies) and reduction in SBP (eight studies).(8) The clinical studies, together with the NMA, provide strong and robust evidence that canagliflozin is effective in lowering HbA1c and has the added benefits of BP lowering and weight loss with a low risk of hypoglycaemia. These results are consistent with conclusions drawn from both the clinical trials and the NMA for canagliflozin in combination therapy, appraised by NICE in 2014.(9) A comprehensive economic analysis of the cost-effectiveness of canagliflozin monotherapy in treating T2DM was conducted using ECHO-T2DM. Results from the economic analysis show SGLT-2 inhibitors to be associated with the greatest QALY gains, with canagliflozin being the most effective (a finding	

Commentator	Comment [sic]	Response
	consistent across all stakeholder submissions with exemption of the pooled analysis submitted by Astra Zeneca) based on 10.039, 10.051, and 10.083 QALYs for 100 mg and 300 mg and 100 mg dose increase, respectively versus current standard of care (sulphonylurea), generating a QALY gain of 9.949 over 40 years. As acknowledged by NICE, the use of pioglitazone in clinical practice is declining in the UK. Further explanation as to why Janssen is confident that its economic analysis, presented in the original submission, is robust in its findings and representative of current clinical practice is provided on pages 8-9, below. Janssen recognises, however, that the original results provided were subject to some uncertainty due to the canagliflozin 300 mg price change and two identified errors after submission and have thus provided the full set of updated results in Appendix 2 on page 15 of this document. In conclusion, canagliflozin is effective in lowering HbA1c and has the added benefits of blood pressure (BP) lowering and weight loss, which helps to minimise the risk of long-term complications associated with the progression of T2DM. Through a robust NMA and rigorous cost-effectiveness analysis, there is compelling evidence for canagliflozin as an efficient use of NHS resources for monotherapy treatment in patients with T2DM unable to take metformin. Both the clinical and economic results generated using the NMA are consistent with results from use of canagliflozin in dual and triple therapy which further strengthens the validity of the analysis.(9)	
Janssen	**2. Evidence which supports the potential differentiation between SGLT2 inhibitors has not been accounted for** In Section 4.18, the ACD summarises the considerations made by the Assessment Group (AG) about the effectiveness of the SGLT-2 inhibitors compared with each other in their NMA. It noted that both doses of canagliflozin lowered HbA1c more than dapagliflozin and both doses of empagliflozin (a finding consistent across all submissions with exemption of the pooled analysis submitted by Astra Zeneca) and noted that this reduction may be because canagliflozin, unlike other SGLT-2 inhibitors, may also have an effect on the SGLT-1 receptor. Though evidence as to the certainty of this mechanistic difference resulting in clinically meaningful transformation is not absolute, Janssen believes that this is an important difference to	The committee heard from the clinical experts that there was no direct evidence available to determine if there are clinically meaningful differences among the SGLT-2 inhibitors. The Committee was aware that some results in the network meta-analyses showed differences between the SGLT-2 inhibitors. For example, some of the

Commentator	Comment [sic]	Response
	consider whilst reviewing the effectiveness evidence presented throughout the appraisal process. Moreover, in section 4.51 on page 28, the ACD notes that the AG acknowledges the SGLT-2 inhibitors were of similar acquisition cost but that overall costs in the canagliflozin arms were cheaper; attributing this to the greater effect of canagliflozin on HbA1c, which meant that treatment, was intensified to the more expensive subsequent lines of treatment with a lag. Indeed, across all stakeholder analyses (with exemption of the pooled analysis submitted by Astra Zeneca) there was a consistent trend that canagliflozin was most cost-effective versus the alternative SGLT2 inhibitors. However, within the summary of cost-effective evidence in section 4.67 on page 39, the first bullet point seems contradictory to these findings. Section 4.56 on page 32 of the ACD summarises two probabilistic analyses conducted by the AG comparing ICERs with DPP-4 inhibitors only assuming an ICER of £20,000 per QALY gained. When assuming no utility gain from the impact of BMI; the probability of being cost effective was reported as: canagliflozin 45%, dapagliflozin 4%, empagliflozin 26%, and sitagliptin 26%. Similarly, however when assuming weight changes were maintained indefinitely, the probability of being cost effective was reported as: canagliflozin 93%, dapagliflozin 0%, empagliflozin 6%, and sitagliptin 0%. In both cases, there was clear separation between the agents. Janssen would ask the Committee to further consider the indirect evidence available. For example, it was demonstrated consistently across all manufacturer submissions (with exemption of the pooled analysis submitted by Astra Zeneca) and the AG analyses that canagliflozin 300 mg was associated with better HbA1c reductions, BP control and weight loss. Furthermore, the NMA demonstrated no additional risk of hypoglycaemia with canagliflozin 300 mg versus alternative SGLT2 inhibitors (as well as placebo). Of particular note, within NICE guidelines on how to prepare information for submission to a NICE appraisal process, it supports the reflection of indirect evidence in the absence of head-to-head data.(10) There is consistent evidence suggesting that canagliflozin is associated with a differential cost-effective profile compared to alternative SGLT2 inhibitors.	network meta-analyses suggested dapagliflozin had a lower HbA1c response than canagliflozin and empagliflozin. However results for dapagliflozin were sensitive to the inclusion of a trial that had different baseline patients characteristics to the others, and when this was removed results were similar to the other SGLT-2 inhibitors. The Committee also noted that the differences in effectiveness between the SGLT2 inhibitors were most pronounced in those receiving the higher doses of canagliflozin and empagliflozin, which were not licensed starting doses. The Committee concluded that from the evidence available it was not possible to determine if there are any differences in effectiveness between the SGLT-2 inhibitors. The Committee also noted that because all the SGLT-2 inhibitors cost the same per tablet and have the same dosing frequency, and the clinical data had not robustly demonstrated that any one SGLT2 inhibitor was more clinically effective than the others (see section 4.6), it could not determine a

Commentator	Comment [sic]	Response
	In addition, there is a Phase I trial that compares the pharmacodynamics of canagliflozin 300 mg and dapagliflozin 10 mg in healthy volunteers. Both medicines were well tolerated. Canagliflozin was, however, associated with higher UGE and greater RTG reductions for the remainder of the day. Overall, in healthy participants, canagliflozin 300 mg provided greater 24-hour UGE, a lower RTG and smaller post prandial glucose (PPG) excursions than dapagliflozin 10 mg.(11)	meaningful way to differentiate treatments by cost. Please see FAD section 4.6 and 4.11.
Janssen	**3. Incorrect reporting of Janssen trial results** On pages 8-9, section 4.4 incorrectly states that "Compared with placebo, all SGLT-2 inhibitors reduced systolic blood pressure; however, no results were statistically significant." Canagliflozin demonstrated statistically significant reductions in systolic blood pressure (SBP) in the trials considered in this appraisal. • Stenlof (2013): canagliflozin 100 and 300 mg were associated with statistically significant reductions from baseline in SBP at week 26 compared with placebo (difference in LS mean changes versus placebo of −3.7 and −5.4 mmHg, respectively; p<0.001 for both canagliflozin doses),(5) • Inagaki (2014): at 24 weeks, reduction in SBP (-7.88 versus -2.72 mmHg) was significantly greater with 100 mg canagliflozin than with placebo (p < 0.05).(4) As further detailed in point 4 below, based on a review of the analyses conducted by the Assessment Group (AG), Janssen previously presented evidence which demonstrated that the incorrect SBP values were used in the network meta-analysis (NMA) and subsequent cost-effectiveness analyses presented in the Assessment Report (AR). Moreover, Janssen received confirmation from the AG during the first appraisal committee meeting that this factual inaccuracy in the data extraction has been used in all further analyses conducted by the AG.	Thank you for your comments. This section has now been reworded to state “Compared with placebo, all SGLT-2 inhibitors reduced systolic blood pressure”. Please see FAD section 3.8.
Janssen	**4. Previously identified error by the AG not corrected and seemingly unaccounted for** In section 4.50, the ACD reports that the AG baseline proportion of ischaemic heart disease prevalence	Thank you for your comments. The Assessment Group has provided updated

Commentator	Comment [sic]	Response
	had been incorrectly set to zero in their modelling and that this has been corrected for in the results presented in the ACD. Janssen believes that there is one further mistake in the economic analysis, which does not appear to have been addressed by the Assessment Group (AG) despite Janssen having raised this as a concern within the Janssen response to the Assessment Report (AR) and at the first Appraisal Committee meeting. Specifically, Janssen noticed that the AR states: "…systolic blood pressure reduction with canagliflozin 300 mg was 0.5 mmHg from baseline, which is 0.9 mmHg more than placebo". For 300 mg, the reduction from baseline was 5.0 mmHg rather than 0.5 mmHg; compared to placebo this should be 5.4 mmHg. Janssen attempted to replicate the NMA conducted by the AG. While exact replication was not achieved (since full details about how missing data were handled were not supplied in the AR report), near replication was achieved, which suggests a high likelihood that this error is not only a typographical error in the text, but an error that has been pulled through to the NMA and subsequent economic modelling (disadvantaging canagliflozin 300 mg).	results for canagliflozin 300 mg. Please see FAD section 3.57.
Janssen	**5. The ACD fails to acknowledge the similarities and focuses on the differences between the modelling approaches used by Janssen and the AG** Section 4.26 of the ACD outlines the differences in the modelling approaches used by Janssen and the AG but it fails to recognise any of the similarities. A detailed list of similarities (and differences) was summarised in section 1 of the 'Additional Information' document provided by Janssen in response to the Assessment Report (AR). Briefly, at a general level, the key similarities between the Janssen and AG analyses are: • Time horizon • Patient baseline characteristics • Efficacy and tolerability data • Early treatment sequencing	Thank you for your comments. The evidence section is intended to provide a brief overview of the available clinical and cost effectiveness evidence.

Commentator	Comment [sic]	Response
	• Acquisition and event costs (in part) • Quality of life data for significant drivers	
Janssen	**6. An inaccurate analysis of the comparative drivers of the Janssen and AG's results led to an inaccurate conclusion, unjustly questioning reliability of the ECHO-T2DM model** Section 4.66 discusses in detail the potential differences between the economic modelling approaches (including the AG model and ECHO-T2DM, but also the way in which the models are applied) and the Committee concluded that the differences in results observed for the comparisons for canagliflozin versus pioglitazone and sulphonylurea were "anomalous" and could not be explained by either differences in the eGFR module or the choice of HbA1c progression modelling; where Janssen chose to model progression assuming a "linear in segment" (but inherently non-linear) approach and the AG chose to use the non-linear UKPDS 68 HbA1c progression equation. Janssen disagrees with this summary of the evidence and believes that further explanation will help to address the Committee's current misconceptions of the ECHO-T2DM model. The choice of using either "linear by segment" or the UKPDS 68 evolution equation to model the progression of HbA1c over time was an important driver of results using the ECHO-T2DM model, with the ICER for canagliflozin 100 mg versus sulphonylurea changing from £3,377 in the base case to £133,274 per QALY gained in scenario analysis 14, in the original submission. The latter value is similar to the base case value arrived at by the AG, also using the UKPDS evolution equation. A similar pattern is found when comparing canagliflozin 100 mg to pioglitazone, the base case ICER changes from ££78,518 to £31,945. It is impossible with the information available for Janssen to assess why using the linear segments did not decrease the ICER in the AGs analysis as would be expected by removing double-counting of the treatment effects associated with rescue medication. Janssen therefore would argue that the lack of difference in the AG analysis is a bigger source of uncertainty than the expected differences, given the changes in the inputs, found in the Janssen analysis. Moreover, Janssen would like to reiterate that the "linear by segments" is its preferred approach, given it is not sensitive to confounding related to	Thank you for your comments. The committee acknowledged there were different advantages and disadvantages to the different modelling approaches, and it agreed with the AG that all models submitted were appropriate and of a reasonable quality. However it concluded that the AG model was most appropriate for decision-making, because of its more accurate reflection of treatment intensification. Please see FAD section 4.8.

Commentator	Comment [sic]	Response
	rescue medication. While Janssen recognises that the AG did inactivate the covariate for Year 2, to reduce the confounding with the treatment effects of the initial treatment, this does not help to mitigate the problem for the remaining (median) 10 years of the trial. Conversely, the ADOPT trial, on which the Janssen analysis is based, was designed to answer specifically the study question at hand, namely the progression of patients' HbA1c over time treated on alternative anti-hyperglycaemic monotherapies in the absence of rescue treatment, to avoid confounding. The finding was that even over approximately 5 years the drift for three important categories of AHAs was almost linear. It is worth noting again that, while Janssen used the "linear by segments"' approach for HbA1c drift, linearity was interrupted with the treatment effects of rescue medication, which yields non-linear mean HbA1c curves on average (i.e. a saw-toothed effect for any individual hypothetical patient, as demonstrated on page 174 of the AR) that look similar to the non-linear (reversion to the mean) curves generated with the UKPDS HbA1c evolution curve.[redacted]. Furthermore, as discussed below on page 9, 12 and in section 4.19 of the ACD, the differential durability of sulphonylureas observed in clinical trials is recognised by the Committee and moreover by clinical experts,(2, 3, 9) which further supports the accuracy of predicting long-term outcomes for alternative AHAs. Whilst Janssen agrees that the effect of disabling the eGFR module resulted in only modest differences	

Commentator	Comment [sic]	Response
	(though in the expected direction) in the results of the exploratory analysis, it is apparent that this was primarily driven by the nature of the patients being explored in the scenario. Patients were relatively young and healthy and only few hypothetical patients were alive and had not progressed to insulin (and hence had already discontinued canagliflozin) when their eGFR became too low to remain on canagliflozin or empagliflozin lower dose therapies. Fewer than 15% of the patients in the canagliflozin arm discontinued because of low eGFR. In other potential applications in which hypothetical patients began with lower eGFR values, this could become an important driver. Moreover, there are a number of other drivers of differences in the results for the comparison with sulphonylurea that were overlooked by the Committee in section 4.66. First, the AG used a greater HbA1c lowering for sulphonylurea as calculated in its NMA (-1.30, inconsistent with the results of other submitted NMAs). Janssen tried to replicate the AG NMA, using the same studies, but found a smaller lowering of about -1.12. Noticeably, the Janssen had the smallest HbA1c lowering for sulphonylurea, which was found to be based on a typographical error in the Janssen NMA. The correct value was computed (-1.04) and the simulation re-run, yielding an ICER as expected somewhat higher than the original of £7,875, for canagliflozin 100 mg versus sulphonylurea. Differences in the rate of drift between canagliflozin and sulphonylurea (as modelled by Janssen but not the AG in the base case) also contribute to differences in health and importantly in the timing of rescue medication. The HbA1c drift in the Janssen model is informed by the intervention treatment and as such varies by agent, whereas the AG model assumption does not per se (see page 9 for further explanation). Both of these features naturally explain some of the distance between the results. Finally, as noted on pages 4-5, Janssen believes that there was an error in the NMA conducted by the AG regarding the SBP improvement associated with canagliflozin 300 mg, inaccurately using a lowering of 0.5 mmHg instead of 5.0 mmHg. A difference of this size is clinically meaningful and it is sufficient to generate noticeable health improvements and cost offsets in this modelling context.	
Janssen	**7. Incomplete explanation of the drivers in the Janssen economic analysis**	Thank you for your comments. This section has

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	In section 4.36 on pages 22 and 23, it is summarised that the ECHO-T2DM model is “very” sensitive to the annual rate of HbA1c progression assumed for canagliflozin and that the AG stated "the changes are likely more because of the time spent on therapy and its immediate effects on treatment cost, weight, adverse events (AEs) and hypoglycaemia than because of any changes in the modelled complications of diabetes". It is important to note that differences in cost, weight profile, and AEs (including hypoglycaemia) are very relevant parameters for a health economic evaluation in T2DM. In fact, patients and their physicians prefer treatments that help to provide additional benefits in terms of weight loss and low risks of hypoglycaemia, in addition to controlling their HbA1c. Like most diabetes outcome prediction models, the simulations presented in the Janssen submission, modelled treatment-to-HbA1c-goal and, thus, led to corresponding bio-marker value convergence (which occurs when agents with worse HbA1c improvements are complemented with rescue medication earlier). Therefore, it may be inaccurate to state that the model itself is “very” sensitive to the annual rate of HbA1c progression. The model may even be conservative regarding the strength of the relationship of HbA1c and the risk of microvascular complications. Nevertheless, Janssen believes that this result, whereby the model outcomes are significantly impacted by the time a patient spends under tight glycaemic, is in accordance with what one would anticipate to observe in clinical practice. It is well-versed in the literature that life-time exposure to hyperglycaemia, sometimes referred to as glycaemic legacy, drives the risk for the complications of diabetes.(13) Thus, the costs related to rescue therapy and AEs such as weight gain and hypoglycaemic rates (higher in patients taking rescue insulin) tend to carry disproportionate weight, while differences in diabetic complications tends to be small because these occur later in a patients disease when costs and QALYs are heavily discounted. Were rescue therapy not to be modelled, which is not consistent with current treatment recommendations [NG28], the situation would be reversed and there would be sustained differences in the bio-markers leading to differences in health outcomes but no cost offsets related to	now been reworded to remove the word “very”. Please see FAD section 3.39.

Commentator	Comment [sic]	Response
	rescue medication.	
Janssen	**8. Incomplete reporting of results, potentially misleading the reader** In Section 4.33 on page 22, the ACD lists only a select number of results from 1 out of the 17 scenario analyses presented in the Janssen submission, which Janssen believes will lead to misinterpretation of the evidence. Janssen does not believe that the scenario analysis results presented give a fair representation of the robustness of the cost-effectiveness analysis conducted using the ECHO-T2DM model and does not demonstrate the true impact of the changes in the input parameters for this scenario analysis. Janssen undertook the particular scenario analysis that was selected for discussion in section 4.33 (in which the HbA1c evolution inputs were switched to the non-linear HbA1c evolution equation from the UKPDS68 trial) to provide the results of an analysis that better approximated the approach that the AG was expected to use. This allowed for a better comparison of the two modelling approaches and to the identification of drivers of cost-effectiveness. Janssen do not, however, believe that the results of this particular scenario analysis are more realistic than those presented in the Janssen base case analysis. For reasons outlined in the original submission and elaborated in the response by Janssen to the AR, Janssen considers a segmented linear agent-varying evolution (source: ADOPT) of HbA1c to be the most relevant approach for the base case. The AG, in fact, expressed “some sympathy” for the serious issue relating to double-counting of the treatment effects related to downstream rescue medication within the AR. Likewise, within section 4.19 on page 15 of the ACD, the evidence summary offers further support to the approach taken by Janssen, whereby the ADOPT trial outputs allows for the investigation of patients HbA1c progression in a treatment specific manner. Of particular interest, the ADOPT trial was indeed designed for the purpose of estimating glycaemic durability of monotherapies, separately from the confounding influences of rescue medication. Specifically, the ADOPT study provided evidence both that HbA1c evolution tends to be linear and that the slope varies by agent.(12) Previously, the National Institute for Health and Care Excellence (NICE) in the	Thank you for your comments. The evidence section is intended to provide a brief overview of the available clinical and cost effectiveness evidence.

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	UK did accept such claims for differing drifts for sulfonylurea and for TZDs in its evaluation of canagliflozin. A number of studies have employed the non-linear HbA1c time path equation from the UKPDS Outcomes Model. While agent-specific differences in evolution are not specified explicitly, the equation specifies current HbA1c as a function of the previous periods HbA1c so any initial drug-specific differences in HbA1c in the simulation will lead the arms to follow different trajectories. This approach appears to have been used by both the manufacturer and the ERG during the NICE technology appraisal for Bydureon,(13) though an unexplained maintained HbA1c gap despite following the expected concave trajectory prompted NICE to question the implementation.(14) One must interpret HbA1c time paths generated in this way carefully, however, as they are heavily confounded by the care that was administered in the UKPDS trial (including agents used, doses, and patterns of intensification), which was not controlled for in the regressions. Indeed, simulation modelling that applies treatment effects explicitly at the time of simulated rescue medication risks double-counting treatment effects (and simulating overly low upward HbA1c drift) because the HbA1c lowering of UKPDS rescue medication is already embedded implicitly in the parameter values of the equation. While inactivating the year 2 covariate mitigates the problem of active treatment change during the initial starting phase of the UKPDS trial, it does not help to alleviate this effect over time. In consideration of this evidence, Janssen is confident in its approach taken in the base case as the majority of the scenario analyses support the robustness of the modelling approach taken, resulting similar outcomes. Furthermore, in order to demonstrate the true implication of changing the assumption around a key driver of the analysis, Janssen believes that all results that are substantially different should be presented in this summary, including those for canagliflozin versus pioglitazone, where the base case ICER of £78,518 changes to £31,945.	Please see FAD section 4.8 for a description of the committee's rationale for its preferred model.
Janssen	**9. Misrepresentation of results given the recent price change of canagliflozin 300 mg** In section 4.46 (pg. 26) the ACD summarises that the Boehringer Ingelheim submission concluded that dapagliflozin was "cheaper but less effective than canagliflozin 300 mg…". While this is true, Janssen	Thank you for your comments. This section has been updated to state that the results use the outdated higher price of canagliflozin

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	believe that it is important to recognise that this particular conclusion was based on the price of canagliflozin 300 mg before the price changed in August 2015. With the lower price of canagliflozin 300 mg, the conclusion is now likely inaccurate. To further demonstrate the impact of this price change, the results from the Janssen model for canagliflozin 300 mg versus dapagliflozin 10 mg are as shown in Table 2 in Appendix 3, page 26.	300mg. Please see FAD section 3.48. In addition, please note that the ACD (section 4.29) and the FAD (section 3.33) states that the "price of canagliflozin 300 mg reduced after the company submissions were received (from approximately £608 to the same price as the 100 mg dose, approximately £477). All the companies used the higher price of canagliflozin 300 mg, whereas the AG was able to use the lower price".
Janssen	**10. Misrepresentation of the manufacturers modelling approach** In section 4.64 on page 37, the ACD states that the manufacturers' submissions were based on switching the treatments being compared when the hypothetical patients intensified treatment. This is not strictly correct for the Janssen modelling. With one exception, the hypothetical patients do not discontinue their first oral agents when rescue medication is first required. For example, a patient receiving canagliflozin monotherapy will add pioglitazone when first intensification is needed, but will not discontinue the canagliflozin. It is only when patients are intensified to insulin that the hypothetical patients discontinue oral therapies being taken. The one exception was repaglinide, which was discontinued at intensification in favour of pioglitazone, though this is consistent with its licence and it should be noted that repaglinide was considered only as a sensitivity analysis in the Janssen submission. This assumption was made based on clinical feedback during interviews used to inform the original submission and was an approach confirmed as appropriate during a further advisory meeting. Evidence within the literature supports both approaches; with a recent publication by Khunti et al highlighting that patients a divided between those that remain on oral AHAs and those that discontinue all other AHAs	Thank you for your comments. The FAD has been updated to note that treatments are switched at either the first or second intensification of the company models. Please see section 3.33.

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	when starting on an insulin regimen.(15, 16)	
Janssen	**11. Misinterpretation of evidence presented in the Janssen submission** In section 4.64 on page 37, the Committee conclude that “all models submitted were appropriate and of a reasonable quality, but the AG model was most appropriate for decision-making, because of its more accurate reflection of treatment intensification”. While Janssen recognises the importance of modelling the most clinically relevant treatment patterns; we are confident that there are additional important aspects of economic modelling that further support the clinical relevance of it to predict outcomes in diabetes. T2DM is chronic, progressive and affects multiple organ systems, thus requiring models that include a large number of inter-related health states and a long time horizon to fully capture the costs and benefits of the disease and its interventions. Moreover, T2DM is characterised by chronic hyperglycaemia, hypertension, and disturbances of blood lipids which have been linked to elevated risks for developing micro- and macro-vascular complications, which is simulated in models of T2DM using risk equations that convert time-varying bio-marker values into the likelihood of developing complications. Thus, in addition to being capable of modelling complex treatment intensification algorithms to treat hyperglycaemia, models must preferably be able to do so for treating hypertension and dyslipidaemia as well. They must be able to extrapolate the effects of interventions observed in short-term trials over long time horizons; and they should be able to model a study baseline for patients moving on to dual or triple (or later) therapies in addition to patients at diagnosis. Models of T2DM must include the treatment-varying risks and consequences of hypoglycaemic events (preferably individually for different event severities) as well as other AE’s relevant to the drugs under comparison, e.g., peripheral oedema for pioglitazone, and genital mycotic infections (GMIs) for SGLT-2 inhibitors. Finally, the treatment and disease history of T2DM has important economic and quality of life implications, which can be influenced by intervention. As the mechanism of action (MoA) is primarily through inhibition of SGLT-2, it is important that the renal function (marked by eGFR) is accounted for in the estimation of efficacy and in the discontinuation of	Thank you for your comments. The Committee acknowledged there were different advantages and disadvantages to the different modelling approaches, and it agreed with the AG that all models submitted were appropriate and of a reasonable quality. However it concluded that the AG model was most appropriate for decision-making, because of its more accurate reflection of treatment intensification. Please see FAD section 4.8.

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	canagliflozin treatment when the patient's eGFR falls below 45 mL/min/1.73 m2 or 60 mL/min/1.73 m2 for canagliflozin 100 mg (empagliflozin 10 mg) and 300 mg (25 mg), respectively. This functionality specific to SGLT-2-i is accounted for in the ECHO-T2DM model. A number of AE's related to excretion of glucose in the urine were also included for simulations of the SGLT-2 inhibitor MoA, including upper and lower UTI's and GMI's (each allow for gender-specific rates, costs, and QALYs and there are separate event rates for the first cycle on agent and subsequent cycles). Using Monte Carlo techniques, ECHO-T2DM simulates a flexible and comprehensive AHA treatment algorithm in addition to accounting for other concomitant complications of T2DM, such as hypertension and dyslipidaemia. All health states accounted for by the model and what they capture are detailed in Section 4.2.1, Appendix 4 of the original Janssen submission. What is more, ECHO-T2DM model uses the macrovascular event rate and mortality equations from the UKPDS-OM2 model [UKPDS82], which allows for more events to be accounted for and the data is arguably more relevant to current treatment strategies and has more patient-years informing it compared to any model informed by earlier data releases, i.e. UKPDS68. Additionally, the UKPDS-OM2 data allow for more specific tailoring to the case of SGLT-2 inhibitors, e.g. the new inclusion of eGFR as a covariate in some of the UKPDS-OM2 equations, to modulate treatment effects for the SGLT-2 inhibitors and to trigger treatment discontinuation. Unlike UKPDS-OM1 (and UKPDS-OM2), ECHO-T2DM also captures the intermediate serious microvascular health states that cause treatment-related costs and impair quality of life (e.g., micro- and macroalbuminuria, diabetic foot ulcers, etc.).	
Janssen	**12. Not all relevant evidence has been accounted for** In section 4.65 on page 38 and on page 48 under "What are the key drivers of cost effectiveness?", "the Committee noted that the evidence had shown that SGLT-2 inhibitors do have a significant effect on weight loss, and felt that the AG's BMI-2 scenario (in which weight gains were maintained and weight losses rebounded to natural history after 1 year) best reflected the treatment effect on weight loss." Janssen is pleased to see that the Committee acknowledge the benefit of weight loss in terms of quality of	The committee noted that there were generally very small quality-adjusted life year (QALY) differences between the various treatments. The Committee agreed that weight loss does affect quality of life and noted that the evidence had shown

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	life improvements for patients with T2DM. Janssen questions, however, the rationale for using scenario analysis BM-2, where patients' weight loss rebounds after 1 year regardless of whether a patient has discontinued treatment or not as the base case. Within the Janssen analysis the assumption is that only after the patient has discontinued treatment will any weight loss (and associated benefits) rebound back to natural history. Whilst there is presently no long-term evidence of weight-loss durability, the approach taken by Janssen has been approved by a clinical expert advisory panel. Furthermore, Janssen has no evidence which suggests patients' weight loss rebounds before discontinuation of treatment. In RCTs investigating monotherapy use of canagliflozin, weight loss is shown to remain sustained from 24/26 week results up to 52 weeks.(6, 7) Similarly, in a RCT investigating canagliflozin dual combination-therapy with metformin, patients were shown to maintain their weight loss achievements through to 104 weeks.(17) In consideration of the above discussion, Janssen would therefore advocate the use of BMI3 as the base case reference ICER.	that SGLT-2 inhibitors do have a significant effect on weight loss. The Committee agreed there is a lack of long term evidence to support firm conclusions about the duration of treatment related weight change. However it noted that NICE's guideline on diabetes used the same assumption for the duration of weight gains and losses as that used in scenario 'BMI-2', because the clinical evidence on treatment-related weight-change was presented at 1 year and 2 years, but was very limited at 2 years. The committee concluded that BMI-2 was the most plausible scenario. Please see FAD section 4.9.
Janssen	**13. Inaccurate interpretation of Janssen network meta-analysis (NMA) results** Section 4.10 (pg.10-11) of the ACD summarises the NMA conducted by Janssen and interprets the results in a Frequentist manner, using the terminology "statistical significance". It is important, however, to recognise that Bayesian statistics are inconsistent with the Frequentist interpretation of results (e.g., it is inappropriate to use credible intervals to assess statistical significance). This is clear in the examples of interpretation in the DSU Technical Support Document 2,(18) where the terminology "statistically significant" is not used. In the Bayesian NMA presented by Janssen within the relative publication(8) and in the original submission, the interpretation is based on Bayesian probabilities rather than on the 95% credibility intervals, which is an appropriate approach for the interpretation of this analysis. Moreover, this is an approach of evidence synthesis that lends itself well to probabilistic decision making under	Thank you for your comments. The evidence section has now been updated. Please see FAD section 3.14

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	uncertainty.	
Janssen	**14. Inaccurate reporting of the included information for the Janssen systematic literature review (SLR)** In section 4.10 on page 10 it states "...several types of DPP-4 inhibitors and sulphonylureas,..." when summarising the inclusion criteria used in the systematic literature review (SLR) conducted by Janssen. Janssen believes that all relevant DPP4 inhibitors and sulphonylureas are included in the Janssen SLR. Alogliptin does not have an indication for monotherapy use and all other DPP4 inhibitors available in the UK, in accordance with those listed in the BNF at time of submission have been included.(19) Similarly, Janssen has included all sulphonylureas listed in the BNF and thus available for prescribing, at time of submission.(19) Janssen believes that the formulation used in the ACD unfairly invites the conclusion that Janssen has not considered all relevant comparators to produce more favourable results.	Thank you for your comments. The evidence section has now been updated. Please see FAD section 3.13 to 3.15.
Janssen	**15. Misinterpretation of evidence presented in the Janssen submission** Within section 4.34 the ACD incorrectly summarises that "The probability of canagliflozin 100 mg being cost effective at an ICER of £20,000 and £30,000 per QALY gained was approximately 70% and 40% respectively." This is interpreting the cost- effectiveness acceptability curve for pioglitazone, not canagliflozin. The interpretation of the canagliflozin line would be "The probability of canagliflozin 100 mg being cost effective at an ICER of £20,000 and £30,000 per QALY gained was approximately 5% and 7% respectively." Janssen is conscious that it may not be entirely appropriate to consider pioglitazone to be considered in this analysis, since its use in the UK is known to be declining and the modelled simulations for pioglitazone in the Janssen economic analysis are conservative with respect to pioglitazone, due to a lack in data to account for long-term HbA1c progression for newer AHAs. Janssen is mindful that the presentation of these results without explaining the influence of running this analysis assessing all	Thank you for your comments. This section has now been updated. Please see FAD section 3.38.

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	medicines simultaneously may lead to misinterpretation of the data.	
Janssen	**16. Incorrect reporting of information provided by Janssen to explain the functioning of the ECHO-T2DM model** In section 4.36 on page 22, the ACD states: "The AG reviewed the model submitted by Janssen. It stated that it was not clear what happened to people who stopped treatment after adverse events". As noted in the Janssen response to the AR this information was provided within the original submission, at the top of page 33 in Appendix 4. Patients who were simulated to discontinue treatment within a cycle because of AEs were started on rescue therapy.	Thank you for your comments. This text has now been removed from the FAD.
Janssen	**17. Misinterpretation of evidence presented in the Janssen submission** In section 4.37 on page 23, the ACD incorrectly summarises that Janssen used patient characteristics from the database used in the NICE's guideline update on type 2 diabetes in one of its scenario analyses. Although the patient characteristics data in this scenario analysis came from the same THIN database, they were collected in a separate analysis conducted by Janssen. Some of these data were published at DUK 2015.(20) Janssen proposes that this description is updated to correctly reflect Janssen' description in the original submission about how the information was generated	Thank you for your comments. This section has now been updated. Please see FAD section 3.40.
Janssen	**Appendix 1** At the first Appraisal Committee Meeting in November 2015, the committee asked the manufacturers for the median values (as well as the ranges) for HbA1c, weight and blood pressure changes. The values are as follows for the two canagliflozin monotherapy trials. All changes are from baseline and sourced from the relative clinical study reports. <u>Stenlof et al (2013) - The CANTATA-M Trial (CANagliflozin Treatment and Trial Analysis – Monotherapy)</u>: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, and tolerability of canagliflozin as monotherapy in the treatment of subjects with type 2 diabetes	Thank you for your comments.

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	mellitus inadequately controlled with diet and exercise (26-week core double-blind period). HbA1c: 100mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] 300mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] Weight: 100mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] 300mg: Mean [redacted] Median [redacted] Range: [redacted] to [redacted] Systolic BP: 100mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] 300mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] NB. Data reported at 26 weeks. Inagaki et al (2014) - A randomised, double-blind, placebo-controlled, parallel-group, multicenter study, to evaluate the efficacy, safety and tolerability of TA-7284 monotherapy in the treatment of subjects with type 2 diabetes mellitus in Japan (24-week core double-blind period) HbA1c: 100mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted]	

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	Weight: 100mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] Systolic BP: 100mg: Mean [redacted] Median [redacted] Range [redacted] to [redacted] NB. Data reported at 24 weeks.	
Janssen	**Appendix 2** The result presented in the original Janssen submission for canagliflozin, summarised in the ACD, must be interpreted with caution. Since the submission the price of canagliflozin 300 mg has changed and Janssen has also corrected two errors identified after submission. A partial update of the affected simulations have thus been corrected to include: (1) the current price for canagliflozin 300 mg (2) the corrected reductions in HbA1c for sulphonylurea and pioglitazone, and (3) the correct eGFR stopping rule for empagliflozin 10 mg (when eGFR falls below 60 mL/min/1.73 m2). Janssen recognises that these changes will consequence in significantly different results and has thus re-run the base case simulations in ECHO-T2DM; the incremental results of which have been presented below. Table 1. Base Case: Corrected from original submission	Thank you for your comments.

Table 1. Base Case: Corrected from original submission

	Total £	Total QALY	ICER versus PIO Value	ICER versus PIO Incremental Interpretation	ICER versus SU Value	ICER versus SU Incremental Interpretation
PIO	£20,211.32	9.960	Lowest cost		Not considered as a comparator	
SU	£22,756.20	9.912	-£52,809.47	PIO Dominates	Lowest cost	
CANA 300	£23,284.36	10.032	£42,782.24	ICER	£4,400.64	ICER
DPP4-i		9.937	-£342.09	CANA 300	-£342.09	CANA 300

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	£23,317.00			Dominates		Dominates
EMPA 25	£23,409.69	9.975	-£2,204.77	CANA 300 Dominates	-£2,204.77	CANA 300 Dominates
CANA incr.	£23,420.64	10.006	-£5,287.37	CANA 300 Dominates	-£5,287.37	CANA 300 Dominates
CANA 100	£23,440.90	9.999	-£4,732.91	CANA 300 Dominates	-£4,732.91	CANA 300 Dominates
DAPA 10	£23,494.98	9.958	-£2,823.73	CANA 300 Dominates	-£2,823.73	CANA 300 Dominates
EMPA 10	£23,513.46	9.967	-£3,514.47	CANA 300 Dominates	-£3,514.47	CANA 300 Dominates

CANA, canagliflozin; CANA incr., canagliflozin 100 mg increased where appropriate to canagliflozin 300 mg; DAPA, dapagliflozin; DPP4-I, dipeptidyl peptidase 4 inhibitor (sitagliptin) ; EMPA, empagliflozin; PIO, pioglitazone; SU, sulphonylurea (gliclazide).

Since pioglitazone use in the UK is known to be declining, removing it from the interpretation of results provides a more valuable insight into the relationship between alternative treatments. Results when pioglitazone has been excluded are described in the far right-hand column of Table 1. These results demonstrate that canagliflozin monotherapy can be considered a cost-effective and efficient use of health care resources in the treatment of T2DM.

Given canagliflozin 300 mg is associated with lower total costs and yields greater QALY gains compared with dapagliflozin, empagliflozin 10 and 25 mg, and DPP-4 inhibitors and is thus more effective, it dominates all SGLT2-i comparators and DPP-4 inhibitors in the analysis.

In line with the summary of product characteristics for both canagliflozin and empagliflozin, patients tolerating the lower doses and with an eGFR ≥ 60 mL/min/1.73 m2 or CrCl ≥ 60 mL/min and need tighter glycaemic control, the dose can be increased . Thus, not all patients will receive the higher doses and the comparator arm considering the dose escalation and canagliflozin 100 mg only are most relevant to the study question. This same rationale applies for the empagliflozin intervention arms, though Janssen has not modelled the dose escalation for empagliflozin, therefore any comparison with the empagliflozin 25 mg

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	only comparator arm must be interpreted cognisant of the fact that this is not an intervention true to clinical practice. Pairwise comparisons show that canagliflozin 100 mg dominates both dapagliflozin and empagliflozin 10 mg, i.e. is both less costly and more effective producing larger QALY gains, and has ICERs of £1,987 and £7,875 versus DPP-4 inhibitors and sulphonylurea, respectively. In summary, qualitatively this means that canagliflozin 100mg can still be considered as an alternative treatment in the appropriate patients that do not require dose escalation to canagliflozin 300mg. The comparator arm modelling the dose escalation of canagliflozin 100 mg to 300 mg produces more QALYs at a reduced cost versus canagliflozin 100 mg and is as such an appropriate cost-effective alternative in the right patients and an efficient use of health care resources in the treatment of T2DM.	
Janssen	**Appendix 3** Table 2 presents the results for canagliflozin 300 mg versus dapagliflozin 10 mg in the original submission and in the update, after correcting for two errors identified in the clinical- and cost-effectiveness analyses and change in price for canagliflozin 300mg. **Table 2. Original and updated results for the pair-wise comparison of canagliflozin 300 mg and dapagliflozin 10 mg** **Original Submission** / **Updated Results** **CANA 300** / **DAPA 10** / **CANA 300** / **DAPA 10** **Total QALY**: 10.069 / 9.994 / 10.032 / 9.958 **Total £**: £24,338 / £23,629 / £23,284 / £23,495 **ICER**: £9,453* / -£2,851* (CANA dominates) **subject to potential rounding error. CANA, canagliflozin; DAPA, dapagliflozin;*	Thank you for your comments.

Commentator	Comment [sic]	Response
Janssen	References 1. [NICE] NIfHaCE. Type 2 diabetes in adults: management [NG28]. NICE guidelines2015. 2. O'Hare JP, Hanif W, Millar-Jones D, Bain S, Hicks D, Leslie RD, et al. NICE guidelines for Type 2 diabetes: revised but still not fit for purpose. Diabetic medicine : a journal of the British Diabetic Association. 2015 Nov;32(11):1398-403. PubMed PMID: 26331592. 3. O'Hare JP, Millar-Jones D, Hanif W, Hicks D, Leslie RD, Bain SC, et al. The revised NICE draft guideline for type 2 diabetes: still a long way to go. The lancet Diabetes & endocrinology. 2015 Sep;3(9):679-80. PubMed PMID: 26254116. 4. Inagaki N, Kondo K, Yoshinari T, Takahashi N, Susuta Y, Kuki H. Efficacy and safety of canagliflozin monotherapy in Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. Expert opinion on pharmacotherapy. 2014 Aug;15(11):1501-15. PubMed PMID: 25010793. 5. Stenlof K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes, obesity & metabolism. 2013 Apr;15(4):372-82. PubMed PMID: 23279307. Pubmed Central PMCID: 3593184. 6. Stenlof K, Cefalu WT, Kim KA, Jodar E, Alba M, Edwards R, et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Current medical research and opinion. 2014 Feb;30(2):163-75. PubMed PMID: 24073995. 7. Inagaki N, Kondo K, Yoshinari T, Kuki H. Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: A 52-week open-label study. Journal of diabetes investigation. 2015 Mar;6(2):210-8. PubMed PMID: 25802729. Pubmed Central	Thanks.

Commentator	Comment [sic]	Response
	PMCID: 4364856. 8. Schroeder MT, V.; Belhadi, D.; Selya-Hammer, C.; Hemels, M.; Nielsen, A.T., editor Bayesian Network Meta-analysis to Assess the Relative Efficacy of Canagliflozin Monotherapy Over 26 Weeks in Patients With Type 2 Diabetes Mellitus. The 20th Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research [ISPOR]; 2015 May 16th -20th, 2015; Philadelphia, Pennsylvania. 9. [NICE] NIfHaCE. Canagliflozin in combination therapy for treating type 2 diabetes [TA315]. In: [NICE] NIfHaCE, editor. NICE technology appraisal guidance2014. 10. [NICE] NIfHaCE. Guide to the methods of technology appraisal 2013. In: [NICE] NIfHaCE, editor. NICE article 2013. 11. Sha S, Polidori D, Farrell K, Ghosh A, Natarajan J, Vaccaro N, et al. Pharmacodynamic differences between canagliflozin and dapagliflozin: results of a randomized, double-blind, crossover study. Diabetes, obesity & metabolism. 2015 Feb;17(2):188-97. PubMed PMID: 25421015. 12. Viberti G, Kahn SE, Greene DA, Herman WH, Zinman B, Holman RR, et al. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes care. 2002 Oct;25(10):1737-43. PubMed PMID: 12351470. 13. Belimumab for the treatment of active autoantibody-positive systemic lupus erythematosus [Internet]. 2011 [cited 26/01/2016]. Available from: http://www.nice.org.uk/guidance/gid-tag273/documents/systemic-lupus-erythematosus-active-belimumab-evidence-review-group-report3. 14. [NICE] NIfHaCE. Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes [TA248]. NICE technology appraisal guidance2012. 15. Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia in intensifying	

Commentator	Comment [sic]	Response
	therapy among people with type 2 diabetes treated with basal insulin. Diabetes, obesity & metabolism. 2016 Jan 7. PubMed PMID: 26743666. 16. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes care. 2013 Nov;36(11):3411-7. PubMed PMID: 23877982. Pubmed Central PMCID: 3816889. 17. Leiter LA, Yoon KH, Arias P, Langslet G, Xie J, Balis DA, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes care. 2015 Mar;38(3):355-64. PubMed PMID: 25205142. 18. Dias SW, N.J.; Sutton, A.J.; Ades, A.E. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. In: Unit DS, editor. NICE DSU Technical Support Documents2011 (Last updated 2014). 19. BMJ Group RPLatRPSoGB. BNF Publications. 2015. 20. Schroeder MB, J.; Girod, I.; Neslusan, C., editor An Analysis of Treatment Patterns and Risk Factor Profiles in a Cohort of 20,300 UK Patients With Newly Diagnosed Type 2 Diabetes. The Diabetes UK Professional Conference; 2015 11th -15th March 2015; London, UK.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
Janssen	I support the recommendations in the ACD as they stand	Thank you for your comments.

Comments received from commentators

Consultee	Comment [sic]	Response
Healthcare Improvement Scotland	**1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted and**	Thank you for your comments.

Consultee	Comment [sic]	Response
	what are the implications of this omission on the results? Yes **2. Do you consider that the analysis of clinical and cost effectiveness has used an appropriate comparator which reflects Scottish practice? If not, please explain.** Yes **3. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. If not, in which areas do you consider that the summaries are not reasonable interpretations?** Yes **4. Are the provisional recommendations of the Appraisal Committee sound, and do they constitute a suitable basis for the preparation of guidance to the NHS.** Yes **5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland?** No **6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales?** No **7. Please add any other information which you think would be useful to the Appraisal Committee, or helpful to us in guiding the Scottish**	

Consultee	Comment [sic]	Response
	response to this assessment. The confusion about the two doses of cana and empa remain – particularly with empa. When should one increase the dosage and why? The role of SUs has been reviewed – although not expensive medications as such – their downstream costs are enormous.	NICE can only make recommendations for a drug within its marketing authorisation. Please see the statements of product characteristics for further information about posology.
Merck Sharp & Dohme	**Incomplete information on adverse reactions** MSD believes that the ACD provides incomplete information of adverse reactions of SGLT2-i. More specifically: • On page 6, the ACD discusses cangliflozin's adverse reactions as follows: "The summary of product characteristics lists the following adverse reactions for canagliflozin as the most commonly reported: vulvovaginal candidiasis, urinary tract infection, and polyuria. For full details of adverse reactions and contraindications, see the summary of product characteristics." MSD requests that all common adverse reactions are listed in this section. Even if the reader is referred to the summary of product characteristics, the way this sentence is written implies that the most commonly reported adverse reactions of cangliflozin are only vulvovaginal candidiasis, urinary tract infection, and polyuria. All most commonly reported adverse reactions should be listed in the ACD – balanitis, dyslipidaemia, haematocrit increase, constipation, thirst and nausea should be also reported here. • On page 6, the ACD discusses dapagliflozin's adverse reactions as follows: "The summary of product characteristics lists the following adverse reactions for dapagliflozin: urinary tract and genital infection, back pain,	Thank you for your comments. This section has now been updated. Please see FAD section 2.

Consultee	Comment [sic]	Response
	dysuria, polyuria, dyslipidaemia and elevated haematocrit." As above, MSD requests that all common adverse reactions are listed in this section - vulvovaginitis, balanitis, dizziness and creatinine renal clearance decreased should be also reported here. • On page 7, the ACD discusses empagliflozin's adverse reactions as follows: "The summary of product characteristics includes the following adverse reactions for empagliflozin: urinary tract infection and polyuria." As above, MSD requests that all common adverse reactions are listed in this section - vulvovaginitis, balanitis and pruritus should be also reported here. • On page 9, the ACD only discusses UTIs and GTIs, but there are no discussion on the risk of cardiovascular events, bone health and diabetic ketoacidosis. MSD believes that all adverse events and warnings associated with SGLT2-i should be reported here. The Assessment Group (AG) dedicated a whole section to diabetic ketoacidosis, cardiovascular events and bone health, and these should be mentioned in the ACD. Moreover, NICE specifically mentions the risk of diabetic ketoacidosis with SGLT2-i in the new NG28 and the ACD should be consistent with the guideline.	
Merck Sharp & Dohme	**<u>Misleading information on adverse reactions</u>** On page 9, the ACD states: "No evidence of a dose-response relationship was found with any treatment". MSD believes that this statement is not true for canagliflozin. The 300mg dose of canagliflozin is associated with higher rates of adverse events, as reported in Schernthaner et al. 20131. More specifically, the study found that "higher incidence of genital mycotic infections and osmotic diuresis-	Thank you for your comments. This section has now been updated. Please see FAD section 3.9 and 3.10.

Consultee	Comment [sic]	Response
	related adverse events were observed with canagliflozin, which led to one discontinuation."	
Merck Sharp & Dohme	**<u>Superior efficacy of SGLT2-i over the DPP4-i</u>** The claims of superior efficacy of the SGLT2-i over the DPP4-i in the ACD are quite difficult to interpret. More specifically: • On page 8, the ACD states: "**The reductions for empagliflozin were also greater than those for sitagliptin (statistical significance was not presented)**" The ACD here is referring to the study of Roden et al. 2013, used by the AG. As we have already stated in our consultation on the Assessment Report (AR), MSD is concerned about the robustness of the conclusions of the AG regarding empagliflozin vs sitagliptin, because (a) the study did not use sitagliptin in line with its UK license (restricted monotherapy in patients who are not controlled or who cannot tolerate metformin); (b) the study applied open-label regime in its study design – this is inappropriate for the purpose of comparison and could bias the results. The authors of the study themselves state that "The comparisons between empagliflozin and sitagliptin were only exploratory and therefore no firm conclusions to be made about the comparative efficacy of these drugs" and (c) the study duration of 24 weeks is relatively short - MSD believes that firm conclusions cannot be drawn from this length of study and that this does not allow the durability of the study drugs to be fully assessed. MSD believes that the only appropriate monotherapy study for sitagliptin is Aschner 2010 where the baseline was much lower (7.2%) and therefore the reduction observed in HbA1c was only 0.43%. Another appropriate study is Aschner 2006, which the Assessment Group rightly	Thank you for your comments. This section has been updated with additional detail about the result, and to clarify that the comparisons with sitagliptin were exploratory in nature. Please see FAD section 3.5 and 3.7.

Consultee	Comment [sic]	Response
	included in the NMA. • On page 11, the document states: "**Compared with DPP-4 inhibitors, it resulted in a greater reduction in HbA1c, weight and systolic blood pressure (all results statistically significant, other than compared with sitagliptin for HbA1c, where there was no difference)**" The ACD here is referring to the NMA that Janssen provided to NICE for their submission. MSD believes that more caution should be applied with the wording of this statement, as none of the sitagliptin studies used in the NMA compared canagliflozin directly with sitagliptin. MSD would welcome the removal of the statement.	The evidence section is intended to provide a brief overview of the available clinical and cost effectiveness evidence. Please also note that this section has been reworded to state "compared with DPP-4 inhibitors, it resulted in a greater reduction in HbA1c, weight and systolic blood pressure (other than when compared with sitagliptin for HbA1c, where there was no difference)". Please see FAD section 3.14.
	• On p. 13 the document states: "**Compared with sitagliptin, SGLT-2 inhibitors were more effective for HbA1c (in some instances this reached statistical significance)**" This statement refers to the NMA conducted by the AG. The studies for sitagliptin were Aschner 2006, Roden 2013 and Stenlof 20132. As mentioned above, MSD believes that Aschner 2006 is an appropriate monotherapy study, but Roden 2013 is not. Regarding Stenlof 2013, the study did not use sitagliptin, but only considered it in extension in a 52-week study (therefore not meeting the inclusion criteria). Moreover, patients were switched to sitagliptin from placebo and sitagliptin was added in the study only for safety purposes. Therefore, MSD believes that results from this study should not be taken into account. Additionally, MSD would like to stress that SGLT2-i studies are generally performed in patients with high baseline HbA1c and therefore the drop is larger (as with any other glucose-lowering medication).	The evidence section is intended to provide a brief overview of the available clinical and cost effectiveness evidence. Please also note that this section has been reworded to state "Compared with sitagliptin, SGLT-2 inhibitors were either more effective for HbA1c (canagliflozin 100 mg and 300 mg, and dapagliflozin) or there was no difference (empagliflozin 10 mg and 25 mg), and all SGLT-2 inhibitors were more effective for weight change". Please see FAD section 3.21.

Consultee	Comment [sic]	Response
Merck Sharp & Dohme	References 1. Schernthaner G et al., Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea – A 52-week randomized trial. Diabetes Care. 2013(36):2508-2515. 2. Stenlof K et al. Long-term efficacy and safety of canagliflozin monotherapy in patients with type 2 diabetes inadequately controlled with diet and exercise: findings from the 52-week CANTATA-M study. Current Medical Research & Opinion. 2014;30(2):163-75.	Thanks.