Single Technology Appraisal

Tirzepatide for treating type 2 diabetes [ID3938]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tirzepatide for treating type 2 diabetes [ID3938]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Eli Lilly and Company
   a. CORE diabetes model cross-comparison report
   b. Appendix A
   c. Appendix B

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Diabetes UK

3. **Comments on the Draft Guidance Document from experts:**
   a. Prof. Stephen C Bain, Professor of Medicine (Diabetes) – clinical expert, nominated by the Association of British Clinical Diabetologists and NovoNordisk

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company response to the Draft Guidance**
   a. SURMOUNT-2 vs SURPASS study comparison

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly & Company Ltd

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive Summary** Eli Lilly welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee detailed in the draft guidance consultation document for tirzepatide for type 2 diabetes (T2D). Whilst Eli Lilly is disappointed that the committee's preliminary decision is to not recommend tirzepatide within its marketing authorisation, we are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the external assessment group (EAG) and committee's key concerns, as outlined in the consultation document and the accompanying letter to company, to enable patients to access this clinically beneficial treatment. [redacted] The [redacted] pricing of tirzepatide is detailed in Table 1, and a summary of the updated EAG preferred base case results for tirzepatide 5 mg, 10 mg and 15 mg versus all comparators is presented in Table 2, Table 3 and Table 4, respectively.

Table 1: [redacted] tirzepatide prices

Dose	[redacted] pack price
Tirzepatide 5 mg	£[redacted]
Tirzepatide 10 mg	£[redacted]
Tirzepatide 15 mg	£[redacted]

Table 2: Summary of base case results for tirzepatide 5 mg versus comparators [redacted]

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	8.715	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	705	0.059	0.100	7,073	0.064

Dulaglutide 3.0 mg	[redacted]	13.076	8.636	644	0.046	0.079	8,182	0.047
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	628	0.030	0.058	10,891	0.026
Semaglutide 0.5 mg	[redacted]	13.075	8.634	682	0.047	0.081	8,401	0.047
Semaglutide 1.0 mg	[redacted]	13.096	8.673	708	0.026	0.042	16,817	0.007
Oral semaglutide 7 mg	[redacted]	13.049	8.595	742	0.073	0.120	6,202	0.083
Oral semaglutide 14 mg	[redacted]	13.074	8.642	719	0.048	0.073	9,873	0.037
Liraglutide 1.2 mg	[redacted]	13.032	8.581	672	0.090	0.134	5,021	0.100
Liraglutide 1.8 mg	[redacted]	13.054	8.600	-409	0.068	0.115	Dominant	0.135

* for tirzepatide versus comparator.
Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Table 3: Summary of base case results for tirzepatide 10 mg versus comparators [redacted]

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.768	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	1,389	0.092	0.153	9,091	0.083
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	1,329	0.079	0.132	10,073	0.065
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	1,312	0.063	0.111	11,843	0.045
Semaglutide 0.5 mg	[redacted]	13.075	8.634	1,367	0.080	0.134	10,171	0.066
Semaglutide 1.0 mg	[redacted]	13.096	8.673	1,393	0.059	0.095	14,616	0.026
Oral semaglutide 7 mg	[redacted]	13.049	8.595	1,427	0.106	0.173	8,254	0.102
Oral semaglutide 14 mg	[redacted]	13.074	8.642	1,403	0.081	0.126	11,140	0.056
Liraglutide 1.2 mg	[redacted]	13.032	8.581	1,356	0.123	0.187	7,254	0.119
Liraglutide 1.8 mg	[redacted]	13.054	8.600	276	0.101	0.168	1,642	0.154

* for tirzepatide versus comparator.
Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Table 4: Summary of base case results for tirzepatide 15 mg versus comparators [redacted]

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.176	8.808	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	2,047	0.113	0.192	10,642	0.090
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	1,987	0.100	0.171	11,586	0.072
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	1,970	0.084	0.150	13,104	0.052
Semaglutide 0.5 mg	[redacted]	13.075	8.634	2,025	0.101	0.174	11,641	0.073
Semaglutide 1.0 mg	[redacted]	13.096	8.673	2,051	0.080	0.135	15,209	0.032
Oral semaglutide 7 mg	[redacted]	13.049	8.595	2,085	0.127	0.212	9,815	0.108
Oral semaglutide 14 mg	[redacted]	13.074	8.642	2,061	0.102	0.166	12,453	0.062
Liraglutide 1.2 mg	[redacted]	13.032	8.581	2,014	0.144	0.227	8,893	0.126
Liraglutide 1.8 mg	[redacted]	13.054	8.600	934	0.122	0.208	4,498	0.161

* for tirzepatide versus comparator.
Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

2

One-way sensitivity analyses for all model inputs in PRIME T2D (tornado diagram)

Incremental cost-effectiveness ratios from the 232 one-way sensitivity analysis simulations for user-editable model inputs are summarized in Table 5 (ICERs ranked from highest to lowest) and a tornado diagram for the ten most influential parameters affecting the ICER is provided in Figure 1.

Table 5: Summary of one-way sensitivity analysis results for the tirzepatide 10 mg versus semaglutide 1.0 mg comparison

Element	Description	ICER
SEMA treatment	HbA1c constant after intensification to insulin	Semaglutide dominant

	SEMA treatment	HbA1c constant during treatment, intensification after 4 years	Semaglutide dominant
	SEMA treatment	SBP constant after intensification to insulin	212,614
	TZP treatment	LDL constant after intensification to insulin	33,302
	SEMA treatment	LDL constant during treatment	26,910
	TZP treatment	SBP follows UKPDS progression during treatment	24,938
	SEMA treatment	QoL decrement on insulin years 2+ decreased by 10%	23,176
	TZP treatment	QoL decrement on insulin years 2+ increased by 10%	22,676
	TZP treatment	Severe hypo rate increased by 10%	19,186
	Cohort	Baseline HbA1c decreased by 10%	19,082
	SEMA treatment	Insulin treatment costs decreased by 10% in years 2+	18,697
	SEMA treatment	HbA1c change increased by 10%	18,544
	TZP treatment	Insulin treatment costs increased by 10% in years 2+	18,543
	SEMA treatment	Severe hypo rate decreased by 10%	18,528
	TZP treatment	BMI constant after intensification to insulin	18,187
	SEMA treatment	Non-severe hypo rate decreased by 10%	17,982
	TZP treatment	Treatment costs increased by 10% in years 2+	17,946
	TZP treatment	Non-severe hypo rate increased by 10%	17,736
	TZP treatment	HbA1c change decreased by 10%	17,091
	SEMA treatment	HDL constant after intensification to insulin	16,974
	SEMA treatment	Treatment costs increased by 10% in years 2+	16,487
	Country	Discount rate set to 6% per annum on costs and benefits	16,442
	TZP treatment	eGFR constant during treatment	16,424
	SEMA treatment	HDL constant during treatment	16,379

	SEMA treatment	WBC constant after intensification to insulin	16,285
	TZP treatment	BMI change decreased by 10%	16,151
	TZP treatment	HbA1c change on insulin decreased by 10%	16,144
	TZP treatment	Treatment costs increased by 10% in year 1	16,142
	TZP treatment	SBP change decreased by 10%	16,114
	SEMA treatment	Heart rate constant during treatment	16,113
	Cohort	Baseline serum lipid levels improved by 10% (TC, HDL and LDL)	16,079
	TZP treatment	BMI follows UKPDS progression during treatment	15,732
	SEMA treatment	Treatment costs increased by 10% in year 1	15,643
	Cohort	Baseline eGFR increased by 10%	15,573
	SEMA treatment	WBC constant during treatment	15,496
	TZP treatment	LDL change increased by 10% on intensification to insulin	15,299
	TZP treatment	BMI change increased by 10% on intensification to insulin	15,286
	SEMA treatment	QoL decrement on treatment years 2+ decreased by 10%	15,276
	SEMA treatment	HDL change increased by 10% on intensification to insulin	15,233
	TZP treatment	QoL decrement on treatment years 2+ increased by 10%	15,107
	SEMA treatment	QoL decrement on insulin year 1 increased by 10%	15,092
	SEMA treatment	Treatment costs decreased by 10% in year 1 of insulin therapy	15,092
	TZP treatment	Treatment costs increased by 10% in year 1 of insulin therapy	15,079
	TZP treatment	QoL decrement on insulin year 1 increased by 10%	15,078
	TZP treatment	HDL change increased by 10% on intensification to insulin	15,059
	TZP treatment	QoL decrement on treatment year 1 increased by 10%	15,052
	SEMA treatment	SBP change increased by 10%	15,020

	SEMA treatment	BMI change increased by 10%	14,944
	Cohort	Baseline BMI decreased by 10%	14,908
	Cohort	Baseline complications all increased by 10%	14,899
	Cohort	Percentage male at baseline increased by 10%	14,885
	TZP treatment	LDL change decreased by 10%	14,870
	Cohort	Baseline haemoglobin decreased by 10%	14,867
	SEMA treatment	Heart rate constant after intensification to insulin	14,858
	Cohort	Baseline haemoglobin increased by 10%	14,822
	Cohort	Baseline eGFR decreased by 10%	14,804
	Cohort	Percentage smokers at baseline increased by 10%	14,778
	SEMA treatment	SBP change decreased by 10%	14,774
	Cohort	No history of complications at baseline (set to 0%)	14,749
	Utilities	Non-severe hypo utility decreased by 10%	14,729
	Utilities	Renal failure utility decreased by 10%	14,729
	Utilities	Severe hypo utility decreased by 10%	14,716
	TZP treatment	WBC constant after intensification to insulin	14,699
	Cohort	Baseline duration of diabetes decreased by 10%	14,692
	Costs	Revascularization cost decreased by 10%	14,672
	Costs	Neuropathy cost decreased by 10%	14,671
	Costs	Severe hypo cost decreased by 10%	14,660
	Utilities	Neuropathy years 2+ utility decreased by 10%	14,658
	Utilities	IHD years 2+ utility decreased by 10%	14,643
	Costs	IHD years 2+ cost decreased by 10%	14,643

	TZP treatment	eGFR constant after intensification to insulin	14,642
	Costs	Heart failure years 2+ cost decreased by 10%	14,640
	Utilities	IHD year 1 utility decreased by 10%	14,638
	Utilities	Stroke years 2+ utility decreased by 10%	14,638
	Costs	Stroke years 2+ cost decreased by 10%	14,638
	Costs	Stroke year 1 cost decreased by 10%	14,638
	Costs	Renal failure cost decreased by 10%	14,633
	Costs	Heart failure year 1 cost decreased by 10%	14,632
	Costs	Myocardial infarction year 1 cost decreased by 10%	14,630
	Utilities	Heart failure years 2+ utility decreased by 10%	14,629
	Utilities	Neuropathy year 1 utility decreased by 10%	14,625
	Costs	IHD year 1 cost decreased by 10%	14,625
	Costs	Amputation year 1 cost decreased by 10%	14,623
	Utilities	Stroke year 1 utility decreased by 10%	14,622
	Utilities	Heart failure year 1 utility decreased by 10%	14,621
	Costs	Blindness years 2+ cost decreased by 10%	14,621
	Costs	Amputation years 2+ cost decreased by 10%	14,621
	Costs	Ulcer cost decreased by 10%	14,621
	Utilities	Ulcer utility decreased by 10%	14,620
	Costs	Blindness year 1 cost decreased by 10%	14,620
	Utilities	Blindness years 2+ utility decreased by 10%	14,619
	Utilities	Macular oedema utility decreased by 10%	14,618
	Utilities	Amputation years 2+ utility decreased by 10%	14,618

	Utilities	Amputation year 1 utility decreased by 10%	14,618
	Utilities	Myocardial infarction year 1 utility decreased by 10%	14,618
	Costs	Macular oedema cost decreased by 10%	14,618
	Utilities	Blindness year 1 utility decreased by 10%	14,617
	Utilities	Myocardial infarction years 2+ utility decreased by 10%	14,617
	Costs	Myocardial infarction years 2+ cost decreased by 10%	14,617
	Utilities	CKD stage 4 utility decreased by 10%	14,616
	Utilities	CKD stage 4 utility increased by 10%	14,616
	Utilities	CKD stage 3 utility decreased by 10%	14,616
	Utilities	CKD stage 3 utility increased by 10%	14,616
	Utilities	Revascularization years 2+ utility decreased by 10%	14,616
	Utilities	Revascularization years 2+ utility increased by 10%	14,616
	Utilities	Revascularization year 1 utility decreased by 10%	14,616
	Utilities	Revascularization year 1 utility increased by 10%	14,616
	Utilities	Myocardial infarction years 2+ utility increased by 10%	14,616
	Costs	CKD stage 4 cost decreased by 10%	14,616
	Costs	CKD stage 4 cost increased by 10%	14,616
	Costs	Myocardial infarction years 2+ cost increased by 10%	14,616
	SEMA treatment	Haemoglobin constant after intensification to insulin	14,616
	SEMA treatment	Haemoglobin constant during treatment	14,616
	TZP treatment	Haemoglobin constant after intensification to insulin	14,616
	TZP treatment	Haemoglobin constant during treatment	14,616
	Cohort	Baseline college education decreased by 10%	14,616

	Cohort	Baseline college education increased by 10%	14,616
	Utilities	Renal failure utility increased by 10%	14,615
	Utilities	Blindness year 1 utility increased by 10%	14,615
	Utilities	Myocardial infarction year 1 utility increased by 10%	14,615
	Costs	Macular oedema cost increased by 10%	14,615
	Utilities	Macular oedema utility increased by 10%	14,614
	Utilities	Amputation years 2+ utility increased by 10%	14,614
	Utilities	Amputation year 1 utility increased by 10%	14,614
	Utilities	Blindness years 2+ utility increased by 10%	14,613
	Utilities	Ulcer utility increased by 10%	14,613
	Utilities	Heart failure year 1 utility increased by 10%	14,612
	Costs	Blindness years 2+ cost increased by 10%	14,612
	Costs	Blindness year 1 cost increased by 10%	14,612
	Costs	Amputation years 2+ cost increased by 10%	14,612
	Costs	Ulcer cost increased by 10%	14,612
	Utilities	Stroke year 1 utility increased by 10%	14,611
	SEMA treatment	LDL change decreased by 10%	14,611
	Costs	Amputation year 1 cost increased by 10%	14,609
	Utilities	Neuropathy year 1 utility increased by 10%	14,608
	Costs	IHD year 1 cost increased by 10%	14,608
	Costs	Non-diabetes related mortality calculated based on BRAVO risk equation	14,604
	Country	Non-diabetes related mortality calculated based on UKPDS OM2 risk equation	14,604
	Country	Heart failure years 2+ utility increased by 10%	14,603

	Costs	Myocardial infarction year 1 cost increased by 10%	14,602
	Costs	Heart failure year 1 cost increased by 10%	14,601
	Costs	Renal failure cost increased by 10%	14,599
	Utilities	IHD year 1 utility increased by 10%	14,595
	Costs	Stroke years 2+ cost increased by 10%	14,595
	Costs	Stroke year 1 cost increased by 10%	14,595
	Utilities	Stroke years 2+ utility increased by 10%	14,594
	Costs	Heart failure years 2+ cost increased by 10%	14,593
	Costs	IHD years 2+ cost increased by 10%	14,590
	Utilities	IHD years 2+ utility increased by 10%	14,589
	TZP treatment	HDL constant after intensification to insulin	14,589
	Utilities	Neuropathy years 2+ utility increased by 10%	14,575
	Costs	Severe hypo cost increased by 10%	14,572
	Cohort	Baseline SBP increased by 10%	14,567
	Cohort	Baseline age increased by 10%	14,563
	Costs	Neuropathy cost increased by 10%	14,562
	Costs	Revascularization cost increased by 10%	14,561
	Utilities	Severe hypo utility increased by 10%	14,518
	Utilities	Non-severe hypo utility increased by 10%	14,505
	TZP treatment	QoL decrement on treatment years 2+ decreased by 10%	14,399
	TZP treatment	HDL change increased by 10%	14,306
	SEMA treatment	BMI change decreased by 10% on intensification to insulin	14,300
	Cohort	Percentage male at baseline decreased by 10%	14,276

	Cohort	Percentage smokers at baseline decreased by 10%	14,269
	SEMA treatment	LDL change increased by 10%	14,268
	TZP treatment	QoL decrement on insulin year 1 decreased by 10%	14,205
	Cohort	Baseline age decreased by 10%	14,199
	TZP treatment	HbA1c change increased by 10% on intensification to insulin	14,197
	SEMA treatment	eGFR constant after intensification to insulin	14,190
	TZP treatment	QoL decrement on insulin year 1 decreased by 10%	14,182
	SEMA treatment	QoL decrement on insulin year 1 increased by 10%	14,170
	Cohort	Baseline BMI increased by 10%	14,166
	TZP treatment	Heart rate constant after intensification to insulin	14,153
	SEMA treatment	Treatment costs increased by 10% in year 1 of insulin treatment	14,141
	SEMA treatment	QoL decrement on treatment year 1 increased by 10%	14,126
	SEMA treatment	BMI change increased by 10% on intensification to insulin	14,118
	SEMA treatment	HDL change increased by 10%	14,114
	TZP treatment	WBC constant during treatment	14,114
	TZP treatment	Treatment costs decreased by 10% in year 1	14,108
	TZP treatment	LDL change increased by 10%	14,063
	Country	Renal failure risk estimated using UKPDS OM2 risk formula	14,060
	TZP treatment	HDL change decreased by 10% on intensification to insulin	14,052
	SEMA treatment	SBP change decreased by 10% on intensification to insulin	14,044
	SEMA treatment	QoL decrement on treatment years 2+ increased by 10%	14,011
	TZP treatment	SBP change decreased by 10% on intensification to insulin	13,965
	Cohort	Baseline serum lipid levels worsened by 10% (TC, HDL and LDL)	13,962

	TZP treatment	LDL change decreased by 10% on intensification to insulin	13,839
	TZP treatment	SBP change increased by 10%	13,826
	SEMA treatment	LDL change increased by 10% on intensification to insulin	13,783
	SEMA treatment	LDL change decreased by 10% on intensification to insulin	13,770
	SEMA treatment	HbA1c change increased by 10% on intensification to insulin	13,740
	TZP treatment	BMI change increased by 10%	13,731
	SEMA treatment	BMI follows UKPDS progression during treatment	13,655
	TZP treatment	SBP change increased by 10% on intensification to insulin	13,600
	SEMA treatment	Treatment costs increased by 10% in year 1	13,590
	SEMA treatment	HDL change decreased by 10% on intensification to insulin	13,589
	TZP treatment	HDL change decreased by 10%	13,550
	SEMA treatment	HDL change decreased by 10%	13,548
	SEMA treatment	SBP change increased by 10% on intensification to insulin	13,541
	Cohort	Baseline race 100% Black	13,454
	Cohort	Baseline race 100% White	13,454
	Cohort	Baseline SBP decreased by 10%	13,440
	Cohort	Baseline race 100% Indian	13,375
	SEMA treatment	BMI change decreased by 10%	13,350
	TZP treatment	BMI change decreased by 10% on intensification to insulin	13,290
	SEMA treatment	HbA1c change decreased by 10% on intensification to insulin	13,178
	TZP treatment	Heart rate constant during treatment	13,068
	SEMA treatment	HbA1c change decreased by 10%	13,048
	Cohort	Baseline duration of diabetes increased by 10%	13,026

	Cohort	Baseline HbA1c increased by 10%	12,911
	SEMA treatment	Treatment costs increased by 10% in years 2+	12,746
	TZP treatment	HDL constant during treatment	12,703
	SEMA treatment	QoL decrement on treatment year 1 decreased by 10%	12,394
	SEMA treatment	Severe hypo rate increased by 10%	12,358
	TZP treatment	Non-severe hypo rate decreased by 10%	12,149
	TZP treatment	Treatment costs decreased by 10% in year 1	12,128
	TZP treatment	HbA1c change increased by 10%	12,049
	SEMA treatment	eGFR constant during treatment	11,927
	TZP treatment	Severe hypo rate decreased by 10%	11,896
	Country	Discount rate set to 0% per annum on costs and benefits	11,842
	SEMA treatment	BMI constant after intensification to insulin	11,739
	TZP treatment	Treatment costs decreased by 10% in years 2+	11,286
	SEMA treatment	Non-severe hypo rate increased by 10%	11,207
	TZP treatment	QoL decrement on insulin years 2+ decreased by 10%	10,784
	TZP treatment	Treatment costs decreased by 10% in years 2+ of insulin treatment	10,689
	SEMA treatment	QoL decrement on insulin years 2+ increased by 10%	10,674
	SEMA treatment	Treatment costs decreased by 10% in years 2+ of insulin treatment	10,536
	SEMA treatment	SBP follows UKPDS progression during treatment	9,377
	TZP treatment	LDL constant during treatment	8,903
	SEMA treatment	LDL constant after intensification to insulin	8,443
	TZP treatment	SBP constant after intensification to insulin	6,349
	TZP treatment	HbA1c constant during treatment, intensification after 4 years	3,153

TZP treatment	HbA1c constant after intensification to insulin	149

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HDL: high density lipoprotein cholesterol; IHD: ischaemic heart disease; LDL: low density lipoprotein cholesterol; QoL: quality of life; SEMA: semaglutide; SBP; systolic blood pressure; TZP: tirzepatide.

ICERs for tirzepatide 10 mg versus semaglutide 1.0 mg were below £20,000 per QALY gained for 224 out of 232 one-way sensitivity analyses performed. There were two scenarios where semaglutide 1.0 mg improved QALYs and cost less than tirzepatide 10 mg, both of which involved substantial changes to the HbA1c profile to favour semaglutide:

- In the sensitivity analysis where HbA1c was held constant in the semaglutide arm following intensification to insulin therapy (whereas HbA1c increased over time in the tirzepatide arm according to the UKPDS OM2 progression equation), there was a large HbA1c benefit for semaglutide from year 10 to year 50 of the simulation leading to improved clinical outcomes
- Similarly, in the sensitivity analysis where HbA1c was held constant at 6.1% during semaglutide treatment (and in the tirzepatide arm HbA1c increased according to the UKPDS OM2 progression equation), there was a large HbA1c benefit for semaglutide from year 2 to year 15 of the simulation leading to improved clinical outcomes

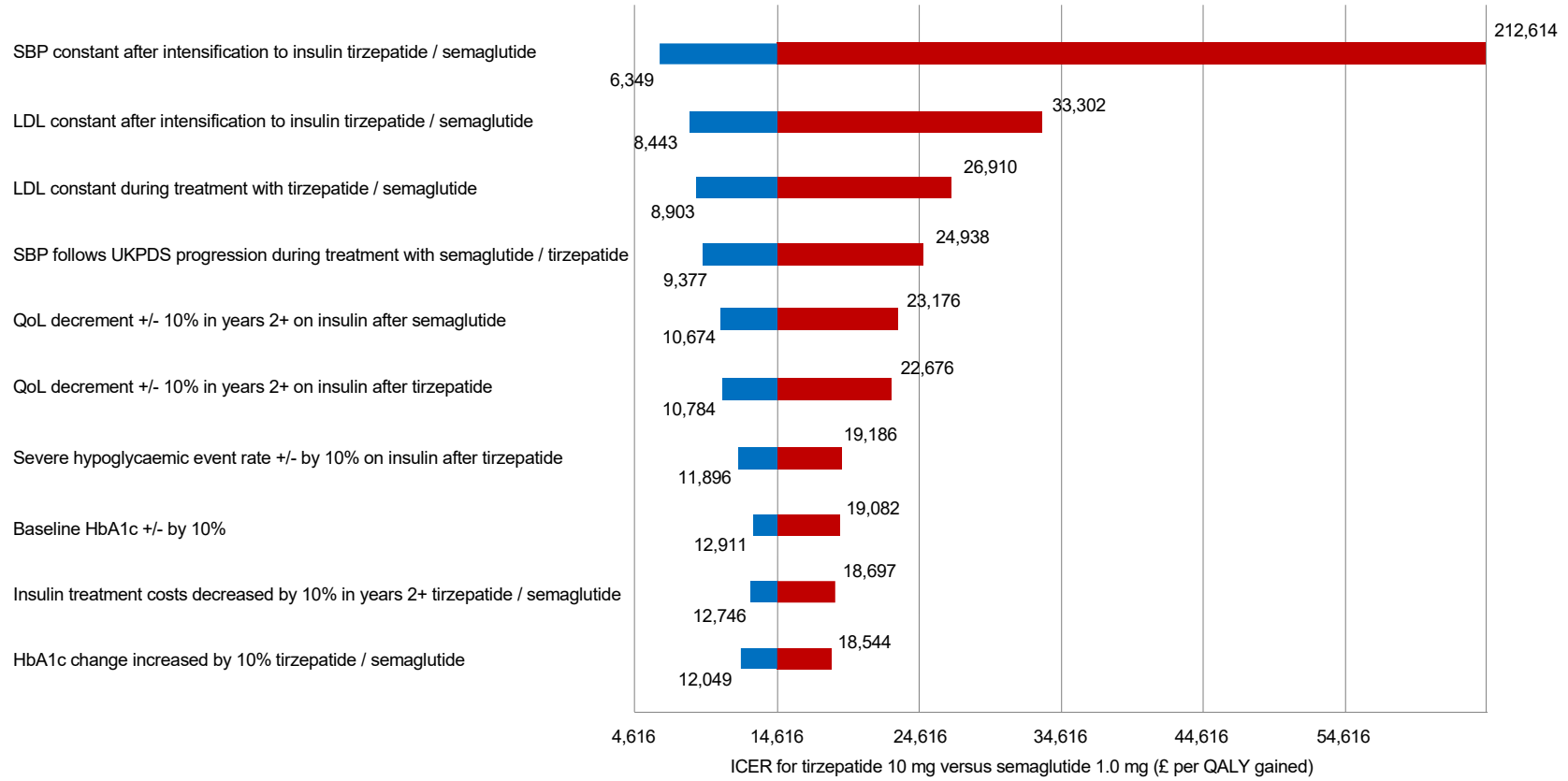
High ICERs were observed when certain risk factors were held constant over time in the semaglutide 1.0 mg and allowed to increase over time in the tirzepatide 10 mg arm. These included:

- In the analysis where SBP was held constant in the semaglutide 1.0 mg treatment arm following intensification to insulin therapy, there was a benefit of over 10 mmHg for semaglutide over approximately 45 years of the simulation leading to only a very small incremental QALY benefit for tirzepatide 10 mg and a high ICER (Figure 1). Incremental costs were a little more than in the base case because there were fewer complications in the semaglutide arm in this analysis due to the SBP benefit. This high ICER, assuming a persistent 10 mmHg benefit over decades after semaglutide treatment, is not a reflection of a possible clinical scenario but rather identifies the effect of stress testing this model input to extreme values. In contrast, holding SBP constant in the tirzepatide 10 mg treatment arm produced an ICER of £6,349 per QALY gained versus semaglutide 1.0 mg, driven by a very high QALY benefit for semaglutide, while the incremental costs were also a little lower than in the base case due to complications avoided in the tirzepatide arm due to the large SBP benefit.
- A similar analysis holding LDL constant over time in the semaglutide 1.0 mg treatment arm produced an ICER of approximately £33,302 per QALY gained, due to the persistent LDL benefit for semaglutide over 40 years of the simulation. When LDL was held constant in the tirzepatide 10 mg treatment arm following insulin intensification, the ICER was £8,443 per QALY gained.
- Holding LDL constant during treatment in the semaglutide 1.0 mg arm whilst LDL increased in the tirzepatide arm according to the UKPDS OM2 progression equation led to notably lower LDL on semaglutide for the first 10 years of the simulation, leading to an ICER of approximately £26,910 per QALY gained. The corresponding approach in the tirzepatide 10 mg arm produced an ICER of £8,903 per QALY gained.
- When SBP was held constant in the semaglutide arm but progressed according to the UKPDS OM2 equation in the tirzepatide arm during treatment,

	the notable difference in SBP levels led to a smaller incremental QALY benefit for tirzepatide and an ICER of £24,938 per QALY gained. In the corresponding analysis (where SBP was constant on tirzepatide and increased on semaglutide), the ICER was £9,377 per QALY gained. • When the disutility associated with BMI in years 2+ of insulin treatment was decreased by 10% in the semaglutide treatment arm or increased by 10% in the tirzepatide treatment arm, the ICERs for tirzepatide versus semaglutide was around £23,000 per QALY gained. Correspondingly, when the same disutility was increased by 10% in the semaglutide arm or decreased in the tirzepatide arm, the ICERs were approximately £10,700 per QALY gained. All other ICERs in the one-way sensitivity analysis were less than £20,000 per QALY gained (Table 5).

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

Figure 1: Tornado diagram of the 10 most influential input parameters (tirzepatide 10 mg versus semaglutide 1.0 mg)



Abbreviations: HbA1c: glycated haemoglobin; ICER: incremental cost effectiveness ratio; LDL: low density lipoprotein; QALY: quality-adjusted life year; QoL: quality of life; SBP: systolic blood pressure; UKPDS: UK Prospective Diabetes Study.

3

A scenario analysis based on direct head-to-head results against semaglutide from SURPASS-2

In response to the request, a scenario analysis using cohort characteristics and treatment effects from the SURPASS-2 trial was performed with the results summarized in Table 6. Long-term projections with the PRIME T2D Model showed that all three doses of tirzepatide were associated with improvements in life expectancy and quality-adjusted life expectancy versus semaglutide 1.0 mg based on the results of the SURPASS-2 trial. For all three doses of tirzepatide, direct costs were higher than with semaglutide 1.0 mg leading to incremental cost-effectiveness ratios (ICERs) ranging from £12,019 to £14,096 per QALY gained (Table 6). ICERs remained relatively stable across all three doses of tirzepatide because increases in incremental costs with increasing doses was balanced by improvements in effectiveness (QALYs) relative to semaglutide 1.0 mg. Evaluation of net health benefit (NHB) assuming a willingness to pay of £20,000 per QALY gained showed tirzepatide 10 mg to be associated with the greatest benefit (0.037 QALYs) over semaglutide 1.0 mg.

Table 6: Summary of SURPASS-2 scenario analysis results for tirzepatide 5, 10 and 15 mg versus semaglutide 1.0 mg

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Semaglutide 1.0 mg	[redacted]	14.993	9.919	--	--	--	--	--
Tirzepatide 5 mg	[redacted]	15.016	9.960	579	0.023	0.041	14,096	0.012
Tirzepatide 10 mg	[redacted]	15.039	10.010	1,103	0.046	0.092	12,019	0.037
Tirzepatide 15 mg	[redacted]	15.048	10.036	1,640	0.055	0.117	14,013	0.035

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * pairwise comparison of tirzepatide versus comparator.

4

Sensitivity analyses around the model averaging approach used to predict the risk of micro- and macrovascular complications

In response to the request, a scenario analysis where UKPDS OM2 risk equations only were used (instead of model averaging) was performed with the results summarized in Table 7. In this scenario analysis, there was a marginally lower risk of diabetes-related complications in general compared with the base case simulation of tirzepatide 10 mg versus semaglutide 1.0 mg. This led to slightly higher overall estimates of life expectancy and quality-adjusted life expectancy in the scenario analysis. Total direct costs were comparable between the analyses as the increased life expectancy (the associated costs of living longer in the simulation) in the scenario analysis off-set the reduced cost of diabetes-related complications.

In the scenario analysis, tirzepatide 10 mg was still associated with improvements in life expectancy and quality-adjusted life expectancy versus semaglutide 1.0 mg, although the benefits were marginally smaller than in the base case analysis (Table 7). Incremental costs with tirzepatide 10 mg versus semaglutide 1.0 mg were comparable with the base case analysis leading to an ICER of £15,521 in the scenario analysis, which is comparable with the base case (£14,616 per QALY gained).

Table 7: Summary of scenario analysis using only UKPDS risk equations results for tirzepatide 10 mg versus semaglutide 1.0 mg

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.439	8.917	--	--	--	--	--
Semaglutide 1.0 mg	[redacted]	13.396	8.830	1,355	0.043	0.087	15,521	0.020
Base case results for comparison								
Tirzepatide 10 mg	[redacted]	*13.155*	*8.768*	--	--	--	--	--
Semaglutide 1.0 mg	[redacted]	*13.096*	*8.673*	*1,393*	*0.059*	*0.095*	*14,616*	*0.026*

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB is calculated assuming a willingness to pay of £20,000 per QALY gained.

5

Scenario analysis in which GLP 1 RAs and tirzepatide are continued (while adding insulin) when intensifying treatment

In response to the request, a scenario analysis where GLP-1 receptor agonist therapy (or tirzepatide) was continued after the initiation of basal insulin was performed with the results summarized in Table 8. The following assumptions were used in this scenario analysis:

- Patients would intensify therapy by adding basal insulin to their existing regimen when HbA1c reached 7.5% or higher. The initiation of basal insulin was associated with a reduction in HbA1c of 0.84% based on the formula published by Willis et al. (2017).[1] Risk factor progressions were aligned with the EAG preferred base case assumptions during therapy with GLP-1 receptor agonist plus basal insulin therapy (systolic blood pressure and body mass index remained constant and other risk factors followed UKPDS OM2 progression curves).
- When HbA1c reached 7.5% for a second time, patients intensified to basal bolus therapy and GLP-1 receptor agonist (or tirzepatide) was stopped. On this second intensification, HbA1c was assumed to be reduced by 0.24% (Willi *et al.* 2017) and all other risk factors returned to baseline levels. All risk factors were assumed to follow UKPDS OM2 progression curves for the remainder of the simulation.

In this scenario analysis, tirzepatide 10 mg was associated with improvements in life expectancy and quality-adjusted life expectancy versus semaglutide 1.0 mg (Table 8). Higher incremental costs with tirzepatide 10 mg versus semaglutide 1.0 mg led to an ICER of £14,720 in this scenario analysis, which is comparable with the base case.

Table 8: Summary of continued GLP-1 receptor agonist treatment scenario analysis results for tirzepatide 10 mg versus semaglutide 1.0 mg

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.211	8.891	--	--	--	--	--
Semaglutide 1.0 mg	[redacted]	13.125	8.766	1,838	0.086	0.125	14,720	0.033

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB is calculated assuming a willingness to pay of £20,000 per QALY gained.

6

Using a baseline utility value that is lower than the utility score for the general population at the same age

The committee requested a scenario analysis using a baseline utility value that is lower than the utility score for the general population at the same age. In response to the request, a scenario analysis using a lower baseline utility than in the submitted base case was performed with the results summarized in Table 9, Table 10 and Table 11. There are a few points to note with respect to this scenario analysis:

- The EAG preferred base case scenario uses an age-adjusted approach to the evaluation of quality-adjusted life expectancy based on the publication by Ara and Brazier (2010).[2] This approach uses a regression function to define baseline utility based on age and gender and incorporates the impact on quality of life with selected complications (macrovascular complications). It is therefore not possible to adjust the baseline utility with this age-adjusted approach, and an additive approach to combining utilities had to be used instead for the lower baseline utility scenario analysis.
- The Ara and Brazier age-adjusted approach suggested by the EAG does not fully capture the benefits of complications avoided (with more efficacious treatments) and, as a result, ICERs for tirzepatide are higher with the age-adjusted approach than with an additive approach to combining utilities (as the latter captures the quality of life impact of all complications modelled), regardless of the specific baseline utility value used in the latter approach.
- Changing the baseline utility has a very modest impact on cost-effectiveness as, essentially, the change is the same in both treatment and incremental quality-adjusted life expectancy remains largely unchanged. The only difference in incremental outcomes is associated with the survival benefit of more effective interventions over less effective comparators.
- For the scenario analysis, a baseline utility value of 0.785 for type 2 diabetes with no complications based on Clarke et al. was used.[3] This value is lower than the value of 0.815 used in previous health economic evaluations performed by NICE and used in the original submission on tirzepatide, which was based on the data reported by Alva et al.[4] It is perhaps noteworthy that a recent systematic review by Redenz *et al.* reported a utility of 0.815 (95% confidence interval 0.808-0.823) based on pooled data from 5-level version of EQ-5D studies for patients with T2D and no complications.[5] The pooled estimate was lower with the 3-level version of the EQ-5D instrument. The authors concluded that, in comparison with direct elicitation

methods, the 5-level EQ-5D showed the best performance among the instruments evaluated.

In the scenario analysis, projections with the PRIME T2D Model over a 50-year time horizon showed that all three doses of tirzepatide were associated with improvements in quality-adjusted life expectancy versus all comparators evaluated. Tirzepatide 5 mg was dominant to liraglutide 1.8 mg and was associated with ICERs ranging between £4,792 to £15,898 per QALY gained (Table 9). Tirzepatide 10 mg was associated with ICERs between £1,576 and £13,902 per QALY gained (Table 10). Tirzepatide 15 mg was associated with ICERs between £3,765 and £13,488 per QALY gained versus comparators (Table 11).

Table 9: Summary of lower baseline utility (0.785) scenario analysis results for tirzepatide 5 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	9.014	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.910	705	0.059	0.104	6,792	0.069
Dulaglutide 3.0 mg	[redacted]	13.076	8.932	644	0.046	0.082	7,900	0.049
Dulaglutide 4.5 mg	[redacted]	13.092	8.954	628	0.030	0.060	10,495	0.028
Semaglutide 0.5 mg	[redacted]	13.075	8.929	682	0.047	0.085	8,059	0.051
Semaglutide 1.0 mg	[redacted]	13.096	8.969	708	0.026	0.045	15,898	0.009
Oral semaglutide 7 mg	[redacted]	13.049	8.889	742	0.073	0.125	5,959	0.087
Oral semaglutide 14 mg	[redacted]	13.074	8.938	719	0.048	0.076	9,444	0.040
Liraglutide 1.2 mg	[redacted]	13.032	8.874	672	0.090	0.140	4,792	0.107
Liraglutide 1.8 mg	[redacted]	13.054	8.895	-409	0.068	0.119	Dominant	0.140

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 10: Summary of lower baseline utility (0.785) scenario analysis results for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	9.070	--	--	--	--	--

Dulaglutide 1.5 mg	[redacted]	13.063	8.910	1,389	0.092	0.159	8,715	0.090
Dulaglutide 3.0 mg	[redacted]	13.076	8.932	1,329	0.079	0.137	9,685	0.071
Dulaglutide 4.5 mg	[redacted]	13.092	8.954	1,312	0.063	0.115	11,367	0.050
Semaglutide 0.5 mg	[redacted]	13.075	8.929	1,367	0.080	0.140	9,742	0.072
Semaglutide 1.0 mg	[redacted]	13.096	8.969	1,393	0.059	0.100	13,902	0.031
Oral semaglutide 7 mg	[redacted]	13.049	8.889	1,427	0.106	0.180	7,918	0.109
Oral semaglutide 14 mg	[redacted]	13.074	8.938	1,403	0.081	0.132	10,652	0.062
Liraglutide 1.2 mg	[redacted]	13.032	8.874	1,356	0.123	0.196	6,926	0.128
Liraglutide 1.8 mg	[redacted]	13.054	8.895	276	0.101	0.175	1,576	0.161

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 11: Summary of lower baseline utility (0.785) scenario analysis results for tirzepatide 15 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.175	9.113	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.910	1,937	0.112	0.203	9,538	0.106
Dulaglutide 3.0 mg	[redacted]	13.076	8.932	1,877	0.099	0.181	10,375	0.087
Dulaglutide 4.5 mg	[redacted]	13.092	8.954	1,860	0.083	0.159	11,689	0.066
Semaglutide 0.5 mg	[redacted]	13.075	8.929	1,915	0.100	0.184	10,406	0.088
Semaglutide 1.0 mg	[redacted]	13.096	8.969	1,941	0.079	0.144	13,488	0.047
Oral semaglutide 7 mg	[redacted]	13.049	8.889	1,975	0.126	0.224	8,820	0.125
Oral semaglutide 14 mg	[redacted]	13.074	8.938	1,951	0.101	0.175	11,122	0.078
Liraglutide 1.2 mg	[redacted]	13.032	8.874	1,904	0.143	0.240	7,950	0.144
Liraglutide 1.8 mg	[redacted]	13.054	8.895	824	0.121	0.219	3,765	0.178

	Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator.
7	**Using the multiplicative method to combine disutilities in the base case or provide a rationale for why a multiplicative approach is not appropriate** A multiplicative approach is not appropriate for this appraisal because (1) it does not align with approved NICE assessments for other incretin therapies, and (2) there is limited evidence to support the use of a multiplicative approach in T2D. The utilities used in the present modelling analysis were originally derived as additive utilities using the EQ-5D instrument (comparing the quality of life utility associated with living with a complication versus without). All of the utilities/disutilities used were published as additive utilities (i.e. occurrence of complication x is associated with a quality of life decrement of y; not a multiplicative reduction of y% in utility score) therefore retaining consistency in our modelling approach. Had the utilities been derived for a multiplicative model, the resulting values would almost certainly be different than the additive values published and used in the present analysis. Previously in diabetes the additive approach for combining utilities has predominated to the extent where it could be considered the standard approach in T2D modelling. Recent NICE appraisals in diabetes have all use the additive approach including the 2022 update to the NICE T2D guideline (NG28) (Table 12). In fact, none of the health economic analyses in T2D available on the NICE website used a multiplicative approach to combine quality of life utilities. Furthermore, appraisals for other incretin therapies (TA664 and TA875) for weight management and obesity have also used the additive approach. The predominant use of the additive approach was described in the NICE appraisal of semaglutide for weight management and obesity (TA875, published 4 months ago in March 2023). In the committee papers, the Southampton EAG acknowledged the research by Gough et al. (2009) which concluded that HRQoL decrements associated with T2D and obesity showed no significant interaction and therefore could be assumed to be additive.[6] Additionally, studies by Sullivan et al. (2011) and Hayes et al. (2016) also reported multiple co-morbidities for diabetes, and considered that it was reasonable to treat co-morbidities as independent and add utility decrements.[7, 8] The EAG concluded that *"we agree with the company and consider it is reasonable to treat co-morbidities as independent and add utility decrements. In addition, we note that this approach was also taken in TA664."* **Table 12: Summary of NICE guideline and technology appraisal health economic analyses in diabetes, weight management and obesity that use and additive approach to combining quality of life utilities**

Example	Year	Title/URL
1	2022	Type 1 and 2 diabetes in adults: diagnosis and management. Economic modelling for periodontal treatment in adults with type 1 and type 2 diabetes. NICE guideline NG17, NG28. Economic model report
		www.nice.org.uk/guidance/ng28/evidence/economic-model-report-on-periodontal-treatment-in-adults-with-type-1-and-type-2-diabetes-pdf-11131191037

2	2022	Type 2 diabetes in adults: management. Economic modelling for continuous glucose monitoring in adults with type 2 diabetes. Economic model report
		www.nice.org.uk/guidance/ng28/evidence/economic-model-report-pdf-11013295213
3	2022	Type 2 diabetes in adults: management (update). Health economic model report [NG28]
		www.nice.org.uk/guidance/ng28/evidence/health-economic-model-report-pdf-10959500845/
4	2013	Dapagliflozin in combination therapy for treating type 2 diabetes. Technology appraisal guidance [TA288]
		https://www.nice.org.uk/guidance/ta288
5	2016	Dapagliflozin in triple therapy for treating type 2 diabetes. Technology appraisal guidance [TA418]
		https://www.nice.org.uk/guidance/ta418
6	2026	Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes
		https://www.nice.org.uk/guidance/ta390
7	2015	Empagliflozin in combination therapy for treating type 2 diabetes. Technology appraisal guidance [TA336]
		https://www.nice.org.uk/guidance/ta336
8	2023	Semaglutide for managing overweight and obesity. Technology appraisal guidance [TA875]
		https://www.nice.org.uk/guidance/ta875
9	2020	Liraglutide for managing overweight and obesity [TA664]
		https://www.nice.org.uk/guidance/TA664

The company acknowledges that NICE has recently changed its manual to state that the multiplicative approach is *"generally preferred"*. The published paper by Dawoud et al. explains the rationale for the change but the evidence underpinning this change is limited.[9] Whilst the paper states that the additive approach can lead to utility values close to zero, or even negative utility scores, this is not a valid concern with respect to the present diabetes modelling analysis or for diabetes models in general. This can be demonstrated by the extreme example of a simulated patient in the model with a history of two conditions experiencing three end-stage complications (myocardial infarction, stroke and onset of blindness) in a single year (Table 13), when the annual utility score does not get close to zero even in such an unlikely scenario.

Table 13: Example additive utility calculation for a patient with a history of two comorbidities experiencing three complications in a given year of the modelling simulation

Health state / event	Utility / disutility	Title / URL
Utility with no complications	0.815	Baseline utility used in the original submission
Comorbidity 1	-0.108	History of heart failure
Comorbidity 2	-0.066	History of neuropathy
Event 1	-0.055	Myocardial infarction event
Event 2	-0.164	Stroke event
Event 3	-0.074	Onset of blindness
Total	**0.348**	**Utility score for the year with two comorbidities and three events**

At this moment in time, there is no evidence that would support the use of a multiplicative approach over an additive approach in T2D in terms of most accurately representing utilities for multiple comorbidities. As stated in the paper from Ara and Brazier 2017 publication for estimating HSUV for comorbidities: *"It is not known which of the additive and multiplicative methods would produce the most accurate estimates for more than two concurrent comorbidities... it seems likely that the multiplicative method might be the preferred method, but this is an area where additional research is justified."*[10] Therefore, there is still a considerable amount of research required to determine the appropriate methods when estimating additional comorbidities.

Given the clear precedent for the use of the additive approach (Table 12), supported by the conclusions of Gough et al. (2009), Sullivan et al. (2011) and Hayes et al. (2016), it would be premature to deviate to the multiplicative approach for the assessment of tirzepatide (and other new treatments in this therapeutic area) in the absence of evidence that the multiplicative approach is more accurate.[6-8] Moreover, it would create inconsistencies in terms of how new interventions are being assessed, particularly in light of NG28 in June, 2022 and TA875 in March, 2023, which are both of relevance to the assessment of tirzepatide.

8	**Cost-effectiveness results when analysis is run in CORE Diabetes Model and/or UKPDS OM2** The committee requested cost-effectiveness results from an analysis is run in CORE Diabetes Model (CDM) and/or UKPDS OM2. Please refer to the CDM report supplied as a standalone file alongside these responses.
9	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B1b. The CS states that a de novo model was developed because *"Models developed prior to 2016, including UKPDS OM1 and OM2 and the IQVIA CORE Diabetes Model, have been shown to under predict CV benefits from the GLP-1 RA class in certain situations. One reason for this could be that models developed earlier than 2016 do not fully capture the benefits of reduced body weight as***

they tend to be based on cohorts using traditional therapies without any weight loss benefit." **This statement is supported by CS reference 140 (Shao et al., Diabetes Care 2020).**

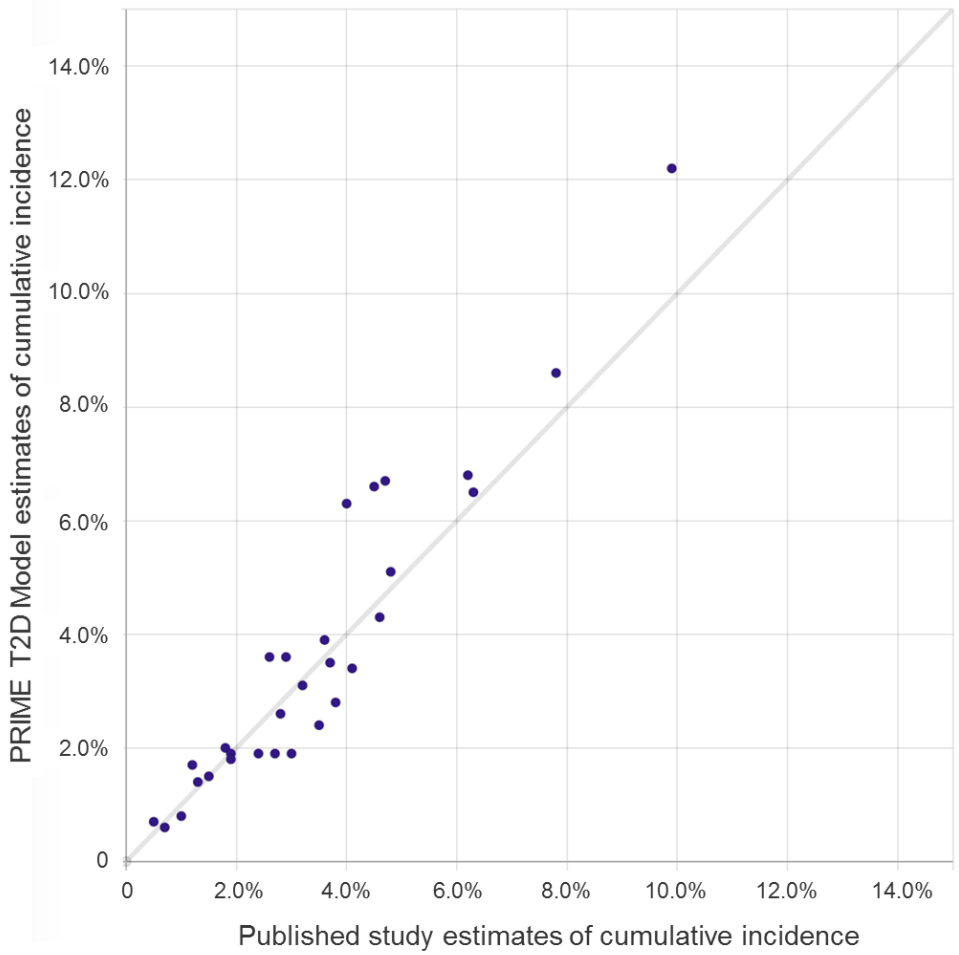
Please provide evidence that the developed de novo model, specifically the current implementation as in the CS, has a better performance to predict complications (including cardiovascular events) compared with existing diabetes models.

Key response points

- The PRIME T2D Model has a recent, published validation analysis that supports its ability to predict complications in real-life clinical studies [for clarity, this is the same version of the model used in the current submission and all validations were performed using model averaging], including CVOTs with GLP-1 receptor agonists (REWIND and LEADER), other CVOTs (EMPA-REG OUTCOME and DEVOTE), UK cohort studies (Shah et al. 2015)[11] and the Lipids in Diabetes Study (LDS)] as well as the ACCORD cardiovascular outcomes study.[12] This validation includes comparisons with UK cohort studies and cardiovascular outcomes trials with GLP-1 receptor agonists, which are both relevant to the current health economic evaluation (details are provided below). Validation scatterplots (below) also demonstrate that the PRIME T2D Model better predicts complications than the CORE Diabetes Model and the UKPDS OM2 for the EMPA-REG OUTCOME study with predicted outcomes matching the published trial outcomes more closely (i.e. closer to the line of 'no difference').
- Data presented at the Ninth Mount Hood Challenge indicated that the CORE Diabetes Model and the UKPDS OM2 provided mixed results in a validation analysis against CVOTs including EMPA-REG OUTCOME and CANVAS, with the authors noting that calibration was required to improve predictive accuracy.[13] The PRIME T2D Model has been shown to validate well against EMPA-REG OUTCOME without the need for any prior calibration (no validation against CANVAS has been performed to date).
- The most recent published validation analysis for the CORE Diabetes Model was in 2014 and showed mixed results, with an overall root mean squared percentage error of 41.3% across all validation analyses (including type 1 and type 2 diabetes validations).[14] This analysis pre-dated validation against any GLP-1 receptor agonist trials. Although an equivalent metric for the PRIME T2D Model is not available, root mean squared deviations (RMSDs)* for all external validations were 3.7% or less, which is generally consistent with a closer match to the published data than that reported by McEwan *et al.* (2014).[14]
- No single extensive validation analysis of the UKPDS OM2 has been published since Hayes et al. first described the model in 2013,[15] although there have been multiple publications describing single validation and/or calibration studies of the model (often against cohorts from other countries).[16-18] In 2022, Keng *et al.* published a validation of the UKPDS OM2 with over 10 years of follow up data from ASCEND (A Study of Cardiovascular Events in Diabetes), one of the largest trials in people with diabetes in the United Kingdom that followed participants from 2005 to 2017.[19] Keng *et al.* claimed that:
    - The UKPDS OM2 overpredicted the risks of myocardial infarction, stroke, heart failure and death
    - The performance of the UKPDS-OM2 was found to be poorer in older patients who received a diagnosis of diabetes at an older age
    - Calibration of risk equations in the UKPDS-OM2 or estimation of new risk equations is needed to predict long-term outcomes for clinical or

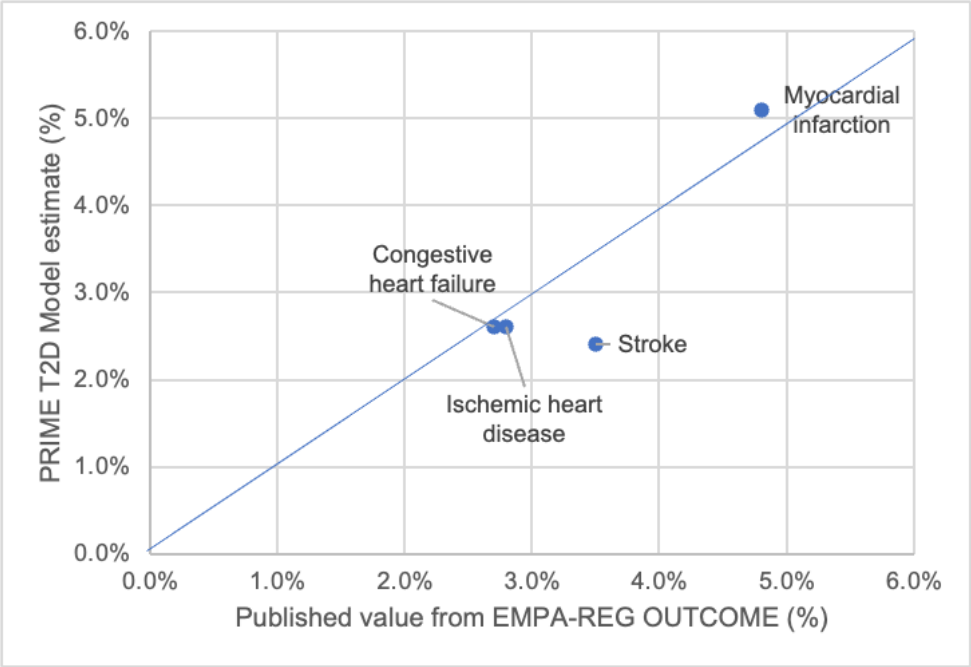
	economic analyses in contemporary cohorts such as in ASCEND ** Root mean squared deviation (RMSDs) is provided as a measure of difference between the modelling results and observed outcomes. It can be considered to reflect the average difference between the cumulative incidence of complications predicted by the model and the cumulative incidence of complications observed in the study. The root mean squared methodology is utilised to avoid positive and negative differences in cumulative incidence cancelling each other out and providing an underestimate of the differences between modelled and observed outcomes (that could occur if only mean differences were reported).* ***Additional detail*** The overall validation of the PRIME T2D Model has been published and was provided as part of the original submission in the model technical report.[12] The validation analysis compared projections using the PRIME T2D Model with published results from a broad range of studies in T2D populations, including UK cohort studies, CVOTs and studies in South East Asian populations. All root mean squared deviation (RMSD) values for the differences between published values and modelled outcomes for internal validations (against published studies used to develop the model) were 1.1% or less and all external validation RMSDs were 3.7% or less. An overall validation scatterplot is provided in Figure 2.

Figure 2: Scatterplot of the PRIME T2D Model overall validation analysis



	Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. ***Describe validation analyses versus GLP-1 CVOTs*** The PRIME T2D Model has been validated against cardiovascular outcomes trials, including EMPA-REG OUTCOME (empagliflozin), REWIND (dulaglutide) and LEADER (liraglutide), using the model averaging approach, and been shown to compare well to published outcomes.[12] In the PRIME T2D Model validation against the intervention arm from the EMPA-REG OUTCOME trial,[20] the root mean squared difference for four endpoints in the active treatment arm was 0.7%, with the PRIME T2D Model generally matching published outcomes well, although slightly underestimating the risk of stroke (see Figure 3 and the PRIME T2D Model Technical Report in the original submission).

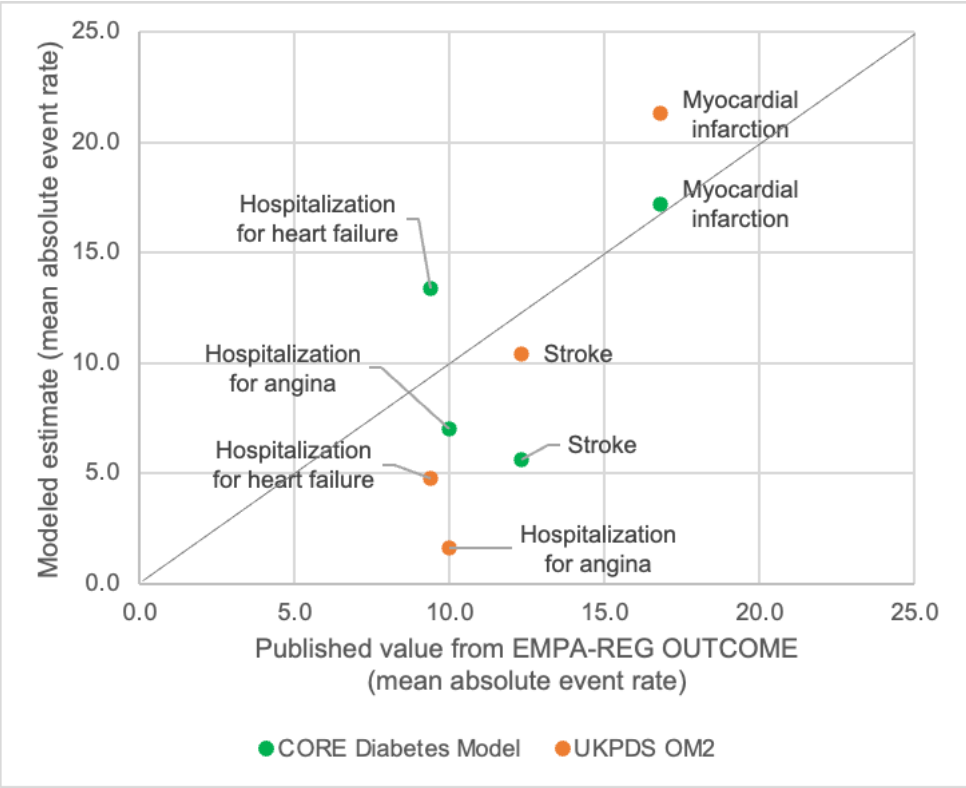
Figure 3: PRIME T2D Model validation scatterplot for the EMPA-REG OUTCOME study



Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

As outlined previously in the original submission and in the response to clarification questions, the CORE Diabetes Model and UKPDS OM2 performed poorly in validations against cardiovascular outcomes trials at the Ninth Mount Hood Challenge Meeting published in 2020.[13] Prior to calibration the CORE Diabetes Model underpredicted the risk of stroke by around 54% and the UKPDS OM2 overpredicted the risk of myocardial infarction by 27% in the active treatment arm of EMPA-REG (Figure 4). Without appropriate calibration, there is a risk that these models may under/overestimate the risk of diabetes-related complications in a cost-effectiveness evaluation, particularly when agents such as GLP-1 receptor agonists are involved that may alter cardiovascular risk profiles.

Figure 4: UKPDS OM2 and CORE Diabetes Model validation scatterplot for the EMPA-REG OUTCOME study

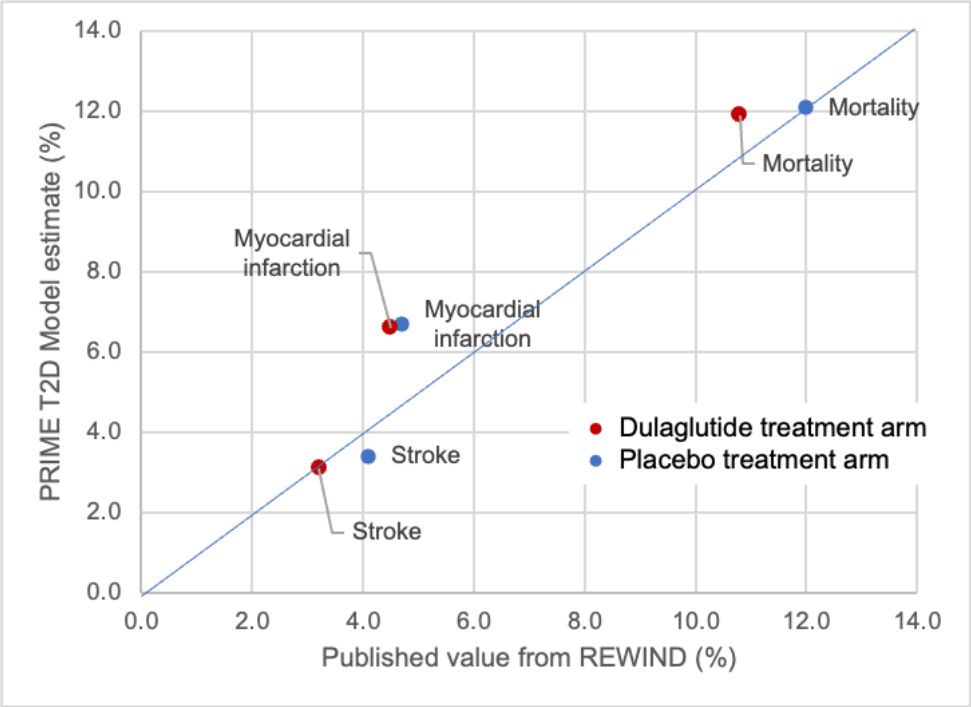


Note: Each point on the graph represents mean absolute event rate estimate from the model and the corresponding published study value for validation. Values from the models are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Crucially, at this moment in time, there are no published data that would allow the appropriate calibration of the UKPDS OM2 or CORE Diabetes Model (or any other model) for the present analysis of tirzepatide. The calibration of existing type 2 diabetes model with hazard ratios from CVOTs is a complex challenge

	with considerable potential to provide misleading results when comparing multiple interventions as recently summarized by Evans *et al.* (2023).[21] Main concerns focus on the heterogeneity of the trials, with different study durations, inclusion criteria, rescue medication protocols and endpoint definitions, which results in significant uncertainty when comparing two or more interventions evaluated in separate CVOTs, as robust adjustment for these differences is very challenging. This is compounded by differences in endpoint definitions in a given diabetes model (which need to match those in the CVOT to be suitable for calibration) and the challenge of double-counting treatment effects (the hazard ratios from CVOTs are typically not adjusted for improvements in conventional risk factors such as HbA1c). The use of unadjusted hazard ratios from multiple CVOTs in a long-term cost-effectiveness analysis has considerable potential to skew the outcomes if these challenges are not appropriately addressed. As outlined by Evans *et al.* it is likely that these challenges can only be overcome by combining patient-level data from CVOTs to prepare novel risk equations that can better model modern therapies for type 2 diabetes. However, at the present moment in time the best approach may be represented by using models that do not require calibration to the same extent that the CORE Diabetes Model and the UKPDS OM2 appear to. Validation evidence of the ability of the PRIME T2D Model to predict outcomes in populations treatment with GLP-1 receptor agonist therapy comes from the REWIND trial (as included in the original submission as part of the PRIME T2D Model Technical Report). REWIND was designed to assess the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control levels.[22] The randomized, controlled trial was conducted at 371 sites in 24 countries and recruited individuals aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes). For the validation analysis, the endpoints of MI (fatal and non-fatal), stroke (fatal and non-fatal) and death were included. Overall, the mean absolute differences between the published REWIND study values and the modelled values were 0.9% in the placebo arm and 1.1% in the dulaglutide arm (Figure 5). The RMSD was 1.2% in the placebo group and 1.4% in the dulaglutide group.

Figure 5: PRIME T2D Model validation scatterplot for the REWIND study

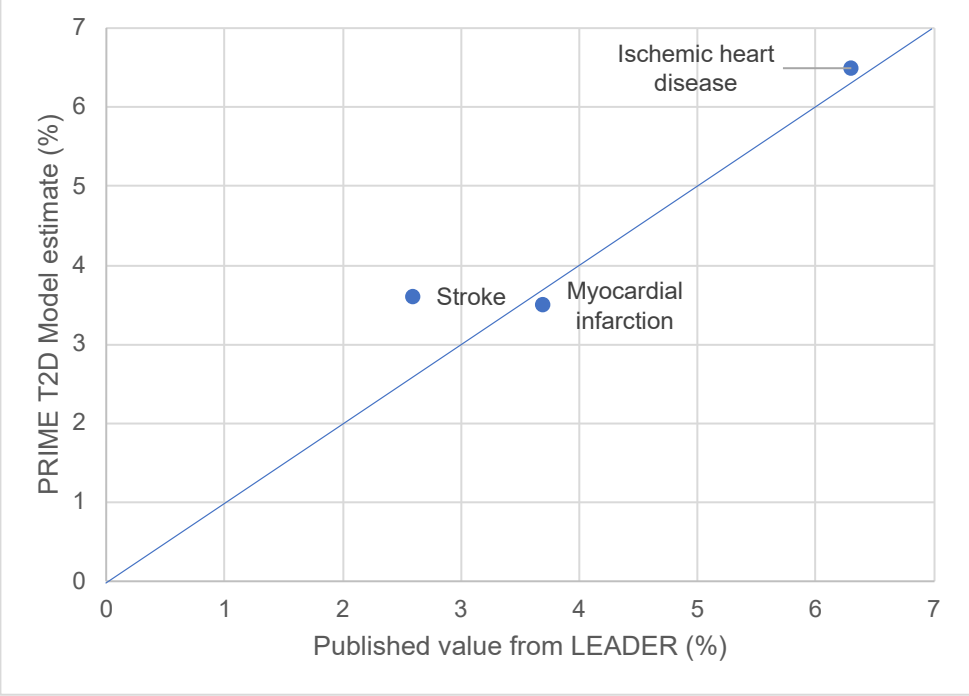


Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Additional evidence of the ability of the PRIME T2D Model to predict outcomes in populations treatment with GLP-1 receptor agonist therapy comes from the LEADER trial, which was designed to evaluate the effect of liraglutide on cardiovascular events when added to existing therapy for type 2 diabetes.[23] Median follow up was 3.8 years, a total of 9,340 patients were randomly allocated to treatment with liraglutide or placebo, and the primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. For the validation

analysis, the endpoints of MI (fatal and non-fatal), stroke (fatal and non-fatal) and ischaemic heart disease in the liraglutide treatment arm were included. Overall, the mean absolute difference between the published LEADER values and the modelled values was 0.5% and the RMSD was 0.6% (Figure 6).

Figure 6: PRIME T2D Model validation scatterplot for the LEADER study



Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

	Taken together, these data provide evidence that the PRIME T2D Model is capable of projecting plausible outcomes for populations with type 2 diabetes, including those treated with GLP-1 receptor agonists. Whilst an extensive head-to-head validation comparison with the UKPDS OM2 and CORE Diabetes Model are not possible in the time frame allowed for this response or without the consent/participation of the other modelling groups, the published evidence on validation against the EMPA-REG OUTCOME trial suggest there may be some limitations around the ability of the CORE Diabetes Model and UKPDS OM2 to project cardiovascular outcomes for a modern diabetes population without prior calibration. Moreover, given the heterogeneous nature of existing CVOT data and the fact that CVOT data on tirzepatide are not currently available, appropriate calibration is not possible within the context of the present submission. Please note that the validation endpoints considered above are focused on cardiovascular endpoints in line with published study data and represent the main contributor to complication costs in the health economic analysis. Validation of other endpoints is provided in the PRIME T2D Model Technical Report (provided as part of the original submission).
10	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B4. In Appendix N it is described that *"a weighted model averaging approach was used in which each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between model cohort and derivation cohort, the larger the weight applied to the risk equation from the respective derivation cohort. The model averaging approach was then optimized by running validation simulations to evaluate predictive performance, measured using the Chi-squared statistic, and using a genetic algorithm to minimize Chi squared by adjusting distance coefficients for each characteristic."*** **Please justify why model averaging is preferred instead of selecting a single predictive model that best matches the decision problem (with alternative models in scenario analyses).** ***Key response points*** • Model averaging is used in the PRIME T2D Model to evaluate the risk of macrovascular complications and blindness. It is designed to tailor the estimates of complication risk to best suit patient characteristics in every year of the simulation. In the present evaluation, risk equations from the UKPDS OM2 and the BRAVO Model were weighted, based on patient characteristics, to provide a combined estimate or complication risk based on the profile of each individual patient. The greater the similarity between simulated patients in the model and derivation cohort the larger the weight applied to the equation. Put most simply, low risk patients will rely more on UKPDS OM2 risk equations (derived from a low risk cohort) and high risk patients more on BRAVO risk equations (derived from a high risk cohort).[24] • Model averaging in the PRIME T2D Model is supported by the published validation analysis demonstrating the model's ability to predict complications in real-life clinical studies (for clarity, this is the same version of the model used in the current submission and all validations were performed using

model averaging).[12] This validation includes comparisons with UK cohort studies and cardiovascular outcomes trials with GLP-1 receptor agonists, which are both relevant to the current health economic evaluation.

- Model averaging offers the potential to increase the predictive power of disease models through the aggregation of multiple models derived from discreet data sets. One particular advantage of this approach is the ability to average out the influence of background risk modifiers, the impact of which are unknown within individual studies. Several publications, including three from academic research groups, have already demonstrated the benefit of model averaging within the healthcare sector.[25-28]
- Risk equations from the UKPDS OM1 and OM2 have formed the cornerstone of many health economic analyses performed by and submitted to NICE in recent years. However, there are question marks about the ability of the UKPDS OM2 risk equations to predict outcomes in CVOTs in type 2 diabetes populations with more advanced disease and receiving medications that were not available at the time of the UKPDS.[13]
- In the absence of risk equations from a long-term UK-based trial comparing tirzepatide with dulaglutide, semaglutide, oral semaglutide and liraglutide in patients with type 2 diabetes, a model averaging approach is preferable to the selection of a single risk model parameterised from a different population receiving different interventions than those relevant to the decision problem. This is because model averaging allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to the target population as well as to change over the time frame of the evaluation as simulated patients progress from having early to advanced disease (with corresponding changes to their risk profile).

Important considerations

In the PRIME T2D Model, weighted model averaging is used in the estimation of macrovascular complication risk (myocardial infarction, stroke, heart failure and ischemic heart disease), and in the risk of blindness. For each endpoint, each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between simulated patients in the model and derivation cohort the larger the weight applied to the equation. In each simulation, weights are calculated using the characteristics on a patient level. This means that different simulated patients will have different weighting of the risk equations in the simulation due to heterogeneity within a modelled cohort. In each year of the simulation, weighting of the risk equations is adjusted for age and duration of diabetes (but not other risk factors) for each patient, so the weighting of equations can change over time in any given simulation. The mathematical explication of the derivations of the weights each year is given in Section 4.3.3 of the PRIME T2D Model Technical Report, which was provided as part of the submission in the Appendices.

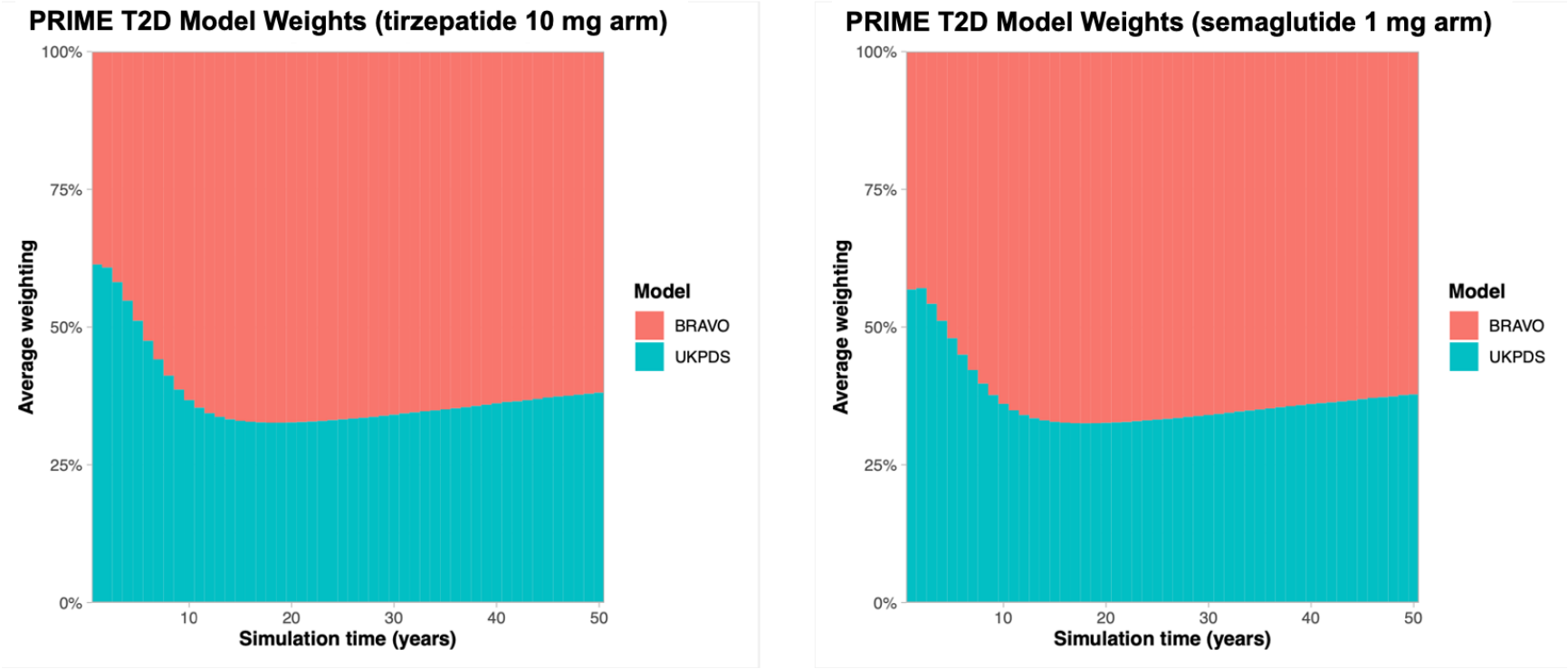
As outlined in the PRIME T2D Model Technical Report, several different published equations that could plausibly be used to estimate the risk of CVD events in patients with type 2 diabetes were identified during the development of the model. Due to the variation between equations in the CVD risk factors considered, no consensus could be reached on the best equation(s) to use in the model; an observation that is in line with previous studies.[29, 30] At an advisory board meeting during model development, it was agreed that for simplicity, comprehension and acceptance by health technology associations, it was highlighted that a single approach should be used if possible (as opposed to offering a choice of risk equations for the model users). In this context, it was agreed that a model

	averaging approach could be used to combine the equations within a single framework, analogous to the approach previously used in the development of the PRIME T1D Model and in other modelling applications.[27, 28] The data sources used in the model averaging approach were selected based on consistency of endpoint definitions and feedback at the advisory board meeting. During the development of the PRIME Type 1 Diabetes Model, it was shown that a model averaging approach, when used to evaluate the risk of cardiovascular endpoints, was superior to any individual risk equations alone. The evidence indicated that risk equations performed well in validations against the derivation populations (or similar populations) but poorly in populations with different characteristics or risk profiles. This is the essential tenet of the model averaging approach: risk equations are weighted to match the risk profile of individual patients to avoid the situations where risk equations from low risk populations (e.g. UKPDS) are applied to high risk patients (e.g. patients in a simulation with long duration of diabetes, advanced disease, history of complications and elevated risk factors). Importantly, validation results to date with the PRIME T2D Model strongly support the weighted model averaging approach currently being used in type 2 diabetes health economic analyses. (See responses 9, 17 and Pollock et al. [2022][12]) The PRIME T2D Model is product and trial-agnostic and model averaging allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to a given cohort. In the absence of risk equations derived directly from the trial or trials in question, we consider this approach to be preferable to the selection of a single risk model parameterised from a different population receiving different interventions than that under investigation. In addition to addressing concerns around the structural uncertainty inherent in using a single risk model, the approach allows the model to adapt risk estimation to different populations at different stages of disease progression. Validation analysis indicates that the model averaging approach is capable of accurately reproducing outcomes from real-life clinical studies in a range of settings. The product and trial-agnostic nature of the PRIME T2D Model necessitates a model averaging approach, as it is the only solution that allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to the cohort and supported by validation analysis. In addition to addressing concerns around the structural uncertainty inherent in using a single specific risk model, the approach allows the model to adapt risk estimation to difference populations at different stages of disease progression. The most prominent diabetes risk models (e.g. UKPDS OM1, UKPDS OM2, the IQVIA Core Diabetes Model, and the Cardiff Model) are all based — at least in part — on the UKPDS population, which was a population with newly-diagnosed type 2 diabetes, with the first patients enrolled in 1977, prior to the existence of statins, insulin analogues, SGLT-2 inhibitors, or GLP-1 receptor agonists. The incorporation, through a model averaging framework, of risk models derived from more modern populations of patients such as ACCORD (in the BRAVO model) allow the model to tailor the weighting of each model to each simulated patient. We believe this approach to be better suited to the decision problem than selecting a single model as the basis of the analysis and validation analysis indicates that the approach may be better suited to predicting long-term clinical outcomes in a modern type 2 diabetes population.

11	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B4. In Appendix N it is described that *"a weighted model averaging approach was used in which each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between model cohort and derivation cohort, the larger the weight applied to the risk equation from the respective derivation cohort. The model averaging approach was then optimized by running validation simulations to evaluate predictive performance, measured using the Chi-squared statistic, and using a genetic algorithm to minimize Chi squared by adjusting distance coefficients for each characteristic."*** **Please provide scenario analyses selecting a single predictive model based on the best match of the derivation cohort to the decision problem.** Please see response in Comment 4 above for details of the scenario analysis with a single predictive model.
12	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B4. In Appendix N it is described that *"a weighted model averaging approach was used in which each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between model cohort and derivation cohort, the larger the weight applied to the risk equation from the respective derivation cohort. The model averaging approach was then optimized by running validation simulations to evaluate predictive performance, measured using the Chi-squared statistic, and using a genetic algorithm to minimize Chi squared by adjusting distance coefficients for each characteristic."*** **To better understand the impact of model averaging, could the company provide the distribution of (normalized) model weights (across all simulated individuals) calculated at baseline.** In response the EAG request, a time series of model weights and a kernel density plot reflecting the number of patients with each weighting of risk equations at baseline are provided in Figure 7 and Figure 8 for the base case simulation of tirzepatide 10 mg versus semaglutide 1.0 mg. The time series shows that UKPDS OM2 risk equations were used predominantly over the first 4–5 years of the simulation before cohort characteristics were more closely matched to the BRAVO derivation population in subsequent years (Figure 7). As patients with more advanced disease experienced a greater mortality risk (and die sooner in the simulation), the weighting towards BRAVO risk equations gradually diminishes after year 15 of the simulation. The weights used in model averaging was comparable in both treatment arms. The distribution of model weights at baseline is represented by the kernel density plot shown in Figure 8, which is analogous to a histogram in certain respects as it can be read as a reflection of the number of patients with that weighting or risk equations. Therefore, the higher a peak on the graph, the more patients

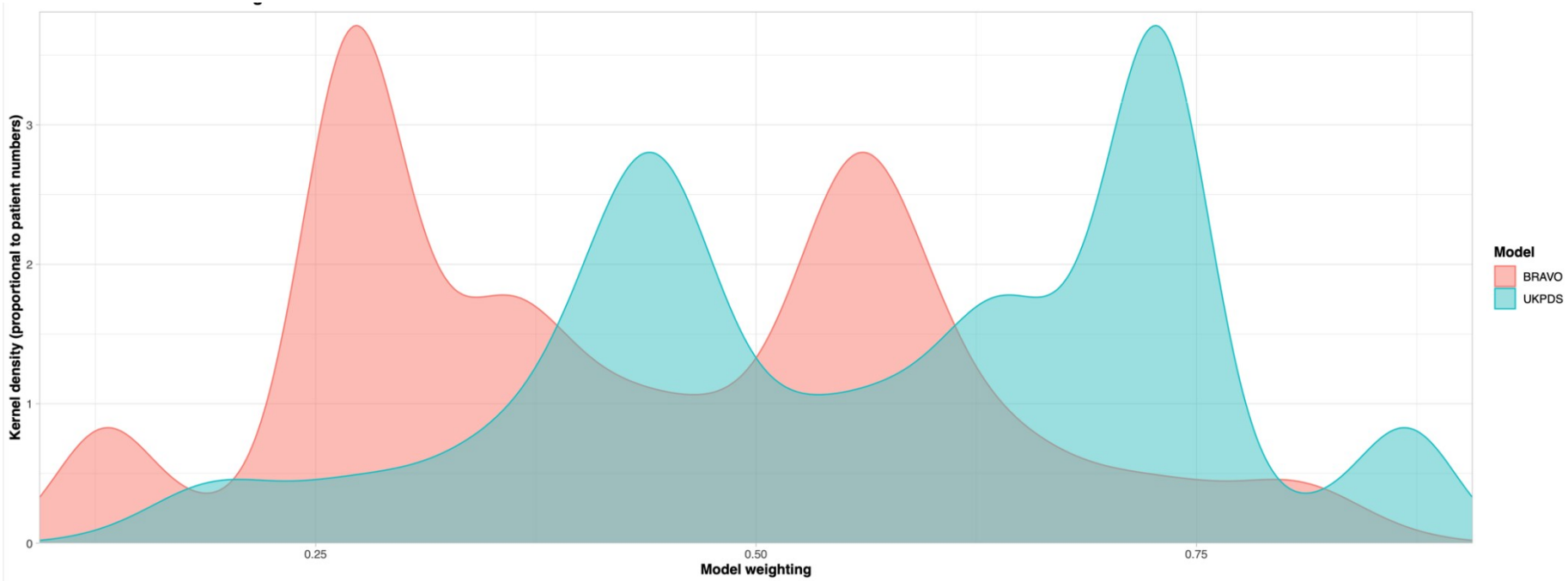
	have that particular weight, read from the x-axis. For any given patient, the sum of weights will always equal one, so if a patient has a UKPDS OM2 weight of 0.7, the BRAVO weight must therefore be 0.3. The plot shows that the most common weighting at baseline was approximately 0.7 UKPDS OM2 plus 0.3 BRAVO. We can see this because the highest peak for UKPDS OM2 is around 0.7 (blue), suggesting that more patients had this weighting for UKPDS OM2 than any other weighting. These patients must also have had a BRAVO weight of 0.3, as the weights must sum to one, and this is reflected in the peak for BRAVO at around 0.3 (red). The fact that these weights must sum to one means that curves are direct, left-to-right mirror images on the kernel density plot (i.e. a peak at 0.7 in one curve must mean at peak at 0.3 in the other curve). We can see this again with the UKPDS peak around 0.42, where we have a corresponding peak for BRAVO around 0.58, which was the second most common weighting: 0.42 UKPDS plus 0.58 BRAVO The distribution of model weights at baseline is a function of the simulated cohort characteristics (based on the THIN second intensification cohort) which are sampled to create individual patient profiles, the cohort characteristics of the UKPDS OM2 and BRAVO model derivation populations and the model averaging weighting algorithm as described by Pollock *et al.* (2022).[12] This corresponded to the UKPDS OM2 risk equations, on average, being weighted more than the BRAVO model risk equations at the start of the simulation.

Figure 7: Average weighting of risk equations over time for the comparison of tirzepatide 10 mg with semaglutide 1.0 mg



Note: Average model weighting over time in the simulated population is shown in blue for UKPDS OM2 risk equations and in red for BRAVO Model risk equations.

Figure 8: Kernel density plot of model weighting at baseline for the comparison of tirzepatide 10 mg with semaglutide 1.0 mg



Note: Kernel density (y-axis) reflects the number of patients in the simulated population with a given weighting (x-axis) at baseline and is shown in blue for UKPDS OM2 risk equations and in red for BRAVO Model risk equations.

13	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B5a and B5b. Appendix N provides descriptions for the generic PRIME T2D Model. However, the appropriateness of the selected predictive models to estimate the risk of complications in patients with type 2 diabetes is not justified (in detail). Nor is the applicability to the specific decision problem (as specified in the CS) justified.** **Please provide a justification that the risk models used, both individually and after model averaging, are appropriate to estimate the risk of complications in patients with type 2 diabetes and are applicable for the specific decision problem (as specified in the CS). Please provide this separately per risk model.** ***Key response points*** • The choice of the UKPDS OM2 risk model is well aligned with previous evaluations performed by NICE to inform the preparation of guidelines, including those analyses performed in 2015 and 2022 to inform NG28.[https://www.nice.org.uk/guidance/ng28/evidence/economic-model-report-on-periodontal-treatment-in-adults-with-type-1-and-type-2-diabetes-pdf-11131191037] The UKPDS OM2 risk equations are derived from a newly-diagnosed, UK-specific cohort with over 30 years of follow up and are widely used in diabetes modelling in general (c.f. the CORE Diabetes Model and the Cardiff Diabetes Model). The fact that the UKPDS risk equations are derived from type 2 diabetes patients in the UK is an important consideration. ○ However, the UKPDS OM2 was not used as a single risk model due to question marks around the ability of the of the model, without calibration, to predict outcomes for modern type 2 diabetes populations receiving interventions such as GLP-1 receptor agonists and with advanced disease (e.g. after second intensification of therapy), which is pertinent to the decision problem[13] ○ The UKPDS OM2 model does not have a risk equation for a revascularization endpoint, which may be an important consideration for a modern type 2 diabetes population[19] • The choice of the BRAVO model risk equations was made to complement the risk profile of the UKPDS OM2 risk equations. The models had comparable endpoints, but the BRAVO risk equations were derived from a cohort with a higher risk profile than the UKPDS population, specifically the ACCORD trial population of over 10,000 patients of whom approximately 35% had a previous cardiovascular event at baseline. The ACCORD cohort had a mean duration of diabetes of over 10 years at baseline, potentially making it better suited to modelling outcomes for patients with more advanced disease than the UKPDS dataset (Table 14). The fact that the BRAVO risk equations have been shown to reproduce outcomes for patients with more advanced disease (e.g. after second intensification) and with existing complication is an important consideration.[31, 32] ○ The BRAVO model was not used as a single risk model due to question marks around its suitability for modelling patients with less advanced disease (and shorter duration of diabetes) and for modelling outcomes for a UK-based population. To the best of our knowledge, no validation data on the BRAVO model exists to address these questions (outside of the use of the risk equations in model averaging in the PRIME T2D Model)

Table 14: Summary of cohort characteristics for the THIN second intensification cohort, the UKPDS cohort and the ACCORD trial cohort

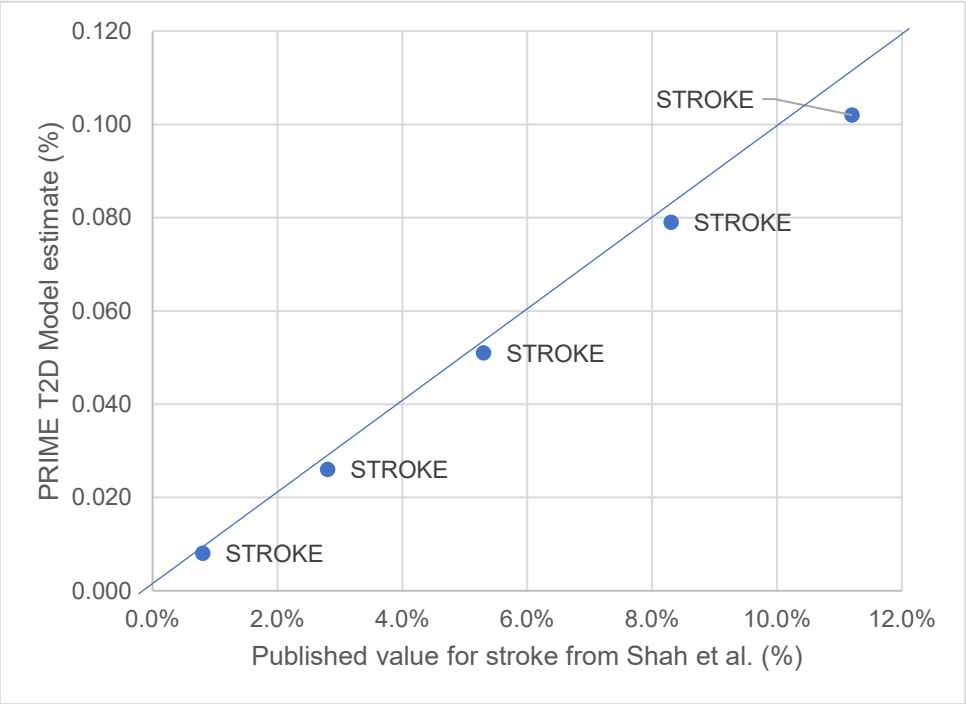
	THIN Second Intensification Cohort	UKPDS Cohort	ACCORD trial cohort (BRAVO)
Mean age (years)	63.95	52.0	62.2
Mean duration of diabetes (years)	8.5	0	10
Percentage male (%)	57	58.2	61
Percentage white (%)	82.4	82.7	64.5
Mean HbA1c (%)	7.5	6.7	8.3
Mean SBP (%)	134.44	135.5	136.3
Mean BMI (%)	30.7	28.8	32.2

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; SBP: systolic blood pressure; UKPDS: The United Kingdom Prospective Diabetes Study.

- The use of model averaging is a key aspect with respect to the selection of risk equations for inclusion in the modelling analysis. As outlined in the response to A.2.b, the use of risk equations in the PRIME T2D Model is weighted based on patient characteristics, to tailor the risk evaluation to individual simulated patients, such that low risk patients will rely more on UKPDS OM2 risk equations and high risk patients more on BRAVO risk equations. Validation analysis has shown that this approach is capable of reproducing outcomes accurately for CVOTs including EMPA-REG OUTCOME, REWIND (dulaglutide) and LEADER (liraglutide), as well as in a UK cohort study and in comparison with the UKPDS OM2 validation on the UK-based Lipids in Diabetes Study (Figure 9, Figure 10 and Figure 11)
- Extensive cross-validation analysis is not possible within the time frame of this submission and/or without the consent/participation of other modelling groups (specifically the UKPDS OM2 and BRAVO Model groups). However, the PRIME T2D Model approach of using risk equations from both UKPDS OM2 and BRAVO in a model averaging approach has been shown to reproduce real-life outcomes from UK cohort studies, GLP-1 receptor agonist studies and CVOTs (for endpoints including mortality, myocardial infarction, stroke, ischaemic heart disease and heart failure which have been shown to be important drivers of cost outcomes), which is not true of the UKPDS OM2 alone, the BRAVO Model or the CORE Diabetes Model. This makes the PRIME T2D Model the most suitable choice with respect to the decision problem in the present health economic evaluation

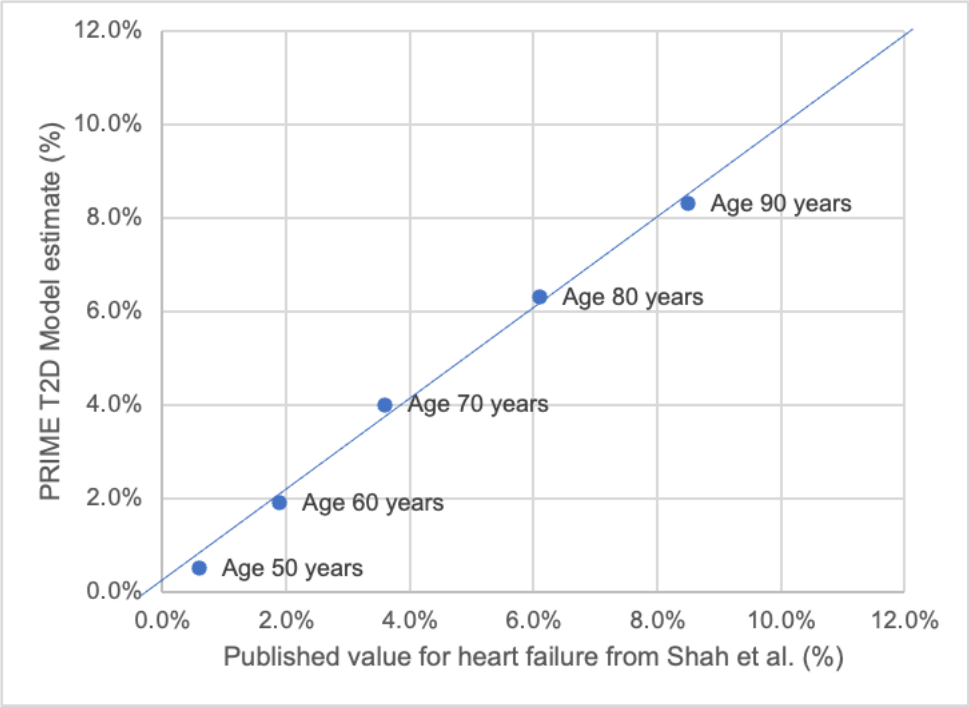
	Additional detail In 2015, Shah *et al*. published data from a cohort study of 1.9 million people in England with a median follow up time of 5.5 years designed to investigate the association between type 2 diabetes and incidence of cardiovascular disease.[11] The study used linked primary care, hospital admission, disease registry, and death certificate records from the CALIBER programme, which links data for people in England recorded in four electronic health data sources and included 34,198 people who had type 2 diabetes. Data for the endpoints of stroke (all) and heart failure were extracted for a validation analysis with the PRIME T2D Model. Other endpoints could not be included due to different endpoint definitions between the model and the Shah et al. analysis and, to match the published data, validations were performed by age (from 50 to 90 years). The PRIME T2D Model projections provided a close match to the published data with a RMSD of 3.7% across all 10 validation points (Figure 9 and Figure 10).

Figure 9: PRIME T2D Model validation scatterplot for the stroke endpoint from the Shah *et al.* cohort study



Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Figure 10: PRIME T2D Model validation scatterplot for the heart failure endpoint from the Shah *et al.* cohort study

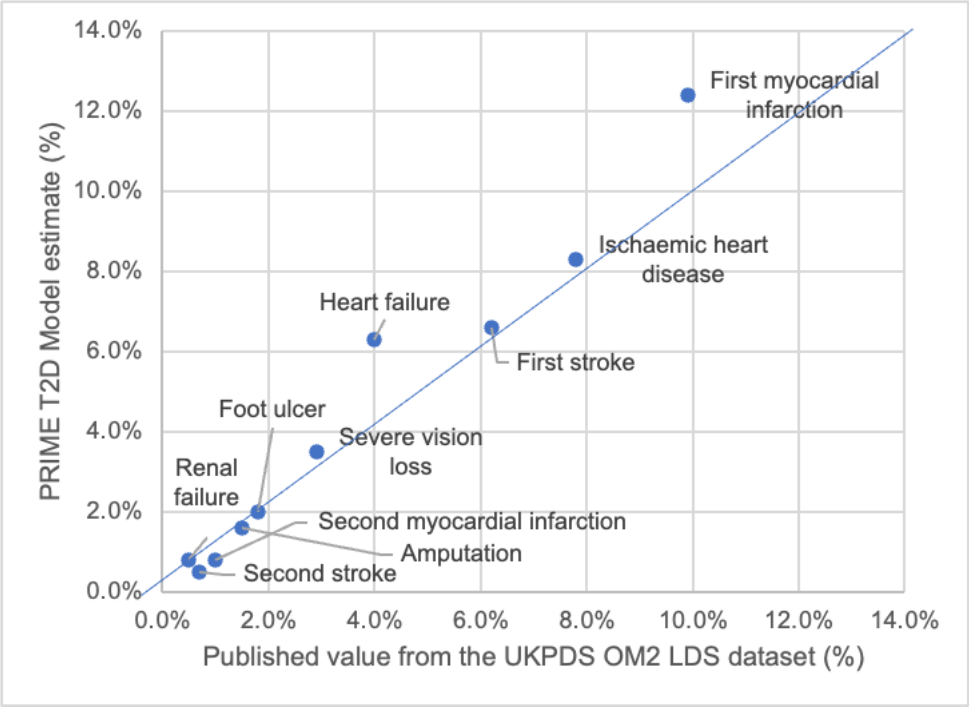


Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

The validation analysis of the UKPDS OM2 published by Hayes et al. in 2013 was based on data from the LDS, a prospective, randomised, placebo-controlled, clinical outcome trial with the principal objective of determining whether lipid reduction with a statin (cerivastatin) or a fibrate (fenofibrate) could substantially reduce cardiovascular related morbidity and mortality in subjects with type 2 diabetes.[15] The trial recruited 4,191 with no previous coronary heart disease but

the study was discontinued when cerivastatin was withdrawn.[33] Hayes *et al.* used the patient characteristics from 3,984 patients with non-missing risk factors from the LDS to make 10-year projections of outcomes with the UKPDS OM1 and OM2.[15] Validation analysis with the PRIME T2D Model was performed on the latter dataset (Figure 11). RMSD for all validation data points was 1.1%, which provides evidence that the PRIME T2D Model can project outcomes comparable with the UKPDS OM2, when the patient characteristics are similar to the UKPDS cohort (as was the case with the LDS cohort).

Figure 11: PRIME T2D Model validation scatterplot for the Lipids in Diabetes Study



	Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.
14	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B30. Further sensitivity analyses/clarification on existing sensitivity analyses would be desirable.** **Please provide sensitivity analysis for all input parameters individually and present results in tornado diagrams.** The requested one-way sensitivity analysis and tornado diagram are presented in the response in Comment 2 above.
15	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B32. Priority question: Further information on validation efforts would be desirable, focusing on this specific implementation of the PRIME T2D model.** **a) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.** The TECHnical VERification (TECH-VER) checklist is described as: "*a comprehensive checklist for the technical verification of decision analytical models, aiming to help identify model implementation errors and their root causes while improving the transparency and efficiency of the verification efforts.*"[34] Extensive verification and validation work has been performed on the PRIME T2D Model (as outlined in the PRIME T2D Model Technical Report) and this is summarized in the context of the TECH-VER checklist in Table 15. There is considerable overlap between the TECH-VER checklist and the internal and external validation analyses completed on the PRIME T2D Model. It should be noted that the TECH-VER checklist is not a standard, pre-defined list of tasks/checks that should be completed and summarized by a model reviewer. Instead, it consists of five verification stages, which have been addressed during the development, verification and validation of the PRIME T2D Model (Table 15): 1. Model input (pre-analysis) calculations. 2. Event/state calculations. 3. Result calculations. 4. Uncertainty analysis calculations. 5. Overall validation/other supplementary checks.

Table 15: Summary of the TECH-VER checklist domains and PRIME T2D Model verification and validation steps

TECH-VER checklist domain	PRIME T2D Model verification/validation step(s)
1. Model input (pre-analysis) calculations: this verification stage checks the pre-analysis calculations that yield direct model inputs (e.g. transition probabilities, cycle-based or event-based costs and utilities) from reference source inputs	All data included in the PRIME T2D Model were independently verified by an external third party during the internal validation step of model development (see below). This included checking all calculation steps as required. For the present analysis, model inputs (and calculation methods where relevant) were described in the original submission. All values entered into the model were cross-checked by a second researcher to match the source values.
2. Event/state calculations: this verification stage checks the event/state calculations that determine the patient flow/disease progression stage as well as the assignment of costs/QALYs or other relevant health/economic outcomes at a given cycle/time	All event/state calculations were independently verified during the internal validation step of model development (see below). Event/state calculations were further verified by test case analysis during the internal validation process.
3. Result calculations: this verification stage checks the result calculations that yield the undiscounted/discounted total and incremental results (e.g. costs, QALYs, other relevant health or economic outcomes and ICER)	All results calculations were independently verified during the internal validation step of model development (see below). Results calculations were further verified by test case analysis during the internal validation process and by one-way and multi-way sensitivity analysis testing internally at Ossian.
4. Uncertainty analysis: this verification stage checks the uncertainty analysis calculations (e.g. one-way, multi-way, probabilistic sensitivity, value of information and scenario analyses)	The approach to handling uncertainty in the PRIME T2D Model was decided at an advisory board meeting and has been independently reviewed through the NICE PRIMA review process. During model development, one-way and multi-way sensitivity analysis was performed on individual model inputs to confirm the expected effects in model outputs during internal validation (described as test case analysis, see below). One-way and multi-way sensitivity analysis as well as scenario analysis form part of every cost-effectiveness evaluation using the PRIME T2D Model, with all results reviewed for consistency and expected outcomes. Probabilistic sensitivity analysis was tested as part of the independent internal validation of the PRIME T2D Model.

		Value of information analysis is not applicable for the present evaluation and was not analysed during model development. Scenario analysis was tested as part of the independent internal validation of the model (described as test case analysis in the PRIME T2D Model Technical Report)
	5. Overall tests (validation or other supplementary tests): these tests include validation efforts from other sources and tests that are applied to the whole model and efforts that do not specifically belong to one of the compartmentalized modules	Multiple validation analyses have been performed with the PRIME T2D Model and are documented in the present response, in the PRIME T2D Model Technical Report and in the Pollock et al. (2022) publication describing the PRIME T2D Model[12]

Internal validation: The PRIME T2D Model Technical Report (in Appendix N of the CS) provides an overview of the internal validation process that addresses much of the TECH-VER checklist. The internal validation of the PRIME T2D Model was performed by HealthMetrics Outcomes Research in Q2, 2020. The validation process took the form of a code audit and followed the procedures outlined below:

1. Test cases were defined for each PRIME T2D Model controller. These tests cases typically consisted of testing at minimum and maximum input values. Testing at the extreme input values allowed for maximum stress on the module.
2. Each controller was independently implemented in Matlab. Matlab (matrix laboratory) is a multi-paradigm numerical computing environment and fourth-generation programming language. Developed by MathWorks, Matlab allows matrix manipulations, plotting of functions and data, implementation of algorithms, creation of user interfaces, and interfacing with programs written in other languages, including Java (the PRIME Model's language), C, C++, Fortran and Python.
3. The test cases were run using both the Java software from the PRIME T2D Model and the Matlab implementations and results are compared to ensure correct implementation in the former.
4. To assess the overall model characteristics, a cohort of 1,000,000 patients was generated using the characteristics defined within the PRIME T2D Model Database Controller (with isCollegeEducationOrAbove and severeHypoHistory initialized to false) and an initial ageAtDiagnosis limited to the range of zero to one year. The complication controllers were then executed. This analysis was performed in MatLab and the only updates to patient characteristics were limited to increasing the patient age and modifying the patient history based on the results of the complications.
5. The findings of this process were detailed in a report and any discrepancies in the PRIME T2D Model code and the MatLab implementation were resolved.

16	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:**

B32. Priority question: Further information on validation efforts would be desirable, focusing on this specific implementation of the PRIME T2D model.

b) Please provide a tabulated overview of all parameters used in the model, including SE/SD/CIs, the probability distribution used, the source, justification for the source, and a specific description of how the parameter was implemented in the model.

Summaries of all model inputs for the base case analysis are provided in Table 1 through to Table 15 of Appendix A (shared as a separate file alongside this response due to its length) in line with the EAG request. The complexity of the model is not possible to capture in a tabular format (e.g. risk factors at baseline are sampled from a distribution, then subjected to treatment effects and progression, may contribute to weighting of risk equations (model averaging) and be associated with the evaluation of complication risk in each model cycle). However, the PRIME T2D Model Technical Report details all of the risk equations used and references the progression functions to elucidate this question and the model code has been provided to detail every parameter and its implementation in any given modelling simulation. With respect to distributions applied for each parameter in the model, the following information can be used to directly identify distributions from the model code:

- Whether sampling of costs is active is governed by a Boolean value named sampleCosts, which is referenced in the EconomicsController Java class.
- Whether sampling of utilities is active is governed by a Boolean value named sampleUtilities, which is referenced in the QualityOfLifeController Java class.
- Whether sampling of treatment effects is active is governed by a Boolean value named sampleTreatmentEffects, which is referenced in the TreatmentController Java class.
- Whether sampling of model coefficients is active is governed by a single line of code in the PatientController.java superclass from which all complication-evaluating Java classes inherit.
- The simulated cohort of patients is generated (based on the user-defined cohort characteristics) in the CohortController Java class. Patient heterogeneity is thereby introduced in this class, which comprises just 250 lines of code (LOC), of which ~180 LOC are responsible for generating the cohort.
- Random walk (stochastic uncertainty) through the model is governed by sampling from uniform distributions in the processPatient() methods of each Java class responsible for modelling a given complication.

The model supports normal, log-normal, uniform and beta distributions and are applied as appropriate and in line with model input data during probabilistic sensitivity analysis. In general, the following schema summarizes the distribution forms used in the model:

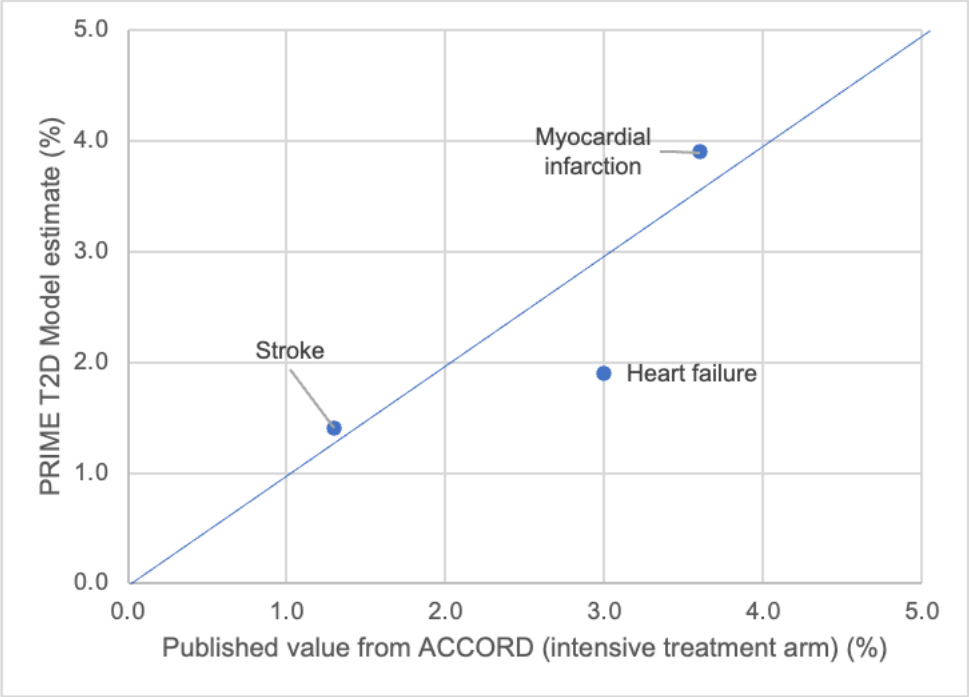
Cohort characteristics

- Normal distribution (with physiological limits) for all parameters defined by mean and standard deviation
- Uniform distribution for all parameters defined by percentages

	• Log-normal distribution for hazard ratios (noted for completeness – not used in the present analysis) Treatment effects • Normal distribution (with physiological limits) for all parameters defined by mean and standard deviation Costs • Normal distribution for all parameters defined by mean and standard deviation Utilities • Normal distribution (with limits) for all parameters defined by mean and standard deviation Risk equation coefficients • Normal distribution unless otherwise indicated in source publication
17	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B35. Priority question: Further external validation of modelled estimates against the SURPASS trials and (potentially available) alternative evidence would be desirable. Please assess the external validity of model inputs, intermediate outcomes and (long-term) disaggregated results (as provided in Appendix J) as well as final outcomes using the SURPASS trials and available alternative evidence sources.** **The EAG noted that it would be informative if the company could provide similar figures as Figure 14 from "ID3938_Eli Lilly_Tirzepatide_Response to EAG Report_v0.2 16May23 [ACIC].docx", based on the current company base-case, for all complications/outcomes considered and compared to more studies (including the ASCEND study).** Previous Comments in this response document (above) have included the following validation scatterplots: • Overall validation analysis (Figure 2) • Validation for MI, stroke, IHD and heart failure against the EMPA-REG OUTCOME study (Figure 3) • Validation of mortality, MI and stroke against the REWIND study (Figure 5) • Validation of MI, stroke and ischaemic heart disease again the LEADER study (Figure 6) • Validation of stroke and heart failure against the Shah et al. cohort study (Figure 9 and Figure 10)

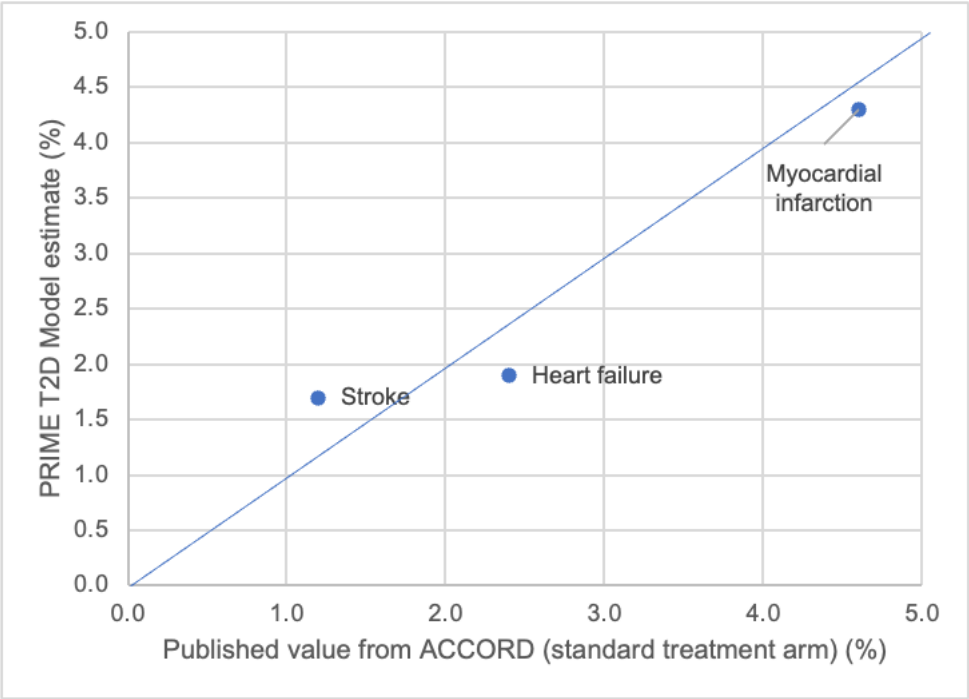
	• Validation of first and second MI, first and second stroke, ischaemic heart disease, heart failure, foot ulcer, amputation and renal failure against the LDS UKPDS OM2 dataset (Figure 11) Validation was also performed against published data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was the derivation cohort for the risk formulae for the BRAVO Model.[31, 35] ACCORD was designed to investigate whether intensive therapy to target normal glycated haemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors. The study recruited 10,251 patients with type 2 diabetes in North America, of whom 35% had a history of cardiovascular disease at baseline, and randomly allocated patients to intensive or standard therapy for a median follow up period of 3.4 years. A finding of higher mortality in the intensive-therapy group led to a discontinuation of the intensive therapy arm after a mean of 3.5 years of follow-up. Validation analysis with the PRIME T2D Model showed that the model predicted outcomes well for the myocardial infarction and stroke endpoints in both treatment groups (Figure 12 and Figure 13). For the heart failure endpoint, the model slightly underpredicted the risk in the intensive treatment group but was closer for the standard therapy arm. The RMSD between cumulative incidence values from the model and the ACCORD intensive treatment group was 0.7%. The corresponding value for the standard care arm was 0.4%.

Figure 12: PRIME T2D Model validation scatterplot for the intensive treatment group in ACCORD



Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Figure 13: PRIME T2D Model validation scatterplot for the standard treatment group in ACCORD

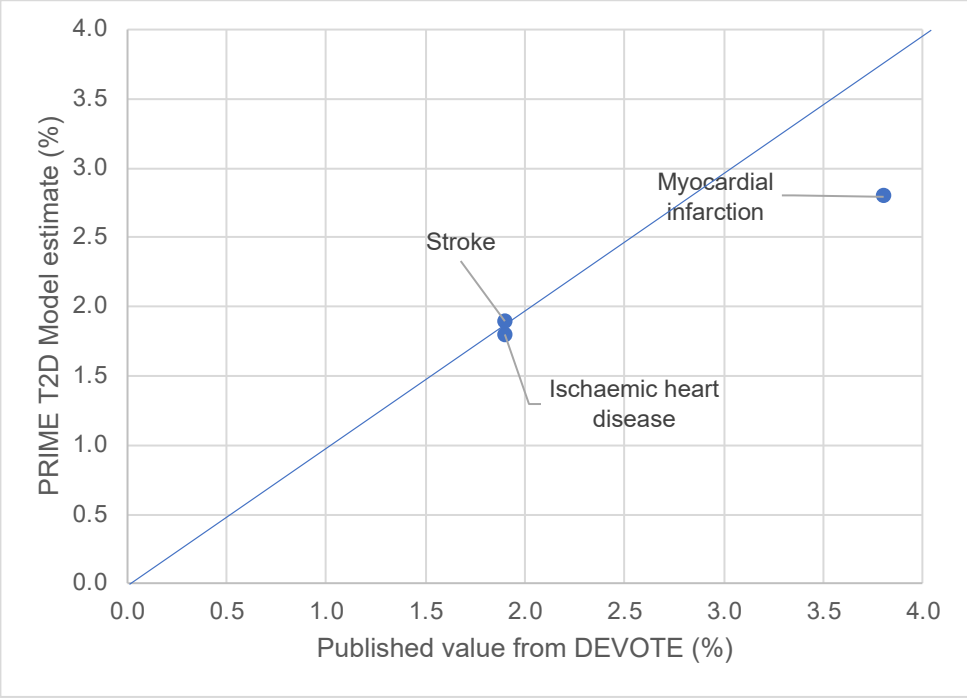


Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Validation analysis has also been performed on the DEVOTE study, the cardiovascular safety trial of insulin degludec.[36] The study recruited a total of 7,637 patients with type 2 diabetes who were randomly assigned to receive either insulin degludec (3,818 patients) or insulin glargine (3,819 patients)

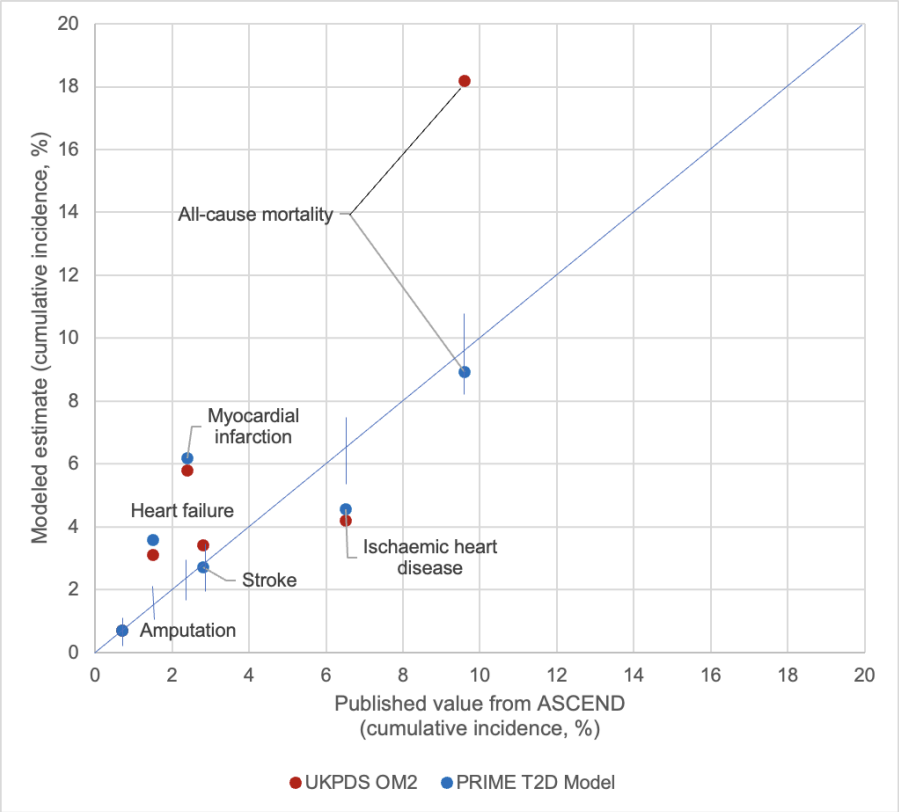
once daily. The study included a total of 438 sites in 20 different countries and had a median follow up time of 1.99 years. Validation was performed against outcomes for the insulin degludec treatment arms and the model showed a good match to published outcomes for stroke and ischaemic heart disease, but slightly underestimated the risk of myocardial infarction in this population Figure 14. The RMSD between modelled outcomes and the trial results for this validation was 0.6%.

Figure 14: PRIME T2D Model validation scatterplot for the DEVOTE study



	Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. At the request of the EAG, a validation analysis was also performed against A Study of Cardiovascular Events in Diabetes (ASCEND), which had been previously used to validate against the UKPDS OM2 as described by Keng et al. (2022).[19] ASCEND was a 2x2 factorial design trial that randomized 15,480 participants with established diabetes mellitus (both type 1 and type 2) but without diagnosed CV disease (CVD) to 100 mg aspirin daily or matching placebo and, separately, to 1 g capsule containing omega-3 fatty acids daily or placebo. Participants were recruited between 2005 and 2011 and followed for an average of 7.4 years. A total of 7,578 patients with type 2 diabetes had complete baseline information and formed the validation cohort. The validation analysis reported in Appendix Table 7 from Keng et al. and supplemented with the corresponding endpoints from the PRIME T2D Model validation is shown in Figure 15. The most notable difference is in terms of mortality estimation, where the PRIME T2D Model was close to the published estimate but the UKPDS OM2 overestimated mortality risk. Amputation estimates were the same with both models. The PRIME T2D Model predicted stroke and ischaemic heart disease a little better than the UKPDS OM2. Both models overpredicted the risk of heart failure and myocardial infarction, with UKPDS OM2 slightly lower than the PRIME T2D Model. The RMSD value (the measure of the average difference between the modelled value and the observed value) for the UKPDS OM2 validation was 3.95% compared with 1.96% with the PRIME T2D Model. Even when the notable outlier for the UKPDS OM2 model is taken out (i.e. all-cause mortality), the RMSD value was 1.99% with the UKPDS OM2, still a little higher than the PRIME T2D Model.

Figure 15: PRIME T2D Model validation scatterplot for the ASCEND study



Each point on the graph represents a cumulative incidence value from a model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the models are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. Vertical lines are shown representing the 95% confidence intervals around the observed endpoint data from ASCEND.

Neither model was able to reproduce the myocardial infarction endpoint from ASCEND accurately. It is not entirely clear why this should be the case. Keng *et al.* speculated that this may be due to the impact of revascularization.[19] However, the publication did not include separate numerical estimates for revascularization and therefore no validation could be performed on this endpoint. It is possible, despite the researchers' best efforts to match the myocardial infarction endpoint by adjudicating all events, that the differences in endpoint definitions drove the differences observed in the myocardial infarction and ischaemic heart disease endpoints(see Table 16).

Table 16: Summary of myocardial infarction and ischaemic heart disease endpoint definitions pertaining to the ASCEND validation

Endpoint	Definition in UKPDS-OM2 and PRIME T2D Model	Definition in ASCEND
Myocardial infarction	WHO clinical criteria with electrocardiogram/enzyme changes or new pathological Q wave ICD-9 codes: 410 (Acute myocardial infarction); ≥ 798 & ≤ 798.9 (Sudden death)	Myocardial infarction (fatal/non-fatal) "Evidence of cardiac necrosis (consistent elevation in cardiac biomarkers or relevant autopsy findings) and there was other evidence of an acute MI (including symptoms of ischemia, recent coronary intervention, death, new ECG changes, evidence of a new myocardial defect on cardiac imaging or an acute coronary occlusion at angiography) and no other diagnosis was likely."
Other ischaemic heart disease	Angina/ischaemic heart disease - WHO clinical criteria confirmed by a new ECG abnormality or an ECG which becomes abnormal on exercise ICD-9 codes: ≥ 411 & ≤ 414.9 (Ischaemic heart disease excluding acute myocardial infarction)	Angina; Coronary revascularizations (coronary artery bypass graft, percutaneous transluminal coronary angioplasty); Death from other coronary heart disease (not myocardial infarction)

There are several points to note with respect to the validation analyses presented above:

- Validation analysis with the PRIME T2D Model to date has focused primarily (but not exclusively) on cardiovascular disease endpoints as these are

	the biggest drivers of cost and are the most important complication in terms of driving outcomes in a cost-effectiveness analysis of diabetes interventions (c.f. the base case analysis). • Validation analyses have also been performed on cohort studies from South-East Asia but these have not been included as they are not relevant to the present modelling analysis. • Root mean squared deviation is provided as a measure of difference between the modelling results and observed outcomes. It can be considered to reflect the average difference between the cumulative incidence of complications predicted by the model and the cumulative incidence of complications observed in the study. The root mean squared methodology is utilised to avoid positive and negative differences in cumulative incidence cancelling each other out and providing an underestimate of the differences between modelled and observed outcomes (that could occur if only mean differences were reported).

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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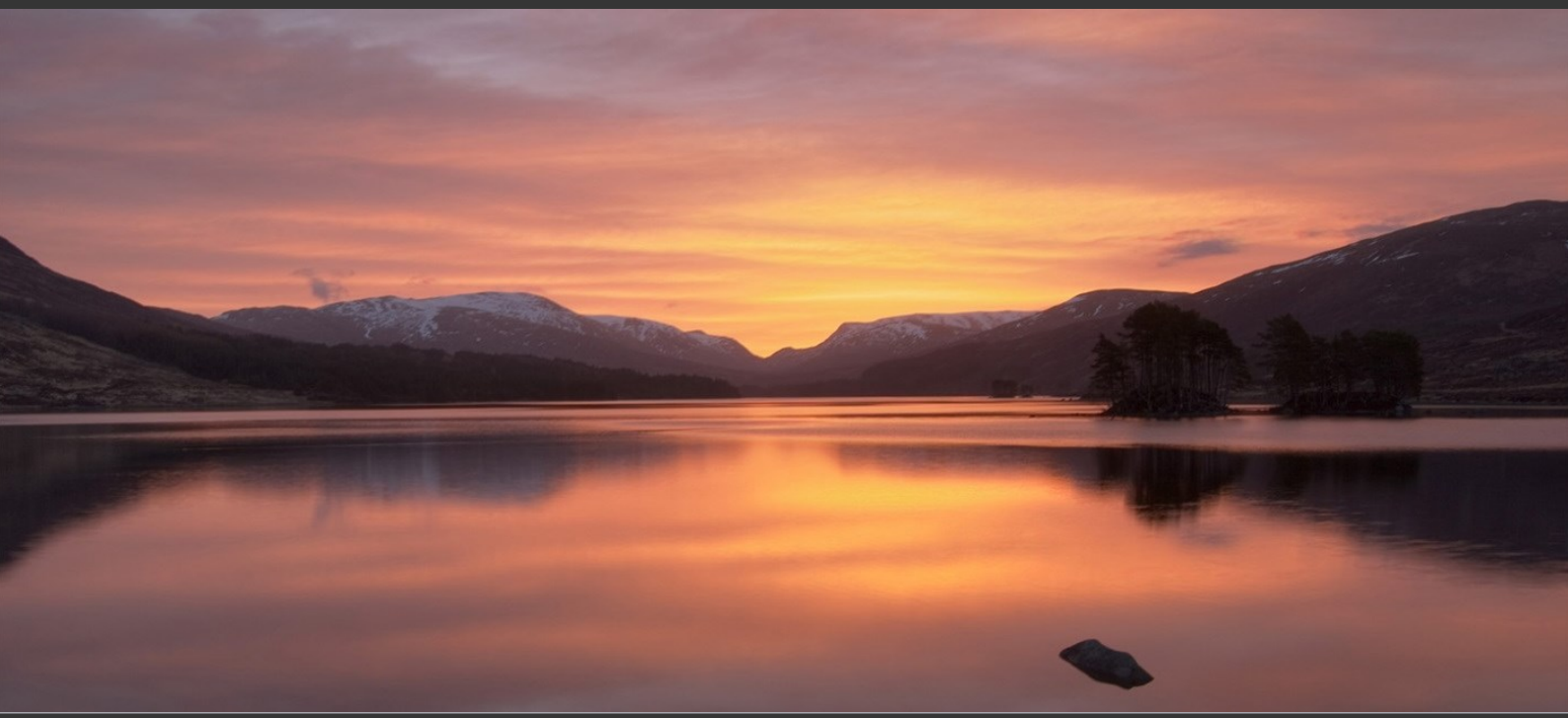
Cross comparison analysis: cost-effectiveness evaluation of tirzepatide using the CORE Diabetes Model



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health economics and communications

Technical report
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1 OVERVIEW AND OBJECTIVES

In response to EAG requests for a cross comparison analysis on the PRIME T2D Model further to the submission on tirzepatide (Single Technology Appraisal ID 3938 - Tirzepatide for the treatment of patients with type 2 diabetes, dated 9th August, 2023), a modeling analysis with IQVIA CORE Diabetes Model has been performed. The modeling analysis was designed to match as closely as possible, the EAG preferred base case analysis provided to NICE ahead of the second committee meeting scheduled for 1st August, 2023.

This report has been prepared to summarize the inputs and results from the CORE Diabetes Model analysis and highlight similarities and differences with the corresponding cost-effectiveness analysis using the PRIME T2D Model.

2 ECONOMIC ANALYSIS

2.1 MODEL STRUCTURE AND OVERVIEW

The IQVIA CORE Diabetes Model was used for this cross comparison analysis at the suggestion of the EAG. The model is a patient-level simulation, coded in C++, accessible online and is described in the publication by Palmer *et al.* (2004).[1] The model source code is proprietary to IQVIA and not available for review (unlike the PRIME T2D Model source code which has been provided in full to the EAG for review). The CORE Diabetes Model is described as being: *based on a series of sub-models that simulate important complications of diabetes (cardiovascular disease, eye disease, hypoglycaemia, nephropathy, neuropathy, foot ulcer, amputation, stroke, ketoacidosis, lactic acidosis and mortality). Each sub-model is a Markov model using Monte Carlo simulation incorporating time, state, time-in state, and diabetes type-dependent probabilities derived from published sources.* The model description was originally published in 2004 and, whilst there have been several updates to the CORE Diabetes Model since then, there is little information available in the published literature to describe how the model functionality has changed since the original publication. A subsequent validation analysis with the CORE Diabetes Model was published by McEwan *et al.* in 2014, which noted the addition of risk equations from the UKPDS 68 and 82 but provided little detail on other updates.[2] Currently, no peer-reviewed publications are available describing the most recent version (version 10) of the CORE Diabetes Model.

All inputs for the CORE Diabetes Model analysis were aligned with the assumptions and model inputs for the EAG preferred base case modeling analysis with the PRIME T2D Model.

Table 1: Overview of EAG preferred base case inputs for the modelling analysis

Simulation element	Change(s) from submitted base case
Cohort	No changes made from the submitted base case analysis in which the cohort characteristics were aligned with the THIN second intensification cohort previously described by NICE
Treatment effects and risk factor progressions	Change from baseline in risk factors were taken from the NMA. Change from baseline in BMI was taken (where available) directly from the NMA results and not calculated from change in body weight. UKPDS risk factor progressions were used for all risk factors with the exceptions of SBP and BMI during treatment with tirzepatide or comparators. SBP and BMI remained constant during treatment with tirzepatide or GLP-1 receptor agonists in line with risk factors progression data from cardiovascular outcomes trials. Following intensification to basal insulin therapy, these risk factors also followed UKPDS-based progression.
Treatment costs	Pack prices for tirzepatide were as follows: • Tirzepatide 5 mg [redacted] (28 days) • Tirzepatide 10 mg [redacted] (28 days) • Tirzepatide 15 mg [redacted] (28 days)
Complication costs	All complication costs were inflated to 2022 values. Costs queried by the EAG were checked against source data and amended if necessary. Variance estimates were extracted from source data wherever possible and included in the model inputs.
Health-related quality of life utilities	An age-adjusted additive approach to utility estimation was used based on Ara and Brazier 2010[3] in the PRIME T2D Model. An age-adjusted approach was not possible with the CORE Diabetes Model and therefore an additive approach to combining utilities was used. Variance estimates were extracted from source data wherever possible and included in the model inputs. No weight loss utility (Boye *et al.* 2021) was used in the EAG preferred base case analysis[4]. No device utilities for tirzepatide or dulaglutide were used in the EAG preferred base case analysis.
Other settings	In both models, a combined approach was used to estimate mortality with complication-related mortality being combined with mortality from other causes from life tables. In the PRIME T2D Model, WHO life tables are cause-subtracted (with mortality from complications captured in the model subtracted) to estimate mortality from non-diabetes-related causes. In the CORE Diabetes Model, the standard approach is to use life tables directly from the WHO (not cause-subtracted).

Abbreviations: BMI: body mass index; EAG: evidence assessment group; NMA: network meta-analysis; SBP: systolic blood pressure; UKPDS: United Kingdom Prospective Diabetes Study.

2.2 PATIENT POPULATION

Cohort characteristics for the analysis with the CORE Diabetes Model were matched as closely as possible to the cohort used in the EAG preferred base case analysis using the PRIME T2D Model (Table 2). On a general level (demographics and key baseline risk factors), the model inputs were well aligned. However, there are several differences between the two sets of model inputs in terms of history of complications at baseline (due to the differences in endpoints included) and additional risk factors required for the CORE Diabetes Model (presumably to populate the many different risk models that can be selected to evaluate complication risk).

Table 2: Summary of cohort characteristics

	PRIME T2D Model value (mean [SD])	CORE Diabetes Model value (mean [SD])	Source
Demographics			
Percentage male	57.0%	0.57 (proportion)	THIN second intensification cohort (Table HE005)
Percentage with college education or higher (%)	25.97	Not applicable	PRIME Model index value[160]
Percentage smokers	17.0%	0.17 (proportion)	THIN second intensification cohort (Table HE005)
Cigarettes per day	Not applicable	9	Office for National Statistics[5]
Age (years)	63.95 [10.4]	63.95 [10.4]	THIN second intensification cohort (Table HE005)
Duration of diabetes (years)	8.5 [6.5]	8.5 [6.5]	THIN second intensification cohort (Section 2.3.1.1)
Alcohol consumption	Not applicable	7.43 oz/week	World Health Organization[6]
Proportion physically active	Not applicable	0.22	CORE Diabetes Model index value (default)
Fasting glucose	Not applicable	180.72 mg/dL	CORE Diabetes Model index value (default)
Proportion with family history of CHD	Not applicable	0.15	CORE Diabetes Model index value (default)
Proportion with family history of stroke	Not applicable	0.04	CORE Diabetes Model index value (default)
Proportion from China – rural area	Not applicable	0.60	CORE Diabetes Model index value (default)
Proportion from China – Northern region	Not applicable	0.38	CORE Diabetes Model index value (default)
Ethnic group			
White	82.4%	0.824 (proportion)	THIN second intensification cohort (Table HE002)
Black	4.5%	0.045 (proportion)	THIN second intensification cohort (Table HE002)
Hispanic	0	0	Assumed
Southeast Asian	0	Not applicable	Assumed
Native American	Not applicable	0	Assumed
Asian/Pacific Islander	Not applicable	0.131 (proportion)	Assumed

	PRIME T2D Model value (mean [SD])	CORE Diabetes Model value (mean [SD])	Source
Indian	13.1%	Not applicable	THIN second intensification cohort (Table HE002)
Afro/Caribbean	0	Not applicable	Assumed
Other	0	Not applicable	Assumed
Australian (south European)	Not applicable	0	Assumed
Percentage Other (%)	Not applicable	0	Assumed
Baseline risk factors			
HbA1c (%)	7.50 [1.03]	7.50 [1.03]	THIN second intensification cohort (Table HE005)
Systolic blood pressure (mmHg)	134.44 [13.8]	134.44 [13.8]	THIN second intensification cohort (Table HE005)
Diastolic blood pressure (mmHg)	Not applicable	80.00 [0]	Assumed
Total cholesterol	4.53 [1.06] mmol/L	175.17 [40.99] mg/dL (equivalent to 4.53 [1.06] mmol/L)	SURPASS-2 CSR, ITT population, Table GPGL.8.43 (converted by multiplying by 38.67)
Low density lipoprotein cholesterol	2.29 [0.89] mmol/L	88.55 [34.42] mg/dL (equivalent to 2.29 [0.89] mmol/L)	THIN second intensification cohort (Table HE005) (converted by multiplying by 38.67)
High density lipoprotein cholesterol	1.23 [0.29] mmol/L	47.56 [11.21] mg/dL (equivalent to 1.23 [0.29] mmol/L)	THIN second intensification cohort (Table HE005) (converted by multiplying by 38.67)
Triglycerides	Not applicable	195.30 [0.00]	Calculated based on cholesterol values
Body mass index (kg/m^2)	30.7 [6.9]	30.7 [6.9]	THIN second intensification cohort (2015 Report Table 20)[138]
Estimated glomerular filtration rate (mL/min/1.73 m^2)	71.37 [17.10]	71.37 [17.10]	THIN second intensification cohort (Table HE005)
White blood cell count (10^6 cells/mL)	7.51 [1.80]	7.51 [1.80]	THIN second intensification cohort (Table HE005)
Heart rate (beats per minute)	72.0 [10.1]	72.0 [10.1]	THIN second intensification cohort (Table HE005)
Haemoglobin (g/dL)	14.5 [1.42]	14.5 [1.42]	THIN second intensification cohort (Table HE005)
Waist:hip ratio	Not applicable	0.93	CORE Diabetes Model index value (default)
Urinary albumin excretion rate	Not applicable	3.10 mg/mmol	CORE Diabetes Model index value (default)
Serum creatinine	Not applicable	1.10 mg/dL	CORE Diabetes Model index value (default)
Serum albumin	Not applicable	3.90 g/dL	CORE Diabetes Model index value (default)

	PRIME T2D Model value (mean [SD])	CORE Diabetes Model value (mean [SD])	Source
Waist circumference	Not applicable	87.84 cm	CORE Diabetes Model index value (default)
Complication history			
Patients with atrial fibrillation at baseline	[redacted]	0.012 (proportion)	SURPASS-2 CSR, ITT population, Table GPGL.8.10
Patients with urinary albumin ≥50mg/L at baseline	22.6%	Not applicable	THIN second intensification cohort (Table HE004)
Patients with peripheral vascular disease at baseline	[redacted]	0.019 (proportion)	SURPASS-2 CSR, ITT population, Table GPGL.8.10
Patients with history of myocardial infarction at baseline	2.0%	0.020 (proportion)	THIN second intensification cohort (Table HE006)
Patients with history of stroke at baseline	1.3%	0.013 (proportion)	THIN second intensification cohort (Table HE006)
Patients with ischemic heart disease at baseline	6.0%	Not applicable	THIN second intensification cohort (Table HE006)
Patients with angina at baseline	Not applicable	0.060 (proportion)	Assumed
Patients with coronary revascularization at baseline	[redacted]	Not applicable	SURPASS-2 CSR, ITT population, Table GPGL.8.10
Patients with heart failure at baseline	1.9%	0.019	THIN second intensification cohort (Table HE006)
Patients with left ventricular hypertrophy at baseline	Not applicable	0	Assumed
Patients with foot ulcer at baseline (%)	0.8%	0.008 (proportion)	THIN second intensification cohort (Table HE006)
Percentage with amputation at baseline (%)	0.2%	0.002 (proportion)	THIN second intensification cohort (Table HE006)
Patients with background diabetic retinopathy at baseline	Not applicable	0	Assumed
Patients with proliferative diabetic retinopathy at baseline	Not applicable	0	Assumed
Percentage with blindness at baseline (%)	1.3%	0.013 (proportion)	THIN second intensification cohort (Table HE006)
Patients with macular edema at baseline	Not applicable	0	Assumed
Patients with cataract at baseline	Not applicable	0	Assumed
Patients with renal failure at baseline	0.4%	0.004 (proportion)	THIN second intensification cohort (Table HE006)

	PRIME T2D Model value (mean [SD])	CORE Diabetes Model value (mean [SD])	Source
Patients with gross proteinuria at baseline	Not applicable	0.006 (proportion)	Assumed (1.5 times greater than proportion with renal failure)
Patients with microalbuminuria at baseline	Not applicable	0.228 (proportion)	Assumed (3.8 times greater than proportion with gross proteinuria)
Patients with SPSL/neuropathy at baseline	9.0%	0.090 (proportion)	SURPASS-2 CSR, ITT population, Table GPGL.8.11

* standard deviation value taken from the SURPASS-2 cohort as value was not reported in the source material. ** value assumed as not reported in source material.
Abbreviations: HbA1c: glycated haemoglobin; SPSL: severe pressure sensation loss.

2.3 TREATMENT EFFECTS

The treatment effects used in the preferred base case analysis are summarized in Table 3 for the PRIME T2D Model with the corresponding values used in the CORE Diabetes Model analysis in Table 4. Modelled change from baseline in HbA1c, SBP, BMI, LDL- and HDL-cholesterol were the same in both modelling analyses and were taken from the NMA. No other risk factor changes were modelled (i.e. change from baseline was assumed to be zero). Nausea and hypoglycaemia rates associated with treatment are described in Section 2.6.

Table 3: Treatment effects applied in the first year of the simulation for tirzepatide and comparators in the PRIME T2D Model

	TZP 5 mg mean (SD)	TZP 10 mg mean (SD)	TZP 15 mg mean (SD)	DULA 1.5 mg mean (SD)	DULA 3.0 mg mean (SD)	DULA 4.5 mg mean (SD)	SEMA 0.5 mg mean (SD)	SEMA 1.0 mg mean (SD)	ORAL SEMA 7 mg mean (SD)	ORAL SEMA 14 mg mean (SD)	LIRA 1.2 mg mean (SD)	LIRA 1.8 mg mean (SD)
HbA1c change from baseline (%)												
SBP change from baseline (mmHg)												
BMI change from baseline (kg/m2)												
HDL change from baseline (mmol/L)												
LDL change from baseline (mmol/L)												

Abbreviations: BMI: body mass index; DULA: dulaglutide; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; LIRA: liraglutide; SBP: systolic blood pressure; SD: standard deviation; SEMA: semaglutide; TZP, tirzepatide.

Table 4: Treatment effects applied in the first year of the simulation for tirzepatide and comparators in the CORE Diabetes Model

	TZP 5 mg mean (SD)	TZP 10 mg mean (SD)	TZP 15 mg mean (SD)	DULA 1.5 mg mean (SD)	DULA 3.0 mg mean (SD)	DULA 4.5 mg mean (SD)	SEMA 0.5 mg mean (SD)	SEMA 1.0 mg mean (SD)	ORAL SEMA 7 mg mean (SD)	ORAL SEMA 14 mg mean (SD)	LIRA 1.2 mg mean (SD)	LIRA 1.8 mg mean (SD)
HbA1c change from baseline (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP change from baseline (mmHg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI change from baseline (kg/m2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HDL change from baseline (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LDL change from baseline (mg/dL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI: body mass index; DULA: dulaglutide; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; LIRA: liraglutide; SBP: systolic blood pressure; SD: standard deviation; SEMA: semaglutide; TZP, tirzepatide.

2.4 TREATMENT INTENSIFICATION

Intensification assumptions were the same in both modelling analyses:

- Simulated patients were assumed to intensify therapy when HbA1c levels rose above 7.5%, in line with NICE guidance for the management of T2D (NG28).
- Simulated patients were assumed to switch to basal insulin therapy on intensification and to remain on basal insulin therapy for the rest of the simulation, also based on NG28 guidance. On initiation of basal insulin therapy:
    - HbA1c was assumed to decrease by a mean of 0.84% based on the formula for "all" input parameters published by Willis *et al.* in 2017.[7]
    - All other risk factors were assumed to return to baseline levels upon initiation of insulin therapy, as there was no evidence on durability of effect at the time of modelling analysis

2.5 LONG-TERM RISK FACTOR PROGRESSION

Comparisons of long-term risk factor progressions between the CORE Diabetes Model and the PRIME T2D Model are provided in Sections 2.5.1 and 2.5.2 where the two models produced comparable outputs. The CORE Diabetes Model also provided outputs for diastolic blood pressure, total cholesterol, triglycerides, waist to hip ratio, heart rate, urinary albumin to creatinine ratio, serum creatinine and serum albumin: all of which were constant over time in the simulation with the exception of total cholesterol (the progression of total cholesterol is presented in Section 2.5.2.3).

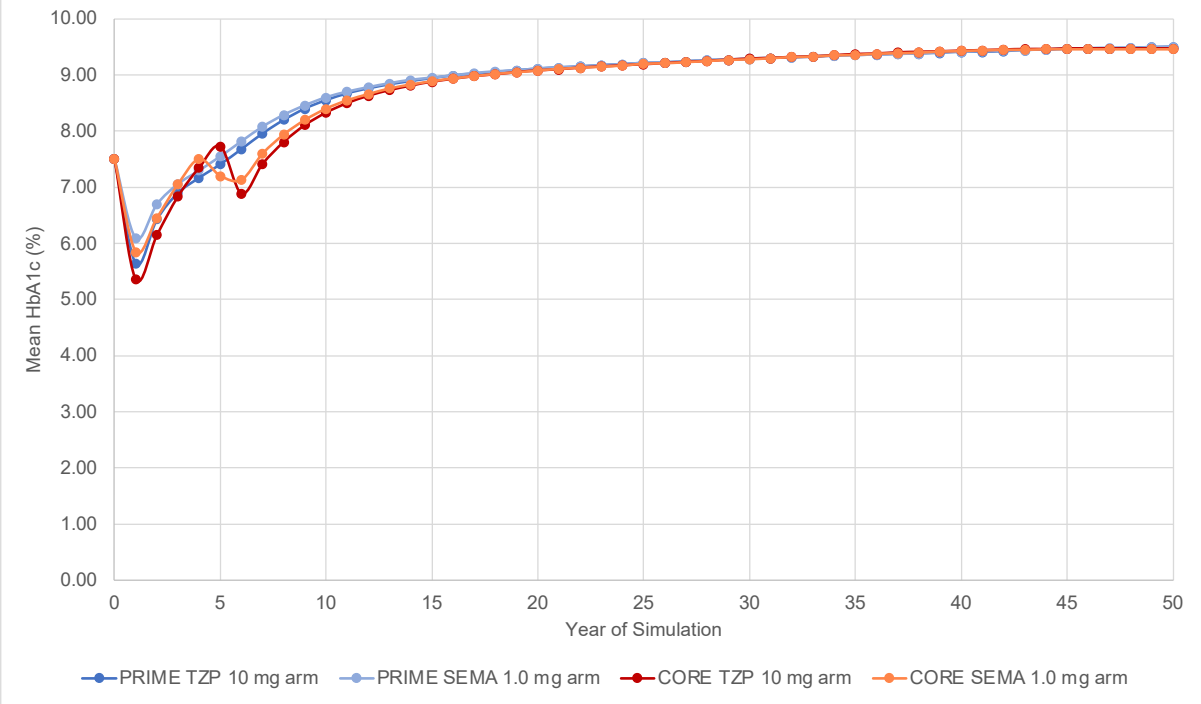
2.5.1 HbA1c progression

A comparison of mean HbA1c values by treatment group for the simulation populations in the PRIME T2D Model and CORE Diabetes Model are provided for the comparison between tirzepatide 10 mg and semaglutide 1.0 mg in Figure 1. The curves are different in the early years of the simulation for two main reasons:

- The UKPDS progression function is only applied in year 2 and onwards in the CORE Diabetes Model, but is already used to adjust HbA1c values in year 1 (after the application of treatment effects) in the PRIME T2D Model; the latter may represent a more conservative approach as HbA1c levels are already increasing in line with the UKPDS progression equation at the end of the first year of the simulation, as opposed to the end of the second year with the CORE Diabetes Model.
- In a standard simulation in the PRIME T2D Model, patient characteristics and treatment effects are sampled to produce a more realistic simulation cohort. This means that different patients will intensify at different times in the simulation (when they reach the HbA1c threshold of 7.5%) just as in real life clinical practice. In the CORE Diabetes Model, all patients are identical and experience an identical treatment effect, resulting in all patients in a given treatment arm intensifying in the same year of the simulation.

These two differences result in different glycemic exposure profiles between the two models, which may have an impact on cost-effectiveness. However, as outlined in Section 3, any impact on the incremental cost-effectiveness ratio (ICER) is likely to have been modest in the context of a long-term simulation given that the two models produced comparable cost-effectiveness profiles for tirzepatide, with ICERs below £20,000 per QALY gained.

Figure 1: Comparison of HbA1c progression in the PRIME T2D Model and the CORE Diabetes Model



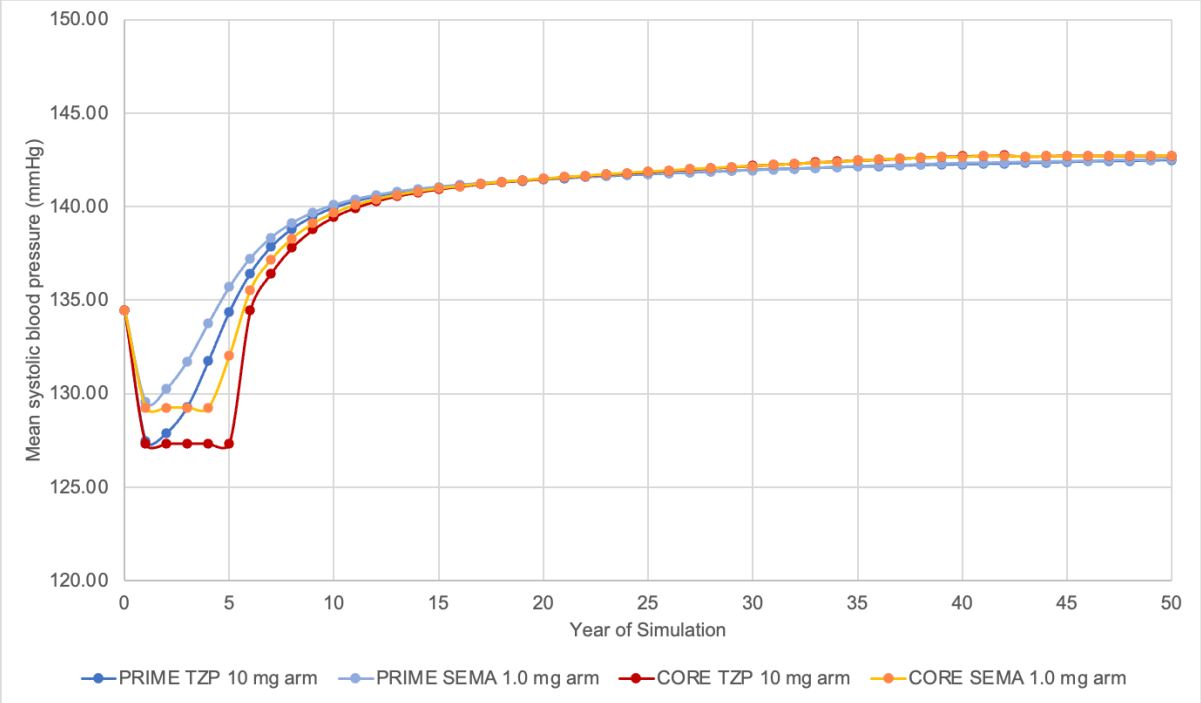
2.5.2 Other risk factors

2.5.2.1 SBP progression

A comparison of mean SBP values over time by treatment group for the simulation populations in the PRIME T2D Model and CORE Diabetes Model is provided for the comparison between tirzepatide 10 mg and semaglutide 1.0 mg in Figure 2. The SBP curves are different in the early years of the simulations due to individual times to intensification in the PRIME T2D Model and identical times to intensification the CORE Diabetes Model, specifically:

- In a standard simulation in the PRIME T2D Model, patient characteristics and treatment effects are sampled to produce a more realistic simulation cohort. This means that different patients will intensify at different times in the simulation (when they reach the HbA1c threshold of 7.5%) just as in real life clinical practice. In the CORE Diabetes Model, all patients are identical and experience an identical treatment effect, resulting in all patients in a given treatment arm intensifying in the same year of the simulation. This results in the population mean SBP curves in the PRIME T2D Model gradually going up over time as more and more patients intensify and SBP returns to baseline. In the CORE Diabetes Model, SBP returns to baseline levels in the same year for all patients in the simulation.

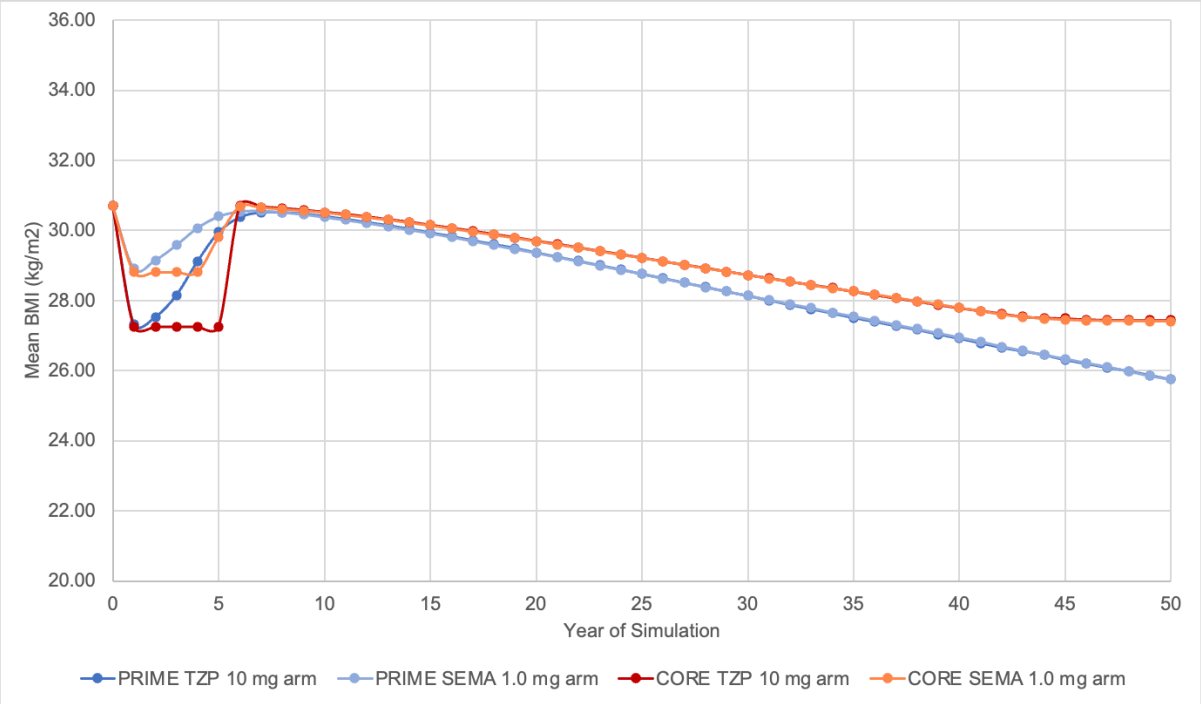
Figure 2: Comparison of SBP progression in the PRIME T2D Model and the CORE Diabetes Model



2.5.2.2 BMI progression

A similar pattern was observed in terms of BMI progression over time in the two models (Figure 3). Different times to intensification between the two models meant that mean BMI was different in the early years of the simulation. Values were similar between the models in years 10 to 15, after which mean BMI in the simulated population was lower in the PRIME T2D Model than in the CORE Diabetes Model. As the source code of the CORE Diabetes Model is not available, it is difficult to explain the difference in later years of the simulation (the implementation of the UKPDS OM2 BMI progression formula has been internally verified in the PRIME T2D Model). One potential explanation is that patients with higher BMI levels are at a higher risk of mortality in the PRIME T2D Model. A similar effect is not evident in the CORE Diabetes Model as all patients have the same BMI.

Figure 3: Comparison of BMI progression in the PRIME T2D Model and the CORE Diabetes Model



2.5.2.3 Serum lipid progressions

Long-term progression of serum lipid levels was comparable between the two models (Figure 4 and Figure 5), although differences were evident in the first 7-8 years of the simulations for the reasons previously outlined. From a cost-effectiveness perspective, the differences between treatment arms were small in both models, which means that any differences in the modeling of the progression of serum lipids over time is unlikely to impact incremental outcomes for tirzepatide versus semaglutide, and therefore cost-effectiveness. The progression of total cholesterol from the CORE Diabetes Model is shown in Figure 6 (the progression of total cholesterol is not modeled in the PRIME T2D Model as this parameter is not included in any of the risk equations used).

Figure 4: Comparison of HDL progression in the PRIME T2D Model and the CORE Diabetes Model

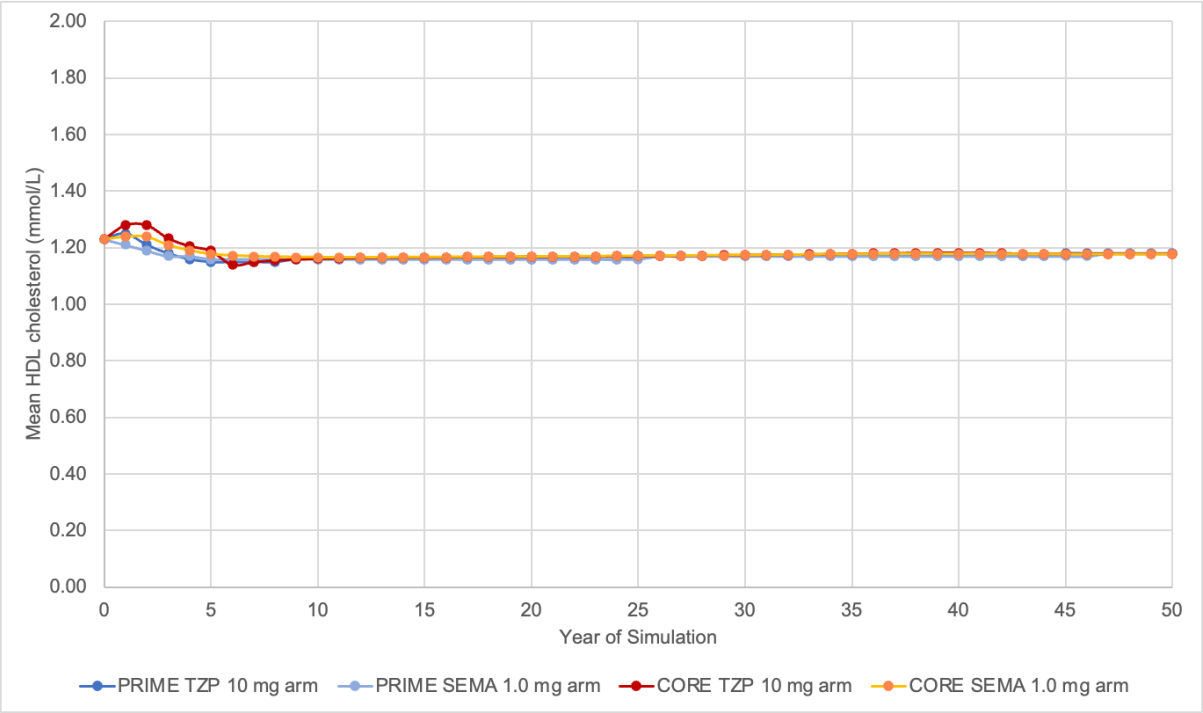


Figure 5: Comparison of LDL progression in the PRIME T2D Model and the CORE Diabetes Model

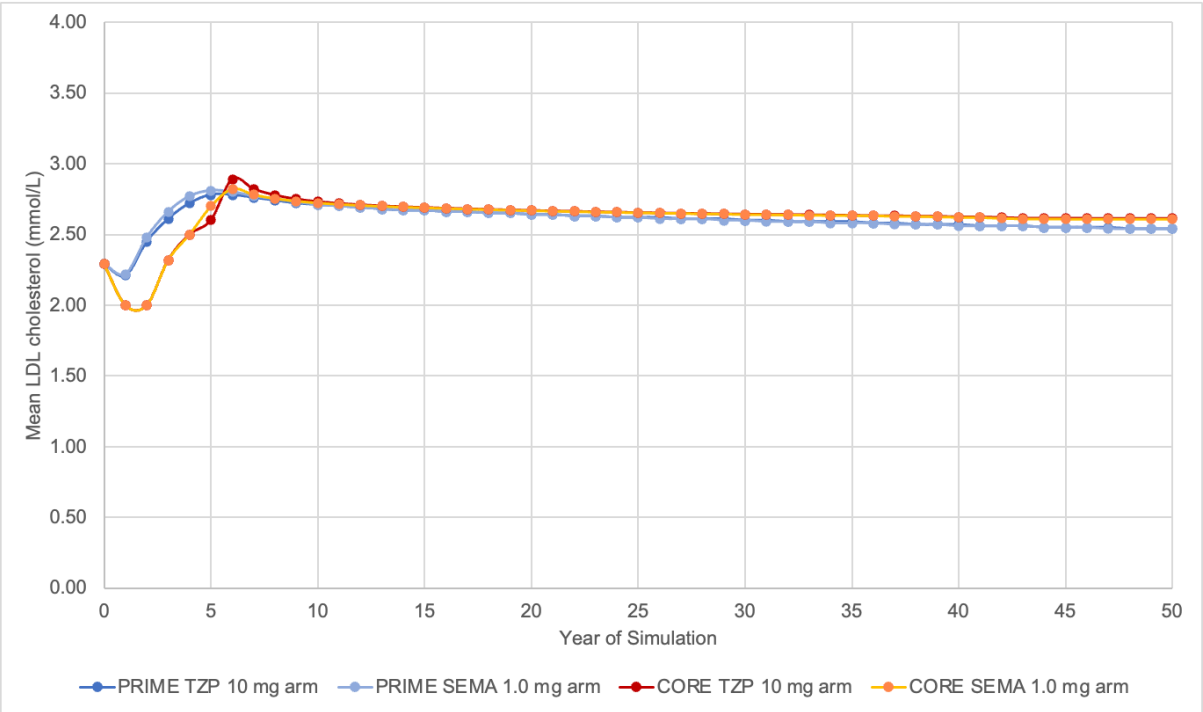
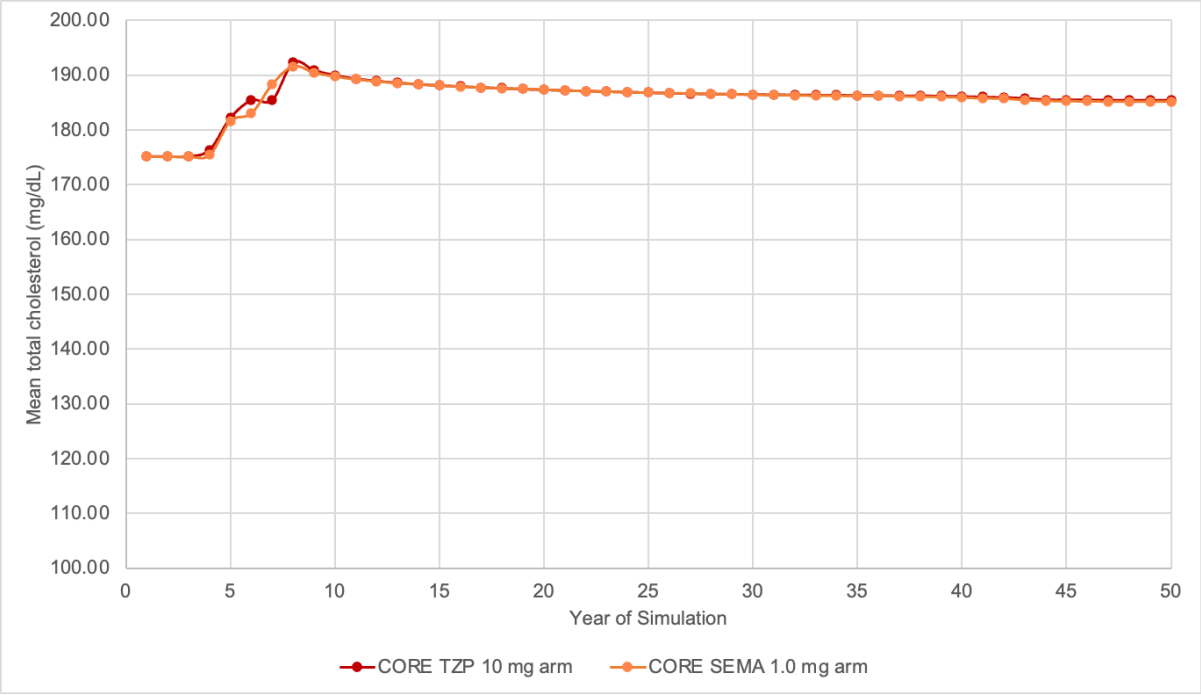


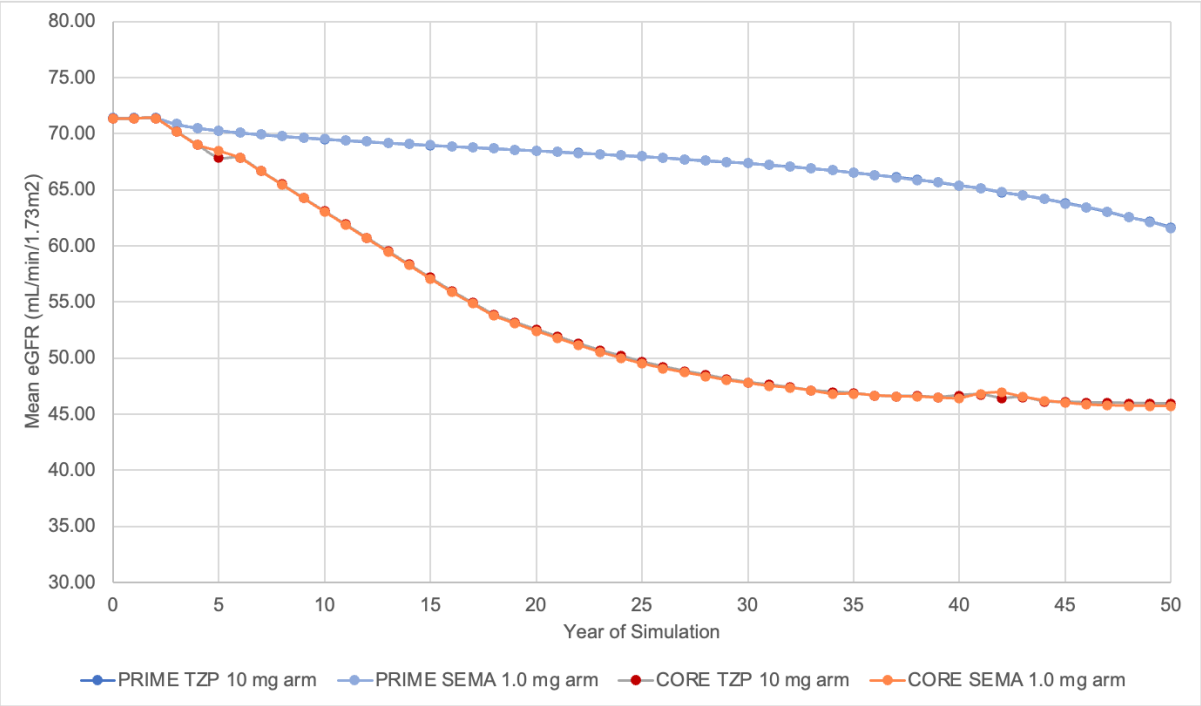
Figure 6: Total cholesterol progression in the CORE Diabetes Model



2.5.2.4 eGFR progression

Progression of eGFR over time appeared to be notably different between the two models (Figure 7). Whilst progression in the PRIME T2D Model followed the UKPDS eGFR progression equation, this option is not available in the CORE Diabetes Model. The only eGFR progression function available there is “Grams et al. 2020 (CRIC registry)”, which was used in the present simulations. The CORE Diabetes Model risk factor progression are a little concerning as it has all patients in a state of KDIGO stage 3 chronic kidney disease after year 25 in the simulation, which is unlikely to reflect clinical reality. However, modeled outcomes suggest that eGFR is not influencing renal disease progression in the CORE Diabetes Model, and which means the impact on cost-effectiveness is likely to be negligible (see Section 4). Moreover, there was very little difference between the treatment arms in either of the two models. Therefore, eGFR is unlikely to be a notable driver of cost-effectiveness in the present analysis.

Figure 7: Comparison of eGFR progression in the PRIME T2D Model and the CORE Diabetes Model



2.5.2.5 Haematology panel progressions

Progressions for haemoglobin and white blood cell count are provided for the PRIME T2D Model and the CORE Diabetes Model in Figure 8 and Figure 9. The values were held constant over time in the CORE Diabetes Model as there was no option to select the UKPDS risk factor progression function. Both of these risk factors followed UKPDS risk factor progression in the PRIME T2D Model analysis. In both modeling analyses, there were no differences in haematology parameters between treatment arms. Therefore, these parameters would not have had a notable impact on incremental outcomes or cost-effectiveness.

Figure 8: Comparison of haemoglobin progression in the PRIME T2D Model and the CORE Diabetes Model

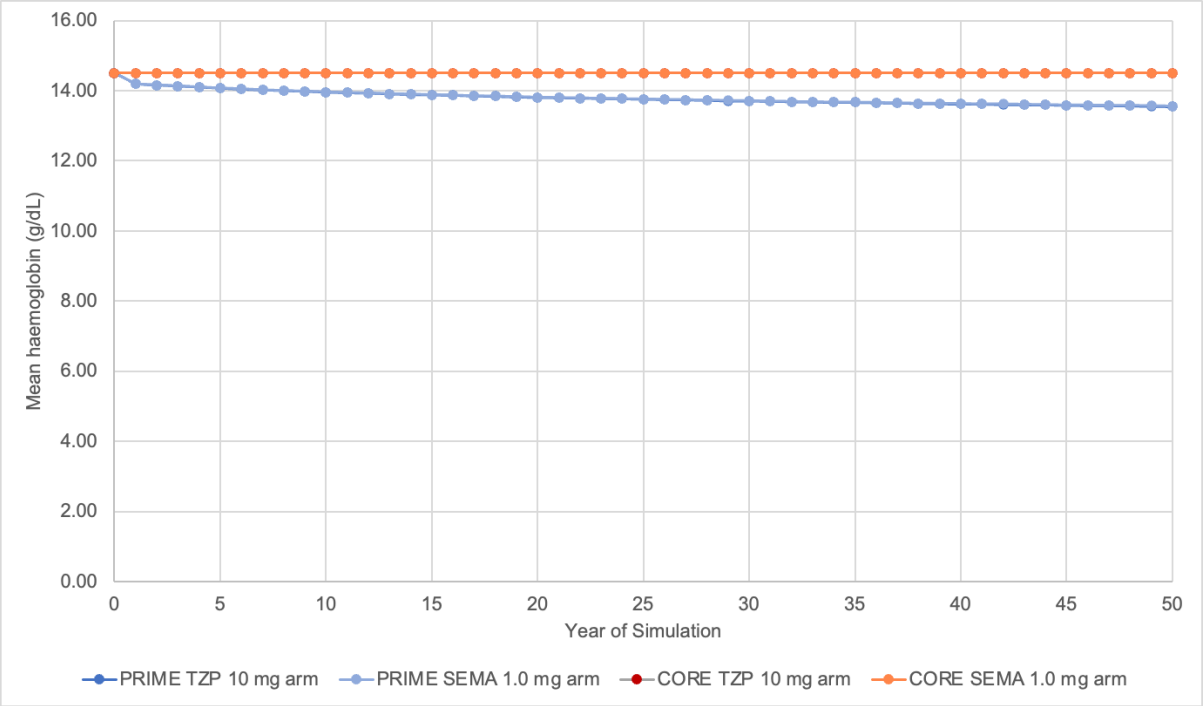
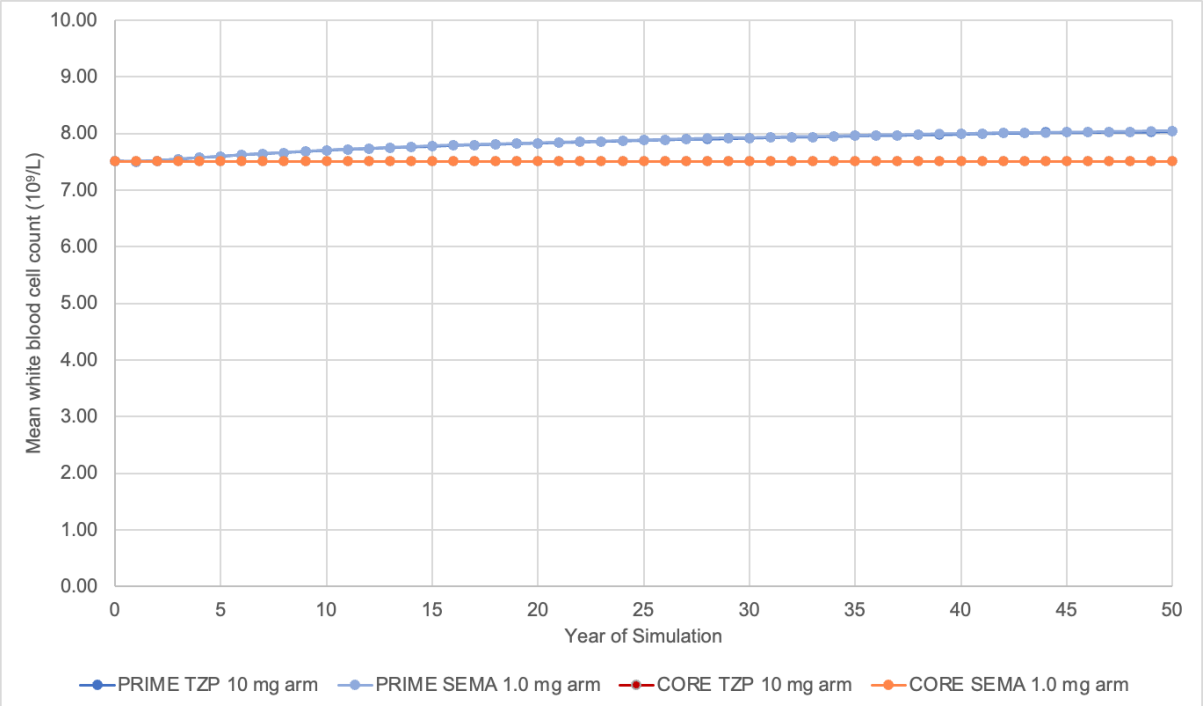


Figure 9: Comparison of white blood cell count progression in the PRIME T2D Model and the CORE Diabetes Model



2.6 HEALTH-RELATED QUALITY-OF-LIFE DATA USED IN THE COST-EFFECTIVENESS ANALYSIS

A summary of the utilities associated with diabetes-related complications and associated variance estimates used in the preferred base case analysis is provided in Table 5. It should be noted that the age-adjusted approach to estimating quality-adjusted life expectancy (requested by the EAG) was not possible with the CORE Diabetes Model as this functionality is not available in the model. Therefore an additive approach to combining utility values was used, as this was the closest match to the approach with the PRIME T2D Model and is aligned with previous NICE evaluations in type 2 diabetes.

Table 5: Utilities and disutilities used in the modelling analysis for diabetes-related complications and hypoglycaemic events

Baseline	**PRIME T2D Model utility**	**CORE Diabetes Model utility**	**Original source**
T2D with no complications	Age-adjusted[3]	0.815 (0.04)	Alva *et al.* Health Econ. 2014;23(4):487-500
Complication/adverse event	**Disutility (SE)**	**Utility / disutility**	**Original source**
Macrovascular complications			
Myocardial infarction event	−0.055 (0.006)	−0.055 (0.006)	Alva *et al.* Health Econ. 2014;23(4):487-500
History of myocardial infraction	−0.055 (0.006)	0.76 (0.04)	Alva *et al.* Health Econ. 2014;23(4):487-500
Stroke event	−0.164 (0.030)	−0.164 (0.03)	Alva *et al.* Health Econ. 2014;23(4):487-500
History of stroke	−0.164 (0.030)	0.651 (0.04)	Alva *et al.* Health Econ. 2014;23(4):487-500
Ischemic heart disease (each year)	−0.090 (0.018)	Not applicable	Alva *et al.* Health Econ. 2014;23(4):487-500
Angina (each year)	Not available	0.725 (0.07)	Alva *et al.* Health Econ. 2014;23(4):487-500
Revascularization	−0.038 (0.011)	Not applicable	Shao et al. Pharmacoeconomics. 2019; 37(7): 921-929
History of revascularization	−0.016 (0.005)	Not applicable	Shao et al. Pharmacoeconomics. 2019; 37(7): 921-929
Congestive heart failure (each year)	−0.108 (0.031)	0.707 (0.04)	Alva *et al.* Health Econ. 2014;23(4):487-500
Peripheral vascular disease (each year)	Not applicable	0.754 (0.04)	Bagust and Beale. Health Econ. 2005;14(3):217-30.
Microvascular complications			
Foot ulcer (year of event)	−0.170 (0.019)	−0.170 (0.019)	Beaudet *et al.* Value Health. 2014;17(4):462-470.
Lower extremity amputation (year of event)	−0.280 (0.056)	−0.280 (0.056)	Alva *et al.* Health Econ. 2014;23(4):487-500

Baseline	PRIME T2D Model utility	CORE Diabetes Model utility	Original source
Lower extremity amputation (subsequent years)	−0.122 (0.025)	0.693 (0.04)	Hayes *et al.* Value Health. 2016;19:36-41
Blindness (each year)	−0.074 (0.025)	0.741 (0.04)	Alva *et al.* Health Econ. 2014;23(4):487-500
Macular oedema (year of event)	−0.047 (0.005)	0.768 (0.04)	Mitchell *et al.* Br J Ophthalmol 2012;96:688-693
Background diabetic retinopathy (each year)	Not applicable	0.775 (0.04)	Fenwick et al. Invest Ophthalmol Vis Sci 2012;53:677-84.
Background diabetic retinopathy, wrongly treated (each year)	Not applicable	0.775 (0.04)	Fenwick et al. Invest Ophthalmol Vis Sci 2012;53:677-84.
Proliferative diabetic retinopathy, laser treated (each year)	Not applicable	0.745 (0.04)	Fenwick et al. Invest Ophthalmol Vis Sci 2012;53:677-84.
Proliferative diabetic retinopathy, no laser (each year)	Not applicable	0.745 (0.04)	Fenwick et al. Invest Ophthalmol Vis Sci 2012;53:677-84.
Cataract (each year)	Not applicable	0.799 (0.04)	Lee et al. Diabet Med. 2005;22(11):1482-6.
Neuropathy/SPSL (each year)	−0.066 (0.007)	0.749 (0.04)	Shao *et al.* Pharmacoeconomics. 2019; 37(7): 921-929
Renal complications			
KDIGO CKD eGFR stage 1	0	Not applicable	Assumed
KDIGO CKD eGFR stage 2	0	Not applicable	Assumed
KDIGO CKD eGFR stage 3	−0.004 (0.010)	Not applicable	Nauck *et al.* Diabetes Obes Metab. 2019;21:525–532.
KDIGO CKD eGFR stage 4	−0.004 (0.010)	Not applicable	Nauck *et al.* Diabetes Obes Metab. 2019;21:525–532.
KDIGO CKD eGFR stage 5 (renal failure)	−0.164 (0.016)	Not applicable	Alva *et al.* Health Econ. 2014;23(4):487-500
Microalbuminuria (each year)	Not applicable	0.815 (0.04)	Assumed
Gross proteinuria (each year)	Not applicable	0.811 (0.04)	Nauck et al. Diabetes Obes Metab. 2019; 21(3): 525-32
Haemodialysis (each year)	Not applicable	0.651 (0.04)	NICE HE Report 2022 (Table HE027: Quality of life parameters)
Peritoneal dialysis (each year)	Not applicable	0.651 (0.04)	NICE HE Report 2022 (Table HE027: Quality of life parameters)
Renal transplant	Not applicable	0.792 (0.04)	Kiberd and Jindal. BMJ 1995;311:1595-9.
Adverse events			

Baseline	PRIME T2D Model utility	CORE Diabetes Model utility	Original source
Severe hypoglycaemic event	−0.062 (0.04)	−0.062 (0.04)	Evans et al. Health Qual Life Outcomes. 2013; 11: 90
Non-severe hypoglycaemic event	−0.005 (0.01)	−0.005 (0.01)	Evans et al. Health Qual Life Outcomes. 2013; 11: 90

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes; SPSL: severe pressure sensation loss; T2D: type 2 diabetes.

Each treatment was associated with an annual disutility designed to capture the effects of nausea and vomiting (in year 1 only) and the impact of BMI on quality of life (Table 6). The BMI-related utility was applied for each year on treatment. In year 1 of the modeling analysis, the utility associated with nausea and vomiting was also added to each patient's utility score. The approach used was the same in the PRIME T2D Model and the CORE Diabetes Model. No utilities associated with devices or weight change (i.e. weight loss) were included in the EAG preferred base case analysis.

Table 6: Utilities and disutilities associated with nausea and vomiting and BMI in the modeling analysis

Treatment	Percentage experiencing nausea (%)	Disutility for nausea and vomiting*	BMI on treatment (kg/m^2)	Disutility for BMI**
Tirzepatide 5 mg	25.8	–0.010	28.28	–0.0200
Tirzepatide 10 mg	34.3	–0.014	27.28	–0.0139
Tirzepatide 15 mg	37.2	–0.015	26.53	–0.0093
Dulaglutide 1.5 mg	28.1	–0.011	29.78	–0.0291
Dulaglutide 3.0 mg	28.1	–0.011	29.61	–0.0281
Dulaglutide 4.5 mg	28.1	–0.011	29.47	–0.0273
Semaglutide 0.5 mg	24.9	–0.010	29.39	–0.0268
Semaglutide 1.0 mg	28.1	–0.011	28.83	–0.0234
Oral semaglutide 7 mg	24.9	–0.010	29.79	–0.0292
Oral semaglutide 14 mg	28.1	–0.011	29.11	–0.0251
Liraglutide 1.2 mg	20.3	–0.008	29.87	–0.0297
Liraglutide 1.8 mg	25.3	–0.010	29.65	–0.0284
Basal insulin	0	0	30.7	–0.0349

* Based on the utility for nausea and vomiting of -0.04 from Matza et al. Qual Life Res 2007; 16:1251–65. ** Based on the utility for each unit of BMI over 25 kg/m2 of -0.0061 from Bagust and Beale. Health Econ 2005; 14(3):217-30

2.7 COSTS USED IN THE COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness analysis in the CORE Diabetes Model and in the PRIME T2D Model have been run based on the pack prices for tirzepatide summarized in Table 7.

Table 7: Pack prices for tirzepatide used in the modeling analysis

Dose	Updated pack price
Tirzepatide 5 mg	[redacted]
Tirzepatide 10 mg	[redacted]
Tirzepatide 15 mg	[redacted]

Annual treatment cost inputs for each intervention were the same in the PRIME T2D Model and in the CORE Diabetes Model, were expressed in 2022 Pounds Sterling (£), and are summarized in Table 8.

Table 8: Annual treatment costs for tirzepatide, comparators and basal insulin therapy used in the modeling analysis

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Dulaglutide (all doses)	Injectable Semaglutide (all doses)	Oral semaglutide (all doses)	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Basal insulin
Study medications									
Annual study medication cost (£)	[redacted]	[redacted]	[redacted]	955.52	955.52	955.00	955.49	1,433.24	-
Annual NPH cost (£)	-	-	-	-	-	-	-	-	185.84
Annual metformin cost (£)	40.18	40.18	40.18	40.18	40.18	40.18	40.18	40.18	40.18
Consumables									
Annual needle costs (£)	0.00	0.00	0.00	0.00	0.00	0.00	18.26	18.26	18.26
Annual SMBG costs (£)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	142.45
Additional costs									
GLP-1 receptor agonist initiation (£)	40.33	40.33	40.33	40.33	40.33	40.33	40.33	40.33	-
Insulin initiation (£)	-	-	-	-	-	-	-	-	141.17
Total annual cost (year 1) (£)	[redacted]	[redacted]	[redacted]	**1,036.03**	**1,036.03**	**1,035.51**	**1,054.27**	**1,532.01**	**527.89**
Total annual cost (years 2+) (£)	[redacted]	[redacted]	[redacted]	**995.70**	**995.70**	**995.18**	**1,013.93**	**1,491.68**	**386.73**

A summary of the complication costs and adverse event unit costs used in the EAG preferred base case analysis (inflated to 2022 values) for the PRIME T2D Model and the CORE Diabetes Model is provided in Table 9. It should be noted that it was not possible to include the variance around each unit cost (as requested by the EAG) in the CORE Diabetes Model as there are no input fields for variance estimates in the CORE Diabetes Model user interface. Therefore, only mean costs are reported.

Table 9: Summary of direct costs associated with diabetes-related complications used in the modelling analysis (2022 values)

	PRIME T2D Model mean (SE) (£)	CORE Diabetes Model mean (£)	Original source
Macrovascular complications			
Myocardial infarction, year 1	8,862 (1,322)	8,862	Alva *et al.* Diabet Med. 2015;32(4):459-66
Myocardial infarction, years 2+	2,203 (250)	2,203	Alva *et al.* Diabet Med. 2015;32(4):459-66
Stroke, year 1	9,530 (2,164)	9,530	Alva *et al.* Diabet Med. 2015;32(4):459-66
Stroke, years 2+	2,270 (379)	2,270	Alva *et al.* Diabet Med. 2015;32(4):459-66
Stroke, death within 30 days	Not applicable	4,651	Alva *et al.* Diabet Med. 2015;32(4):459-66
Ischemic heart disease, year 1	12,831 (1,799)	Not applicable	Alva *et al.* Diabet Med. 2015;32(4):459-66
Ischemic heart disease, years 2+	2,256 (248)	Not applicable	Alva *et al.* Diabet Med. 2015;32(4):459-66
Revascularization, year 1	3,593 (359)	Not applicable	NHS Reference Costs 2019/20 (weighted mean of Standard Percutaneous Transluminal Coronary Angioplasty, HRG codes EY41A, EY41B, EY41C, EY41D),no variance reported, 10% assumed
Revascularization, years 2+	0 (0)	Not applicable	Assumed
Angina, year 1	Not applicable	2,513	Alva *et al.* Diabet Med. 2015;32(4):459-66
Angina, years 2+	Not applicable	421	Alva *et al.* Diabet Med. 2015;32(4):459-66
Congestive heart failure, year 1	5,033 (1,127)	5,033	Alva *et al.* Diabet Med. 2015;32(4):459-66
Congestive heart failure, years 2+	2,952 (510)	2,952	Alva *et al.* Diabet Med. 2015;32(4):459-66

	PRIME T2D Model mean (SE) (£)	CORE Diabetes Model mean (£)	Original source
Peripheral vascular disease, year 1	Not applicable	2,304	2022/23 National Tariff Payment System, Averge of YQ50A-F Peripheral Vascular Disorders with CC Score 0-15
Peripheral vascular disease, years 2+	Not applicable	2,304	2022/23 National Tariff Payment System, Averge of YQ50A-F Peripheral Vascular Disorders with CC Score 0-15
Microvascular complications			
Foot ulcer, year 1	3,705 (371)	3,705	Kerr *et al.* Diabet. Med. 2019;36: 995-1002, no variance reported, 10% assumed
Foot ulcer, years 2+	0 (0)	0	Assumed
Amputation, year 1	14,779 (2,962)	14,779	Alva et al. Diabet Med. 2015;32(4):459-66
Amputation, years 2+	4,107 (837)	4,107	Alva et al. Diabet Med. 2015;32(4):459-66
Blindness, year 1	3,796 (1,409)	3,796	Alva et al. Diabet Med. 2015;32(4):459-66
Blindness, years 2+	1,438 (229)	1,438	Alva et al. Diabet Med. 2015;32(4):459-66
Macular oedema	696 (70)	Not applicable	NHS reference costs 2019/2020*, no variance reported, 10% assumed
Neuropathy/SPSL, all years	1,098 (110)	1,098	Hunt et al. Diabetes Ther. 2017;8(1):129-147, no variance reported, 10% assumed
Laser treatment	Not applicable	99	2022/23 National Tariff Payment System, BZ87A Minor Vitreous Retinal Procedures, 19 years and over as outpatient procedure
Cataract surgery, year 1	Not applicable	823	Alva et al. Diabet Med. 2015;32(4):459-66
Cataract surgery, years 2+	Not applicable	899	Alva et al. Diabet Med. 2015;32(4):459-66
Neuropathy/SPSL, all years	1,098 (110)	1,098	Hunt et al. Diabetes Ther. 2017;8(1):129-147, no variance reported, 10% assumed

	PRIME T2D Model mean (SE) (£)	CORE Diabetes Model mean (£)	Original source
Renal complications			
KDIGO CKD eGFR stage	0 (0)	Not applicable	Assumed
KDIGO CKD eGFR stage 2	0 (0)	Not applicable	Assumed
KDIGO CKD eGFR stage 3	0 (0)	Not applicable	Assumed
KDIGO CKD eGFR stage 4	472 (31)	Not applicable	Kent et al. BMC Nephrol. 2015;16:65.
KDIGO CKD eGFR stage 5	21,996 (2,200)	Not applicable	Alva et al. Diabet Med. 2015;32(4):459-66
Haemodialysis, year 1	Not applicable	21,996	Alva et al. Diabet Med. 2015;32(4):459-66
Haemodialysis, years 2+	Not applicable	21,996	Alva et al. Diabet Med. 2015;32(4):459-66
Peritoeal dialysis, year 1	Not applicable	21,996	Alva et al. Diabet Med. 2015;32(4):459-66
Peritoeal dialysis, years 2+	Not applicable	21,996	Alva et al. Diabet Med. 2015;32(4):459-66
Renal transplant, year 1	Not applicable	21,541	NICE HE Report 2022 (Table HE018: Management and complication costs)
Renal transplant, years 2+	Not applicable	8,589	NICE HE Report 2022 (Table HE018: Management and complication costs)
Adverse events			
Severe hypoglycaemia	393 (0)	393	NICE HE Report 2022 (Table HE023: Hypoglycemia costs)
Non-severe hypoglycaemia	0 (0)	0	NICE HE Report 2022 (Table HE023: Hypoglycemia costs)
Nausea and vomiting	0 (0)	0	Assumed

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SPSL: severe pressure sensation loss; KDIGO: Kidney Disease Improving Global Outcomes.
*Day Case, BZ87A, Minor vitreous retinal procedures, 19 years and over.[34]

2.8 MODELING APPROACH

Simulations with the CORE Diabetes Model were run using the default approach of 1,000 iterations of cohorts of 1,000 identical patients over a 50-year time horizon (first order Monte Carlo simulation). The same approach was used in both recent NICE evaluations performed using the CORE Diabetes Model.[8,9] The approach used in the PRIME T2D Model was to generate individual patients by sampling baseline characteristics and treatment effects for a population of 300,000 for each treatment arm and simulating their progression using a first order Monte Carlo simulation approach over a 50-year time horizon. The UKPDS 82 risk equations

were selected in the CORE Diabetes Model to evaluate the risk of diabetes-related complications. A model averaging approach was used in the PRIME T2D Model analysis.

Discount rates for future costs and clinical benefits were set to 3.5% *per annum* in the CORE Diabetes Model as well as in the PRIME T2D Model analysis.

3 COST-EFFECTIVENESS RESULTS USING THE TIRZEPATIDE EAG PREFERRED BASE CASE SETTINGS WITH THE CORE DIABETES MODEL

Long-term projections with the CORE Diabetes Model indicated that use of all three doses of tirzepatide was associated with improvements in life expectancy and quality-adjusted life expectancy versus all comparators evaluated (Table 10, Table 11 and Table 12). Tirzepatide 5 mg was associated with greater lifetime direct costs than all but one of the comparators, with incremental costs ranging between £761 and £1,088 and incremental cost-effectiveness ratios (ICERs) ranging between £5,982 and £19,779 per QALY gained (Table 10). Tirzepatide 5 mg was cost-saving versus liraglutide 1.8 mg (reducing costs by approximately £922), making it dominant in this comparison.

Tirzepatide 10 mg was also associated with higher direct costs than all but one of the comparators, with ICERs for tirzepatide 10 mg ranged between £9,105 and £19,204 per QALY gained (Table 11). Tirzepatide 10 mg was also dominant to liraglutide 1.8 mg. A similar pattern of results was projected for tirzepatide 15 mg, with higher direct costs than all comparators and ICERs ranging between £3,178 and £20,286 per QALY gained versus comparators (Table 12).

For purposes of comparison, summary cost-effectiveness results from the PRIME T2D Model are provided in Table 13, Table 14 and Table 15. In general, life expectancy estimates and total costs were higher with the PRIME T2D Model than with the CORE Diabetes Model. However, incremental quality-adjusted life expectancy estimates were comparable between the models, indicating similarities in incremental risk evaluation between the models, and leading to comparable cost-effectiveness outcomes and ranking of interventions. Incremental costs were a little lower in the PRIME T2D Model analysis than with the CORE Diabetes Model, leading to slightly lower ICERs overall.

Cost-effectiveness scatterplots with cost-effectiveness frontiers are provided for each dose of tirzepatide from the CORE Diabetes Model (Figure 10, Figure 11 and Figure 12) and the PRIME T2D Model (Figure 13, Figure 14 and Figure 15). In all three cases, the frontier was found between tirzepatide and semaglutide, with all other comparators above (to the North West of) the frontier represented by the ICER for tirzepatide versus semaglutide 1.0 mg.

Table 10: Summary of EAG preferred base case results for tirzepatide 5 mg versus comparators from the CORE Diabetes Model

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	11.599	8.247	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	11.553	8.128	936	0.047	0.119	7,851	0.072
Dulaglutide 3.0 mg	[redacted]	11.568	8.163	894	0.031	0.084	10,607	0.039
Dulaglutide 4.5 mg	[redacted]	11.561	8.163	975	0.038	0.084	11,635	0.035
Semaglutide 0.5 mg	[redacted]	11.554	8.142	1,088	0.045	0.105	10,369	0.051
Semaglutide 1.0 mg	[redacted]	11.580	8.194	1,052	0.020	0.053	19,779	0.000
Oral semaglutide 7 mg	[redacted]	11.543	8.132	817	0.056	0.115	7,090	0.074
Oral semaglutide 14 mg	[redacted]	11.575	8.177	1,080	0.024	0.071	15,321	0.017
Liraglutide 1.2 mg	[redacted]	11.545	8.120	761	0.054	0.127	5,982	0.089
Liraglutide 1.8 mg	[redacted]	11.553	8.128	-922	0.047	0.119	Dominant	0.165

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB was calculated assuming a willingness to pay of £20,000 per QALY gained.

Table 11: Summary of EAG preferred base case results for tirzepatide 10 mg versus comparators from the CORE Diabetes Model

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	11.614	8.290	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	11.553	8.128	1,719	0.062	0.162	10,640	0.076
Dulaglutide 3.0 mg	[redacted]	11.568	8.163	1,678	0.046	0.127	13,242	0.043
Dulaglutide 4.5 mg	[redacted]	11.561	8.163	1,759	0.053	0.126	13,935	0.038
Semaglutide 0.5 mg	[redacted]	11.554	8.142	1,871	0.060	0.147	12,704	0.053
Semaglutide 1.0 mg	[redacted]	11.580	8.194	1,836	0.035	0.096	19,204	0.004

Oral semaglutide 7 mg	[redacted]	11.543	8.132	1,600	0.071	0.158	10,155	0.078
Oral semaglutide 14 mg	[redacted]	11.575	8.177	1,864	0.039	0.113	16,508	0.020
Liraglutide 1.2 mg	[redacted]	11.545	8.120	1,545	0.069	0.170	9,105	0.093
Liraglutide 1.8 mg	[redacted]	11.553	8.128	-139	0.062	0.161	Dominant	0.168

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB was calculated assuming a willingness to pay of £20,000 per QALY gained.

Table 12: Summary of EAG preferred base case results for tirzepatide 15 mg versus comparators from the CORE Diabetes Model

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	11,629	8.322	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	11.553	8.128	2,472	0.076	0.194	12,762	0.070
Dulaglutide 3.0 mg	[redacted]	11.568	8.163	2,430	0.060	0.159	15,305	0.038
Dulaglutide 4.5 mg	[redacted]	11.561	8.163	2,511	0.068	0.158	15,864	0.032
Semaglutide 0.5 mg	[redacted]	11.554	8.142	2,624	0.075	0.179	14,634	0.048
Semaglutide 1.0 mg	[redacted]	11.580	8.194	2,588	0.049	0.128	20,286	-0.001
Oral semaglutide 7 mg	[redacted]	11.543	8.132	2,353	0.086	0.190	12,404	0.072
Oral semaglutide 14 mg	[redacted]	11.575	8.177	2,616	0.054	0.145	18,044	0.014
Liraglutide 1.2 mg	[redacted]	11.545	8.120	2,298	0.084	0.202	11,392	0.087
Liraglutide 1.8 mg	[redacted]	11.553	8.128	614	0.076	0.193	3,178	0.162

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator. NHB was calculated assuming a willingness to pay of £20,000 per QALY gained.

Table 13: Summary of EAG preferred base case results for tirzepatide 5 mg versus comparators from the PRIME T2D Model

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	8.715	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	705	0.059	0.100	7,073	0.064
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	644	0.046	0.079	8,182	0.047
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	628	0.030	0.058	10,891	0.026
Semaglutide 0.5 mg	[redacted]	13.075	8.634	682	0.047	0.081	8,401	0.047
Semaglutide 1.0 mg	[redacted]	13.096	8.673	708	0.026	0.042	16,817	0.007
Oral semaglutide 7 mg	[redacted]	13.049	8.595	742	0.073	0.120	6,202	0.083
Oral semaglutide 14 mg	[redacted]	13.074	8.642	719	0.048	0.073	9,873	0.037
Liraglutide 1.2 mg	[redacted]	13.032	8.581	672	0.090	0.134	5,021	0.100
Liraglutide 1.8 mg	[redacted]	13.054	8.600	-409	0.068	0.115	Dominant	0.135

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB was calculated assuming a willingness to pay of £20,000 per QALY gained.

Table 14: Summary of EAG preferred base case results for tirzepatide 10 mg versus comparators from the PRIME T2D Model

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.768	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	1,389	0.092	0.153	9,091	0.083
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	1,329	0.079	0.132	10,073	0.065
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	1,312	0.063	0.111	11,843	0.045
Semaglutide 0.5 mg	[redacted]	13.075	8.634	1,367	0.080	0.134	10,171	0.066
Semaglutide 1.0 mg	[redacted]	13.096	8.673	1,393	0.059	0.095	14,616	0.026

Oral semaglutide 7 mg	[redacted]	13.049	8.595	1,427	0.106	0.173	8,254	0.102
Oral semaglutide 14 mg	[redacted]	13.074	8.642	1,403	0.081	0.126	11,140	0.056
Liraglutide 1.2 mg	[redacted]	13.032	8.581	1,356	0.123	0.187	7,254	0.119
Liraglutide 1.8 mg	[redacted]	13.054	8.600	276	0.101	0.168	1,642	0.154

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB was calculated assuming a willingness to pay of £20,000 per QALY gained.

Table 15: Summary of EAG preferred base case results for tirzepatide 15 mg versus comparators from the PRIME T2D Model

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.176	8.808	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	2,047	0.113	0.192	10,642	0.090
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	1,987	0.100	0.171	11,586	0.072
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	1,970	0.084	0.150	13,104	0.052
Semaglutide 0.5 mg	[redacted]	13.075	8.634	2,025	0.101	0.174	11,641	0.073
Semaglutide 1.0 mg	[redacted]	13.096	8.673	2,051	0.080	0.135	15,209	0.032
Oral semaglutide 7 mg	[redacted]	13.049	8.595	2,085	0.127	0.212	9,815	0.108
Oral semaglutide 14 mg	[redacted]	13.074	8.642	2,061	0.102	0.166	12,453	0.062
Liraglutide 1.2 mg	[redacted]	13.032	8.581	2,014	0.144	0.227	8,893	0.126
Liraglutide 1.8 mg	[redacted]	13.054	8.600	934	0.122	0.208	4,498	0.161

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator. NHB was calculated assuming a willingness to pay of £20,000 per QALY gained.

Figure 10: Cost-effectiveness frontier for tirzepatide 5 mg versus comparators using the CORE Diabetes Model

The broken line indicates the cost-effectiveness frontier with the corresponding incremental cost-effectiveness ratio for tirzepatide versus the most-effective comparator. Comparators above the line can be considered less cost-effective.
Abbreviations: GBP: Great British Pounds; QALY: quality-adjusted life year; TZP: tirzepatide.

Figure 11: Cost-effectiveness frontier for tirzepatide 10 mg versus comparators using the CORE Diabetes Model

The broken line indicates the cost-effectiveness frontier with the corresponding incremental cost-effectiveness ratio for tirzepatide versus the most-effective comparator. Comparators above the line can be considered less cost-effective.
Abbreviations: GBP: Great British Pounds; QALY: quality-adjusted life year; TZP: tirzepatide.

Figure 12: Cost-effectiveness frontier for tirzepatide 15 mg versus comparators using the CORE Diabetes Model

The broken line indicates the cost-effectiveness frontier with the corresponding incremental cost-effectiveness ratio for tirzepatide versus the most-effective comparator. Comparators above the line can be considered less cost-effective.
Abbreviations: GBP: Great British Pounds; QALY: quality-adjusted life year; TZP: tirzepatide.

Figure 13: Cost-effectiveness frontier for tirzepatide 5 mg versus comparators using the PRIME T2D Model

The broken line indicates the cost-effectiveness frontier with the corresponding incremental cost-effectiveness ratio for tirzepatide versus the most-effective comparator. Comparators above the line can be considered less cost-effective.
Abbreviations: GBP: Great British Pounds; QALY: quality-adjusted life year; TZP: tirzepatide.

Figure 14: Cost-effectiveness frontier for tirzepatide 10 mg versus comparators using the PRIME T2D Model

The broken line indicates the cost-effectiveness frontier with the corresponding incremental cost-effectiveness ratio for tirzepatide versus the most-effective comparator. Comparators above the line can be considered less cost-effective.
Abbreviations: GBP: Great British Pounds; QALY: quality-adjusted life year; TZP: tirzepatide.

Figure 15: Cost-effectiveness frontier for tirzepatide 15 mg versus comparators using the PRIME T2D Model

The broken line indicates the cost-effectiveness frontier with the corresponding incremental cost-effectiveness ratio for tirzepatide versus the most-effective comparator. Comparators above the line can be considered less cost-effective.
Abbreviations: GBP: Great British Pounds; QALY: quality-adjusted life year; TZP: tirzepatide.

4 INTERPRETATION AND CONCLUSIONS

Long-term cost-effectiveness analyses using the CORE Diabetes Model to compare tirzepatide with GLP-1 RAs in common use in the UK setting, based on NMA data, have shown that:

- All three doses of tirzepatide (5, 10 and 15 mg) were associated with improvements in life expectancy and quality-adjusted life expectancy over the evaluated comparators.

- Direct costs were generally higher for tirzepatide than for comparators. Higher lifetime costs versus comparators were driven by higher treatment costs in the tirzepatide arms due to higher drug acquisition costs and a longer time on therapy. The longer time on therapy was driven by greater improvements in HbA1c with tirzepatide, resulting in a longer time to reach the basal insulin intensification threshold of 7.5%. Higher treatment costs with tirzepatide were partially offset by reduced complication costs, in particular the reduced costs associated with macrovascular complications on tirzepatide versus comparators.

- All doses of tirzepatide were associated with ICERs below £20,000 per QALY gained against the comparators, with tirzepatide 5 and 10 mg being dominant to liraglutide 1.8 mg, with one exception: the comparison of tirzepatide 15 mg with semaglutide 1.0 mg produced an ICER of £20,286 per QALY in the evaluation with the CORE Diabetes Model.

Broadly speaking, the models are conceptually similar, in that they run patient level simulations and use published data to evaluate the risk of diabetes-related complications and mortality on patients with type 2 diabetes. The models share many endpoints, particularly in relation to end-stage complications (e.g. myocardial infarction, stroke, heart failure, blindness, renal failure, neuropathy, foot ulcer and amputation) and report comparable outcomes for cost-effectiveness analysis (life expectancy, quality-adjusted life expectancy, direct costs and incremental outcomes from head-to-head comparisons). However, there are differences between the models that may influence simulation outcomes:

- There were differences in some of the endpoints evaluated by the two models:

    - The CORE Diabetes Model uses an angina endpoint but not ischaemic heart disease (IHD) endpoint, whereas the PRIME T2D Model includes IHD but not angina. It is not clear how angina is estimated in the CORE Diabetes Model as this is not an endpoint available from UKPDS OM2 risk equations (but IHD is).

    - Revascularization is included in the PRIME T2D Model but is not included in the CORE Diabetes Model.

    - The intermediate endpoint peripheral vascular disease (PVD) is included in the CORE Diabetes Model but is not modelled in the PRIME T2D Model (although history of PVD is included as a baseline risk factor). The decision not to included PVD in the PRIME T2D Model was made at the Advisory Board Meeting in 2019 based on the evidence that PVD incidence rates are so low in routine clinical practice (in addition to the complexity associated with multiple related endpoint definitions), that including PVD would have a negligible impact on costs, quality of life and cost-effectiveness. This approach is consistent with most other type 2 diabetes models, which similarly do not include PVD as an endpoint (e.g. UKPDS

OM2, BRAVO, ECHO-T2DM, Cardiff Diabetes Model, MDM-TTM, Michigan Diabetes Model, etc.).[10]

  - Renal disease modelling is different in the two models. In the CORE Diabetes Model, patients progress through states of microalbuminuria and gross proteinuria to reach renal failure. At this point, they can receive haemodialysis, peritoneal dialysis or a renal transplant. As the UKPDS OM2 only provides a risk equation for the onset of renal failure, it's not clear exactly how this progression is modelled in the CORE Diabetes Model and how the treatment modalities during renal failure are distributed. In the PRIME T2D Model, the development of renal disease is dictated by eGFR progression (in the present analysis using UKPDS based risk factor progression for eGFR and the UKPDS risk equations for the onset of renal failure). It is assumed that eGFR did not influence the risk of renal disease progression in the CORE Diabetes Model as, despite a rapid decline in eGFR, the cumulative incidence of gross proteinuria was around 4% and the cumulative incidence of end-stage renal disease was around 0.5% at the end of the simulations, suggesting that the difference between the two models in terms of eGFR progression did not directly influence cost-effectiveness.

  - The CORE Diabetes Model simulates the progression to blindness through intermediates stages of background and proliferative retinopathy, again with different treatment modalities. It is unclear how this progression is integrated with the UKPDS risk equation for the onset of blindness. The PRIME T2D Model simulates the onset of blindness without the intermediate stages. Macular edema is modelled in the PRIME T2D Model but not in the CORE Diabetes Model.

- In general, the approach to mortality estimation is similar in both models. The PRIME T2D Model uses UKPDS mortality risk equations to evaluate the risk of mortality following diabetes-related complications, and simulates mortality from other causes based on cause-subtracted life tables. The CORE Diabetes Model also uses life tables (although typically these are not cause-subtracted) to evaluate the risk of mortality from non-diabetes causes. It is assumed that UKPDS mortality equations are used to evaluate the risk of mortality following diabetes-related complications, but it is not clear whether this is true of all complications or only selected complications.

- Differences between the two models in terms of the characteristics of simulated patients are evident in the model outputs. The default approach in the CORE Diabetes Model is to simulate the progression of disease in cohorts of identical patients through multiple iterations. The PRIME T2D Model generated individual patient characteristics by sampling at baseline (along with treatment effect), meaning that the progression of disease is simulated in a cohort of non-identical patients with mean values matching the cohort characteristics and treatment effects entered by the user. This has an impact on two main areas that could influence cost-effectiveness results:

  - The mean time to treatment intensification may be different in the two models as individual patients intensify at different times in the PRIME T2D Model (based on individual HbA1c levels) and all identical patients intensify at the same time in the CORE Diabetes Model.

  - Different times to intensification mean that the progression of risk factors over time are different between the two models (see Sections 2.5.1 and 2.5.2),

potentially leading to differences in glycaemic exposure and incremental differences in exposure to other risk factors, including SBP and BMI.

    - Different times to intensification may also influence the estimation of pharmacy costs, with longer times on more costly therapies potentially increasing incremental costs and influencing cost-effectiveness.

- For the evaluation of complication risk, the CORE Diabetes Model uses risk equations from the UKPDS OM2 for (most) complications. The PRIME T2D Model uses a model averaging approach, weighting risk equations from UKPDS OM2 and BRAVO in line with individual patient characteristics, to estimate the risk of diabetes-related complications in a way that better "fits" the simulation cohort than a single risk equation alone. The PRIME T2D Model is product and trial-agnostic, and model averaging allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to a given cohort. In the absence of risk equations derived directly from the trial(s) in question, we consider this approach to be preferable to the selection of a single risk model parameterised from a different population receiving different interventions than that under investigation. In addition to addressing concerns around the structural uncertainty inherent in using a single risk model, the approach allows the model to adapt risk estimation to different populations at different stages of disease progression. Validation analysis indicates that the model averaging approach is capable of accurately reproducing outcomes from real-life clinical studies in a range of settings.

- The approach to combining utilities was different in the two modelling analyses. In the CORE Diabetes Model analysis, an additive approach to combining utilities for complications was used as no age-adjusted approach was available. In the PRIME T2D Model, an age-adjusted additive approach to combining utility scores was used in line with a recommendation from the EAG.

- The CORE Diabetes Model has management inputs that purport to influence the risk of diabetes-related complications in relation to concomitant medication use and screening. It is not clear how much influence, if any, these parameters have on modelled outcomes (as they don't play a role in the UKPDS OM2 risk equations).

In terms of model outputs, differences and similarities were noted between the two modeling approaches:

- Life expectancy was higher in the PRIME T2D Model than in the CORE Diabetes Model. This may be due to the use of cause-subtracted life tables in the PRIME T2D Model and unadjusted life tables (with the risk of double-counting mortality events) in the CORE Diabetes Model. However, as neither model provided outputs on cause of death, more detailed analysis was not possible.

- Direct costs were higher in the PRIME T2D Model than in the CORE Diabetes Model, primarily due to higher macrovascular complication costs (Table 16).

- Different times to intensification and different life expectancies led to modest differences in treatment costs between the two models.

- More cardiovascular events (principally IHD, revascularization and heart failure) led to higher overall costs and greater cost savings with tirzepatide in the PRIME T2D Model

than in the CORE Diabetes Model. In this context, it should be noted that cost of IHD (with the PRIME T2D Model) was notably higher than the cost associated with angina (with the CORE Diabetes Model) used in the modeling analyses.

- More amputation and neuropathy in the PRIME T2D Model led to higher costs, but with a smaller difference between treatments than in the CORE Diabetes Model.

Table 16: Breakdown of costs for the comparison of tirzepatide 10 mg with semaglutide 1.0 mg in the PRIME T2D Model and the CORE Diabetes Model

	PRIME T2D Model			CORE Diabetes Model		
	TZP 10 mg	SEMA 1.0 mg	Difference	TZP 10 mg	SEMA 1.0 mg	Difference
Total direct cost	[redacted]	31,402	[redacted]	[redacted]	23,883	[redacted]
Treatment	[redacted]	7,102	[redacted]	[redacted]	7,207	[redacted]
CVD	14,017	14,197	-178	8,058	8,178	-119
Renal disease	672	688	-16	766	758	8
Ulcer / Amputation / Neuropathy	7,224	7,291	-67	5,458	5,619	-161
Ocular complications	1,031	1,041	-10	1,062	1,089	-28
Hypoglycaemia	1,041	1,083	-42	984	1,032	-48

Abbreviations: TZP: tirzepatide, SEMA: semaglutide

Crucially, despite the differences between the models, the evaluation of incremental risk between the intervention and comparators was comparable in the two modelling environments, which produced broadly similar findings in terms of cost-effectiveness for tirzepatide versus comparators. This finding (in terms of the importance of incremental risk in a cost-effectiveness evaluation) has also been reported in the publications from the Mount Hood Challenge meetings, where the results of several diabetes models have been compared.[11,12]

In both modelling environments, tirzepatide, a GIP/GLP-1 RA, represents a new treatment option that can improve the glycaemic control and weight loss of patients with T2D who have an unmet need in these areas on currently-available treatments. Tirzepatide was shown to represent a cost-effective use of NHS resources versus commonly used GLP-1 RAs in England. Tirzepatide represents a valuable new addition to the clinical pathway of care for T2D, providing patients with an effective, tolerable therapy for T2D that addresses the unmet needs as outlined in the original submission.

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Appendix A

Table 1: Tabulated overview of all model inputs – cohort characteristics

Input	Mean	Standard deviation	Units	Reference	Justification
Demographics					
Percentage male	57.0	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with college education or higher	25.97	Not required	%	PRIME default (set to index value so this does not influence results)	Set to the model index value to have no effect on complication risk
Percentage smokers	17.0%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Age	63.95	10.4	Years	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Duration of diabetes	8.5	6.50	Years	NICE HE Report 2022, Second Intensification Cohort (page 13) median duration of diabetes, SD taken from the SURPASS-2 cohort	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Race					
Percentage White	82.4	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE002: Baseline ethnic characteristics)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage Black	4.5	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE002: Baseline ethnic characteristics)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage Hispanic	0.0	Not required	%	Assumed	Assumed based on proportion White, Black and Indian
Percentage Southeast Asian	0.0	Not required	%	Assumed	Assumed based on proportion White, Black and Indian

Input	Mean	Standard deviation	Units	Reference	Justification
Percentage Indian	13.1	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE002: Baseline ethnic characteristics)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage Afro/Caribbean	0.0	Not required	%	Assumed	Assumed based on proportion White, Black and Indian
Percentage Other	0.0	Not required	%	Assumed	Assumed based on proportion White, Black and Indian
Baseline risk factors					
Glycated haemoglobin (HbA1c)	7.50	1.03	%	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort (CSR Table GPGL.4.5, page 92)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Systolic blood pressure	134.44	13.8	mmHg	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort (CSR Table GPGL.4.5, page 92)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Total cholesterol	4.53	1.06	mmol/L	SURPASS-2 CSR, ITT population, Table GPGL.8.43, page 1225 (arithmetic mean and standard deviation)	Value not available from the THIN second intensification cohort, so supplemented from population eligible for tirzepatide with comparable duration of diabetes
Low density lipoprotein cholesterol	2.29	0.89	mmol/L	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort, CSR page 1255, Table GPGL.8.43	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
High density lipoprotein cholesterol	1.23	0.29	mmol/L	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort, CSR page 1240, Table GPGL.8.43	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem

Input	Mean	Standard deviation	Units	Reference	Justification
Estimated glomerular filtration rate	71.37	17.10	ml/min/1.73 m^2	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort (CSR Table GPGL.4.5, page 92)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Body mass index	30.7	6.90	kg/m2	NICE HE Report 2015, Second Intensification Cohort (Table 20: Baseline THIN data used to populate the original health economic model), SD taken from the SURPASS-2 cohort	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
White blood cell count	7.51	1.8	10^6 cells/mL	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from UKPDS 68	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Heart rate	72.0	10.1	bpm	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort (CSR Table GPGL.4.5, page 92)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Hemoglobin	14.5	1.42	g/dL	NICE HE Report 2022, Second Intensification Cohort (Table HE005: Baseline characteristics), SD taken from the SURPASS-2 cohort (CSR Table GPGL.8.140, page 3398)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem

Input	Mean	Standard deviation	Units	Reference	Justification
Complication history					
Percentage with atrial fibrillation at baseline	1.2%	Not required	%	SURPASS-2 CSR, ITT population, Table GPGL.8.10, page 782	Value not available from the THIN second intensification cohort, so supplemented from population eligible for tirzepatide with comparable duration of diabetes
Percentage with urinary albumin ≥50mg/L at baseline	22.6%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE004: albuminuria prevalence), assume albuminuria definition of ≥50mg/L	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with peripheral vascular disease at baseline	1.9%	Not required	%	SURPASS-2 CSR, ITT population, Table GPGL.8.10, page 782	Value not available from the THIN second intensification cohort, so supplemented from population eligible for tirzepatide with comparable duration of diabetes
Percentage with history of myocardial infarction at baseline	2.0%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with history of stroke at baseline	1.3%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with ischemic heart disease at baseline	6.0%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with revascularization at baseline	3.0%	Not required	%	SURPASS-2 CSR, ITT population, Table GPGL.8.10, page 782	Value not available from the THIN second intensification cohort, so supplemented from population eligible for tirzepatide with comparable duration of diabetes
Percentage with heart failure at baseline	1.9%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence) - NICE report states "CHD" but means "CHF"	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem

Input	Mean	Standard deviation	Units	Reference	Justification
Percentage with foot ulcer at baseline	0.8%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with amputation at baseline	0.2%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with blindness at baseline	1.3%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with renal failure at baseline	0.4%	Not required	%	NICE HE Report 2022, Second Intensification Cohort (Table HE006: Baseline risk factor prevalence)	Matched to the THIN second intensification cohort previously used by NICE and in line with the decision problem
Percentage with SPSL/neuropathy at baseline	9.0%	Not required	%	SURPASS-2 CSR, ITT population, Table GPGL.8.11, page 787	Value not available from the THIN second intensification cohort, so supplemented from population eligible for tirzepatide with comparable duration of diabetes

Abbreviations: HE: health economic; CSR: clinical study report; ITT, intent to treat.

Table 2: Tabulated overview of all model inputs – tirzepatide 5 mg treatment

Input (TZP 5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (TZP 5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies [Gerstein et al. Lancet. 2019; 394(10193): 121-13, Marso et al. N Engl J Med. 2016; 375(4): 311-22, Marso et al. N Engl J Med. 2016; 375(19): 1834-44]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (TZP 5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of TZP 5 mg in year 1	[redacted]	Not required	£	Eli Lilly and Company, tirzepatide 5 mg pack price NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for tirzepatide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of TZP 5 mg in year 2 onwards	[redacted]	Not required	£	Eli Lilly and Company, tirzepatide 5 mg pack price	Based on the pack price for tirzepatide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with TZP 5 mg in year 1	-0.0303	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 25.8% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with TZP 5 mg in year 2 onwards	-0.0200	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (TZP 5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (TZP 5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (TZP 5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

Table 3: Tabulated overview of all model inputs – tirzepatide 10 mg treatment

Input (TZP 10 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (TZP 10 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (TZP 10 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of TZP 10 mg in year 1	[redacted]	Not required	£	Eli Lilly and Company, tirzepatide 10 mg pack price NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for tirzepatide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of TZP 10 mg in year 2 onwards	[redacted]	Not required	£	Eli Lilly and Company, tirzepatide 5 mg pack price	Based on the pack price for tirzepatide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with TZP 10 mg in year 1	-0.0276	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 34.3% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with TZP 10 mg in year 2 onwards	-0.0139	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (TZP 10 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (TZP 10 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (TZP 10 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

Table 4: Tabulated overview of all model inputs – tirzepatide 15 mg treatment

Input (TZP 15 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (TZP 15 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (TZP 15 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of TZP 15 mg in year 1	[redacted]	Not required	£	Eli Lilly and Company, tirzepatide 15 mg pack price NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for tirzepatide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of TZP 15 mg in year 2 onwards	[redacted]	Not required	£	Eli Lilly and Company, tirzepatide 5 mg pack price	Based on the pack price for tirzepatide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with TZP 15 mg in year 1	-0.0242	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 37.2% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with TZP 15 mg in year 2 onwards	-0.0093	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (TZP 15 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (TZP 15 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (TZP 15 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

Table 5: Tabulated overview of all model inputs – dulaglutide 1.5 mg treatment

Input (DULA 1.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (DULA 1.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (DULA 1.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of DULA 1.5 mg in year 1	1,036.03	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for dulaglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of DULA 1.5 mg in year 2 onwards	995.70	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for dulaglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with DULA 1.5 mg in year 1	-0.0404	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 28.1% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with DULA 1.5 mg in year 2 onwards	-0.0291	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (DULA 1.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (DULA 1.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (DULA 1.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

Table 6: Tabulated overview of all model inputs – dulaglutide 3.0 mg treatment

Input (DULA 3.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (DULA 3.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (DULA 3.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of DULA 3.0 mg in year 1	1,036.03	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for dulaglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of DULA 3.0 mg in year 2 onwards	995.70	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for dulaglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with DULA 3.0 mg in year 1	-0.0394	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 28.1% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with DULA 3.0 mg in year 2 onwards	-0.0281	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (DULA 3.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (DULA 3.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (DULA 3.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 7: Tabulated overview of all model inputs – dulaglutide 4.5 mg treatment

Input (DULA 4.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (DULA 4.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (DULA 4.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of DULA 4.5 mg in year 1	1,036.03	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for dulaglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of DULA 4.5 mg in year 2 onwards	995.70	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for dulaglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with DULA 4.5 mg in year 1	-0.0385	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 28.1% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with DULA 4.5 mg in year 2 onwards	-0.0273	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (DULA 4.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (DULA 4.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (DULA 4.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 8: Tabulated overview of all model inputs – semaglutide 0.5 mg treatment

Input (SEMA 0.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (SEMA 0.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (SEMA 0.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of SEMA 0.5 mg in year 1	1,036.03	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for semaglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of SEMA 0.5 mg in year 2 onwards	995.70	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for semaglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with SEMA 0.5 mg in year 1	-0.0367	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 24.9% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with SEMA 0.5 mg in year 2 onwards	-0.0268	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis

Input (SEMA 0.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (SEMA 0.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (SEMA 0.5 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 9: Tabulated overview of all model inputs – semaglutide 1.0 mg treatment

Input (SEMA 1.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (SEMA 1.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (SEMA 1.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of SEMA 1.0 mg in year 1	1,036.03	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for semaglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of SEMA 1.0 mg in year 2 onwards	995.70	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for semaglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with SEMA 1.0 mg in year 1	-0.0346	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 28.1% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with SEMA 1.0 mg in year 2 onwards	-0.0234	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (SEMA 1.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (SEMA 1.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (SEMA 1.0 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 10: Tabulated overview of all model inputs – oral semaglutide 7 mg treatment

Input (O_SEMA 7 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (O_SEMA 7 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (O_SEMA 7 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of O_SEMA 7 mg in year 1	1,035.51	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation and oral semaglutide pack price)	Based on the pack price for oral semaglutide (NICE NG28 health economic analysis), metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of O_SEMA 7 mg in year 2 onwards	995.18	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for oral semaglutide (NICE NG28 health economic analysis) and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with O_SEMA 7 mg in year 1	-0.0351	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 24.9% of patients experiencing nausea in year 1, oral medication (+0.004, NICE NG28 health economic analysis) and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with O_SEMA 7 mg in year 2 onwards	-0.0251	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach and oral medication (+0.004, NICE NG28 health economic analysis)

Input (O_SEMA 7 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin

Input (O_SEMA 7 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (O_SEMA 7 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 11: Tabulated overview of all model inputs – oral semaglutide 14 mg treatment

Input (O_SEMA 14 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022*	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (O_SEMA 14 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (O_SEMA 14 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of O_SEMA 14 mg in year 1	1,035.51	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation and oral semaglutide pack price)	Based on the pack price for oral semaglutide (NICE NG28 health economic analysis), metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of O_SEMA 14 mg in year 2 onwards	995.18	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for oral semaglutide (NICE NG28 health economic analysis) and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with O_SEMA 14 mg in year 1	-0.0322	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 28.1% of patients experiencing nausea in year 1, oral medication (+0.004, NICE NG28 health economic analysis) and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with O_SEMA 14 mg in year 2 onwards	-0.0209	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach and oral medication (+0.004, NICE NG28 health economic analysis)

Input (O_SEMA 14 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin

Input (O_SEMA 14 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (O_SEMA 14 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 12: Tabulated overview of all model inputs – liraglutide 1.2 mg treatment

Input (LIRA 1.2 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (LIRA 1.2 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (LIRA 1.2 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of LIRA 1.2 mg in year 1	1,054.27	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for liraglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of LIRA 1.2 mg in year 2 onwards	1,013.93	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for liraglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with LIRA 1.2 mg in year 1	-0.0378	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 20.3% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with LIRA 1.2 mg in year 2 onwards	-0.0297	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (LIRA 1.2 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (LIRA 1.2 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (LIRA 1.2 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 13: Tabulated overview of all model inputs – liraglutide 1.8 mg treatment

Input (LIRA 1.8 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Treatment effects					
HbA1c	[redacted]	[redacted]	%	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Treatment effects for all comparators were taken from the network meta-analysis
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (LIRA 1.8 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Adverse event rates					
Severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Non-severe hypoglycemia rate	0	0	events per patient year	Assumed (not available from the NMA)	The analysis assumed no differences between treatments in hypoglycaemia rates
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	Constant	Not required	Not required	Assumed based on CVOT data	SBP remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	Constant	Not required	Not required	Assumed based on CVOT data	BMI remained (approximately) constant on GLP-1 receptor agonist therapy in CVOT studies[2-4]
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (LIRA 1.8 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of LIRA 1.8 mg in year 1	1,532.01	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for GLP-1 receptor agonist initiation)	Based on the pack price for liraglutide, metformin costs from the NHS 2022 Electronic Drug Tariff and initiation costs
Annual cost of LIRA 1.8 mg in year 2 onwards	1,491.68	Not required	£	NHS 2022 Electronic Drug Tariff	Based on the pack price for liraglutide and metformin costs from the NHS 2022 Electronic Drug Tariff
Quality of life (QoL)					
QoL change with LIRA 1.8 mg in year 1	-0.0385	Not required	Utility score	Matza et al. (2007)[5] Bagust and Beale (2005)[6]	Utility adjustment for 25.3% of patients experiencing nausea in year 1 and utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with LIRA 1.8 mg in year 2 onwards	-0.0284	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	Above HbA1c 7.5%	Not required	Not required	Assumed	In line with recommendations in NG28
Subsequent treatment effects					
HbA1c	-0.84	0.15	%	Willis et al. (2017)[7]	HbA1c changes estimated based on insulin initiation in insulin naïve patients
SBP	[redacted]	[redacted]	mmHg	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy

Input (LIRA 1.8 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Body mass index	[redacted]	[redacted]	kg/m2	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
High density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Low density lipoprotein cholesterol	[redacted]	[redacted]	mmol/L	Europe Network 2 NMA, March 7, 2022	Returns to baseline level after intensification to basal insulin therapy
Estimated glomerular filtration rate	0	0	ml/min/1.73 m^2	Assumed	The analysis assumed no differences between treatments in eGFR
White blood cell count	0	0	10^6 cell/ml	Assumed	The analysis assumed no differences between treatments in white blood cell count
Haemoglobin	0	0	g/dL	Assumed	The analysis assumed no differences between treatments in haemoglobin
Cardiovascular risk modifiers					
Myocardial infarction	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Stroke	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Heart failure	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis
Cardiovascular death	1	Not required	Relative risk	Assumed	No model calibration was used in the analysis

Input (LIRA 1.8 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Adverse event rates					
Severe hypoglycemia rate	0.32	0.03	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Non-severe hypoglycemia rate	3.84	0.38	events per patient year	Mean rate from NICE 2022 HE Report Table HE013 (page 24), SD assumed to be approximately 10% of mean value	Matched to the hypoglycaemia rates used by NICE in the NG28 health economic analysis
Risk factor progression					
HbA1c	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Systolic blood pressure	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Low-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
High-density lipoprotein cholesterol	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Body mass index	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Estimated glomerular filtration rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
White blood cell count	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Heart rate	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG

Input (LIRA 1.8 mg)	Mean / Selection	Standard deviation	Units	Reference	Justification
Hemoglobin	UKPDS OM2	Not required	Not required	UKPDS risk factor progression[1]	Recommended by the EAG
Treatment costs					
Annual cost of basal insulin in year 1	527.89	Not required	£	NHS 2022 Electronic Drug Tariff NICE 2022 HE Report (assumptions on nursing time for insulin initiation)	Based on NPH insulin costs (daily dose 40 IU), including needles, self-monitoring of blood glucose and initiation costs
Annual cost of basal insulin in year 2 onwards	386.73	Not required	£	NHS 2022 Electronic Drug Tariff	Based on NPH insulin costs (daily dose 40 IU), including needles, and self-monitoring of blood glucose
Quality of life (QoL)					
QoL change with basal insulin in year 1	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
QoL change with basal insulin in year 2 onwards	-0.0349	Not required	Utility score	Bagust and Beale (2005)[6]	Utility adjustment for each unit of BMI over 25 in line with previous NICE approach
Treatment switch					
Risk factor threshold	None	Not required	Not required	Assumed	No further treatment intensification after basal insulin therapy in the base case.

* uses nearest neighbour approach for missing values (as described in the original submission)

Table 14: Tabulated overview of all model inputs – complication costs

Input	Mean	Standard deviation	Units	Reference	Justification
Macrovascular complications					
Myocardial infarction, year 1	8,862	1,322	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Myocardial infarction, years 2+	2,203	250	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Stroke, year 1	9,530	2,164	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Stroke, years 2+	2,270	379	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Ischemic heart disease, year 1	12,831	1,799	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Ischemic heart disease, years 2+	2,256	248	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Revascularization, year 1	3,593	359	£, 2022	NHS Reference Costs 2019/20 (weight mean of Standard Percutaneous Transluminal Coronary Angioplasty)	NHS reference cost used in the absence of annual cost estimate previously used by NICE
Revascularization, years 2+	0	0	£, 2022	Assumed (no cost identified in the literature)	Health should be improved by revascularization and in most cases no routine follow up is needed
Congestive heart failure, year 1	5,033	1,127	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Congestive heart failure, years 2+	2,952	510	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis

Input	Mean	Standard deviation	Units	Reference	Justification
Macrovascular complications					
Foot ulcer, year 1	3,705	371	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Foot ulcer, years 2+	0	0	£, 2022	Assumed	No routine follow up or sequelae expected (beyond routine care) after resolution of foot ulcer episode
Amputation, year 1	14,779	2,962	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Amputation, years 2+	4,107	837	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Blindness, year 1	3,796	1,409	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Blindness, years 2+	1,438	229	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Macular oedema, year 1	696	70	£, 2022	National Schedule of NHS Costs 2019/20 (Day Case, BZ87A, Minor vitreous retinal procedures, 19 years and over) - https://www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/	NHS reference cost used in the absence of annual cost estimate previously used by NICE
Macular oedema, years 2+	0	0	£, 2022	Assumed	No routine follow up or sequelae expected (beyond routine care) after resolution of macular oedema
Neuropathy/SPSL, all years	1,098	110	£, 2022	Hunt et al. (2017)[8]	Annual cost estimate in line with pain management and regular visits
Renal complications					
KDIGO CKD eGFR stage 1	0	0	£, 2022	Assumed	No additional routine care costs anticipated for stage 1 chronic kidney disease

Input	Mean	Standard deviation	Units	Reference	Justification
KDIGO CKD eGFR stage 2	0	0	£, 2022	Assumed	No additional routine care costs anticipated for stage 2 chronic kidney disease
KDIGO CKD eGFR stage 3	0	0	£, 2022	Assumed	No additional routine care costs anticipated for stage 3 chronic kidney disease
KDIGO CKD eGFR stage 4	472	31	£, 2022	Kent et al. (2015)[9]	Annual cost estimate in line with routine monitoring and regular visits
KDIGO CKD eGFR stage 5	21,996	2,200	£, 2022	NICE HE Report 2022 (Table HE018: Management and complication costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Adverse events					
Severe hypoglycaemic event	393	39	£, 2022	NICE HE Report 2022 (Table HE023: Hypoglycemia costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis
Non-severe hypoglycaemic event	0	0	£, 2022	NICE HE Report 2022 (Table HE023: Hypoglycemia costs)	Matched to the cost estimates previously used by NICE in the NG28 health economic analysis

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes., SPSL: severe pressure sensation loss

Table 15: Tabulated overview of all model inputs – Disutilities associated with diabetes-related complications and hypoglycaemia

Input	Mean	Standard deviation	Units	Reference	Justification
Baseline utility					
Type 2 diabetes, no complications	Adjusted for age	Not required	Utility score	Ara and Brazier (2010)[10]	Requested by the EAG
Macrovascular complications					
Myocardial infarction event	-0.055	0.006	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
History of myocardial infraction	-0.055	0.006	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Stroke event	-0.164	0.030	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
History of stroke	-0.164	0.030	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Ischemic heart disease (each year)	-0.090	0.018	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Revascularization event	-0.038	0.011	Utility score	Shao et al. (2019)[13]	Only disutility estimates identified by literature review for revascularization specific to patients with type 2 diabetes
History of revascularization	-0.016	0.005	Utility score	Shao et al. (2019)[13]	Only disutility estimates identified by literature review for revascularization specific to patients with type 2 diabetes
Congestive heart failure (each year)	-0.108	0.031	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis

Input	Mean	Standard deviation	Units	Reference	Justification
Microvascular complications					
Foot ulcer (year of event)	-0.170	0.019	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Foot ulcer (subsequent years)	0	0	Utility score	Assumed	Foot ulcer episode was assumed to be resolved and have no impact on quality of life in years after the event
Lower extremity amputation (year of event)	-0.280	0.056	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Lower extremity amputation (subsequent years)	-0.122	0.025	Utility score	Hayes et al. (2016)[11]	Utility derived from EQ-5D data in a population with type 2 diabetes (ADVANCE study)
Blindness (first year)	-0.074	0.025	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Blindness (subsequent years)	-0.074	0.025	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Macular edema (first year)	-0.047	0.005	Utility score	Mitchell et al. (2012)[12]	Value specific to macular oedema in population with type 2 diabetes (RESTORE-1 trial), corresponding to correspond to best corrected visual acuity change from 76-85 to 66-75
Macular edema (subsequent years)	0	0	Utility score	Assumed resolved	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Neuropathy / SPSL (all years)	-0.066	0.007	Utility score	Shao et al. (2019)[13]	Recent estimate of neuropathy/SPSL impact on quality of life specific to a type 2 diabetes population

Input	Mean	Standard deviation	Units	Reference	Justification
Renal complications					
KDIGO CKD eGFR stage 1	0	0	Utility score	Assumed	Assumed to have a negligible impact on quality of life (no values identified by literature review)
KDIGO CKD eGFR stage 2	0	0	Utility score	Assumed	Assumed to have a negligible impact on quality of life (no values identified by literature review)
KDIGO CKD eGFR stage 3	-0.004	0.010	Utility score	Nauck et al. Diabetes Obes Metab. 2019; 21(3): 525-32[14]	Utility values specific to chronic kidney disease in patients with type 2 diabetes
KDIGO CKD eGFR stage 4	-0.004	0.010	Utility score	Nauck et al. Diabetes Obes Metab. 2019; 21(3): 525-32[14]	Utility values specific to chronic kidney disease in patients with type 2 diabetes
KDIGO CKD eGFR stage 5	-0.164	0.016	Utility score	NICE HE Report 2022 (Table HE027: Quality of life parameters)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Hypoglycaemia					
Severe hypoglycemic event	-0.062	0.004	Utility score	NICE HE Report 2022 (Section 2.3.5.3 Hypolgycemia)	Matched to the utility estimates previously used by NICE in the NG28 health economic analysis
Non-severe hypoglycemic event	-0.005	0.001	Utility score	Evans et al. (2013)[15]	Utility values specific to hypoglycaemia in patients with type 2 diabetes in the UK

Abbreviations: CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; KDIGO: Kidney Disease Improving Global Outcomes., SPSL: severe pressure sensation loss

Table 16: Tabulated overview of all model inputs – Country inputs

Input	Mean / selection	Standard deviation	Units	Reference	Justification
Analysis settings					
Cost discount rate	3.5	Not required	% per annum	NICE Health Technology Evaluations Manual	Recommended discount rate for the base case analysis
Effectiveness discount rate	3.5	Not required	% per annum	NICE Health Technology Evaluations Manual	Recommended discount rate for the base case analysis
Complications					
Complication risk model	PRIME default	Not required	Not applicable	Pollock et al. J Med Econ. 2022; 25(1): 393-402[16]	Model averaging approach is supported by external validation analysis for modelling GLP-1 receptor agonists and UK cohorts
Complications					
Background mortality modeling approach	Life tables	Not required	Not applicable	Pollock et al. J Med Econ. 2022; 25(1): 393-402[16]	Hybrid approach to mortality estimation is supported by external validation analysis for modelling GLP-1 receptor agonists and UK cohorts
Life table for background mortality	UK 2019	Not required	Not applicable	https://www.who.int/data/gho/data/indicators/indicator-details/GHO/gho-ghe-life-tables-by-country	Hybrid approach to mortality estimation is supported by external validation analysis for modelling GLP-1 receptor agonists and UK cohorts
Complication-specific mortality modeling approach	UKPDS OM2	Not required	Not applicable	Hayes et al. Diabetologia. 2013; 56: 1925-33[17]	Hybrid approach to mortality estimation is supported by external validation analysis for modelling GLP-1 receptor agonists and UK cohorts
Complications					
Renal failure approach	eGFR decline model	Not required	Not applicable	Pollock et al. J Med Econ. 2022; 25(1): 393-402[16]	Model default approach based on eGFR levels mapped to renal function health states

Abbreviations: eGFR: estimated glomerular filtration rate; UKPDS OM2: United Kingdom Prospective Diabetes Study Outcomes Model.

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NICE National Institute for Health and Care Excellence

Tirzepatide for treating type 2 diabetes [ID3938]

Draft guidance comments form – Appendix B

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 25 July 2023. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
18	**Please provide rationale for not including the SURMOUNT-2 and SURMOUNT-CN studies in the company submission. Please also provide a tabulated summary of SURMOUNT and SURPASS trials, focusing on population enrolled, trial design and key outcomes (highlighting any key differences and similarities) to help us assess the impact of not including these studies** The SURMOUNT trials are recent studies in a different indication (weight loss) to the current appraisal and will be assessed in the upcoming appraisal for obesity and are not relevant for this appraisal. The majority of the SURMOUNT trials are not relevant to this appraisal because SURMOUNT-1, -3, -4, -MMO, -OSA and -CN all excluded diabetes patients. Only SURMOUNT-2 included diabetes patients, although that trial was specifically designed (and powered) to assess weight reduction as the primary outcome rather than HbA1c reduction and T2D was secondary to the trial. Patients included in the SURMOUNT-2 trial, have a much higher BMI than the current submission T2D population, as the SURMOUNT studies are assessing patients with overweight/obesity (median BMI 36; a minimum BMI of 27 was needed to be eligible for inclusion in the trial). Importantly, the SURMOUNT-2 trial would not have been included in the NMA for the current appraisal, as the definition of background therapies permitted is not directly relevant to the current decision problem. Finally, the SURMOUNT-2 data have only recently been published (26th June 2023),[1] and the SURMOUNT-CN data have not yet been published so these results were not available before the company submission (CS) in August 2022 or during the first appraisal committee meeting on 6th June 2023. Please see Table 10 at the end of this document for a tabulated summary of the SURMOUNT and SURPASS trials.
19	**Rationale for selecting UKPDS OM2, BRAVO Model and Hong Kong Diabetes Registry out of all possible risk models, when estimating the rates of micro- and macrovascular complications** The final choice of risk models for inclusion in the model averaging code for evaluation of macrovascular complication risk in the PRIME T2D Model was based on a number of factors following full-text review of relevant hits from the model development literature review (an overview of the literature review is described in the PRIME T2D Model Technical Report previously provided). The key criteria for inclusion were: • The publication describes (a) risk formula(e) that was derived from a population with type 2 diabetes • The risk formula(e) can be used to estimate the annual risk of one or more diabetes-related complications • The risk formula(e) can be used to estimate annual risk without transformation (e.g. assuming proportional hazards) from a multi-year risk score • Endpoint definitions must be closely matched between different publications to be included in model averaging and the outcomes should not be a

composite endpoint (without a means to separate individual endpoints)

The literature searches identified several publications that were reviewed in detail for potential inclusion in the model averaging approach (Table 1). The majority of publications identified were not suitable for inclusion in model averaging, primarily due to reporting risk scores (e.g. 5-year estimate or risk) and/or reporting only composite endpoints with no individual endpoint delineation. This left the UKPDS OM2, BRAVO and Hong Kong Registry equations for inclusion in model averaging at the time of model development. Validation analysis has indicated that the present model averaging approach performs well in comparison with published clinical study data across different populations (presented previously in Comment 10 of the response to draft guidance and in the PRIME T2D Model Technical Report found in Appendix N of the original company submission).

Table 1: Summary of publications identified by literature searches for potential inclusion in the model averaging approach

Publication	Model/study	Cardiovascular endpoints	Comments
Hayes *et al.* (2013)[2]	UKPDS OM2/UKPDS	Myocardial infarction, stroke, heart failure and ischaemic heart disease	Included in model averaging
Shao *et al.* (2018)[3]	BRAVO/ACCORD	Myocardial infarction, stroke, heart failure, angina and revascularization	Included in model averaging
Yang *et al.* (2008)[4]	Hong Kong Diabetes Registry	Coronary heart disease (composite of myocardial infarction and ischaemic heart disease)	Included in model averaging in Asian populations for ischaemic heart disease endpoint
Yang *et al.* (2007)[5]	Hong Kong Diabetes Registry	First stroke (fatal and non-fatal)	Included in model averaging in Asian populations for stroke endpoint
Yang *et al.* (2008)[4]	Hong Kong Diabetes Registry	Hospitalization for heart failure	Included in model averaging in Asian populations for heart failure endpoint
Tanaka *et al.* (2013)[6]	JJ Risk Engine/Japan Diabetes Complications Study (JDCS)	Coronary heart disease (composite) and stroke	Not included: risk equations could not be reproduced from the publication
Elley *et al.* (2010)[7]	NZDCS	Composite first CVD event (ischemic heart disease, cerebrovascular accident/transient ischemic attack, or peripheral arterial disease)	Not included: reported 5-year risk of “first CVD event” (composite)
Donnan *et al.* (2006)[8]	Diabetes Audit and Research in Tayside (DARTS)	Coronary heart disease (composite of myocardial infarction and coronary heart disease death)	Not included: reported "first CHD"(composite)

	Schramm *et al.* (2016)[9]	PROSIT	Stroke and coronary heart disease (composite)	Not included: Relies on UKPDS Risk Engine and older data / coronary heart disease composite endpoint
	Kengne *et al.* (2011)[10]	Action in Diabetes and Vascular disease: preterax and diamicron-MR controlled evaluation (ADVANCE)	Composite of all CVD events	Not included: reported 4-year risk of major CVD events
	Davis *et al.* (2010)[11]	Freemantle Diabetes Study	Composite of all CVD events	Not included: reported 5-year risk of CVD events
	Cederholm *et al.* (2008)[12]	Swedish National Diabetes Registry	Composite of all CVD events	Not included: reported 5-year risk of CVD events
	Folsom *et al.* (2003)[13]	Atherosclerosis Risk in Communities (ARIC)	Coronary heart disease composite endpoint (including myocardial infarction, coronary heart disease death and revascularization)	Not included: reported 10-year risk of coronary heart disease composite endpoint
	Abbreviations: ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; ARIC: Atherosclerosis Risk in Communities; CVD: cardiovascular disease; DARTS: Diabetes Audit and Research in Tayside; JDCS: Japan Diabetes Complications Study; UKPDS: United Kingdom Prospective Diabetes Study; UKPDS OM2: United Kingdom Prospective Diabetes Study Outcomes Model 2.			
20	**Rationale for a decrease in incremental life years but an increase in incremental QALYs when running analysis in CORE Diabetes Model, compared with PRIME T2D Model** Whilst it is difficult to be prescriptive about specific differences in outcomes between the two models, this observation is most likely explained by different approach to the estimation of quality-adjusted life expectancy between the two models. In line with the EAG recommendation, an age-adjusted approach to utility estimation was used in the PRIME T2D Model. However, an age-adjusted approach is not available in the CORE Diabetes Model and therefore an additive approach was used to combining utilities in that model (as this was considered the closest match to the approach used in the PRIME T2D Model). The additive approach in the CORE Diabetes Model would likely provide higher estimates of incremental QALYs than the age-adjusted approach in the PRIME T2D Model (as utilities are not decreased in older patients with the additive approach). This increase in incremental QALYs with the additive approach is likely to have offset the smaller incremental life years benefit observed with the CORE Diabetes Model.			
21	**Scenario analysis using the EAG's preferred baseline utility value for people with type 2 diabetes (0.772; Redenz, 2023)** Results from the scenario analysis using the baseline utility of 0.772 are summarized in Table 2, Table 3 and Table 4. It should be noted that, as discussed in Comment 6 of the response to draft guidance, using a fixed baseline utility of 0.772 is not compatible with the age-adjusted approach. This is because the age-adjusted approach relies on a regression equation to define the annual baseline utility each year as opposed to a fixed value. Therefore an additive approach to combining utilities was used as this represents the closest match to the base case analysis.[14] As lowering the baseline utility had little			

impact on incremental differences between treatment arms, ICERs were close to those reported in the base case analysis for tirzepatide versus comparators (Table 2, Table 3 and Table 4).

Table 2: Summary of lower baseline utility (0.772) scenario analysis results for tirzepatide 5 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	8.836	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.733	705	0.059	0.103	6,840	0.068
Dulaglutide 3.0 mg	[redacted]	13.076	8.755	644	0.046	0.081	7,956	0.049
Dulaglutide 4.5 mg	[redacted]	13.092	8.777	628	0.030	0.059	10,563	0.028
Semaglutide 0.5 mg	[redacted]	13.075	8.752	682	0.047	0.084	8,115	0.050
Semaglutide 1.0 mg	[redacted]	13.096	8.792	708	0.026	0.044	16,016	0.009
Oral semaglutide 7 mg	[redacted]	13.049	8.713	742	0.073	0.124	6,003	0.087
Oral semaglutide 14 mg	[redacted]	13.074	8.761	719	0.048	0.076	9,520	0.040
Liraglutide 1.2 mg	[redacted]	13.032	8.697	672	0.090	0.139	4,830	0.105
Liraglutide 1.8 mg	[redacted]	13.054	8.718	−409	0.068	0.119	Dominant	0.139

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 3: Summary of lower baseline utility (0.772) scenario analysis results for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.891	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.733	1,389	0.092	0.158	8,779	0.089
Dulaglutide 3.0 mg	[redacted]	13.076	8.755	1,329	0.079	0.136	9,757	0.070
Dulaglutide 4.5 mg	[redacted]	13.092	8.777	1,312	0.063	0.115	11,446	0.049

Semaglutide 0.5 mg	[redacted]	13.075	8.752	1,367	0.080	0.139	9,812	0.071
Semaglutide 1.0 mg	[redacted]	13.096	8.792	1,393	0.059	0.099	14,007	0.030
Oral semaglutide 7 mg	[redacted]	13.049	8.713	1,427	0.106	0.179	7,977	0.108
Oral semaglutide 14 mg	[redacted]	13.074	8.761	1,403	0.081	0.131	10,735	0.061
Liraglutide 1.2 mg	[redacted]	13.032	8.697	1,356	0.123	0.194	6,981	0.126
Liraglutide 1.8 mg	[redacted]	13.054	8.718	276	0.101	0.174	1,587	0.160

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 4: Summary of lower baseline utility (0.772) scenario analysis results for tirzepatide 15 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.175	8.935	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.733	1,937	0.112	0.202	9,605	0.105
Dulaglutide 3.0 mg	[redacted]	13.076	8.755	1,877	0.099	0.180	10,447	0.086
Dulaglutide 4.5 mg	[redacted]	13.092	8.777	1,860	0.083	0.158	11,767	0.065
Semaglutide 0.5 mg	[redacted]	13.075	8.752	1,915	0.100	0.183	10,478	0.087
Semaglutide 1.0 mg	[redacted]	13.096	8.792	1,941	0.079	0.143	13,582	0.046
Oral semaglutide 7 mg	[redacted]	13.049	8.713	1,975	0.126	0.222	8,883	0.124
Oral semaglutide 14 mg	[redacted]	13.074	8.761	1,951	0.101	0.174	11,203	0.077
Liraglutide 1.2 mg	[redacted]	13.032	8.697	1,904	0.143	0.238	8,010	0.143
Liraglutide 1.8 mg	[redacted]	13.054	8.718	824	0.121	0.217	3,791	0.176

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator.

22	**Scenario analysis using a multiplicative approach for combining disutilities** [redacted]

Results from the scenario analysis using a multiplicative approach for combining utilities for tirzepatide 10 mg versus comparators are summarized in Table 5. Across all comparisons, tirzepatide 10 mg was associated with an ICER of less than £20,000 per QALY gained. It is notable, that comparison of tirzepatide 10 mg with semaglutide 1.0 mg produced an ICER of £18,337 per QALY gained, in this scenario which the company considers to be very conservative.

This scenario is not considered appropriate, because given the clear precedent for the use of the additive approach in previous analyses in type 2 diabetes, including those by NICE and as supported by the conclusions of Gough et al. (2009), Sullivan et al. (2011) and Hayes et al. (2016),[15-17] it may be premature to deviate to the multiplicative approach for the assessment of tirzepatide (and other new treatments in this therapeutic area) in the absence of evidence that the multiplicative approach is more accurate. Please refer to Comment 7 of the response to draft guidance for more information on why a multiplicative approach is not appropriate for this appraisal.

Table 5: Summary of scenario analysis results using a multiplicative approach for combining disutilities for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	9.393	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	9.274	1,389	0.092	0.119	11,634	0.050
Dulaglutide 3.0 mg	[redacted]	13.076	9.289	1,329	0.079	0.105	12,704	0.038
Dulaglutide 4.5 mg	[redacted]	13.092	9.305	1,312	0.063	0.088	14,848	0.023
Semaglutide 0.5 mg	[redacted]	13.075	9.288	1,367	0.080	0.105	13,039	0.036
Semaglutide 1.0 mg	[redacted]	13.096	9.317	1,393	0.059	0.076	18,337	0.006
Oral semaglutide 7 mg	[redacted]	13.049	9.261	1,427	0.106	0.132	10,835	0.060
Oral semaglutide 14 mg	[redacted]	13.074	8.642	1,403	0.081	0.751	1,868	0.681
Liraglutide 1.2 mg	[redacted]	13.032	9.246	1,356	0.123	0.147	9,206	0.080
Liraglutide 1.8 mg	[redacted]	13.054	9.263	,276	0.101	0.130	2,123	0.116

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

23	**Scenario analysis incorporating diarrhoea as an adverse event (as in company response to clarification comments, updated)**

As requested, scenario analysis simulations were run incorporating rates of diarrhoea from the NMA. Literature review failed to identify appropriate utilities for diarrhoea in the target population and therefore the nausea and vomiting utility published by Matza *et al*. and used in the base case analysis was used as a proxy (-0.04 for each patient experiencing diarrhoea).[18] This was applied to the proportion of patients who experienced diarrhoea and to the proportion of patients who experiencing nausea based on the NMA in year 1 of the simulations. The total proportions for each treatment are summarized in Table 6.

Table 6: Summary of proportions of patients with nausea and diarrhoea for the scenario analysis

Intervention	Proportion of patients experiencing nausea (%)	Proportion of patients experiencing diarrhoea (%)	Combined proportion to receive -0.04 disutility (%)
Tirzepatide 5 mg	25.8	17.1	42.8
Tirzepatide 10 mg	34.3	19.5	53.8
Tirzepatide 15 mg	37.2	17.7	55.0
Dulaglutide 1.5 mg	28.1	15.1	43.2
Dulaglutide 3.0 mg	28.1*	15.1*	43.2
Dulaglutide 4.5 mg	28.1*	15.1*	43.2
Semaglutide 0.5 mg	24.9	12.3	37.3
Semaglutide 1.0 mg	28.1	14.3	42.4
Oral semaglutide 7 mg	24.9*	12.3*	37.3
Oral semaglutide 14 mg	28.1*	14.3*	42.2
Liraglutide 1.2 mg	20.3	7.7	28.1
Liraglutide 1.8 mg	25.3	12.5	37.8

Any apparent discrepancies in the combined proportion column are due to rounding. * nearest neighbour approach used to estimate the proportion of patients experiencing events.

Including the diarrhoea utility for all treatments based on data from the NMA had a modest impact on incremental quality-adjusted life expectancy and, therefore, on cost-effectiveness relative to the base case analysis (Table 7, Table 8 and Table 9).

Table 7: Summary of scenario including disutility for diarrhoea analysis results for tirzepatide 5 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	8.708	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.610	705	0.059	0.098	7,163	0.063
Dulaglutide 3.0 mg	[redacted]	13.076	8.631	644	0.046	0.078	8,290	0.046
Dulaglutide 4.5 mg	[redacted]	13.092	8.651	628	0.030	0.057	11,048	0.025
Semaglutide 0.5 mg	[redacted]	13.075	8.629	682	0.047	0.079	8,621	0.045
Semaglutide 1.0 mg	[redacted]	13.096	8.667	708	0.026	0.041	17,312	0.005
Oral semaglutide 7 mg	[redacted]	13.049	8.591	742	0.073	0.117	6,343	0.080
Oral semaglutide 14 mg	[redacted]	13.074	8.637	719	0.048	0.071	10,094	0.035
Liraglutide 1.2 mg	[redacted]	13.032	8.579	672	0.090	0.130	5,176	0.096
Liraglutide 1.8 mg	[redacted]	13.054	8.596	−409	0.068	0.113	Dominant	0.133

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 8: Summary of scenario including disutility for diarrhoea analysis results for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.760	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.610	1,389	0.092	0.150	9,233	0.081
Dulaglutide 3.0 mg	[redacted]	13.076	8.631	1,329	0.079	0.130	10,237	0.063
Dulaglutide 4.5 mg	[redacted]	13.092	8.651	1,312	0.063	0.109	12,050	0.043
Semaglutide 0.5 mg	[redacted]	13.075	8.629	1,367	0.080	0.131	10,416	0.063
Semaglutide 1.0 mg	[redacted]	13.096	8.667	1,393	0.059	0.093	14,978	0.023

Oral semaglutide 7 mg	[redacted]	13.049	8.591	1,427	0.106	0.169	8,437	0.098
Oral semaglutide 14 mg	[redacted]	13.074	8.637	1,403	0.081	0.123	11,382	0.053
Liraglutide 1.2 mg	[redacted]	13.032	8.579	1,356	0.123	0.182	7,458	0.114
Liraglutide 1.8 mg	[redacted]	13.054	8.596	276	0.101	0.165	1,676	0.151

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 9: Summary of scenario including disutility for diarrhoea analysis results for tirzepatide 15 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.175	8.803	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.610	1,937	0.112	0.193	10,041	0.096
Dulaglutide 3.0 mg	[redacted]	13.076	8.631	1,877	0.099	0.172	10,894	0.078
Dulaglutide 4.5 mg	[redacted]	13.092	8.651	1,860	0.083	0.151	12,290	0.058
Semaglutide 0.5 mg	[redacted]	13.075	8.629	1,915	0.100	0.174	11,024	0.078
Semaglutide 1.0 mg	[redacted]	13.096	8.667	1,941	0.079	0.135	14,327	0.038
Oral semaglutide 7 mg	[redacted]	13.049	8.591	1,975	0.126	0.212	9,333	0.113
Oral semaglutide 14 mg	[redacted]	13.074	8.637	1,951	0.101	0.166	11,772	0.068
Liraglutide 1.2 mg	[redacted]	13.032	8.579	1,904	0.143	0.224	8,489	0.129
Liraglutide 1.8 mg	[redacted]	13.054	8.596	824	0.121	0.207	3,977	0.166

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator.

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Tirzepatide for treating type 2 diabetes [ID3938]

Draft guidance comments form – Appendix B

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 25 July 2023. Please submit via NICE Docs.

Table 10: Comparison of SURPASS and SURMOUNT trials

	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5	SURPASS-6	SURMOUNT-CN	SURMOUNT-2
Intervention	Tirzepatide						
Comparator	Injectable semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo	Insulin Lispro	Placebo	Placebo
Background Therapy	Metformin	Metformin ± SGLT2i	Metformin ± SU ± SGLT2i	Insulin glargine ± metformin	Insulin glargine ± metformin	N/A – diabetes patients were **excluded** from this trial	Any oral glycaemic-lowering agent (as per local labelling) EXCEPT dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon like peptide-1 receptor agonists (GLP-1 RAs)
Population	Patients with T2D, who had inadequate glycaemic control with metformin monotherapy (≥1500 mg/day) and had not been treated with any other OADs during the 3 months prior to the start of the study	Patients with T2D, who had inadequate glycaemic control on stable doses of metformin with or without an SGLT2i	Patients with T2D with high CVD risk, who had inadequate glycaemic control on stable doses of at least 1 and no more than 3 oral antidiabetic drugs (OADs), including metformin, an SGLT2i and/or an SU	Patients with T2D, with background therapy of insulin glargine with or without metformin	Patients with T2D treated with insulin glargine, with or without metformin	**Chinese-only population.** Patients with a BMI ≥28 kg/m², or ≥24 kg/m² and previous diagnosis with at least one of the following comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, CVD, and a history of at least	Patients (aged ≥18 years) with a body-mass index (BMI) of 27 kg/m2 or higher and glycated haemoglobin (HbA1c) of 7–10% (53–86 mmol/mol)

						one self-reported unsuccessful dietary effort to lose body weight	
Trial Design	Randomised, open-label, dose-blind, active-controlled, international, multicentre phase 3 trial assessing the efficacy and safety of tirzepatide for the treatment of T2D, compared to semaglutide	Randomised, open-label, international, multicentre phase 3 trial assessing the efficacy and safety of tirzepatide for the treatment of T2D, compared to insulin degludec	Randomised, open-label, international, multicentre phase 3 trial assessing the efficacy and safety of tirzepatide for the treatment of T2D, compared to insulin glargine	Randomised, double-blind, international, multicentre phase 3 trial assessing the efficacy and safety of tirzepatide for the treatment of T2D, compared to placebo	Randomized, phase 3,open-label trial comparing the effect of the addition of tirzepatide once weekly versus Insulin lispro (U100) three times daily in T2D	Phase 3 trial, randomised, double-blind, multicentre, placebo-controlled trial of once-weekly tirzepatide in 210 Chinese participants who have obesity (BMI ≥ 28 kg/m2) or are overweight (BMI ≥ 24 kg/m2) with weight-related comorbidities and without T2DM.	Phase 3, randomised, double-blind, multi-centre, placebo-controlled trial of once-weekly tirzepatide in 938 participants with obesity or are overweight (BMI ≥27 kg/m²) and with T2DM.
Primary Outcomes	Mean change in HbA1c values from baseline to 40 weeks for tirzepatide 10 mg and 15 mg.	Mean change in HbA1c values from baseline to 52 weeks for tirzepatide 10 mg and 15 mg.	Mean change in HbA1c values from baseline to 52 weeks for tirzepatide 10 mg and 15 mg.	Mean change in HbA1c values from baseline to 40 weeks.	Mean change in HbA1c values from baseline to 52 weeks	Mean percent change from randomisation in body weight and percentage of participants who achieve ≥5% body weight reduction	Mean percent change from randomisation in body weight and percentage of participants who achieve ≥5% body weight reduction
Secondary and exploratory outcomes	**Key secondary efficacy endpoints**	**Key secondary efficacy endpoints**	**Key secondary efficacy endpoints**	**Key secondary efficacy endpoints**	• Mean CfB in body weight • Proportion of patients	• Mean change from randomisation in body weight	• Percentage of participants who achieve ≥10% body

	(controlled for type 1 error) • Mean CfB in HbA1c for tirzepatide 5 mg • Mean CfB in body weight for all tirzepatide doses • Proportion of patients achieving a target HbA1c <7% (53 mmol/mol) for all tirzepatide doses • Proportion of patients achieving HbA1c <5.7% (39 mmol/mol) for tirzepatide 10 mg and 15 mg **Additional secondary efficacy endpoints (not**	**(controlled for type 1 error)** • Mean CfB in HbA1c for tirzepatide 5 mg • Mean CfB in body weight for all tirzepatide doses • Proportion of patients achieving a target of HbA1c <7% (53 mmol/mol) for all tirzepatide doses **Additional secondary efficacy endpoints (not controlled for type 1 error; for all tirzepatide doses)** • Proportion of patients achieving target	**(controlled for type 1 error)** • Mean CfB in HbA1c for tirzepatide 5 mg • Mean CfB in body weight for all tirzepatide doses • Proportion of patients achieving a target of HbA1c <7% (53 mmol/mol) for all tirzepatide doses **Additional secondary efficacy endpoints (not controlled for type 1 error; for all tirzepatide doses)** • Proportion of patients achieving	**(controlled for type 1 error)** • Mean CfB in HbA1c for tirzepatide 5 mg • Mean CfB in body weight for all tirzepatide doses • Mean CfB in FSG for all tirzepatide doses • Proportion of patients achieving a target HbA1c <7% (53 mmol/mol) for all tirzepatide doses • Proportion of patients achieving HbA1c <5.7% (39 mmol/mol) for tirzepatide 10 mg and 15 mg	achieving a target HbA1c <7% (53 mmol/mol) for all tirzepatide doses • Proportion of patients achieving HbA1c ≤6.5% (48 mmol/mol) for tirzepatide 10 mg and 15 mg • Proportion of patients achieving HbA1c <5.7% (39 mmol/mol) for tirzepatide 10 mg and 15 mg **Safety assessments** • Hypoglycaemic events • Treatment-emergent adverse events	• Percentage of participants who achieve ≥10% body weight reduction • Percentage of participants who achieve ≥15% body weight reduction • Mean change from randomisation in waist circumference • Mean change from randomisation in body weight • Mean change from randomisation in body mass index (BMI) • Mean change from randomisation in haemoglobin a1c (HbA1c)	weight reduction from randomisation • Percentage of participants who achieve ≥15% body weight reduction from baseline • Change from randomisation in absolute body weight • Change from randomisation in body mass index (BMI) • Change from randomisation in HbA1c • Percentage of participants who achieve HbA1c <7% • Percentage of participants who achieve HbA1c ≤6.5% • Percentage of

	controlled for type 1 error; for all tirzepatide doses unless otherwise specified) • Proportion of patients achieving a target HbA1c of ≤6.5% (48 mmol/mol) • Proportion of patients achieving HbA1c <5.7% (39 mmol/mol) for tirzepatide 5 mg • Mean CfB in FSG • Mean CfB in 7-point SMBG profiles • Proportion of patients who achieved weight loss ≥5%, ≥10% and ≥15%	HbA1c ≤6.5% (48 mmol/mol) and <5.7% (39 mmol/mol) • Mean CfB in FSG, measured in the central laboratory • Mean CfB in 7-point SMBG profiles • Proportion of patients who achieved weight loss ≥5%, ≥10% and ≥15% • Mean CfB in patient-reported outcomes, including DTSQs/DTSQc, IW-SP, and APPADL **Tertiary or exploratory efficacy endpoints (for all tirzepatide doses)**	target HbA1c ≤6.5% (48 mmol/mol) and <5.7% (39 mmol/mol) • Mean CfB in FSG, measured in the central laboratory • Mean CfB in 7-point SMBG profiles • Proportion of patients who achieved weight loss ≥5%, ≥10% and ≥15% • Mean CfB in patient-reported outcomes, including DTSQs/DTSQc, IW-SP, and APPADL **Tertiary or exploratory efficacy**	**Additional secondary efficacy endpoints (not controlled for type 1 error; for all tirzepatide doses unless elsewhere specified)** • Proportion of patients achieving a target HbA1c of ≤6.5% (48 mmol/mol) • Proportion of patients achieving HbA1c <5.7% (39 mmol/mol) for tirzepatide 5 mg • Mean CfB in 7-point SMBG profiles • Proportion of patients who achieved weight loss ≥5%, ≥10% and	• Serious adverse events • Change in blood pressure and pulse rate	• Mean change from randomisation in fasting glucose (FSG) • Mean change from randomisation in short-form-36 health survey version 2 (SF-36 v2) acute form physical functioning domain score • Mean change from randomisation in impact of weight on quality of life-lite clinical trials version (IWQOL-lite-CT) physical function composite score • Mean change from randomisation	participants who achieve HbA1c <5.7% • Change from randomisation in fasting glucose • Change from randomisation in waist circumference • Change from randomisation in total cholesterol • Change from randomisation in low density lipid (LDL)-cholesterol • Change from randomisation in high density lipid (HDL) Cholesterol • Change from randomisation in very low density lipid (VLDL) cholesterol

	• Mean CfB in patient-reported outcomes, including DTSQs/DTSQc, IW-SP, and APPADL **Tertiary or exploratory efficacy endpoints (for all tirzepatide doses)** • Mean change in fasting glucose, C-peptide and insulin levels • Mean CfB in lipids (total cholesterol, HDL, VLDL, and triglycerides) • Mean CfB in BMI and waist circumference • Mean CfB in	• Mean CfB in lipids (total cholesterol, HDL, LDL, VLDL, and triglycerides) • Mean CfB in BMI • Mean CfB in waist circumference • Mean CfB in biomarkers • Mean CfB in EQ-5D-5L scores **Safety assessments** • AEs • Patient diaries • Concomitant medications • Dilated fundoscopic examinations were performed at baseline for all patients;	**endpoints (for all tirzepatide doses)** • Mean CfB in lipids (total cholesterol, HDL, LDL, VLDL, and triglycerides) • Mean CfB in BMI • Mean CfB in waist circumference • Mean CfB in patient-reported outcomes, including APPADL, IW-SP, DTSQs/DTSQc and EQ-5D-5L scores **Safety assessments** • AEs • CV events (time to first	≥15% • Mean CfB in daily mean insulin glargine dose **Tertiary or exploratory efficacy endpoints (for all tirzepatide doses)** • Mean CfB in lipids (total cholesterol, HDL, LDL, VLDL, and triglycerides) • Mean CfB in waist circumference • Mean CfB in BMI • Mean CfB in patient-reported outcomes, including APPADL, DTSQs/DTSQc		in diastolic blood pressure (DBP) • Mean change from randomisation in systolic blood pressure (SBP) • Mean change from randomisation in total cholesterol • Mean change from randomisation in high density lipoprotein (HDL) cholesterol • Mean change from randomisation in low density lipoprotein (LDL) cholesterol • Mean change from randomisation	• Change from randomisation in triglycerides • Change from randomisation in free fatty acids • Change from randomisation in systolic blood pressure (SBP) • Change from randomisation in diastolic blood pressure (DBP) • Change from randomisation in fasting insulin • Change from randomisation in Short Form 36 Health Survey version 2 (SF-36v2) acute form physical functioning domain score

	biomarkers • Mean CfB in patient-reported outcomes, including EQ-5D-5L scores and IWQOL-Lite-CT **Safety assessments** • AEs • Patient diaries • Concomitant medications • Dilated fundoscopic examinations were performed at baseline for all patients; follow-up dilated fundoscopic examinations were performed as deemed appropriate by the investigator	follow-up dilated fundoscopic examinations were performed as deemed appropriate by the investigator • Vital signs • ECGs • Laboratory tests, including hepatic safety monitoring	occurrence of MACE-4) • Patient diaries • Concomitant medications • Dilated fundoscopic examinations were performed at baseline for all patients; follow-up dilated fundoscopic examinations were performed as deemed appropriate by the investigator • Vital signs • ECGs • Laboratory tests, including hepatic safety monitoring	, and EQ-5D-5L scores **Safety assessments** • AEs • Patient diaries • Concomitant medications • Dilated fundoscopic examinations were performed at baseline for all patients; follow-up dilated fundoscopic examinations were performed as deemed appropriate by the investigator • Vital signs • ECGs • Laboratory tests, including hepatic safety monitoring		in very low density lipoprotein (VLDL) cholesterol • Mean change from randomisation in triglycerides • Mean change from randomisation in free fatty acids • Mean change from randomisation in fasting insulin	• Change from randomisation in impact of weight on quality of life-lite-clinical trials version (IWQOL Lite-CT) physical function composite score • Pharmacokinetics (PK): steady state area under the concentration curve (AUC) of tirzepatide

	• Vital signs • ECGs • Laboratory tests, including hepatic safety monitoring						

Abbreviations: AE: adverse event; ALT: alanine transaminase; APPADL: ability to perform physical activities of daily living; BMI: body mass index; CDK-EPI: chronic Kidney Disease-Epidemiology; CfB: change from baseline; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; DPP: dipeptidyl peptidase; DTSQ(c/s): diabetes treatment satisfaction questionnaire (change/status); ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EQ-5D-5L: EuroQol-5 dimension-5 level descriptive system; FSG: fasting serum glucose; GLP-1 RA: glucagon-like peptide-1 receptor agonist; HbA1c: glycated haemoglobin; HDL: high density lipoprotein; IW-SP: impact of weight on self-perception; IWQOL-Lite-CT: impact of weight on quality of life lite clinical trials version; IWRS: Interactive Web Response System; LDL: low density lipoprotein; MACE: major adverse cardiovascular event; MTC: medullary thyroid cancer; OUS: outside the USA; SBP: systolic blood pressure; SGLT2i: sodium glucose cotransporter 2 inhibitor; SU: sulphonylurea; T2D: type 2 diabetes; ULN: upper limit of normal; VLDL: very low density lipoprotein.
Source: SURPASS-2 CSR,[19] SURPASS-3 CSR,[20] SURPASS-4 CSR,[21] SURPASS-5 CSR,[22] Rosenstock et al. (2023),[23] Garvey *et al.* (2023),[1] ClinicalTrials.gov NCT05024032,[24] ClinicalTrials.gov NCT04657003.[25]

NICE National Institute for Health and Care Excellence

Tirzepatide for treating type 2 diabetes [ID3938]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Diabetes UK

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NICE National Institute for Health and Care Excellence

Tirzepatide for treating type 2 diabetes [ID3938]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Eli Lilly - £229,259 supporting our CPD programme <u>Comparator Funding</u> Novo Nordisk £174,345 supporting our Clinical Champions programme and as a conference exhibitor Sanofi £70,500 as a conference sponsor All are ongoing partnerships
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here] NONE
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are supportive of Tirzepatide being approved as the trial data supporting this is strong and the medication shows clear improvements in its ability to reduce body weight and HbA1c when compared to currently approved medications for type 2 diabetes. We are concerned that this

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	recommendation not to approve tirzepatide for type 2 diabetes will result in fewer and less effective treatment options for people with type 2 diabetes.
2	We are concerned that the current shortage of GLP-1 receptor agonists within the UK is preventing people with type 2 diabetes from accessing GLP-1s. The latest guidance from NHS England and the Department of Health and Social Care is not to issue any new prescriptions of GLP-1 RAs until the shortage is resolved. This supply issue is unlikely to be resolved until mid-2024 and has the potential to impact, not only people with type 2 who are prescribed GLP-1 RAs, but could also people who take other treatment for diabetes. Approval of this drug, therefore, increases the options available to prescribers and potentially provides further solutions to the shortage of GLP-1s, this should be considered as an equality issue.
3	Tirzepatide also provides a variation to the existing type 2 drugs currently available as it contains both GLP-1 and GIP hormones. This will increase the options available to prescribers for treatment where other medications may not be viable due to existing contraindications.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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NICE Tirzepatide response on behalf of ABCD
Professor S C Bain

Thank you for allowing access to the draft guidance consultation and recommendation for 'Tirzepatide for treating type 2 diabetes'

My comments, having attended the meeting on 6th June, 2023 are as follows:

Section 3.2 Treatment options; the draft guidance consultation points out that current NICE guidelines allow the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) for people that have failed to achieve glycaemic targets on a triple therapy oral combination including metformin. In addition, there are also BMI limitations. The committee should appreciate that this guidance bares no relation to the licences for GLP-1RAs and is not advocated by any other national guideline in the world. For these reasons, the global phase 3 clinical trial programme of tirzepatide does not focus on the patient cohort of greatest interest to the committee (highlighted in section 3.5).

The criticism that the company sponsor did not apply for use in the totality of tirzepatide's licenced indication seems harsh, given that all GLP-1RAS have a similar broad licence but have been allocated a niched and late positioning in NG28, the current NICE guideline for managing type 2 diabetes (updated March 2022). For information, the Association of British Clinical Diabetologists (ABCD) favours an earlier use of GLP-1RAs, as is advocated by the joint consensus statement of the American Diabetes Association and European Association for the Study of Diabetes (ADA/EASD 2022).

Furthermore, two of the 'relevant comparators' (section 3.4) dulaglutide and semaglutide, have never had appraisals performed by NICE (TA10437 and ID1451, both scheduled for 2018, were cancelled in anticipation of the 2022 update).

Section 3.9 NMA misalignment and decision problem; the draft guidance consultation points out that only one direct comparison has been performed between tirzepatide and a GLP-1RA (SURPASS-2). However, the GLP-1RA molecule in that trial, semaglutide, is the most potent GLP-1RA currently available, in terms of both glucose lowering and weight reduction (confirmed in head-to-head clinical trials with comparators).

The company's economic model (3.10); the sponsor company produced outcomes based on a new model (PRIME T2D) which apparently uses more up-to-date population data than UKPDS data (first published in 1998). This model was not accepted by the external assessment group (EAG) and further analyses have been requested, presumably based on the CORE Diabetes Model and the UK Prospective Diabetes Study (UKPDS) model. It was unclear why the EAG could not have unambiguously disclosed this decision to the sponsor company so that acceptable analyses could have been discussed at the meeting (especially given that this had been delayed by four months from the original scheduled date).

Single Technology Appraisal

Tirzepatide for treating type 2 diabetes [ID3938]

Comments on the draft guidance received through the NICE website

Name	
Role	
Organisation	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

"A. The systemic literature reviews (SLRs) included as part of the evidence package appear to exclude a key publication and relevant clinical trials for tirzepatide with no clear rationale as to why.

In section 3.11 of the draft guidance, the NICE committee states that no comparative data on micro- and macrovascular complications of diabetes, including cardiovascular (CV) outcomes, was available. However, a paper published by Sattar et al. 2022 reports data from a pre-specified cardiovascular meta-analysis which included all seven randomised controlled trials with a duration of at least 26 weeks from the tirzepatide T2D clinical development program, SURPASS.3 This data was requested from both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Data from a pre-specified meta-analysis and post-hoc safety analysis across one phase 2 and five 3 trials was conducted based on prospectively collected and centrally adjudicated MACE events from the trials. A total of 7,215 patients with type 2 diabetes were analysed and compared to a pooled comparator group followed up over a median duration of 55.3 weeks. In total, 2,187 (34.9%) participants had a history of cardiovascular disease which also included data from SURPASS 4 which recruited patients with type 2 diabetes, of which 86.9% had established cardiovascular disease.3

In addition, the draft guidance states that the clinical evidence for tirzepatide came from four trials, SURPASS-2 to -5, however, another two clinical trials with tirzepatide including patients with type 2 diabetes have been completed:

- SURMOUNT-2: NCT046570034
- SURMOUNT-CN: NCT050240325

These trials contain important outcome data that could be used in the modelling to inform cost-effectiveness in potential subgroups, particularly around patients with obesity and different ethnic groups as well as complimentary safety data.

The rationale for exclusion of such evidence from the current submission is unclear. Therefore, for the reasons outlined above, it is unclear whether the SLRs conducted as part of this appraisal are inclusive of all available evidence for tirzepatide.

B. It is unclear whether the resource utilisation associated with the prolonged titration or up titration of tirzepatide have been considered in the economic modelling approach.

In section 3.7 and 3.8 of the draft guidance, the clinical experts noted that the titration of tirzepatide will be much slower than it is with GLP-1 RAs, which is more resource intensive, however it is unclear whether this anticipated increase in resource utilisation has been taken into account within the economic modelling.

Published literature indicates that there is a degree of therapeutic inertia with the slow up titration GLP-1 RAs to mitigate adverse events.6 If patients are not moved on to maintenance doses for concerns due to factors such as gastrointestinal tolerability or blood glucose optimisation and remained on non-maintenance doses of tirzepatide, further NHS resources would likely be required. This is further demonstrated in Section 3.7 of the draft guidance consultation, where the clinical experts further explained that, in clinical practice, if someone has any gastrointestinal problems, dose increases may be delayed, or they may remain on their current dose. Furthermore, in section 3.8, the clinical experts explained that, in NHS practice, the focus is on blood glucose levels, so if the target HbA1c is met, people would stay at the current dose of tirzepatide.

Based on the above, it is unclear whether the anticipated impact on NHS resources has been considered in the economic analysis for tirzepatide.

References

1. Frias JP, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021; 5;385(6):503-515. doi: 10.1056/NEJMoa2107519.
2. Gogtay NJ, et al. Understanding estimands. Perspect Clin Res. 2021; 12(2): 106–112. doi: 10.4103/picr.picr_384_20
3. Sattar N, et al. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nat Med. 2022; 28(3):591-598. doi: 10.1038/s41591-022-01707-4.
4. ClinicalTrial.gov. A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Who Have Obesity or Are Overweight (SURMOUNT-2) [NCT04657003]. Available from: https://clinicaltrials.gov/ct2/show/NCT04657003 [accessed July 2023]
5. ClinicalTrial.gov. A Study of Tirzepatide (LY3298176) in Chinese Participants Without Type 2 Diabetes Who Have Obesity or Overweight (SURMOUNT-CN) [NCT05024032]. Available from: https://www.clinicaltrials.gov/study/NCT05024032 [accessed July 2023]

6. Arx, LBV, et al. Therapeutic inertia related to the injectable glucagon-likepeptide-1 receptor agonists dulaglutide and semaglutide inpatients with type 2 diabetes in UK primary care. Diabetes Obes Metab. 2023 May;25(5):1331-1340. doi: 10.1111/dom.14985."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

"A. The modelling of adverse events appears to only include nausea rates, however diarrhoea is a very common adverse event from incretin-analogue therapies including tirzepatide (GLP-1/GIP) and other GLP-1 receptor analogues.1

In SURPASS 2, which compared tirzepatide 5 mg, 10 mg and 15 mg to semaglutide 1 mg, the rates of diarrhoea were 13.2%, 16.4%, 13.8% and 11.5%, respectively.2 These adverse events were frequent enough to warrant additional consideration, and although typically mild to moderate in nature and occurring during the prolonged dose-escalation period, this adverse event appears to be inadequately captured in the assessment. This is particularly important given the potential impact the management of diarrhoea may have on clinical practice, patient quality of life, and the use of NHS resources due to the slower dose escalation of treatment with tirzepatide than currently available GLP-1 receptor agonists as well as the monitoring requirements.

B. The modelling of adverse events appears to only include severe and non-severe hypoglycaemic rates for basal insulin therapy. However, given the proposed positioning of tirzepatide, it would remain plausible that a proportion of patients would use tirzepatide in combination with insulin secreatagogues, insulin or sulphonylureas.

Evidence from a recent UKCPRD analysis indicates that >39% and >21% of patients with type 2 diabetes taking GLP-1 receptor agonists (dulaglutide or semaglutide) also use concomitant sulphonylureas and insulin, respectively.3 When used in combination with sulphonylurea or insulin, incretin-analogue therapies including tirzepatide (GLP-1/GIP) and other GLP-1 receptor analogues are known to increase the risk of hypoglycaemia-related adverse events. 1

Data from the SURPASS 5 trial indicates that hypoglycaemia rates for all doses of tirzepatide added on top of insulin glargine, exhibited higher rates of hypoglycaemia (<3 mmol/L) than placebo. The proportion of patients experiencing hypoglycaemia were 15.5%, 19.3%, 14.2% and 12.5% for tirzepatide 5 mg, 10 mg, 15 mg and placebo, respectively. In addition, severe hypoglycaemia episodes requiring assistance from a third-party to administer rescue medication also occurred at higher rates at 1.6% and 0.8% of patients on 10 mg and 15 mg tirzepatide, respectively, compared to placebo at 0%.4

The occurrence and management of nausea and hypoglycaemic events will have an impact on NHS resources because additional blood glucose monitoring is required when tirzepatide is used in combination with sulphonylurea or insulin, while carrying out any potential blood glucose adjustments.1 Therefore, it appears that the summaries of clinical and cost effectiveness at present are not reasonable interpretations of the evidence.

References

1. Elli Lilly. Mounjaro® (Tirzepatide). Summary of Product Characteristics. 2023. Available from: https://www.medicines.org.uk/emc/product/14203/smpc [Accessed: 09-July-2023].
2. Frias JP, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021. 5;385(6):503-515. doi: 10.1056/NEJMoa2107519.
3. Arx, LBV, et al. Therapeutic inertia related to the injectable glucagon-likepeptide-1 receptor agonists dulaglutide and semaglutide inpatients with type 2 diabetes in UK primary care. Diabetes Obes Metab. 2023 May;25(5):1331-1340. doi: 10.1111/dom.14985.
4. Dahl D, Onishi Y, Norwood P, et al. Effect of Subcutaneous Tirzepatide vs Placebo Added to Titrated Insulin Glargine on Glycemic Control in Patients With Type 2 Diabetes: The SURPASS-5 Randomized Clinical Trial. JAMA. 2022;327(6):534–545. doi:10.1001/jama.2022.0078."

NICE National Institute for Health and Care Excellence

Tirzepatide for treating type 2 diabetes [ID3938]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eli Lilly & Company Ltd

NICE National Institute for Health and Care Excellence

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

NICE National Institute for Health and Care Excellence

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PART 1 (comments 1-17)

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.	EAG response
1	**Executive Summary** Eli Lilly welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee detailed in the draft guidance consultation document for tirzepatide for type 2 diabetes (T2D). Whilst Eli Lilly is disappointed that the committee's preliminary decision is to not recommend tirzepatide within its marketing authorisation, we are, however, committed to working with the National Institute for Health and Care Excellence (NICE) to address the external assessment group (EAG) and committee's key concerns, as outlined in the consultation document and the accompanying letter to company, to enable patients to access this clinically beneficial treatment. [redacted] The [redacted] pricing of tirzepatide is detailed in Table 1, and a summary of the updated EAG preferred base case results for tirzepatide 5 mg, 10 mg and 15 mg versus all comparators is presented in Table 2, Table 3 and Table 4, respectively. **Table 1: [redacted] tirzepatide prices** Dose | [redacted] pack price Tirzepatide 5 mg | £[redacted] Tirzepatide 10 mg | £[redacted] Tirzepatide 15 mg | £[redacted] **Table 2: Summary of base case results for tirzepatide 5 mg versus comparators [redacted]** [redacted] | Direct costs (£) | Life expectancy (years) | Quality-adjusted life | Incremental costs (£)* | Incremental life years* | Incremental QALYs* | ICER* (£ per QALY gained) | NHB (QALYs)	No comment, these are updated company's base-case results [redacted]

			expectancy (QALYs)					
Tirzepatide 5 mg	[redacted]	13.122	8.715	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	705	0.059	0.100	7,073	0.064
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	644	0.046	0.079	8,182	0.047
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	628	0.030	0.058	10,891	0.026
Semaglutide 0.5 mg	[redacted]	13.075	8.634	682	0.047	0.081	8,401	0.047
Semaglutide 1.0 mg	[redacted]	13.096	8.673	708	0.026	0.042	16,817	0.007
Oral semaglutide 7 mg	[redacted]	13.049	8.595	742	0.073	0.120	6,202	0.083
Oral semaglutide 14 mg	[redacted]	13.074	8.642	719	0.048	0.073	9,873	0.037
Liraglutide 1.2 mg	[redacted]	13.032	8.581	672	0.090	0.134	5,021	0.100
Liraglutide 1.8 mg	[redacted]	13.054	8.600	-409	0.068	0.115	Dominant	0.135

* for tirzepatide versus comparator.
Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Table 3: Summary of base case results for tirzepatide 10 mg versus comparators [redacted]

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.768	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	1,389	0.092	0.153	9,091	0.083
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	1,329	0.079	0.132	10,073	0.065
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	1,312	0.063	0.111	11,843	0.045

Semaglutide 0.5 mg	[redacted]	13.075	8.634	1,367	0.080	0.134	10,171	0.066
Semaglutide 1.0 mg	[redacted]	13.096	8.673	1,393	0.059	0.095	14,616	0.026
Oral semaglutide 7 mg	[redacted]	13.049	8.595	1,427	0.106	0.173	8,254	0.102
Oral semaglutide 14 mg	[redacted]	13.074	8.642	1,403	0.081	0.126	11,140	0.056
Liraglutide 1.2 mg	[redacted]	13.032	8.581	1,356	0.123	0.187	7,254	0.119
Liraglutide 1.8 mg	[redacted]	13.054	8.600	276	0.101	0.168	1,642	0.154

* for tirzepatide versus comparator.
Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

Table 4: Summary of base case results for tirzepatide 15 mg versus comparators [redacted]

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.176	8.808	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.615	2,047	0.113	0.192	10,642	0.090
Dulaglutide 3.0 mg	[redacted]	13.076	8.636	1,987	0.100	0.171	11,586	0.072
Dulaglutide 4.5 mg	[redacted]	13.092	8.657	1,970	0.084	0.150	13,104	0.052
Semaglutide 0.5 mg	[redacted]	13.075	8.634	2,025	0.101	0.174	11,641	0.073
Semaglutide 1.0 mg	[redacted]	13.096	8.673	2,051	0.080	0.135	15,209	0.032
Oral semaglutide 7 mg	[redacted]	13.049	8.595	2,085	0.127	0.212	9,815	0.108
Oral semaglutide 14 mg	[redacted]	13.074	8.642	2,061	0.102	0.166	12,453	0.062

Liraglutide 1.2 mg	[redacted]	13.032	8.581	2,014	0.144	0.227	8,893	0.126
Liraglutide 1.8 mg	[redacted]	13.054	8.600	934	0.122	0.208	4,498	0.161

* for tirzepatide versus comparator.
Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year.

2

One-way sensitivity analyses for all model inputs in PRIME T2D (tornado diagram)

Incremental cost-effectiveness ratios from the 232 one-way sensitivity analysis simulations for user-editable model inputs are summarized in Table 5 (ICERs ranked from highest to lowest) and a tornado diagram for the ten most influential parameters affecting the ICER is provided in Figure 1.

Table 5: Summary of one-way sensitivity analysis results for the tirzepatide 10 mg versus semaglutide 1.0 mg comparison

Element	Description	ICER
SEMA treatment	HbA1c constant after intensification to insulin	Semaglutide dominant
SEMA treatment	HbA1c constant during treatment, intensification after 4 years	Semaglutide dominant
SEMA treatment	SBP constant after intensification to insulin	212,614
TZP treatment	LDL constant after intensification to insulin	33,302
SEMA treatment	LDL constant during treatment	26,910
TZP treatment	SBP follows UKPDS progression during treatment	24,938
SEMA treatment	QoL decrement on insulin years 2+ decreased by 10%	23,176
TZP treatment	QoL decrement on insulin years 2+ increased by 10%	22,676
TZP treatment	Severe hypo rate increased by 10%	19,186

Thank you for providing these one-way sensitivity analyses. The results indicate that risk factors (HbA1c, SBP, LDL, HDL), the utility decrement on insulin years 2+, insulin treatment costs, hypoglycaemia rate and treatment costs can have a substantial impact on the estimated ICER. It should be noted that the one-way sensitivity analyses were predominantly performed using alternative assumptions (e.g. assuming 10% increase or decrease or constant risk factor after intensification) rather on the estimated standard error (or 95% confidence interval) of the specific parameter of interest. Additionally, the individual parameters of the risk models (including the UKPDS risk factor progression) were not

	Cohort	Baseline HbA1c decreased by 10%	19,082	included in the one-way sensitivity analyses.
	SEMA treatment	Insulin treatment costs decreased by 10% in years 2+	18,697	
	SEMA treatment	HbA1c change increased by 10%	18,544	
	TZP treatment	Insulin treatment costs increased by 10% in years 2+	18,543	
	SEMA treatment	Severe hypo rate decreased by 10%	18,528	
	TZP treatment	BMI constant after intensification to insulin	18,187	
	SEMA treatment	Non-severe hypo rate decreased by 10%	17,982	
	TZP treatment	Treatment costs increased by 10% in years 2+	17,946	
	TZP treatment	Non-severe hypo rate increased by 10%	17,736	
	TZP treatment	HbA1c change decreased by 10%	17,091	
	SEMA treatment	HDL constant after intensification to insulin	16,974	
	SEMA treatment	Treatment costs increased by 10% in years 2+	16,487	
	Country	Discount rate set to 6% per annum on costs and benefits	16,442	
	TZP treatment	eGFR constant during treatment	16,424	
	SEMA treatment	HDL constant during treatment	16,379	
	SEMA treatment	WBC constant after intensification to insulin	16,285	
	TZP treatment	BMI change decreased by 10%	16,151	
	TZP treatment	HbA1c change on insulin decreased by 10%	16,144	
	TZP treatment	Treatment costs increased by 10% in year 1	16,142	
	TZP treatment	SBP change decreased by 10%	16,114	
	SEMA treatment	Heart rate constant during treatment	16,113	
	Cohort	Baseline serum lipid levels improved by 10% (TC, HDL and LDL)	16,079	
	TZP treatment	BMI follows UKPDS progression during treatment	15,732	

SEMA treatment	Treatment costs increased by 10% in year 1	15,643
Cohort	Baseline eGFR increased by 10%	15,573
SEMA treatment	WBC constant during treatment	15,496
TZP treatment	LDL change increased by 10% on intensification to insulin	15,299
TZP treatment	BMI change increased by 10% on intensification to insulin	15,286
SEMA treatment	QoL decrement on treatment years 2+ decreased by 10%	15,276
SEMA treatment	HDL change increased by 10% on intensification to insulin	15,233
TZP treatment	QoL decrement on treatment years 2+ increased by 10%	15,107
SEMA treatment	QoL decrement on insulin year 1 increased by 10%	15,092
SEMA treatment	Treatment costs decreased by 10% in year 1 of insulin therapy	15,092
TZP treatment	Treatment costs increased by 10% in year 1 of insulin therapy	15,079
TZP treatment	QoL decrement on insulin year 1 increased by 10%	15,078
TZP treatment	HDL change increased by 10% on intensification to insulin	15,059
TZP treatment	QoL decrement on treatment year 1 increased by 10%	15,052
SEMA treatment	SBP change increased by 10%	15,020
SEMA treatment	BMI change increased by 10%	14,944
Cohort	Baseline BMI decreased by 10%	14,908
Cohort	Baseline complications all increased by 10%	14,899
Cohort	Percentage male at baseline increased by 10%	14,885
TZP treatment	LDL change decreased by 10%	14,870
Cohort	Baseline haemoglobin decreased by 10%	14,867
SEMA treatment	Heart rate constant after intensification to insulin	14,858
Cohort	Baseline haemoglobin increased by 10%	14,822

Cohort	Baseline eGFR decreased by 10%	14,804
Cohort	Percentage smokers at baseline increased by 10%	14,778
SEMA treatment	SBP change decreased by 10%	14,774
Cohort	No history of complications at baseline (set to 0%)	14,749
Utilities	Non-severe hypo utility decreased by 10%	14,729
Utilities	Renal failure utility decreased by 10%	14,729
Utilities	Severe hypo utility decreased by 10%	14,716
TZP treatment	WBC constant after intensification to insulin	14,699
Cohort	Baseline duration of diabetes decreased by 10%	14,692
Costs	Revascularization cost decreased by 10%	14,672
Costs	Neuropathy cost decreased by 10%	14,671
Costs	Severe hypo cost decreased by 10%	14,660
Utilities	Neuropathy years 2+ utility decreased by 10%	14,658
Utilities	IHD years 2+ utility decreased by 10%	14,643
Costs	IHD years 2+ cost decreased by 10%	14,643
TZP treatment	eGFR constant after intensification to insulin	14,642
Costs	Heart failure years 2+ cost decreased by 10%	14,640
Utilities	IHD year 1 utility decreased by 10%	14,638
Utilities	Stroke years 2+ utility decreased by 10%	14,638
Costs	Stroke years 2+ cost decreased by 10%	14,638
Costs	Stroke year 1 cost decreased by 10%	14,638
Costs	Renal failure cost decreased by 10%	14,633
Costs	Heart failure year 1 cost decreased by 10%	14,632

Costs	Myocardial infarction year 1 cost decreased by 10%	14,630
Utilities	Heart failure years 2+ utility decreased by 10%	14,629
Utilities	Neuropathy year 1 utility decreased by 10%	14,625
Costs	IHD year 1 cost decreased by 10%	14,625
Costs	Amputation year 1 cost decreased by 10%	14,623
Utilities	Stroke year 1 utility decreased by 10%	14,622
Utilities	Heart failure year 1 utility decreased by 10%	14,621
Costs	Blindness years 2+ cost decreased by 10%	14,621
Costs	Amputation years 2+ cost decreased by 10%	14,621
Costs	Ulcer cost decreased by 10%	14,621
Utilities	Ulcer utility decreased by 10%	14,620
Costs	Blindness year 1 cost decreased by 10%	14,620
Utilities	Blindness years 2+ utility decreased by 10%	14,619
Utilities	Macular oedema utility decreased by 10%	14,618
Utilities	Amputation years 2+ utility decreased by 10%	14,618
Utilities	Amputation year 1 utility decreased by 10%	14,618
Utilities	Myocardial infarction year 1 utility decreased by 10%	14,618
Costs	Macular oedema cost decreased by 10%	14,618
Utilities	Blindness year 1 utility decreased by 10%	14,617
Utilities	Myocardial infarction years 2+ utility decreased by 10%	14,617
Costs	Myocardial infarction years 2+ cost decreased by 10%	14,617
Utilities	CKD stage 4 utility decreased by 10%	14,616
Utilities	CKD stage 4 utility increased by 10%	14,616

Utilities	CKD stage 3 utility decreased by 10%	14,616
Utilities	CKD stage 3 utility increased by 10%	14,616
Utilities	Revascularization years 2+ utility decreased by 10%	14,616
Utilities	Revascularization years 2+ utility increased by 10%	14,616
Utilities	Revascularization year 1 utility decreased by 10%	14,616
Utilities	Revascularization year 1 utility increased by 10%	14,616
Utilities	Myocardial infarction years 2+ utility increased by 10%	14,616
Costs	CKD stage 4 cost decreased by 10%	14,616
Costs	CKD stage 4 cost increased by 10%	14,616
Costs	Myocardial infarction years 2+ cost increased by 10%	14,616
SEMA treatment	Haemoglobin constant after intensification to insulin	14,616
SEMA treatment	Haemoglobin constant during treatment	14,616
TZP treatment	Haemoglobin constant after intensification to insulin	14,616
TZP treatment	Haemoglobin constant during treatment	14,616
Cohort	Baseline college education decreased by 10%	14,616
Cohort	Baseline college education increased by 10%	14,616
Utilities	Renal failure utility increased by 10%	14,615
Utilities	Blindness year 1 utility increased by 10%	14,615
Utilities	Myocardial infarction year 1 utility increased by 10%	14,615
Costs	Macular oedema cost increased by 10%	14,615
Utilities	Macular oedema utility increased by 10%	14,614
Utilities	Amputation years 2+ utility increased by 10%	14,614
Utilities	Amputation year 1 utility increased by 10%	14,614

Utilities	Blindness years 2+ utility increased by 10%	14,613	
Utilities	Ulcer utility increased by 10%	14,613	
Utilities	Heart failure year 1 utility increased by 10%	14,612	
Costs	Blindness years 2+ cost increased by 10%	14,612	
Costs	Blindness year 1 cost increased by 10%	14,612	
Costs	Amputation years 2+ cost increased by 10%	14,612	
Costs	Ulcer cost increased by 10%	14,612	
Utilities	Stroke year 1 utility increased by 10%	14,611	
SEMA treatment	LDL change decreased by 10%	14,611	
Costs	Amputation year 1 cost increased by 10%	14,609	
Utilities	Neuropathy year 1 utility increased by 10%	14,608	
Costs	IHD year 1 cost increased by 10%	14,608	
Costs	Non-diabetes related mortality calculated based on BRAVO risk equation	14,604	
Country	Non-diabetes related mortality calculated based on UKPDS OM2 risk equation	14,604	
Country	Heart failure years 2+ utility increased by 10%	14,603	
Costs	Myocardial infarction year 1 cost increased by 10%	14,602	
Costs	Heart failure year 1 cost increased by 10%	14,601	
Costs	Renal failure cost increased by 10%	14,599	
Utilities	IHD year 1 utility increased by 10%	14,595	
Costs	Stroke years 2+ cost increased by 10%	14,595	
Costs	Stroke year 1 cost increased by 10%	14,595	
Utilities	Stroke years 2+ utility increased by 10%	14,594	

Costs	Heart failure years 2+ cost increased by 10%	14,593
Costs	IHD years 2+ cost increased by 10%	14,590
Utilities	IHD years 2+ utility increased by 10%	14,589
TZP treatment	HDL constant after intensification to insulin	14,589
Utilities	Neuropathy years 2+ utility increased by 10%	14,575
Costs	Severe hypo cost increased by 10%	14,572
Cohort	Baseline SBP increased by 10%	14,567
Cohort	Baseline age increased by 10%	14,563
Costs	Neuropathy cost increased by 10%	14,562
Costs	Revascularization cost increased by 10%	14,561
Utilities	Severe hypo utility increased by 10%	14,518
Utilities	Non-severe hypo utility increased by 10%	14,505
TZP treatment	QoL decrement on treatment years 2+ decreased by 10%	14,399
TZP treatment	HDL change increased by 10%	14,306
SEMA treatment	BMI change decreased by 10% on intensification to insulin	14,300
Cohort	Percentage male at baseline decreased by 10%	14,276
Cohort	Percentage smokers at baseline decreased by 10%	14,269
SEMA treatment	LDL change increased by 10%	14,268
TZP treatment	QoL decrement on insulin year 1 decreased by 10%	14,205
Cohort	Baseline age decreased by 10%	14,199
TZP treatment	HbA1c change increased by 10% on intensification to insulin	14,197
SEMA treatment	eGFR constant after intensification to insulin	14,190
TZP treatment	QoL decrement on insulin year 1 decreased by 10%	14,182

SEMA treatment	QoL decrement on insulin year 1 increased by 10%	14,170
Cohort	Baseline BMI increased by 10%	14,166
TZP treatment	Heart rate constant after intensification to insulin	14,153
SEMA treatment	Treatment costs increased by 10% in year 1 of insulin treatment	14,141
SEMA treatment	QoL decrement on treatment year 1 increased by 10%	14,126
SEMA treatment	BMI change increased by 10% on intensification to insulin	14,118
SEMA treatment	HDL change increased by 10%	14,114
TZP treatment	WBC constant during treatment	14,114
TZP treatment	Treatment costs decreased by 10% in year 1	14,108
TZP treatment	LDL change increased by 10%	14,063
Country	Renal failure risk estimated using UKPDS OM2 risk formula	14,060
TZP treatment	HDL change decreased by 10% on intensification to insulin	14,052
SEMA treatment	SBP change decreased by 10% on intensification to insulin	14,044
SEMA treatment	QoL decrement on treatment years 2+ increased by 10%	14,011
TZP treatment	SBP change decreased by 10% on intensification to insulin	13,965
Cohort	Baseline serum lipid levels worsened by 10% (TC, HDL and LDL)	13,962
TZP treatment	LDL change decreased by 10% on intensification to insulin	13,839
TZP treatment	SBP change increased by 10%	13,826
SEMA treatment	LDL change increased by 10% on intensification to insulin	13,783
SEMA treatment	LDL change decreased by 10% on intensification to insulin	13,770
SEMA treatment	HbA1c change increased by 10% on intensification to insulin	13,740
TZP treatment	BMI change increased by 10%	13,731
SEMA treatment	BMI follows UKPDS progression during treatment	13,655

TZP treatment	SBP change increased by 10% on intensification to insulin	13,600
SEMA treatment	Treatment costs increased by 10% in year 1	13,590
SEMA treatment	HDL change decreased by 10% on intensification to insulin	13,589
TZP treatment	HDL change decreased by 10%	13,550
SEMA treatment	HDL change decreased by 10%	13,548
SEMA treatment	SBP change increased by 10% on intensification to insulin	13,541
Cohort	Baseline race 100% Black	13,454
Cohort	Baseline race 100% White	13,454
Cohort	Baseline SBP decreased by 10%	13,440
Cohort	Baseline race 100% Indian	13,375
SEMA treatment	BMI change decreased by 10%	13,350
TZP treatment	BMI change decreased by 10% on intensification to insulin	13,290
SEMA treatment	HbA1c change decreased by 10% on intensification to insulin	13,178
TZP treatment	Heart rate constant during treatment	13,068
SEMA treatment	HbA1c change decreased by 10%	13,048
Cohort	Baseline duration of diabetes increased by 10%	13,026
Cohort	Baseline HbA1c increased by 10%	12,911
SEMA treatment	Treatment costs increased by 10% in years 2+	12,746
TZP treatment	HDL constant during treatment	12,703
SEMA treatment	QoL decrement on treatment year 1 decreased by 10%	12,394
SEMA treatment	Severe hypo rate increased by 10%	12,358
TZP treatment	Non-severe hypo rate decreased by 10%	12,149
TZP treatment	Treatment costs decreased by 10% in year 1	12,128

TZP treatment	HbA1c change increased by 10%	12,049
SEMA treatment	eGFR constant during treatment	11,927
TZP treatment	Severe hypo rate decreased by 10%	11,896
Country	Discount rate set to 0% per annum on costs and benefits	11,842
SEMA treatment	BMI constant after intensification to insulin	11,739
TZP treatment	Treatment costs decreased by 10% in years 2+	11,286
SEMA treatment	Non-severe hypo rate increased by 10%	11,207
TZP treatment	QoL decrement on insulin years 2+ decreased by 10%	10,784
TZP treatment	Treatment costs decreased by 10% in years 2+ of insulin treatment	10,689
SEMA treatment	QoL decrement on insulin years 2+ increased by 10%	10,674
SEMA treatment	Treatment costs decreased by 10% in years 2+ of insulin treatment	10,536
SEMA treatment	SBP follows UKPDS progression during treatment	9,377
TZP treatment	LDL constant during treatment	8,903
SEMA treatment	LDL constant after intensification to insulin	8,443
TZP treatment	SBP constant after intensification to insulin	6,349
TZP treatment	HbA1c constant during treatment, intensification after 4 years	3,153
TZP treatment	HbA1c constant after intensification to insulin	149

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HDL: high density lipoprotein cholesterol; IHD: ischaemic heart disease; LDL: low density lipoprotein cholesterol; QoL: quality of life; SEMA: semaglutide; SBP; systolic blood pressure; TZP: tirzepatide.

ICERs for tirzepatide 10 mg versus semaglutide 1.0 mg were below £20,000 per QALY gained for 224 out of 232 one-way sensitivity analyses performed. There were two scenarios where semaglutide 1.0 mg improved QALYs and cost less than tirzepatide 10 mg, both of which involved substantial changes to the HbA1c profile to favour semaglutide:

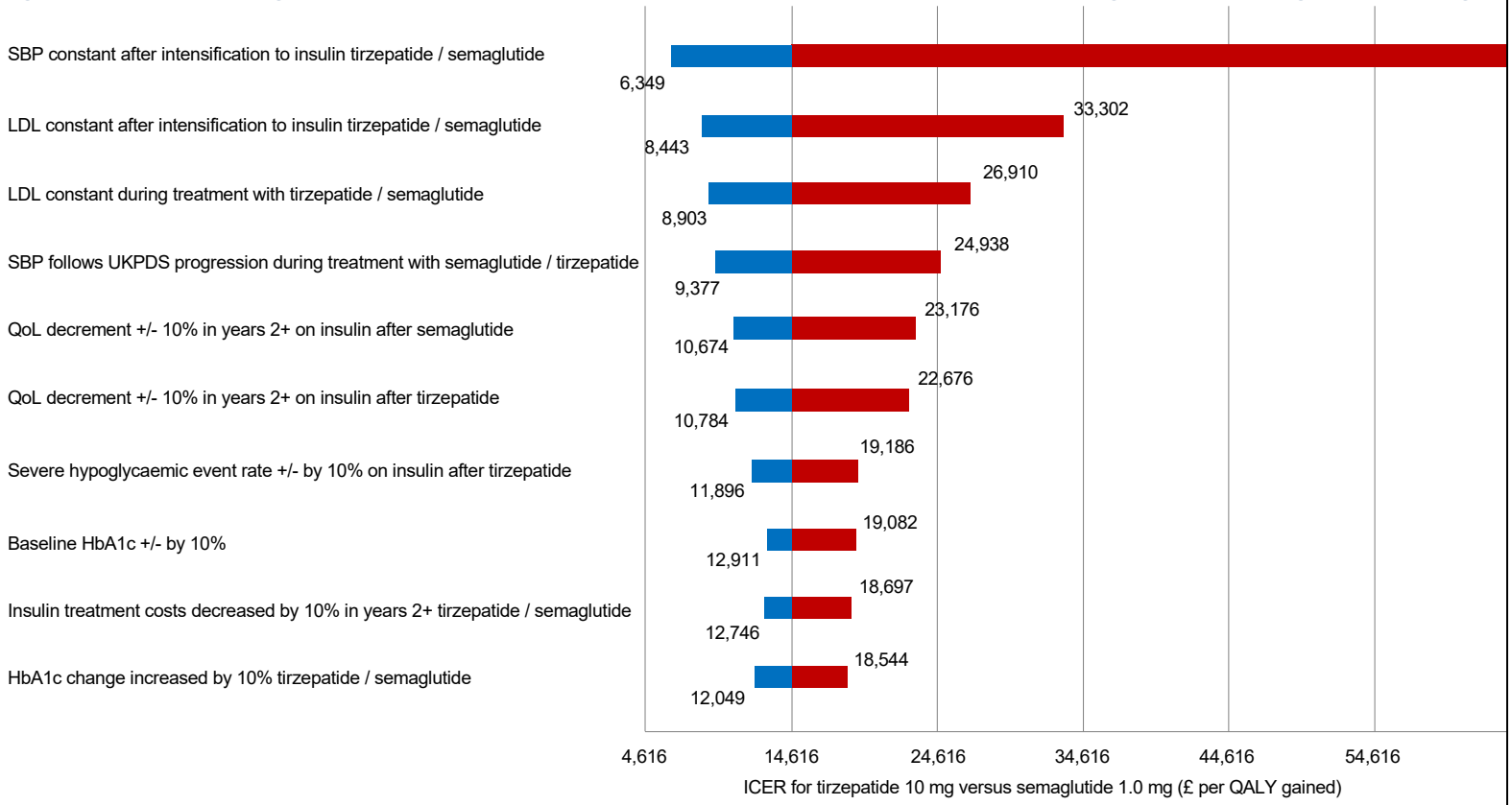
- In the sensitivity analysis where HbA1c was held constant in the semaglutide arm following intensification to insulin therapy

	(whereas HbA1c increased over time in the tirzepatide arm according to the UKPDS OM2 progression equation), there was a large HbA1c benefit for semaglutide from year 10 to year 50 of the simulation leading to improved clinical outcomes • Similarly, in the sensitivity analysis where HbA1c was held constant at 6.1% during semaglutide treatment (and in the tirzepatide arm HbA1c increased according to the UKPDS OM2 progression equation), there was a large HbA1c benefit for semaglutide from year 2 to year 15 of the simulation leading to improved clinical outcomes High ICERs were observed when certain risk factors were held constant over time in the semaglutide 1.0 mg and allowed to increase over time in the tirzepatide 10 mg arm. These included: • In the analysis where SBP was held constant in the semaglutide 1.0 mg treatment arm following intensification to insulin therapy, there was a benefit of over 10 mmHg for semaglutide over approximately 45 years of the simulation leading to only a very small incremental QALY benefit for tirzepatide 10 mg and a high ICER (Figure 1). Incremental costs were a little more than in the base case because there were fewer complications in the semaglutide arm in this analysis due to the SBP benefit. This high ICER, assuming a persistent 10 mmHg benefit over decades after semaglutide treatment, is not a reflection of a possible clinical scenario but rather identifies the effect of stress testing this model input to extreme values. In contrast, holding SBP constant in the tirzepatide 10 mg treatment arm produced an ICER of £6,349 per QALY gained versus semaglutide 1.0 mg, driven by a very high QALY benefit for semaglutide, while the incremental costs were also a little lower than in the base case due to complications avoided in the tirzepatide arm due to the large SBP benefit. • A similar analysis holding LDL constant over time in the semaglutide 1.0 mg treatment arm produced an ICER of approximately £33,302 per QALY gained, due to the persistent LDL benefit for semaglutide over 40 years of the simulation. When LDL was held constant in the tirzepatide 10 mg treatment arm following insulin intensification, the ICER was £8,443 per QALY gained. • Holding LDL constant during treatment in the semaglutide 1.0 mg arm whilst LDL increased in the tirzepatide arm according to the UKPDS OM2 progression equation led to notably lower LDL on semaglutide for the first 10 years of the simulation, leading to an ICER of approximately £26,910 per QALY gained. The corresponding approach in the tirzepatide 10 mg arm produced an ICER of £8,903 per QALY gained. • When SBP was held constant in the semaglutide arm but progressed according to the UKPDS OM2 equation in the tirzepatide arm during treatment, the notable difference in SBP levels led to a smaller incremental QALY benefit for tirzepatide and an ICER of £24,938 per QALY gained. In the corresponding analysis (where SBP was constant on tirzepatide and increased on semaglutide), the ICER was £9,377 per QALY gained. • When the disutility associated with BMI in years 2+ of insulin treatment was decreased by 10% in the semaglutide treatment arm or increased by 10% in the tirzepatide treatment arm, the ICERs for tirzepatide versus semaglutide was around	

£23,000 per QALY gained. Correspondingly, when the same disutility was increased by 10% in the semaglutide arm or decreased in the tirzepatide arm, the ICERs were approximately £10,700 per QALY gained.

All other ICERs in the one-way sensitivity analysis were less than £20,000 per QALY gained (Table 5).

Figure 1: Tornado diagram of the 10 most influential input parameters (tirzepatide 10 mg versus semaglutide 1.0 mg)



Abbreviations: HbA1c: glycated haemoglobin; ICER: incremental cost effectiveness ratio; LDL: low density lipoprotein; QALY: quality-adjusted life year; QoL: quality of life; SBP: systolic blood pressure; UKPDS: UK Prospective Diabetes Study.

3

A scenario analysis based on direct head-to-head results against semaglutide from SURPASS-2

In response to the request, a scenario analysis using cohort characteristics and treatment effects from the SURPASS-2 trial was performed with the results summarized in Table 6. Long-term projections with the PRIME T2D Model showed that all three doses of tirzepatide were associated with improvements in life expectancy and quality-adjusted life expectancy versus semaglutide 1.0 mg based on the results of the SURPASS-2 trial. For all three doses of tirzepatide, direct costs were higher than with semaglutide 1.0 mg leading to incremental cost-effectiveness ratios (ICERs) ranging from £12,019 to £14,096 per QALY gained (Table 6). ICERs remained relatively stable across all three doses of tirzepatide because increases in incremental costs with increasing doses was balanced by improvements in effectiveness (QALYs) relative to semaglutide 1.0 mg. Evaluation of net health benefit (NHB) assuming a willingness to pay of £20,000 per QALY gained showed tirzepatide 10 mg to be associated with the greatest benefit (0.037 QALYs) over semaglutide 1.0 mg.

Table 6: Summary of SURPASS-2 scenario analysis results for tirzepatide 5, 10 and 15 mg versus semaglutide 1.0 mg

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Semaglutide 1.0 mg	[redacted]	14.993	9.919	--	--	--	--	--
Tirzepatide 5 mg	[redacted]	15.016	9.960	579	0.023	0.041	14,096	0.012
Tirzepatide 10 mg	[redacted]	15.039	10.010	1,103	0.046	0.092	12,019	0.037
Tirzepatide 15 mg	[redacted]	15.048	10.036	1,640	0.055	0.117	14,013	0.035

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * pairwise comparison of tirzepatide versus comparator.

Thank you for providing this scenario analysis. To increase understanding of this scenario analysis, it might be helpful to provide an overview of input parameters that were modified for this scenario (as well as the updated parameter values).

4

Sensitivity analyses around the model averaging approach used to predict the risk of micro- and macrovascular complications

In response to the request, a scenario analysis where UKPDS OM2 risk equations only were used (instead of model averaging) was performed with the results summarized in Table 7. In this scenario analysis, there was a marginally lower risk of diabetes-related

The scenario analysis where UKPDS OM2 risk equations only were used (instead of model averaging) has a minor

complications in general compared with the base case simulation of tirzepatide 10 mg versus semaglutide 1.0 mg. This led to slightly higher overall estimates of life expectancy and quality-adjusted life expectancy in the scenario analysis. Total direct costs were comparable between the analyses as the increased life expectancy (the associated costs of living longer in the simulation) in the scenario analysis off-set the reduced cost of diabetes-related complications.

In the scenario analysis, tirzepatide 10 mg was still associated with improvements in life expectancy and quality-adjusted life expectancy versus semaglutide 1.0 mg, although the benefits were marginally smaller than in the base case analysis (Table 7). Incremental costs with tirzepatide 10 mg versus semaglutide 1.0 mg were comparable with the base case analysis leading to an ICER of £15,521 in the scenario analysis, which is comparable with the base case (£14,616 per QALY gained).

Table 7: Summary of scenario analysis using only UKPDS risk equations results for tirzepatide 10 mg versus semaglutide 1.0 mg

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.439	8.917	--	--	--	--	--
Semaglutide 1.0 mg	[redacted]	13.396	8.830	1,355	0.043	0.087	15,521	0.020
Base case results for comparison								
Tirzepatide 10 mg	[redacted]	*13.155*	*8.768*	--	--	--	--	--
Semaglutide 1.0 mg	[redacted]	*13.096*	*8.673*	*1,393*	*0.059*	*0.095*	*14,616*	*0.026*

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB is calculated assuming a willingness to pay of £20,000 per QALY gained.

impact on the estimated ICER. This is reassuring to the EAG. Ideally, a scenario analysis including the BRAVO model would also have been provided (without model averaging), as both models are used in the model averaging approach.

5

Scenario analysis in which GLP 1 RAs and tirzepatide are continued (while adding insulin) when intensifying treatment

In response to the request, a scenario analysis where GLP-1 receptor agonist therapy (or tirzepatide) was continued after the initiation of basal insulin was performed with the results summarized in Table 8. The following assumptions were used in this scenario analysis:

- Patients would intensify therapy by adding basal insulin to their existing regimen when HbA1c reached 7.5% or higher. The initiation of basal insulin was associated with a reduction in HbA1c of 0.84% based on the formula published by Willis et al.

Thank you for providing this scenario analysis, adding continuation with tirzepatide or GLP-1 receptor agonist after the initiation of basal insulin, when HbA1c reached 7.5% for tirzepatide and the comparator respectively.

(2017).[1] Risk factor progressions were aligned with the EAG preferred base case assumptions during therapy with GLP-1 receptor agonist plus basal insulin therapy (systolic blood pressure and body mass index remained constant and other risk factors followed UKPDS OM2 progression curves).

- When HbA1c reached 7.5% for a second time, patients intensified to basal bolus therapy and GLP-1 receptor agonist (or tirzepatide) was stopped. On this second intensification, HbA1c was assumed to be reduced by 0.24% (Willi *et al.* 2017) and all other risk factors returned to baseline levels. All risk factors were assumed to follow UKPDS OM2 progression curves for the remainder of the simulation.

In this scenario analysis, tirzepatide 10 mg was associated with improvements in life expectancy and quality-adjusted life expectancy versus semaglutide 1.0 mg (Table 8). Higher incremental costs with tirzepatide 10 mg versus semaglutide 1.0 mg led to an ICER of £14,720 in this scenario analysis, which is comparable with the base case.

Table 8: Summary of continued GLP-1 receptor agonist treatment scenario analysis results for tirzepatide 10 mg versus semaglutide 1.0 mg

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.211	8.891	--	--	--	--	--
Semaglutide 1.0 mg	[redacted]	13.125	8.766	1,838	0.086	0.125	14,720	0.033

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator. NHB is calculated assuming a willingness to pay of £20,000 per QALY gained.

It is however unclear to the EAG how treatment effectiveness was modelled in this scenario, e.g. whether treatment effectiveness was based on the NMA (or only SURPASS-2) and what the company's assumptions regarding treatment effectiveness of continuation with tirzepatide or GLP-1 receptor agonist.

6

Using a baseline utility value that is lower than the utility score for the general population at the same age

The committee requested a scenario analysis using a baseline utility value that is lower than the utility score for the general population at the same age. In response to the request, a scenario analysis using a lower baseline utility than in the submitted base case was performed with the results summarized in Table 9, Table 10 and Table 11. There are a few points to note with respect to this scenario analysis:

- The EAG preferred base case scenario uses an age-adjusted approach to the evaluation of quality-adjusted life expectancy based on the publication by Ara and Brazier (2010).[2] This approach uses a regression function to define baseline utility

Thank you for providing this scenario analysis, it is however unclear to the EAG why the utility value of 0.772 (mentioned in ACD section 3.15) was not used by the company in this scenario as

based on age and gender and incorporates the impact on quality of life with selected complications (macrovascular complications). It is therefore not possible to adjust the baseline utility with this age-adjusted approach, and an additive approach to combining utilities had to be used instead for the lower baseline utility scenario analysis.

- The Ara and Brazier age-adjusted approach suggested by the EAG does not fully capture the benefits of complications avoided (with more efficacious treatments) and, as a result, ICERs for tirzepatide are higher with the age-adjusted approach than with an additive approach to combining utilities (as the latter captures the quality of life impact of all complications modelled), regardless of the specific baseline utility value used in the latter approach.
- Changing the baseline utility has a very modest impact on cost-effectiveness as, essentially, the change is the same in both treatment and incremental quality-adjusted life expectancy remains largely unchanged. The only difference in incremental outcomes is associated with the survival benefit of more effective interventions over less effective comparators.
- For the scenario analysis, a baseline utility value of 0.785 for type 2 diabetes with no complications based on Clarke et al. was used.[3] This value is lower than the value of 0.815 used in previous health economic evaluations performed by NICE and used in the original submission on tirzepatide, which was based on the data reported by Alva et al.[4] It is perhaps noteworthy that a recent systematic review by Redenz *et al.* reported a utility of 0.815 (95% confidence interval 0.808-0.823) based on pooled data from 5-level version of EQ-5D studies for patients with T2D and no complications.[5] The pooled estimate was lower with the 3-level version of the EQ-5D instrument. The authors concluded that, in comparison with direct elicitation methods, the 5-level EQ-5D showed the best performance among the instruments evaluated.

In the scenario analysis, projections with the PRIME T2D Model over a 50-year time horizon showed that all three doses of tirzepatide were associated with improvements in quality-adjusted life expectancy versus all comparators evaluated. Tirzepatide 5 mg was dominant to liraglutide 1.8 mg and was associated with ICERs ranging between £4,792 to £15,898 per QALY gained (Table 9). Tirzepatide 10 mg was associated with ICERs between £1,576 and £13,902 per QALY gained (Table 10). Tirzepatide 15 mg was associated with ICERs between £3,765 and £13,488 per QALY gained versus comparators (Table 11).

Table 9: Summary of lower baseline utility (0.785) scenario analysis results for tirzepatide 5 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	9.014	--	--	--	--	--

baseline utility. This appears to be consistent with committee preferences "It concluded that it preferred to use the lower baseline utility value identified by the EAG" (ACD section 3.15)

Dulaglutide 1.5 mg	[redacted]	13.063	8.910	705	0.059	0.104	6,792	0.069
Dulaglutide 3.0 mg	[redacted]	13.076	8.932	644	0.046	0.082	7,900	0.049
Dulaglutide 4.5 mg	[redacted]	13.092	8.954	628	0.030	0.060	10,495	0.028
Semaglutide 0.5 mg	[redacted]	13.075	8.929	682	0.047	0.085	8,059	0.051
Semaglutide 1.0 mg	[redacted]	13.096	8.969	708	0.026	0.045	15,898	0.009
Oral semaglutide 7 mg	[redacted]	13.049	8.889	742	0.073	0.125	5,959	0.087
Oral semaglutide 14 mg	[redacted]	13.074	8.938	719	0.048	0.076	9,444	0.040
Liraglutide 1.2 mg	[redacted]	13.032	8.874	672	0.090	0.140	4,792	0.107
Liraglutide 1.8 mg	[redacted]	13.054	8.895	-409	0.068	0.119	Dominant	0.140

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 10: Summary of lower baseline utility (0.785) scenario analysis results for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	9.070	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.910	1,389	0.092	0.159	8,715	0.090
Dulaglutide 3.0 mg	[redacted]	13.076	8.932	1,329	0.079	0.137	9,685	0.071
Dulaglutide 4.5 mg	[redacted]	13.092	8.954	1,312	0.063	0.115	11,367	0.050
Semaglutide 0.5 mg	[redacted]	13.075	8.929	1,367	0.080	0.140	9,742	0.072
Semaglutide 1.0 mg	[redacted]	13.096	8.969	1,393	0.059	0.100	13,902	0.031
Oral semaglutide 7 mg	[redacted]	13.049	8.889	1,427	0.106	0.180	7,918	0.109

Oral semaglutide 14 mg	[redacted]	13.074	8.938	1,403	0.081	0.132	10,652	0.062
Liraglutide 1.2 mg	[redacted]	13.032	8.874	1,356	0.123	0.196	6,926	0.128
Liraglutide 1.8 mg	[redacted]	13.054	8.895	276	0.101	0.175	1,576	0.161

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 11: Summary of lower baseline utility (0.785) scenario analysis results for tirzepatide 15 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)*	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.175	9.113	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.910	1,937	0.112	0.203	9,538	0.106
Dulaglutide 3.0 mg	[redacted]	13.076	8.932	1,877	0.099	0.181	10,375	0.087
Dulaglutide 4.5 mg	[redacted]	13.092	8.954	1,860	0.083	0.159	11,689	0.066
Semaglutide 0.5 mg	[redacted]	13.075	8.929	1,915	0.100	0.184	10,406	0.088
Semaglutide 1.0 mg	[redacted]	13.096	8.969	1,941	0.079	0.144	13,488	0.047
Oral semaglutide 7 mg	[redacted]	13.049	8.889	1,975	0.126	0.224	8,820	0.125
Oral semaglutide 14 mg	[redacted]	13.074	8.938	1,951	0.101	0.175	11,122	0.078
Liraglutide 1.2 mg	[redacted]	13.032	8.874	1,904	0.143	0.240	7,950	0.144
Liraglutide 1.8 mg	[redacted]	13.054	8.895	824	0.121	0.219	3,765	0.178

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator.

7	**Using the multiplicative method to combine disutilities in the base case or provide a rationale for why a multiplicative approach is not appropriate** A multiplicative approach is not appropriate for this appraisal because (1) it does not align with approved NICE assessments for other incretin therapies, and (2) there is limited evidence to support the use of a multiplicative approach in T2D. The utilities used in the present modelling analysis were originally derived as additive utilities using the EQ-5D instrument (comparing the quality of life utility associated with living with a complication versus without). All of the utilities/disutilities used were published as additive utilities (i.e. occurrence of complication x is associated with a quality of life decrement of y; not a multiplicative reduction of y% in utility score) therefore retaining consistency in our modelling approach. Had the utilities been derived for a multiplicative model, the resulting values would almost certainly be different than the additive values published and used in the present analysis. Previously in diabetes the additive approach for combining utilities has predominated to the extent where it could be considered the standard approach in T2D modelling. Recent NICE appraisals in diabetes have all use the additive approach including the 2022 update to the NICE T2D guideline (NG28) (Table 12). In fact, none of the health economic analyses in T2D available on the NICE website used a multiplicative approach to combine quality of life utilities. Furthermore, appraisals for other incretin therapies (TA664 and TA875) for weight management and obesity have also used the additive approach. The predominant use of the additive approach was described in the NICE appraisal of semaglutide for weight management and obesity (TA875, published 4 months ago in March 2023). In the committee papers, the Southampton EAG acknowledged the research by Gough et al. (2009) which concluded that HRQoL decrements associated with T2D and obesity showed no significant interaction and therefore could be assumed to be additive.[6] Additionally, studies by Sullivan et al. (2011) and Hayes et al. (2016) also reported multiple co-morbidities for diabetes, and considered that it was reasonable to treat co-morbidities as independent and add utility decrements.[7, 8] The EAG concluded that *"we agree with the company and consider it is reasonable to treat co-morbidities as independent and add utility decrements. In addition, we note that this approach was also taken in TA664."* **Table 12: Summary of NICE guideline and technology appraisal health economic analyses in diabetes, weight management and obesity that use and additive approach to combining quality of life utilities** **Example** | **Year** | **Title/URL** 1 | 2022 | Type 1 and 2 diabetes in adults: diagnosis and management. Economic modelling for periodontal treatment in adults with type 1 and type 2 diabetes. NICE guideline NG17, NG28. Economic model report	Thank you for providing this information. This is a matter of judgement, the EAG comments from the EAG report are still applicable and the EAG still believes that a scenario analysis, using the multiplicative approach is informative.

		www.nice.org.uk/guidance/ng28/evidence/economic-model-report-on-periodontal-treatment-in-adults-with-type-1-and-type-2-diabetes-pdf-11131191037
2	2022	Type 2 diabetes in adults: management. Economic modelling for continuous glucose monitoring in adults with type 2 diabetes. Economic model report
		www.nice.org.uk/guidance/ng28/evidence/economic-model-report-pdf-11013295213
3	2022	Type 2 diabetes in adults: management (update). Health economic model report [NG28]
		www.nice.org.uk/guidance/ng28/evidence/health-economic-model-report-pdf-10959500845/
4	2013	Dapagliflozin in combination therapy for treating type 2 diabetes. Technology appraisal guidance [TA288]
		https://www.nice.org.uk/guidance/ta288
5	2016	Dapagliflozin in triple therapy for treating type 2 diabetes. Technology appraisal guidance [TA418]
		https://www.nice.org.uk/guidance/ta418
6	2026	Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes
		https://www.nice.org.uk/guidance/ta390
7	2015	Empagliflozin in combination therapy for treating type 2 diabetes. Technology appraisal guidance [TA336]
		https://www.nice.org.uk/guidance/ta336
8	2023	Semaglutide for managing overweight and obesity. Technology appraisal guidance [TA875]
		https://www.nice.org.uk/guidance/ta875
9	2020	Liraglutide for managing overweight and obesity [TA664]
		https://www.nice.org.uk/guidance/TA664

The company acknowledges that NICE has recently changed its manual to state that the multiplicative approach is *"generally preferred"*. The published paper by Dawoud et al. explains the rationale for the change but the evidence underpinning this change is limited.[9] Whilst the paper states that the additive approach can lead to utility values close to zero, or even negative utility scores, this is not a valid concern with respect to the present diabetes modelling analysis or for diabetes models in general. This can be demonstrated by the extreme example of a simulated patient in the model with a history of two conditions experiencing three end-

stage complications (myocardial infarction, stroke and onset of blindness) in a single year (Table 13), when the annual utility score does not get close to zero even in such an unlikely scenario.

Table 13: Example additive utility calculation for a patient with a history of two comorbidities experiencing three complications in a given year of the modelling simulation

Health state / event	Utility / disutility	Title / URL
Utility with no complications	0.815	Baseline utility used in the original submission
Comorbidity 1	-0.108	History of heart failure
Comorbidity 2	-0.066	History of neuropathy
Event 1	-0.055	Myocardial infarction event
Event 2	-0.164	Stroke event
Event 3	-0.074	Onset of blindness
Total	**0.348**	**Utility score for the year with two comorbidities and three events**

At this moment in time, there is no evidence that would support the use of a multiplicative approach over an additive approach in T2D in terms of most accurately representing utilities for multiple comorbidities. As stated in the paper from Ara and Brazier 2017 publication for estimating HSUV for comorbidities: *"It is not known which of the additive and multiplicative methods would produce the most accurate estimates for more than two concurrent comorbidities... it seems likely that the multiplicative method might be the preferred method, but this is an area where additional research is justified."*[10] Therefore, there is still a considerable amount of research required to determine the appropriate methods when estimating additional comorbidities.

Given the clear precedent for the use of the additive approach (Table 12), supported by the conclusions of Gough et al. (2009), Sullivan et al. (2011) and Hayes et al. (2016), it would be premature to deviate to the multiplicative approach for the assessment of tirzepatide (and other new treatments in this therapeutic area) in the absence of evidence that the multiplicative approach is more accurate.[6-8] Moreover, it would create inconsistencies in terms of how new interventions are being assessed, particularly in light of NG28 in June, 2022 and TA875 in March, 2023, which are both of relevance to the assessment of tirzepatide.

8	**Cost-effectiveness results when analysis is run in CORE Diabetes Model and/or UKPDS OM2**	The EAG would like to applaud the company for this effort. According to the EAG,

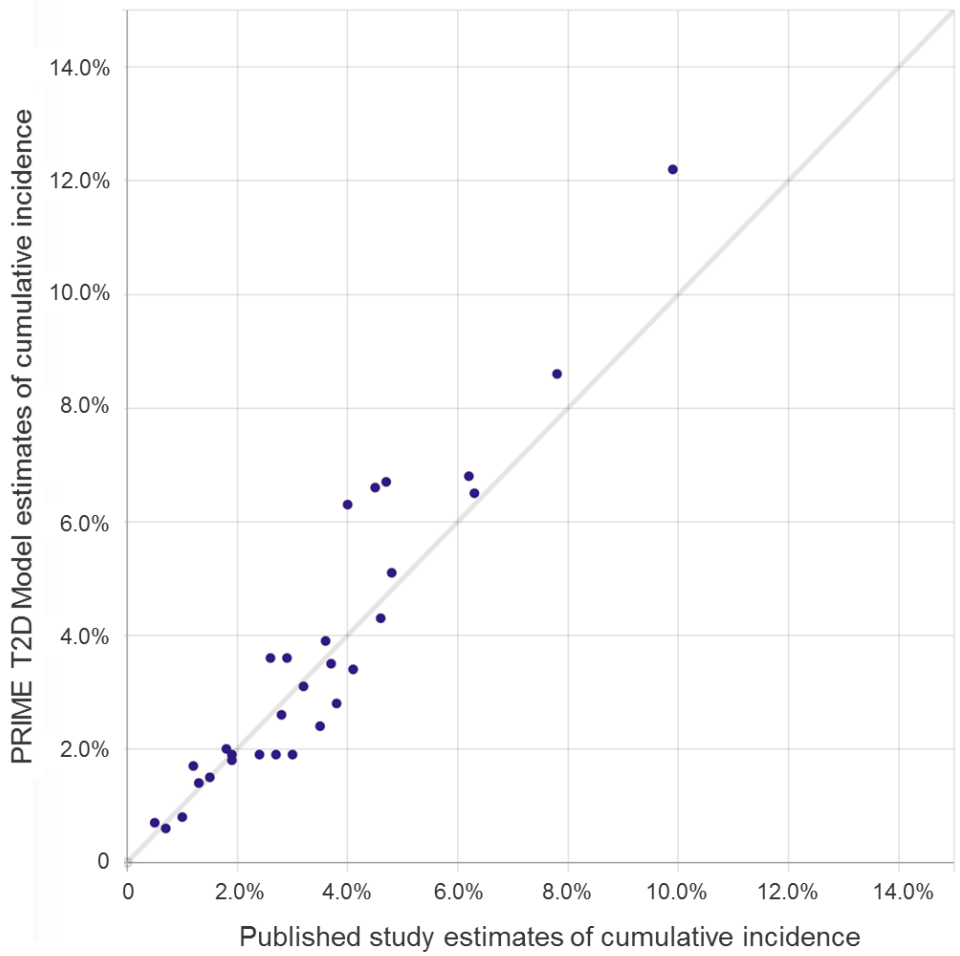
	The committee requested cost-effectiveness results from an analysis is run in CORE Diabetes Model (CDM) and/or UKPDS OM2. Please refer to the CDM report supplied as a standalone file alongside these responses.	this increased the credibility of the analyses provided in the CS. Nevertheless, some issues might warrant further clarification: - Considering Tables 10-15 of the additional file submitted by the company, it becomes clear that using the CORE diabetes model (compared with the PRIME model), in general resulted in lower absolute costs and (quality-adjusted) life years. Moreover, the incremental costs were typically larger while the incremental life years were typically smaller. In contrast the incremental quality-adjusted life years were typically larger. This finding (difference between incremental QALYs and LYs) would warrant further clarification by the company - The CORE model uses utility values instead of disutility values for certain health states where (e.g. history of MI, history of stroke etc.). the EAG noted that the utility values are comparable

		to the baseline utility – disutility in the PRIME model. It is, however, unclear to the EAG how quality of life was calculated in case of multiple complications. More specifically, how was the additive approach implemented and was it comparable to the PRIME model.
9	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B1b. The CS states that a de novo model was developed because *"Models developed prior to 2016, including UKPDS OM1 and OM2 and the IQVIA CORE Diabetes Model, have been shown to under predict CV benefits from the GLP-1 RA class in certain situations. One reason for this could be that models developed earlier than 2016 do not fully capture the benefits of reduced body weight as they tend to be based on cohorts using traditional therapies without any weight loss benefit."* This statement is supported by CS reference 140 (Shao et al., Diabetes Care 2020).** **Please provide evidence that the developed de novo model, specifically the current implementation as in the CS, has a better performance to predict complications (including cardiovascular events) compared with existing diabetes models.** ***Key response points*** • The PRIME T2D Model has a recent, published validation analysis that supports its ability to predict complications in real-life clinical studies [for clarity, this is the same version of the model used in the current submission and all validations were performed using model averaging], including CVOTs with GLP-1 receptor agonists (REWIND and LEADER), other CVOTs (EMPA-REG OUTCOME and DEVOTE), UK cohort studies (Shah et al. 2015)[11] and the Lipids in Diabetes Study (LDS)] as well as the ACCORD cardiovascular outcomes study.[12] This validation includes comparisons with UK cohort studies and cardiovascular outcomes trials with GLP-1 receptor agonists, which are both relevant to the current health economic evaluation (details are provided below). Validation scatterplots (below) also demonstrate that the PRIME T2D Model better predicts complications than the CORE Diabetes Model and the UKPDS OM2 for the EMPA-REG OUTCOME study with	Many thanks for providing additional evidence, together with the company's response to comment 17, this is supporting the predictive performance of the PRIME T2D model in general. The company considered multiple UK populations to compare with, including long term cohorts and cohorts with other GLP1 Ras. However, the applicability to this specific decision problem (i.e. for adults with T2D that is inadequately controlled with three or more antidiabetic agents) is uncertain according to the EAG (potentially given the unavailability of data to provide evidence of predictive

	predicted outcomes matching the published trial outcomes more closely (i.e. closer to the line of 'no difference').
	• Data presented at the Ninth Mount Hood Challenge indicated that the CORE Diabetes Model and the UKPDS OM2 provided mixed results in a validation analysis against CVOTs including EMPA-REG OUTCOME and CANVAS, with the authors noting that calibration was required to improve predictive accuracy.[13] The PRIME T2D Model has been shown to validate well against EMPA-REG OUTCOME without the need for any prior calibration (no validation against CANVAS has been performed to date).
	• The most recent published validation analysis for the CORE Diabetes Model was in 2014 and showed mixed results, with an overall root mean squared percentage error of 41.3% across all validation analyses (including type 1 and type 2 diabetes validations).[14] This analysis pre-dated validation against any GLP-1 receptor agonist trials. Although an equivalent metric for the PRIME T2D Model is not available, root mean squared deviations (RMSDs)* for all external validations were 3.7% or less, which is generally consistent with a closer match to the published data than that reported by McEwan *et al.* (2014).[14]
	• No single extensive validation analysis of the UKPDS OM2 has been published since Hayes et al. first described the model in 2013,[15] although there have been multiple publications describing single validation and/or calibration studies of the model (often against cohorts from other countries).[16-18] In 2022, Keng *et al.* published a validation of the UKPDS OM2 with over 10 years of follow up data from ASCEND (A Study of Cardiovascular Events in Diabetes), one of the largest trials in people with diabetes in the United Kingdom that followed participants from 2005 to 2017.[19] Keng *et al.* claimed that:
	  ○ The UKPDS OM2 overpredicted the risks of myocardial infarction, stroke, heart failure and death
	  ○ The performance of the UKPDS-OM2 was found to be poorer in older patients who received a diagnosis of diabetes at an older age
	  ○ Calibration of risk equations in the UKPDS-OM2 or estimation of new risk equations is needed to predict long-term outcomes for clinical or economic analyses in contemporary cohorts such as in ASCEND
	** Root mean squared deviation (RMSDs) is provided as a measure of difference between the modelling results and observed outcomes. It can be considered to reflect the average difference between the cumulative incidence of complications predicted by the model and the cumulative incidence of complications observed in the study. The root mean squared methodology is utilised to avoid positive and negative differences in cumulative incidence cancelling each other out and providing an underestimate of the differences between modelled and observed outcomes (that could occur if only mean differences were reported).*
	
	Additional detail
		performance in this specific population).

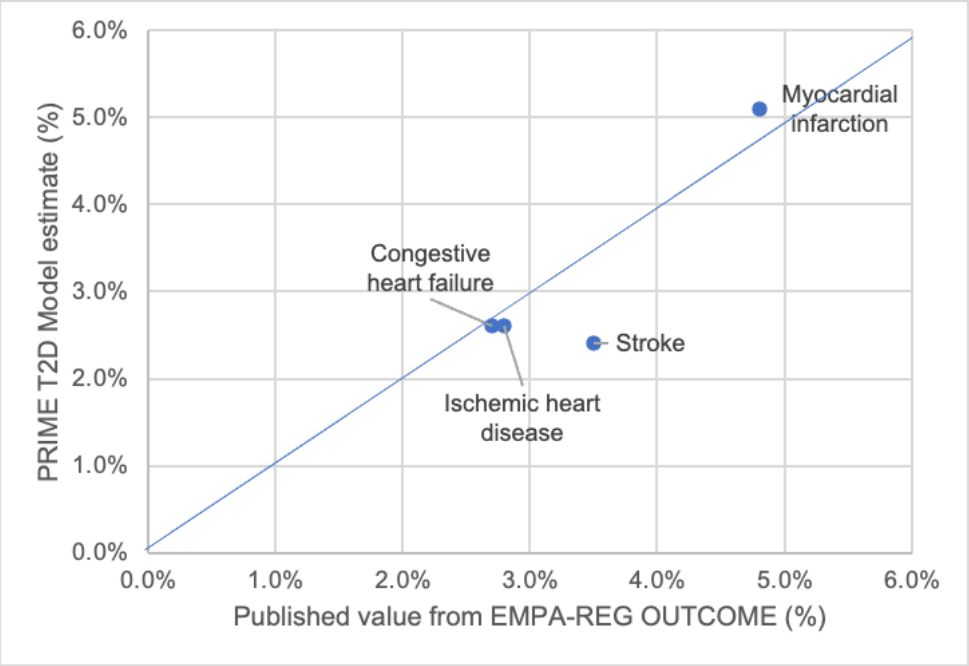
	The overall validation of the PRIME T2D Model has been published and was provided as part of the original submission in the model technical report.[12] The validation analysis compared projections using the PRIME T2D Model with published results from a broad range of studies in T2D populations, including UK cohort studies, CVOTs and studies in South East Asian populations. All root mean squared deviation (RMSD) values for the differences between published values and modelled outcomes for internal validations (against published studies used to develop the model) were 1.1% or less and all external validation RMSDs were 3.7% or less. An overall validation scatterplot is provided in Figure 2.	

Figure 2: Scatterplot of the PRIME T2D Model overall validation analysis



	Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. ***Describe validation analyses versus GLP-1 CVOTs*** The PRIME T2D Model has been validated against cardiovascular outcomes trials, including EMPA-REG OUTCOME (empagliflozin), REWIND (dulaglutide) and LEADER (liraglutide), using the model averaging approach, and been shown to compare well to published outcomes.[12] In the PRIME T2D Model validation against the intervention arm from the EMPA-REG OUTCOME trial,[20] the root mean squared difference for four endpoints in the active treatment arm was 0.7%, with the PRIME T2D Model generally matching published outcomes well, although slightly underestimating the risk of stroke (see Figure 3 and the PRIME T2D Model Technical Report in the original submission).	

Figure 3: PRIME T2D Model validation scatterplot for the EMPA-REG OUTCOME study

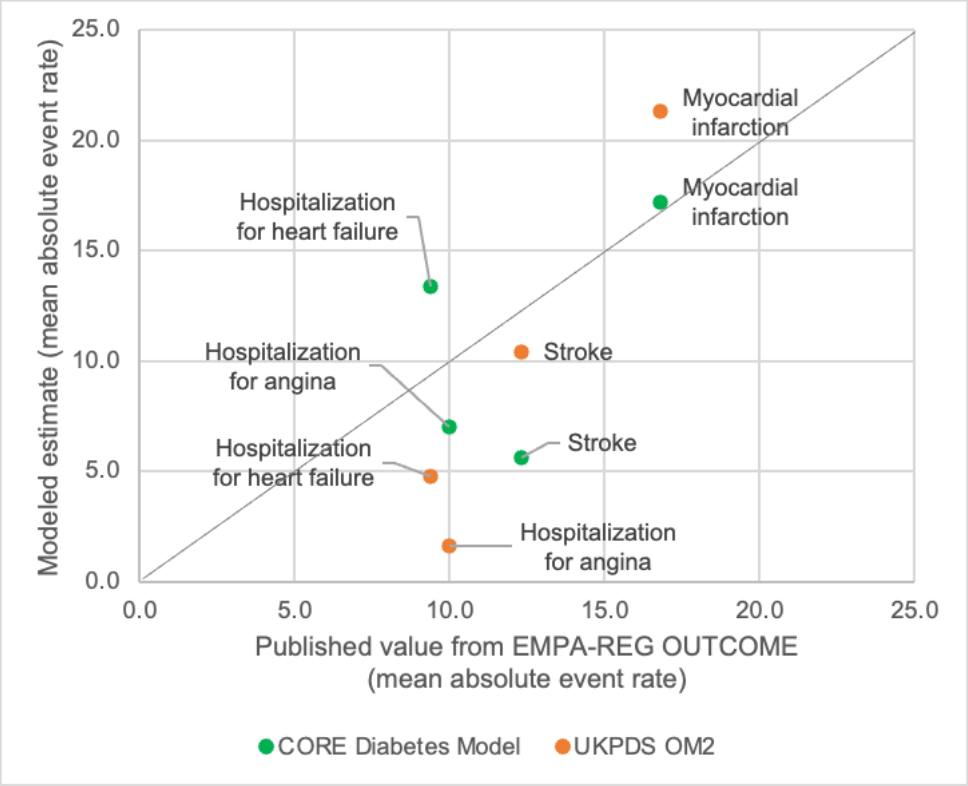


Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

As outlined previously in the original submission and in the response to clarification questions, the CORE Diabetes Model and UKPDS OM2 performed poorly in validations against cardiovascular outcomes trials at the Ninth Mount Hood Challenge Meeting published in 2020.[13] Prior to calibration the CORE Diabetes Model underpredicted the risk of stroke by around 54% and the UKPDS OM2 overpredicted the risk of myocardial infarction by 27% in the active treatment arm of EMPA-REG (Figure 4). Without

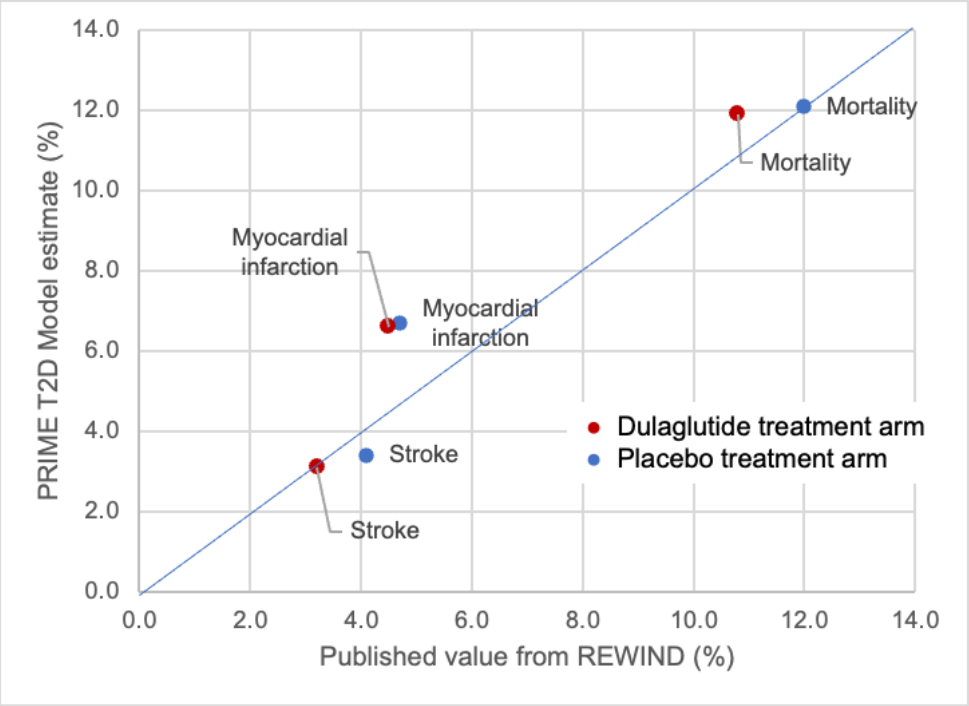
appropriate calibration, there is a risk that these models may under/overestimate the risk of diabetes-related complications in a cost-effectiveness evaluation, particularly when agents such as GLP-1 receptor agonists are involved that may alter cardiovascular risk profiles.

Figure 4: UKPDS OM2 and CORE Diabetes Model validation scatterplot for the EMPA-REG OUTCOME study



	Note: Each point on the graph represents mean absolute event rate estimate from the model and the corresponding published study value for validation. Values from the models are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. Crucially, at this moment in time, there are no published data that would allow the appropriate calibration of the UKPDS OM2 or CORE Diabetes Model (or any other model) for the present analysis of tirzepatide. The calibration of existing type 2 diabetes model with hazard ratios from CVOTs is a complex challenge with considerable potential to provide misleading results when comparing multiple interventions as recently summarized by Evans *et al.* (2023).[21] Main concerns focus on the heterogeneity of the trials, with different study durations, inclusion criteria, rescue medication protocols and endpoint definitions, which results in significant uncertainty when comparing two or more interventions evaluated in separate CVOTs, as robust adjustment for these differences is very challenging. This is compounded by differences in endpoint definitions in a given diabetes model (which need to match those in the CVOT to be suitable for calibration) and the challenge of double-counting treatment effects (the hazard ratios from CVOTs are typically not adjusted for improvements in conventional risk factors such as HbA1c). The use of unadjusted hazard ratios from multiple CVOTs in a long-term cost-effectiveness analysis has considerable potential to skew the outcomes if these challenges are not appropriately addressed. As outlined by Evans *et al.* it is likely that these challenges can only be overcome by combining patient-level data from CVOTs to prepare novel risk equations that can better model modern therapies for type 2 diabetes. However, at the present moment in time the best approach may be represented by using models that do not require calibration to the same extent that the CORE Diabetes Model and the UKPDS OM2 appear to. Validation evidence of the ability of the PRIME T2D Model to predict outcomes in populations treatment with GLP-1 receptor agonist therapy comes from the REWIND trial (as included in the original submission as part of the PRIME T2D Model Technical Report). REWIND was designed to assess the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control levels.[22] The randomized, controlled trial was conducted at 371 sites in 24 countries and recruited individuals aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes). For the validation analysis, the endpoints of MI (fatal and non-fatal), stroke (fatal and non-fatal) and death were included. Overall, the mean absolute differences between the published REWIND study values and the modelled values were 0.9% in the placebo arm and 1.1% in the dulaglutide arm (Figure 5). The RMSD was 1.2% in the placebo group and 1.4% in the dulaglutide group.	

Figure 5: PRIME T2D Model validation scatterplot for the REWIND study

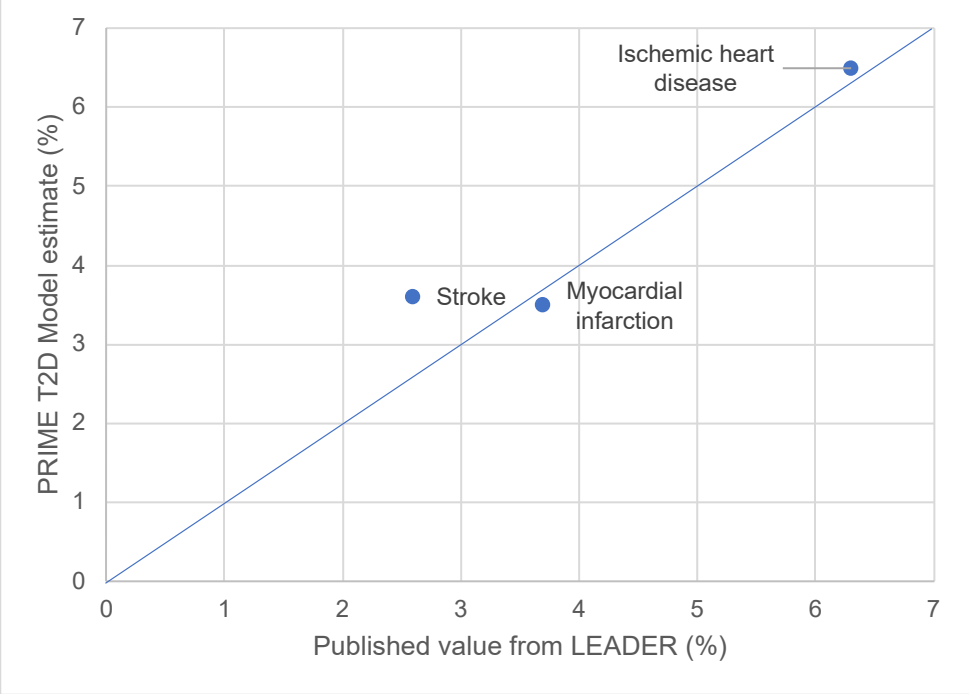


Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Additional evidence of the ability of the PRIME T2D Model to predict outcomes in populations treatment with GLP-1 receptor agonist therapy comes from the LEADER trial, which was designed to evaluate the effect of liraglutide on cardiovascular events when added to existing therapy for type 2 diabetes.[23] Median follow up was 3.8 years, a total of 9,340 patients were randomly allocated to

treatment with liraglutide or placebo, and the primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. For the validation analysis, the endpoints of MI (fatal and non-fatal), stroke (fatal and non-fatal) and ischaemic heart disease in the liraglutide treatment arm were included. Overall, the mean absolute difference between the published LEADER values and the modelled values was 0.5% and the RMSD was 0.6% (Figure 6).

Figure 6: PRIME T2D Model validation scatterplot for the LEADER study



	Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. Taken together, these data provide evidence that the PRIME T2D Model is capable of projecting plausible outcomes for populations with type 2 diabetes, including those treated with GLP-1 receptor agonists. Whilst an extensive head-to-head validation comparison with the UKPDS OM2 and CORE Diabetes Model are not possible in the time frame allowed for this response or without the consent/participation of the other modelling groups, the published evidence on validation against the EMPA-REG OUTCOME trial suggest there may be some limitations around the ability of the CORE Diabetes Model and UKPDS OM2 to project cardiovascular outcomes for a modern diabetes population without prior calibration. Moreover, given the heterogeneous nature of existing CVOT data and the fact that CVOT data on tirzepatide are not currently available, appropriate calibration is not possible within the context of the present submission. Please note that the validation endpoints considered above are focused on cardiovascular endpoints in line with published study data and represent the main contributor to complication costs in the health economic analysis. Validation of other endpoints is provided in the PRIME T2D Model Technical Report (provided as part of the original submission).	
10	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B4. In Appendix N it is described that *"a weighted model averaging approach was used in which each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between model cohort and derivation cohort, the larger the weight applied to the risk equation from the respective derivation cohort. The model averaging approach was then optimized by running validation simulations to evaluate predictive performance, measured using the Chi-squared statistic, and using a genetic algorithm to minimize Chi squared by adjusting distance coefficients for each characteristic."*** **Please justify why model averaging is preferred instead of selecting a single predictive model that best matches the decision problem (with alternative models in scenario analyses).** ***Key response points*** • Model averaging is used in the PRIME T2D Model to evaluate the risk of macrovascular complications and blindness. It is	No compelling new arguments and/or evidence were provided, hence the EAG comments from the original EAG report on model averaging (whether it should be preferred instead of selecting a single predictive model) are still applicable. See also response to comment 4 above.

designed to tailor the estimates of complication risk to best suit patient characteristics in every year of the simulation. In the present evaluation, risk equations from the UKPDS OM2 and the BRAVO Model were weighted, based on patient characteristics, to provide a combined estimate or complication risk based on the profile of each individual patient. The greater the similarity between simulated patients in the model and derivation cohort the larger the weight applied to the equation. Put most simply, low risk patients will rely more on UKPDS OM2 risk equations (derived from a low risk cohort) and high risk patients more on BRAVO risk equations (derived from a high risk cohort).[24]

- Model averaging in the PRIME T2D Model is supported by the published validation analysis demonstrating the model's ability to predict complications in real-life clinical studies (for clarity, this is the same version of the model used in the current submission and all validations were performed using model averaging).[12] This validation includes comparisons with UK cohort studies and cardiovascular outcomes trials with GLP-1 receptor agonists, which are both relevant to the current health economic evaluation.
- Model averaging offers the potential to increase the predictive power of disease models through the aggregation of multiple models derived from discreet data sets. One particular advantage of this approach is the ability to average out the influence of background risk modifiers, the impact of which are unknown within individual studies. Several publications, including three from academic research groups, have already demonstrated the benefit of model averaging within the healthcare sector.[25-28]
- Risk equations from the UKPDS OM1 and OM2 have formed the cornerstone of many health economic analyses performed by and submitted to NICE in recent years. However, there are question marks about the ability of the UKPDS OM2 risk equations to predict outcomes in CVOTs in type 2 diabetes populations with more advanced disease and receiving medications that were not available at the time of the UKPDS.[13]
- In the absence of risk equations from a long-term UK-based trial comparing tirzepatide with dulaglutide, semaglutide, oral semaglutide and liraglutide in patients with type 2 diabetes, a model averaging approach is preferable to the selection of a single risk model parameterised from a different population receiving different interventions than those relevant to the decision problem. This is because model averaging allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to the target population as well as to change over the time frame of the evaluation as simulated patients progress from having early to advanced disease (with corresponding changes to their risk profile).

Important considerations

In the PRIME T2D Model, weighted model averaging is used in the estimation of macrovascular complication risk (myocardial infarction, stroke, heart failure and ischemic heart disease), and in the risk of blindness. For each endpoint, each equation was

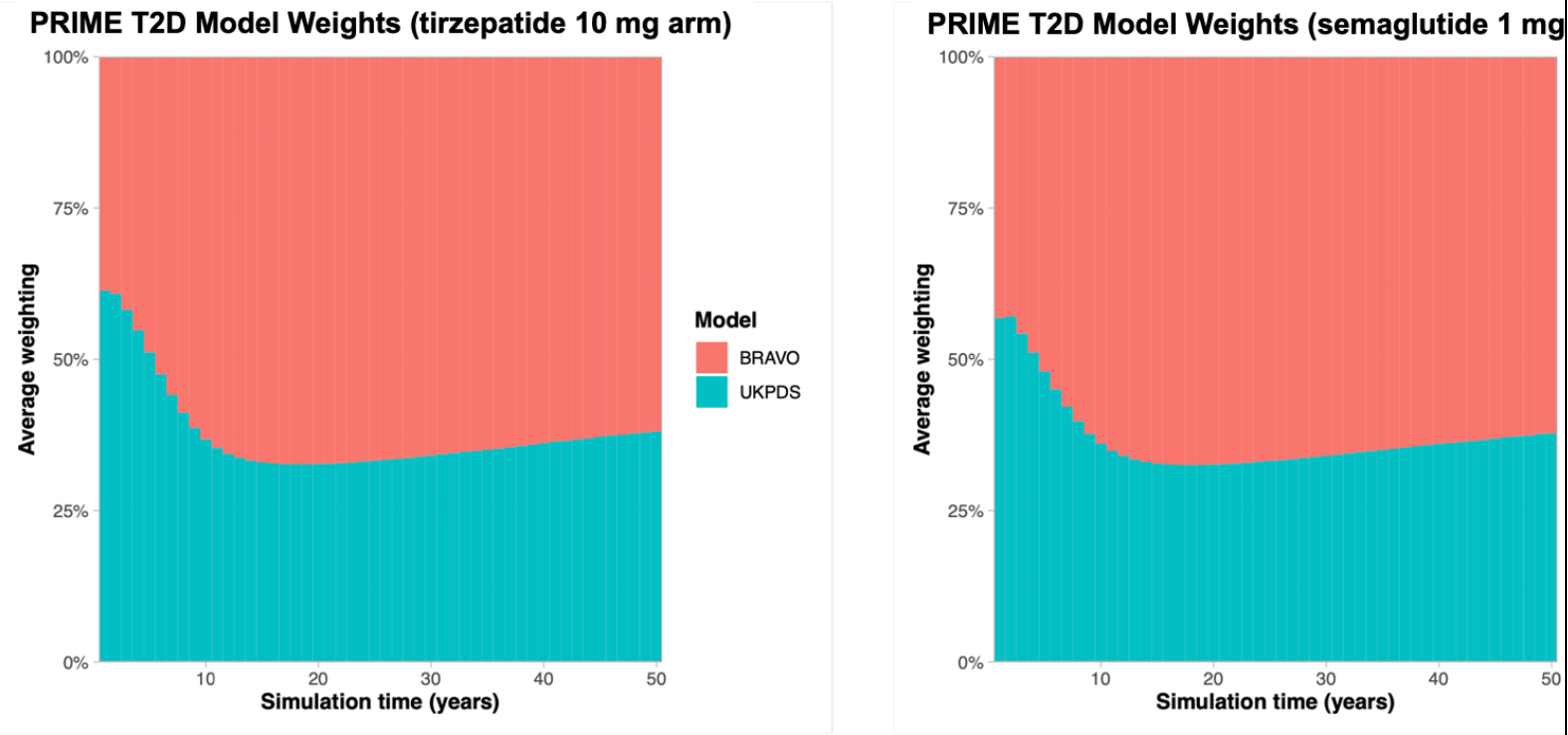
	assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between simulated patients in the model and derivation cohort the larger the weight applied to the equation. In each simulation, weights are calculated using the characteristics on a patient level. This means that different simulated patients will have different weighting of the risk equations in the simulation due to heterogeneity within a modelled cohort. In each year of the simulation, weighting of the risk equations is adjusted for age and duration of diabetes (but not other risk factors) for each patient, so the weighting of equations can change over time in any given simulation. The mathematical explication of the derivations of the weights each year is given in Section 4.3.3 of the PRIME T2D Model Technical Report, which was provided as part of the submission in the Appendices. As outlined in the PRIME T2D Model Technical Report, several different published equations that could plausibly be used to estimate the risk of CVD events in patients with type 2 diabetes were identified during the development of the model. Due to the variation between equations in the CVD risk factors considered, no consensus could be reached on the best equation(s) to use in the model; an observation that is in line with previous studies.[29, 30] At an advisory board meeting during model development, it was agreed that for simplicity, comprehension and acceptance by health technology associations, it was highlighted that a single approach should be used if possible (as opposed to offering a choice of risk equations for the model users). In this context, it was agreed that a model averaging approach could be used to combine the equations within a single framework, analogous to the approach previously used in the development of the PRIME T1D Model and in other modelling applications.[27, 28] The data sources used in the model averaging approach were selected based on consistency of endpoint definitions and feedback at the advisory board meeting. During the development of the PRIME Type 1 Diabetes Model, it was shown that a model averaging approach, when used to evaluate the risk of cardiovascular endpoints, was superior to any individual risk equations alone. The evidence indicated that risk equations performed well in validations against the derivation populations (or similar populations) but poorly in populations with different characteristics or risk profiles. This is the essential tenet of the model averaging approach: risk equations are weighted to match the risk profile of individual patients to avoid the situations where risk equations from low risk populations (e.g. UKPDS) are applied to high risk patients (e.g. patients in a simulation with long duration of diabetes, advanced disease, history of complications and elevated risk factors). Importantly, validation results to date with the PRIME T2D Model strongly support the weighted model averaging approach currently being used in type 2 diabetes health economic analyses. (See responses 9, 17 and Pollock et al. [2022][12])	

	The PRIME T2D Model is product and trial-agnostic and model averaging allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to a given cohort. In the absence of risk equations derived directly from the trial or trials in question, we consider this approach to be preferable to the selection of a single risk model parameterised from a different population receiving different interventions than that under investigation. In addition to addressing concerns around the structural uncertainty inherent in using a single risk model, the approach allows the model to adapt risk estimation to different populations at different stages of disease progression. Validation analysis indicates that the model averaging approach is capable of accurately reproducing outcomes from real-life clinical studies in a range of settings. The product and trial-agnostic nature of the PRIME T2D Model necessitates a model averaging approach, as it is the only solution that allows the model to derive weights on a per-patient basis to tailor the overall modelling approach to the cohort and supported by validation analysis. In addition to addressing concerns around the structural uncertainty inherent in using a single specific risk model, the approach allows the model to adapt risk estimation to difference populations at different stages of disease progression. The most prominent diabetes risk models (e.g. UKPDS OM1, UKPDS OM2, the IQVIA Core Diabetes Model, and the Cardiff Model) are all based — at least in part — on the UKPDS population, which was a population with newly-diagnosed type 2 diabetes, with the first patients enrolled in 1977, prior to the existence of statins, insulin analogues, SGLT-2 inhibitors, or GLP-1 receptor agonists. The incorporation, through a model averaging framework, of risk models derived from more modern populations of patients such as ACCORD (in the BRAVO model) allow the model to tailor the weighting of each model to each simulated patient. We believe this approach to be better suited to the decision problem than selecting a single model as the basis of the analysis and validation analysis indicates that the approach may be better suited to predicting long-term clinical outcomes in a modern type 2 diabetes population.	
11	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B4. In Appendix N it is described that *"a weighted model averaging approach was used in which each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between model cohort and derivation cohort, the larger the weight applied to the risk equation from the respective derivation cohort. The model averaging approach was then optimized by running validation simulations to evaluate predictive performance, measured using the Chi-squared statistic, and using a genetic algorithm to minimize Chi squared by adjusting distance coefficients for each characteristic."***	See response to comment 4 above

	Please provide scenario analyses selecting a single predictive model based on the best match of the derivation cohort to the decision problem. Please see response in Comment 4 above for details of the scenario analysis with a single predictive model.	
12	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B4. In Appendix N it is described that *"a weighted model averaging approach was used in which each equation was assigned a weight based on the similarity of mean cohort characteristics at baseline between the model cohort and the cohort used to derive the equation (derivation cohort). The greater the similarity between model cohort and derivation cohort, the larger the weight applied to the risk equation from the respective derivation cohort. The model averaging approach was then optimized by running validation simulations to evaluate predictive performance, measured using the Chi-squared statistic, and using a genetic algorithm to minimize Chi squared by adjusting distance coefficients for each characteristic."*** **To better understand the impact of model averaging, could the company provide the distribution of (normalized) model weights (across all simulated individuals) calculated at baseline.** In response the EAG request, a time series of model weights and a kernel density plot reflecting the number of patients with each weighting of risk equations at baseline are provided in Figure 7 and Figure 8 for the base case simulation of tirzepatide 10 mg versus semaglutide 1.0 mg. The time series shows that UKPDS OM2 risk equations were used predominantly over the first 4–5 years of the simulation before cohort characteristics were more closely matched to the BRAVO derivation population in subsequent years (Figure 7). As patients with more advanced disease experienced a greater mortality risk (and die sooner in the simulation), the weighting towards BRAVO risk equations gradually diminishes after year 15 of the simulation. The weights used in model averaging was comparable in both treatment arms. The distribution of model weights at baseline is represented by the kernel density plot shown in Figure 8, which is analogous to a histogram in certain respects as it can be read as a reflection of the number of patients with that weighting or risk equations. Therefore, the higher a peak on the graph, the more patients have that particular weight, read from the x-axis. For any given patient, the sum of weights will always equal one, so if a patient has a UKPDS OM2 weight of 0.7, the BRAVO weight must therefore be 0.3. The plot shows that the most common weighting at baseline was approximately 0.7 UKPDS OM2 plus 0.3 BRAVO. We can see this because the highest peak for UKPDS OM2 is around 0.7 (blue), suggesting that more patients had this weighting for UKPDS OM2 than any other weighting. These patients must also have had a BRAVO weight of 0.3, as the weights must sum to one, and this is reflected in the peak for BRAVO at around 0.3 (red). The fact that these weights must sum to one means that curves are direct, left-to-right mirror images on the kernel density plot (i.e. a peak at 0.7 in one curve must mean at peak at 0.3 in the other curve). We	According to the EAG he response to this question indicates that the sampling of events in individual patients is driven by a mixture of BRAVO and UKPDS (no model is dominating the predicted outcome risks). In other words, the PRIME T2D Model will simulate events according to a predicted risk that lies (roughly halfway) between the predictions of BRAVO and UKPDS. This may be undesirable if these two models substantially differ (e.g., in terms of included variables, or source population) and tend to generate predictions that exhibit little correlation within individuals. If this situation is likely, it may be helpful to consider a sensitivity analysis that uses a single model (rather than the weighting approach) for each endpoint (see also comments 4 and 10). The choice of an

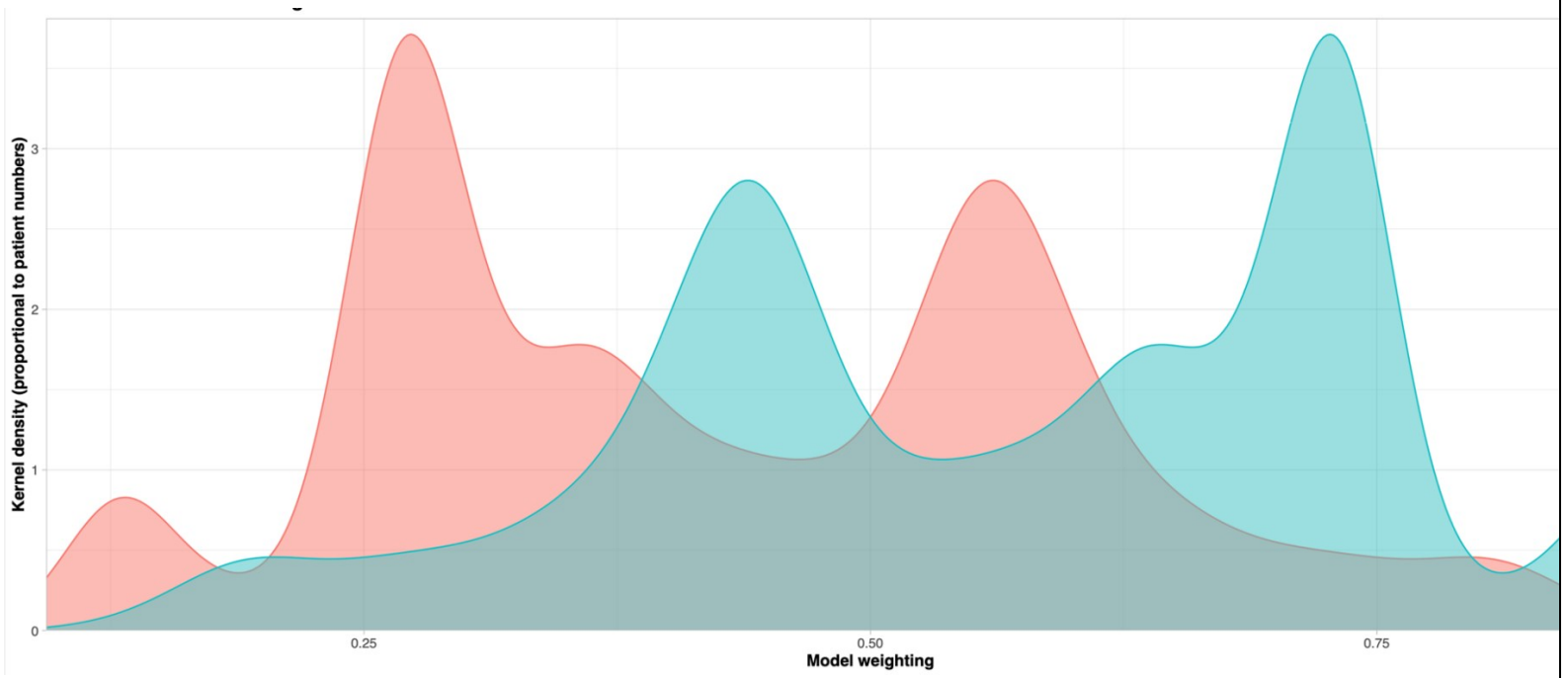
	can see this again with the UKPDS peak around 0.42, where we have a corresponding peak for BRAVO around 0.58, which was the second most common weighting: 0.42 UKPDS plus 0.58 BRAVO The distribution of model weights at baseline is a function of the simulated cohort characteristics (based on the THIN second intensification cohort) which are sampled to create individual patient profiles, the cohort characteristics of the UKPDS OM2 and BRAVO model derivation populations and the model averaging weighting algorithm as described by Pollock *et al.* (2022).[12] This corresponded to the UKPDS OM2 risk equations, on average, being weighted more than the BRAVO model risk equations at the start of the simulation.	appropriate risk model could be driven by various criteria, such as quality of the development study but also applicability of the model's predictions to the targeted setting/population (see also response to comment 13). Although the model averaging approach seems to have a good prediction of cadiovascular events, there are many elements that could affect the face validity and applicability of these equations, the PROBAST checklist could be used to facilitate selection of an appropriate equation.

Figure 7: Average weighting of risk equations over time for the comparison of tirzepatide 10 mg with semaglutide 1.0 mg



Note: Average model weighting over time in the simulated population is shown in blue for UKPDS OM2 risk equations and in red for BRAVO Model risk equations.

Figure 8: Kernel density plot of model weighting at baseline for the comparison of tirzepatide 10 mg with semaglutide 1.0 mg



Note: Kernel density (y-axis) reflects the number of patients in the simulated population with a given weighting (x-axis) at baseline and is shown in blue for UKPDS OM2 risk equations and in red for BRAVO Model risk equations.

13	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B5a and B5b. Appendix N provides descriptions for the generic PRIME T2D Model. However, the appropriateness of the selected predictive models to estimate the risk of complications in patients with type 2 diabetes is not justified (in detail). Nor is the applicability to the specific decision problem (as specified in the CS) justified.** **Please provide a justification that the risk models used, both individually and after model averaging, are appropriate to estimate the risk of complications in patients with type 2 diabetes and are applicable for the specific decision problem (as specified in the CS). Please provide this separately per risk model.** ***Key response points*** • The choice of the UKPDS OM2 risk model is well aligned with previous evaluations performed by NICE to inform the preparation of guidelines, including those analyses performed in 2015 and 2022 to inform NG28.[https://www.nice.org.uk/guidance/ng28/evidence/economic-model-report-on-periodontal-treatment-in-adults-with-type-1-and-type-2-diabetes-pdf-11131191037] The UKPDS OM2 risk equations are derived from a newly-diagnosed, UK-specific cohort with over 30 years of follow up and are widely used in diabetes modelling in general (c.f. the CORE Diabetes Model and the Cardiff Diabetes Model). The fact that the UKPDS risk equations are derived from type 2 diabetes patients in the UK is an important consideration. ○ However, the UKPDS OM2 was not used as a single risk model due to question marks around the ability of the of the model, without calibration, to predict outcomes for modern type 2 diabetes populations receiving interventions such as GLP-1 receptor agonists and with advanced disease (e.g. after second intensification of therapy), which is pertinent to the decision problem[13] ○ The UKPDS OM2 model does not have a risk equation for a revascularization endpoint, which may be an important consideration for a modern type 2 diabetes population[19] • The choice of the BRAVO model risk equations was made to complement the risk profile of the UKPDS OM2 risk equations. The models had comparable endpoints, but the BRAVO risk equations were derived from a cohort with a higher risk profile than the UKPDS population, specifically the ACCORD trial population of over 10,000 patients of whom approximately 35% had a previous cardiovascular event at baseline. The ACCORD cohort had a mean duration of diabetes of over 10 years at baseline, potentially making it better suited to modelling outcomes for patients with more advanced disease than the UKPDS dataset (Table 14). The fact that the BRAVO risk equations have been shown to reproduce outcomes for patients	Thank you for providing this information. As stated in the EAG report *"Appendix N of the CS provides descriptions for the generic PRIME T2D Model. However, the appropriateness of the selected predictive models to estimate the risk of complications in patients with T2D is not justified (in detail). Nor is the applicability to the specific decision problem (as specified in the CS) justified"* Moreover, also reiterating the EAG report: *"Unfortunately, the company did not provide justifications (requested in clarification question B5), that the risk models used, both individually and after model averaging, are appropriate to*

with more advanced disease (e.g. after second intensification) and with existing complication is an important consideration.[31, 32]

- The BRAVO model was not used as a single risk model due to question marks around its suitability for modelling patients with less advanced disease (and shorter duration of diabetes) and for modelling outcomes for a UK-based population. To the best of our knowledge, no validation data on the BRAVO model exists to address these questions (outside of the use of the risk equations in model averaging in the PRIME T2D Model)

Table 14: Summary of cohort characteristics for the THIN second intensification cohort, the UKPDS cohort and the ACCORD trial cohort

	THIN Second Intensification Cohort	UKPDS Cohort	ACCORD trial cohort (BRAVO)
Mean age (years)	63.95	52.0	62.2
Mean duration of diabetes (years)	8.5	0	10
Percentage male (%)	57	58.2	61
Percentage white (%)	82.4	82.7	64.5
Mean HbA1c (%)	7.5	6.7	8.3
Mean SBP (%)	134.44	135.5	136.3
Mean BMI (%)	30.7	28.8	32.2

Abbreviations: BMI: body mass index; HbA1c: glycated haemoglobin; SBP: systolic blood pressure; UKPDS: The United Kingdom Prospective Diabetes Study.

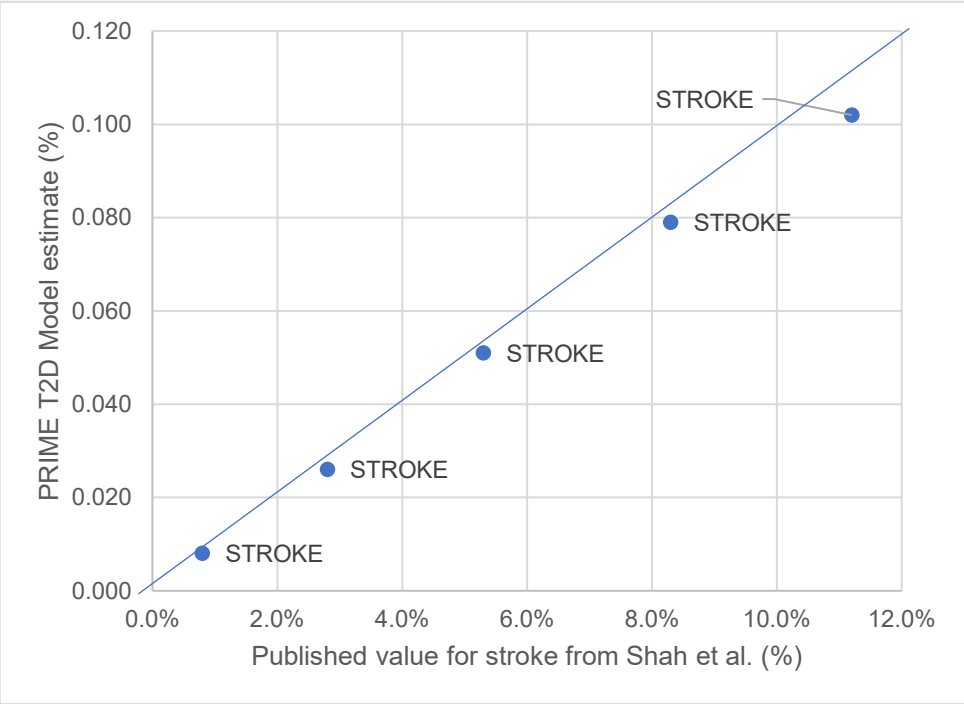
- The use of model averaging is a key aspect with respect to the selection of risk equations for inclusion in the modelling analysis. As outlined in the response to A.2.b, the use of risk equations in the PRIME T2D Model is weighted based on patient characteristics, to tailor the risk evaluation to individual simulated patients, such that low risk patients will rely more on UKPDS OM2 risk equations and high risk patients more on BRAVO risk equations. Validation analysis has shown that this approach is capable of reproducing outcomes accurately for CVOTs including EMPA-REG OUTCOME, REWIND (dulaglutide) and LEADER (liraglutide), as well as in a UK cohort study and in comparison with the UKPDS OM2 validation on the UK-based Lipids in Diabetes Study (Figure 9, Figure 10 and Figure 11)

estimate the risk of complications for the population as specified in the CS."

The EAG would have expected a description of the process to select the risk models (i.e. a systematic review) with selection criteria (and how the risk models did comply with those criteria) as well as a description of the applicability and performance of the risk models, separately per individual complication, for the population as specified in the CS.

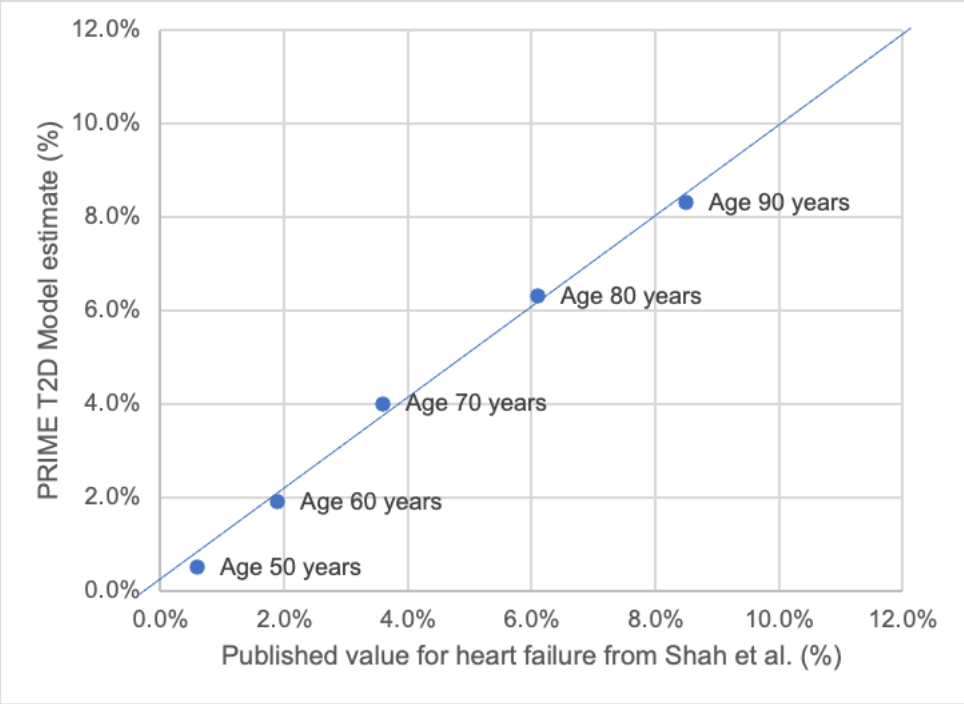
	• Extensive cross-validation analysis is not possible within the time frame of this submission and/or without the consent/participation of other modelling groups (specifically the UKPDS OM2 and BRAVO Model groups). However, the PRIME T2D Model approach of using risk equations from both UKPDS OM2 and BRAVO in a model averaging approach has been shown to reproduce real-life outcomes from UK cohort studies, GLP-1 receptor agonist studies and CVOTs (for endpoints including mortality, myocardial infarction, stroke, ischaemic heart disease and heart failure which have been shown to be important drivers of cost outcomes), which is not true of the UKPDS OM2 alone, the BRAVO Model or the CORE Diabetes Model. This makes the PRIME T2D Model the most suitable choice with respect to the decision problem in the present health economic evaluation **Additional detail** In 2015, Shah *et al*. published data from a cohort study of 1.9 million people in England with a median follow up time of 5.5 years designed to investigate the association between type 2 diabetes and incidence of cardiovascular disease.[11] The study used linked primary care, hospital admission, disease registry, and death certificate records from the CALIBER programme, which links data for people in England recorded in four electronic health data sources and included 34,198 people who had type 2 diabetes. Data for the endpoints of stroke (all) and heart failure were extracted for a validation analysis with the PRIME T2D Model. Other endpoints could not be included due to different endpoint definitions between the model and the Shah et al. analysis and, to match the published data, validations were performed by age (from 50 to 90 years). The PRIME T2D Model projections provided a close match to the published data with a RMSD of 3.7% across all 10 validation points (Figure 9 and Figure 10).	

Figure 9: PRIME T2D Model validation scatterplot for the stroke endpoint from the Shah *et al.* cohort study



Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Figure 10: PRIME T2D Model validation scatterplot for the heart failure endpoint from the Shah *et al.* cohort study

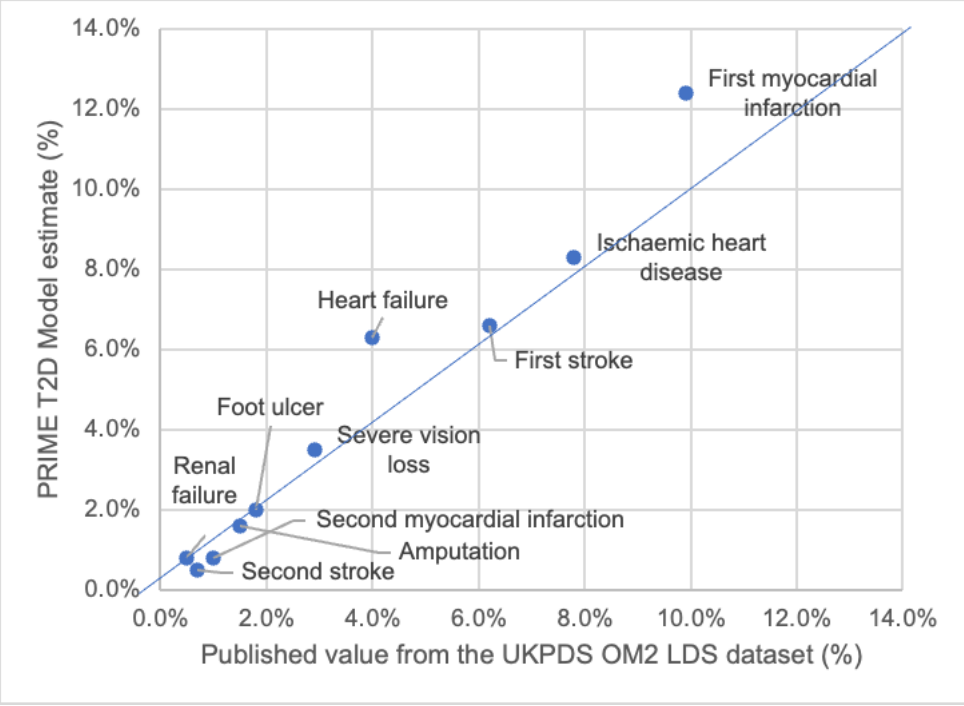


Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

The validation analysis of the UKPDS OM2 published by Hayes et al. in 2013 was based on data from the LDS, a prospective, randomised, placebo-controlled, clinical outcome trial with the principal objective of determining whether lipid reduction with a statin

(cerivastatin) or a fibrate (fenofibrate) could substantially reduce cardiovascular related morbidity and mortality in subjects with type 2 diabetes.[15] The trial recruited 4,191 with no previous coronary heart disease but the study was discontinued when cerivastatin was withdrawn.[33] Hayes *et al.* used the patient characteristics from 3,984 patients with non-missing risk factors from the LDS to make 10-year projections of outcomes with the UKPDS OM1 and OM2.[15] Validation analysis with the PRIME T2D Model was performed on the latter dataset (Figure 11). RMSD for all validation data points was 1.1%, which provides evidence that the PRIME T2D Model can project outcomes comparable with the UKPDS OM2, when the patient characteristics are similar to the UKPDS cohort (as was the case with the LDS cohort).

Figure 11: PRIME T2D Model validation scatterplot for the Lipids in Diabetes Study



	Note: Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.	
14	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B30. Further sensitivity analyses/clarification on existing sensitivity analyses would be desirable.** **Please provide sensitivity analysis for all input parameters individually and present results in tornado diagrams.** The requested one-way sensitivity analysis and tornado diagram are presented in the response in Comment 2 above.	See response to comment 2
15	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B32. Priority question: Further information on validation efforts would be desirable, focusing on this specific implementation of the PRIME T2D model.** **a) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.** The TECHnical VERification (TECH-VER) checklist is described as: "*a comprehensive checklist for the technical verification of decision analytical models, aiming to help identify model implementation errors and their root causes while improving the transparency and efficiency of the verification efforts.*"[34] Extensive verification and validation work has been performed on the PRIME T2D Model (as outlined in the PRIME T2D Model Technical Report) and this is summarized in the context of the TECH-VER checklist in Table 15. There is considerable overlap between the TECH-VER checklist and the internal and external validation analyses completed on the PRIME T2D Model. It should be noted that the TECH-VER checklist is not a standard, pre-defined list of tasks/checks that should be completed and summarized by a model reviewer. Instead, it consists of five verification stages, which have been addressed during the development, verification and validation of the PRIME T2D Model (Table 15): 1. Model input (pre-analysis) calculations. 2. Event/state calculations. 3. Result calculations.	The EAG is satisfied with the additional information provided on the technical verification of the PRIME model (also given the responses to comments 4, 8, 9 and 17).

4. Uncertainty analysis calculations.
5. Overall validation/other supplementary checks.

Table 15: Summary of the TECH-VER checklist domains and PRIME T2D Model verification and validation steps

TECH-VER checklist domain	PRIME T2D Model verification/validation step(s)
1. Model input (pre-analysis) calculations: this verification stage checks the pre-analysis calculations that yield direct model inputs (e.g. transition probabilities, cycle-based or event-based costs and utilities) from reference source inputs	All data included in the PRIME T2D Model were independently verified by an external third party during the internal validation step of model development (see below). This included checking all calculation steps as required. For the present analysis, model inputs (and calculation methods where relevant) were described in the original submission. All values entered into the model were cross-checked by a second researcher to match the source values.
2. Event/state calculations: this verification stage checks the event/state calculations that determine the patient flow/disease progression stage as well as the assignment of costs/QALYs or other relevant health/economic outcomes at a given cycle/time	All event/state calculations were independently verified during the internal validation step of model development (see below). Event/state calculations were further verified by test case analysis during the internal validation process.
3. Result calculations: this verification stage checks the result calculations that yield the undiscounted/discounted total and incremental results (e.g. costs, QALYs, other relevant health or economic outcomes and ICER)	All results calculations were independently verified during the internal validation step of model development (see below). Results calculations were further verified by test case analysis during the internal validation process and by one-way and multi-way sensitivity analysis testing internally at Ossian.
4. Uncertainty analysis: this verification stage checks the uncertainty analysis calculations (e.g. one-way, multi-way, probabilistic sensitivity, value of information and scenario analyses)	The approach to handling uncertainty in the PRIME T2D Model was decided at an advisory board meeting and has been independently reviewed through the NICE PRIMA review process. During model development, one-way and multi-way sensitivity analysis was performed on individual model inputs to confirm the

	expected effects in model outputs during internal validation (described as test case analysis, see below). One-way and multi-way sensitivity analysis as well as scenario analysis form part of every cost-effectiveness evaluation using the PRIME T2D Model, with all results reviewed for consistency and expected outcomes. Probabilistic sensitivity analysis was tested as part of the independent internal validation of the PRIME T2D Model. Value of information analysis is not applicable for the present evaluation and was not analysed during model development. Scenario analysis was tested as part of the independent internal validation of the model (described as test case analysis in the PRIME T2D Model Technical Report)	
5. Overall tests (validation or other supplementary tests): these tests include validation efforts from other sources and tests that are applied to the whole model and efforts that do not specifically belong to one of the compartmentalized modules	Multiple validation analyses have been performed with the PRIME T2D Model and are documented in the present response, in the PRIME T2D Model Technical Report and in the Pollock et al. (2022) publication describing the PRIME T2D Model[12]	

Internal validation: The PRIME T2D Model Technical Report (in Appendix N of the CS) provides an overview of the internal validation process that addresses much of the TECH-VER checklist. The internal validation of the PRIME T2D Model was performed by HealthMetrics Outcomes Research in Q2, 2020. The validation process took the form of a code audit and followed the procedures outlined below:

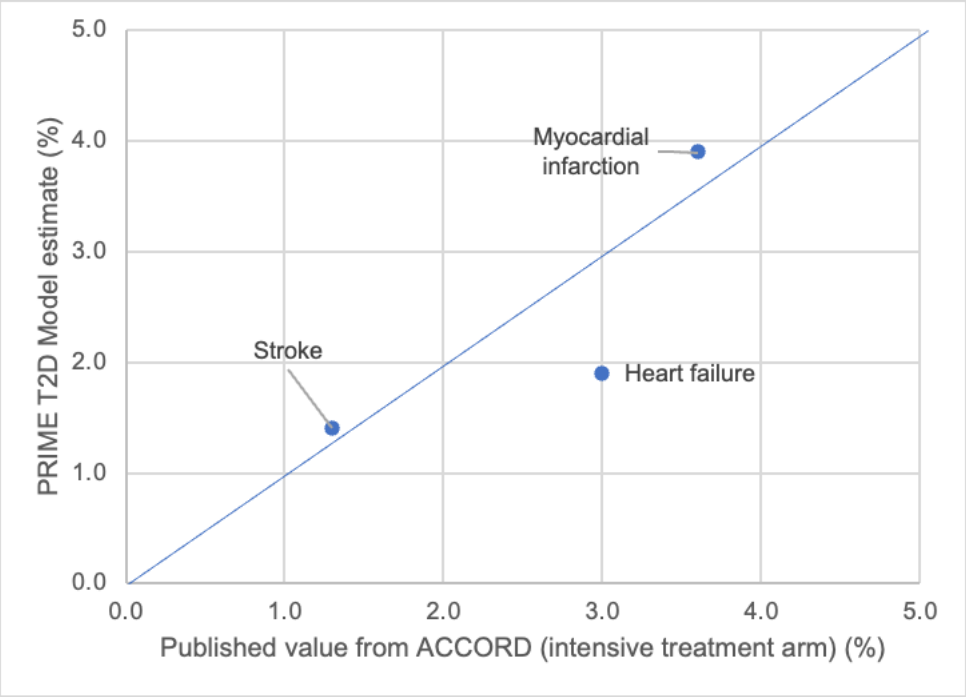
1. Test cases were defined for each PRIME T2D Model controller. These tests cases typically consisted of testing at minimum and maximum input values. Testing at the extreme input values allowed for maximum stress on the module.
2. Each controller was independently implemented in Matlab. Matlab (matrix laboratory) is a multi-paradigm numerical computing environment and fourth-generation programming language. Developed by MathWorks, Matlab allows matrix manipulations, plotting of functions and data, implementation of algorithms, creation of user interfaces, and interfacing with programs written in other languages, including Java (the PRIME Model's language), C, C++, Fortran and Python.

	3. The test cases were run using both the Java software from the PRIME T2D Model and the Matlab implementations and results are compared to ensure correct implementation in the former. 4. To assess the overall model characteristics, a cohort of 1,000,000 patients was generated using the characteristics defined within the PRIME T2D Model Database Controller (with isCollegeEducationOrAbove and severeHypoHistory initialized to false) and an initial ageAtDiagnosis limited to the range of zero to one year. The complication controllers were then executed. This analysis was performed in MatLab and the only updates to patient characteristics were limited to increasing the patient age and modifying the patient history based on the results of the complications. 5. The findings of this process were detailed in a report and any discrepancies in the PRIME T2D Model code and the MatLab implementation were resolved.	
16	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B32. Priority question: Further information on validation efforts would be desirable, focusing on this specific implementation of the PRIME T2D model.** **b) Please provide a tabulated overview of all parameters used in the model, including SE/SD/CIs, the probability distribution used, the source, justification for the source, and a specific description of how the parameter was implemented in the model.** Summaries of all model inputs for the base case analysis are provided in Table 1 through to Table 15 of Appendix A (shared as a separate file alongside this response due to its length) in line with the EAG request. The complexity of the model is not possible to capture in a tabular format (e.g. risk factors at baseline are sampled from a distribution, then subjected to treatment effects and progression, may contribute to weighting of risk equations (model averaging) and be associated with the evaluation of complication risk in each model cycle). However, the PRIME T2D Model Technical Report details all of the risk equations used and references the progression functions to elucidate this question and the model code has been provided to detail every parameter and its implementation in any given modelling simulation. With respect to distributions applied for each parameter in the model, the following information can be used to directly identify distributions from the model code: • Whether sampling of costs is active is governed by a Boolean value named sampleCosts, which is referenced in the EconomicsController Java class. • Whether sampling of utilities is active is governed by a Boolean value named sampleUtilities, which is referenced in the QualityOfLifeController Java class. • Whether sampling of treatment effects is active is governed by a Boolean value named sampleTreatmentEffects, which is	We would like to thank the company for providing an overview of input parameters in Appendix A. However, this overview is incomplete, for instance the individual parameters of the risk models (including the UKPDS risk factor progression) were not included. In addition, the distribution used (per parameter) was not specified in Appendix A. Moreover, the general summary of distributions used, raised some concerns for the EAG: why is an uniform distribution used for percentages (and not a BETA distributions), why are normal distributions used for costs and utilities (and not GAMMA and BETA distributions)

	referenced in the TreatmentController Java class. • Whether sampling of model coefficients is active is governed by a single line of code in the PatientController.java superclass from which all complication-evaluating Java classes inherit. • The simulated cohort of patients is generated (based on the user-defined cohort characteristics) in the CohortController Java class. Patient heterogeneity is thereby introduced in this class, which comprises just 250 lines of code (LOC), of which ~180 LOC are responsible for generating the cohort. • Random walk (stochastic uncertainty) through the model is governed by sampling from uniform distributions in the processPatient() methods of each Java class responsible for modelling a given complication. The model supports normal, log-normal, uniform and beta distributions and are applied as appropriate and in line with model input data during probabilistic sensitivity analysis. In general, the following schema summarizes the distribution forms used in the model: Cohort characteristics • Normal distribution (with physiological limits) for all parameters defined by mean and standard deviation • Uniform distribution for all parameters defined by percentages • Log-normal distribution for hazard ratios (noted for completeness – not used in the present analysis) Treatment effects • Normal distribution (with physiological limits) for all parameters defined by mean and standard deviation Costs • Normal distribution for all parameters defined by mean and standard deviation Utilities • Normal distribution (with limits) for all parameters defined by mean and standard deviation Risk equation coefficients • Normal distribution unless otherwise indicated in source publication	
17	**A detailed response to the following clarification question, providing more justification/evidence/elaboration then was provided in the clarification responses:** **B35. Priority question: Further external validation of modelled estimates against the SURPASS trials and (potentially available) alternative evidence would be desirable. Please assess the external validity of model**	See response to comment 9

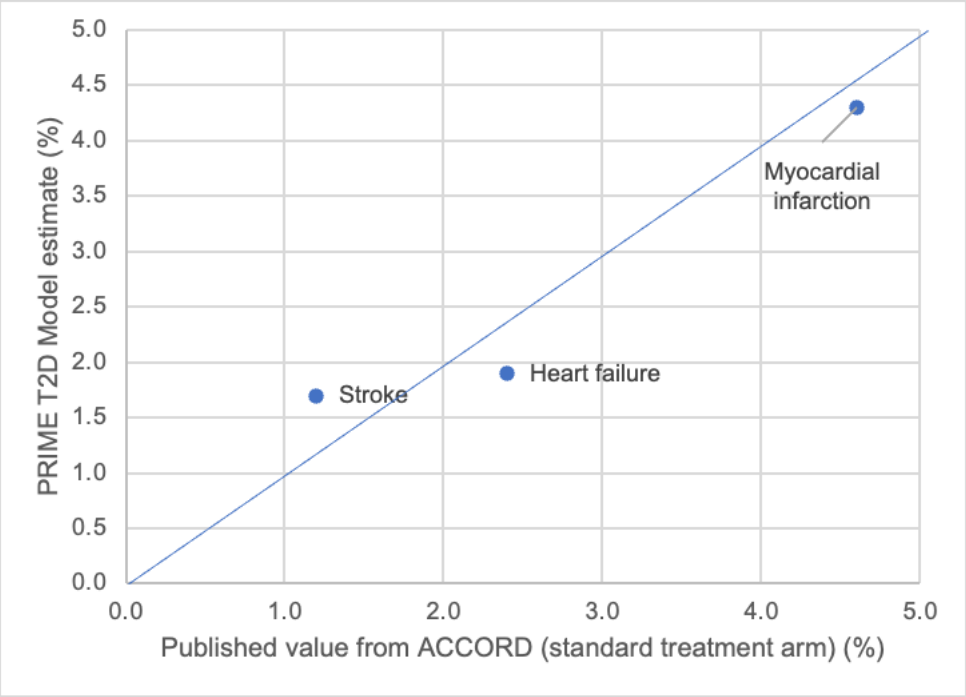
	inputs, intermediate outcomes and (long-term) disaggregated results (as provided in Appendix J) as well as final outcomes using the SURPASS trials and available alternative evidence sources. **The EAG noted that it would be informative if the company could provide similar figures as Figure 14 from "ID3938_Eli Lilly_Tirzepatide_Response to EAG Report_v0.2 16May23 [ACIC].docx", based on the current company base-case, for all complications/outcomes considered and compared to more studies (including the ASCEND study).** Previous Comments in this response document (above) have included the following validation scatterplots: • Overall validation analysis (Figure 2) • Validation for MI, stroke, IHD and heart failure against the EMPA-REG OUTCOME study (Figure 3) • Validation of mortality, MI and stroke against the REWIND study (Figure 5) • Validation of MI, stroke and ischaemic heart disease again the LEADER study (Figure 6) • Validation of stroke and heart failure against the Shah et al. cohort study (Figure 9 and Figure 10) • Validation of first and second MI, first and second stroke, ischaemic heart disease, heart failure, foot ulcer, amputation and renal failure against the LDS UKPDS OM2 dataset (Figure 11) Validation was also performed against published data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was the derivation cohort for the risk formulae for the BRAVO Model.[31, 35] ACCORD was designed to investigate whether intensive therapy to target normal glycated haemoglobin levels would reduce cardiovascular events in patients with type 2 diabetes who had either established cardiovascular disease or additional cardiovascular risk factors. The study recruited 10,251 patients with type 2 diabetes in North America, of whom 35% had a history of cardiovascular disease at baseline, and randomly allocated patients to intensive or standard therapy for a median follow up period of 3.4 years. A finding of higher mortality in the intensive-therapy group led to a discontinuation of the intensive therapy arm after a mean of 3.5 years of follow-up. Validation analysis with the PRIME T2D Model showed that the model predicted outcomes well for the myocardial infarction and stroke endpoints in both treatment groups (Figure 12 and Figure 13). For the heart failure endpoint, the model slightly underpredicted the risk in the intensive treatment group but was closer for the standard therapy arm. The RMSD between cumulative incidence values from the model and the ACCORD intensive treatment group was 0.7%. The corresponding value for the standard care arm was 0.4%.	

Figure 12: PRIME T2D Model validation scatterplot for the intensive treatment group in ACCORD



Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Figure 13: PRIME T2D Model validation scatterplot for the standard treatment group in ACCORD

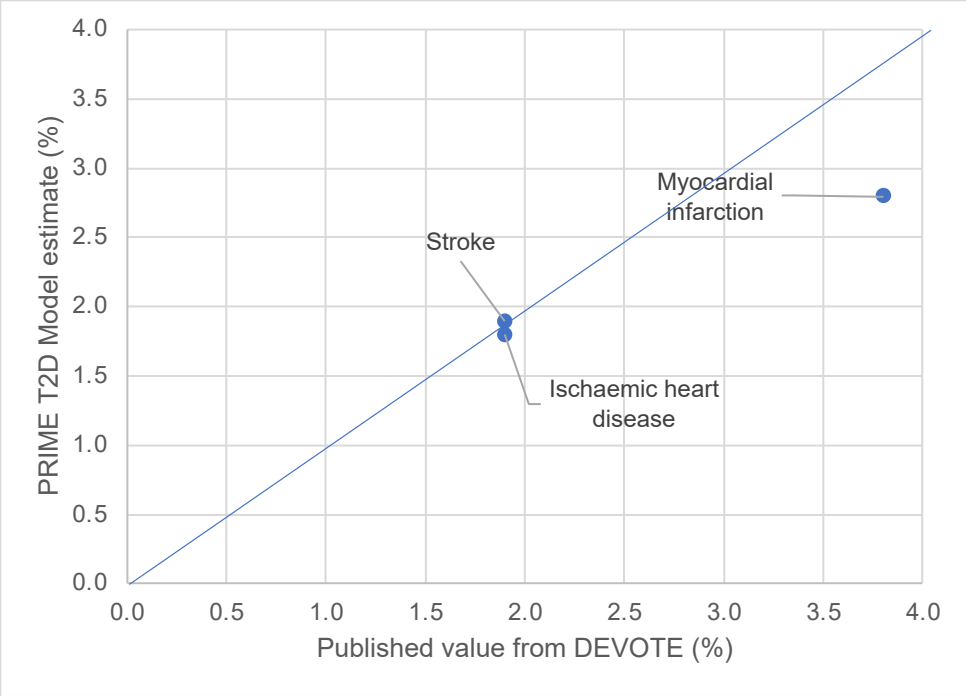


Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line.

Validation analysis has also been performed on the DEVOTE study, the cardiovascular safety trial of insulin degludec.[36] The study recruited a total of 7,637 patients with type 2 diabetes who were randomly assigned to receive either insulin degludec

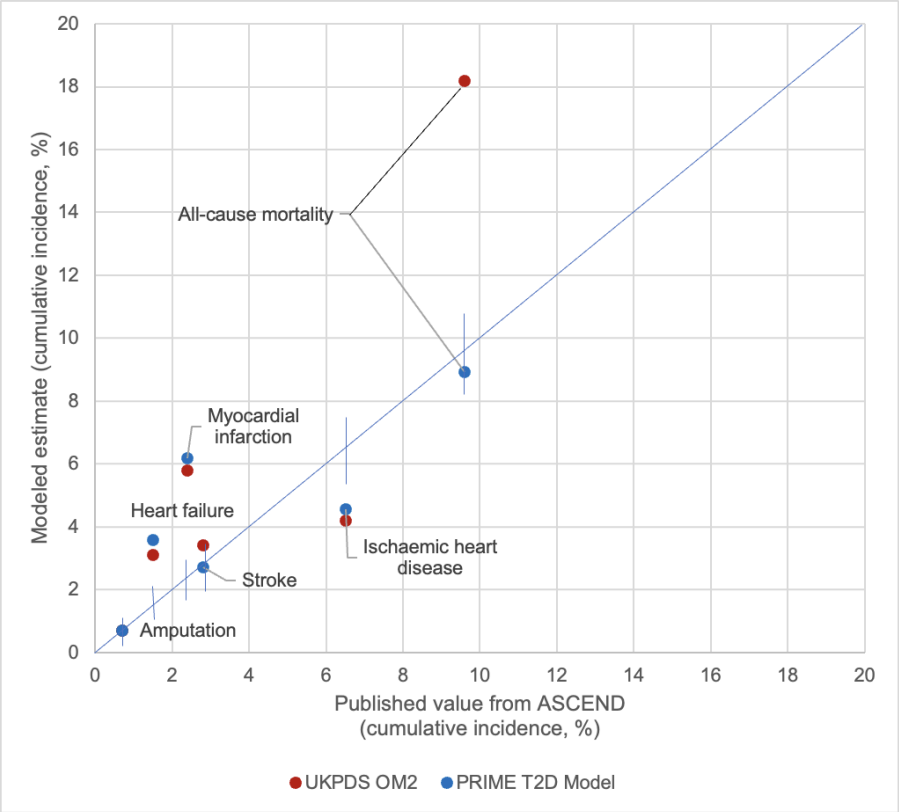
(3,818 patients) or insulin glargine (3,819 patients) once daily. The study included a total of 438 sites in 20 different countries and had a median follow up time of 1.99 years. Validation was performed against outcomes for the insulin degludec treatment arms and the model showed a good match to published outcomes for stroke and ischaemic heart disease, but slightly underestimated the risk of myocardial infarction in this population Figure 14. The RMSD between modelled outcomes and the trial results for this validation was 0.6%.

Figure 14: PRIME T2D Model validation scatterplot for the DEVOTE study



	Each point on the graph represents a cumulative incidence value from the PRIME T2D Model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the PRIME T2D Model are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. At the request of the EAG, a validation analysis was also performed against A Study of Cardiovascular Events in Diabetes (ASCEND), which had been previously used to validate against the UKPDS OM2 as described by Keng et al. (2022).[19] ASCEND was a 2x2 factorial design trial that randomized 15,480 participants with established diabetes mellitus (both type 1 and type 2) but without diagnosed CV disease (CVD) to 100 mg aspirin daily or matching placebo and, separately, to 1 g capsule containing omega-3 fatty acids daily or placebo. Participants were recruited between 2005 and 2011 and followed for an average of 7.4 years. A total of 7,578 patients with type 2 diabetes had complete baseline information and formed the validation cohort. The validation analysis reported in Appendix Table 7 from Keng et al. and supplemented with the corresponding endpoints from the PRIME T2D Model validation is shown in Figure 15. The most notable difference is in terms of mortality estimation, where the PRIME T2D Model was close to the published estimate but the UKPDS OM2 overestimated mortality risk. Amputation estimates were the same with both models. The PRIME T2D Model predicted stroke and ischaemic heart disease a little better than the UKPDS OM2. Both models overpredicted the risk of heart failure and myocardial infarction, with UKPDS OM2 slightly lower than the PRIME T2D Model. The RMSD value (the measure of the average difference between the modelled value and the observed value) for the UKPDS OM2 validation was 3.95% compared with 1.96% with the PRIME T2D Model. Even when the notable outlier for the UKPDS OM2 model is taken out (i.e. all-cause mortality), the RMSD value was 1.99% with the UKPDS OM2, still a little higher than the PRIME T2D Model.	

Figure 15: PRIME T2D Model validation scatterplot for the ASCEND study



Each point on the graph represents a cumulative incidence value from a model and the corresponding published study value for validation (expressed as cumulative incidence of a given diabetes-related complication). Values from the models are plotted as the y-axis and the corresponding cumulative incidence values from the published study on the x-axis. A perfect match would see all points on the y=x line. Vertical lines are shown representing the 95% confidence intervals around the observed endpoint data from ASCEND.

Neither model was able to reproduce the myocardial infarction endpoint from ASCEND accurately. It is not entirely clear why this should be the case. Keng *et al.* speculated that this may be due to the impact of revascularization.[19] However, the publication did not include separate numerical estimates for revascularization and therefore no validation could be performed on this endpoint. It is possible, despite the researchers' best efforts to match the myocardial infarction endpoint by adjudicating all events, that the differences in endpoint definitions drove the differences observed in the myocardial infarction and ischaemic heart disease endpoints(see Table 16).

Table 16: Summary of myocardial infarction and ischaemic heart disease endpoint definitions pertaining to the ASCEND validation

Endpoint	Definition in UKPDS-OM2 and PRIME T2D Model	Definition in ASCEND
Myocardial infarction	WHO clinical criteria with electrocardiogram/enzyme changes or new pathological Q wave ICD-9 codes: 410 (Acute myocardial infarction); ≥ 798 & ≤ 798.9 (Sudden death)	Myocardial infarction (fatal/ "Evidence of cardiac necrosis (consistent eleva relevant autopsy findings) and there was oth (including symptoms of ischemia, recent coron ECG changes, evidence of a new myocardial de acute coronary occlusion at angiography) and n
Other ischaemic heart disease	Angina/ischaemic heart disease - WHO clinical criteria confirmed by a new ECG abnormality or an ECG which becomes abnormal on exercise ICD-9 codes: ≥ 411 & ≤ 414.9 (Ischaemic heart disease excluding acute myocardial infarction)	Angina; Coronary revascularizations (coronary artery transluminal coronary angi Death from other coronary heart disease (r

There are several points to note with respect to the validation analyses presented above:

	• Validation analysis with the PRIME T2D Model to date has focused primarily (but not exclusively) on cardiovascular disease endpoints as these are the biggest drivers of cost and are the most important complication in terms of driving outcomes in a cost-effectiveness analysis of diabetes interventions (c.f. the base case analysis). • Validation analyses have also been performed on cohort studies from South-East Asia but these have not been included as they are not relevant to the present modelling analysis. • Root mean squared deviation is provided as a measure of difference between the modelling results and observed outcomes. It can be considered to reflect the average difference between the cumulative incidence of complications predicted by the model and the cumulative incidence of complications observed in the study. The root mean squared methodology is utilised to avoid positive and negative differences in cumulative incidence cancelling each other out and providing an underestimate of the differences between modelled and observed outcomes (that could occur if only mean differences were reported).	

Tirzepatide for treating type 2 diabetes [ID3938]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

PART 2 (comments 18-23)

Company's response submitted on July 27 2023		
18	**Please provide rationale for not including the SURMOUNT-2 and SURMOUNT-CN studies in the company submission. Please also provide a tabulated summary of SURMOUNT and SURPASS trials, focusing on population enrolled, trial design and key outcomes (highlighting any key differences and similarities) to help us assess the impact of not including these studies** The SURMOUNT trials are recent studies in a different indication (weight loss) to the current appraisal and will be assessed in the upcoming appraisal for obesity and are not relevant for this appraisal. The majority of the SURMOUNT trials are not relevant to this appraisal because SURMOUNT-1, -3, -4, -MMO, -OSA and -CN all excluded diabetes patients. Only SURMOUNT-2 included diabetes patients, although that trial was specifically designed (and powered) to assess weight reduction as the primary outcome rather than HbA1c reduction and T2D was secondary to the trial. Patients included in the SURMOUNT-2 trial, have a much higher BMI than the current submission T2D population, as the SURMOUNT studies are assessing patients with overweight/obesity (median BMI 36; a minimum BMI of 27 was needed to be eligible for inclusion in the trial). Importantly, the SURMOUNT-2 trial would not have been included in the NMA for the current appraisal, as the definition of background therapies permitted is not directly relevant to the current decision problem. Finally, the SURMOUNT-2 data have only recently been published (26th June 2023),[1] and the SURMOUNT-CN data have not yet been published so these results were not available before the company submission (CS) in August 2022 or during the first appraisal committee meeting on 6th June 2023. Please see **Error! Reference source not found.** at the end of this document for a tabulated summary of the SURMOUNT and SURPASS trials.	As stated in the document produced by the EAG, 'SURMOUNT-2 vs SURPASS study comparison [ACIC]', the allowance of change in concomitant medication during SURMOUNT-2 is a key difference to the SURPASS trials. Perhaps most importantly, unlike in the SURPASS trials, as well as all of the other trials in the NMA, patients in SURMOUNT-2 were not required to have inadequate glycaemic control on entry.
19	**Rationale for selecting UKPDS OM2, BRAVO Model and Hong Kong Diabetes Registry out of all possible risk models, when estimating the rates of micro- and macrovascular complications** The final choice of risk models for inclusion in the model averaging code for evaluation of macrovascular complication risk in the PRIME T2D Model was based on a number of factors following full-text review of relevant hits from the model development literature review (an overview of the literature review is described in the PRIME T2D Model Technical Report previously provided). The key criteria for inclusion were: • The publication describes (a) risk formula(e) that was derived from a population with type 2 diabetes • The risk formula(e) can be used to estimate the annual risk of one or more diabetes-related complications • The risk formula(e) can be used to estimate annual risk without transformation (e.g. assuming proportional hazards) from a	Thank you for providing the inclusion criteria for the model selection. The EAG notes that the model selection process was based on a systematic literature review and clear inclusion criteria. As stated in the EAG report "*the appropriateness of the selected predictive*

multi-year risk score

- Endpoint definitions must be closely matched between different publications to be included in model averaging and the outcomes should not be a composite endpoint (without a means to separate individual endpoints)

The literature searches identified several publications that were reviewed in detail for potential inclusion in the model averaging approach (Table 17). The majority of publications identified were not suitable for inclusion in model averaging, primarily due to reporting risk scores (e.g. 5-year estimate or risk) and/or reporting only composite endpoints with no individual endpoint delineation. This left the UKPDS OM2, BRAVO and Hong Kong Registry equations for inclusion in model averaging at the time of model development. Validation analysis has indicated that the present model averaging approach performs well in comparison with published clinical study data across different populations (presented previously in Comment 10 of the response to draft guidance and in the PRIME T2D Model Technical Report found in Appendix N of the original company submission).

Table 17: Summary of publications identified by literature searches for potential inclusion in the model averaging approach

Publication	Model/study	Cardiovascular endpoints	Comments
Hayes *et al.* (2013)[2]	UKPDS OM2/UKPDS	Myocardial infarction, stroke, heart failure and ischaemic heart disease	Included in model averaging
Shao *et al.* (2018)[3]	BRAVO/ACCORD	Myocardial infarction, stroke, heart failure, angina and revascularization	Included in model averaging
Yang *et al.* (2008)[4]	Hong Kong Diabetes Registry	Coronary heart disease (composite of myocardial infarction and ischaemic heart disease)	Included in model averaging in Asian populations for ischaemic heart disease endpoint
Yang *et al.* (2007)[5]	Hong Kong Diabetes Registry	First stroke (fatal and non-fatal)	Included in model averaging in Asian populations for stroke endpoint
Yang *et al.* (2008)[4]	Hong Kong Diabetes Registry	Hospitalization for heart failure	Included in model averaging in Asian populations for heart failure endpoint
Tanaka *et al.* (2013)[6]	JJ Risk Engine/Japan Diabetes Complications Study (JDCS)	Coronary heart disease (composite) and stroke	Not included: risk equations could not be reproduced from the publication

models to estimate the risk of complications in patients with T2D is not justified (in detail [e.g. using PROBAST as mentioned in response to comment 12]*). Nor is the applicability to the specific decision problem (as specified in the CS) justified."* However, the company's responses provided in the first part of this document are reassuring to the EAG regarding the appropriateness of the predictive performance.

	Elley *et al.* (2010)[7]	NZDCS	Composite first CVD event (ischemic heart disease, cerebrovascular accident/transient ischemic attack, or peripheral arterial disease)	Not included: reported 5-year risk of "first CVD event" (composite)	
	Donnan *et al.* (2006)[8]	Diabetes Audit and Research in Tayside (DARTS)	Coronary heart disease (composite of myocardial infarction and coronary heart disease death)	Not included: reported "first CHD"(composite)	
	Schramm *et al.* (2016)[9]	PROSIT	Stroke and coronary heart disease (composite)	Not included: Relies on UKPDS Risk Engine and older data / coronary heart disease composite endpoint	
	Kengne *et al.* (2011)[10]	Action in Diabetes and Vascular disease: preterax and diamicron-MR controlled evaluation (ADVANCE)	Composite of all CVD events	Not included: reported 4-year risk of major CVD events	
	Davis *et al.* (2010)[11]	Freemantle Diabetes Study	Composite of all CVD events	Not included: reported 5-year risk of CVD events	
	Cederholm *et al.* (2008)[12]	Swedish National Diabetes Registry	Composite of all CVD events	Not included: reported 5-year risk of CVD events	
	Folsom *et al.* (2003)[13]	Atherosclerosis Risk in Communities (ARIC)	Coronary heart disease composite endpoint (including myocardial infarction, coronary heart disease death and revascularization)	Not included: reported 10-year risk of coronary heart disease composite endpoint	
	Abbreviations: ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; ARIC: Atherosclerosis Risk in Communities; CVD: cardiovascular disease; DARTS: Diabetes Audit and Research in Tayside; JDCS: Japan Diabetes Complications Study; UKPDS: United Kingdom Prospective Diabetes Study; UKPDS OM2: United Kingdom Prospective Diabetes Study Outcomes Model 2.				
20	**Rationale for a decrease in incremental life years but an increase in incremental QALYs when running analysis in CORE Diabetes Model, compared with PRIME T2D Model** Whilst it is difficult to be prescriptive about specific differences in outcomes between the two models, this observation is most likely explained by different approach to the estimation of quality-adjusted life expectancy between the two models. In line with the EAG recommendation, an age-adjusted approach to utility estimation was used in the PRIME T2D Model. However, an age-adjusted approach is not available in the CORE Diabetes Model and therefore an additive approach was used to combining utilities in that model (as this was considered the closest match to the approach used in the PRIME T2D Model). The additive approach in the				Thank you for this explanation. The EAG agrees that age-adjustment could have caused this difference. Other reasons might also play a role here, such as the correction of mortality rates in

	CORE Diabetes Model would likely provide higher estimates of incremental QALYs than the age-adjusted approach in the PRIME T2D Model (as utilities are not decreased in older patients with the additive approach). This increase in incremental QALYs with the additive approach is likely to have offset the smaller incremental life years benefit observed with the CORE Diabetes Model.	the PRIME model, which could explain the difference in incremental life years. Nevertheless, the EAG finds that the comparability of the outcomes of the CORE model and the PRIME model reassuring.
21	**Scenario analysis using the EAG's preferred baseline utility value for people with type 2 diabetes (0.772; Redenz, 2023)** Results from the scenario analysis using the baseline utility of 0.772 are summarized in Table 18, Table 19 and Table 20. It should be noted that, as discussed in Comment 6 of the response to draft guidance, using a fixed baseline utility of 0.772 is not compatible with the age-adjusted approach. This is because the age-adjusted approach relies on a regression equation to define the annual baseline utility each year as opposed to a fixed value. Therefore an additive approach to combining utilities was used as this represents the closest match to the base case analysis.[14] As lowering the baseline utility had little impact on incremental differences between treatment arms, ICERs were close to those reported in the base case analysis for tirzepatide versus comparators (Table 18, Table 19 and Table 20). **Table 18: Summary of lower baseline utility (0.772) scenario analysis results for tirzepatide 5 mg versus comparators**	Thank you for providing this scenario analysis. The EAG notes that the ICERs increase slightly (and more with higher doses of tirzepatide)

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 5 mg	[redacted]	13.122	8.836	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.733	705	0.059	0.103	6,840	0.068
Dulaglutide 3.0 mg	[redacted]	13.076	8.755	644	0.046	0.081	7,956	0.049
Dulaglutide 4.5 mg	[redacted]	13.092	8.777	628	0.030	0.059	10,563	0.028
Semaglutide 0.5 mg	[redacted]	13.075	8.752	682	0.047	0.084	8,115	0.050
Semaglutide 1.0 mg	[redacted]	13.096	8.792	708	0.026	0.044	16,016	0.009

Oral semaglutide 7 mg	[redacted]	13.049	8.713	742	0.073	0.124	6,003	0.087
Oral semaglutide 14 mg	[redacted]	13.074	8.761	719	0.048	0.076	9,520	0.040
Liraglutide 1.2 mg	[redacted]	13.032	8.697	672	0.090	0.139	4,830	0.105
Liraglutide 1.8 mg	[redacted]	13.054	8.718	−409	0.068	0.119	Dominant	0.139

Abbreviations: ICER: incremental cost-effectiveness ratio; NHB: net health benefit; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 19: Summary of lower baseline utility (0.772) scenario analysis results for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.891	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.733	1,389	0.092	0.158	8,779	0.089
Dulaglutide 3.0 mg	[redacted]	13.076	8.755	1,329	0.079	0.136	9,757	0.070
Dulaglutide 4.5 mg	[redacted]	13.092	8.777	1,312	0.063	0.115	11,446	0.049
Semaglutide 0.5 mg	[redacted]	13.075	8.752	1,367	0.080	0.139	9,812	0.071
Semaglutide 1.0 mg	[redacted]	13.096	8.792	1,393	0.059	0.099	14,007	0.030
Oral semaglutide 7 mg	[redacted]	13.049	8.713	1,427	0.106	0.179	7,977	0.108
Oral semaglutide 14 mg	[redacted]	13.074	8.761	1,403	0.081	0.131	10,735	0.061
Liraglutide 1.2 mg	[redacted]	13.032	8.697	1,356	0.123	0.194	6,981	0.126
Liraglutide 1.8 mg	[redacted]	13.054	8.718	276	0.101	0.174	1,587	0.160

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 20: Summary of lower baseline utility (0.772) scenario analysis results for tirzepatide 15 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.175	8.935	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.733	1,937	0.112	0.202	9,605	0.105
Dulaglutide 3.0 mg	[redacted]	13.076	8.755	1,877	0.099	0.180	10,447	0.086
Dulaglutide 4.5 mg	[redacted]	13.092	8.777	1,860	0.083	0.158	11,767	0.065
Semaglutide 0.5 mg	[redacted]	13.075	8.752	1,915	0.100	0.183	10,478	0.087
Semaglutide 1.0 mg	[redacted]	13.096	8.792	1,941	0.079	0.143	13,582	0.046
Oral semaglutide 7 mg	[redacted]	13.049	8.713	1,975	0.126	0.222	8,883	0.124
Oral semaglutide 14 mg	[redacted]	13.074	8.761	1,951	0.101	0.174	11,203	0.077
Liraglutide 1.2 mg	[redacted]	13.032	8.697	1,904	0.143	0.238	8,010	0.143
Liraglutide 1.8 mg	[redacted]	13.054	8.718	824	0.121	0.217	3,791	0.176

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator.

22	**Scenario analysis using a multiplicative approach for combining disutilities** [redacted] Results from the scenario analysis using a multiplicative approach for combining utilities for tirzepatide 10 mg versus comparators are summarized in Table 21. Across all comparisons, tirzepatide 10 mg was associated with an ICER of less than £20,000 per	Thank you for providing this scenario analysis with the multiplicative method. This scenario inflates the ICER for tirzepatide 10mg vs.

	QALY gained. It is notable, that comparison of tirzepatide 10 mg with semaglutide 1.0 mg produced an ICER of £18,337 per QALY gained, in this scenario which the company considers to be very conservative. This scenario is not considered appropriate, because given the clear precedent for the use of the additive approach in previous analyses in type 2 diabetes, including those by NICE and as supported by the conclusions of Gough et al. (2009), Sullivan et al. (2011) and Hayes et al. (2016),[15-17] it may be premature to deviate to the multiplicative approach for the assessment of tirzepatide (and other new treatments in this therapeutic area) in the absence of evidence that the multiplicative approach is more accurate. Please refer to Comment 7 of the response to draft guidance for more information on why a multiplicative approach is not appropriate for this appraisal.	Semaglutide 1mg with £3.721 pound. Whether the additive or multiplicative method is most applicable remails a matter of judgement, the EAG comments from the EAG report are still applicable.

Table 21: Summary of scenario analysis results using a multiplicative approach for combining disutilities for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	9.393	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	9.274	1,389	0.092	0.119	11,634	0.050
Dulaglutide 3.0 mg	[redacted]	13.076	9.289	1,329	0.079	0.105	12,704	0.038
Dulaglutide 4.5 mg	[redacted]	13.092	9.305	1,312	0.063	0.088	14,848	0.023
Semaglutide 0.5 mg	[redacted]	13.075	9.288	1,367	0.080	0.105	13,039	0.036
Semaglutide 1.0 mg	[redacted]	13.096	9.317	1,393	0.059	0.076	18,337	0.006
Oral semaglutide 7 mg	[redacted]	13.049	9.261	1,427	0.106	0.132	10,835	0.060
Oral semaglutide 14 mg	[redacted]	13.074	8.642	1,403	0.081	0.751	1,868	0.681
Liraglutide 1.2 mg	[redacted]	13.032	9.246	1,356	0.123	0.147	9,206	0.080
Liraglutide 1.8 mg	[redacted]	13.054	9.263	,276	0.101	0.130	2,123	0.116

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

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Scenario analysis incorporating diarrhoea as an adverse event (as in company response to clarification comments, updated)

As requested, scenario analysis simulations were run incorporating rates of diarrhoea from the NMA. Literature review failed to identify appropriate utilities for diarrhoea in the target population and therefore the nausea and vomiting utility published by Matza *et al*. and used in the base case analysis was used as a proxy (-0.04 for each patient experiencing diarrhoea).[18] This was applied to the proportion of patients who experienced diarrhoea and to the proportion of patients who experiencing nausea based on the NMA in year 1 of the simulations. The total proportions for each treatment are summarized in Table 22.

Many thanks for providing this additional scenario analysis. The EAG notes that this has only a minor impact on the ICER.

Table 22: Summary of proportions of patients with nausea and diarrhoea for the scenario analysis

Intervention	Proportion of patients experiencing nausea (%)	Proportion of patients experiencing diarrhoea (%)	Combined proportion to receive -0.04 disutility (%)
Tirzepatide 5 mg	25.8	17.1	42.8
Tirzepatide 10 mg	34.3	19.5	53.8
Tirzepatide 15 mg	37.2	17.7	55.0
Dulaglutide 1.5 mg	28.1	15.1	43.2
Dulaglutide 3.0 mg	28.1*	15.1*	43.2
Dulaglutide 4.5 mg	28.1*	15.1*	43.2
Semaglutide 0.5 mg	24.9	12.3	37.3
Semaglutide 1.0 mg	28.1	14.3	42.4
Oral semaglutide 7 mg	24.9*	12.3*	37.3
Oral semaglutide 14 mg	28.1*	14.3*	42.2
Liraglutide 1.2 mg	20.3	7.7	28.1
Liraglutide 1.8 mg	25.3	12.5	37.8

Any apparent discrepancies in the combined proportion column are due to rounding. * nearest neighbour approach used to estimate the proportion of patients experiencing events.

Including the diarrhoea utility for all treatments based on data from the NMA had a modest impact on incremental quality-adjusted life expectancy and, therefore, on cost-effectiveness relative to the base case analysis (Table 23, Table 24 and Table 25).

Table 23: Summary of scenario including disutility for diarrhoea analysis results for tirzepatide 5 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)

			expectancy (QALYs)					
Tirzepatide 5 mg	[redacted]	13.122	8.708	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.610	705	0.059	0.098	7,163	0.063
Dulaglutide 3.0 mg	[redacted]	13.076	8.631	644	0.046	0.078	8,290	0.046
Dulaglutide 4.5 mg	[redacted]	13.092	8.651	628	0.030	0.057	11,048	0.025
Semaglutide 0.5 mg	[redacted]	13.075	8.629	682	0.047	0.079	8,621	0.045
Semaglutide 1.0 mg	[redacted]	13.096	8.667	708	0.026	0.041	17,312	0.005
Oral semaglutide 7 mg	[redacted]	13.049	8.591	742	0.073	0.117	6,343	0.080
Oral semaglutide 14 mg	[redacted]	13.074	8.637	719	0.048	0.071	10,094	0.035
Liraglutide 1.2 mg	[redacted]	13.032	8.579	672	0.090	0.130	5,176	0.096
Liraglutide 1.8 mg	[redacted]	13.054	8.596	−409	0.068	0.113	Dominant	0.133

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 24: Summary of scenario including disutility for diarrhoea analysis results for tirzepatide 10 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 10 mg	[redacted]	13.155	8.760	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.610	1,389	0.092	0.150	9,233	0.081
Dulaglutide 3.0 mg	[redacted]	13.076	8.631	1,329	0.079	0.130	10,237	0.063
Dulaglutide 4.5 mg	[redacted]	13.092	8.651	1,312	0.063	0.109	12,050	0.043
Semaglutide 0.5 mg	[redacted]	13.075	8.629	1,367	0.080	0.131	10,416	0.063

Semaglutide 1.0 mg	[redacted]	13.096	8.667	1,393	0.059	0.093	14,978	0.023
Oral semaglutide 7 mg	[redacted]	13.049	8.591	1,427	0.106	0.169	8,437	0.098
Oral semaglutide 14 mg	[redacted]	13.074	8.637	1,403	0.081	0.123	11,382	0.053
Liraglutide 1.2 mg	[redacted]	13.032	8.579	1,356	0.123	0.182	7,458	0.114
Liraglutide 1.8 mg	[redacted]	13.054	8.596	276	0.101	0.165	1,676	0.151

Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. * for tirzepatide versus comparator.

Table 25: Summary of scenario including disutility for diarrhoea analysis results for tirzepatide 15 mg versus comparators

	Direct costs (£)	Life expectancy (years)	Quality-adjusted life expectancy (QALYs)	Incremental costs (£)	Incremental life years*	Incremental QALYs*	ICER* (£ per QALY gained)	NHB (QALYs)
Tirzepatide 15 mg	[redacted]	13.175	8.803	--	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	13.063	8.610	1,937	0.112	0.193	10,041	0.096
Dulaglutide 3.0 mg	[redacted]	13.076	8.631	1,877	0.099	0.172	10,894	0.078
Dulaglutide 4.5 mg	[redacted]	13.092	8.651	1,860	0.083	0.151	12,290	0.058
Semaglutide 0.5 mg	[redacted]	13.075	8.629	1,915	0.100	0.174	11,024	0.078
Semaglutide 1.0 mg	[redacted]	13.096	8.667	1,941	0.079	0.135	14,327	0.038
Oral semaglutide 7 mg	[redacted]	13.049	8.591	1,975	0.126	0.212	9,333	0.113
Oral semaglutide 14 mg	[redacted]	13.074	8.637	1,951	0.101	0.166	11,772	0.068
Liraglutide 1.2 mg	[redacted]	13.032	8.579	1,904	0.143	0.224	8,489	0.129
Liraglutide 1.8 mg	[redacted]	13.054	8.596	824	0.121	0.207	3,977	0.166

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

	Abbreviations: NHB: net health benefit; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; * for tirzepatide versus comparator.	

NICE National Institute for Health and Care Excellence

Tirzepatide for treating type 2 diabetes [ID3938]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 18 July 2023. Please submit via NICE Docs.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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STUDY COMPARISSON; SURMOUNT-2 versus the SURPASS trials (2 to 5)

This summary provides a brief comparison between the SURPASS trial series (2 to 5) and the SURMOUNT-2 trial{Garvey, 2023 #501}, both reporting on efficacy and safety outcomes of Tirzepatide. The objectives of the trials were different and as such key aspects of their design was different. SURMOUNT-2 focused on the treatment of obesity in people with T2D having as key outcomes the percent change in bodyweight from baseline and weight reduction from baseline (of at least 5%) until the end of the trial. On the other hand, the SURPASS trials focused on the treatment of T2D as a whole, having as key outcome the change in the glycated haemoglobin (HbA1c) level from baseline to the end of the trials.

The SURPASS trials were multicentre, randomised, open-label trials running for 40 to 104 weeks, while SURMOUNT-2 was a multicentre, randomised, double-blind trial, running for 72 weeks. The intervention under investigation of SURMOUNT-2 was Tirzepatide alone while all the SURPASS trials combined Tirzepatide with other T2D treatments (metformin, SGLT2i, sulfonylurea, insulin glargine). Three doses of Tirzepatide were administered in the SURPASS trials (5, 10, 15 mg) but only two in SURMOUNT-2 (10, 15 mg). SURMOUNT-2 and SURPASS-5 were placebo controlled, the rest of the SURPASS trials had active comparators. It should also be noted that people treated with insulin were excluded from participation in SURMOUNT-2 and that a specific lifestyle intervention was also implemented which included regular lifestyle counselling sessions.

Since the focus of the SURMOUNT-2 trial was treatment of obesity other medication for weight management were not permitted as concurrent therapy. On the other hand, the use of antihyperglycemic medication (AHM) was permitted at randomization, with some exceptions (GLP-1R agonists, DPP-4 inhibitors), and they were to be continued at their current dose. New AHMs could be initiated as a rescue therapy for persistent hypoglycaemia, in study patients that discontinued Tirzepatide permanently and during the safety follow-up period with no restrictions. In fact, the change in the number of AHMs taken by the study participants from baseline to the end of the trial was an endpoint of the trial based on post-hoc analysis. This is a key difference between the trials since the concurrent anti-diabetic therapies changed in the course of the trial. Anti-diabetic therapies at baseline are presented in Table 1. In SURMOUNT-2 more than 2 concurrent oral AHMs at baseline were received by 32% of the study population while 7% received ≥3, in this aspect the trial is only comparable to SURPASS-4.

The population of the trials also differ. SURMOUNT-2 included T2D adult patients with a BMI ≥27 kg/m^2 and an HbA1c between 7-10%. On the other hand, the SURPASS trials (2-4) allowed patients with a lower BMI of ≥25 kg/m^2 and an HbA1c between 7-10.5% (SURPASS-5: BMI of ≥23 kg/m^2). Nevertheless, the major difference between the trials' populations is that the SURPASS-2 to -4 trials required that the patients with T2D had inadequate glycaemic control with metformin monotherapy or metformin in combination with other anti-diabetic medication, which was not a requirement in SURMOUNT-2. This additional eligibility criterion has the potential to alter the population in terms of line of treatment which was key in the current submission. A comparison of key baseline characteristics is presented in Table 2, where we see that indeed the duration of diabetes (years) and the level of HbA1c (% and mmol/mol) is less in SURMOUNT-2, while weight (Kg) and BMI (% and category) is higher.

Key outcomes of the trials are presented in Tables 3 and 4. Regarding SURMOUNT-2, in terms of change in HbA1c (%), there was a reduction but the change from baseline to 72 weeks was smaller than in the SURPASS trials, while the estimated treatment difference from placebo was smaller than SURPASS-5 (placebo controlled) but still present. A reduction was also observed regarding body weight. The change from baseline (%) was higher than the SURPASS trials as was the estimated

treatment difference from placebo compared to SURPASS-5. These outcomes might reflect the differences in the baseline characteristics. Nevertheless, a direct comparison between the trials is not advisable due to the key differences described above.

Table 1: Concomitant treatments at baseline

Characteristics	TZP 5 mg	TZP 10 mg	TZP 15 mg	Comparator	Overall population
SURPASS-2					
Metformin	100%				
SURPASS-3					
Metformin alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin plus SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	458 (31.9)
SURPASS-4					
Metformin alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin plus SU, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin plus SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin plus SU plus SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SU alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGLT-2i alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SU + SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURPASS-5					
Insulin dose mean ± SD	39.1 ± 25.4	34.7 ± 15.4	40.5 ± 29.1	36.3 ± 18.0	37.6 ± 22.7
Metformin, n (%)	99 (85.3)	99 (83.2)	97 (80.8)	99 (82.5)	394 (82.9)
SURMOUNT-2					
Biguanides, n (%)	-	282 (90%)	276 (89%)	274 (87%)	832 (89%)
Sulfonylureas, n (%)	-	78 (25%)	78 (25%)	94 (30%)	250 (27%)
Sodium–glucose cotransporter 2 inhibitors, n (%)	-	63 (20%)	62 (20%)	66 (21%)	191 (20%)
Thiazolidinediones, n (%)	-	11 (4%)	11 (4%)	11 (3%)	33 (4%)
α–Glucosidase inhibitors, n (%)	-	2 (1%)	2 (1%)	4 (1%)	8 (1%)
Other, n (%)	-	0	1 (<1%)	1 (<1%)	2 (<1%)
CS = company submission; SD = standard deviation; SGLT-2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide					

Table 2: Baseline characteristics of patients included in the SURPASS-2, 3, 4 and 5 trials and SURMOUNT-2 trial.

Intervention/comparator	TZP 5 mg				TZP 10 mg				TZP 15 mg				SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Overall population				TZP 10 mg	TZP 15 mg	Placebo	Overall population
SURPASS trial	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**SURMOUNT-2**			
N	**470**	**358**	**329**	**116**	**469**	**360**	**328**	**119**	**470**	**359**	**338**	**120**	**469**	**360**	**1000**	**120**	**1,878**	**1,437**	**1,995**	**475**	**312**	**311**	**315**	**938**
Demographics																								
Age (years), mean ± SD	56.3 ± 10.0	57.2 ± 10.1	62.9 ± 8.6	61.5 ± 9.8	57.2 ± 10.5	57.4 ± 9.7	63.7 ± 8.7	60.4 ± 10.2	55.9 ± 10.4	57.5 ± 10.2	63.7 ± 8.6	60.5 ± 9.9	56.9 ± 10.8	57.5 ± 10.1	63.8 ± 8.5	60.0 ± 9.6	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9	54.3 ± 10.7	53.6 ± 10.6	54.7 ± 10.5	54.2 ± 10.6
Female, n (%)	265 (56.4)	158 (44.1)	131 (39.8)	55 (47.4)	231 (49.3)	165 (45.8)	119 (36.3)	47 (39.5)	256 (54.5)	165 (46.0)	135 (39.9)	55 (45.8)	244 (52.0)	147 (40.8)	364 (36.4)	54 (45.0)	996 (53.0)	635 (44.2)	749 (37.5)	211 (44.4)	158 (51)	159 (51)	159 (50)	476 (51)
Race, n (%)																								
White	382 (81.3)	323 (90.2)	260 (79.3)	95 (81.9)	376 (80.2)	328 (91.1)	259 (79.0)	94 (79.0)	392 (83.4)	327 (91.1)	285 (84.6)	94 (78.3)	401 (85.5)	329 (91.4)	825 (82.7)	97 (80.8)	1551 (82.6)	1307 (91.0)	1629 (81.8)	380 (80.0)	228 (73)	234 (75)	248 (79)	710 (76)
American Indian or Alaska native	53 (11.3)	0	[redacted]	[redacted]	53 (11.3)	1 (0.3)	[redacted]	[redacted]	57 (12.1)	1 (0.3)	[redacted]	[redacted]	45 (9.6)	2 (0.6)	[redacted]	[redacted]	208 (11.1)	4 (0.3)	[redacted]	[redacted]	-	-	-	-
Asian	6 (1.3)	20 (5.6)	15 (4.6)	20 (17.2)	11 (2.3)	19 (5.3)	16 (4.9)	21 (17.6)	5 (1.1)	20 (5.6)	8 (2.4)	22 (18.3)	3 (0.6)	17 (4.7)	31 (3.1)	22 (18.3)	25 (1.3)	76 (5.3)	70 (3.5)	85 (17.9)	44 (14)	42 (14)	39 (12)	125 (13)
Black or African American	28 (6.0)	13 (3.6)	13 (4.0)	1 (0.9)	21 (4.5)	12 (3.3)	17 (5.2)	2 (1.7)	15 (3.2)	8 (2.2)	11 (3.3)	3 (2.5)	15 (3.2)	11 (3.1)	32 (3.2)	0	79 (4.2)	44 (3.1)	73 (3.7)	6 (1.3)	33 (11)	22 (7)	22 (7)	77 (8)
Multiple	1 (0.2)	1 (0.3)	[redacted]	[redacted]	8 (1.7)	0	[redacted]	[redacted]	0	1 (0.3)	[redacted]	[redacted]	3 (0.6)	0	[redacted]	[redacted]	12 (0.6)	2 (0.1)	[redacted]	[redacted]	6 (2)	12 (4)	5 (2)	23 (2)
Native Hawaiian or other Pacific Islander	0	1 (0.3)	[redacted]	-	0	0	[redacted]	-	1 (0.2)	2 (0.6)	[redacted]	-	2 (0.4)	1 (0.3)	[redacted]	-	3 (0.2)	4 (0.3)	[redacted]	-	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Missing	-	-	[redacted]	-	-	-	[redacted]	-	-	-	[redacted]	-	-	-	[redacted]	-	-	-	[redacted]	-	-	-	-	-

Intervention/comparator	TZP 5 mg				TZP 10 mg				TZP 15 mg				SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo	Overall population				TZP 10 mg	TZP 15 mg	Placebo	Overall population
SURPASS trial	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**-2**	**-3**	**-4**	**-5**	**SURMOUNT-2**			
N	**470**	**358**	**329**	**116**	**469**	**360**	**328**	**119**	**470**	**359**	**338**	**120**	**469**	**360**	**1000**	**120**	**1,878**	**1,437**	**1,995**	**475**	**312**	**311**	**315**	**938**
Weight (kg), mean ± SD	92.5 ± 21.8	94.43 ± 18.86	90.3 ± 20.3	95.8 ± 19.8	94.8 ± 22.7	93.80 ± 19.81	90.6 ± 18.2	94.5 ± 22.2	93.8 ± 21.8	94.90 ± 20.98	90.0 ± 16.3	96.3 ± 22.8	93.7 ± 21.1	93.98 ± 20.59	90.2 ± 19.0	94.1 ± 21.8	93.7 ± 21.9	94.28 ± 20.06	90.3 ± 18.7	95.2 ± 21.6	100.9 ±20.9	99.6 ±20.1	101.7 ±22.3	100.7 ±21.1
BMI (kg/m²), mean ± SD	33.8 ± 6.9	33.58 ± 5.87	32.6 ± 6.1	33.6 ± 5.9	34.3 ± 6.6	33.41 ± 6.21	32.8 ± 5.5	33.4 ± 6.2	34.5 ± 7.1	33.68 ± 6.11	32.5 ± 5.0	33.4 ± 5.9	34.2 ± 7.2	33.42 ± 6.06	32.5 ± 5.5	33.2 ± 6.3	34.2 ± 6.9	33.52 ± 6.06	32.6 ± 5.5	33.4 ± 6.1	36 ± 6.4	35.7 ± 6.1	36.6 ± 7.3	36.1 ± 6.6
BMI category, n (%)																								
<30	[redacted]	104 (29.1)	[redacted]	[redacted]	[redacted]	116 (32.2)	[redacted]	[redacted]	[redacted]	109 (30.4)	[redacted]	[redacted]	[redacted]	117 (32.5)	[redacted]	[redacted]	[redacted]	446 (31.0)	[redacted]	[redacted]	60 (19)	51 (16)	52 (17)	163 (17)
30 to <35	[redacted]	136 (38.0)	[redacted]	[redacted]	[redacted]	119 (33.1)	[redacted]	[redacted]	[redacted]	121 (33.7)	[redacted]	[redacted]	[redacted]	120 (33.3)	[redacted]	[redacted]	[redacted]	496 (34.5)	[redacted]	[redacted]	92 (29)	114 (37)	105 (33)	311 (33)
≥35	[redacted]	118 (33.0)	[redacted]	[redacted]	[redacted]	125 (34.7)	[redacted]	[redacted]	[redacted]	129 (35.9)	[redacted]	[redacted]	[redacted]	123 (34.2)	[redacted]	[redacted]	[redacted]	495 (34.4)	[redacted]	[redacted]	160 (51)	146 (47)	158 (51)	464 (50)
Disease Characteristics																								
Duration of diabetes (years), mean ± SD	9.1 ± 7.2	8.47 ± 5.83	11.14 ± 7.08	14.1 ± 8.1	8.4 ± 5.9	8.43 ± 6.59	11.96 ± 7.45	12.6 ± 6.2	8.7 ± 6.9	8.52 ± 6.47	11.48 ± 7.54	13.7 ± 7.5	8.3 ± 5.8	8.12 ± 6.04	12.03 ± 7.66	12.9 ± 7.4	8.6 ± 6.5	8.38 ± 6.24	11.78 ± 7.51	13.3 ± 7.3	8.8 ± 6.9	8 ± 6.4	8.8 ± 6.2	8.5 ± 6.5
HbA1c (%), mean ± SD	8.32 ± 1.08	8.17 ± 0.89	8.52 ± 0.84	8.30 ± 0.88	8.30 ± 1.02	8.18 ± 0.89	8.59 ± 0.91	8.36 ± 0.83	8.26 ± 1.00	8.21 ± 0.94	8.52 ± 0.98	8.23 ± 0.86	8.25 ± 1.01	8.12 ± 0.94	8.50 ± 0.85	8.37 ± 0.84	8.28 ± 1.03	8.17 ± 0.91	8.52 ± 0.88	8.31 ± 0.85	8 ± 0.84	8.07 ± 0.99	7.89 ± 0.84	8.02 ± 0.89
HbA1c (mmol/mol), mean ± SD	67.46 ± 1.84	65.81 ± 9.69	69.59 ± 9.21	[redacted]	67.20 ± 11.20	65.91 ± 9.76	70.43 ± 9.95	[redacted]	66.78 ± 10.97	66.18 ± 10.24	69.63 ± 10.68	[redacted]	66.69 ± 10.99	65.20 ± 10.28	69.41 ± 9.32	[redacted]	67.03 ± 11.25	65.78 ± 9.99	69.65 ± 9.65	[redacted]	64 ± 9.1	64.7 ± 10.8	63.7 ± 9.2	64.1 ± 9.7

BMI = body mass index; HbA1c = glycated haemoglobin; SD = standard deviation; SEMA = semaglutide; TZP = tirzepatide; % = percentage

Table 3: Change in HbA1c, percentage

Characteristics	TZP 5 mg	TZP 10 mg	TZP 15 mg	Comparator
SURPASS-2 (versus semaglutide 1 mg)				
N	470	469	469	468
Change from baseline to 40 weeks	−2.09*	−2.37*	−2.46*	−1.86*
Change difference from SEMA (95% CI) to 40 weeks	−0.23** (−0.36, −0.10)	−0.51** (−0.64, −0.38)	−0.60** (−0.73, −0.47)	n/a
SURPASS-3 (versus insulin degludec)				
N	358	360	358	359
Change from baseline to 52 weeks	−1.93*	−2.20*	−2.37*	−1.34*
Change difference from insulin degludec (95% CI) at 52 weeks	−0.59** (−0.73, −0.45)	−0.86** (−1.00, −0.72)	−1.04** (−1.17, −0.90)	n/a
SURPASS-4 (versus insulin glargine)				
N	326	321	334	978
Change from baseline to 52 weeks	−2.24*	−2.43*	−2.58*	−1.44*
Change difference from insulin glargine (95% CI) at 52 weeks	−0.80** (−0.92, −0.68)	−0.99** (−1.11, −0.87)	−1.14** (−1.26, −1.02)	n/a
SURPASS-5 (versus placebo)				
N	116	118	118	119
Change from baseline to 40 weeks	−2.23*	−2.59*	−2.59*	−0.93*
Change difference from placebo (95% CI) at 40 weeks	−1.30** (−1.52, −1.07)	−1.66** (−1.88, −1.43)	−1.65** (−1.88, −1.43)	n/a
SURMOUNT-2 (versus placebo)				
N	-	312	311	315
Change from baseline to 72 weeks	-	-2.07	-2.08	-0.51
Estimated treatment difference from placebo (95% CI) at 72 weeks	-	-1.55*** (-1.74, -1.37)	-1.57 *** (-1.76, -1.37)	n/a

Table 26, 32, 36, 40 of the CS[3]
CI = confidence interval; CS = company submission; HbA1c = glycated haemoglobin; SEMA = semaglutide; TZP = tirzepatide
*p<0.001 vs. baseline; **p<0.001 vs. comparator; ***p<0.0001 vs. comparator

Table 4: Body weight change from baseline, percentage (kg)

Characteristics	TZP 5 mg	TZP 10 mg	TZP 15 mg	Comparator
SURPASS-2 (versus semaglutide 1 mg)				
N	470	469	469	468

Characteristics	TZP 5 mg	TZP 10 mg	TZP 15 mg	Comparator
Baseline	92.6	94.6	93.9	93.8
Change from baseline to 40 weeks	−7.8[a]	−10.3[a]	−12.4[a]	−6.2[a]
Change difference from SEMA (95% CI) to 40 weeks	−1.7[b] (−2.6, −0.7)	−4.1[b] (−5.0, −3.2)	−6.2[b] (−7.1, −5.3)	N/A
SURPASS-3 (versus insulin degludec)				
N	358	360	358	359
Baseline	94.5	94.3	94.9	94.2
Change from baseline to 52 weeks	−7.5[a]	−10.7[a]	−12.9[a]	2.3[a]
Change difference from insulin degludec (95% CI) at 52 weeks	−9.8[c] (−10.8, −8.8)	−13.0[c] (−14.0, −11.9)	−15.2[c] (−16.2, −14.2)	N/A
SURPASS-4 (versus insulin glargine)				
N	326	321	334	978
Baseline	90.3	90.7	90.0	90.3
Change from baseline to 52 weeks	−7.1[a]	−9.5[a]	−11.7[a]	1.9
Change difference from insulin glargine (95% CI) at 52 weeks	−9.0[d] (−9.8, −8.3)	−11.4[d] (−12.1, −10.6)	−13.5[d] (−14.3, −12.8)	N/A
SURPASS-5 (versus placebo)				
N	116	118	118	119
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline to 40 weeks	−6.2[a]	−8.2[a]	−10.9[a]	1.7[e]
Change difference from placebo (95% CI) at 40 weeks	[redacted]	[redacted]	[redacted]	[redacted]
SURMOUNT-2 (versus placebo)				
N	-	312	311	315
Baseline	-	100.9	99.6	101.7
Change from baseline to 72 weeks	-	-12.8	-14.7	-3.2
Estimated treatment difference from placebo (95% CI) at 72 weeks	-	-9.6[g] (-11.1, -8.1)	-11.6[g] (-13, -10.1)	N/A

Table 27, 33, 37, 42 of CS[3]
CI = confidence interval; CS = company submission; SEMA = semaglutide; TZP = tirzepatide; N/A = not applicable
[a]p<0.001; [b]p<0.001 versus semaglutide 1 mg; [c]p<0.001 versus insulin degludec for the mean change difference; [d]p<0.001 versus insulin glargine; [e]p<0.01 versus baseline; [f]p<0.001 versus placebo for the mean change difference; [g] p<0.0001 versus placebo