NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Dapagliflozin in Triple Therapy

Submitted as an addendum to HTA submission Dapagliflozin for the treatment of type 2 diabetes

Submitted by

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Single technology appraisal (STA)

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Contents

Introduction

The following document is an **Addendum** to the previously submitted HTA document **Dapagliflozin for the treatment of type 2 diabetes** submitted to the Institute on the 17th July 2012.

This document presents the clinical efficacy and safety and cost effectiveness data, relating to dapagliflozin as a third-line add-on after metformin and sulphonylurea (SU) in the treatment of type 2 diabetes (T2DM).

Background

As presented in the main submission, diabetes is a significant health issue; in 2009-10 there were an estimated 3.1 million adults with diabetes in England. Diabetes occurs when blood glucose, which can be measured by HbA1c, is not controlled. Lowering HbA1c reduces the risk of complications such as nephropathy, retinopathy, heart attacks and strokes.

Unfortunately current therapies have some inherent shortcomings, such as causing weight gain and hypoglycaemia (too low a level of blood sugar). In addition, despite a wide variety of treatment options, a considerable number of people with T2DM continue to fail to meet treatment targets, with over one-third of patients failing to reach an appropriate HbA1c target. Additionally, around half of patients with T2DM failed to reach NICE recommended blood pressure targets and over three quarters were overweight or obese. These additional CV risk factors increase the risk of mortality. A recent National Audit Office report estimates that up to 24,000 people die each year from avoidable causes related to their diabetes.

Around 90% of people with diabetes have T2DM. There are a number of existing treatment options for T2DM patients and clinical guidelines (NICE CG87) recommend a step-wise approach to treatment, as the disease is progressive over time: start with diet modifications and exercise; progress to monotherapy; then to dual-therapy; then to treatment with insulin. However, triple therapy with sitagliptin or pioglitazone can be considered instead of insulin, if insulin is unacceptable (because of employment, social, recreational or other personal issues, or obesity). Exenatide can be added to metformin and SU if the above is true, as well as the patient meeting specific Body Mass Index (BMI) thresholds.

Efficacy, safety and cost-effectiveness data for dapagliflozin in triple therapy

The efficacy and safety of dapagliflozin after metformin and SU are still being evaluated in a prospective, randomised controlled trial (RCT) which is expected to complete in late 2013 [NCT01392677].

However, following discussion with the Institute (21 June, 2012), BMS/AZ have provided this report to allow consideration of the use of dapagliflozin in the triple therapy setting. However, BMS/AZ initially did not intend to provide these analyses as part of the ongoing STA appraisal because, as noted in our response to the scope, a full RCT is ongoing and will report in 2013. The 6 months' data from this trial will form the basis of regulatory evaluation by EMA/CHMP to include triple combination data in SmPC Section 5.1 'Pharmacodynamic particulars' to supplement the approved dual combination therapies. The expected launch indication for the use of dapagliflozin in combination with other glucose lowering

medicinal products, including insulin, will be supported by the clinical data presented in Section 5.1 of the SmPC. The add on therapy combinations for which we are seeking an approval at launch are; add on to metformin, add on to SU and add on to insulin (for guidance on the indication of dapagliflozin as an add on combination therapy (please see SmPC Section 5.1).

BMS/AZ have therefore endeavoured to provide an assessment of the potential efficacy, safety and cost-effectiveness of dapagliflozin in the triple therapy setting after extrapolating data from the overall clinical trial programme and an analysis for NICE (a pooled post hoc analysis of a subset of T2DM patients at high risk of CV events failing to reach glycaemic targets despite being treated with metformin and SU) derived from data available from two studies (Study 18 and Study 19).

Limitations:

In providing this analysis, BMS/AZ note the following caveats:

- This report has been provided to allow a consideration of the use of dapagliflozin in the triple therapy setting. BMS/AZ did not initially intend to provide these analyses as part of the ongoing STA appraisal because, as noted in our response to the scope, a full triple therapy RCT is on-going and will complete in late 2013. Data from this RCT will provide definitive evidence for the assessment of dapagliflozin in a triple therapy regimen.
- However, following discussion with the Institute, we respect that some clinicians may wish to use dapagliflozin in this setting and without this information the submission may not fully address the appraisal scope.
- In providing these analyses we stress that the most suitable data available at this time are provided from a post-hoc analysis, considering a subset of patients from 2 clinical studies (Studies 18 & 19) and these studies were not designed to directly assess the use of dapagliflozin in triple therapy but to assess efficacy and safety of dapagliflozin in high-risk CV patients. The clinical results presented here should therefore be treated as exploratory until data from the on-going triple therapy RCT report in late 2013.

Further caveats should be noted with respect to the economic analyses presented:

- In considering the economic analyses presented here, it should be noted that comparator evidence has been drawn from a published systematic review and meta-analysis, and data for dapagliflozin has been drawn from a post hoc analysis of a subset of patients from the two clinical trials as described above. The two sets of data have not been formally assessed for comparability and differences between the populations considered will exist.
- The published meta-analysis did not provide some of the data inputs required for the model (SBP, TC, HDL-C, and AE's) and these values are therefore set to zero within the analyses presented.
- Given these caveats, it should be noted that both the evidence base for the triple therapy analyses presented here and the results of the triple therapy economic evaluation should be considered less robust than the analyses presented within the main submission document.
- This additional analysis has been prepared in a relatively short time frame following the Decision Problem Meeting with NICE. The analyses presented here have not been subject to

the same quality control checks as those included in the main submission and, as noted for the clinical data, should therefore be considered exploratory.

Dapagliflozin clinical trial programme

The dapagliflozin trial programme has studied the use of the drug in a range of clinical scenarios including diabetes drug-naive patients to those with established cardiovascular disease.

For a detailed list of the appropriate studies, please see Section 1.6 in the main HTA submission document. However, in practical terms these studies encompassed the following designs:

- monotherapy study (included a high HbA1c baseline cohort and monotherapy arms in initial combination)
- dual therapy (add on to metformin, add on to SU, add on to met vs SU)
- dual/triple therapy (add on to DPP-4 inhibitor and/or metformin). [Not included in Section 5.1 of SPC].
- add on to insulin and or 1 or 2 oral antidiabetics (OADs)
- add on to diabetes background therapy in patients with established cardiovascular disease and/or hypertension. [Not included in Section 5.1 of SPC].

With regards to dapagliflozin being used in the triple therapy setting, the following clinical trials are of particular interest (Table 1). These studies contain various subgroups of patients specifically looking at the use of dapagliflozin in triple therapy. However, it should be emphasised that the data from these studies have a number of limitations with respect to the appropriate extrapolation of the results into the triple therapy domain, and these are discussed below.

Table 1: Studies involving dapagliflozin in triple combination

Study number	Description of study	Comments
Study 10 double-blind RCT (NCT00984867)	Effect of Dapagliflozin in patients with type 2 diabetes failing DPP-4 inhibitor ± metformin	Prespecified stratum of patients already on metformin and DPP4 inhibitor
Study 18 placebo controlled, double-blind RCT (NCT01031680)	Effect of Dapagliflozin in patients with type 2 diabetes with existing cardiovascular disease and hypertension	Post hoc sub group analysis of population previously on stable metformin and sulphonylurea
Study 19 placebo controlled, double-blind RCT (NCT01042977)	Effect of Dapagliflozin in patients with type 2 diabetes with existing cardiovascular disease	Post hoc analysis of population previously on stable metformin and sulphonylurea
Add on to metformin and SU (NCT01392677)	Prospective evaluation of the efficacy and safety of dapagliflozin vs placebo in patients failing on metformin and sulphonylurea,	Trial currently ongoing, expected to report in late 2013

Limitations of current Phase 3 data in determining the efficacy of dapagliflozin in the triple therapy setting data

Study 10 (NCT00984867)
This study included 2 pre-specified strata (groups) of patients failing to reach glycaemic control:

1. DPP4 monotherapy
2. Metformin + DPP4

NICE CG87 generally recommends metformin to be followed by SU (second line). While Study 10 Stratum 2 patients provide "triple therapy" data, the population characteristics of this group do not reflect those of the population failing on metformin and SU, because they have already been pre-selected for DPP4 treatment on the basis of their being unsuitable for SU (i.e. have risk of hypoglycaemia, or weight gain).

Consequently, BMS/AZ determined that the Study 10 data was not appropriate to be used as part of the triple therapy database, due to the trial population not being representative of the metformin + SU population able to receive triple therapy as recommended by CG87.

Studies 18 (NCT01031680) and 19 (NCT01042977)
Studies 18 and 19 differ from the remaining dapagliflozin trials in that, as well as T2DM, these trials required patients to have documented cardiovascular disease (prior MI, stroke etc.) and /or hypertension. As such these T2DM patients are older (average age 63-64 years), and approximately 5-6 years from the most recent qualifying cardiovascular event (Cefalu et al 1056-P ADA 2012, Philadelphia USA; Leiter et al Poster 1114-P ADA 2012, Philadelphia USA).

[redacted] This is not unexpected in patients of this age or degree of co-morbidity and their presence in the study population may have a negative impact of the efficacy of the drug. [redacted]

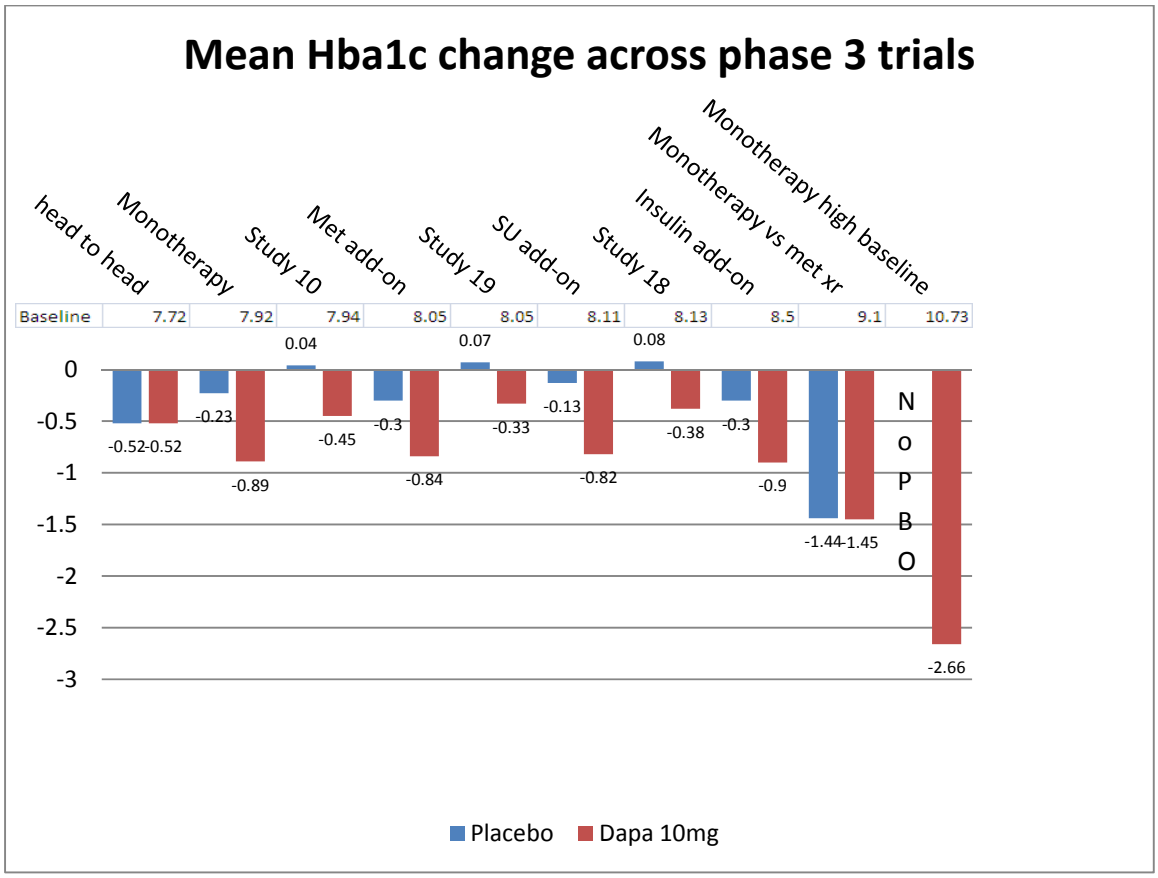
Nevertheless these two studies do include a large cohort of patients [redacted] who were being treated with metformin and SU at baseline, and who were stratified at study entry into an oral anti-diabetic category (OAD), and so are potentially a triple therapy population as defined by the Institute.

Consequently, BMS/AZ determined that the patient subset from Studies 18 and 19, despite their greater age and poorer cardiovascular history, would be most appropriate to be used as part of the triple therapy database as this subset of patients was reasonably representative of the treatment pathway for triple therapy as recommended by CG87.

Effect of baseline HbA1c on efficacy of dapagliflozin in the Phase 3 studies
At this stage it is appropriate to remind ourselves of the primary and secondary endpoints from the Phase 3 studies.

The mean change in HbA1c across these Phase 3 trials are shown in Figure 1

Figure 1 Mean change in HbA1c across Phase 3 trials using dapagliflozin (10mg)

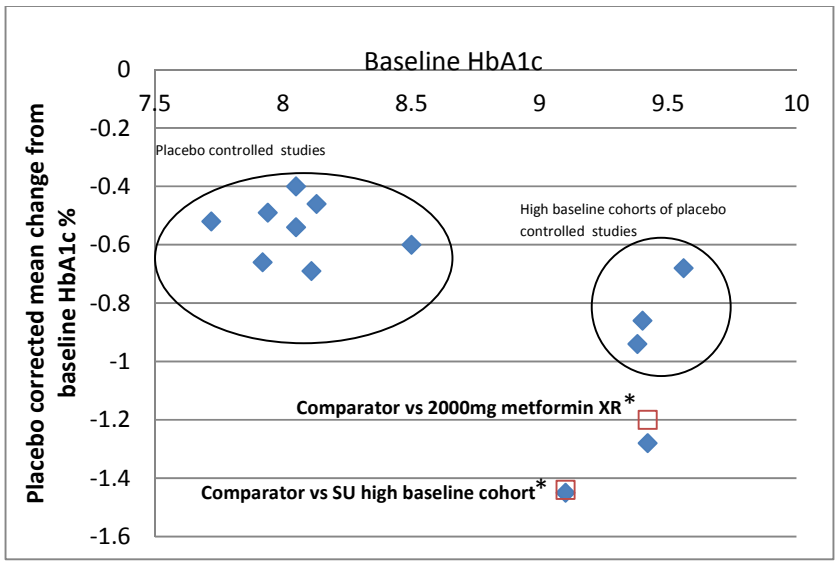


The results of these studies show a consistent effect of dapagliflozin on glycaemic control, which is independent of the duration of diabetes (in the studies displayed above duration ranges from 0.5 to 14 years) and the type of add on therapy (metformin, SU, insulin and or other OAD).

However, the data show that the effect of dapagliflozin is dependent on baseline HbA1c. For example, the greatest effect is seen in the monotherapy (high baseline) trial with the highest base line HbA1c (10.73%). This observation is consistent with the mechanism of action of dapagliflozin – i.e. a higher baseline HbA1c level results in a greater amount of glucose filtration with, consequently, a higher excretion of glucose.

Figure 2 (below) displays these same data in a slightly different format, where it can be clearly seen that the baseline HbA1c does have a critical effect on likely efficacy.

Figure 2 Placebo-controlled mean change from baseline HbA1c across the dapagliflozin phase 3 trials

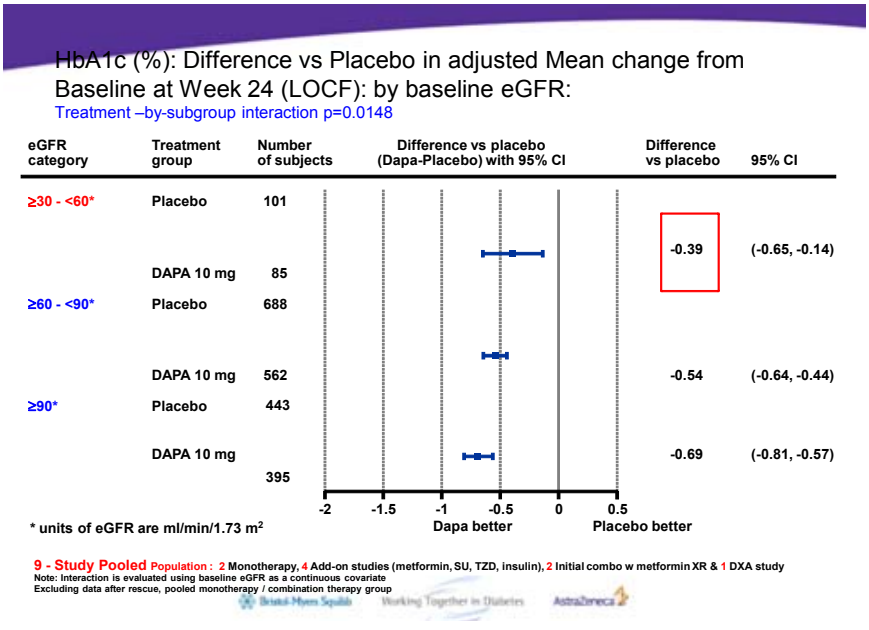


*active comparator studies vs SU and metformin XR 2000mg (comparator results shown as squares)

Effect of baseline eGFR on efficacy of dapagliflozin in the Phase 3 studies

The only other parameter that has been found to affect the efficacy of dapagliflozin is baseline eGFR (Figure 3).

Figure 3 The effect of eGFR on the efficacy of dapagliflozin



In keeping with the mechanism of action of dapagliflozin, a lower baseline eGFR results in lower amount of glucose filtration and therefore reduced dapagliflozin efficacy. The efficacy of dapagliflozin was also assessed separately in a dedicated study of diabetic subjects with moderate renal impairment (252 subjects with mean eGFR of 44ml/min/1.73m^2). The mean change from baseline in HbA1c at 24 weeks was -0.44% and -0.32%, for dapagliflozin 10mg and placebo respectively. [redacted].

In conclusion, BMS/AZ anticipate that the efficacy of dapagliflozin after metformin and SU [redacted] should depend purely on their baseline HbA1c.

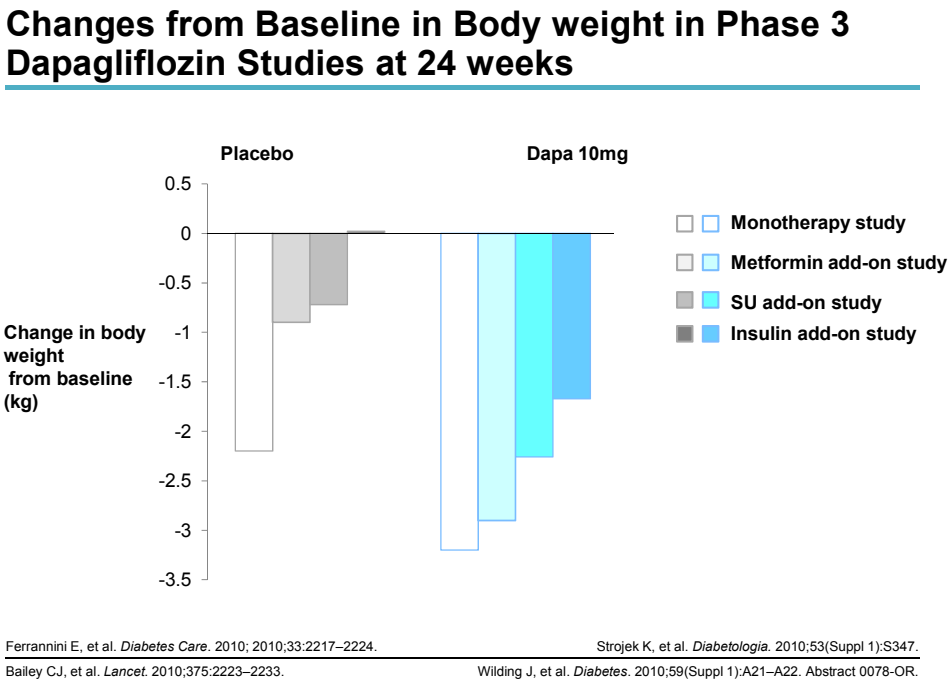
Effect of baseline HbA1c on efficacy of dapagliflozin in Studies18/19

[redacted]

This shows that, as expected, the efficacy of dapagliflozin in the “triple therapy” population is dependent on baseline HbA1c. BMS/AZ anticipate that the ongoing triple therapy RCT in patients failing on metformin and SU will deliver similar results.

Weight loss associated with dapaglflozin across the Phase 3 studies
Dapagliflozin has the secondary benefit of weight loss. This has been consistently demonstrated across the Phase 3 studies regardless of the therapy setting (Figure 5).

Figure 5 Changes from baseline in body weight in the Phase 3 dapagliflozin studies



A similar drop in weight would be expected in patients receiving dapagliflozin as an add-on to metformin and SU

[redacted]

This shows that dapagliflozin causes weight loss in the “triple therapy” population in keeping with the rest of the Phase 3 trials. BMS/AZ anticipate that the ongoing RCT in patients failing on metformin and SU will deliver similar results.

Blood pressure
A key safety endpoint across the dapagliflozin clinical trial programme was changes in blood pressure, as described in the main HTA submission. In the triple therapy cohort the changes observed are presented in Table 5.

[redacted]

It should be noted that in Studies 18 and 19 no changes in background antihypertensive medications were allowed except when certain rescue criteria were met (SBP >160 mmHg or DBP >100 mmHg). Because of this, BMS/AZ feel the data presented above are robust and in keeping with the rest of the trial programme (see main HTA submission).

Safety of dapagliflozin in combination with metformin and SU

Hypoglycaemia
A key safety endpoint across the dapagliflozin clinical trial programme was the rate of hypoglycaemia. As described in the main HTA submission, when added to metformin, dapagliflozin does not significantly increase the rates of hypoglycaemia (Bailey 2010). When added to agents that are known to cause hypoglycaemia (such as SU or insulin) dapagliflozin is associated with small increases in the background rate of hypoglycaemia (Strojek 2011 and Wilding 2012).

Based on these data, BMS/AZ would anticipate that the rate of hypoglycaemia may be slightly increased when dapagliflozin is added to metformin and SU. [redacted]

[redacted]

Other safety endpoints of interest
These are genital infections (GTIs) and urinary tract infections (UTIs).

GTIs were considered events of special interest in the dapagliflozin development program given that, due to its mechanism of action, dapagliflozin causes glucosuria and that these infections are known to be more common in diabetic patients than in the general population. Events of GTI were reported in a

higher proportion of patients treated with dapagliflozin compared with control. In all treatment groups, most events (first event) of GTI were reported in the first 24 weeks. The majority of events of GI were non-serious, mild to moderate in intensity, responded to initial standard treatment and were not recurrent. Few events of GTI resulted in discontinuation.

UTIs were considered events of special interest in the dapagliflozin development program due to dapagliflozin's mechanism of action which causes glucosuria, and that these infections are known to be more common in diabetic patients than in the general population.

[redacted]

These data are in keeping with the safety profile of dapagliflozin in the rest of the Phase 3 trials (see main HTA submission) showing an increase in events suggestive of GI – mainly in females – and small increase in events suggestive of UTI.

Other adverse events summary

[redacted]

[redacted]

Overview of clinical data for the use of dapagliflozin in triple therapy

- At this time, there is no prospective data available from the Phase 3 clinical programme trials to assess the efficacy and safety of dapagliflozin in the triple therapy setting
  - [redacted]

Comparators in the third line add-on setting

As RCT data for dapagliflozin in this setting are yet to report, BMS/AZ had not planned a systematic review of the appropriate publication database. Instead, therefore, BMS/AZ have used the Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review of third line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea as a substitute (REF).

This systematic review and MTC has some limitations for application here: the literature search extended to 2009 and since then new data in the triple therapy space have been published. Below is a list of known studies published since review:

- Linagliptin (Owens et al Diabetic Medicine 2011)
- Saxagliptin (Moses et al Poster 1094-P, ADA 2012, Philadelphia)

These studies both report similar efficacy and safety findings to those of the single sitagliptin study included in the systematic review. BMS/AZ do not expect the results of these 2 studies to unduly influence the findings of the MTC. There may, of course, be other studies that have been published in the interim and would be identified via a full updated search. While the full document is attached as an Appendix, we present the sections/data most relevant to this submission below.

Third line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea

A systematic review was conducted by the Canadian Agency for drugs and technologies in health(CADTH) for third line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea.

The systematic review of third-line anti-diabetes drugs included 33 unique RCTs (reported in 36 full-text articles) which identified evidence for the following eight drug classes:

- alpha-glucosidase inhibitors (four RCTs),
- meglitinides (one RCT), TZDs (nine RCTs),
- DPP-4 inhibitors (one RCT),
- GLP-1 analogues (six RCTs),
- basal insulin (18 RCTs), bolus insulin (one RCT),
- biphasic insulin (12 RCTs).

The evidence within these eight drug classes was further stratified based upon the following three scenarios:

1. addition of a third-line agent while continuing metformin and sulfonylurea
2. treatment with a third-line agent upon discontinuation of metformin or sulfonylurea (but not both)
3. treatment with a third-line agent upon discontinuation of both metformin and sulfonylurea (e.g., insulin monotherapy).

The first scenario was the most common amongst the included RCTs, with 26 RCTs reporting comparisons of interventions added onto existing metformin and sulfonylurea therapy, and is the most relevant to this submission.

Key Outcomes

Patient characteristics

Table 4 Summary of patient characteristics from the CADTH systematic review for third line therapy in patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea (reproduced from original paper)

Table 5: Summary of Patient Characteristics	
Patient Characteristics	Range Across All Included Studies
Mean age (years)	51.2[27] to 69.4[13]
Gender (% male)	27.6[21] to 75.4[20]
Mean duration of diabetes (years)	3.5[28] to 12.7[28]
Mean A1C at baseline (%)	8.1[20,22,28] to 11.3[12,21]

Long-term complications of diabetes

There were no adequately powered RCTs evaluating the comparative efficacy of any class of third-line anti-diabetes drug for reducing clinically important long-term complications of diabetes. Longer-term studies with larger sample sizes are required to determine if any of the agents have an advantage over another in limiting diabetes-related complications.

Haemoglobin HbA1C:

- Compared with metformin and a SU alone, basal insulin, biphasic insulin, DPP-4 inhibitors, GLP-1 analogues, TZDs, or bolus insulin combined with metformin and a sulfonylurea produced statistically significant reductions in A1C (range: -0.9% to -1.2%). However, meglitinides and alphaglucosidase inhibitors did not. Biphasic insulin was also effective in reducing HbA1C (-1.9%) when given in combination with metformin alone (i.e., patients ceased taking sulfonylureas).
- There were no statistically significant differences in HbA1C reductions between basal insulin, biphasic insulin, DPP-4 inhibitors, GLP-1 analogues, TZDs, and bolus insulin.
- Overall, the amount and quality of evidence was insufficient to draw conclusions regarding the relative efficacy of the add-on, partial-switch, and switch regimens in the initiation of insulin.

Body weight

- When added to metformin and sulfonylurea therapy, treatment with basal insulin, biphasic insulin, bolus insulin, and TZDs was associated with statistically significantly greater increases in body weight than treatment with metformin and SU alone.
- DPP-4 inhibitors, and alpha-glucosidase inhibitors were not associated with significant weight gain, and GLP-1 analogues were associated with statistically significant weight loss.

Hypoglycemia

- TZDs, GLP-1 analogues, DPP-4 inhibitors, and basal insulin were associated with a significantly greater risk of overall hypoglycaemia than placebo when given in combination with metformin and a sulfonylurea.
- The various insulin-containing strategies were typically associated with a greater risk of overall hypoglycemia relative to other active comparators, with biphasic and bolus insulins associated with a significantly greater risk of overall hypoglycaemia than basal insulin.
- Overall, events of severe and nocturnal hypoglycaemia were relatively rare for all drug classes, limiting the ability to make meaningful comparisons between drug classes.

Withdrawals due to adverse events:

- GLP-1 analogues were associated with a higher incidence of withdrawals because of adverse events than placebo, basal insulin, and biphasic insulin. Nausea and vomiting were cited as the primary reasons for these withdrawals.
- Low event rates and a lack of consistent reporting prevented meaningful comparisons regarding the occurrence of serious or severe adverse events in the included RCTs.

Conclusions
Evidence has been presented in three different formats based on differing levels of aggregation:

  - MTC meta-analysis
  - direct pairwise meta-analysis
  - individual study-level results.

Direct evidence was available for many comparisons including five of the eight possible comparisons against placebo. The good alignment between direct and indirect estimates in most comparisons supports the validity of the MTC meta-analysis results. The robustness of the results was demonstrated with extensive sensitivity analyses and meta-regression, while alternative modelling was used to ensure that pooling of trials reflected differences between trials in the concomitant use of metformin and sulfonylurea (i.e. primary analysis of add-on therapies only versus secondary analysis of all treatment strategies).

However, it should be noted that there were limited data for clinically relevant complications of diabetes.

- The primary methodological limitations of the included RCTs were failure to report adequate methods for allocation concealment, and the use of analyses other than intention-to-treat.

- Key limitations with respect to external validity of trials included the relatively short duration of trials, small sample sizes, failure to report definitions for hypoglycemia and adverse events,

blood glucose targets that were different from those suggested in the Canadian Diabetes Association Clinical Practice Guidelines, and a level of contact between trial subjects and health care professionals that likely exceeds routine clinical practice.

- There was between-study heterogeneity with regard to baseline A1C, duration of diabetes, reporting of metformin and sulfonylurea dosing at baseline, glycemic targets specified in the included RCTs, inclusion, and characteristics of run-in periods. However, through sensitivity analyses and metaregression, the impact of these factors on MTC meta-analysis results was found to be limited.

Summary of comparator data in the triple therapy setting

There was insufficient evidence to evaluate the comparative efficacy of third-line anti-diabetes drugs in reducing clinically important long-term complications of diabetes. Compared with continued treatment with metformin and sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, TZDs, and bolus insulin produced statistically significant reductions in HbA1c in combination with metformin and sulfonylureas, whereas meglitinides and alpha-glucosidase inhibitors did not. Basal insulin, biphasic insulin, bolus insulin, and TZDs all resulted in an increase in body weight, while DPP-4 inhibitors, alpha-glucosidase inhibitors, and GLP-1 analogues were not associated with significant weight gain. The various insulin-containing strategies were typically associated with a greater risk of hypoglycemia relative to other active comparators.

Cost Effectiveness

Using the same model, approach and baseline characteristics presented in the main submission dossier, an economic analysis was performed to provide a preliminary assessment of the cost effectiveness of dapagliflozin compared to DPP-4 inhibitors, GLP-1 analogues and TZD. For details of the general approach to implementation of clinical data within the economic model please refer to the main submission. A number of scenarios analyses are presented focussing on the impact of varying utility weights. Probabilistic sensitivity analyses are also presented.

Clinical Parameters and variables

Treatment Sequences

The treatment sequences implemented in the model are summarised in the following table:

	Treatment arm		**Control arm**		
First line	MET+SU		MET+SU	MET+SU	MET+SU
Second line	MET+SU+Dapagliflozin	**vs**	MET+SU+DPP4	MET+SU+TZD	MET+SU+GLP1
Third line	MET+INS		MET+INS	MET+INS	MET+INS
HbA1c switching threshold	Same as HbA1c baseline (i.e. 7.72%)				

Each sequence is modelled to start with MET + SU and to add either dapagliflozin, DPP-4, TZD or GLP-1 as triple therapy. For all sequences, treatment on progression is assumed to be MET + INS.

Each treatment sequence is initiated with MET + SU because the systematic review pools data from a variety of studies and therefore no single set of baseline characteristics are available to re-base the analyses. Baseline characteristics for Study 4 are therefore assumed in each sequence. As a result, the 'true' cost effectiveness estimates will be distorted as the assessment would ideally initiate with the triple therapy comparison, however, any effect will apply equally to all comparisons.

The following tables summarise the model inputs used within the analysis and reported standard errors from two clinical trials as described above. As noted, the two sets of data used here have not been formally assessed for comparability and differences between the populations considered will exist. Given the methods applied, it has not been possible to adjust for baseline characteristics.

Model Inputs:

	Treatment arm		Control arm		
[redacted]	[redacted]		MET+SU+DPP4	MET+SU+TZD	MET+SU+GLP1
[redacted]	[redacted]		-0.89	-0.96	-1.06
[redacted]	[redacted]		1.11	3.10	-1.59
[redacted]	[redacted]		*0.00*	*0.00*	*0.00*
[redacted]	[redacted]		*0.00*	*0.00*	*0.00*
[redacted]	[redacted]	**vs**	*0.00*	*0.00*	*0.00*
[redacted]	[redacted]		0.00	0.00	0.01
[redacted]	[redacted]		0.16	0.23	0.25
[redacted]	[redacted]		*0.00*	*0.00*	*0.00*
[redacted]	[redacted]		*0.00*	*0.00*	*0.00*
[redacted]	[redacted]		0.02	0.04	0.07

Dapagliflozin arm: Clinical study 18 & 19
Comparator arms: Canadian HTA assessment OAD triple therapy (CADTH Therapeutic Review)
*Data not available for the control arms; these values were therefore assumed to be zero for both treatment and control arm.

Standard Errors:

	Treatment arm		Control arm		
	[redacted]		MET+SU+DPP4	MET+SU+TZD	MET+SU+GLP1
[redacted]	[redacted]		0.0316	0.0199	0.0199
[redacted]	[redacted]		0.1260	0.0699	0.0724
[redacted]	[redacted]	**vs**	0.0328	0.0460	0.0500
[redacted]	[redacted]		na	na	0.0093
[redacted]	[redacted]		na	na	na
[redacted]	[redacted]		na	na	na
[redacted]	[redacted]		na	na	na

Dapagliflozin arm: Clinical study 18 & 19
Comparator arms: Canadian HTA assessment OAD triple therapy (CADTH Therapeutic Review)

Results

Clinical outcomes from the model

Add-on to metformin and SU: dapagliflozin versus DPP-4

The following table shows the predicted lifetime (40 year) cumulative number of diabetes related complications per patient for both treatment arms, as well as the predicted number of treatment related AEs.

	Dapagliflozin		**Control**		***Incremental***	
Event	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	***Non-Fatal***	***Fatal***
Macrovascular						
IHD	[redacted]	[redacted]	0.1321	0.0000	[redacted]	[redacted]
MI	[redacted]	[redacted]	0.2039	0.1211	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	0.0916	0.0165	[redacted]	[redacted]
CHF	[redacted]	[redacted]	0.0587	0.0165	[redacted]	[redacted]
Microvascular						
Blindness	[redacted]	[redacted]	0.0774	0.0000	[redacted]	[redacted]
Nephropathy	[redacted]	[redacted]	0.0148	0.0160	[redacted]	[redacted]
Amputation	[redacted]	[redacted]	0.0271	0.0276	[redacted]	[redacted]
AE_UTI	[redacted]		0.2371		[redacted]	
AE_GenI	[redacted]		0.0999		[redacted]	
Symptomatic hypoglycemia	[redacted]		2.2670		[redacted]	
Severe hypoglycemia	[redacted]		0.5393		[redacted]	

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; UTI, urinary tract infection.

The following table presents the average duration on each treatment line simulated in the model with a lifetime horizon for the MET+SU+dapagliflozin strategy and the MET+SU+DPP-4 strategy.

Treatment line	**Dapa sequence (years)**	**Control sequence (years)**
1st line	3.71	3.71
2nd line	2.74	3.71
3rd line	15.03	14.07
Total	21.48	21.49

Add-on to metformin and SU: dapagliflozin versus TZD

The following table shows the predicted lifetime (40 year) cumulative number of diabetes related complications per patient for both treatment arms, as well as the predicted number of treatment related AEs.

	Dapagliflozin		**Control**		***Incremental***	
Event	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	***Non-Fatal***	***Fatal***

Macrovascular						
IHD	[redacted]	[redacted]	0.1321	0.0000	[redacted]	[redacted]
MI	[redacted]	[redacted]	0.2041	0.1210	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	0.0916	0.0165	[redacted]	[redacted]
CHF	[redacted]	[redacted]	0.0587	0.0165	[redacted]	[redacted]
Microvascular						
Blindness	[redacted]	[redacted]	0.0775	0.0000	[redacted]	[redacted]
Nephropathy	[redacted]	[redacted]	0.0149	0.0160	[redacted]	[redacted]
Amputation	[redacted]	[redacted]	0.0271	0.0276	[redacted]	[redacted]
AE_UTI	[redacted]		0.2369		[redacted]	
AE_GenI	[redacted]		0.1001		[redacted]	
Symptomatic hypoglycemia	[redacted]		2.4956		[redacted]	
Severe hypoglycemia	[redacted]		0.5421		[redacted]	

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; UTI, urinary tract infection

The following table presents the average duration on each treatment line simulated in the model with a lifetime horizon for the MET+SU+dapagliflozin strategy and the MET+SU+TZD strategy.

Treatment line	**Dapa sequence (years)**	**Control sequence (years)**
1st line	3.71	3.71
2nd line	2.74	3.64
3rd line	15.03	14.14
Total	21.48	21.49

Add-on to metformin and SU: dapagliflozin versus GLP-1

The following table shows the predicted lifetime (40 year) cumulative number of diabetes related complications per patient for both treatment arms, as well as the predicted number of treatment related AEs.

	Dapagliflozin		**Control**		***Incremental***	
Event	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	***Non-Fatal***	***Fatal***
Macrovascular					[redacted]	[redacted]
IHD	[redacted]	[redacted]	0.1321	0.0000	[redacted]	[redacted]
MI	[redacted]	[redacted]	0.2041	0.1209	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	0.0917	0.0165	[redacted]	[redacted]
CHF	[redacted]	[redacted]	0.0587	0.0165	[redacted]	[redacted]
Microvascular						
Blindness	[redacted]	[redacted]	0.0776	0.0000	[redacted]	[redacted]
Nephropathy	[redacted]	[redacted]	0.0147	0.0160	[redacted]	[redacted]
Amputation	[redacted]	[redacted]	0.0272	0.0276	[redacted]	[redacted]

	Dapagliflozin		Control		*Incremental*	
Event	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	***Non-Fatal***	***Fatal***
AE_UTI	[redacted]		0.2371		[redacted]	[redacted]
AE_GTI	[redacted]		0.1000		[redacted]	[redacted]
Symptomatic hypoglycemia	[redacted]		2.5380		[redacted]	[redacted]
Severe hypoglycemia	[redacted]		0.5778		[redacted]	[redacted]

Abbreviations: CHF, congestive heart failure; GTI, genital infection; IHD, ischaemic heart disease; MET, metformin; MI, myocardial infarction; UTI, urinary tract infection

The following table presents the average duration on each treatment line simulated in the model with a lifetime horizon for the MET+SU+dapagliflozin strategy and the MET+SU+GLP-1 strategy.

Treatment line	Dapa sequence (years)	Control sequence (years)
1st line	3.71	3.71
2nd line	2.74	3.51
3rd line	15.03	14.27
Total	21.48	21.50

Cost outcomes from the model

The costs by category per patient for the dapagliflozin strategy and the comparator strategies are presented below.

Add-on to metformin and SU: dapagliflozin versus DPP-4

Parameter	**Dapa sequence**	**Control sequence**	***Incremental***
Tx related			
Drug treatment (total)	[redacted]	£3,298	[redacted]
BMI costs	[redacted]	£ -	[redacted]
Hypoglycemia	[redacted]	£125	[redacted]
Other AE related costs (incl. renal monitoring)	[redacted]	£14	[redacted]
Event related			
IHD	[redacted]	£1,195	[redacted]
MI	[redacted]	£2,349	[redacted]
Stroke	[redacted]	£617	[redacted]
CHF	[redacted]	£589	[redacted]
Blindness	[redacted]	£395	[redacted]
Nephropathy	[redacted]	£2,876	[redacted]
Amputation	[redacted]	£515	[redacted]
Total	[redacted]	**£11,974**	[redacted]

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MI, myocardial infarction

Add-on to metformin and SU: dapagliflozin versus TZD

Parameter	Dapa sequence	Control sequence	*Incremental*
Tx related			
Drug treatment (total)	[redacted]	£3,255	[redacted]
BMI costs	[redacted]	£ -	[redacted]
Hypoglycemia	[redacted]	£126	[redacted]
Other AE related costs (incl. renal monitoring)	[redacted]	£ 15	[redacted]
Event related			
IHD	[redacted]	£1,194	[redacted]
MI	[redacted]	£2,355	[redacted]
Stroke	[redacted]	£617	[redacted]
CHF	[redacted]	£590	[redacted]
Blindness	[redacted]	£395	[redacted]
Nephropathy	[redacted]	£2,890	[redacted]
Amputation	[redacted]	£515	[redacted]
-			
Total	[redacted]	**£11,951**	[redacted]

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MI, myocardial infarction

Add-on to metformin and SU: dapagliflozin versus GLP-1

Parameter	Dapa sequence	Control sequence	*Incremental*
Tx related			
Drug treatment (total)	[redacted]	£4,563	[redacted]
BMI costs	£ -	£ -	[redacted]
Hypoglycemia	£136	£137	[redacted]
Other AE related costs (incl. renal monitoring)	£22	£16	[redacted]
Event related			
IHD	£1,193	£1,195	[redacted]
MI	£2,336	£2,352	[redacted]
Stroke	£618	£617	[redacted]
CHF	£587	£589	[redacted]
Blindness	£391	£395	*-£4*
Nephropathy	£2,909	£2,864	*£45*
Amputation	£512	£516	*-£4*
-			
Total	**£11,865**	**£13,244**	***-£1,380***

Abbreviations: CHF, congestive heart failure; GI, genital infection; IHD, ischaemic heart disease; MI, myocardial infarction

Base-case analysis
Summary of results

The base case results for the model are presented in the following tables:

Outcome	**MET+SU+dapagliflozin**	**MET+SU+DPP-4**	***Incremental***
Life years (discounted)	14.69	14.70	*-0.01*
QALYs (discounted)	11.710	11.468	*0.242*
Costs (£)	11,865	11,974	*-109*
ICER (£) Incremental cost per QALY gained			Dominant

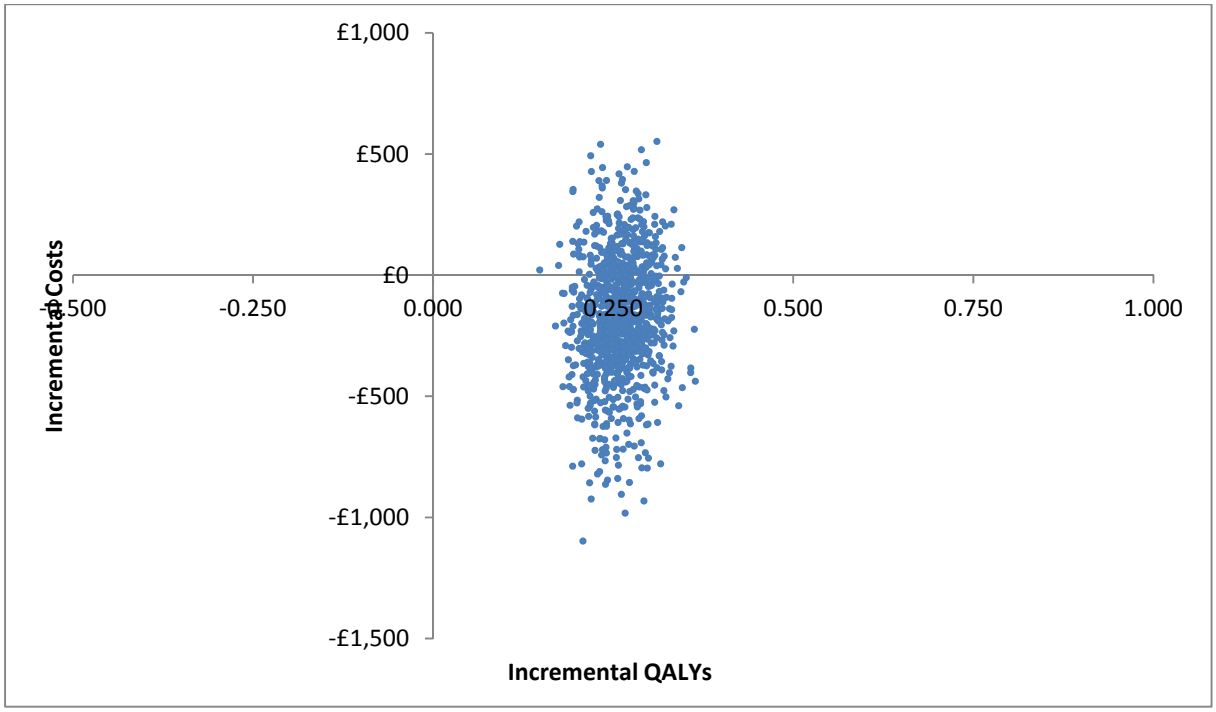
Outcome	**MET+SU+dapagliflozin**	**MET+SU+TZD**	***Incremental***
Life years (discounted)	14.69	14.70	*-0.01*
QALYs (discounted)	11.710	11.088	*0.622*
Costs (£)	11,865	11,951	*-86*
ICER (£) Incremental cost per QALY gained			Dominant

Outcome	**MET+SU+dapagliflozin**	**MET+SU+GLP-1**	***Incremental***
Life years (discounted)	14.69	14.70	*-0.01*
QALYs (discounted)	11.710	11.689	*0.021*
Costs (£)	11,865	13,244	*-£1,380*
ICER (£) Incremental cost per QALY gained			Dominant

Probabilistic sensitivity analysisAdd-on to metformin and SU: dapagliflozin versus DPP-4

The figure below presents the scatterplot of the ICER estimates of the PSA. Approximately two-thirds of the estimates are in the lower right-hand quadrant, with dapagliflozin having a 75% probability of being dominant compared to DPP-4. The 95% confidence intervals around the point estimates for incremental QALY's and costs were estimated accordingly (see corresponding table).

Scatterplot of the ICER estimates of the PSA:



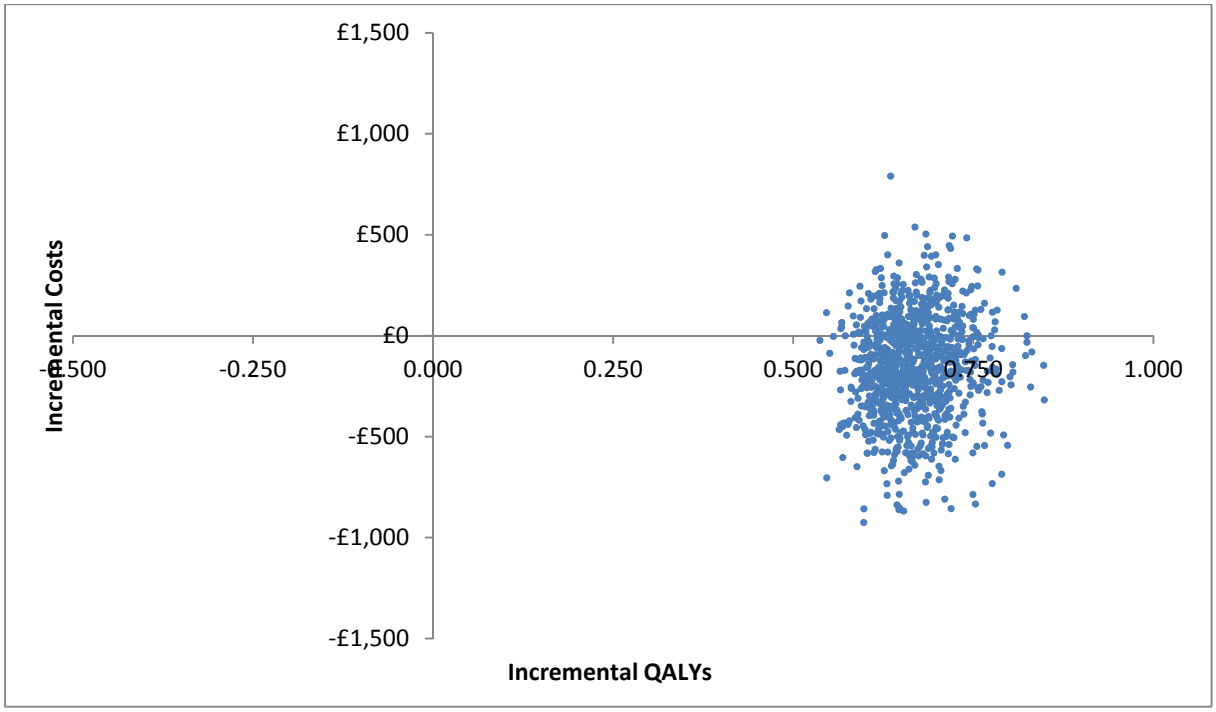
Results of the PSA: 95% CI around incremental QALYs and costs:

Outcome	LL_95% CI	UL_95% CI
Δ QALY	0.194	0.326
Δ Costs	-£723	£308

Add-on to metformin and SU: dapagliflozin versus TZD

The figure below presents the scatterplot of the ICER estimates of the PSA. Approximately two-thirds of the estimates are in the lower right-hand quadrant, with dapagliflozin having a 72% probability of being dominant compared to TZD. The 95% confidence intervals around the point estimates for incremental QALY's and costs were estimated accordingly (see corresponding table).

Scatterplot of the ICER estimates of the PSA:



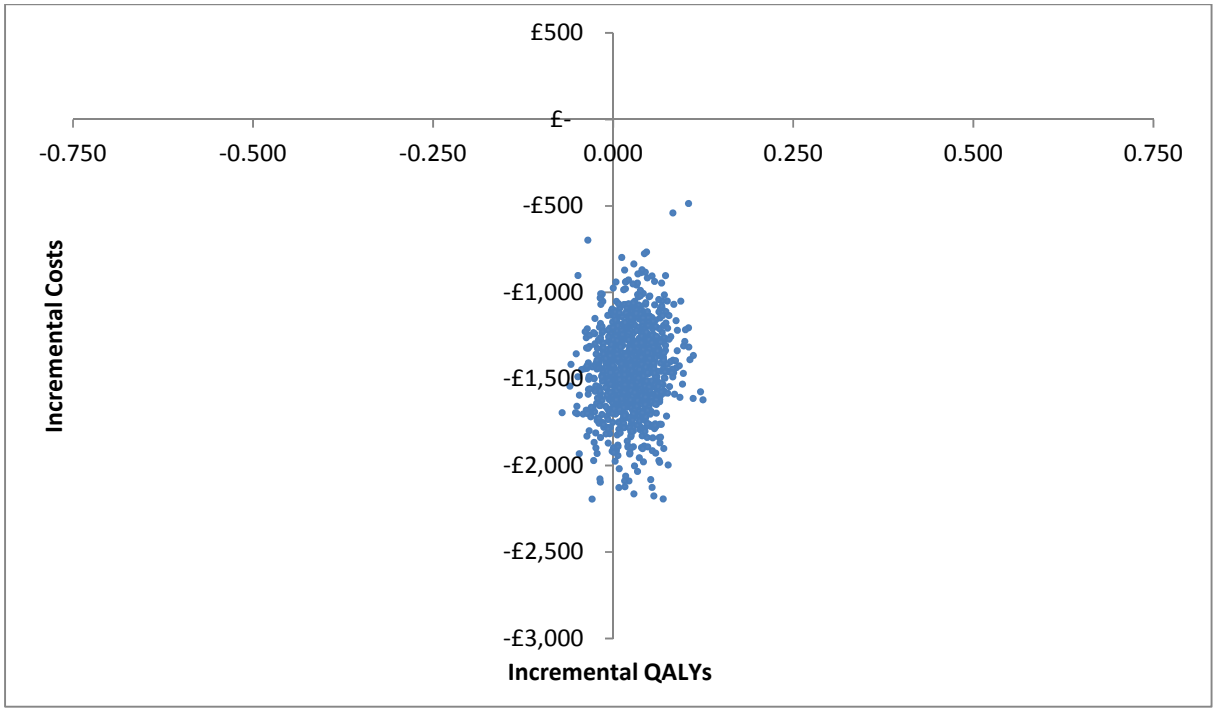
Results of the PSA: 95% CI around incremental QALYs and costs:

Outcome	LL_95% CI	UL_95% CI
Δ QALY	0.194	0.326
Δ Costs	-£723	£308

Add-on to metformin and SU: dapagliflozin versus GLP-1

The figure below presents the scatterplot of the ICER estimates of the PSA. Approximately four-fifths of the estimates are in the lower right-hand quadrant, with dapagliflozin having a 80% probability of being dominant compared to GLP-1. In 20% of the simulations dapagliflozin was estimated to be both less effective and less costly.The 95% confidence intervals around the point estimates for incremental QALY's and costs were estimated accordingly (see corresponding table).

Scatterplot of the ICER estimates of the PSA:



Outcome	LL_95% CI	UL_95% CI
Δ QALY	-0.035	0.083
Δ Costs	-£1,931	-£973

Scenario Analysis

The results of the scenario analyses are summarised in the following tables:

Add-on to metformin and SU: dapagliflozin versus DPP-4

Scenario	ΔCosts	ΔQALYs	ICUR (£/QALY)
Base case	-£109	0.242	Dominant
BMI utility decrements decreased by 10%	-£109	0.218	Dominant
BMI utility decrements decreased by 50%	-£109	0.121	Dominant
BMI utility decrements decreased by 100%	-£109	0.000	£2,358,369
BMI utility decrements based on Bagust et al.	-£109	0.031	Dominant

Add-on to metformin and SU: dapagliflozin versus TZD

Scenario	ΔCosts	ΔQALYs	ICUR (£/QALY)
Base case	-£86	0.622	Dominant
BMI utility decrements decreased by 10%	-£86	0.560	Dominant
BMI utility decrements decreased by 50%	-£86	0.312	Dominant
BMI utility decrements decreased by 100%	-£86	0.003	Dominant
BMI utility decrements based on Bagust et al.	-£86	0.083	Dominant

Add-on to metformin and SU: dapagliflozin versus GLP-1

Scenario	ΔCosts	ΔQALYs	ICUR (£/QALY)
Base case	-£1,380	0.021	Dominant
BMI utility decrements decreased by 10%	-£1,380	0.019	Dominant
BMI utility decrements decreased by 50%	-£1,380	0.012	Dominant
BMI utility decrements decreased by 100%	-£1,380	0.004	Dominant
BMI utility decrements based on Bagust et al.	-£1,380	0.006	Dominant

Summary of Cost Effectiveness

Key points:

- The results of this preliminary analysis confirm the findings of those submitted for dapagliflozin in the dual therapy setting and the add-on to insulin setting. There is a high likelihood that dapagliflozin would be considered cost effective in this setting at conventional thresholds. In each base case comparison, versus DPP-4, TZD and GLP-1, dapagliflozin is dominant.
- Probabilistic sensitivity analyses show dapagliflozin is always likely to be provide superior clinical benefits compared to the DPP-4 class and TZDs. Compared to GLP-1, dapagliflozin is consistently less costly and in 80% of simulations is more effective
- The key variable identified in the main submission as driving the cost effectiveness results is the utility associated with changes in BMI. This variable is therefore extensively tested here by reducing the base case utility decrement by 10%, 50% and 100% in each comparison. Dapagliflozin remains the most economically efficient treatment alternative with the exception of the scenario reducing the BMI utility decrement by 100% in comparison with DPP-4. The apparently high resultant ICER is simply an artefact of the near equivalence of the therapies in this scenario. The impact of the choice of utilities on the ICER is tested further by employing the Bagust et al published values and again, in each comparison dapagliflozin remains dominant.

References

Bailey C et al Lancet 2010 vol. 375 (9733) pp. 2223-33

Cefalu W et al 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, PA, USA, June 8-12 2012; Poster #1056P

Leiter L et al 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, PA, USA, June 8-12 2012; poster #1114

Strojek K et al Diabetes, obesity & metabolism 2011 vol. 13 (10) pp. 928-38

Wilding JPH et al Ann Intern Med 2012 vol. 156 (6) pp. 405-415

CADTH Therapeutic Review Clinical Review: Third-Line Therapy for Patients with Type 2 Diabetes Inadequately Controlled with Metformin and a Sulfonylurea August 2010. Available at http://www.cadth.ca/media/pdf/Diabetes_TR_Clinical_Report_Final_e.pdf

Appendix 1

A systematic review was conducted by the Canadian Agency for drugs and technologies in health(CADTH) for third line therapy for patients with type 2 diabetes inadequately controlled with metformin and sulfonylurea

canadian+triple.unlocked.pdf

http://www.cadth.ca/media/pdf/Diabetes_TR_Clinical_Report_Final_e.pdf