DAPAGLIFLOZIN FOR THE TREATMENT OF TYPE 2 DIABETES: ADDITIONAL ANALYSES REQUESTED BY THE COMMITTEE FOLLOWING THE SECOND MEETING

REPORT BY THE DECISION SUPPORT UNIT

2nd April 2013

Sarah Davis
School of Health and Related Research, University of Sheffield

Decision Support Unit, ScHARR, University of Sheffield, Regent Court, 30 Regent Street
Sheffield, S1 4DA

Tel (+44) (0)114 222 0734
E-mail dsuadmin@sheffield.ac.uk
Website www.nicedsu.org.uk

ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Clinical Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

The production of this document was funded by NICE through its Decision Support Unit. The views, and any errors or omissions, expressed in this document are of the authors only. NICE may take account of part or all of this document if it considers it appropriate, but it is not bound to do so.

Acknowledgements

We thank Jefferson Sheard for his work adapting the C++ code to implement the DSU's changes to the weight profiles within the PSA version of the model.

EXECUTIVE SUMMARY

Following the second committee meeting, NICE asked the decision support unit to further review the economic analysis provided in response to consultation and to perform exploratory analyses, particularly in relation to how changes in weight are modelled over time for the different treatments.

The settings within the manufacturer's models submitted following the ACD for the comparisons of dapagliflozin in combination with metformin (Dapa+MET) against Dipeptidyl peptidase-4 in combination with metformin (DDP4+MET) and sulphonylurea in combination with metformin (SU+MET) did not ensure that the treatment related weight losses for the Dapa+MET and DPP4+MET treatment strategies were regained. Amending the settings to ensure regain of treatment related weight losses in the year following the maintenance period, or at first therapy switch if this occurs first, resulted in substantive changes to the ICERs for Dapa+MET when compared to DPP4+MET and SU+MET. This demonstrated that the relative cost-effectiveness of the add-on to metformin strategies can be changed substantially by changes made to the weight profile over time.

Efficacy data were not available from the 24 week network meta-analysis (NMA) for the SU+MET strategy. We examined whether it was possible to apply the 52 week NMA data to the SU+MET strategy in order to produce a full incremental analysis, but this was not considered appropriate as the incremental cost-effectiveness ratios (ICERs) under this assumption varied substantively from those generated using the pair-wise comparison from Study 4. Therefore a full incremental analysis was only possible for the scenario analysis which used 52 week NMA data.

The cost-effectiveness results are sensitive to changes in the weight profile over time which itself is dependent on the timing of treatment switches. Treatment switches are dependent on the relationship between the baseline HbA1c, treatment related HbA1c changes and the HbA1c threshold for switching therapies. Therefore, the cost-effectiveness of Dapa in dual therapy indications, either as an add-on to metformin or an add-on to insulin, is particularly sensitive to the HbA1c switching threshold, the baseline characteristics and the choice of efficacy estimates (e.g 24 week NMA vs 52 week NMA).

In the version of the model which uses mean parameter values, a small difference in the HbA1c treatment effect between two therapies may result in one having an earlier treatment switch. In the PSA version of the model, the HbA1c treatment effects for the first-line therapies are sampled giving more variation in the duration of time spent on the first therapy and a higher mean duration of treatment.

The scenario analyses conducted demonstrate that the comparisons of Dapa+MET against TZD+MET (thiazolidinedione in combination with metformin) and SU+MET were sensitive to changes made to the weight profiles to achieve weight convergence at the last therapy switch. Scenario analyses were also conducted using the manufacturer's original approach to modelling the relationship between hypoglycaemia episodes and utility which relates the two through a hypoglycaemia fear score (HFS). The cost-effectiveness results were not found to be particularly sensitive to changes in the utility decrements applied in the HFS. It was noted that in many of the scenarios considered, a large proportion of the QALY gain associated with Dapa+MET was attributable to patient preferences regarding weight changes over and above their impact on diabetes complications.

Under the DSU's basecase assumptions, Dapa+MET has an ICER under £20,000 per QALY compared to TZD+MET and SU+MET for both the PSA and mean parameter values versions of the model. The costs and QALYs for DPP4+MET are very similar to those for Dapa+MET, such that both strategies have similar ICERs compared to TZD+MET. In the scenario analysis examining weight convergence at last therapy switch the ICER for Dapa+MET versus TZD+MET was above £30,000 per QALY, but the ICER for Dapa+MET versus SU+MET was still under £30,000 per QALY. Dapa+MET is not cost-effective when conducting a full incremental analysis using the 52 week NMA data, but this may be due to the application of different baseline and efficacy estimates applied, rather than simply due to the addition of the SU+MET comparator within the incremental analysis.

Under the DSU's basecase assumptions, Dapa+INS had an ICER under £20,000 per QALY compared to DPP4+INS for both the PSA and mean values versions of the model. None of the scenario analyses for the add-on to insulin therapy comparison generated ICERs above £20,000 per QALY.

CONTENTS

TABLES & FIGURES

ABBREVIATIONS AND DEFINITIONS

ACD	Appraisal consultation document
BMI	Body mass index
BMS/AZ	Bristol-Myers Squibb / AstraZeneca
CHF	Congestive heart failure
DPP4	Dipeptidyl peptidase-4
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
ICER	Incremental cost-effectiveness ratio
IHD	Ischaemic heart disease
INS	Insulin
MET	Metformin
MRACD	Manufacturer response to the appraisal consultation document
MS	Manufacturer submission
MI	Myocardial infarction
NB	Net benefit
PSA	Probabilistic sensitivity analysis
SBP	Systolic blood pressure
SE	Standard error
SU	Sulphonylurea
TC	Total cholesterol
TZD	Thiazolidinedione
UTI	Urinary tract infection
VBA	Visual basic application
QALY	Quality adjusted life-years

1. INTRODUCTION

1.1. BACKGROUND

In the appraisal consultation document (ACD) the Committee was minded not to recommend dapagliflozin in combination therapy for treating type 2 diabetes and requested further clarification and analyses from the manufacturers (as outlined in section 1.2-1.4 of the ACD). In the manufacturer's response to the ACD (MRACD), the manufacturer provided a revised economic model and analyses which attempted to address the issues raised by the Committee. At the second committee meeting the Committee discussed the MRACD, but concluded that its concerns about the economic model had not been fully resolved. In particular it was unclear about how changes in weight were modelled over time for the different treatments. Because of time constraints in the post-consultation period, the ERG had not been able to explore this issue fully or to conduct any further sensitivity analyses. The Committee concluded that it was unable to decide on the most plausible ICERs or to make a recommendation on dapagliflozin in combination therapy (as add-on to metformin or insulin) for treating type 2 diabetes until these issues have been resolved.

The DSU was requested to review the manufacturers' additional analyses in response to the ACD request, to assess how changes in weight are modelled over time for different treatments within the manufacturer's revised economic model. A description of the data inputs and process used to generate weight profiles is given in Section 2 of this report, followed by some exploratory analyses to show how making different assumptions regarding weight evolution affects the ICER.

The DSU was also requested to conduct a range of further analyses using the revised economic model in order to help the Committee decide on the most plausible ICERs for dapagliflozin in combination therapy as an add-on to insulin and as an add-on to metformin.

The DSU's basecase assumptions, which were made according to the details in the DSU specification document, are described in section 3. The weight profiles under the DSU's base case assumptions and the cost-effectiveness results for the base case scenario and several

scenario analyses are presented in section 4 for the add-on to metformin indication and section 5 for the add-on to insulin therapy comparison.

2. EVOLUTION OF WEIGHT

2.1. INTRODUCTION TO WEIGHT MODELLING

Diabetes treatments have the potential to cause either weight gain or weight loss. In the economic model submitted by Bristol-Myers Squibb / AstraZeneca (BMS/AZ), weight influences cost-effectiveness directly through a health utility change related to BMI changes and indirectly through its influence on the risk of diabetes complications.

Five parameters are used to determine the weight profile for each individual drug in the treatment sequence.

- Starting weight: This is the weight before any treatment related or natural weight gain is applied.
- Treatment related weight change: this is an efficacy outcome which, depending on the scenario, is taken either from a pair wise comparison of trials or from a network meta-analysis
- Years of maintained weight loss / gain: this is a user input
- Years to loss of weight effect: this is a user input
- Natural weight gain of 100g per annum

The process used to generate the weight profile for each treatment in the sequence is as follows;

1) Start weight is set. This is the baseline weight for the first line therapy and the weight for the previous therapy at the time of treatment switch for second and third line therapies
2) Treatment related weight gain is applied in a linear manner during the first year of treatment (in the original submission it was applied immediately, but this assumption was amended to a linear gain over 1 year in in the MRACD).

3) The weight is then fixed at a constant value until the model time is equal to the 'years of maintained weight loss / gain'.
4) The model then uses the 'years to loss of weight effect' variable as a switch to apply two different sets of assumptions depending on whether the value is zero or non-zero as follows;
    a. **When 'years to loss of weight effect' is set to zero**, the weight after the maintenance period is returned to the value expected when applying the treatment related loss (or gain) plus 100g per year. **i.e any treatment related weight change is not reversed.**
    b. **When 'years to loss of weight effect' is non-zero** a linear weight re-gain (or loss) is applied to achieve baseline weight plus weight gain of 100g per year over the number of 'years to loss of weight effect' specified**. i.e treatment related weight changes are reversed over the time period specified.**

    [NB in both 3a and 3b above the 100g per year is applied from end of year 1 not from baseline].
5) When a treatment switch occurs due to loss of HbA1c control, the treatment related weight change is applied to the weight predicted for the previous therapy at the time of treatment switch. Changes made to either the HbA1c control or to the threshold for switching treatment can therefore affect the evolution of weight over time.

2.2. ASSUMPTIONS APPLIED IN THE MANUFACTURER'S ORIGINAL SUBMISSION

The assumptions applied in the manufacturer's original submission are detailed in Table 1. 'Years to loss of weight effect' is set to zero for treatments associated with weight gain. In treatments associated with weight loss, 'years to loss of weight effect' has been set such that the weight regain is completed 1 year before first treatment switch. This ensures that the weight on starting second-line therapy is equivalent to baseline line weight plus 100g per year, over the time from end of year 1 to starting second-line therapy. The data in the last column of Table 1 have been manually adjusted to achieve the assumption that weight regain occurs before first treatment switch. Different values would be required in the final column if any of the data in the previous columns (apart from baseline weight) were to be changed.

The DSU are satisfied that the weight profiles applied in the original submission are consistent with the description provided by the manufacturer in the MRCL and the MRACD. [The comments made by the DSU in their first report regarding 'deltaBMI' values being based on mean rather than sampled parameter values, which were fully addressed in the MRACD].

Table 1 Data inputs for weight profiles in the manufacturer's original submission.

Comparison	Treatment arm	Baseline weight	Treatment related weight change	Years of maintained treatment related weight change	HbA1c threshold (first switch)	Time of first treatment switch (HbA1c> threshold)	Years to loss of weight effect
SU+MET vs Dapa+MET	SU+MET	88.02	1.44	1	8.9	4	0
	Dapa+MET	88.02	-3.22	2	8.9	4	1
DPP4+MET vs TZD+MET vs Dapa+MET	DPP4+MET	90.14	-0.510	2	8.17	6	3
	Dapa+MET	90.14	-2.790	2	8.17	5	2
	TZD+MET	90.14	1.720	1	8.17	7	0
INS+DPP4 Vs INS+Dapa	DPP4+MET	91.40	0.190	1	8.9	7	0
	Dapa+MET	91.40	-1.630	2	8.9	8	5

2.3. ASSUMPTIONS APPLIED IN THE MODELS SUBMITTED FOLLOWING THE ACD

2.3.1. Years to loss of weight effect

The ERG noted in their review of the MRACD that, "the revised dual therapy comparisons with SU and the DPP-IV appear to retain much of the initial weight reduction from dapagliflozin and do not reverse this at therapy switch". This was noted when the ERG examined the models used to generate Scenario (B) in Table 2.3.2.1 of the MRACD. The DSU investigated the cause of this by examining the submitted models. The assumptions applied are given in Table 2. The TZD+MET vs Dapa+MET comparison has been separated from the other add-on to metformin comparisons as the assumptions for dapagliflozin are different in this comparison. The TZD+MET vs Dapa+MET comparison and the add-on to insulin therapy comparison both appear to apply assumptions consistent with those described in the original assumption, in that for treatments associated with weight loss, the 'years to loss of weight effect' is set to a value ensuring weight regain before first treatment switch. However, for the comparisons of SU+MET and DPP4+MET against Dapa+MET the 'years to loss of weight effect' has been set to zero.

The manufacturer states that the 'years to loss of weight effect' variable should be set to zero for any treatment causing weight gain, as it would not be reasonable for treatment related weight gain to reverse when a treatment is finished (see pages 34 and 35 of the MRACD). The application of a zero value to treatments associated with weight loss appears to be an error. It contradicts the description on page 40 of the MRACD where it states, "In the absence of a slope parameter to regulate the rate of loss of weight effect, in order to simulate a linear, gradual regain of weight, the 'years to loss of weight effect' were set to a value such that weight is fully regained by the time of switch to the next treatment line." Furthermore, the MRACD describes this parameter being set to zero only for weight gaining treatments (Table 3.1.2.4 of the MRACD).

Table 2 Data inputs for weight profiles applied for Scenario (B) in Table 2.3.2.1 of the MRACD

Comparison	Treatment arm	Baseline weight	Treatment related weight change	Years of maintained treatment related weight change	HbA1c threshold (first switch)	Time of first treatment switch (HbA1c> threshold)	Years to loss of weight effect
SU+MET vs DPP4+MET vs Dapa+MET	SU+MET	87.84	0.110	1	7.5	3	0
	DPP4+MET	87.84	-1.810	2	7.5	2	**0**
	Dapa+MET	87.84	-4.550	2	7.5	3	**0**
TZD+MET vs Dapa+MET	TZD+MET	87.84	0	1	7.5	3	0
	Dapa+MET	87.84	-4.550	2	7.5	3	1
INS+DPP4 Vs INS+Dapa	DPP4+MET	91.15	0.180	1	9.04	8	0
	Dapa+MET	91.15	-1.640	1	9.04	8	6

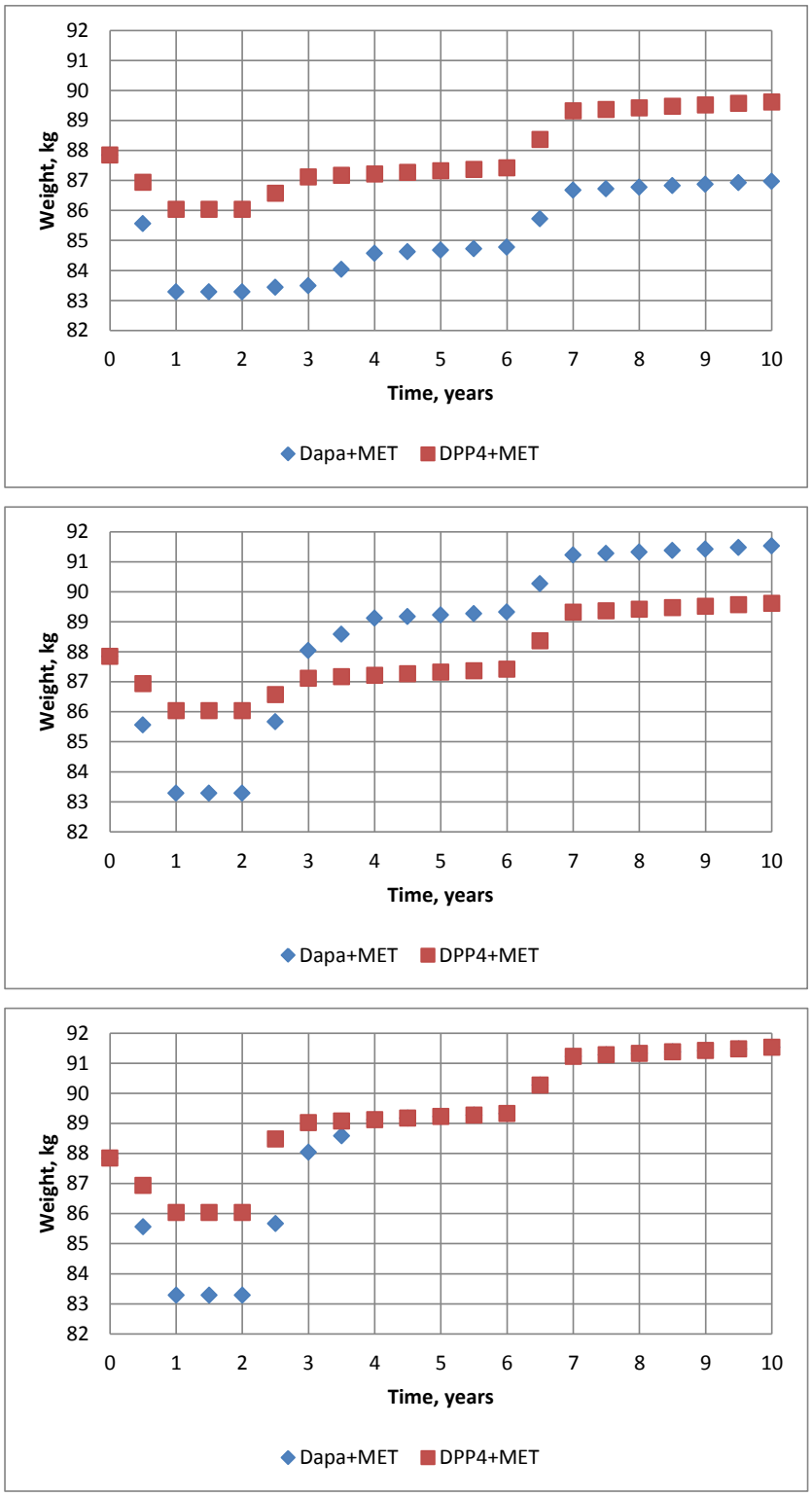
The DSU has explored the impact of setting the 'years to loss of weight effect' to 1 for the DPP4+MET and SU+MET comparisons against Dapa+MET. The impact of this on the weight profiles for DPP4+MET and Dapa+MET can be seen in Figure 1. The weight loss for Dapa+MET is now regained between years 2 and 3 reaching a value 200g over the baseline weight at year 3. A treatment switch to MET+INS occurs at 3 years resulting in a further linear increase in weight to year 4. However, for the DPP4+MET comparator it can be seen that the weight loss is still not regained. The reason for this lies with the way in which the starting weight is set for treatment 2.

Figure 1: Alternative weight profiles for Dapa+MET vs DPP4+MET.

Upper panel:'Years to loss of weight effect' set to zero for both arms.

Central panel: 'Years to loss of weight effect' set to 1 for both arms.

Lower panel: As for central panel but with VBA code amended to ensure regain prior to treatment switch



2.3.1. Starting weight for second-line treatment

For the first-line treatment the starting weight is given by the baseline weight, but for second and third-line therapies it is based on the weight at the time of switching from the previous therapy. This is problematic if the HbA1c rises above the treatment switching threshold before the treatment related weight loss has had time to be regained. An example of this can be seen in the DPP4+MET arm of the comparison against Dapa+MET shown in Figure 1. The HbA1c value on DPP4+MET reaches just over the threshold of 7.5% at year 2 resulting in a therapy switch before the weight loss associated with DPP4+MET has been regained. The starting weight for therapy 2 is therefore the second year weight for therapy 1, before the weight regain has occurred, plus the weight gain associated with therapy 2. This generates a weight difference between the treatment arms which is maintained throughout the model duration.

The DSU has amended the way in which the weight profiles are generated in the VBA (for the mean parameter values model) and in the C++ source code (for the PSA model). In the revised weight profiles, for treatments which cause weight loss, a check is made to see whether the treatment switch occurs prior to the weight loss being regained. If an early treatment switch has occurred, the starting weight of the new therapy is set equal to the weight that would have been achieved after the weight regain period for the previous therapy. The lower panel of Figure 1 shows the impact of this change to the VBA code. It can be seen that for the DPP4+MET comparator, the weight in the year following the first treatment switch includes both the regain of weight loss associated with stopping DPP4+MET at 2 years and a linear increase in weight from year 2 to 3 due to initiation the of MET+INS at 2 years.

2.3.2. Treatment switches for reasons other than loss of HbA1c control

For the ‘mean parameter values’ version of the model, the weight profiles are determined upfront and are then drawn into the PLS. For second and third line therapies, the starting weight and therefore it’s subsequent evolution are dependent on the weight at the time of treatment switches due to loss of HbA1c control. However, within the PLS, treatment

switches can also occur due to treatment discontinuation, but the only data available to the PLS to determine weight at start of next treatment is that based on treatment switches resulting from loss of HbA1c control. So, for example if the model projects 4 years of dapagliflozin treatment with weight regain by year 3, a patient discontinuing first-line therapy at the start of the model will have the weight predicted for a patient starting second-line therapy at 4 years. In effect, they will have jumped ahead several years in terms of their weight progression and therefore their weight on starting second-line treatment will include some natural weight progression from baseline which is unlikely if discontinuation occurs rapidly at the start of a new therapy. Patients experiencing treatment discontinuations will therefore have an additional disutility associated with weight gain, but as the weight changes due to natural weight progression are small compared to those associated with therapy, this is likely to have a small impact on the ICER, and no attempt was made to correct this aspect of the model behaviour.

2.3.3. Impact on the ICERS of changing the assumptions on weight regain

The DSU has explored the impact on the ICERS of setting the time to weight regain to 1 for the comparisons of SU+MET and DPP4+MET against Dapa+MET. This was shown in Figure 1 to have a significant impact on the weight profiles, resulting in much higher weights from year 3 in the Dapa+MET arm. This had a corresponding impact on the ICERs with a substantial rise in the ICER for Dapa+MET vs SU+MET, and a reversal in the direction of incremental costs and benefits for Dapa+MET vs DPP4+MET.

The DSU also explored the impact of amending the code used to generate the weight profiles to ensure that any treatment related weight loss is regained even if a treatment switch occurs before the specified period for weight regain. This was shown in Figure 1 to have a substantial impact on the weight profile or DPP4+MET, bringing it closer to that of Dapa+MET for which a treatment switch occurs at year 3 rather than year 2. This can be seen to have a corresponding impact on the ICER, taking DPP4+MET from dominating Dapa+MET to having an ICER of £23,089.

These exploratory analyses demonstrate that the relative cost-effectiveness of the strategies can be changed substantially by changes made to the weight profile over time.

Table 3 Impact on the ICER of varying weight profiles

Scenario index	Scenario description	DAPA+MET vs SU+MET	DAPA+MET vs DPP4+MET
1	B from Table 2.3.2.1 of the MRACD	£7,735	£3,337
2	Scenario 1 but with 'years to loss of weight effect' set to 1 in both arms	£33,630	Dapa+MET is dominated by DPP4+MET
3	Scenario 2 but with VBA code amended to ensure weight regain by time of therapy switch	£33,630	£23,089

3. DESCRIPTION OF DSU BASE CASE SCENARIO

3.1. DSU BASE CASE SCENARIO

The following assumptions have been applied in the DSU base case scenario to reflect the requests made in section 1.3 of the ACD:

- An annual average cost of £69.09 for pioglitazone based on the latest February 2013 NHS drug tariff.
- An annual cost of £483 (taken from the UKPDS 65 study) for people not experiencing diabetic complications (adjusting the cost for those with complications accordingly to avoid double counting).
- Utility decrements for hypoglycaemia (-0.012 for severe -0.004 for symptomatic) and BMI changes (±0.0061 per unit of BMI).
- Efficacy estimates from the revised 24 week NMA, which incorporates the manufacturer's changes to the WinBUGs programme code to bring it in-line with the recommendations in TSD2.
- Treatment related weight loss is regained during year 3 (retaining the 2 year maintenance of treatment related weight loss) to the level expected in a patient with weight gain since baseline of 0.1kg per year. This assumption is applied to any dual therapy associated with weight loss.
- Zero prevalence of diabetes complications at baseline (as per the manufacturer's original submission).
- HbA1c switching threshold of 7.5% for first and second switch in add-on to metformin indication and for first switch in the add-on to insulin comparison (there is no third line therapy in the add-on to insulin comparison so the threshold is set to 11% to prevent triggering a second switch).

Furthermore, the amendments to the VBA and C++ code to ensure that any treatment related weight losses are regained at first treatment switch, as described in Section 2, were included in the DSU base case assumptions.

4. ADD-ON TO METFORMIN COMPARISON

4.1. DSU BASECASE SCENARIO

4.1.1. Clinical data applied and weight profiles generated

Efficacy estimates from the 24 week NMA were not available for all comparators. It was specified a-priori, in the DSU specification document, that where there was a lack of 24 week NMA estimates from a particular comparator (e.g weight / HbA1c data for MET+ SUA), data from the 52 week NMA would be indirectly applied to allow a full incremental comparison using the 24 week efficacy evidence. The 24 week efficacy evidence was chosen for use in the base case in preference over the 52 week efficacy evidence due to a greater number of studies reporting data at 24 weeks. The efficacy estimates from the 24 week NMA and 52 week NMA are provided in Table 4. The treatment effects for HbA1c, SBP and weight were based primarily on the data found in Tables 11 and 12, on pages 97 to 98 of the appendices to the MRACD. For these outcomes the efficacy results applied in the model are based on the revised NMA using random effects. The unadjusted model was used for weight and SBP, but the baseline adjusted estimates were used for HbA1c. These data were selected by the DSU to ensure consistency with those presented in the MRACD.

We could not see how the data presented in the appendices to the MRACD on symptomatic and severe hypoglycaemia episodes related to the event rates within the submitted models. Therefore, to maintain consistency with the cost-effectiveness results presented in the MRACD, we have applied the event rates from within the submitted models, with those for the 24 week time point being based on the original NMA rather than the revised NMA. The hypoglycaemia event rates are summarised in Table 5.

Table 4 Efficacy estimates applied in the 52 week and 24 week models [adapated from Tables 11 and 12, on pages 97 and p98 of the appendices to the MRACD]

	52 week Absolute treatment effects WMD versus baseline				24 week Absolute treatment effects WMD versus baseline			
	WMD	95% CrI (lower)	95% CrI (upper)	SE	WMD	95% CrI (lower)	95% CrI (upper)	SE
Change in HbA1c (covariate adjustment)†								
	WMD	95% CrI (lower)	95% CrI (upper)	SE	WMD	95% CrI (lower)	95% CrI (upper)	SE
Dapa	-0.92	-1.12	-0.714	0.11	[redacted]	[redacted]	[redacted]	[redacted]
DPP4	-0.84	-0.98	-0.6968	0.07	[redacted]	[redacted]	[redacted]	[redacted]
TZD	-0.90	-1.10	-0.6887	0.11	[redacted]	[redacted]	[redacted]	[redacted]
SU[a]	-0.92	-1.04	-0.80	0.06*	-	-	-	-
Change in weight (kg)								
	WMD	95% CrI (lower)	95% CrI (upper)	SE	WMD	95% CrI (lower)	95% CrI (upper)	SE
Dapa	-4.55	-6.90	-2.204	1.15	[redacted]	[redacted]	[redacted]	[redacted]
DPP4	-1.81	-3.01	-0.6824	0.57	[redacted]	[redacted]	[redacted]	[redacted]
TZD	-	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]
SU[b]	0.11	-0.10	-0.32	0.06*	-	-	-	-
Change in SBP								
	WMD	95% CrI (lower)	95% CrI (upper)	SE	WMD	95% CrI (lower)	95% CrI (upper)	SE
Dapa	-	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]
DPP4	-	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]
TZD	-	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]
SU	-	-	-	-	-	-	-	-

[a] Not presented in Table 11, so taken from Table 8 (Appendix 4 of MRACD)

[b] Not presented in Table 11, so taken from Table 9 (Appendix 4 of MRACD)

All results from unadjusted random-effects models except HbA1c at base

† - random-effects model adjusted for mean HbA1c at baseline (study arm-level);

All data from NMA except hypoglycaemia rates

* calculated from upper and lower CIs

Table 5 Hypoglycaemia rates applied in the 52 week and 24 week models

	52 week Absolute treatment effects WMD versus baseline		24 week Absolute treatment effects WMD versus baseline	
Hypoglycaemia[C]: Symptomatic event rates per annum				
	Mean	SE	Mean	SE
SU	40.3%	2.4%	-	-
Dapa	4.673%	0.62%	7.5%	1.50%
DPP4	4.673%	0.92%	4.9%	0.98%
TZD	8.348%	1.2%	2.3%	0.46%
Hypoglycaemia[C]: Proportion of symptomatic events that are severe				
	Mean	SE	Mean	SE
SU	0.463%	0	-	-
Dapa	0.054%	2.323%	0.0077%	0
DPP4	2.981%	1.701%	0.005%	0
TZD	0.096%	0.310%	0.0024%	0

[C]Hypoglycaemia rates are taken directly from the models submitted and are therefore based on original and not revised 24 week NMA, and the revised 52 week NMA)

The baseline characteristics for the 24 week NMA, 52 week NMA and study 4 populations are provided in Table 6. The choice of baseline characteristics applied in the model is an important factor in determining cost-effectiveness as patients only remain on treatment whist their HbA1c remains below the threshold for treatment switches. Therefore applying a higher baseline HbA1c makes it harder for patients to achieve HbA1c control and remain on a particular treatment even if the efficacy of that treatment is unchanged.

Table 6 Comparison of baseline data for 52 week and 24 week NMA and Study 4

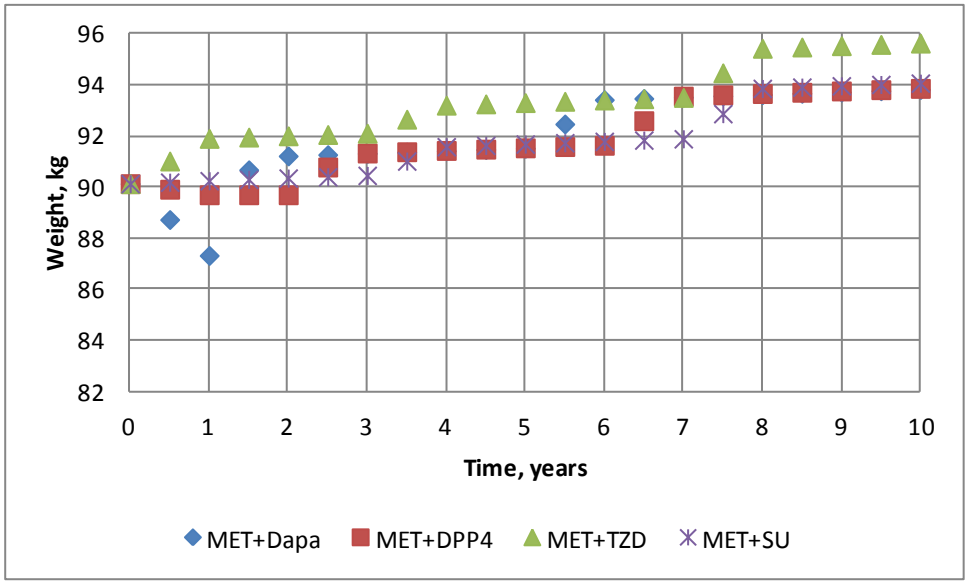
	Data source		
Baseline variable	**Study 4 population**	**24 week NMA population**	**52 week NMA population**
Age	58.4	55.16	57.51
Female	44.9%	44.2%	47.0%
Diabetes duration	6.32	5.03	5.17
Height (m)	1.67	1.7	1.69
Afro-Caribbean	6.2%	6.2%	6.2%
Smokers	17.6%	55.0%	36.9%
HbA1c (%)	7.72	8.17	8.05
Total cholesterol	182.54	185	199.57
HDL-cholesterol	45.87	45.53	44.09
SBP (mmHg)	133.3	133.83	133.3
Weight (kg)	88.02	90.14	87.84

Changes to the efficacy data influence the weight profiles, both directly through differences in the treatment related weight changes and indirectly through differences in the time of treatment switches which are determined by the baseline HbA1c, the treatment effect on HbA1c and the threshold for treatment switches. The weight profiles when using the 24 week efficacy data (52 week for SU+MET) and 24 week baseline characteristics are shown in Figure 2 for a treatment switching threshold of 7.5%. In the manufacturer's original submission, the HbA1c thresholds for treatment switches were set equal to the HbA1c at baseline for the population used to determine the efficacy. In the DSU basecase assumptions, the switching threshold has been set to 7.5% to reflect the HbA1c levels that are currently recommended in the NICE guideline, 'Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87)'. Under the manufacturer's original basecase assumption, any first-line therapy with a negative HbA1c change will be considered to have achieved the treatment target. Whilst under the DSU's assumption, HbA1c reductions of 0.22, 0.67 and 0.55 are required to achieve the HbA1c treatment target of 7.5% for the Study 4, 24 week NMA and 52 week NMA populations respectively.

It can be seen in Figure 2, that the application of the 7.5% HbA1c threshold for switching therapies results in a treatment switch from Dapa+MET to INS+MET in the second year,

whilst in the comparator strategies, the first treatment switch happens at 3 years. The second treatment switch also occurs at different times for the different strategies.

Figure 2 Weight profiles when using the 24 week efficacy data and 24 week baseline data (as per manufacturer's original submission) except for MET+SU which uses 52 week efficacy data.



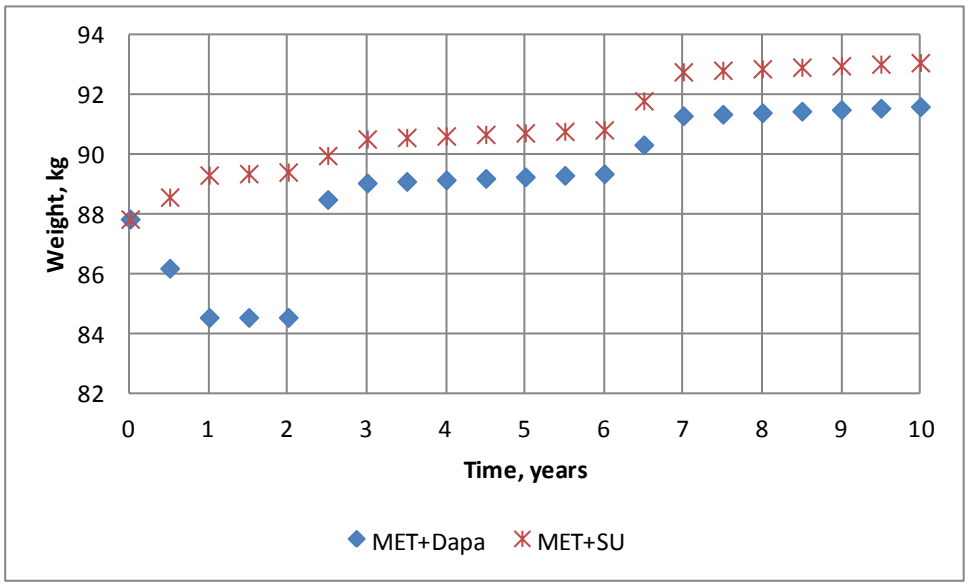
The application of the 52 week NMA data to replace the missing 24 week data NMA for SU+MET was validated by comparing the ICERs generated with those produced when using data from the within trial pair-wise comparison (i.e Study 4) at 24 weeks. In both cases the baseline characteristics from the 24 week NMA population were applied to isolate the influence of the efficacy data from any changes resulting in different baseline characteristics. The results are summarised in Table 7. This showed that the ICER was substantially different when using the efficacy data from Study 4. It was therefore not considered to be appropriate to include SU+MET in the base case incremental analysis by indirectly applying data from the 52 week NMA.

Table 7 Validation of indirect comparison of SU+MET vs Dapa+MET (with baseline characteristics as per 24 week NMA)

Technologies	Total per treatment arm		Incremental vs SU+MET		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	ICER
Using 24 week NMA for Dapa+MET and 52 week NMA for SU+MET					
SU+MET	£14,884	11.830			
Dapa+MET	£14,497	11.829	£613	-0.001	Dapa+MET is dominated by SU+MET
Using Study 4 efficacy data for both arms					
SU+MET	15,103	11.773			
Dapa+MET	15,478	11.826	£367	0.053	£7,149

Instead a separate pair-wise comparison was conducted using the baseline and efficacy data from Study 4, which is consistent with the approach taken in the manufacturer's original submission. The weight profiles for the pair wise comparison using clinical data from Study 4 are given in Figure 3.

Figure 3 Weight profiles for Dapa+MET and SU+MET using clinical data from Study 4



4.1.2. Incremental comparison of DPP4+MET, TZD+MET and Dapa+MET based on 24 week NMA

The cost-effectiveness results for the incremental comparison DPP4+MET, TZD+MET and Dapa+MET based on 24 week NMA are given in Table 8. The incremental costs and QALYs vs the TZD+MET strategy which has the lowest costs and QALYs are shown in Figure 4. A detailed breakdown of the events and costs for the three strategies in the indirect comparison is given in Appendix A.

The incremental comparison shows that whilst Dapa+MET has an ICER under £20,000 per QALY when compared to TZD+MET, DPP4+MET also has an ICER under £20,000 per QALY when compared to Dapa+MET. Therefore, Dapa+MET would not be the most cost-effective treatment when applying a threshold of £20,000 per QALY.

The proportion of the QALY gain attributable to patient preferences regarding weight changes over and above their impact on diabetes complications was estimated by setting the utility/disutility per unit of BMI change to zero (formerly 0.0061 in the DSU assumptions). For this scenario, the lifetime discounted QALY gain for TZD+MET was greater than that for Dapa+MET or DPP4+MET resulting in TZD+MET dominating the other two dual therapy options. This is expected from the clinical data, as TZD+MET has a greater effect on both HbA1c and SBP than the other two dual therapy option, but is associated with weight gain rather than the weight loss associated with the other two strategies. Under the DSU's assumptions, in which the latest drug tariff cost for pioglitazone is applied, the annual drug cost for TZD is much lower than that for either DPP4 or Dapagliflozin. These results suggests that the cost-effectiveness of both Dapa+MET and DPP4+MET when compared to TZD+MET is being driven by their impact on weight, and patient preferences regarding weight changes over and above their impact on diabetes complications.

Figure 4 Cost-effectiveness plane for DSU base case scenario

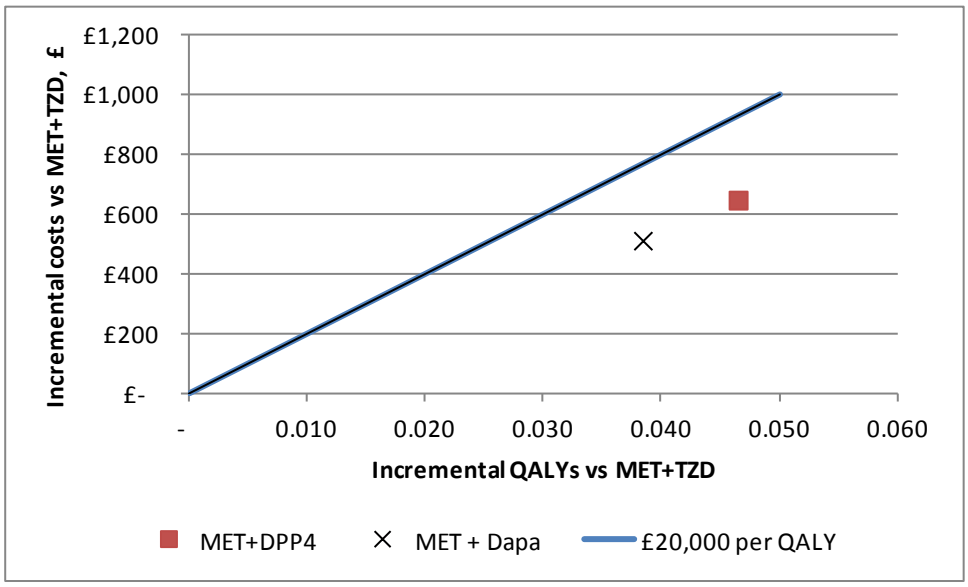


Table 8 Cost effectiveness results for DSU assumptions using mean parameter values

Technologies	Total per treatment arm		Incremental vs TZD+MET		ICER vs TZD+MET	Incremental analysis*
	Costs (£)	QALYs	Costs (£)	QALYs		ICER (£)
TZD+MET	£14,985	11.790	-	-		
Dapa+MET	£15,497	11.829	£ 513	0.038[a]	£13,338	£13,338
DPP4+MET	£15,633	11.837	£ 648	0.046[a]	£13,947	£16,847

*ICER vs next least effective non-dominated strategy

[a]Incremental QALY is <0 when excluding patient preferences regarding weight changes over and above their impact on diabetes complications

The results of the incremental analysis based on mean outputs from 1000 PSA samples are given in Table 9. From this it can be seen that the incremental cost of Dapa+MET is greater when using the mean output of the PSA model, than when using the model that uses mean parameter values. The differences in costs appear to be due to a longer duration of treatment for all first-line therapies which results in higher treatment costs and a higher incremental cost between Dapa+MET and TZD+MET. We believe that this is due to the interaction between baseline HbA1c values, the treatment switching threshold and the efficacy data resulting in a different mean duration on first-line therapy. In the mean values version of the

model, the duration spent on the first therapy is essentially fixed, but in the PSA it varies with variation in the HbA1c effect estimated for the first treatment. This causes a corresponding change to the weight profiles which has a great influence on the cost-effectiveness. This is particularly noticeable in the comparison between DPP4+MET and Dapa+MET, where there is an early first switch in the Dapa+MET strategy when applying the mean effect on HbA1c, but this is due to a very small difference in HbA1c between the two arms with DPP4+Met falling just below the threshold at 1 year and Dapa+Met falling above the threshold at one year. This explains why the absolute costs and QALYs for the Dapa+MET strategy and the DPP4+MET strategy are much closer Table 9, which presents mean outcomes from the PSA, than in Table 8 which presents outcomes based on mean parameters values.

Table 9 Cost-effectiveness results for DSU assumptions: mean results across 1000 parameter samples

Technologies	Total per treatment arm		Incremental vs TZD+MET		ICER vs TZD+MET	Incremental analysis*	Likelihood of having maximum NB at £20K /£30K per QALY
	Costs (£)	QALYs	Costs (£)	QALYs		ICER (£)	
TZD+MET	£14,937	11.741	-	-			24.1% / 15.8%
Dapa+MET	£15,584	11.784	£647	0.042	£15,257	£15,257	40.4% / 42.7%
DPP4+MET	£15,601	11.784	£664	0.043	£15,511	£41,654	35.5% / 41.5%

*ICER vs next least effective non-dominated strategy

4.1.3. Pair-wise comparison of Dapa+MET and SU+MET using clinical data from Study 4

The pair-wise comparison of Dapa+MET against SU+MET using data from Study 4 gives an ICER of £12,405 as shown in Table 10. A detailed breakdown of the event rates and costs are given in Appendix A for the pair-wise comparison using study 4.

It should be noted that 84% of the incremental QALY gain is related to patient preferences regarding weight changes.

Table 10 Cost-effectiveness results for Dapa+MET versus SU+MET using DSU assumptions and clinical data from Study 4: Results based on mean parameter values

Technologies	Total per treatment arm		Incremental vs SU+MET		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	ICER
Using Study 4 efficacy data for both arms, with baseline characteristics as per Study 4					
SU+MET	13,827	11.172			
Dapa+MET	14,579	11.232	£752	0.061*	£12,405

*84% of QALY gain is attributable to patient preferences regarding weight changes over and above their impact on diabetes complications. Without BMI related utility the incremental QALY is 0.010

Table 11 Cost-effectiveness results for Dapa+MET versus SU+MET using DSU assumptions and clinical data from Study 4: mean results across 1000 parameter samples

Technologies	Total per treatment arm		Incremental vs SU+MET		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	ICER
Using Study 4 efficacy data for both arms, with baseline characteristics as per Study 4					
SU+MET	13,747	11.103			
Dapa+MET	14,673	11.164	£926	0.061	£15,148

The results for the PSA when using Study 4 to provide both efficacy and baseline characteristics for the comparison of Dapa+MET against SU+MET are given in Table 11. The incremental costs are higher than the results based on the mean parameter values resulting in an ICER of £15,148. The increase in the incremental cost is due to a longer duration of first-line treatment in both arms of the model when using the PSA version of the model. In the model which uses mean parameter values, there is a treatment switch at 2 years due to the HbA1c being just above threshold. However, in the PSA model, the HbA1c treatment effect is sampled giving more variation in the timing of the first treatment switch

and leading to a higher mean treatment duration for the first therapy in the sequence. Dapa+MET has the highest NB for 61.0% of parameter samples when valuing a QALY at £20,000 and 72.7% of samples when valuing a QALY at £30,000.

4.2. ADD ON TO METFORMIN: SCENARIO ANALYSES

Each of the scenario analyses presented below explores a single change to the DSU basecase scenario presented in section 3.1 and maintains all other DSU assumptions described in section 3.1.

4.2.1. Scenario analyses using original HFS

In the DSU's basecase scenario the relationship between hypoglycaemic events and utility which is based on the HFS was amended by dividing the utility coefficients in the HFS by 4. In this scenario analysis, this change was reversed to give the manufacturer's original relationship between hypoglycaemia events and utility.

In the incremental analysis of TZD+MET, DPP4+MET and Dapa+MET, shown in Table 12, it can be seen that Dapa+MET is extendedly dominated. The incremental QALY gain of Dapa+MET vs TZD+MET is reduced due to a the larger disutility associated with hypoglycaemia which affects the QALYs gained for Dapa+MET more than TZD+MET due to the higher rate of hypoglycaemia episodes and a greater chance that they are severe under Dapa+MET compared to TZD+MET. Dapa+MET is still cost-effective compared to TZD+MET when considering a pair-wise comparison rather than a full incremental analysis.

Table 12 Cost effectiveness results for DSU assumptions but applying original HFS

Technologies	Total per treatment arm		Incremental vs TZD+MET		ICER vs TZD+MET	Incremental analysis*
	Costs (£)	QALYs	Costs (£)	QALYs	ICER	ICER (£)
TZD+MET	£14,985	11.688	-	-	-	-
Dapa+MET	£15,497	11.720	£ 513	0.032[a]	£16,195	Extendedly dominated
DPP4+MET	£15,633	11.736	£ 648	0.048[a]	£13,535	£8,359

*ICER vs next least effective non-dominated strategy

[a] Incremental QALY gain (vs TZD+MET) is <0 when patient preferences regarding weight changes over and above their impact on diabetes complications are removed.

The cost-effectiveness results for Dapa+MET compared to SU+MET when using the pair-wise comparison based on Study 4 and the manufacturer's original HFS, are summarised in Table 13. The ICER is £10,317 when using the manufacturer's original HFS whereas it was £12,405 when applying the changes to the HFS specified in the ACD.

Dapa+MET has a lower hypoglycaemia risk than SU+MET (40.8% vs 3.5% based on the data in the submitted model which uses Study 4 clinical data) and therefore the incremental QALY gain is increased when applying a greater utility decrement for hypoglycaemia. Consequently a smaller proportion of the overall QALY gain is directly attributable to patient preferences regarding weight changes (70% down from 84%).

Table 13 Pair wise comparison for SU+MET vs Dapa+MET using data from Study 4 and DSU assumptions but applying original HFS

Technologies	Total per treatment arm		Incremental vs SU+MET		ICER
	Costs (£)	QALYs	Costs (£)	QALYs	ICER
Using Study 4					
SU+MET	13,827	11.066			
Dapa+MET	14,579	11.139	£752	0.073[a]	£10,317

[a]70% of incremental QALY attributable to patient preferences regarding weight changes over and above their impact on diabetes complications. Without BMI related utility the incremental QALY is 0.022

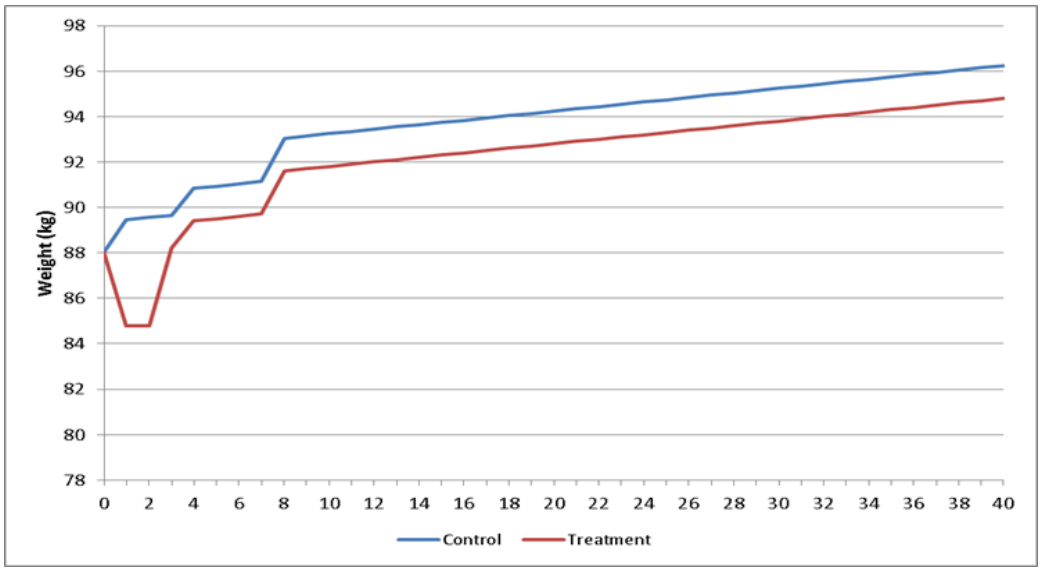
4.2.2. Scenario analysis with weight convergence at last therapy switch

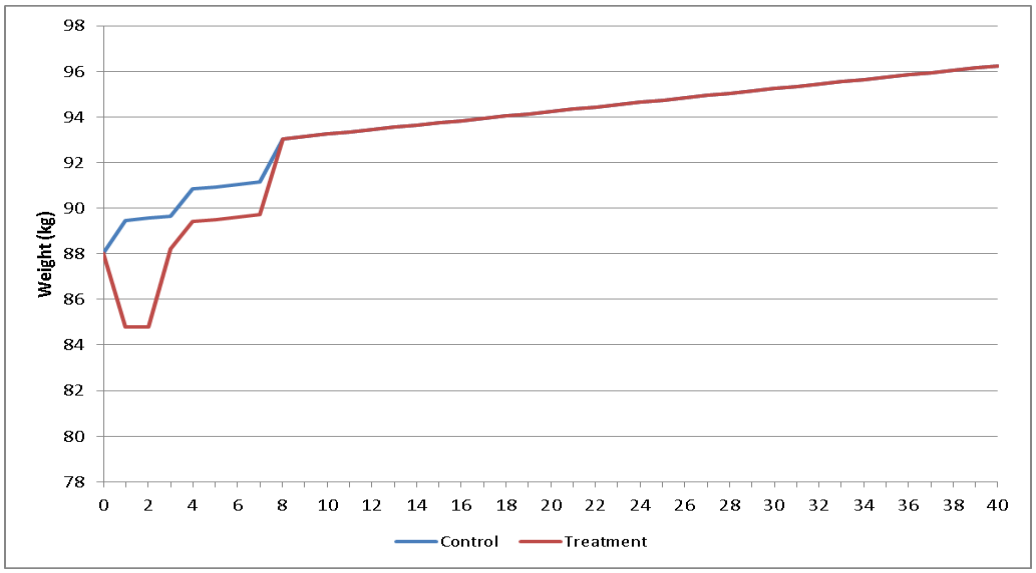
The MRACD included a description of how to achieve weight convergence at last therapy switch by adjusting the weight gain of the last treatment in the sequence. In the manufacturer's example (Figure 3.1.2.5 on page 37 of the MRACD), the treatment arm (Dapa+MET) was associated with weight loss and the comparator arm (SU+MET) was associated with weight gain. Weight convergence was therefore achieved by increasing the weight gain for the last treatment in the sequence (insulin therapy) for the treatment sequence starting with Dapa+MET. The impact of this assumption on the weight profile for SU+MET vs Dapa+MET when using the baseline and efficacy data from Study 4 can be seen by comparing the upper and lower panels of Figure 5 which reproduces Figures 3.1.2.4 and 3.1.2.5 from the MRACD.

Figure 5 Predicted progression of weight over time; Dapa+MET vs SU+MET (clinical data from Study 4)

Upper panel: basecase scenario

Lower panel: scenario analysis with weight convergence achieved by altering the weight gain associated with insulin therapy for the strategy starting with Dapa+MET

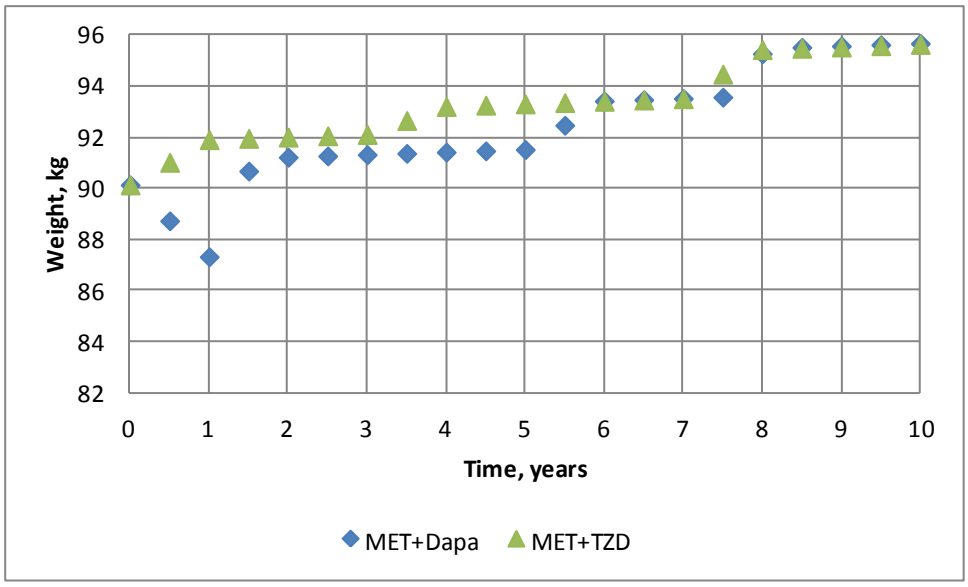




In the comparison between SU+MET and Dapa+MET, the treatment switch for both therapies occurs at the same time meaning that any additional weight gain applied to the Dapa+MET arm at the start of insulin therapy coincides with the weight gain at the start of insulin therapy for the comparator strategy. However, for the other comparisons, once the data from the revised 24 week NMA and the revised threshold for switching treatments have

been applied, this results in different switching times between the strategies being compared. It did not seem appropriate for the Dapa+MET arm to have an additional weight gain at the start of insulin therapy which is applied prior to the treatment switch to insulin in the comparator strategy. We have therefore amended the VBA code to set the starting weight for the last treatment in the Dapa+MET strategy equal to the starting weight for last treatment in the comparator strategy at the time that the comparator treatment switches to the last treatment. For the comparisons against DPP4+MET this did not have a large impact on the weight profiles as the weights were already similar at last treatment switch. However, for the comparisons against, TZD+MET, this had a large impact on the weight profile as an additional weight gain was applied in the Dapa+MET strategy at the time of last therapy switch in the TZD+MET strategy to achieve weight convergence. The weight profile achieved by the changes to the VBA is shown in Figure 6 for the TZD+MET and Dapa+MET comparison.

Figure 6 Weight profiles for Dapa+MET and TZD+MET when requiring weight convergence at last therapy switch.



The weight profiles achieved for the comparison of SU+MET against Dapa+MET with the DSU's changes to the VBA code are shown in Figure 7. These are similar to the profiles achieved using the manufacturer's approach, with slight differences at 2.5 years and 6.5 years in the Dapa+MET strategy due to the DSU modifications to the VBA.

Figure 7 Weight profiles for SU+MET and Dapa+MET when using clinical data from Study 4.

Upper panel: DSU base case assumptions.

Lower panel: Weight convergence at last therapy switch.

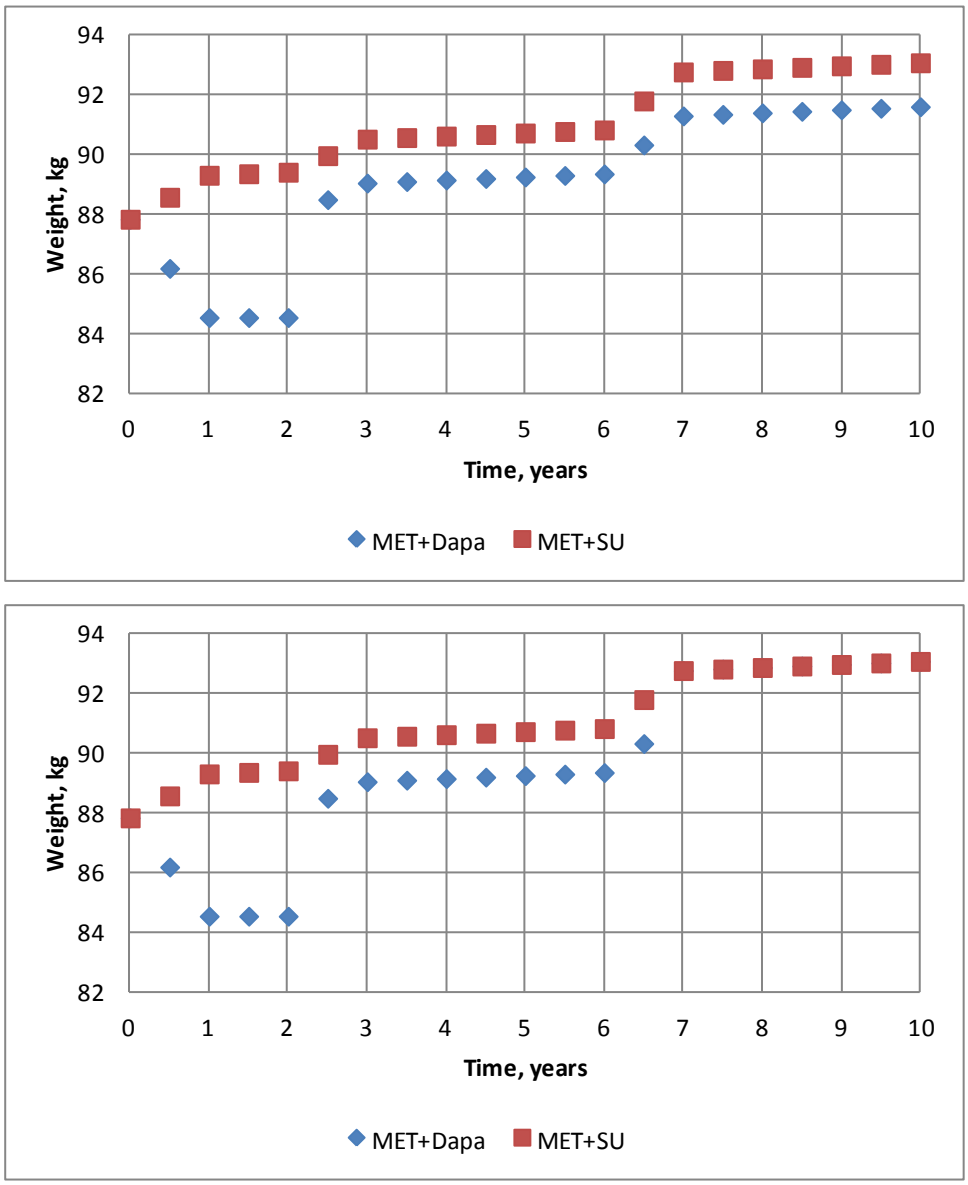


Table 14 shows pair-wise comparisons for the add-on to metformin indication. An incremental analysis is not appropriate for this scenario as the weight profiles for Dapa+MET are not consistent between the different pair-wise comparisons.

It can be seen that the ICER for Dapa+MET vs TZD+MET has been substantially increased from£13,338 to £60,965 by the assumption that weight should converge at last therapy switch. Conversely applying this assumption to the comparison between DPP4+MET and

Dapa+MET had no noticeable impact on the ICER as the weights were already very similar at last therapy switch under the base case assumptions. For the pair-wise comparison of SU+MET against Dapa+MET, the ICER is increased from £12,403 to £21,200 when requiring weight convergence at last therapy switch.

Table 14 Cost effectiveness results for DSU assumptions but with weight convergence at last therapy switch: results based on mean parameters values

Technologies	Efficacy and baseline data	Total per treatment arm		Incremental		ICER
		Costs (£)	QALYs	Costs (£)	QALYs	
TZD+MET	24 week NMA	£14,984	11.791	-	-	
Dapa+MET		£15,536	11.800	£552	0.009[a]	£60,965
Dapa+MET	24 week NMA	£15,499	11.827	-	-	
DPP4+MET		£15,633	11.837	£134	0.010[a]	£16,847^
SU+MET	Study 4	13,827	11.172	-	-	
Dapa+MET		14,611	11.209	£784	0.037[a]	£21,200

*ICER vs next least effective non-dominated strategy

^ for DPP4+MET vs Dapa+MET

[a]When excluding patient preferences regarding weight changes over and above their impact on diabetes complications, the incremental QALY gain is <0 vs TZD+MET, 0.006 vs DPP4+MET and 0.010 vs SU+MET

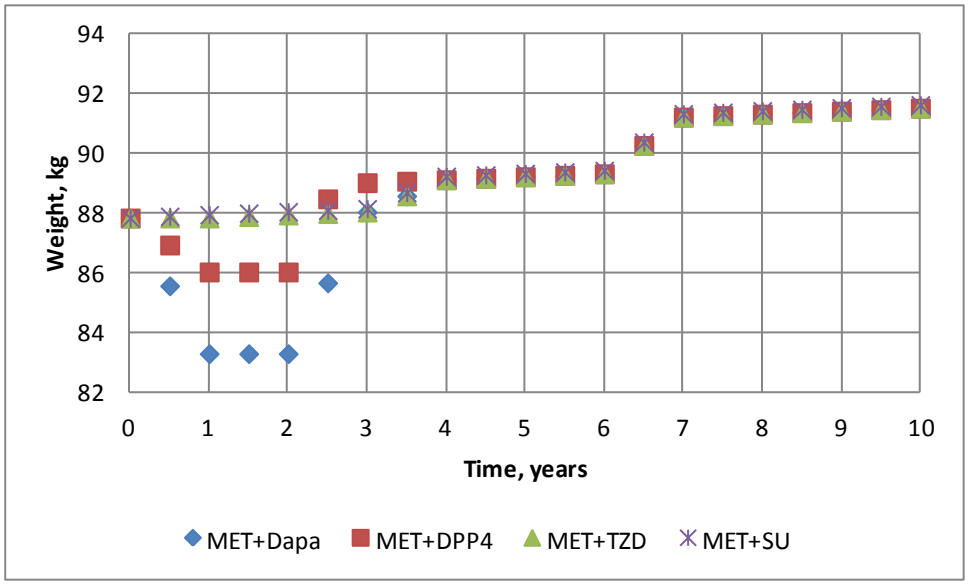
NB: The DSU were unable to extract PSA results for the weight convergence scenario in the time frame available.

4.2.3. Scenario analysis using 52 week NMA

A scenario analysis using the 52 week NMA data in place of the 24 week NMA has been conducted. The 52 week NMA data were taken directly from the models submitted by the manufacturer following the ACD.

The weight profiles when applying the efficacy and baseline values from the 52 week NMA are shown in Figure 8. It can be seen that there is treatment switch in the DPP4+MET arm at year 2 resulting in an earlier rise in weight than in the other arms where the first treatment switch occurs at year 3.

Figure 8 Weight profiles when applying the 52 week NMA efficacy and baseline data



The results for this scenario, presented in Table 15 and Figure 9, show that Dapa+MET is not cost-effective when conducting a full incremental analysis using the 52 week NMA data. Dapa+MET has an ICER substantially over £30,000 per QALY when making pair-wise comparisons against either SU+MET (£61,988 per QALY) or TZD+MET (£94,466 per QALY). The higher mean duration of first-line therapy for Dapa+MET in this scenario compared to the basecase scenario, which used the 24 week NMA data, results in Dapa+MET having a higher incremental cost compared to the lower cost SU+MET and TZD+MET strategies. Dapa+MET has an ICER of £25,604 when compared directly to DPP4+MET, but

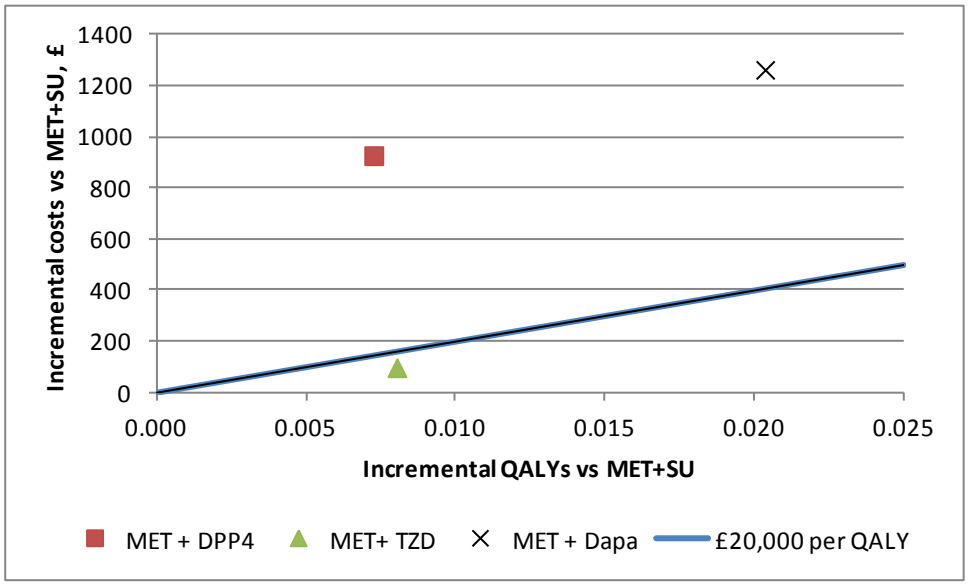
DPP4+MET is dominated by TZD+MET. A detailed breakdown of the costs and event rates for this scenario is given in Appendix A.

Table 15 Cost-effectiveness results for DSU basecase but using 52 week efficacy data instead of 24 week efficacy data:based on mean parameter values

Technologies	Total per treatment arm		Incremental vs SU+MET			Incremental analysis
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£) Incremental cost per QALY gained	ICER (£) Incremental cost per QALY gained
SU+MET	14009	11.294	-	-	-	
DPP4+MET	14936	11.301	927	0.007[a]	127,738	Dominated by TZD+MET
TZD+MET	14107	11.302	97	0.008[a]	12,108	12,108
Dapa+MET	15272	11.314	1263	0.020[a]	61,988	94,466

[a]When patient preferences regarding weight changes, over and above those related to diabetes complications are removed, incremental QALY gain (versus SU+MET) is <0 for DPP4+MET, 0.005 for TZD+MET and 0.001 for Dapa+MET

Figure 9 Cost-effectiveness plane for DSU basecase but using 52 week efficacy data instead of 24 week efficacy data



5. ADD ON TO INSULIN COMPARISON

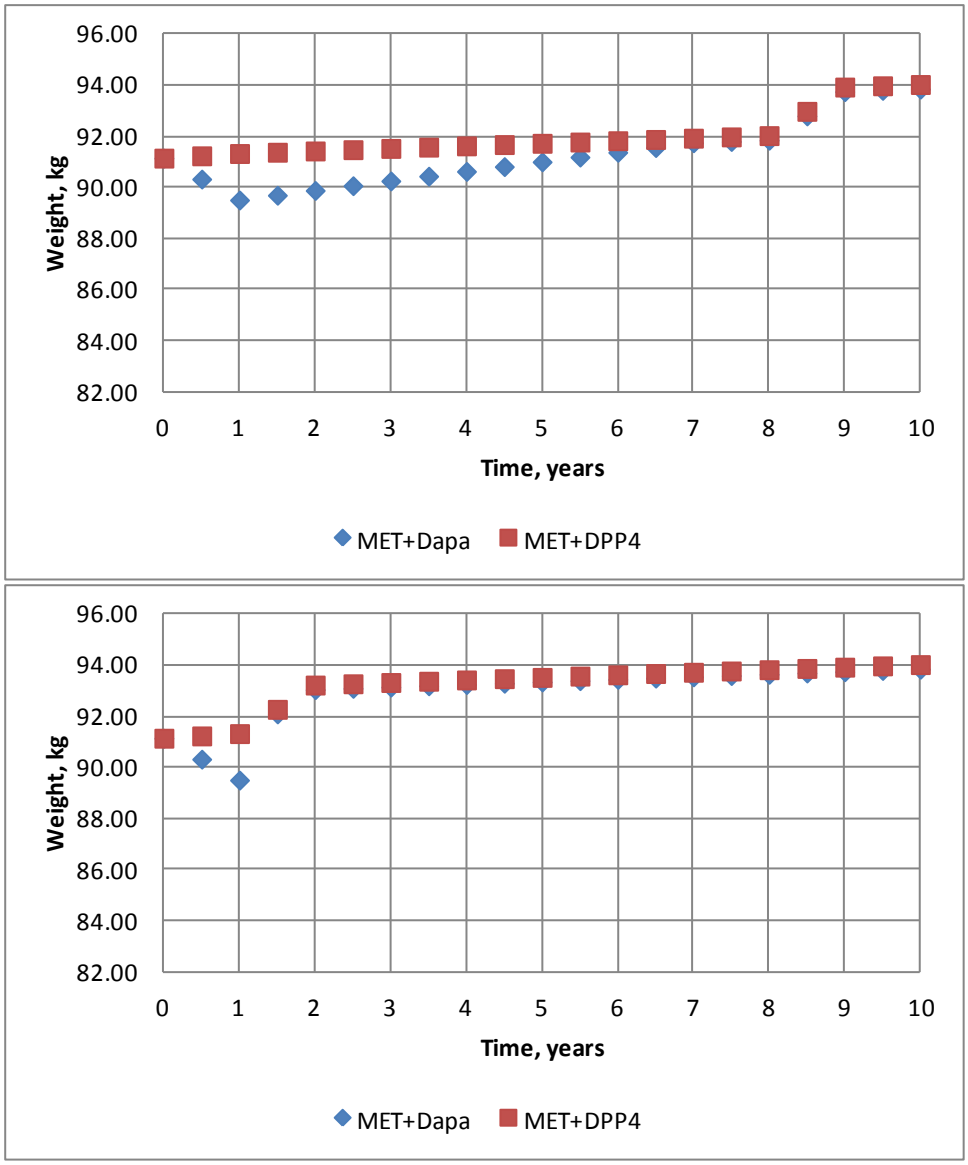
5.1. WEIGHT PROFILES WHEN APPLYING THE DSU'S BASECASE ASSUMPTIONS

In the manufacturer's original and revised base case scenario for the add-on to insulin indication, the time to weight regain was set to occur before first treatment switch. The HbA1c threshold for treatment switching was set to 9.04% in the manufacturer's revised basecase which gave a treatment switch at 8 years.

In line with the DSU's base case scenario described in section 3.1, we have explored the impact of setting the time to weight regain to 1 year and the switching threshold to 7.5%. As can be seen from Figure 10, these changes result in a substantial change in the weight profile due to a treatment switch at 1 year. Weight regain would have occurred at year 3 in the absence of a therapy switch due to loss of HbA1c control.

The results for the DSU basecase assumptions are presented in Section 5.1. Given that changes to the weight profiles were found to have a large impact on the ICERs, in the exploratory analyses conducted for the add-on to metformin indication, results for the manufacturer's assumptions regarding weight regain are presented in a scenario analysis (Section 5.2.1).

Figure 10 Weight profiles for the manufacturer's revised basecase (upper panel) and the DSU's assumptions (lower panel). Both have treatment related weight losses regained at first treatment switch but this occurs at 8 years and 1 year respectively.



5.2. RESULTS FOR DSU ASSUMPTIONS

Dapa+INS has an ICER of £3,706 compared to DPP4+INS when using the version of the model that applies mean parameter values, as shown in Table 16. The incremental cost is low as DPP4 and dapagliflozin have similar drug costs, and the time spent on the first treatment combination in the sequence is only 1 year under the DSU's base case assumptions. A detailed breakdown of event rates and costs are provided in Appendix B.

Table 16 Cost-effectiveness of Dapa+INS vs DPP4+INS using DSU assumptions: results based on mean parameter values

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
DPP4	£ 17,553	11.497	-	-	
Dapagliflozin	£ 17,609	11.512	+£ 56	0.015*	£ 3,706

*50% of QALY gain is attributable to patient preferences regarding weight changes over and above their impact on diabetes complications. Without BMI related utility the incremental QALY is 0.008

The PSA results averaged across 1000 parameter samples are given in Table 17. The incremental cost is greater in the PSA results than in the results based on mean parameter values. This is mainly due to a higher incremental treatment cost. The average duration of time spent on the first treatment in the sequence is around 1.5 years for both arms in the PSA and just under 1 year in the model which uses mean parameter values. This increase in time spent on first-line therapy increases the incremental cost of the Dapa+INS strategy. The longer duration on first-line therapy occurs because the difference between the starting HbA1c (9.04%) and the threshold (7.5%) is greater than the HbA1c treatment effect for both Dapa+INS (mean -0.84%, SE 1.72%) and DPP4+INS (mean -0.73%, SE 1.24%). In the mean values version of the model, the treatment effect is fixed and so all patients switch treatment

at 1 year, whereas in the PSA, the treatment effect is sampled allowing some patients to have a greater reduction in HbA1c and to switch treatment at a later time point. The longer time spent on first-line therapies results in an increase in both incremental costs and incremental QALYs, but on balance the ICER is increased.

Table 17 Cost-effectiveness of Dapa+INS vs DPP4+INS using DSU assumptions: results based on mean across 1000 PSA samples

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
DPP4	£ 17,750	11.411	-	-	
Dapagliflozin	£ 17,887	11.430	+£ 137	0.019	£ 7,402

5.3. ADD-ON TO INSULIN: SCENARIO ANALYSES

5.3.1. Results for manufacturer weight profile

The results when applying the manufacturer's weight profile are given in Table 18. A detailed breakdown of event rates and costs are provided in Appendix B.

It can be seen that the weight profile applied in the manufacturer's basecase results in higher incremental costs than the weight profile applied under the DSU's basecase assumptions for weight regain. This is due to patients spending more years on dual therapy prior to switching to insulin monotherapy. The manufacturer's weight profile also results in higher QALY gains which appear to be driven by fewer complications being prevented under the DSU's assumptions.

Table 18 Cost-effectiveness of Dapa+INS vs DPP4+INS using DSU assumptions but manufacturer weight profile: results based on mean parameter values

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
DPP4	£ 19,594	11.471	-	-	
Dapagliflozin	£ 19,878	11.493	+£ 293	+0.022*	£ 12,879

*71% of QALY gain is attributable to patient preferences regarding weight changes over and above their impact on diabetes complications. Without BMI related utility the incremental QALY is 0.006

5.3.2. Scenario analysis using original HFS

Cost-effectiveness results are presented in Table 19 for the scenario analysis which uses the manufacturer's original HFS values to calculate the utility of hypoglycaemia. All other DSU changes to the manufacturer's basecase scenario have been maintained including the DSU's weight profile. All costs and events are the same as for the DSU's base case assumptions. It can be seen that the QALY gains are increased from 0.015 to 0.019, which lowers the ICER from £3,706 to £2,959.

Table 19 Cost-effectiveness of Dapa+INS vs DPP4+INS using DSU assumptions but manufacturer's approach to HFS (discounted results per patient based on mean parameter values)

Technologies	Total		Incremental		ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs	Incremental cost per QALY gained
DPP4	£ 17,553	11.330	-	-	
Dapagliflozin	£ 17,609	11.349	+£ 56	0.019*	£ 2,959

*40% of QALY gain is attributable to patient preferences regarding weight changes over and above their impact on diabetes complications. Without BMI related utility the incremental QALY is 0.011.

5.3.3. Scenario analysis using 52 week efficacy data

Scenario analyses using 52 week efficacy data were not possible for this comparison as these data were not presented in Appendix 4 of the MRACD.

5.3.4. Scenario analysis with weight convergence at last therapy switch

Scenario analyses examining convergence at last therapy switch were not conducted as the weight difference between treatment and control at last therapy switch was only 0.18kg in the two scenarios already considered. Removing this small difference is not expected to result in a significant change in the ICER.

6. CONCLUSIONS

The settings within the manufacturer's models submitted following the ACD for the comparisons of Dapa+MET against DDP+MET and SU+MET did not ensure that the treatment related weight losses for the Dapa+MET and DPP4+MET treatment strategies were regained. Amending the settings to ensure regain of treatment related weight losses in the year following the maintenance period, or at first therapy switch if this occurs first, resulted in substantive changes to the ICERs for Dapa+MET when compared to DPP4+MET and SU+MET. This demonstrated that the relative cost-effectiveness of the add-on to metformin strategies can be changed substantially by changes made to the weight profile over time.

Efficacy data were not available from the 24 week NMA for the SU+MET strategy. We examined whether it was possible to apply the 52 week NMA data to the SU+MET strategy in order to produce a full incremental analysis, but this was not considered appropriate as the ICERs under this assumption varied substantively from those generated using the pair-wise comparison from Study 4. Therefore a full incremental analysis was only possible for the scenario analysis which used 52 week NMA data.

The cost-effectiveness results are sensitive to changes in the weight profile over time which itself is dependent on the timing of treatment switches. Treatment switches are dependent on the relationship between the baseline HbA1c, treatment related HbA1c changes and the HbA1c threshold for switching therapies. Therefore, the cost-effectiveness of Dapa in dual therapy indications, either as an add-on to metformin or an add-on to insulin, is particularly sensitive to the HbA1c switching threshold, the baseline characteristics and the choice of efficacy estimates (e.g 24 week NMA vs 52 week NMA).

In the version of the model which uses mean parameter values, a small difference in the HbA1c treatment effect between two therapies may result in one therapy having an earlier treatment switch. In the PSA version of the model, the HbA1c treatment effects for the first-line therapies are sampled giving more variation in the duration of time spent on the first therapy and a higher mean duration of treatment.

The scenario analyses conducted demonstrate that the comparisons of Dapa+MET against TZD+MET and SU+MET were sensitive to changes made to the weight profiles to achieve weight convergence at the last therapy switch. Scenario analyses were also conducted using the manufacturer's original HFS. The cost-effectiveness results were not found to be particularly sensitive to changes in the utility decrements applied in the HFS. It was noted that in many of the scenarios considered, a large proportion of the QALY gain associated with Dapa in combination with metformin was attributable to patient preferences regarding weight changes over and above their impact on diabetes complications.

Under the DSU's basecase assumptions, Dapa+MET has an ICER under £20,000 per QALY compared to TZD+MET and SU+MET for both the PSA and mean parameter values versions of the model. The costs and QALYs for DPP4+MET are very similar to those for Dapa+MET, such that both strategies have similar ICERs compared to TZD+MET. In the scenario analysis examining weight convergence at last therapy switch the ICER for Dapa+MET versus TZD+MET was above £30,000 per QALY, but the ICER for Dapa+MET versus SU+MET was still under £30,000 per QALY. Dapa+MET is not cost-effective when conducting a full incremental analysis using the 52 week NMA data, but this may be due to the application of different baseline and efficacy estimates applied, rather than simply due to the addition of the SU+MET comparator within the incremental analysis.

Under the DSU's basecase assumptions, Dapa+INS had an ICER under £20,000 per QALY compared to DPP4+INS for both the PSA and mean values versions of the model. None of the scenario analyses for the add-on to insulin therapy comparison generated ICERs above £20,000 per QALY.

APPENDICES

APPENDIX A: BREAKDOWN OF RESULTS FOR ADD-ON TO METFORMIN INDICATION

Table A 1 Cost breakdown for DSU basecase – clinical data from 24 week NMA

Variable	DPP4+MET	TZD+MET	Dapa+MET
Treatment related			
Drug treatment (total)	£ 3,875.76	£ 3,247.94	£ 3,726.29
Severe hypoglycaemia	£ 122.43	£ 123.22	£ 131.53
Other AE & renal monitoring	£ 5.15	£ 1.46	£ 46.01
Diabetes complications			
IHD	£ 637.42	£ 637.39	£ 635.03
MI	£ 1,107.59	£ 1,108.13	£ 1,108.09
Stroke	£ 323.25	£ 321.90	£ 320.39
CHF	£ 332.10	£ 332.60	£ 331.78
Blindness	£ 154.15	£ 153.44	£ 154.89
Nephropathy	£ 2,005.15	£ 1,987.46	£ 1,973.36
Amputation	£ 406.52	£ 405.05	£ 407.82
No complications	£ 6,663.64	£ 6,666.10	£ 6,662.04
Total	£ 15,633.15	£ 14,984.70	£ 15,497.23

Table A 2 Breakdown of events for DSU basecase assumptions – clinical data from 24 week NMA

	DPP4+MET		TZD+MET		Dapa+MET	
Variable	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**
Macrovascular events						
IHD	0.1115	0.0000	0.1116	0.0000	0.1112	0.0000
MI	0.1234	0.1630	0.1236	0.1627	0.1232	0.1627
Stroke	0.0677	0.0198	0.0676	0.0198	0.0674	0.0195
CHF	0.0682	0.0072	0.0682	0.0073	0.0680	0.0072
Microvascular events						
Blindness	0.0622	0.0000	0.0622	0.0000	0.0622	0.0000
Nephropathy	0.020	0.0022	0.0202	0.0021	0.0201	0.0021
Amputation	0.0420	0.0046	0.0419	0.0046	0.0420	0.0046
Adverse events						
UTI	0.1023		0.0000		0.0988	
GI	0.000		0.0000		0.1126	
Hypoglycaemia (sympt)	8.4054		8.4728		8.9370	
Hypoglycaemia (severe)	0.4390		0.4412		0.4611	

Table A 3 Cost breakdown for DSU basecase – clinical data from 24 week NMA

Variable	SU+MET	Dapa+MET
Treatment related	£ 2,918.83	
Drug treatment (total)	£ 2,918.83	£ 3,689.30
Severe hypoglycaemia	£ 122.02	£ 117.66
Other AE & renal monitoring	£ 8.14	£ 53.13
Diabetes complications		
IHD	£ 605.38	£ 596.96
MI	£ 945.09	£ 937.48
Stroke	£ 297.91	£ 297.52
CHF	£ 359.44	£ 355.51
Blindness	£ 155.51	£ 156.70
Nephropathy	£ 1,720.62	£ 1,677.35
Amputation	£ 353.20	£ 354.15
No complications	£ 6,341.08	£ 6,343.52
Total	£ 13,827.22	£ 14,579.26

Table A 4: Breakdown of events for DSU basecase assumptions – Clinical data from Study 4

	SU+MET		Dapa+MET	
Variable	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**
Macrovascular events				
IHD	0.1070	0.0000	0.1062	0.0000
MI	0.1051	0.1504	0.1042	0.1499
Stroke	0.0614	0.0188	0.0611	0.0194
CHF	0.0732	0.0084	0.0727	0.0083
Microvascular events				
Blindness	0.0632	0.0000	0.0635	0.0000
Nephropathy	0.0180	0.0021	0.0178	0.0021
Amputation	0.0355	0.0043	0.0357	0.0042
Adverse events				
UTI	0.1199		0.1949	
GI	0.0506		0.2226	
Hypoglycaemia (sympt)	8.3190		7.6600	
Hypoglycaemia (severe)	0.4242		0.4129	

Table A 5 Cost breakdown for DSU basecase but with 52 week NMA data

Variable	SU+MET	DPP4+MET	TZD+MET	Dapa+MET
Treatment related				
Drug treatment (total)	£ 2,771.07	£ 3,647.63	£ 2,877.68	£ 3,973.57
Severe hypoglycaemia	£ 109.67	£ 139.40	£ 105.60	£ 106.04
Other AE & renal monitoring	£ 10.67	£ 5.17	£ 1.47	£ 60.37
Diabetes complications				
IHD	£ 663.54	£ 664.22	£ 662.51	£ 659.91
MI	£ 1,114.85	£ 1,113.20	£ 1,112.98	£ 1,116.43
Stroke	£ 334.52	£ 335.63	£ 335.67	£ 333.62
CHF	£ 345.22	£ 349.06	£ 344.38	£ 346.51
Blindness	£ 163.87	£ 162.66	£ 163.99	£ 162.74
Nephropathy	£ 1,737.65	£ 1,764.50	£ 1,745.53	£ 1,754.15
Amputation	£ 372.25	£ 371.93	£ 371.40	£ 374.80
No complications	£ 6,386.13	£ 6,382.85	£ 6,385.49	£ 6,383.80
Total	£ 14,009.44	£ 14,936.25	£14,106.68	£ 15,271.95

Table A 6 Breakdown of events for DSU basecase assumptions but using 52 week NMA data

	SU+MET		DPP4+MET		TZD+MET		Dapa+MET	
Variable	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**
Macrovascular events								
IHD	0.1178	0.0000	0.1176	0.0000	0.1176	0.0000	0.1174	0.0000
MI	0.1236	0.1728	0.1233	0.1725	0.1233	0.1730	0.1236	0.1725
Stroke	0.0689	0.0212	0.0689	0.0214	0.0691	0.0213	0.0690	0.0211
CHF	0.0722	0.0083	0.0726	0.0082	0.0722	0.0082	0.0725	0.0081
Microvascular events								
Blindness	0.0665	0.0000	0.0661	0.0000	0.0665	0.0000	0.0662	0.0000
Nephropathy	0.0185	0.0020	0.0187	0.0020	0.0185	0.0020	0.0184	0.0022
Amputation	0.0379	0.0044	0.0378	0.0043	0.0378	0.0044	0.0381	0.0043
Adverse events								
UTI	0.1815		0.1027		0.0000		0.2947	
GI	0.0767		0.0000		0.0000		0.3366	
Hypoglycaemia (sympt)	8.8141		7.7317		7.8982		7.8553	
Hypoglycaemia (severe)	0.3929		0.4721		0.3822		0.3829	

APPENDIX B: BREAKDOWN OF RESULTS FOR ADD-ON TO INSULIN THERAPY COMPARISON

Table B 1Cost breakdown for Dapa+INS vs DPP4+INS using DSU assumptions (discounted results per person using mean parameter values)

Variable	Dapagliflozin	DPP4	Difference
Treatment related			
Drug treatment (total)	£ 5,904.89	£ 5,878.16	£ 26.72
Severe hypoglycaemia	£ 108.64	£ 108.97	-£ 0.33
Other AE & renal monitoring	£ 43.73	£ 3.03	£ 40.70
Diabetes complications			
IHD	£ 689.50	£ 689.97	-£ 0.48
MI	£ 963.96	£ 963.98	-£ 0.02
Stroke	£ 300.48	£ 301.11	-£ 0.62
CHF	£ 374.80	£ 375.87	-£ 1.07
Blindness	£ 157.86	£ 158.23	-£ 0.37
Nephropathy	£ 2,063.60	£ 2,074.21	-£ 10.60
Amputation	£ 494.88	£ 495.67	-£ 0.79
No complications	£ 6,506.88	£ 6,503.54	£ 3.34
Total	£ 17,609.21	£ 17,552.74	£ 56.47

Table B 2 Lifetime predicted events of Dapa+INS vs DPP4+INS using DSU assumptions

	INS+dapagliflozin		INS+DPP4		Incremental	
Variable	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	**ΔNon-fatal**	**ΔFatal**
Macrovascular events						
IHD	0.1184	0.0000	0.1184	0.0000	0.0000	0.0000
MI	0.1054	0.1550	0.1053	0.1550	0.0001	-0.0001
Stroke	0.0612	0.0194	0.0612	0.0195	0.0001	-0.0001
CHF	0.0747	0.0087	0.0748	0.0088	-0.0001	0.0000
Microvascular events					0.0000	0.0000
Blindness	0.0628	0.0000	0.0629	0.0000	-0.0001	0.0000
Nephropathy	0.0213	0.0025	0.0213	0.0025	0.0000	0.0000
Amputation	0.0492	0.0058	0.0492	0.0058	0.0000	0.0000
Adverse events						
UTI	0.0542		0.0615		-0.0073	
GI	0.0898		0.0030		0.0868	
Hypoglycaemia (sympt)	12.8395		13.4157		-0.5762	
Hypoglycaemia (severe)	0.3913		0.3921		-0.0008	

Table B 3 Cost breakdown for Dapa+INS vs DPP4+INS using DSU assumptions but manufacturer weight profile (discounted results per person using mean parameter values)

Variable	Dapagliflozin	DPP4	Difference
Treatment related			
Drug treatment (total)	£ 8,098.16	£ 7,862.63	£ 235.53
Severe hypoglycaemia	£ -	£ -	£ -
Other AE & renal monitoring	£ 69.42	£ 72.65	-£ 3.23
Diabetes complications			
IHD	£ 699.34	£ 703.66	-£ 4.32
MI	£ 970.95	£ 970.95	£ 0.00
Stroke	£ 302.07	£ 302.55	-£ 0.48
CHF	£ 375.77	£ 375.83	-£ 0.06
Blindness	£ 164.27	£ 163.68	£ 0.59
Nephropathy	£ 2,111.55	£ 2,109.87	£ 1.68
Amputation	£ 514.22	£ 517.48	-£ 3.26
No complications	£ 6,497.80	£ 6,498.43	-£ 0.63
Total	£ 19,877.52	£ £19,594.43	£ 283.10

Table B 4 Lifetime predicted events of Dapa+INS vs DPP4+INS using DSU assumptions but manufacturer weight profile

	INS+dapagliflozin		INS+DPP4		Incremental	
Variable	**Non-Fatal**	**Fatal**	**Non-Fatal**	**Fatal**	**ΔNon-fatal**	**ΔFatal**
Macrovascular events						
IHD	0.1196	0.0000	0.1199	0.0000	-0.0003	0.0000
MI	0.1065	0.1552	0.1061	0.1557	0.0004	-0.0005
Stroke	0.0614	0.0196	0.0616	0.0194	-0.0003	0.0002
CHF	0.0752	0.0086	0.0747	0.0087	0.0006	-0.0002
Microvascular events					0.0000	0.0000
Blindness	0.0650	0.0000	0.0647	0.0000	0.0003	0.0000
Nephropathy	0.0217	0.0025	0.0217	0.0026	-0.0001	-0.0001
Amputation	0.0512	0.0059	0.0514	0.0059	-0.0002	0.0000
Adverse events						
UTI	0.4189		0.4755		-0.0566	
GI	0.6860		0.0231		0.6630	
Hypoglycaemia (sympt)	22.0809		26.5829		-4.5020	
Hypoglycaemia (severe)	0.2760		0.2856		-0.0095	