Janssen Response to the Appraisal Consultation Document

Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes

January 2016

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.

1. **Janssen believes the evidence base considered in this appraisal process does not support the provisional recommendations made for guidance to the NHS**

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 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 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)

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 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.

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)

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.

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 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).

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

- Acquisition and event costs (in part)
- Quality of life data for significant drivers

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 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]

[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 (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.

7. Incomplete explanation of the drivers in the Janssen economic analysis

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 rescue medication.

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 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 HbA_{1c} as a function of the previous periods HbA_{1c} so any initial drug-specific differences in HbA_{1c} 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.

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 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.

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 when starting on an insulin regimen.(15, 16)

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 canagliflozin treatment when the patient's eGFR falls below 45 mL/min/1.73 m^2 or 60 mL/min/1.73 m^2 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.).

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 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.

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 uncertainty.

Points of Clarification

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.

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 medicines simultaneously may lead to misinterpretation of the data.

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.

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.

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.

Stenlof et al (2013) - The CANTATA-M Trial (CANagliflozin Treatment and Trial Analysis – Monotherapy): 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 mellitus inadequately controlled with diet and exercise (26-week core double-blind period).

[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)

[redacted]

NB. Data reported at 24 weeks.

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 m^2). 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

	Total £	Total QALY	ICER versus PIO		ICER versus SU	
			Value	Incremental Interpretation	Value	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	£23,317.00	9.937	-£342.09	CANA 300 Dominates	-£342.09	CANA 300 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 m^2 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 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.

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;*

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