Dapagliflozin STA: ERG comments on economics of manufacturer ACD submission

General ERG commentary on revised modelling that has been submitted

A substantial additional amount of information and models were submitted by the manufacturer, with only a short period for the ERG to review them. The documentation of the revised model inputs and model structure was also quite poor within the manufacturer ACD submission. The summary tables presented below are the best effort of the ERG in the time available to outline the changes made to the modelling, and their impacts upon results. But these have been drawn from the electronic copies of the model submitted by the manufacturer, and have not been error checked by the manufacturer.

Some considerations about the revised modelling are outlined. This is then followed by a presentation of the inputs to the DCEM modelling, then the DCEM results followed by the CORE validation exercise results. Due to the centrality of the evolution of weight within the modelling, this is graphed for each comparison in an appendix.

Dual therapy modelling: move from 24 week NMA to revised 52 week NMA

This relies upon the 52 week NMA which changes the model inputs quite considerably from the original modelling. In particular, in terms of HbA1c dapagliflozin is now estimated to be superior to the TZD and the DPP-IV when the original modelling suggested the reverse. Modelling for the revised 24 week NMA has not been submitted.

Triple therapy modelling

While the manufacturer ACD submission addresses a number of the concerns of the ACD, the triple therapy modelling does not consistently adopt the same approach. Notable among the discrepancies are:

- The baseline patient characteristics have been altered for reasons that are unclear.
- The Lane et al BMI utility decrements being retained.
- The (incorrect) adjustment to the costs of complications not being applied.
- Non-zero baseline prevalences of complications being introduced.

Therapy switch and BMI

It should be borne in mind that in the context of most of the QALY gains arising from the direct BMI effects, having a short duration of initial therapy may improve the estimated cost effectiveness. The duration of therapy is linked to the HbA1c switch threshold, with a lower HbA1c switch threshold causing patients to switch therapy sooner. As a consequence, a patient may come off dapagliflozin more quickly, reducing costs in the dapagliflozin arm while maintaining a weight advantage into the

longer term. Changing the HbA1c switch threshold cannot be considered without also considering the assumed evolutions of weight.

Modelling of BMI in DCEM

Due to the centrality of the evolution of weight to the modelling, this has been graphed for all the comparisons in an appendix. These are taken directly from the submitted models. There may be problems with the revisions to the modelling of weight progression. The manufacturer ACD submission notes that "*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. By "fully regained" it is meant that the patient weight is at a level that it would be if no weight effect had occurred in the first year after therapy start*". The ERG interpretation of this is that therapies that cause a loss of weight have this weight loss reversed at therapy switch.

There are some concerns about this. In particular, 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.

The evolution of weight in the triple therapy comparison with the GLP-1 is also difficult to understand. Despite the GLP-1 having a superior evolution of weight up to the first therapy switch at year 6, which is somewhat later than the first therapy switch for dapagliflozin, the longer term effect is that the GLP-1 has a worse weight profile than dapagliflozin.

The treatment of the evolution of weight in the dapagliflozin arm is not consistently applied within the dual therapy pairwise comparisons, and is also is not consistently applied within the triple therapy pairwise comparisons.

Note also that despite two not particularly well documented sensitivity analyses, the manufacturer ACD submission does not address the ACD concern around limiting the duration of differential weight effects within the modelling. This also applies with as much if not more force within the CORE validation exercise.

The CORE validation exercise

The implementation within the CORE model differs from the revised DCEM submitted subsequent to the ACD in certain key areas. Based upon table 1 of the validation report:

- BMI is modelled as an initial treatment effect followed by weight gain on switch to insulin. While the text is not explicit (4.3.4) it appears that the absolute differences in BMI after the initial treatment effect are maintained over the time horizon of CORE. For the DCEM the

BMI is modelled in a more ad hoc manner, but one that tends to reduce but not eliminate over time the initial differences modelled in BMI.

- CORE models the progression of lipids based upon the Framingham Heart Study rather than the UKPDS 68.
- CORE has a more explicit consideration of the possibility of eye disease than the one eye blindness of UKPDS 68 and the DCEM
- Some difference in the treatment of utility decrements from complications
- The CORE modelling applies the reduced disutilities for hypoglycaemic events.

Note that it appears that the progression of BMI within CORE is taken from "Table values from clinical database". The ERG has not sourced these tables, in part because the CORE user interface has changed considerably since last used by the ERG. But based upon the results sheet of the dual therapy comparison of dapagliflozin with the SU[1], CORE models an initial treatment effect upon weight and retains this treatment effect over the time horizon of the modeling[2]. Given this, it appears that CORE will typically be estimating a larger net QALY gain from the direct weight effects than the DCEM. For simulations where the net QALY gain is similar between the DCEM and CORE, this would appear to suggest that CORE is estimating a smaller net QALY or possibly even a net QALY loss from the complications of diabetes compared to the DCEM.

The costs of diabetic complications

For the costs of complications of diabetes, the ERG report noted that the UKPDS 65 also gives a £483 cost for those without complications. These are not within the model structure, but as further noted in the ERG report the simplest means of approximating to this would be to subtract £483 from the costs of the complications to give the additional net cost of the complications. In addition to this, it would be more accurate to also add the £483 to the costs of all treatments, though this was not noted within the ERG report.

Unfortunately, the manufacturer revisions to the model have added rather than subtracted £483 to the costs of the complications, though only within the dual therapy and add-on to insulin comparisons and not within the triple therapy comparisons. Due to the dual therapy comparisons using the revised 52 week NMA results which now suggest that dapagliflozin is superior to the DPP-IV and the TZD in terms of HbA1c, further increasing the costs of complications is likely to further favour dapagliflozin. But the triple therapy comparisons still estimate dapagliflozin to be worse than the comparators for

[1] BMS-933667_DapaDouble_ST4_thres7.5_TEST simulation2-UK-TEST

[2] In this example, a net gain of 1.67kgm^2 is applied over the 50 year time horizon. The other simulations may have slightly different evolutions between the arms based upon different timings of switch of therapy, but the broad point that the initial absolute net treatment effect will be maintained over the time horizon of the model appears to apply.

HbA1c. Increasing the costs of complications in this context may work against dapagliflozin which may be why it has not been implemented in the comparisons.

Disutility and hypos

Despite the ERG having re-read Currie et al a number of times, it is still unclear on the point being made by the manufacturer about how the utility decrements from hypos in Currie should be applied. Note that the ERG report suggested decrement per severe hypo of -0.012 is broadly in line with the -0.01 applied within CG87: Type 2 diabetes - newer agents.

While the appropriate value is still pertinent, it should be borne in mind that in the previous analyses the net QALY impact of hypos was typically a very small proportion of the total net QALY impact in the simulations where hypos contributed to the net QALY gain from dapagliflozin. If the ERG interpretation were to be applied, the impact of it upon dual therapy results would be slight. The impact for add-on to insulin is more notable, as outlined in table 2.3.2.2 of the manufacturer ACD submission, though this may mainly relate to non-severe hypos as the rates of these in the revised NMA are somewhat different from before.

Further ERG sensitivity analyses

Due to the possible problems around the modelling of the evolution of weight, coupled with time constraints, the ERG has not undertaken any further sensitivity analyses.

These would probably require:

- The new £69.09 cost for pioglitazone to be applied.
- The costs of complications to be reduced by £483 compared to the values of the original submission, coupled with the annual costs of treatment all being increased by £483.
- The triple therapy modelling being brought into line with the other modelling:
    - Applying the 0.0061 BMI disutility of Bagust et al.
    - Applying a zero prevalence of complications for the base case.
- Quantification of the impact upon the ICERs of sensitivity analyses that equalise weights at first therapy switch.
- Quantification of the impact upon the ICERs of sensitivity analyses that apply the 24 week NMA results.
- A combination of the above two bullets.

Dual therapy comparisons

Revised NMA

The dual therapy modelling revises both the 24 week NMA and the 52 week NMA. The original manufacturer submission relied upon the 24 week NMA, while the manufacturer ACD submission relies upon the 52 week NMA. The revisions to the NMAs make relatively little difference, but the switch from the 24 week NMA to the 52 week NMA has rather larger impacts. Based upon a simple summation of the central values reported in tables 3.2.1.1 to 3.2.1.7 the total impact (i.e. relative to baseline rather than relative to placebo or the SU) can be derived.

Table 01: 24 week NMA: HbA1c

		Original (relative)		Revised (relative)		Original (total)		Revised (total)	
		Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
DPP4 vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZD vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GLP1 vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo vs baseline	Unadjusted	[redacted]		[redacted]	[redacted]				
	Adjusted			[redacted]	[redacted]				

Table 02: 52 week NMA: HbA1c

		Original (relative)		Revised (relative)		Original (total)		Revised (total)	
		Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
DPP4 vs SU	Unadjusted	0.08	0.08	0.08	0.08	-0.61	-0.61	-0.84	-0.84
	Adjusted	0.07	0.07	0.07	0.08	-0.62	**-0.62**	-0.85	**-0.84**
TZD vs SU	Unadjusted	0.02	0.02	0.02	0.02	-0.67	-0.67	-0.90	-0.90
	Adjusted	0.03	0.03	0.03	0.01	-0.66	**-0.66**	-0.89	**-0.91**
Dapa vs SU	Unadjusted	0.00	0.00	0.00	0.00	-0.69	-0.69	-0.92	-0.92
	Adjusted	-0.01	0.00	-0.01	0.00	-0.70	**-0.69**	-0.93	**-0.92**
SU vs baseline	Unadjusted	-0.69		-0.92	-0.92			-0.92	-0.92
	Adjusted			-0.92	-0.92			-0.92	**-0.92**

Compared to the 24 week NMA results within which dapagliflozin was estimated to have a worse central estimate for the impact upon HbA1c than both the DPP-IV and the TZD, the 52 week NMA results suggest that dapagliflozin is superior to both the DPP-IV and the TZD.

Table 03: 24 week NMA: weight

		Original (relative)		Revised (relative)		Original (total)		Revised (total)	
		Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
DPP4i vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TZD vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GLP1 vs placebo	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo vs baseline	Unadjusted	[redacted]	[redacted]	[redacted]	[redacted]				

Table 04: 52 week NMA: weight

		Original (relative)		Revised (relative)		Original (total)		Revised (total)	
		Fixed	Random	Fixed	Random	Fixed	Random	Fixed	Random
DPP4i vs SU	Unadjusted	-1.81	-1.92	-1.81	-1.92		**-0.61**	-1.70	**-1.81**
TZD vs SU	Unadjusted	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Dapa vs SU	Unadjusted	-4.66	-4.67	-4.66	-4.66		**-3.36**	-4.55	**-4.55**
SU vs baseline	Unadjusted		1.31	0.11	0.11		**1.31**	0.11	**0.11**

Original model inputs

Table 05: Table 9 of ERG report: Baseline characteristics and effects

Study	Study 4			NMA			
	Baseline	Dapa	SU	Baseline	Dapa	DPP-IV	TZD
Baseline characteristics							
Age	58.4	..	..	55.16	..	..	..
Female	44.9%	..	..	44.2%	..	..	..
Diabetes duration	6.32	..	..	5.03	..	..	..
Height (m)	1.67	..	..	1.7	..	..	..
Afro-Caribbean	6.2%	..	..	6.2%	..	..	..
Smokers	17.6%	..	..	55.0%	..	..	..
Risk factors							
HbA1c	7.72%	-0.52%	-0.52%	8.17%	-0.58%	-0.74%	-0.90%
Cholesterol (mg/dL)	182.54	0.071	-0.028	185	n.a.	n.a.	n.a.
HDL (mg/dL)	45.87	0.070	-0.002	45.53	n.a.	n.a.	n.a.
SBP (mmHg)	133.3	-4.3	0.8	133.83	-4.5	-1.37	-2.87
Weight (kg)	88.02	-3.22	1.44	90.14	-2.79	-0.51	1.72
Weight plateau (yrs)	..	2	1	..	2	2	1
Loss of effect (yrs)	..	1	..	..	2	3	..
Adverse Events							
Discontinuation	..	9.10%	5.90%	..	2.20%	3.10%	6.00%
Hypoglycaemia	..	3.50%	40.80%	..	7.50%	4.90%	2.30%
Severe hypoglycaemia	..	0.00%	0.74%	..	0.01%	0.01%	0.00%
UTI	..	10.80%	6.40%	..	6.70%	5.20%	n.a.
GI	..	12.30%	2.70%	..	8.90%	0.50%	n.a.

Additional elements relevant to the ACD

- Rick factor evolution having values at diagnosis differing between the arms.
- HbA1c switching value 7.72% for SU comparison and 8.17% for other dual therapy comparisons.
- The BMI utilities of -0.0472 for weight gain and 0.0171 for weight loss as drawn from Lane.
- TZD cost does not reflect the revised cost of pioglitazone.
- Treatment of costs does not address costs for those with no complications.

Table 06: Revised model inputs: Baseline characteristics and effects

Study	Study 4			NMA			
	Baseline	Dapa	SU	Baseline	Dapa	DPP-IV	TZD
Baseline characteristics							
Age	57.51	..	..	57.51	..	..	..
Female	47.0%	..	..	47.0%	..	..	..
Diabetes duration	5.17	..	..	5.17	..	..	..
Height (m)	1.69	..	..	1.69	..	..	..
Afro-Caribbean	6.2%	..	..	6.2%	..	..	..
Smokers	36.9%	..	..	36.9%	..	..	..
Risk factors							
HbA1c	8.05%	-0.92%	-0.92%	8.05%	-0.92%	-0.84%	-0.90%
Cholesterol (mg/dL)	199.57	0.000	0.000	199.57	0.000	0.000	0.000
HDL (mg/dL)	44.09	0.000	0.000	44.09	0.000	0.000	0.000
SBP (mmHg)	133.3	0.0	0.0	133.3	0.0	0.0	0.0
Weight (kg)	87.84	-4.55	0.11	87.84	-4.55	-1.81	0.00
Weight plateau (yrs)	..	2	1	..	2	2	1
Loss of effect (yrs)	..	0	0	..	0*	0	0
Adverse Events							
Discontinuation	..	8.10%	4.70%	..	8.10%	4.30%	4.10%
Hypoglycaemia	..	4.67%	40.30%	..	4.67%	4.67%	8.35%
Severe hypoglycaemia	..	0.05%	0.46%	..	0.05%	2.98%	0.10%
UTI	..	10.80%	6.40%	..	10.80%	5.40%	0.00%
GI	..	12.30%	2.70%	..	12.30%	0.00%	0.00%

* For the comparison with the TZD the loss of effect for dapagliflozin is set to 1, resulting in a different weight evolution. As a consequence the evolution of weight for the dapagliflozin arm is not the same across the comparisons (see appendix for graphs of weight over time). The ERG does not understand how the weight evolution within the comparison within the TZD has been implemented, but for this comparison it appears to equalise the weight between the TZD arm and the dapagliflozin arm at switch of therapy and so be more in line with the ACD.

Additional elements relevant to the ACD

- Rick factor evolution having equal values at diagnosis. The ERG has only had time to inspect the visual basic code for this, and has not compared the risk factor evolutions of the DCEM with separate ERG calculations.
- HbA1c switching value 7.5% for all dual therapy comparisons.
- The BMI utilities of 0.0061 for weight changes as drawn from Bagust.

- TZD cost does reflect the revised cost of pioglitazone: £112.18 as per the ERG report, but not the current drug tariff[3] price of £69.09.
- Treatment of costs does not address costs for those with no complications, and the costs of complications have been increased by £483.

The revised inputs somewhat increase the effect upon HbA1c from both dapagliflozin and the sulfonylurea. This is to the extent that in contract to the previous analysis which saw dapagliflozin being worse than both the DPP-IV and the TZD, the revised analysis estimates that dapagliflozin is slightly superior in terms of its HbA1c effect than both the DPP-IV and the TZD.

The impacts upon weight are also somewhat larger in the revised analysis, though the net differences between dapagliflozin and the other treatments are broadly the same. There is a slight increase in the net effect for dapagliflozin compared to the DPP-IV: previously 2.28kg , but 2.74kg in the revised analysis.

Another difference is the very much higher discontinuation rate for dapagliflozin when being compared with the DPP-IV and the TZD.

Table 07: Results: Cost effectiveness: DCEM: 7.5% threshold: 52 week NMA

	Dapa	SU	Net	DPP-IV	Net	Dapa	TZD	Net
Cost	£10,885	£9,752	£1,132	£10,628	£256	£11,014	£9,968	£1,045
QALY	11.33	11.18	0.15	11.25	0.08	11.22	11.21	0.01
ICER			£7,735		£3,337			£77,615

Note that due to the different approach adopted for the evolution of weight in the comparison with the TZD, there is a slight increase in costs in the dapagliflozin arm and a reduction in the total QALYs. The evolution of weight within the TZD comparison can be seen as being more in line with the thrust of the ACD.

There are concerns about the modelled evolution of weight in the revised analysis of dual therapy, as graphed in the appendix. For both the comparison with the SU and the comparison with the DPP-IV weight in the dapagliflozin arm does not appear to revert towards the baseline value at therapy as broadly occurred in the original modelling [figure 12 on page 66 of the ERG report].

The DCEM results can be compared with the results of the CORE validation exercise.

[3] http://www.ppa.org.uk/edt/March_2013/mindex.htm accessed 02 March 2013

Table 08: Results: Cost effectiveness: CORE: 7.5% threshold: 52 week NMA

	Dapa	SU	Net	DPP-IV	Net	TZD	Net
Cost	£23,537	£22,065	£1,472	£23,341	£196	£22,344	£1,193
QALY	9.16	8.99	0.17	9.06	0.10	8.99	0.17
ICER			£8,879		£2,014		£7,093

The costs are very much higher within CORE and the total QALYs quite a lot lower, but the net amounts are reasonably in line with those of the DCEM. This is with the exception of the comparison with the TZD which is an outlier in terms of the DCEM modelling approach adopted, probably due to the evolution of weight changes within the DCEM for this comparison.

As with the DCEM modelling, the cost effectiveness of dapagliflozin worsens if the HbA1c switch threshold is increased from 7.5% to 8.5%, as per table 2.3.2.1 of the manufacturer ACD submission and table 39 of the CORE validation report.

The CORE validation exercise also estimates the cost effectiveness of dapagliflozin based upon the study 4 results for the comparison with the SU, and using the 24 week NMA results for the comparisons with the DPP-IV and the TZD.

Table 09: Results: Cost effectiveness: CORE: 7.5% threshold: Study 4

	Dapa	SU	Net
Cost	£22,457	£21,109	£1,348
QALY	9.02	8.78	0.23
ICER			£5,747

The ICER worsens to £7,467 per QALY for a 7.72% HbA1c switch threshold.

Table 10: Results: Cost effectiveness: CORE: 7.5% threshold: 24 week NMA

	Dapa	DPP-IV	Net	TZD	Net
Cost	£24,226	£24,220	£5	£23,431	£795
QALY	9.35	9.25	0.09	9.25	0.09
ICER			£57		£8,401

The ICER versus the DPP-IV worsens to £4,359 per QALY for an 8.17% HbA1c switch threshold, and to £14,922 per QALY versus the TZD.

Triple therapy comparisons

Original model inputs

Table 11: Table 10 of ERG report: Baseline characteristics and effects

Study	Triple therapy review				
	Baseline	Dapa	DPP-IV	TZD	GLP1
Baseline characteristics					
Age	58.4	..	..	..	..
Female	44.9%	..	..	..	..
Diabetes duration	6.32	..	..	..	..
Height (m)	1.67	..	..	..	..
Afro-Caribbean	6.2%	..	..	..	..
Smokers	17.6%	..	..	..	..
Baseline risk factors					
HbA1c	7.72%	[redacted]	-0.89%	-0.96%	-1.06%
Cholesterol (mg/dL)	182.54	[redacted]	n.a.	n.a.	n.a.
HDL (mg/dL)	45.87	[redacted]	n.a.	n.a.	n.a.
SBP (mmHg)	133.3	[redacted]	n.a.	n.a.	n.a.
Weight (kg)	88.02	[redacted]	1.11	3.10	-1.59
Weight plateau (yrs)	..	1	1	1	1
Loss of effect (yrs)	..	..	..	..	..
Adverse Events					
Discontinuation	..	[redacted]	1.70%	3.70%	7.30%
Hypoglycaemia	..	[redacted]	16.40%	23.00%	25.00%
Severe hypoglycaemia	..	[redacted]	0.00%	0.00%	0.88%
UTI	..	[redacted]	0.00%	0.00%	0.00%
GI	..	[redacted]	0.00%	0.00%	0.00%

Additional elements relevant to the ACD

- Rick factor evolution having values at diagnosis differing between the arms.
- HbA1c switching value 7.72%.
- The BMI utilities of -0.0472 for weight gain and 0.0171 for weight loss as drawn from Lane.
- TZD cost does not reflect the revised cost of pioglitazone.
- Treatment of costs does not address costs for those with no complications.
- Zero prevalence of complications at baseline.

Revised model inputs

Table 12: Dapagliflozin in triple therapy: Baseline characteristics and effects

Study	Triple therapy review				
	Baseline	Dapa	DPP-IV	TZD	GLP1
Baseline characteristics					
Age	57.7	..	..	..	..
Female	43.0%	..	..	..	..
Diabetes duration	9.5	..	..	..	..
Height (m)	1.69	..	..	..	..
Afro-Caribbean	4.3%	..	..	..	..
Smokers	23.9%	..	..	..	..
Baseline risk factors					
HbA1c	8.61%	[redacted]	-0.89%	-0.96%	-1.06%
Cholesterol (mg/dL)	175.5	[redacted]	0.000	0.000	0.000
HDL (mg/dL)	39	[redacted]	0.000	0.000	0.000
SBP (mmHg)	139	[redacted]	0.0	0.0	0.0
Weight (kg)	89	[redacted]	1.10	3.10	-1.59
Weight plateau (yrs)	..	[redacted]	1	1	2
Loss of effect (yrs)	..	[redacted]	0	0	4
Adverse Events					
Discontinuation	..	[redacted]	2.00%	4.00%	7.00%
Hypoglycaemia	..	[redacted]	16.00%	23.00%	25.00%
Severe hypoglycaemia	..	[redacted]	0.00%	0.00%	1.00%
UTI	..	[redacted]	0.00%	0.00%	0.00%
GI	..	[redacted]	0.00%	0.00%	0.00%
* For the comparison with the GLP1 the loss of effect for dapagliflozin is lengthened to 3 years. As a consequence the evolution of weight for the dapagliflozin arm is not the same across the comparisons (see appendix for graphs of weight over time). For reasons that are unclear this also results in the long term weight profile for the GLP1 being worse than for dapagliflozin, despite the somewhat longer time before therapy switch and presumably a longer time plateauing and avoiding the annual weight gain.					

Additional elements relevant to the ACD

- Rick factor evolution having equal values at diagnosis. The ERG has only had time to inspect the visual basic code for this, and has not compared the risk factor evolutions of the DCEM with separate ERG calculations.
- HbA1c switching value 8.61% for all triple therapy comparisons.
- The BMI utilities of -0.0472 for weight gain and 0.0171 for weight loss as drawn from Lane.

- TZD cost does not reflect the revised cost of pioglitazone.
- Treatment of costs does not address costs for those with no complications, though the costs of complications have not been increased by £483 as in the other analyses.
- Note also that the baseline prevalences of complications have been revised from zero to those of the table below.

Table 13: Revised baseline complications' prevalences in triple therapy modelling

Percentage with Clinical history	Study 4
AF	4.00%
PVD	3.00%
IHD	8.80%
MI	2.40%
CHF	4.80%
STROKE	2.20%
AMP	0.60%
BLIND	0.20%
ESRD	0.50%

The triple therapy modelling was the most poorly documented in the revised analyses submitted. The baseline characteristics have been revised, and it is unclear why. The treatment effects have not been revised, but there appear to be changes to the assumed evolutions of weight. The discontinuation rates have also been slightly revised for no obvious reason, though this does serve to equalise them between dapagliflozin and the TZD.

It seems peculiar that the Lane BMI disutilities have been retained and the revisions to the costs of complications made for the other analyses have not also been implemented in the triple therapy modelling. The baseline prevalences of complications are also revised from zero to a total of 26.5%. This needs to be read in the context of dapagliflozin being estimated to be inferior to the other treatments in terms of HbA1c.

Table 14: Results: Cost effectiveness: DCEM: 8.16% HbA1c switch threshold

	Dapa	DPP-IV	Net	TZD	Net	Dapa	GLP-1	Net
Cost	£13,296	£13,309	-£13	£13,380	-£84	£13,283	£15,656	-£2,373
QALY	10.04	9.85	0.19	9.45	0.59	10.14	10.10	0.03
ICER			Dom.		Dom.			Dom.

Note that if the costs and effects from the dapagliflozin comparisons with the DPP-IV and the TZD are retained, the cost effectiveness of the GLP-1 compared to dapagliflozin is £38,251 per QALY due mainly to the total QALYs for dapagliflozin falling from 10.14 QALYs to 10.04 QALYs.

Also note that if the £112.18 price for pioglitazone is applied, the cost effectiveness of dapagliflozin compared to the TZD is £2,464 per QALY.

All these analyses retain the Lane BMI disutilities.

Table 15: Results: Cost effectiveness: CORE 8.16% HbA1c switch threshold

	Dapa	DPP-IV	Net	TZD	Net	Dapa	GLP-1	Net
Cost	£30,081	£29,986	£95	£28,375	£1,706	£30,081	£32,338	-£2,257
QALY	7.61	7.55	0.05	7.50	0.11	7.61	7.68	-0.07
ICER			£1,759		£16,054			£32,243sw

The cost effectiveness of £32,243 per QALY is most simply interpreted as the cost effectiveness of the GLP-1 compared to dapagliflozin.

Note that for an HbA1c threshold switch of 7.5% CORE estimates dapagliflozin to be dominated by the DPP-IV due to a small loss of -0.003 QALYs but an additional cost of £417. Similarly, the cost effectiveness compared to the TZD worsens, with a 0.038 QALY gain at a cost of £688 to yield a cost effectiveness estimate of £18,077 per QALY. The GLP-1 is estimated to yield an additional 0.126 QALYs at a cost of £103 to yield a cost effectiveness of £817 per QALY compared to dapagliflozin.

Add-on to insulin

Original model inputs

Table 16: Table 11 of ERG report: Baseline characteristics and effects

Study	NMA		
	Baseline	Dapa	DPP-IV
Baseline characteristics			
Age	57.8	..	..
Female	53.0%	..	..
Diabetes duration	12.8	..	..
Height (m)	1.675	..	..
Afro-Caribbean	6.2%	..	..
Smokers	17.6%	..	..
Risk factors			
HbA1c	8.90%	-0.82%	-0.69%
Cholesterol (mg/dL)	195.04	n.a.	n.a.
HDL (mg/dL)	45.07	n.a.	n.a.
SBP (mmHg)	134.5	n.a.	n.a.
Weight (kg)	91.4	-1.63	0.19
Weight plateau (yrs)	..	2	1
Loss of effect (yrs)	..	5	..
Adverse Events			
Discontinuation	..	n.a.	n.a.
Hypoglycaemia	..	140.00%	144.00%
Severe hypoglycaemia	..	0.68%	0.70%
UTI	..	5.60%	6.30%
GI	..	9.20%	0.30%

Additional elements relevant to the ACD

- Rick factor evolution having values at diagnosis differing between the arms.
- HbA1c switching value 8.90%.
- The BMI utilities of -0.0472 for weight gain and 0.0171 for weight loss as drawn from Lane.
- Treatment of costs does not address costs for those with no complications.

Revised model inputs

Table 17: Dapagliflozin as an add-on to insulin: Baseline characteristics and effects

Study	NMA		
	Baseline	Dapa	DPP-IV
Baseline characteristics			
Age	56.51	..	..
Female	55.1%	..	..
Diabetes duration	6.67	..	..
Height (m)	1.68	..	..
Afro-Caribbean	6.2%	..	..
Smokers	17.6%	..	..
Risk factors			
HbA1c	9.04%	-0.84%	-0.73%
Cholesterol (mg/dL)	201.99	0.000	0.000
HDL (mg/dL)	45.01	0.000	0.000
SBP (mmHg)	140.3	-2.9	-0.4
Weight (kg)	91.15	-1.64	0.18
Weight plateau (yrs)	..	1	1
Loss of effect (yrs)	..	6	0
Adverse Events			
Discontinuation	..	3.06%	1.97%
Hypoglycaemia	..	204.00%	262.00%
Severe hypoglycaemia	..	0.44%	0.57%
UTI	..	5.60%	6.30%
GI	..	9.20%	0.30%

Additional elements relevant to the ACD

- Rick factor evolution having values at diagnosis differing between the arms. CHECK
- HbA1c switching value 9.04%.
- The BMI utilities of 0.0061 for weight changes as drawn from Bagust.
- Treatment of costs does not address costs for those with no complications, and the costs of complications have been increased by £483.

The revised inputs are broadly in line with those previously submitted. While the rates of adverse events differ, the net effects between the arms are broadly as before with the exception of the rates of hypoglycaemia.

Table 18: Results: Cost effectiveness: DCEM: 9.0% HbA1c switch threshold

	Dapa	DPP-IV	Net
Cost	£15,556	£15,280	£276
QALY	11.26	11.21	0.05
ICER			£5,634

These can be compared with the CORE validation exercise results.

Table 19: Results: Cost effectiveness: CORE: 9.0% HbA1c switch threshold

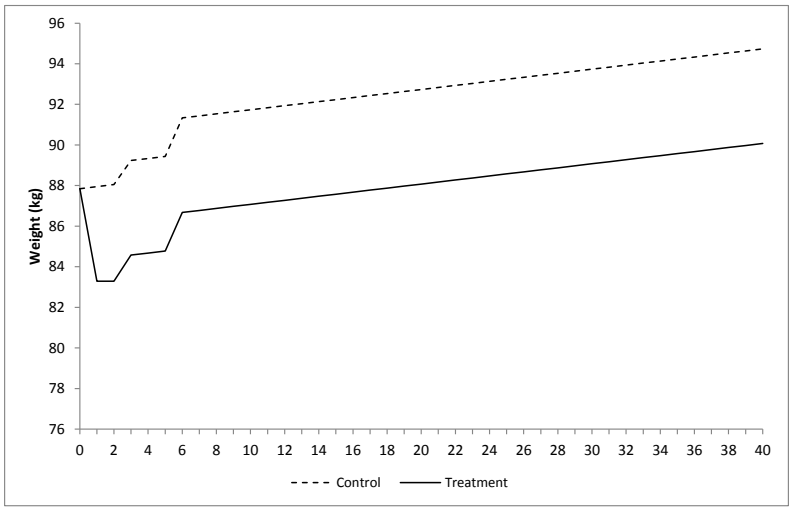
	Dapa	DPP-IV	Net
Cost	£31,789	£31,578	£211
QALY	8.39	8.26	0.13
ICER			£1,675

Note that for an HbA1c therapy switch threshold of 7.5%, CORE estimates a gain of 0.120 QALYs and a cost saving of £88 resulting in dapagliflozin dominating the DPP-IV.

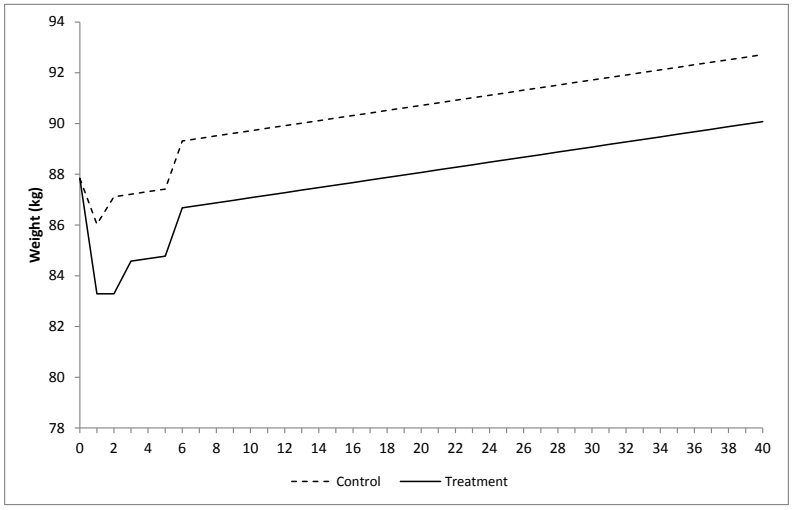
Appendix: Evolution of weight changes

Evolution of weight in the base cases: Dual therapy

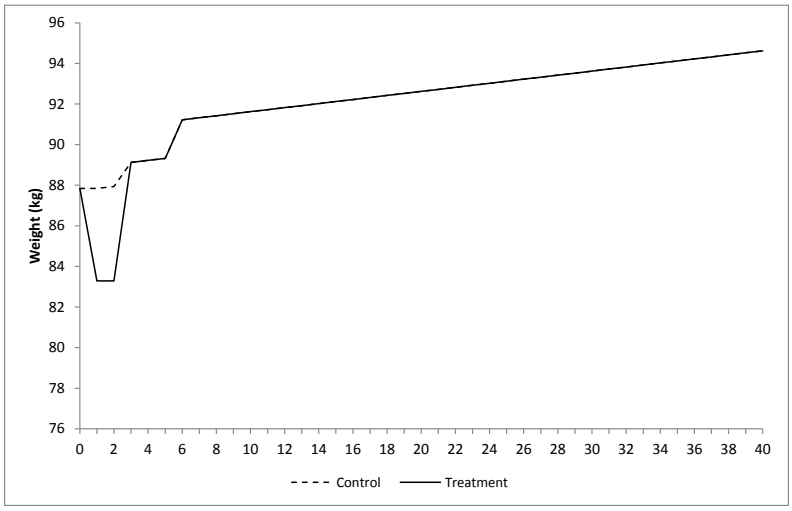
Dual therapy: SU control versus DAPA treatment



Dual therapy: DPPIV control versus DAPA treatment

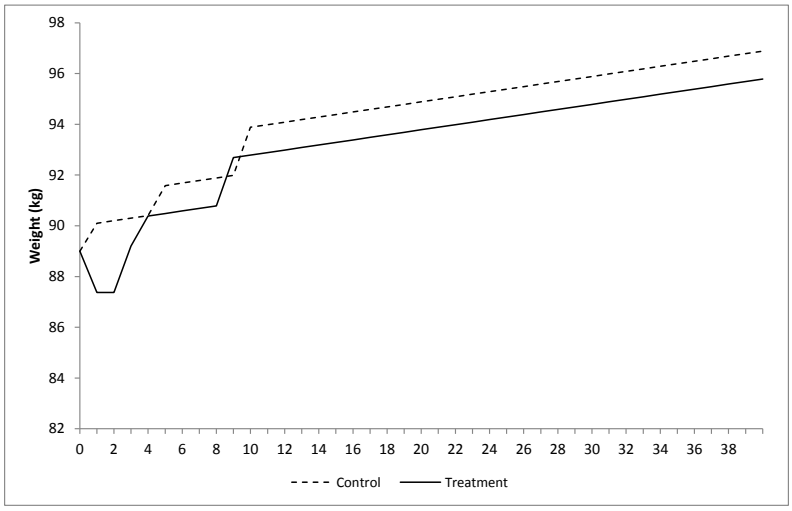


Dual therapy: TZD control versus DAPA treatment

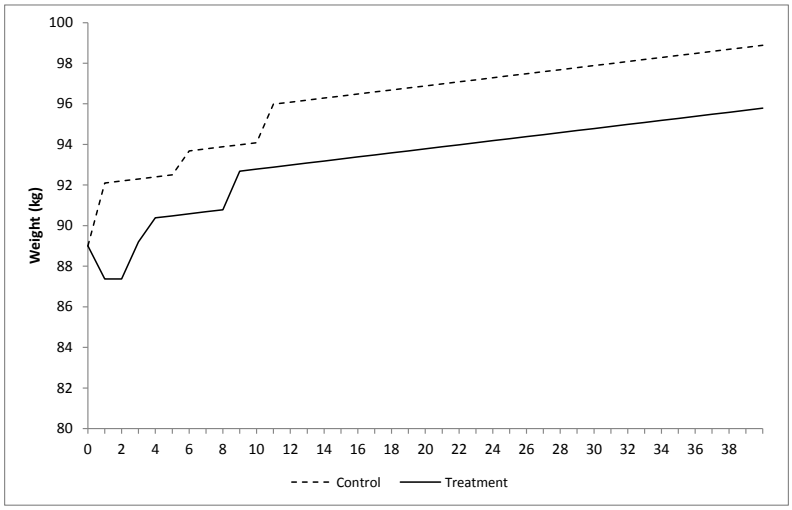


Evolution of weight in the base cases: Triple therapy

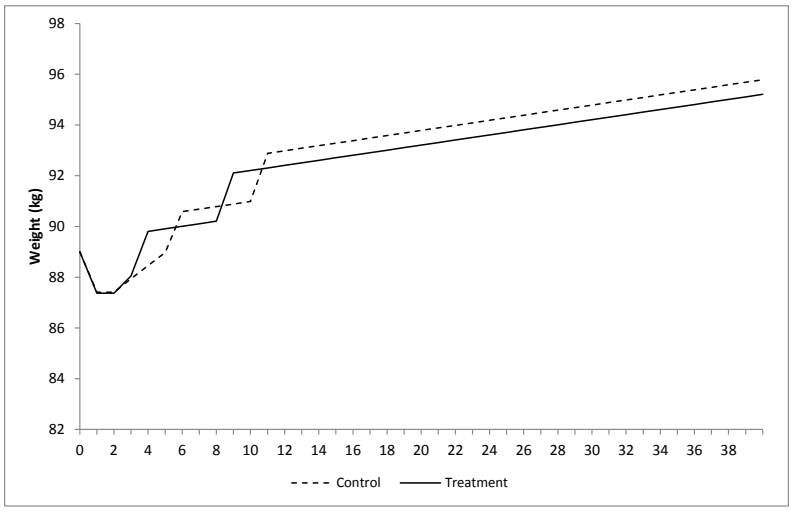
Triple therapy: DPP4 control versus DAPA treatment

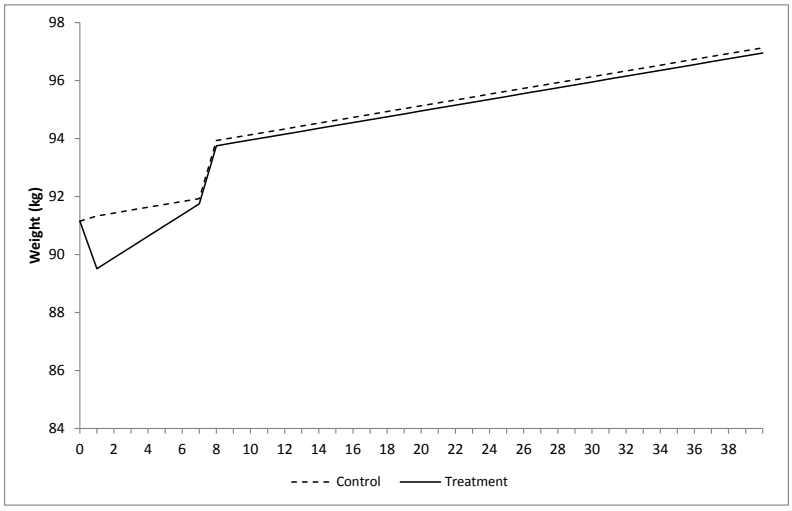


Triple therapy: TZD control versus DAPA treatment



Triple therapy: GLP1 control versus DAPA treatment



Evolution of weight in the base cases: Add-on to insulin

Add-on to insulin: DPP4 control versus DAPA treatment