Assessment Group comments on responses to ACD. 8th February, Final.

Astrazeneca comments:

The AG is still not clear why there are the discrepancies between the Astrazeneca unit costs and the AG unit costs derived from the UKPDS84. The AG report is explicit about their derivation in table 61 and Astrazeneca does not question this.

Astrazeneca suggests that omitting the inpatient and outpatient costs for those with no complications will have minimal impact because the survival estimates are similar for all the arms modelled. The AG views this as incorrect. To see this consider two patients with identical survival of 10 years, but one patient having no complications throughout the 10 years and the other with no complications at baseline but who develops blindness in one eye for the remaining 9 years. Based upon the AG costs of table 61 and the Astrazeneca method the undiscounted inpatient and outpatient costs for the first patient are estimated to be £0 when they should be £10,190. The undiscounted inpatient and outpatient costs for other patient are estimated to be £14,259. The estimated difference in undiscounted costs between the two patients is £14,259 using the Astrazeneca method and £4,069 using the AG method. 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.

Boehringer Ingelheim

The AG welcomes the clarification around the halving of the costs of complications in model B. But this may raise further concerns about the validity of the results of model B.

Point 2. The statistical significance was not reported by the AG but we accept that it was provided in the Roden paper. The ACD should distinguish between the two doses of empagliflozin. There was no difference in HbA1c lowering between empagliflozin 10 and sitagliptin, but there was slightly greater lowering (0.12%) with 25mg.

Point 3 – accepted.

Janssen

The most substantial comments come from Janssen. In what follows, we refer to their numbered points by J and their number

J1. Relative restriction on use of the flozins and the gliptins (DPP4 inhibitors).

Page 2, paragraph 1, last two sentences. Janssen point out that the new Type 2 Guideline (December 2015) states that the gliptins (DPP4 inhibitors) can be used as first line in patients

who cannot take metformin, without the requirement to consider or try a sulfonylurea and pioglitazone first. The guideline says;

- If HbA1c rises to 6.5% on lifestyle, consider one of the following: a DPP4 inhibitor, pioglitazone or a sulfonylurea.

Whereas the ACD says that a flozin is recommended only if pioglitazone or a sulfonylurea is not appropriate. Janssen state that clinicians do not have to consider the appropriateness of pioglitazone or sulfonylureas before prescribing a gliptin as monotherapy.
The gliptins are only slightly less expensive than the flozins, so it would seem inequitable to have a tighter restriction on the flozins. However the ACD does say that a flozin can be considered when

"a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed"

J2. Relative effectiveness.

Page 2, para 3. Janssen repeat the results from the CANTATA-M trial with HbA1c reduction of 1.16% on 300mg, but it should be noted that patients in the trial started on 300mg, whereas patients treated according to licence would start with 100mg and only increase dose if response was insufficient. Those with insufficient response to 100mg might not get as large a reduction in HbA1c.
On pages 2 and 3, Janssen summarise their NMA which found that canagliflozin 300mg gave the greatest reduction in HbA1c, with canagliflozin 100mg third after pioglitazone. They argue that canagliflozin is the most potent of the flozins. Table 1 below shows the AG NMA which had similar results.

Table 1: AG NMA results.

Pairwise comparison	**Mean difference (95% Credible Intervals)**
Compared with Placebo	
Canagliflozin 300mg	-1.19 (-1.34 to -1.04)
Pioglitazone	-1.13 (-1.49 to -0.78)
Canagliflozin 100mg	-0.95 (-1.06 to -0.84)
Gliclazide	-0.95 (-1.27 to -0.64)
Empagliflozin 25mg	-0.88 (-0.99 to -0.77)
Sitagliptin 100mg	-0.76 (-0.87 to -0.65)
Empagliflozin 10mg	-0.76 (-0.87 to -0.65)
Vildagliptin 50mg	-0.72 (-0.98 to -0.46)
Linagliptin 5mg	-0.61 (-0.71 to -0.51)
Dapagliflozin 10mg	-0.59 (-0.70 to -0.48)

However, the dapagliflozin figure below is pulled down by inclusion of the Kaku trial with its low baseline HbA1c of 7.5%. Exclusion of that trial would increase the dapagliflozin HbA1c reduction to 0.75% (Astra Zeneca calculation). The AG included trials with baseline HbA1c of 7.5% or over, in line with the NICE intensification threshold.

J1 QALY gains

On page 3 of their responses, Janssen report using QALY results of 10.039, 10.051 and 10.083 for 100mg, 300mg and 100 mg increased to 300 respectively. The last figure looks odd – people who have an insufficient response to 100mg canagliflozin and have it increased to 300mg would be likely to include poor responders to the drug and would therefore be expected to have a lower response than the brOHAer group started on 300mg. so we would expect fewer QALYS in the 100mg-increased-to-300mg group. (It could be argued that had Janssen adhered to the licence, they should not have included the 300mg starting group in the submission at all.)

J2. SGLT 1

Jansen also remind us that canagliflozin has some activity against the SGLT1 transport system which is found in the gut and in the kidneys. The renal SGLT1 system is normally only responsible for a small percentage of glucose reabsorption but this is increased after the upstream SGTL2 system is inhibited.

The Janssen comments cite the recent (2015) study by Sha and colleagues from Janssen Research and Development. This was a short cross-over trial in healthy volunteers randomised to have canagliflozin 300mg for four days then dapagliflozin 10mg for four days, to assess the effects on (amongst other variables) urinary glucose excretion and post-prandial glucose levels. Sha et al report that the effects of the two flozins on glucose excretion were similar for the first 4 hours after taking them, but that canagliflozin 300mg then lasted longer, leading to a 25% greater excretion of glucose over 24 hours (51g versus 41g). They also noted that there was a 10% lower rise in post-prandial glucose after canagliflozin 300mg which was unrelated to plasma canagliflozin levels, confirming that the effect is an intra-intestinal one occurring with the first meal after taking canagliflozin.
Dapagliflozin is highly selective for SGLT2, whereas canagliflozin has some effect on SGLT1.

The authors then use their results to estimate the relative effects of dapagliflozin and canagliflozin 100mg, and conclude that
"the available data suggest that the PD differences observed between canagliflozin 300 mg and dapagliflozin 10 mg might translate into differences in HbA1c lowering in patients with T2DM that are similar to the differences observed between canagliflozin 300 mg and canagliflozin 100 mg."
In other words, they think that canagliflozin 100 mg might be equivalent to dapagliflozin 10mg.

When considering relative potencies, the small number of trials and the heterogenous results need to be considered. In the dapagliflozin trials, HbA1c fell in the placebo groups, by 0.29% and 0.23% in the Ji and Ferrannini trials. In the placebo groups in the canagliflozin trials, HbA1c rose by 0.29% (Inagaki) and 0.14% (Stenlof CANTATA-M). Two of the dapagliflozin trials were done in East Asians who may have a different form of type 2 diabetes. Chinese people with type 2 tend to have lower BMI and a more insulin-deficient pattern, compared to Western diabetics who are usually overweight or obese with initial insulin resistance. If we restricted the canagliflozin versus dapagliflozin evidence to trials done predominantly in western countries, we would have only two trials, CANTATA-M (Stenlof 2103) and Ferrannini 2010. Full details are in the assessment report, but for convenience Table 1 summarises baseline characteristics and key results.

Table 2. The Stenlof and Ferrannini trials

	Stenlof canagliflozin 100mg	Ferrannini dapagliflozin 10mg
Baseline HbA1c	8.1%	8.0%
Reduction in HbA1c 24-26 weeks	0.77%	0.84%
Baseline BMI	31.6	33.6
Weight reduction 24-26 weeks	2.5kg	3.15kg
Reduction in SBP	3.3 mmHg	3.6 mmHg

So restricting the evidence base to trials in Western countries (including Russia) would show dapagliflozin 10mg being slightly more effective than canagliflozin 100mg, before adjustment for placebo effect. However the differences are insignificant so it would be better to describe them as equivalent.

Adjustment of HbA1c changes for placebo changes gives reductions of 0.91% on canagliflozin and 0.61% on dapagliflozin.

J6, 7 and 8 – modelling

The AG used the OMford model version 1 (OM1), partly because it is freely available to academic units, partly because of familiarity with it from previous appraisals, but mainly because it is a well-established and validated model. We were unable to get access to the updated version, OM2, in time.

The OMford Model 1 was chosen by the NICE CG support team after consideration of other models. The reasons for the choice of OM1 are given in the Full Economics Report of the Type 2 guideline (appendix F, pages 24-26). The NICE CG for T2DM preferred the UKPDS OM model over the alternatives in no small part due to it being derived from a single trial rather than drawing a range of modelling inputs together from a variety of sources. The cost and quality of life impacts of the

modelled complications of diabetes are also drawn from the same source. This was also in large part the reason for the UKPDS OM model being specified in the protocol for the assessment of flozins as monotherapy.

The AG report notes that "*The ECHO-T2DM model is an individual patient simulation model developed by staff of the Swedish Institute for Health Economics. It has been routinely submitted to the Mt. Hood challenges … But the ECHO-T2DM submissions to the Mt. Hood challenges were probably with different assumptions than those used for the Janssen submission, in particular with regards the evolution of HbA1c*.". Janssen accepts that the outputs of the ECHO-T2DM model are very sensitive to whether HbA1c is assumed to evolve according to the UKPDS equation or to the assumed linear evolutions as derived from the ADOPT study by Janssen.

If it is accepted that the most reasonable modelling of HbA1c is to adopt a linear segments approach with the rate of linear increase differentiated by treatment it should be borne in mind the Janssen derives the linear rates of increase from the ADOPT study which compared rosiglitazone, glibenclamide (called glyburide in the USA) and metformin. None of the treatments under consideration were examined in the ADOPT study, with Janssen assuming equivalence as below.

Table 3: Janssen annual rates of HbA1c drift by monotherapy

Monotherapy	ADOPT equivalent	Annual HbA1c drift
Flozin	Metformin	0.14%
DPP IV: Sitagliptin	Metformin	0.14%
SU: Gliclazide	SU: Glyburide	0.24%
Repaglinide	SU: Glyburide	0.24%
Pioglitazone	Rosiglitazone	0.07%

The AG report noted the 6 year difference in starting insulin among those on glybenclamide compared to gliclazide (Satoh et al). This is likely to have biased the Janssen analysis against gliclazide. They assumed that the drift with rosiglitazone could be used for pioglitazone which seems reasonable since for HbA1c, they work in the same way. They assumed that drift on sitagliptin was the same as on metformin, which may not be the case, since the action of sitagliptin depends partly on stimulating insulin release, and it may be less durable than metformin. But we have no long-term data on the durability of the gliptins.

Janssen notes that section 4.51 of the ACD states that the AG estimated lower acquisition costs for canagliflozin with this arising due to slightly greater efficacy and hence a lag in intensification

compared to other treatments. But if as in section 4.67 of the ACD the AC has reasonably concluded that the clinical evidence does not support any difference between the flozins there would be no lag in intensification under canagliflozin. It consequently follows that there would be no evidence to support a difference in cost effectiveness. This would also flow through to the probabilistic analysis.

J5, pages 5-6, comparison of modelling.

Janssen highlights certain similarities with the AG modelling. It is not immediately obvious that the similarities are as strong as Janssen suggests. The central clinical effectiveness estimates for HbA1c are quite different, and changes in HbA1c are key to the modelling. The clinical effectiveness estimates for SU are very different though as Janssen notes this was in part due to a transcription error in the Janssen NMA.

Table 4: Central clinical effectiveness estimates: HbA1c

	Janssen	AG
Cana. 100mg	-0.97	
Cana. 300mg	-1.20	-1.153
Dapa. 10mg	-0.64	-0.704
Empa. 10mg	-0.73	
Empa. 25mg	-0.85	-0.870
Sita. 100mg	-0.72	-0.723
Pioglitazone	-0.78	-1.200
Sulfonylurea	-0.59	-1.301

The costs of complications and quality of life values are also not really quite aligned between Janssen and the AG.

Table 5: Complication costs during year of event

	Janssen	AG
No complications	£0	£1,019
Complications 1st year		
Fatal MI	£1,566	£1,564
Fatal IHD	£3,818	£3,873
Fatal stroke	£4,255	£4,066
Fatal CHF	£3,366	n.a.
Non-fatal MI	£6,665	£7,550
Non-fatal IHD	£10,116	£10,932
Non-fatal stroke	£7,247	£8,120
Non-fatal CHF	£3,337	£4,288
Amputation	£11,810	£12,592

Blindness	£2,260	£3,234
ESRD	£26,297	£36,801

Table 6: Complication costs in subsequent years

	Janssen	AG
MI	£875	£1,877
IHD	£920	£1,922
Stroke	£934	£1,934
CHF	£1,527	£2,515
Amputation	£2,531	£3,499
Blindness	£215	£1,225
ESRD	£26,152	£36,801

As noted in the AG comment on Astrazeneca, assuming no outpatient and inpatient costs for those with no complications does seem to be something of an omission.

Table 7: Complication quality of life impacts

	Janssen	AG
No complications	0.843	0.801
MI year	-0.028	-0.055
MI history	-0.028	-0.055
IHD	-0.028	-0.090
Stroke	-0.115	-0.164
CHF	-0.028	-0.108
Amputation	-0.272	-0.280
Blindness	-0.057	-0.074
ESRD	-0.175	-0.263

The AG agrees that the adoption of the linear segments assumption for HbA1c rather than the UKPDS equation appears to be a key driver of the Janssen results. But the AG has demonstrated that it is not a key driver of the AG results in scenario analysis 09 of the AG report. Janssen notes that the ECHO-T2DM model uses the updated UKPDS equations. It also accepts that the eGFR module of the ECHO-T2DM model did not particularly drive its results.

As a consequence, some or all of the following would seem to have to apply:

- The AG modelling of the linear segments is incorrect.
- The Janssen modelling of the linear segments is incorrect.

- The ECHO-T2DM model is not particularly driven by the updated UKPDS equations but by other equations and modules within it.
- There are other elements which differ between scenario 09 of the AG report and the Janssen modelling of the linear segments evolution of HbA1c.

Janssen notes that it is impossible with the information available for Janssen to assess why using linear segments did not decrease the ICER in the AGs analysis as would be expected. This is incorrect as the ICERs were reduced as shown in table 94 of the AG report as compared with table 66. The AG model was supplied to Janssen at consultation and was sufficient to cross check the AG base case. In the opinion of the AG it is very much simpler and more intuitive to use than the ECHO-T2DM. But the user guide supplied with it did not specify that to cross check the AG scenario 09 the linear evolutions for each treatment should be inputted to the *HBA1cLin* values of the treatment sample sheets for each treatment at each line of therapy that is modelling and the option(s) of linear evolutions of HbA1c applied within the *Model* worksheet. The AG hopes that this is sufficient for Janssen to cross check the correctness of AG modelling of linear segments for HbA1c using the UKPDS OM1[1].

Elements that appear to differ between scenario 09 of the AG report and the Janssen modelling are:

- The clinical effectiveness estimates for HbA1c as outlined above.
- To some degree the cost and quality of life impacts as outlined above.
- The assumption of whether patients stop their OHAs when intensifying to insulin or continue with them. This is a key cost driver.
- The rebound assumption for when patients stop their OHAs.

The AG remains unclear quite what rebound assumptions Janssen has assumed for when patients stop their OHAs when starting insulin, the AG report noting some ambiguity around this. Rebound may assume that the initial treatment effects are lost or that patients rebound to baseline value, prior to having the insulin treatment effect applied. The AG interpretation is that the Janssen modelling may assume rebound to baseline.

Rebound to baseline would be incorrect. Take for example someone whose HbA1c rises above 7.5% of lifestyle measures alone. Suppose addition of a flozin reduced this to 6.5%. But given progression of disease, HbA1c rises to above 7.5% again and gliclazide is added. Assume a 0.5% reduction in HbA1c with gliclazide (based on the low baseline of 7.5%) so HbA1c is reduced to 7.0%. It then

[1] Note that to replicate the revised SBP estimate for canagliflozin 300mg in theTreatment_1st_Line_Inputs worksheet set cell P4=-5.5.

drifts up again. So if both drugs were stopped once it reaches 7.5%, the effect lost is 1.5% and HbA1c would be 9%.

The mean baseline HbA1c in the Janssen model was 8.0% but patient heterogeneity is modelled and there is a range of patient values. Consider three patients with baseline values of 7.5%, 8.0% and 8.5%. The central clinical effectiveness estimates of Janssen for canagliflozin 300mg, SU and insulin are reductions of -1.2%, -0.59% and -0.9% respectively. The AG would expect that within the Janssen modelling the three patients will receive the initial canagliflozin reduction, then their HbA1c will worsen until at 7.5% they intensify by adding SU and so fall back to 6.9%. Their HbA1c continues to worsen until it again reaches 7.5%, at which point they intensify to insulin but they stop the two oral agents and lose the reduction of 1.5% in HbA1c.

However, the AG's interpretation of the Janssen modelling is that when the OHAs are withdrawn they initially rebound back to their baseline values of 7.5%, 8.0% and 8.5% before having the -0.9% reduction associated with insulin applied causing their HbA1c to drop to 6.6%, 7.1% and 7.6%, though for the latter patient dose escalation may cause a further reduction to 7.5%.

So if the AG correctly understands the Janssen rebound assumptions when patients intensify to insulin due to their HbA1c breaching 7.5%, the vast majority of patients are modelled as having a reduction of somewhat less than the -0.9% reduction associated with insulin because they have lost the effect of the oral agents. Some patients experience no reduction in their HbA1c when intensifying to insulin until the dose is titrated upwards.

The rebound assumptions of the Janssen model may be a key difference in terms of the modelling assumptions that Janssen applied. The reasonableness of these rebound assumptions has not been explored.

Due to the AG modelling assuming the intensification to insulin adds insulin to the existing OHA therapy mix, within the AG modelling there is no particular need to consider whether any rebound assumptions are required.

J10 discontinuation of oral agents.

Janssen cite Khunti et al (2013) and Khunti et al (2016) as providing evidence that "*patients are divided between those that remain on oral AHAs and those that discontinue all other AHAs when starting on an insulin regimen*".

These papers do not provide such evidence.

Khunti et al (2013), supported by Novo Nordisk, is a study of clinical inertia among 81,573 UK patients with type 2 diabetes who were recorded on the UK Clinical Practice Research Datalink database as having started therapy with at least one OHA between 2004 and 2006, with an end of follow-up of 2011. Of these patients 62% were receiving 1 OHA, 31% were receiving 2 OHAs and 7% were receiving 3 OHAs. People treated with T1DM or people treated only with insulin are excluded from the analysis. An OHA regimen is defined as the time period in which the same OHAs were used without the use of insulin. The end of an OHA regimen is classified as treatment intensification, end due to receiving fewer OHAs, or end of follow-up or lack of acceptable data. Treatment intensification is defined as either adding further OHAs to the existing OHA regimen or initiation of insulin irrespective of changes in the OHA regimen. Time in poor control is defined as the time spent above a given HbA1c cut-off until control went back below the cut-off, or until treatment was intensified, or censoring. The HbA1c cut-off defining poor control is varied to 7.0%, 7.5% and 8.0%.

Khunti et al (2013) then go on to examine the time to intensifications. These are analysed by whether intensification added further OHAs to the existing OHA regimen or initiated insulin irrespective of changes in the OHA regimen. For instance among thosewith HBA1c >= 7.0%, of those taking one OHA the median time to intensification was with an additional OHA was 2.9 years while the median time to intensification with insulin irrespective of changes in the OHA regimen was more than 7.2 years. Khunti et al (2013) provides evidence that intensification to insulin occurs among those receiving one, two and three OHAs. The AG can find no support within Khunti et al (2013) to support Janssen arguments about whether those starting basal insulin discontinue OHAs.

Khunti et al (2016), supported by Novo Nordisk, is a study of clinical inertia among 11,696 UK patients with type 2 diabetes who were recorded on the UK Clinical Practice Research Datalink database as having started basal insulin between 2004 and 2011, with an end of follow-up of 2013. The paper goes on to report the various times to intensification by adding bolus or a premix or a GLP-1. The number of OHAs was recorded as being a significant predictor of the time to intensification with increased OHA usage being associated with a longer time to intensification.

Khunti et al (2016) note the following distributions between the number of OHAs patients were receiving at the baseline of start of basal insulin among all patients and among those eligible for intensification.

Table 8: Khunti et al (2016) number of OHAs when starting basal insulin

	All patients	HbA1c≥7.5%

N	11,696	6,072
0 OHA	4.8%	9.6%
1 OHA	15.0%	45.8%
≥ 2 OHAs	80.3%	44.6%

The all patient data suggests that the vast majority of patients starting basal insulin were receiving at least 2 OHAs at that point, with a minority receiving only one OHA and a smaller proportion none. The data does not appear to say anything about whether patients remain on their OHAs or discontinue them when starting basal insulin. The AG can find no support within Khunti et al (2016) to support Janssen arguments about whether those starting basal insulin discontinue OHAs.

The study which Janssen might have cited is the Novo Nordisk SOLVD (Study of once daily levemir) by Vora, Khunti et al (Journal of Clinical Pharmacy and Therapeutics, 2014, 39, 136–143), although the results don't support their comment about discontinuation of all OHAs, partly because the protocol specified that at least one OHA should be continued. SOLVD was a very large observational study in 10 countries of the commencement on detemir insulin in people failing on oral agents. It provides two sets of data that are of interest. Firstly, it provides data on which OHAs patients were on at the point of intensification to insulin. In the UK 79 were on metformin, 77% on a sulphonylurea, 21% on a TZD, and 10% on a DPP4 inhibitor.
Secondly, it provides, for all countries except the UK, data on the number of OHAs continued after insulin was started. Overall there was no change in the number – the most common approach was to leave them unchanged. However it was only a 24-week study, and given longer time for titration of insulin, more changes might occur.
One other finding worth noting is that intensification to insulin occurred at HbA1c of around 8.9% - more evidence of clinical inertia.

J9. Recent price change of canagliflozin 300mg

As far as the AG can ascertain the Janssen response to the ACD which updates the canagliflozin 300mg price and corrects the Janssen NMA errors does not present any modelling results for the AC preferred set of assumptions and the AC preference for the AG clinical effectiveness estimates. Janssen does not question the correctness of the other AG inputs to the economic modelling, but also does not explore the impact of these inputs upon its results.

Janssen appear to suggest that weight and hypoglycaemia drive results. The AG agrees that weight does drive results, as shown by the No BMI and BMI-1 to BMI-5 scenarios that the AG presents for each analysis in the AG report. It is less clear that hypoglycaemia events should drive results. The AG modelling has included treatment specific estimates of hypoglycaemia event rates with costs and

quality of life impacts attached to these. Janssen do not question these event rates, costs or quality of life impacts. The other main AEs are also modelled using treatment specific estimates. Given their limited duration they have little impact upon results which is as would be expected.

Janssen selectively identifies two STAs, one of which is a Janssen submission for canagliflozin, where linear evolutions of HbA1c or treatment specific trajectories of HbA1c have been accepted by NICE. The AG has not checked these but thinks this is an unbalanced presentation. It does not reflect the large number of STAs and MTAs, including the recent NICE CG, which have adopted the UKPDS68 equation for the evolution of HbA1c. Janssen appears to argue that NICE precedents should determine the approach to modelling HbA1c. In the opinion of the AG this is rather likely to argue for using the UKPDS68 HbA1c evolution.

J3 Systolic blood pressure on canagliflozin 300mg

As confirmed by the AG at the first Appraisal Committee meeting, an incorrect SBP value for canagliflozin 300mg in the AG NMA was carried through to the economic analysis. The correct reduction for canagliflozin 300mg of 5.0mmHg (not 0.5mm Hg), hence a reduction of 5.5mmHg compared to baseline, is applied in the results reported below. Given the Janssen concerns around the most appropriate method of modelling HbA1c the AG has reanalysed the base case and scenario analysis 09 of the AG report which applies the Janssen linear HbA1c evolutions.

Before reporting these results the AG has identified an error within the AG report. Table 95 of the AG report for the scenario analysis 09 cost effectiveness estimates for the flozins compared to sitagliptin incorrectly replicates the results of Table 91 of scenario analysis 08. This AG error was carried through to the PMB document table 25. Table 95 of the AG report should have been as follows.

Table 9: Corrected Table 95 of AG report: SA09: Flozins vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£2,073	£582	£1,501	£998	£1,819	£1,095
Empa. 25	£12,206	£3,557	£9,713	£6,653	£10,803	£7,020
Dapa. 10	£41,718	£6,978	£32,466	£17,541	£31,850	£17,363

The above does not affect any of the conclusions of the AC.

Turning to the results of the AG running the model with the old and the revised SBP estimate for canagliflozin 300mg this results in the following base case estimates for canagliflozin 300mg.

Table 10: AG base case estimates: Canagliflozin 300mg vs SU

	Net cost	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5

Old SBP							
Net cost/QALY	£5,362	-0.012	0.147	0.057	0.074	0.000	0.028
ICER		Dom	£36,491	£93,384	£72,315	Dom	£193k
New SBP							
Net cost/QALY	£5,224	0.005	0.163	0.074	0.090	0.016	0.044
ICER		£1.1mn	£32,015	£71,038	£57,865	£330k	£118k

Due to the improved SBP estimate canagliflozin 300mg is no longer dominated under the scenario of BMI changes having no quality of life impact. The revised SBP estimate improve the ICERs for canagliflozin compared to gliclazide. But the conclusions to be drawn from the revised estimates appear to be the same as those that were drawn from the old estimates.

Table 11: AG base case estimates: Canagliflozin 300mg vs sitagliptin

	Net cost	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Old SBP							
Net cost/QALY	£318	0.025	0.123	0.036	0.052	0.031	0.048
ICER		£12,623	£2,590	£8,913	£6,111	£10,256	£6,627
New SBP							
Net cost/QALY	£187	0.042	0.139	0.052	0.068	0.048	0.064
ICER		£4,401	£1,341	£3,586	£2,729	£3,929	£2,896

The net cost compared to sitagliptin falls with the new estimate and the QALY gains increase, again improving the ICERs for canagliflozin 300mg compared to sitagliptin. The conclusions to be drawn from the revised estimates appear to be the same as those that were drawn from the old estimates.

For the scenario analysis 09 which applies the Janssen preferred linear segments for HbA1c the estimates are as follows.

Table 12: AG SA09: Canagliflozin 300mg vs SU

	Net cost	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Old SBP							
Net cost/QALY	£5,399	-0.011	0.148	0.059	0.087	0.001	0.050
ICER		Dom	£36,446	£91,603	£61,897	£4.3mn	£108k
New SBP							
Net cost/QALY	£5,282	0.007	0.165	0.075	0.104	0.018	0.066
ICER		£810k	£32,093	£70,174	£50,993	£298k	£79,667

Due to the improved SBP estimate canagliflozin 300mg is no longer dominated under the scenario of BMI changes having no quality of life impact. The revised estimate improves the ICERs for

canagliflozin compared to gliclazide. But the conclusions to be drawn from the revised estimates appear to be the same as those that were drawn from the old estimates.

Table 13: AG SA09: Canagliflozin 300mg vs sitagliptin

	Net cost	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Old SBP							
Net cost/QALY	£82	0.040	0.142	0.055	0.083	0.045	0.075
ICER		£2,073	£582	£1,501	£998	£1,819	£1,095
New SBP							
Net cost/QALY	-£42	0.055	0.156	0.070	0.097	0.060	0.090
ICER		Domin	Domin	Domin	Domin	Domin	Domin

The small net cost for canagliflozin 300mg compared to sitagliptin is revised to a small cost saving. Given the QALY gains this results in canagliflozin 300mg being estimated to dominate sitagliptin. Again, the conclusions are unaffected.

MSD

Page 2, relative efficacy of SGLT2 inhbitors and sitagliptin. The third paragraph mentions the Aschner 2010 trial. Because of the low baseline HbA1c, this was an exclusion from our NMA.
Page 2, last paragraph. The Stenlof sitagliptin arm was not included in our NMA – the diagram on page 81 of the assessment report should not have included the link.

Summary

The main comments on cost effectiveness are those of Janssen.

- The use of the UKPDS OM1 was specified in the assessment protocol. It was preferred by the recent NICE CG due to it being estimated from a single trial rather than being a compendium of estimates from a variety of different sources. Related to this the cost and quality of life estimates for the complications that are modelled are also from the same source.
- Janssen identified two precedent STAs where treatment specific HbA1c trajectories may have been applied. This is not a balanced reflection of the NICE precedents. While it has not reviewed all previous NICE assessments in T2DM, in the opinion of the AG the weight of precedents will strongly favour applying the UKPDS68 evolution of HbA1c and not the preferred Janssen linear segments approach.
- The Janssen linear segments approach is likely to be biased against gliclazide, since the estimate for gliclazide is based upon the ADOPT glibenclamide estimate.

- The AG modelling using the UKPDS OM1 is not particularly sensitive to whether the base case UKPDS68 evolution of HbA1c is applied or the Janssen preferred linear segments approach. The conclusions that would be drawn from both are the same.
- Janssen state that the ECHO-T2DM uses the revised UKPDS event equations. If anything these should be more conservative than the AG OM1 modelling. In the light of this the sensitivity of the Janssen modelling to whether the AG base case UKPDS68 evolution of HbA1c is applied or the Janssen preferred linear segments approach seems surprising. Given the AG results this sensitivity of the ECHO-T2DM would appear to be due to other reasons than the effects upon the UKPDS event equations.
- The AG remains unclear quite what the Janssen rebound assumptions are. These may affect modelling results. Due to the uncertainty around them have not particularly been reviewed by the AC.
- Janssen cites two papers by Khunti as supporting the view that whether patients continue or discontinue OHAs at intensification to insulin is mixed. The AG can find no support for this assertion in the cited papers. Nor does a more relevant paper of which Khunit was an author provide support.
- Janssen does not appear to have tried to model the AC preferred base case using either its or the AG clinical effectiveness estimates:
    - Continuation of OHAs when intensifying to insulin.
    - AG other cost and quality of life inputs.
- The AG modelling did apply an incorrect SBP reduction for canagliflozin 300mg. Correcting this error improves the cost effectiveness estimates for canagliflozin 300mg but does not alter the conclusions that would be drawn from either the AG base case modelling or the scenario analysis that applies the Janssen preferred linear segments approach to model HbA1c.

There are uncertainties about the relative effectiveness of the three drugs because of ethnic differences in type 2 diabetes amongst participants in the trials, different baseline HbA1c, and differing changes in the placebo groups.