Single Technology Appraisal

Tirzepatide for managing overweight and obesity [ID6179]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tirzepatide for managing overweight and obesity [ID6179]

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   a. Royal College of General Practitioners
   b. Royal College of Physicians (RCP)
   c. Hertfordshire and West Essex Integrated Care Board
   d. On behalf of ICBs along with Anurita Rohilla
   e. Novo Nordisk Ltd
   f. NHS England (NHSE)
   g. Weight Management Unit (WMU) comments to be considered as part of DHSC response

3. **Comments on the Draft Guidance from experts:**
   a. Jonathan Pinkney, Clinical Expert – Nominated by Eli Lilly & Company

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 25 June 2024. 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 and Company

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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.	No disclosures.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures.
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** Lilly would like to thank NICE for the opportunity to respond to the preliminary recommendation made by the Committee detailed in the draft guidance document (DGD) for tirzepatide in obesity. In summary, Lilly is pleased that the Committee have concluded that tirzepatide should be recommended for patients with a body mass index (BMI) ≥35 kg/m^2 with at least one weight-related comorbidity across both primary care and secondary care setting without a long-term stopping rule. However, Lilly wish to re-iterate that there remains a substantial unmet need in managing this chronic disease for the broader population of patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity. Whilst the primary care and secondary care positioning will help reduce the inequity of access for patients with BMI ≥35 kg/m^2, Lilly is committed to working with NICE to address the key areas of uncertainty raised by the EAG and Committee in the DGD and the accompanying cover letter, to enable this broader patient population to also access and benefit from this potentially life-changing treatment and to reduce inequalities in the care of the chronic disease. This response will focus on responding to the key areas of uncertainty outlined in the DGD and presenting any relevant cost effectiveness analyses. Results are presented for patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity, as this remains the Company's target population; in addition, to address the Committee's specific request, Lilly have also presented cost-effectiveness results for the narrower subpopulation with a BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity. Lilly wishes to re-iterate that the wider population of patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity should be used for the decision making ICERs and this narrower subgroup is provided in order to allay the Committee's concerns of uncertainty.

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	To reflect the additional evidence and justifications presented in this response, Lilly have presented a revised Company base case post-DGD in Section 2. Finally, it should be noted that for completeness, Lilly have presented any requested scenario analysis (including scenarios for diet and exercise HCRU and the findings of Haase *et al.)* applied to both the Company and Committee base case. A summary of the key uncertainties that Lilly will seek to address in this response are provided below, with full details provided in the following sections of this response: **Perceived system challenges with mitigation strategies (Section 3)** • Primary care physicians are well equipped to deliver tirzepatide in primary care for obesity, given that tirzepatide is already being prescribed in primary care alongside diet and exercise for patients with type 2 diabetes mellitus (T2DM), many of whom have comorbid obesity.[1] • Relevant health bodies should seek to leverage and align with existing models of care, ensuring that appropriate levels of support are available, but without the need for complex or overly intensive programmes that may impede patient access to tirzepatide. • Capacity concerns should be alleviated by the fact that individuals who would become eligible for tirzepatide will already be receiving treatment for their comorbidities. Effective management of obesity in a primary care setting will also alleviate capacity concerns in specialist weight management services (SWMS) and potentially across all other areas of the NHSE (especially GPs in primary care) in the longer term. **Scenario analysis: HCRU for diet and exercise (Section 4)** • Lilly urge the Committee to discount a scenario in which no HCRU costs are applied for diet and exercise as this assumption implies that diet and exercise does not incur any HCRU cost, yet has the same efficacy as the diet and exercise intervention provided in SURMOUNT-1 – where patients received a light-touch intervention resulting in some observable efficacy. • If the HCRU associated with diet and exercise is excluded, the Company consider that such a scenario should necessarily have implications on the modelled efficacy. Alternatively, if the efficacy of the diet and exercise intervention from SURMOUNT-1 is retained, HCRU costs should be included which reflect the SURMOUNT-1 diet and exercise support. **BMI distribution (Section 5)** • The Company maintain that BMI should have a gamma distribution (rather than normal) in the model, as this better reflects the BMI category distribution reported for Community Weight Management Services (CWMS) and data from the SURMOUNT-1 target population, both of which represent robust evidence for patients with obesity who are seeking treatment in clinical practice.

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	• The EAG's suggestion that BMI would be normally distributed implies that those with the least severe disease and lowest risk of comorbidities will *vastly* outnumber those with the most severe disease who have most to gain from treatment; this lacks face validity. • The Committee may also wish to consider data from the IMPACT-O study, which collected BMI data for 1,734,788 patients at UK primary care clinics between January 2018–September 2022; these data appear to display a trend lying between the Health Survey England (HSE) and CWMS data. **Applying a natural progressive increase in weight while receiving tirzepatide treatment after 72 weeks (Section 6)** • Lilly strongly disagrees that a natural increase in weight should be applied to patients still receiving tirzepatide after 72 weeks or at any point in the model, as this assumes (based on no evidence or rationale) that the treatment effect of tirzepatide wanes over time whilst patients are still on treatment. • Data from SCALE do not represent a robust evidence source on which to base long-term treatment effect assumptions for tirzepatide as the reduction in treatment effect observed in SCALE may be due to the analyses including patients who discontinued liraglutide. Liraglutide is also a substantially less effective treatment than tirzepatide with a markedly different half-life. • Longer-term data from the first on-treatment analysis from the SELECT trial for semaglutide in obesity demonstrate that, in patients adhering to treatment, there is no loss of treatment effect over 221 weeks – this same trend would be expected for patients receiving tirzepatide in the longer term.[2] **Factual accuracy correction to T2DM cost inflation (Section 7)** • The costs from the UKPDS (unadjusted £484 for males and £647 for females) have been inflated by the EAG from a 2012/13 cost with an inflation factor of 14%, resulting in an inflated figure of £674. • The Company consider that this is a factual inaccuracy, since the standard practice for inflating costs is to use the Pay and Prices (P&P) index as reported in the PSSRU; using the P&P Index excluding capital results in a calculated value of £803 (£656 for males and £876 for females). **Scenario analysis: Long-term impact of obesity based on Haase et al. (Section 8)** • Incorporating the findings from Haase *et al.* in the model has significant limitations, and the Company are concerned that this study has provoked undue uncertainty in the cost effectiveness results for tirzepatide. Lilly are also concerned with the EAG's implementation of residual risk in the model.

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	• Whilst there are limitations with incorporating Haase *et al.* in the model, the study findings indicate that there may be important uncaptured benefits associated with treating patients with obesity *before* their BMI progresses to later disease stages – the model may therefore be underestimating the benefits associated with tirzepatide treatment for patients with BMI 30–34.9 kg/m^2. **Consideration of identified uncertainties within the wider context of the obesity policy in the United Kingdom (Section 9)** • Lilly would like the Committee to consider the identified uncertainty in the wider context of UK obesity policy – whilst NICE Reference Case stipulates that costs considered in the ICER are from the perspective of the NHS and PSS, many of the direct costs borne by HM Government budget fall outside the NHS budget but would be reduced if tirzepatide was available in the NHS. • Were the Committee to find itself also able to recommend tirzepatide in the target population, similar to the Scottish Medicines Consortium, this would represent a paradigm shift in access for patients to effective therapy for their obesity and a crucial step towards reducing health inequalities, not just in England and Wales, but throughout the United Kingdom.[3]
2.	**Revised Company base case following DGD** Table 1 details any assumptions which differ between the Committee and Company base case, whilst Table 2 presents the accompanying ICERs for the Committee and Company base case vs. diet and exercise for each population of interest. Full Company and Committee base case results (including total/incremental costs/QALYs) can be found in the Appendix (Section 10). Overall, these results demonstrate that tirzepatide represents a cost-effective use of NHS resources in the target population of BMI ≥30 kg/m^2 with at least one weight-related comorbidity (Table 1). As expected, cost-effectiveness results for the population with a BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity are less favourable than the broader population with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity, given their lower baseline risk. However, Lilly urge the Committee to interpret the ICERs presented for this population in the context of the important paradigm shift that tirzepatide could offer these patients – from the prospect of having a chronically elevated BMI without access to highly effective treatments until further progression, to the early alleviation of current comorbidities, the prevention of future comorbidities, and the avoidance of the long-term health impacts caused by previously having a BMI over 35 kg/m^2.[4]

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Table 1. Assumptions that differ between Company and Committee base case

	Committee-preferred assumption	Company-preferred assumption	Rationale
UKPDS T2DM cost, inflated to 2022/23	£674	£803	Lilly has included factual accuracy correction of T2DM costs in its base case. For more details see Section 7
Long-term efficacy of tirzepatide	Application of natural weight regain whilst patients remains on treatment from 72 weeks	No weight regain whilst patients remain on tirzepatide	Lilly maintain that patients receiving tirzepatide would not experience any natural weight regain while on treatment. For more details see Section 6
Distribution for BMI	Normal	Gamma	Lilly maintain that gamma better reflects the BMI distribution of people with obesity seeking treatment in NHS clinical practice. For more details see Section 5

Abbreviations: BMI: body mass index; T2DM: type 2 diabetes mellitus; UKPDS: UK Prospective Diabetes Study.

Table 2. Company and Committee base case results (vs. diet and exercise)

Treatment	Committee-preferred base case	Company-preferred base case
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£18,529	£13,623
Tirzepatide (10.0 mg)	£17,334	£13,251
Tirzepatide (15.0 mg)	£19,514	£14,735
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£24,265	£17,612
Tirzepatide (10.0 mg)	£23,552	£19,896
Tirzepatide (15.0 mg)	£27,699	£23,425

Footnotes: Full results (including total/incremental costs/QALYs) can be found in the Appendix (Section 10).
Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

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3.	**Perceived system challenges with mitigation strategies** In the cover letter shared alongside the DGD, it was indicated that the Committee were interested in receiving comments regarding the potential system challenges that may warrant an extension to the typical period in which relevant health bodies must comply with the recommendations made, as well as any potential solutions to these challenges. Lilly do not consider it within their remit to define the precise mode of delivery for tirzepatide and the diet and exercise support provided alongside it, nor how relevant health bodies may overcome any challenges faced. However, Lilly acknowledges the Committee's concerns, and as such, would like to echo the sentiments of the clinical experts at Appraisal Committee meeting (ACM) 2. Specifically, any concerns with introducing tirzepatide to primary care should be alleviated by the fact that tirzepatide is **already available and prescribed in primary care alongside diet and exercise** – in the same medical product and at the same doses – for T2DM following NICE TA924.[1] Given the vast majority of patients with T2DM also have obesity, primary care providers are therefore already well-equipped to prescribe and manage patients in this indication in a primary care setting. Whilst in the obesity indication tirzepatide must be provided alongside 'a reduced-calorie diet and increased physical activity' (as opposed to 'alongside diet and exercise' in T2DM), the level of diet and exercise support provided in SURMOUNT-1 was **light-touch, aligned with what is already recommended in CG189, and was less intense than what is currently provided in a primary care Tier 2 setting**.[5] Relevant health bodies should therefore seek to leverage and align with existing models of care, ensuring that appropriate levels of support are available (as in the management of other chronic diseases in primary care), but without the need for complex or overly intensive programmes that may impede patient access to this treatment. It is anticipated that simple approaches to implementation and light-touch support will be critical in ensuring that treatment with tirzepatide reaches the full spectrum of patients with obesity and comorbidities, maximising patient access and reducing inequalities in care. Furthermore, with regards to capacity concerns, Lilly wish to re-iterate that patients with comorbidities who would become eligible for treatment with tirzepatide will already be known to their primary care physician as they are already receiving care for their comorbidities. In addition, whilst a recommendation for tirzepatide will allow more people to receive effective pharmacological treatment for their obesity in a primary care setting, it is expected that this would alleviate capacity constraints within specialist weight management services (SWMS), allowing those most in need of this service to access it. In the longer-term, more effective management of obesity at the population level through availability and use of effective pharmacological treatments would also be expected to reduce the number of people requiring care for obesity-related comorbidities and complications, potentially reducing capacity constraints across all areas of the National Health Service in England (NHSE). This is underscored in the previously discussed Lilly Market Research in England and Wales (n=381), in which 100% of GPs responded that offering patients with obesity additional effective treatments in primary care would add value to their patients. 93% of GPs responded that offering patients with obesity additional

	effective treatments in primary care would add value to their GP practice. When asked about the extent to which this would help them tackle capacity constraints, 87% responded between 4 to 7 on a scale of 1 to 7 (1 being 'Not at all' and 7 being 'To a great extent'). Moreover, a recent study estimated that a 20% decrease in the prevalence of BMI ≥30 kg/m^2 in the UK would lead to a cost saving of around £12 billion every year (considering direct costs, costs due to loss of health-related quality of life [HRQoL] and wider costs to society due to loss of productivity and social care) – more than double the annual NHSE costs for cancer treatment.[6]
4.	**Scenario analysis: Implications of the EAG's preference for no HCRU for diet and exercise comparator** In relation to the HCRU associated with diet and exercise (alone or as an adjunct to tirzepatide), the DGD notes that the EAG prefers to apply "*all the proposed resource to the tirzepatide arm for the duration of tirzepatide treatment and assumed no resource costs for the diet and exercise arm*". The Committee conclude that this is likely to "*result in the highest likely cost-effectiveness estimates for tirzepatide"* and as such that they will consider a range of scenarios in decision making. Whilst a range of scenarios may be considered in light of implementation uncertainties, Lilly strongly disagree that this scenario should be included as part of such a range, and would instead urge the Committee to discount it entirely. This is because the application of this assumption **implies that diet and exercise does not incur any HCRU cost, yet has the same efficacy as the diet and exercise intervention provided in SURMOUNT-1 – where patients received a light-touch intervention resulting in some observable efficacy**. As such, **the costs considered (or lack thereof) in this scenario do not correspond with the modelled efficacy**, strongly biasing the analysis in favour of diet and exercise and resulting in ICERs that are inappropriate for decision-making. If the EAG's preference is to exclude the costs and HCRU associated with diet and exercise based on the argument that there is "*no service use for people having diet and exercise support alone*" (which directly contradicts the recommendations in CG189 and the input from clinical experts during ACM1 and ACM2), the Company consider that such a scenario should necessarily have implications on the modelled efficacy of the comparator – Lilly have therefore explored a scenario in which there are no costs associated with diet and exercise and no efficacy (to reflect the lack of intervention; Table 4). Compared to the EAG-preferred assumption (Table 3), this scenario reduces the ICERs for tirzepatide by approximately ~£10,000 across all three doses, highlighting the extent of the bias when the modelled efficacy does not correspond with the costs of the diet and exercise arm. To further explore this concept, Lilly have also presented an inverse scenario in Table 5, in which the efficacy of the diet and exercise intervention from SURMOUNT-1 is retained, but costs are included which reflect those specified by NHSE to reflect the SURMOUNT-1 diet and exercise support. It should be noted that when NHSE costs are applied to the diet and exercise arm, no tirzepatide-specific costs are included (e.g. titration

appointments, administration training appointments). Finally, Lilly have presented a scenario in Table 6 which includes light-touch HCRU which is aligned with the SURMOUNT-1 protocol; the Company consider that this scenario better reflects the level of support that would be required in clinical practice.

Table 3. EAG-preferred assumption – no costs in the diet and exercise arm but efficacy from SURMOUNT-1; NHSE-proposed resource use applied to tirzepatide arm only (vs. diet and exercise)

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£24,250	£17,981
Tirzepatide (10.0 mg)	£21,962	£16,949
Tirzepatide (15.0 mg)	£24,170	£18,381
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£31,507	£23,127
Tirzepatide (10.0 mg)	£29,727	£25,300
Tirzepatide (15.0 mg)	£34,191	£29,098

Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Table 4. No costs and no efficacy in the diet and exercise arm; NHSE-proposed resource use in the tirzepatide arm

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£17,319	£12,942
Tirzepatide (10.0 mg)	£16,733	£12,879
Tirzepatide (15.0 mg)	£18,706	£14,289

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BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£19,872	£15,226
Tirzepatide (10.0 mg)	£20,332	£17,426
Tirzepatide (15.0 mg)	£23,474	£20,177

Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Table 5. NHSE-proposed resource use in diet and exercise without appointments specific to tirzepatide with SURMOUNT-1 efficacy; NHSE-proposed resource use in the tirzepatide arm

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£18,455	£13,567
Tirzepatide (10.0 mg)	£17,448	£13,344
Tirzepatide (15.0 mg)	£19,774	£14,943
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£24,163	£17,535
Tirzepatide (10.0 mg)	£23,701	£20,027
Tirzepatide (15.0 mg)	£28,064	£23,744

Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Table 6. Light-touch SURMOUNT-1 HCRU

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		

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	Tirzepatide (5.0 mg)	£19,289	£14,173
	Tirzepatide (10.0 mg)	£17,904	£13,683
	Tirzepatide (15.0 mg)	£20,071	£15,144
	BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
	Tirzepatide (5.0 mg)	£25,273	£18,355
	Tirzepatide (10.0 mg)	£24,369	£20,603
	Tirzepatide (15.0 mg)	£28,535	£24,148
	Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.		
5.	**BMI distribution** In the DGD, the Committee concludes that further analyses on the BMI distribution in the target population (BMI ≥30 kg/m^2) is required and requests that a detailed graduation of the BMI distribution in SURMOUNT-1 is presented to better understand how well the BMI distribution in the SURMOUNT-1 trial matches the distribution in clinical practice. The Company have therefore provided in Figure 1 the requested breakdown of BMI from the target population from SURMOUNT-1.		

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	Figure 1. BMI distribution of patients with a BMI ≥30 kg/m^2 with at least one comorbidity in SURMOUNT-1 **Abbreviations:** BMI: body mass index. In line with these data, the Company maintain that the most appropriate modelling assumption is that BMI has a gamma distribution, rather than adopting a normal distribution for BMI as proposed by the EAG. This is because the EAG's proposed sampling distribution does not reflect the available evidence for the demographic characteristics of patients with obesity who are seeking treatment in NHSE clinical practice.

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Specifically, whilst the EAG's normal distribution scenario applies the Health Survey England (HSE) data "assuming BMI to be normally distributed", no evidence is provided that the HSE data is normally distributed. Crucially, the EAG have also not provided any evidence that the general population distribution is likely to reflect those presenting for treatment with tirzepatide or diet and exercise in the NHSE. In fact, the BMI category distribution reported for Community Weight Management Services (CWMS) (which specifically reports data for patients presenting for treatment) is very similar to the data in the model (Table 8). The CWMS data are also broadly aligned with those from the SURMOUNT-1 trial target population (Figure 1, Table 8) – again, those enrolling in a clinical trial are, by definition, seeking treatment for their obesity and similarly have a BMI distribution that is more aligned with gamma sampling.

Lilly consider that there is clinical rationale for the difference observed between the general population and SURMOUNT-1 and CWMS data (and thus the most appropriate sampling approach in the model) – those with a higher BMI are more likely to be aware of and driven to seek a potentially life-long treatment, as it is likely these individuals would be most affected by their obesity. Accordingly, it is logical that the model should sample a relatively higher proportion of patients within the combined BMI ≥35 kg/m^2 categories (as per the SURMOUNT-1 and CWMS data). In contrast, the EAG's suggestion that BMI would be normally distributed implies that those with the least severe disease and lowest risk of comorbidities will *vastly* outnumber those with the most severe disease who have most to gain from treatment. This assumption lacks face validity and ultimately leads to unrealistic and extremely skewed results; Lilly therefore maintain that gamma sampling is the most appropriate assumption in the model.

Table 7. Gamma sampling distribution – Company-preferred assumption

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£18,748	N/A – already applied in Company base case
Tirzepatide (10.0 mg)	£16,355	N/A – already applied in Company base case
Tirzepatide (15.0 mg)	£17,729	N/A – already applied in Company base case
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£24,412	N/A – already applied in Company base case
Tirzepatide (10.0 mg)	£23,209	N/A – already applied in Company base case

Tirzepatide (15.0 mg)	£27,295	N/A – already applied in Company base case

Abbreviations: BMI: body mass index; D&E: diet and exercise; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Additional evidence

Additional data that may be relevant for the Committee to consider are from the IMPACT-O study, in which data from the UK IQVIA Medical Research Database and The Health Improvement Network database were analysed, with BMI data collected for 1,734,788 patients at primary care clinics throughout the UK between January 2018–September 2022. Overall, of the total proportion of patients with BMI data collected in primary care with overweight/obesity (n=1,110,830), 30.4% had Class I obesity (BMI 30–<35 kg/m^2), 14.4% has Class II obesity (BMI 35–<40 kg/m^2) and 10.1% had Class III obesity (BMI 30–<35 kg/m^2).[7] As shown in Table 8, these data (when adjusted) appear to display a trend lying in between the HSE and the CWMS data.

Table 8. BMI distributions in relevant sources

BMI (kg/m^2)	SURMOUNT-1 (ITT)[8]	SURMOUNT-1 (target population)[8]	Community Weight Management Services	Model (gamma distribution) – Company preference	General Population (HSE general population survey)	Model (normal distribution) – EAG preference	IMPACT-O[7]
30.0–34.9 (Class I)	37%	35%	40%	35%	66%	65%	55.6%
35.0–39.9 (Class II)	30%	29%	30%	32%	27%	29%	25.9%
40+ (Class III)	33%	35%	30%	33%	7%	7%	18.5%

Footnotes: data from IMPACT-O have been adjusted to total 100%
Abbreviations: BMI: body mass index; EAG; external assessment group: HSE; Health and Safety Executive; ITT: intention-to-treat.

Relevant scenarios

Based on data from IMPACT-O, Lilly have explored a scenario where the BMI sampling is based on the IMPACT-O mean and SDs. For this scenario, a gamma distribution is selected as this was considered to better reflect the distribution of data in IMPACT-O. The results from this scenario are presented in Table 9. As expected, this scenario results in ICERs that lie between the scenarios that reflect the CWMS and HSE data.

Table 9. BMI sampling in line with IMPACT-O data

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£17,809	£18,021
Tirzepatide (10.0 mg)	£16,438	£17,636
Tirzepatide (15.0 mg)	£18,273	£19,717
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£24,237	£17,564
Tirzepatide (10.0 mg)	£22,730	£19,432
Tirzepatide (15.0 mg)	£26,758	£22,831

Abbreviations: BMI: body mass index; D&E: diet and exercise; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

6.

Applying a natural progressive increase in weight while receiving tirzepatide treatment after 72 weeks

In the Committee-preferred base case, it was assumed that the impact of age-related natural increase in weight would, *to some extent*, also impact someone taking tirzepatide over the time horizon in the model; accordingly, the Committee-preferred base case applies a natural increase in weight to patients still receiving tirzepatide after 72 weeks (the SURMOUNT-1 trial period). Lilly strongly disagrees with this assumption given that it implies that the treatment effect of tirzepatide wanes over time whilst patients **are still receiving treatment**. Key justifications and evidence are presented below to allay any uncertainty surrounding the longer-term effects of tirzepatide and support the removal of this assumption from the Committee base case.

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	Relevance of data from the SCALE prediabetes extension study Lilly understands that the primary driver behind the EAG and Committee's exploration into treatment effect waning in the model was Week 60 data from the SCALE prediabetes extension study (which the EAG reproduced in Figure 3 in their report). However, these data do not represent a robust source of evidence on which to base long-term treatment effect assumptions for tirzepatide. Firstly and most pertinently, Lilly wish to highlight that the reduction in treatment effect observed in the SCALE study may be due to the analyses **including patients who discontinued liraglutide** rather than due to a treatment waning effect. In contrast to the description provided in the EAG report (which refers to last observation carried forward [LOCF]), the week-by-week data presented from the SCALE prediabetes extension are the observed mean relative change in body weight for individuals in the full analysis set who completed each scheduled visit, the number of which has roughly halved over the 160 weeks due to withdrawals from the trial. Furthermore, as the SCALE prediabetes extension study was conducted before the widespread usage of, and regulatory requirement for, estimands (which specifically provide a description of how the efficacy of treatment is calculated in the presence of intercurrent events, such as whether a person remains on the intervention or discontinues), the observed data from SCALE are not specified to have been taken only from patients remaining on treatment and are assumed to therefore include patients who stopped treatment but did not withdraw from the trial – the SCALE trial reports that "The prespecified efficacy analyses used data from the full analysis set of all randomised individuals who received at least one treatment dose and had at least one post-baseline assessment". This statement implies that the observed data may include patients who were no longer taking liraglutide. Beyond these significant limitations associated with these data, it should also be noted that liraglutide represents a substantially less effective treatment than tirzepatide with a markedly different half-life (requiring daily, rather than weekly, injections); in SURMOUNT-1, mean weight loss for tirzepatide was −16.0%, −21.4% and −22.5% for tirzepatide 5, 10 and 15 mg, respectively, whereas in SCALE, mean weight loss was −6.1%. The applicability of any findings from SCALE to tirzepatide, which represents a more effective and longer-acting incretin therapy than liraglutide, is therefore likely to be extremely limited. ***Lack of rationale for loss of treatment effect whilst on treatment***

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	Considering the above, Lilly maintain that there is no evidence nor rationale for patients receiving tirzepatide to experience a loss of treatment effect over time such that they would experience a natural increase in weight whilst on treatment. In fact, Lilly encourage the Committee to consider this issue from the perspective of obesity as a chronic progressive disease: *untreated* obesity has been shown in literature already presented to lead to a gradual increase in BMI over time, however tirzepatide is known to have mechanism of action that acts directly on two incretin hormone receptors regulating satiety and appetite which should be considered disease-modifying. Accordingly, the Company do not consider that there is biological rationale for a person remaining on treatment to experience a reduction in the effect on satiety and appetite over time that would lead to weight regain. The Company-preferred assumption (presented in Table 10) is therefore that absolute weight loss would be maintained in the tirzepatide arm for the duration of the modelled time horizon while patients remain on treatment. ***Additional evidence*** To support the Company's position, Lilly wish to highlight longer-term data from the first on-treatment analysis from the SELECT trial for semaglutide in obesity has recently been published (Lincoff ***et al.***, 2024), which demonstrate that in patients adhering to treatment, there is no loss of treatment effect over 221 weeks, with percentage body weight at 221 weeks remaining consistent with the 65 week data (at which point the majority of participants had reached a plateau of effect; Figure 2).[2] Given that both medicines are incretin analogues (while acknowledging that tirzepatide is a dual agonist and semaglutide single agonist), this same trend to plateauing would be expected to be generalisable patients receiving tirzepatide in the longer term. As such, in contrast to the Committee's preferred assumption, these data suggest that weight loss for patients remaining on tirzepatide would be maintained at least until 221 weeks, and if extrapolated, suggest that weight loss would be maintained over the long term.

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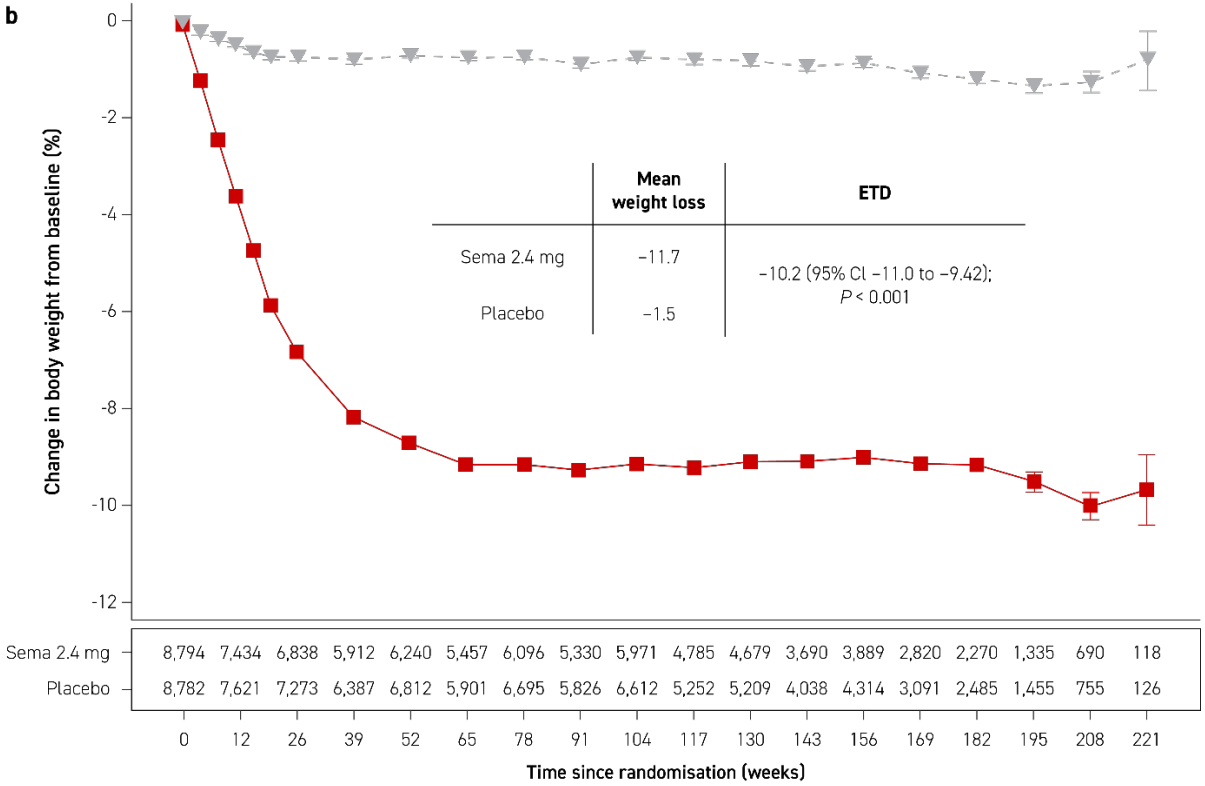
Figure 2. Percentage change in body weight over time in SELECT (semaglutide in obesity; Week 221 – on-treatment analysis)



Footnotes: Data presented is from a first on-treatment analysis (observation period until the first time being off treatment for >35 days), which provides an estimate of weight loss in those adhering to treatment (corresponding to the efficacy estimand in SURMOUNT-1)
Abbreviations: SD : standard deviation.
Source: Lincoff *et al*. 2024[2]

Relevant scenario analyses

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Whilst Lilly has assumed in their base case that patients receiving tirzepatide would not experience a natural progressive weight regain whilst on treatment, several other scenarios have been explored, in which a waning assumption has been applied.

Table 11 presents results when an annual natural increase in BMI is applied from 10 years, whilst Table 12 presents scenarios that explore application of treatment waning from 20 years. Table 10 presents the cost-effectiveness results when no annual natural increase in BMI is included whilst still on tirzepatide treatment (Company-preferred assumption). As expected, the application of a net increase in BMI over time whilst patients remain on treatment increases the ICER for tirzepatide, since it assumes (based on no evidence) that weight regain whilst on tirzepatide would occur at the same rate as someone who is receiving no treatment (in the diet and exercise arm) at arbitrary timepoints.

Table 10. No annual natural increase in BMI whilst still on tirzepatide treatment (Company-preferred assumption)

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£14,452	N/A – already applied in Company base case
Tirzepatide (10.0 mg)	£14,866	N/A – already applied in Company base case
Tirzepatide (15.0 mg)	£17,143	N/A – already applied in Company base case
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£18,278	N/A – already applied in Company base case
Tirzepatide (10.0 mg)	£20,839	N/A – already applied in Company base case
Tirzepatide (15.0 mg)	£24,511	N/A – already applied in Company base case

Abbreviations: BMI: body mass index; D&E: diet and exercise; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Table 11. Constant annual natural increase in BMI after 10 years

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		

Tirzepatide (5.0 mg)	£15,909	£15,118
Tirzepatide (10.0 mg)	£15,697	£14,262
Tirzepatide (15.0 mg)	£18,008	£15,691
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£20,506	£19,954
Tirzepatide (10.0 mg)	£21,460	£20,614
Tirzepatide (15.0 mg)	£25,178	£24,274

Abbreviations: BMI: body mass index; D&E: diet and exercise; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Table 12. Constant annual natural increase in BMI after 20 years

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI ≥30 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£14,738	£13,991
Tirzepatide (10.0 mg)	£15,131	£13,466
Tirzepatide (15.0 mg)	£17,335	£15,001
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£18,746	£18,196
Tirzepatide (10.0 mg)	£20,784	£20,100
Tirzepatide (15.0 mg)	£24,395	£23,668

Abbreviations: BMI: body mass index; D&E: diet and exercise; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

7.	**Factual Accuracy Correction to T2DM cost inflation**

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	Lilly welcomes that the Committee-preferred T2DM costs include non-hospital costs in addition to drug costs. However, Lilly would like to highlight that the current costs obtained from UKPDS have not been correctly inflated to the current cost year. The costs from the UKPDS (unadjusted £484 for males and £647 for females) have been inflated by the EAG from a 2012 cost with an inflation factor of 14%, resulting in an inflated figure of £674. However, standard practice for inflating costs is to use the P&P index as reported in the PSSRU. Using the P&P Index excluding capital results in a calculated value of £803, which the Company have adopted in place of the Committee-preferred value in their base case.
8.	**Scenario analysis: Long-term impact of obesity** As detailed in the DGD, the EAG has suggested that it may be unreasonable for the model to assume there is no long-term impact from having previously had a higher BMI, based on evidence from Haase *et al*.[9] As a result, the Committee concluded that there was uncertainty in the model, and that the base case ICERs presented were likely to be higher if residual risk was accounted for in the model. Whilst Lilly notes that the Committee discussed that Haase *et al.* may have "potential biases", Lilly consider that incorporating the findings from Haase *et al.* into the model has significant limitations, and has provoked undue uncertainty in the cost effectiveness results for tirzepatide. Lilly are also concerned with the EAG's implementation of residual risk in the model and has therefore presented a corrected scenario that better aligns with the findings from Haase *et al*. With regards to the uncertainty in the model, Lilly wish to highlight that the findings of Haase *et al*. – that having an elevated BMI results in a long-term irreversible impact – indicate the direction of the uncertainty may in fact be in favour of early use of tirzepatide, since these findings suggest there are **important benefits associated with treating patients with obesity *before* their BMI progresses to later disease stages**; benefits which are currently uncaptured in the model. In the context of this appraisal, these findings therefore indicate that the model may be underestimating the benefits associated with tirzepatide treatment for patients with BMI 30–34.9 kg/m^2. Furthermore, they support Lilly's proposed positioning for patients with a ≥30 kg/m^2 with at least one weight-related comorbidity, as treatment with tirzepatide may enable patients with BMI 30–34.9 kg/m^2 to benefit from long-term weight loss and thereby avoid any residual irreversible health impacts associated with previously having a BMI ≥35 kg/m^2. ***Limitations associated with Haase et al. and its utility in the model*** As noted above, Lilly consider that Haase *et al.* has several key limitations which may limit its usability within the economic analysis underpinning this appraisal. In particular, the residual risk observations in Haase *et al*. are based on a median weight loss of 13% from a baseline BMI of exactly 35 kg/m^2 – Lilly therefore consider that the residual risk data from Haase *et al*. are not representative of the modelled population, where mean weight

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	loss in the tirzepatide 15 mg arm (which the majority of patients will receive) is −22.5%.[9] The utility of this study in the economic model is also limited by the fact that in Haase *et al.* patients with a BMI <25 kg/m^2 (even at the end of year 4 of the index period) are excluded, meaning that anyone who experienced weight loss which took them into a normal BMI range were excluded. As a result, Haase *et al.* excludes those with significantly higher magnitudes of weight loss (such as those who would receive tirzepatide) who are known to have the greatest benefit.[9] Importantly, Lilly would also like to note that the model is based on risk equations derived from large population data sets which include coefficients related to weight/BMI at the time points observed in the datasets, and therefore are likely not compatible with these adjustments. Specifically, the population the risk equations are derived from are likely to be a combination of patients who with 'stable' BMI and those who have gained or lost weight, and therefore are not an appropriate baseline for the application of this paper's findings. Other key concerns associated with the study and study reporting are detailed below, which further cast doubt on the robustness of this study and its usability for informing decision-making: • Haase *et al*. excluded patients with a weight loss between 5–10% – it is unclear why these patients are excluded, given that the study itself notes that clinical guidelines in the UK and USA suggest that weight loss between 5 and 10% is sufficient to have a clinical impact on outcomes, and that such weight loss would be relevant to the comparator arm in the model. • It is well-established that obesity is one of the leading causes of heart failure, atrial fibrillation or unstable angina/myocardial infarction (MI), yet Haase *et al.* failed to observe a clear reduction in the risk of these comorbidities/complications after weight loss, suggesting that the duration of follow-up may not have been adequate to capture changes in the incidence of these events. • The median follow-up for the weight loss group (5.7 years, with an IQR 2.8, 8.3) was shorter than the stable weight loss group (6.4 years, with an IQR 3.4, 9.3). • A relatively higher proportion of individuals in the weight-loss cohort had comorbidities at baseline compared with the stable cohort (see Figure 2 in Haase *et al*.) which may have resulted in a higher risk of cardiovascular (CV) outcomes in the weight loss cohort, but may also have been an impetus for weight loss, confounding comparisons with the stable-weight cohort. • A relatively lower proportion of individuals in the weight loss group were male (37.1%) compared with the stable cohort (50.3%), which may have influenced the results given that there are well-established sex differences in terms of complication risk.[10]

- Based on Supplementary Figure 1, only ~50% of people in the stable group had a BMI calculation 2 years after their baseline measurement compared with ~96% in the weight loss group. It is therefore unclear whether the other ~50% of the stable weight cohort group did in fact remain a stable weight over the follow-up period.
- With regards to the weight loss intervention, the paper states "27% weight loss medication, 1.1% bariatric surgery, 52.7% weight loss diet" – this leaves 19.2% (n=9,374) of patients who are not accounted for.
- The study did not capture whether people with T2D were receiving SGLT2i or GLP-1 RA therapies which may have directly confounded other observed risks, given their known efficacy profiles.
- Based on the study reporting, there appears to be no adjustment for location/socioeconomic status/ethnicity in the analyses, which are known to influence obesity-related outcomes.

Findings from Khunti et al.

With regards to the applicability of the findings from Haase *et al.* Lilly wish to draw the Committee's attention to a recently published study by Khunti *et al*., which appears to be an extension of the Haase *et al.* paper, in which Khunti *et al.* sought to identify associations between weight loss/gain and the risk of developing the same obesity-related complications as Haase *et al*., also using data from adults with obesity form the UK Clinical Practice Research Datalink GOLD database (N=418,774).[4] Importantly, this study identified that the weight loss benefit on obesity-related complications was dependent on weight loss magnitude (with the paper comparing changes from baseline of −10% vs. −20%), further supporting the sentiment that the residual risk data from Haase *et al*. paper cannot be applied in this appraisal.

When considering residual risk specifically, this paper indicates that when estimating a patients' risk of future events, it is important to consider both whether they had an elevated BMI initially (as per Haase *et al*.), as well as the extent of the weight loss achieved to reach their new BMI. Notably, this study identified a significant additional benefit of 20% vs. 10% weight loss for T2DM and OSA, regardless of baseline BMI. For example, for a baseline BMI of 40 kg/m^2, a 10% and 20% weight loss was associated with a ~25% and ~50% reduction, respectively, in the hazard ratio of T2DM relative to maintaining a stable body weight (Figure 3 in Khunti *et al*.).[4] Given these findings and the fact that tirzepatide is associated with notably greater weight loss than diet and exercise alone, and notably greater weight loss than was tested in Haase *et al*., Lilly considers the use of Haase *et al*. for scenario analysis to be unsupportable.

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	Implementation of residual risk in the model In addition to the limitations highlighted above, Lilly are concerned with the EAG's implementation of the findings from Haase *et al.* in the model. In their report post-ACM2, the EAG explain that they use the following classifications for the residual risk findings in Haase *et al*: • Residual risk, assume 75% effect (and 50% effect as a further scenario) • No residual risk, assume 100% effect • Superior, assume 125% effect, and 100% effect as a scenario However, the EAG have not explained that these modifications are only applied as adjustment factors to the costs and utilities for each event, rather than modifying the actual risk of event – whilst Lilly appreciate this is likely applied as a simplification, it should be noted that this approach does not account for the wider implications of these events in the model. For instance, the risk of T2DM does not just affect the costs/QALYs, it also impacts the risk of future CV events. In their report post ACM2, the EAG states that the Company's alternative approach of amending the risk of an events within the Visual Basic for Applications (VBA) "does not limit the complications' effects to lie somewhere between no effect and 100% effect", but then fails to explain how their own method addresses this limitation. In addition, it should be noted that when the EAG apply the findings of Haase *et al.* they do so by applying an adjustment factor of 0.75 to cost and utilities for comorbidities, where Haase *et al*. report a residual risk (e.g. T2DM). Lilly do not consider that this approach is logical – "residual risk" by definition implies that even after a patient loses weight, their risk of the event is **elevated** compared to that estimated by the risk equation (which in this case represents the risk of someone with a "stable" BMI). If a patient's risk of an event is increased compared to what is estimated by the risk equation (i.e. they have residual risk), this would **increase** costs and disutilities across **all** arms. This is not what the EAG's method achieves; instead, their method reduces total costs and utilities for these events by applying an adjustment factor of 0.75, which essentially removes a quarter of the costs and disutilities for these events. In a similar vein, for events classified as having "no residual risk" (e.g. MI and angina), the EAG applies an adjustment factor of zero. The result of this adjustment is that there are **no longer any costs or disutilities** applied in the model for these events. To illustrate this, the Company have provided a breakdown of costs associated with each event in the model before and after the EAG's Haase *et al.* scenario is run (Table 13) – the same pattern is observed for QALYs.

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Table 13. Comparison of costs in the model before and after EAG's implementation of residual risk in the model; BMI ≥30 kg/m^2 with at least one weight-related comorbidity

Treatment	T2DM	Angina	MI	Stroke	OSA	NAFLD
Committee-preferred base case						
TZP 5 mg	£3,066	£654	£1,019	£622	£1,475	£1,550
TZP 10 mg	£2,658	£679	£1,000	£602	£1,496	£1,487
TZP 15 mg	£2,635	£653	£995	£623	£1,484	£1,501
Diet and Exercise	£5,740	£723	£1,058	£622	£1,485	£1,505
EAG implementation of Haase *et al.*						
TZP 5 mg	£2,299	£0	£0	£622	£1,107	£1,550
TZP 10 mg	£1,994	£0	£0	£602	£1,122	£1,487
TZP 15 mg	£1,976	£0	£0	£623	£1,113	£1,501
Diet and Exercise	£4,305	£0	£0	£622	£1,114	£1,505

Abbreviations: NAFLD; non-alcoholic fatty liver disease; MI: myocardial infarction; OSA: obstructive sleep apnoea; T2DM: type 2 diabetes mellitus.

Since Lilly do not consider the EAG's adjustment factors to be logical, nor reflect the study's findings, Lilly have presented cost-effectiveness in which the adjustment factor applied to costs/utilities has been corrected (Table 14). Specifically, where Haase *et al.* reports a residual risk, Lilly have applied an adjustment factors of 1.25 to costs/utilities (rather than the EAG's 0.75) – this means that costs/disutilities are increased for these events across all arms, reflecting the fact that these patients are at an elevated risk of these events even after losing weight. Similarly, Lilly has applied an adjustment factor of 1 to events where these is no difference between individuals at a stable weight and those who previously had higher BMI – this means costs/disutilities remain the same as that estimated by the risk equations, reflecting the fact that patients who previously had a higher BMI are at the same risk as those who did not. As per the EAG's scenarios, results have not been presented for the target population, as the findings in Haase *et al.* are only reported for/relevant for subgroups of the target population.

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Table 14. Correction of EAG method for Haase scenario

Treatment	ICER (applied to Committee base case; cost/QALY)	ICER (applied to Company base case; cost/QALY)
BMI 30–34.9 kg/m^2 with at least one weight-related comorbidity		
Tirzepatide (5.0 mg)	£22,239	£15,939
Tirzepatide (10.0 mg)	£21,726	£18,173
Tirzepatide (15.0 mg)	£25,652	£21,504

Footnotes: Results have not been presented for the target population, as the findings in Haase *et al.* are only reported for/relevant for subgroups of the target population
Abbreviations: D&E: diet and exercise; QALY: quality-adjusted life years; ICER: incremental cost effectiveness ratio.

9.

Consideration of identified uncertainties within the wider context of obesity policy in the United Kingdom

Lilly trust that their responses on the detail of the identified uncertainties above will allow the Committee to conclude that ICERs in the target population of BMI ≥30 kg/m^2 with at least one weight-related comorbidity do represent a cost-effective use of NHS resources, but they would also like the Committee to consider uncertainty in the wider context of UK obesity policy. The NICE Reference Case stipulates that costs considered in the ICER are from the perspective of the NHS and PSS – but in obesity it is well recognised that many of the direct costs borne by HM Government budget fall outside the NHS budget but would be reduced if effective treatment for obesity were available in the NHS.[11] The Committee may therefore consider that these cost benefits not captured within the Reference Case, but available to HM Government budget, allow it further confidence that any remaining uncertainties in the ICER are balanced by uncaptured cost benefits. Were the Committee to find itself also able to recommend tirzepatide in the target population, similar to the Scottish Medicines Consortium, this would represent a paradigm shift in access for patients to effective therapy for their obesity and a crucial step towards reducing health inequalities, not just in England and Wales, but throughout the United Kingdom.[3]

10.

Appendix – full cost-effectiveness results

Table 15. Company-preferred base case

Treatment	Total Costs	Total QALYs	vs. D&E

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			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
BMI ≥30 kg/m² with at least one weight-related comorbidity					
Diet and Exercise	£20,976	15.582			
Tirzepatide (5.0 mg)	£35,141	16.622	£14,165	1.040	£13,623
Tirzepatide (10.0 mg)	£37,986	16.866	£17,010	1.284	£13,251
Tirzepatide (15.0 mg)	£40,967	16.939	£19,991	1.357	£14,735
BMI 30–34.9 kg/m² with at least one weight-related comorbidity					
Diet and Exercise	£17,816	16.196			
Tirzepatide (5.0 mg)	£32,182	17.012	£14,365	0.816	£17,612
Tirzepatide (10.0 mg)	£35,599	17.090	£17,783	0.894	£19,896
Tirzepatide (15.0 mg)	£38,242	17.068	£20,426	0.872	£23,425

Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.

Table 16. Committee-preferred base case

Treatment	Total Costs	Total QALYs	vs. D&E		
			Incremental Costs	Incremental QALYs	ICER (Cost/QALY)
BMI ≥30 kg/m² with at least one weight-related comorbidity					
Diet and Exercise	£19,297	16.270			
Tirzepatide (5.0 mg)	£34,200	17.074	£14,903	0.804	£18,529
Tirzepatide (10.0 mg)	£37,335	17.310	£18,039	1.041	£17,334
Tirzepatide (15.0 mg)	£40,327	17.347	£21,031	1.078	£19,514
BMI 30–34.9 kg/m² with at least one weight-related comorbidity					
Diet and Exercise	£17,148	16.228			

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	Tirzepatide (5.0 mg)	£32,222	16.850	£15,073	0.621	£24,265
	Tirzepatide (10.0 mg)	£35,568	17.010	£18,420	0.782	£23,552
	Tirzepatide (15.0 mg)	£38,245	16.990	£21,097	0.762	£27,699
	Abbreviations: BMI: body mass index; D&E: diet and exercise; NHSE: National Health Service England; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years.					

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- 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.
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Tirzepatide for managing overweight and obesity [ID6179]

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References

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Royal College of General Practitioners

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures
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	Overall, we are concerned that the recommendations are not a suitable basis for guidance to the NHS due to insignificant emphasis on support required for improvement in **food quality** – this is a particular risk to those from more deprived communities who face rising food insecurity and are most likely to suffer with **obesity and malnutrition** (the double burden of obesity). A “caloric

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	restriction" only approach to weight loss in these groups risks greater adverse effects from malnutrition including poor metabolic health outcomes, vitamin deficiencies and sarcopenia. It is important to recognise the risks of managing obesity with pharmacotherapy and the risks in older people living with frailty of reductions in muscle mass as well as bone density. (Mwala NN, et al, Challenges in identifying malnutrition in obesity; An overview of the state of the art and directions for future research. Nutrition Research Reviews. Published online 2024:1-10)
2	**Support for improved dietary quality omitted from guidance** Section 1. 1.1 The statement "alongside a reduced-calorie diet and increased physical activity" does not adequately reflect the need for support to improve dietary quality rather than just a focus on a reduction in calories. See wider and extensive literature on ultra-processed food and obesity and work of Kevin Hall proving causality of UPF in obesity (metabolic ward studies). This is a particular concern as the SURMOUNT studies did not include the UK population which is known to have the highest UPF consumption in Europe/OECD countries. Malnutrition is a risk particularly in those with obesity (many with obesity are already malnourished i.e. have vitamin, mineral and fibre deficiencies as well as dysbiosis of microbiome and sarcopenia – see WHO work on double burden of obesity). Malnutrition is a significant risk if a poor quality diet continues to be consumed but in smaller quantities due to appetite suppression with Tirzepatide – in real world practice this is likely to be a greater risk than seen in trial populations. (this may also explain why people with prediabetes in the SURMOUNT trials who lost weight with Tirzepatide and reversed pre-diabetes, saw it return at 2/3 years when the support for diet and physical activity stopped see section 3.19 "prediabetes reversal loss") We would suggest an increased emphasis on dietary quality and a holistic assessment. So an improved statement might include "alongside a holistic assessment including support for improved dietary quality with reduced caloric intake with increased physical activity".
3	**Guidance needs to include new and wider roles in the NHS that have weight management expertise e.g. GP with Extended Role in Lifestyle Medicine** Section 3.2 Treatment pathways; the guidance would benefit from reflecting the increasing skill diversity within health care teams that now include clinicians of many backgrounds with Lifestyle Medicine training. Of particular note this guidance should explicitly list the GP with extended role in Lifestyle Medicine as a suitable provider of weight management services (see https://www.rcgp.org.uk/your-career/gp-extended-roles/Lifestyle-medicine-framework-practice). Although there may be some support of an MDT through ARRS-funded roles, the skills and capacity of dieticians and other team members may be limited in many areas to deliver a universal service. This would need careful consideration if the teams are devolved down to a local or PCN level.
4	**Guidance needs greater emphasis on recognition of the increasing safety risks and need for deprescribing in the case of significant rapid weight loss (particularly for those with polypharmacy)** Section 3.2 Weight management services prescribing Tirzepatide will need the support of the patient's own GP/employ a GP to review the need for deprescribing for those on multiple medications. This already occurs for some digital weight management services and additional medication reviews and titration of medication as a result of this work needs to be considered and funded for General Practice. Evidence suggests that significant weight loss can improve or even reverse many health conditions including hypertension, sleep apnoea, type-2 diabetes (although these patients will receive medications through other pathways) heart failure, osteoarthritis, chronic pain, depression, atrial fibrillation etc. Therefore deprescribing or down-titration of medications for these conditions is likely to be needed and in some cases, without deprescribing, serious harms can result e.g. from hypotensive falls, hypoglycaemia, sedation, rises in INR whilst on warfarin etc Polypharmacy is common in real life practice and uncommon in trial based participants so the risks of these complications are unlikely to have been fully understood. We need to be mindful of an approach which takes into account realistic medicine / prudent health principles / personalised care approach.

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5	**Need for appropriate <u>medical screening</u> of high risk patients particularly those with polypharmacy and multi-morbidity through a holistic medical review ideally by a medical generalist prior to starting Tirzepatide.** Section 3.2 Rapid, significant weight loss is also strongly associated with an increased risk of biliary disease which in some cases can be serious/life threatening e.g. acute cholecystitis. Patients will need to be screened for biliary disease and advised of the symptoms and risks. Similarly, contraception may need to be reviewed as women with obesity have reduced fertility and may have stopped relying on contraception – patients need to be advised about a potential rapid return in fertility that can occur with significant weight loss and to use appropriate contraception. Complex co-morbidity in those with obesity may not have been identified in the medical record or by a medical professional previously – these may only be identified after a comprehensive assessment by an experienced medical clinician e.g. GP or weight management doctor.
6	**The Guidance needs to reflect the uncertainty around risks and benefits of Tirzepatide for those from more <u>deprived communities</u> who are more likely to have multiple co-morbidities and polypharmacy** – these groups were not well represented in the trial data and are more likely to have greater risks of side effects from polypharmacy, malnutrition, treatment failure and need for deprescribing of other medications. This group is also most likely to be facing food insecurity and therefore be at risk of malnutrition with obesity which can be exacerbated by an overall food reduction approach than a food quality approach. This should be reflected in guidance that requires a comprehensive medical and food quality (rather than just caloric quantity) assessment for higher risk groups such as these. We need to ensure that we don't widen the health inequality gap unintentionally for deprived communities who may not have access to wider MDT teams for weight management services and the personalised approach and intensive support which might be required.
7	**The Guidance should be stronger around statements on the needs for <u>investment and implementation support</u> particularly in primary care –** There is a clear consensus amongst primary care leaders and policy makers that General Practice is not in a position to carry out any extra unfunded work and not currently in the position to prioritise weight management support services without significant additional training and long term investment. The guidance team should be aware that complications arising from rapid and significant weight loss e.g. biliary disease, medication side effects (those prescribed for other conditions improved by weight loss) will default to primary care teams without proper planning.
8	**The guidance should offer <u>prioritisation guidelines</u> that could be used whilst stocks or services are in short supply (section 3.30)** – these could include, as suggested, those patients awaiting surgery, infertility, IVF, or suffering severe complications etc.
9	**The guidance should be clearer that there <u>will</u> be system challenges (as opposed to may be) due to severe challenges in local availability of appropriate staff, training and services as well a funding limitations. (section 4.1)**
10	3.7 – It is unclear whether this can be prescribed in primary care or requires referral to secondary care for diabetes and weight management
11	3.7 – for generalisability - Would depression/mental health issues be included in co-morbidities for those patients with a slightly lower weight/BMI?
12	3.22 – If a patient stops the medication, is there a time limit within which they can re-start the medication, or does it each time require a first review for weight loss over 6months.

Insert extra rows as needed

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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]

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	The draft guidance clearly demonstrates the process and evidence used in making the recommendation. The External Assessment Group have clearly identified the relevant challenges posed by the company submission for the use of Tirzepatide in the management of obesity. Our main concerns relate to questions 5 and 6:

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	5. Please specify any potential challenges with implementing these recommendations and the associated reasons. 6. Please also provide any ways to overcome these potential challenges, any estimate of the time period within which the recommendation can be complied with, and any approaches to phase in funding to manage access to tirzepatide during any potential extended funding variation period. These concerns are outlined below:
2	The current proposal that Tirzepatide be delivered in both primary and secondary care in some respects is welcomed in that it will increase access to medication for the management of obesity and hence improve health inequalities that are already so apparent due to variability in provision of weight management services. It also recognises the growing need and the longer term implications in restricting access to definitive treatments in obesity and the benefits for weight loss. However, the ability for primary care to meet the demand is not achievable given the number of people that would be eligible using the guidance proposed. It would be helpful to know if a feasibility study (in terms of workforce and financial) has been conducted with primary care partners to see how this could be delivered in primary and secondary care. Not only will workforce likely be an issue but also funding constraints, especially given the wrap around care required. In reality, the only way that Tirzepatide can be delivered in primary care for the management of obesity would be for a full re-structure of weight management services in England and review of medical therapies and surgery with guidance from NICE about the place of Tirzepatide alongside Wegovy, Saxenda and surgical procedures. Currently it is unclear how Tirzepatide fits in with the available medication (Wegovy) and how its application differs in terms of clinical pathways and referral criteria. If the current guidance goes ahead – it is not clear what the role of Wegovy will be especially given that it appears to cost more and less effective compared to Tirzepatide (making allowance for the fact that there is no head to head data and the population groups studied are different). The proposal of ongoing, long-term prescription (rather than two year cut-off) is welcome in that from a clinician's perspective, it feels morally wrong and unethical to stop a medication that has obvious medical benefits, especially given that there is good evidence of the weight re-gain on discontinuation. However, I would suggest that further 'stop criteria' are required other than the initial 6 month 5% requirement. Weight re-gain in subsequent years needs guidance and when to stop Tirzepatide. It might be that these patients would be more suitable for bariatric surgical procedures and this should be considered at every review with guidance about when to refer. Following the experience of Ozempic and the demand that ensued, it would be helpful to know whether the company is genuinely able to meet demand. Given the ongoing National Patient Safety alert for GLP-1 analogues which came about due to the popularity of Ozempic, it would seem prudent to consider a phasing in approach to assess the ability to meet demand (as per Society for Endocrinology position statement on the phasing in of Wegovy). The problem with this approach however is that Tirzepatide for diabetes is unrestricted (although it is clear where in the diabetes management pathway where it sits) and yet for obesity it may be restricted due to the number of people eligible and financial implications for ICBs. While all the above challenges need to be rectified and weight management services in England reviewed, perhaps one solution would be a phasing in approach of Tirzepatide and a Funding variation application would be supported. There are several options however ultimately the guidance presented will cause significant challenges to primary care colleagues, create confusion about the role of Wegovy in secondary care and create significant pressure on already strained resources within primary are and the community that will need significant funding and time to embed. Hence a

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	phased approach and increased time to implementation (beyond the three months) would be preferable. There also needs to be a feasibility study about the wrap around care, how it can be delivered, costs involved and a realistic level of support. The proposed company model of wrap around care is unlikely to be deliverable in primary care however the use of group, virtual session, allied healthcare professionals and the use of digital technologies can be utilised for the majority of patients. There is however little mention about the provision of psychological support which has a significant predominance in people living with obesity and how this might be accessed. In terms of clinical need and the evidence available (particularly in cardiovascular disease) for improved outcomes – it is worth noting that for comorbidities such as hypertension and lipid lowering – there are already established and much cheaper treatment options for management of these conditions and therefore more evidence is needed about the additional benefit that Tirzepatide offers when doing cost analysis. In summary therefore there will be significant challenges in being able to deliver Tirzepatide to all people that would be eligible using this guidance. It is also unclear what the role of Wegovy is going forwards given that this is restricted largely to secondary care services. A feasibility study is required and review of weight management services in order to aim for primary care provision of medical therapies in future. It would also be helpful for guidance on a phased approach and how this might be enabled based on clinical need and the evidence available.
3	
4	
5	
6	

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Hertfordshire and West Essex Integrated Care Board

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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.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that there are gaps in the evidence considered relating to the relevant population group, the intervention and outcomes.
2	With regard the population:

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	The evidence considered by the Committee was based on the SURMOUNT-1 trial which excluded cohorts of patients including those with diabetes, a change in body weight of more than 5 kg within 90 days before screening, previous or planned surgical treatment for obesity, treatment with a medication that promotes weight loss within 90 days before screening, significant active or unstable major depressive disorder or other severe psychiatric disorders within the last 2 years. These same cohorts should be excluded in the TA recommendations, unless additional evidence can be considered which will support their inclusion. This would mitigate the committee's concerns regarding "uncertainty about the generalisability of the clinical-effectiveness results" which "may have affected the reliability of the cost-effectiveness results" and also NHSE who commented that the "generalisabiliy of the trial should be considered with caution because there is no clinical evidence to show the effectiveness of tirzepatide in this group of people". Despite not considering any additional evidence on tirzepatide for people with type 2 diabetes compared to the NICE TA924 on tirzepatide for type 2 diabetes, this draft TA makes very different recommendations and widens the cohort of people with type 2 diabetes who would be eligible for tirzepatide. As per NICE TA924, tirzepatide is only recommended if a patient with type 2 diabetes and a BMI of 35 or more has insufficiently controlled type 2 diabetes AND specific psychological or other medical problems associated with obesity AND triple therapy with metformin and 2 other oral antidiabetic drugs is ineffective, not tolerated or contraindicated. In this draft TA, tirzepatide is recommended for anyone with type 2 diabetes (which is a weight related co-morbidity) and a BMI of at least 35. The committee discussed that more people with type 2 diabetes would be eligible under the draft recommendations but it is not clear what the evidence base for this is. Pre-diabetes is included in the marketing authorisation for tirzepatide as a weight related co-morbidity which would widen the eligible population even further! "The committee noted that people with some types of severe psychiatric disorders (such as bipolar or schizoaffective disorder) who may be on antipsychotic medicine did not appear to have been included in SURMOUNT-1". From a commissioning perspective, this is a priority cohort for obesity treatment as people with severe mental illness are more likely to experience obesity and obesity is an important contributor to the excess morbidity and mortality experienced by this cohort. Whist the committee seem to have considered whether this group may require additional psychological support, it is not documented that the committee have considered the safety or effectiveness of tirzepatide in this group. 40% of SURMOUNT-1 participants had a BMI <35 and would therefore be ineligible under the draft recommendations. The strength of the evidence when limited to the subgroup of participants with a BMI of 35 or more and an obesity related co-morbidity is not transparently documented. There were no trial sites in England and the ethnic or racial profile of participants was very different to the English population. This creates additional uncertainty in generalising the findings to the English population who will be seen in clinical practice. The relationship between obesity and ethnicity is complex, with differences in the prevalence of obesity, prevalence of obesity related co-morbidities, health behaviours, and experience of obesity-related stigma.1
3	With regard to the intervention: Tirzepatide is recommended as an option for managing overweight and obesity, alongside a reduced-calorie diet and increased physical activity. In the SURMOUNT trial, lifestyle intervention included regular lifestyle counselling sessions, delivered by a dietitian or a qualified health care professional, to help the participants adhere to healthful, balanced meals, with a deficit of 500 calories per day, and at least 150 minutes of physical activity per week. NICE considered the "evidence from a survey of GPs in England and Wales, suggesting that 78% of the GPs that responded always or very frequently offer specific diet and exercise advice, 67% have access to a dietitian and 80% have access to an exercise professional". This survey is insufficient evidence that the same level of support is or can be delivered in primary care or outside of a weight management service, such as tier 2. It is noted that the Committee "concluded that it was uncertain if the diet and exercise support included in SURMOUNT-1 was similar to the obesity weight management services that could be delivered in primary care, especially regarding the

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	length of availability, intensity and consistency across the country". The majority of Commissioners/ICBs can confirm that this level of support cannot be delivered in primary care. As commissioners, we also disagree with the company's expectation that this support could feasibly be incorporated into the ongoing care patients receive for obesity related co-morbidities, which would involve significant service changes to multiple specialities. "They [a clinical expert] also explained that there is evidence to suggest that the weight loss seen in the trial would likely be similar without the diet and exercise support provided." If this point is to be considered, the evidence needs to be referenced and appraised. The idea that a medication should be used first line medicalises a public health issue without understanding the long term safety risks] and also disadvantages patients from gaining the wider benefits from lifestyles changes e.g., mental health improvements and gut health, which will be more sustainable longer term.
4	With regard to the outcomes: The clinical experts suggested that it is likely that, over time, people on tirzepatide would regain weight even while on treatment, and there is no evidence for making the recommendation for treatment long term. No evidence for safety and clinical effectiveness has been considered beyond the length of the trial. Therefore, the recommendation for long term use is not evidence-based. There have been reports of fatal pancreatitis associated with tirzepatide use in the United States of America. The MHRA and EMA are seeking intensive ongoing pharmacovigilance in the post marketing period particularly regarding pancreatic malignancy, medullary thyroid cancer, diabetic retinopathy complications, suicide and suicidal ideation and safety of tirzepatide in pregnancy and breast feeding. Although the SURMOUNT-1 trial considered these adverse outcomes, the trial is insufficient to demonstrate that there is not increased risk of these outcomes with tirzepetide. The SURMOUNT-1 trial also suggested increased severe hypoglycaemia in treatment arms (blood glucose <54 mg/dl (<3mmol/mol) (1.4-1.6% of participants on tirzepetide vs 0.2% of control participants). This is a significant risk in patients who are not routinely monitoring their blood glucose or educated in how to manage it. Hypoglycaemia this severe would be expected to lead to emergency healthcare use including ambulance call-outs. Evidence that Incretin-Based weight loss drugs can cause significant loss of lean mass was also not considered. This is a significant risk factor for the development of frailty in older individuals. It could be harmful to patients to recommend its indefinite use for such large cohort of patients in a primary care setting. In particular, patients cannot be adequately informed of the risks of the medication, especially when used long term. There is also a lack of evidence for patient-orientated outcomes. Trial evidence is limited to proxy measures (i.e. loss of weight, waist circumference, BP, fasting insulin, lipids, prediabetes). There is significant uncertainty in the size of any impact on relevant disease outcomes (e.g. cardiovascular disease, sleep apnoea etc) and healthcare utilisation for obesity related co-morbidities. This is acknowledged but not mitigated. The recommendation is largely based on the Company presented evidence and although the gaps in the evidence are recognised they do not appear to have been adequately mitigated or considered in the decision making.
5	We are concerned the summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence for the following reasons: The model excluded patients with diabetes, however the recommendation does not.

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	It is noted that patients with type 2 diabetes were also excluded from the economic model and yet are not excluded from the recommendation. Co-morbidities The BMI distribution in SURMOUNT-1 was different to the population who would be eligible for tirzepatide in clinical practice and that this does limit the generalisability of the results. It would be people at the lower end of the BMI range that would access this treatment if this TA was published with the recommendation suggested and this needs to be considered. The TA Committee recognised that three years after stopping treatment, original weight would be regained in most patients. Therefore, it is likely that lifelong maintenance treatment will be required for most patients. It is not clear how the cost effectiveness of ongoing continuous treatment beyond three years to maintain weight loss has been assessed. Long term effectiveness and safety beyond the trial duration remains unknown and therefore clinical and cost effectiveness beyond this limit also remains unknown. It is not clear how the clinical and cost effectiveness of ongoing continuous treatment beyond three years to maintain weight loss (life-long) has been assessed. The NICE TA for semaglutide is limited to 2 years because of restricted time in specialist weight management services and lack of evidence for longer use. There is significant uncertainty in the size of any potential efficiencies with a lack of long term data on impact on comorbidities and healthcare use. Relying on potential financial savings due to potential reduced obesity related comorbidities is insufficient.
6	We are concerned that these are not sound and reasonable recommendations for the NHS for the following reasons: 1. Publishing this TA as it stands reputationally damages the relationship of the NHS and NICE as it is not useable and this cannot be practically implemented and is overly medicalising a public health issue. Representatives from Integrated Care Boards across the Country are extremely worried and concerned by this draft publication and are seriously losing confidence in the ability of NICE to make decisions for the NHS. 2. This is overly medicalising what is essentially a public health issue. Obesity is a public health issue and medical and treatments should be considered in the context of wider recommendations on obesity prevention and as part of the overall recommendations for obesity management rather than as a mandatory TA. The NHS is trying to take a holistic approach to patient management however this does not support that approach. 3. Publishing this TA will create a lot of patient demand and expectation which the NHS cannot meet. 4. Recommendation for use in such a large cohort is unaffordable for the NHS and the NHS do not have the resource, workforce or capacity to deliver this. The recommendations should be for the patients most likely to benefit from treatment which the Committee does not have the evidence for based on the evidence presented.
7	These TA recommendations are impossible to implement in practice for the NHS, due to workforce, capacity and resource issues so will inadvertently lead to unlawful discrimination.
8	The challenges with this recommendation are that this is a treatment for which 1 in 3 adult patients will be eligible for which makes it impossible to implement. Obesity services need to be defined

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	and developed with appropriate investment in staffing and infrastructure. Qualifying co-morbidities for eligibility need to be defined further. This drug is not suitable for primary care initiation and management for obesity where a wrap around service including counselling and pastoral support is a requirement for its success. There is no capacity in primary care to deliver the GP appointments, nursing appointments, clinical pharmacist support, dietetic support or psychological support. The stopping rule would be very difficult to implement in practice as it is a 'consider' recommendation. The Committee noted concerns around regaining weight lost after stopping and the psychological impact of this. This will also, make it very difficult to implement in practice, particularly in primary care
9	This treatment is not suitable for primary care without significant time consuming service redesign, which requires additional funding and staffing resources. This would be best managed in a dedicated service, to ensure those who are most likely to benefit from the treatment receive it. This may be through an enhanced service framework if it still recommended to delivered in primary care. However, it should be noted that GP practices are already struggling with workload, resource and capacity constraints and may choose not to sign up to deliver this service as a result. Training will also be required as primary care are not skilled in managing obesity. Patients would need to demonstrate adherence to a reduced-calorie diet and increased physical activity prior to being initiated on this treatment. A patient decision aid outlining the benefits and risks of treatment should accompany this guidance.

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 confidential in turquoise. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'confidential 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.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	On behalf of ICBs along with Anurita Rohilla

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	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.
1	The patient cohort in SURMOUNT -1 is not indicative of the patients who will be eligible to access these treatments in the real-world setting. The exclusions for SURMOUNT-1 trial were very broad and excluded patients with severe psychological disorders and those waiting for related surgery. Consequently, there is limited evidence to confirm cost effectiveness of tirzepatide in a real world setting or to support use of tirzepatide in a phased way which implements and targets tirzepatide treatment at those at highest

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	risk first. More robust evidence and analysis is required to confirm that the overall results in SURMOUNT -1 were not skewed by the possible high proportion of patients with prediabetes as stated in the trial cohort. The long-term safety of tirzepatide and other GLP-1s has not been considered adequately. Outcomes from the SURMOUNT- 4 have not been considered adequately. SURMOUNT-MAINTAIN is not due to complete until April 2026 and timescales for publication of results are unknown at this time. We have significant concerns that tirzepatide is being recommended for long term treatment of a large cohort of patients without evidence of long term safety and efficacy.
2	The only evidence that has been considered is evidence presented in the base case by the marketing authorisation holder (Eli Lilly). There is not enough long-term data to confirm clinical and cost effectiveness over a patient's lifetime. The 2 year limit specified in TA875 for semaglutide was not just due to current capacity within current weight management service arrangements as stated in this consultation, but also because cost effectiveness beyond 2 years for semaglutide was not established. The committee discussion states that 'semaglutide is limited to 2 years because of restricted time in specialist weight management services and **lack of evidence for longer use'**. It is the same with tirzepatide – long term effectiveness and safety beyond 88 weeks remains unknown and therefore cost effectiveness beyond this limit also remains unknown. These limits need to be built into both this NICE TA or the analysis should be adjusted for lifetime use and cost effectiveness re -calculated. The process and procedures for the assessment of this drug are not consistent with those applied to other drugs in the same class. A 2-year duration rule and recommendations for targeted cohorts of patients as have been applied for Saxenda and Wegovy should be applied to this drug for consistency,
3	Advice provided is not useful or useable. Tirzepatide is recommended alongside a reduced-calorie diet and increased physical activity in adults, with no further detail as to what this entails. In its submission, the company proposed that tirzepatide could be used either in primary or secondary care, and that the appropriate diet and exercise support that should be accessed alongside tirzepatide could be delivered in both settings. In the trials patients were highly medically supervised to ensure compliance with their reduced-calorie diet and physical exercise undertaken. The guidance as written contains no specification as to what is required in respect of diet and exercise support and is therefore not implementable in a cost-effective, consistent and equitable manner across the country. No duration of treatment has been specified. The 2 year limit specified in TA875 for semaglutide was not just due to current capacity within current weight management service arrangements as stated in this consultation, but also because cost effectiveness beyond 2 years for semaglutide was not established. The committee discussion states that 'semaglutide is limited to 2 years because of restricted time in specialist weight management services and lack of evidence for longer use'. It is the same with tirzepatide – long term effectiveness and safety beyond 88 weeks remains unknown and therefore cost effectiveness beyond this limit also remains unknown. These limits need to be built into both this NICE TA or the analysis should be adjusted for lifetime use and cost effectiveness re -calculated. The guidance as written is not implementable within any care setting-secondary care, community care or primary care, and will have a severe impact on capacity- particularly in primary care. Patients will need highly supervised continuous long term monitoring to ensure safety of patients and that the drug is used in the cost-effective manner as detailed in the trials upon which this recommendation is made. Publishing the guidance as it stands will result in unrealistic patient

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	demand which will further add to pressures in the primary care setting and other services will inevitably be disadvantaged. Primary care does not have the resources to manage the number of patients who will be eligible in a safe and cost-effective manner. Whilst recognising that affordability of implementing this guidance falls outside the remit of NICE, implementation of this NICE TA as recommended is totally unaffordable and will have a detrimental impact on other ICB priority areas for investment.
4	The proposed NICE TA recommendations are too broad, unrestricted and unaffordable, leading to the need for a funding variation to be put in place to ensure systems can start to implement and meet their legal obligations. However, phased implementation arrangements could lead to unlawful discrimination. Whilst NICE states that its current remit does not include the need to assess affordability, it is clear that this should be an essential part of its assessment process and function.
5	It is not possible to implement this guidance within 3 months of final guidance being published and an extension to this normal period will be required, which will require a considerable period of time. A five year period for implementation with additional centrally provided funding-as was agreed for Hybrid Closed Loop NICE TA - would support implementation.
6	Advice/recommendation provided in the draft TA is neither useful or useable. The guidance as it stands is unimplementable. To implement this TA as its stands would require total system reform. Specifically, this is because of the issues around prescribing and monitoring this drug in primary care. Currently many ICBs do not have the funding, systems, infrastructure or staff required. The funding and staffing pressure would result in destabilisation of other services and put patients at risk. The criteria is too broad and encompass too many eligible patients leading to overwhelming numbers of patients who would be eligible for treatment. The eligible cohort needs to be tightened to focus on those at highest risk of harm from their obesity. Need to consider overlap of diabetes guidance and place in pathway for tirzepatide and use as a weight loss drug. More specific guidance needs to be provided in respect of the reduced-calorie diet- who provides advice and supervision and should be dietitian; what sort of exercise, how much and who supervises- potentially health coach. Many locally commissioned Tier 2 services exclude patients who meet the current NICE TA BMI eligibility criteria from their services. Recommend that like Saxenda and Wegovy that this drug is only available through specialist weight management services like Tier 3 to ensure that dietetic and psychology advice and support is available for patients in a consistent manner to support the lifestyle and behavioural changes which is crucial to address obesity. Mandate stopping tirzepatide if less than 5% of the initial weight has been lost after 6 months of treatment. This is much clearer for clinicians than the current 'consider' and more equitable for patients. Cost-effectiveness has not been proven when used for longer than 2 years so introducing a 2 year duration of treatment rule will support management of numbers and help with capacity of commissioned weight management services.
7	The use of weight management drugs should form part of an overarching Public Health strategy which has considered the ethical and practical issues around medicalising lifestyle choices, and the limited resources available to the NHS. Greater clarity should be provided in respect of local authorities responsibilities for supporting the implementation of this guidance.

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	Obesity services need to be defined and developed with appropriate investment in staffing and infrastructure, before guidance is published that mandates the use of a weight management drug in a large cohort of patients. Even given a phased introduction over an extended period e.g. 5 years, it is unlikely that systems will be able to afford to fund treatment for the cohort of patients specified in the draft TA. The patient cohort needs to be revised and targeted to make sure that the patients who will gain the greatest healthcare benefits are given access to this treatment. Targeted cohorts for a phased implementation needs to focus on those who derive greatest overall benefit and should start with those of highest clinical risk using for example using evidence-based frameworks: • Edmonton Criteria • King's Criteria Central funding will be required to ensure relevant workforce resources are in place, and funding for the drug will also be necessary. Reimbursement based on coding and evidence of use- particularly if used in primary care where same product is used for diabetes and weight loss. Develop a shared decision tool to support patients and clinicians agree the risks and benefits of using the drug, and what non-drug alternatives can be accessed to support them in their weight loss journey. This should include some kind of contract with the patient to ensure both parties comply with their agreed actions and understanding that failure to do so will result in the medication being stopped. Even where the patient complies, there should be an agreed de-prescribing plan with timescales. If access to this drug is to be via primary care, there needs to be formal nationally funded Weight Management LES, with optional sign up for practices and which defines the level of service provision-dietetic, health coach, psychological support and based on resource available allows the practice to limit the number of patients being managed at any one time- important that there is a 2 year duration of treatment to manage this.

Insert extra rows as needed

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

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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]

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1	**Requirement for a wraparound service to facilitate tirzepatide delivery** The ongoing use of pharmacotherapies such as tirzepatide rely on the effective and consistent delivery of a wider wraparound obesity management service. In that context we note comments from the NHS commissioning expert who stated that access to lifestyle weight management services and the level of support provided in primary care services varies drastically across the country. This variability is a challenge not just for

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	the delivery of lifestyle weight management services, but the ability to initiate, titrate and monitor the use of tirzepatide safely and appropriately in clinical practice. Further, while the draft guidance details the wraparound services required to prescribe tirzepatide (section 3.16), this wording is not reflected in the committee's overall recommendation. This creates an inconsistency across guidance documents for obesity treatments (TA664, TA875) where more specificity is detailed in the terms of the recommendation outlined in Section 1 of the guidance. We are concerned that if tirzepatide is prescribed in a care setting without the resources to adequately provide this wraparound service it is likely that the treatment benefits will not be realised, risking both patient safety and the inefficient use of NHS resources. As such, to avoid creating confusion with clinicians and local payers we request that specific wording be added to Section 1 of the guidance stating tirzepatide should be prescribed only in settings that can provide the necessary multidisciplinary specialist support, as described by NHSE, for a sustained period.
	Target population The recommendation of tirzepatide for a higher BMI group than the one considered in the company submission is sensible given the cost-effectiveness results that have been presented so far. All of the ICERs presented by the EAG for the BMI≥30 with ≥1 comorbidity exceeded the £20,000 per QALY threshold which NICE considered acceptable.
2	**Additional sensitivity analyses required** **Treatment duration** has not been thoroughly explored in the sensitivity analyses and it is not clear if it is actually lifetime or a period that is expected to resemble lifetime. Novo Nordisk requests clarification on the treatment duration and proposes sensitivity analyses looking at different treatment duration periods to further validate the model. **Bariatric surgery** has not been tested as extensively as in previous appraisals. Novo Nordisk proposes that different scenarios for bariatric surgery are presented including using the assumptions from the semaglutide 2.4mg appraisal to better understand the effect of this intervention in the modelled results. **Weight regain** has not been extensively examined in the sensitivity analyses, and the influence of the alternative scenario on the absolute cost and QALY estimates for semaglutide 2.4mg and tirzepatide is not reported in the considered sensitivity analysis. Novo Nordisk suggests conducting sensitivity analyses presenting longer weight regain patterns to enhance the validation of the model.
3	**Clarity on ICERs used to determine the cost-effectiveness of Tirzepatide.** The Company presented a number of ICERs for the relevant population of BMI ≥35 with ≥1 comorbidities, but there are some discrepancies between the results presented in the ACM2 slides and the Company Response to Committee-Preferred Assumptions Post-ACM2. Particularly, the company preferred base-case was higher in the ACM2 slides (slide 46, £11,184) compared with the company response post-ACM2 (Committee Papers page 894, Table 1: £10,679).

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	Further, the ICER including the EAG preferred assumptions is higher in ACM2 slides (slide 47, £21,450) than the value stated for the EAG-preferred base case including resource use described in Committee Papers page 900, Table 4 (£18,433). It would be useful if the guidance could be updated to clearly reflect the Committee preferred assumptions and impact on the ICERs used to determine cost-effectiveness at the willingness-to-pay threshold of £20,000. In reviewing the Committee-preferred settings we noticed that removing the mortality modifiers applied in the company's model for history of angina, myocardial infarction and stroke because the increased risk of death from these events is covered by the BMI mortality modifier (Committee Papers page 894, Table 1, ICER changes from £10,679 to £10,568) decreased the ICER where intuitively it would be expected to have the opposite effect. Novo Nordisk would appreciate clarification on this.
4	**Difference in cost-effectiveness according to tirzepatide dose** Tirzepatide is available at various doses ranging from 2.5mg to 15mg. Although we agree that it is likely that most patients would titrate to the highest tolerated dose of tirzepatide (15mg) in clinical practice, as per data reported from SURMOUNT-1, there remains substantial differences in the efficacy of tirzepatide depending on the dose received. In the current guidance wording, it is unclear whether NICE consider tirzepatide to be a cost-effective use of NHSE resources regardless of the dose received, or whether the recommendations made exclusively relate to the use of the 15mg dose. We request that this be made clear in Section 1 of the guidance, particularly in the context that the 15mg dose was the primary focus of Committee decision-making. If NICE's recommendation applies to all available doses, we propose comparing the cost-effectiveness of tirzepatide 5mg, 10mg and 15mg doses with each other to understand if they are priced appropriately.
5	**Long-term impact of prior obesity** We recognise the relevance of the consideration given to the long-term impact of prior obesity on the interpretation of both the costs and outcomes calculated in the company economic analyses. However, Section 3.20 of the draft guidance states '*The committee discussed that if the residual impact of having previously had a higher BMI was not included in the model, as was the case with the company and EAG base cases, the QALY gain is likely to be overestimated*'. Whilst in isolation this point may be accurate, it is worth noting that the complex nature of obesity means it would be impossible to capture fully all of the expected benefits associated with weight reduction (such as a decreased risk of adverse events associated with respiratory infections, a reduction in social isolation and stigma associated with obesity, improvement in fertility or success rate for *in vitro* fertilisation). To some degree, the modelling presented will always be a simplification of reality through this inability to fully capture the multifaceted impact of the condition and therefore it is potentially misleading for the guidance to suggest the QALY gain included in the company and EAG base cases is likely to be overestimated, when on balance, given the inability to capture all the benefits of weight-loss, the QALY gains will still more likely be

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	underestimated than overestimated. For transparency we would recommend the wording be updated to reflect this.
6	**Dose de-escalation** Current wording*: 'The committee also concluded that dose escalation and de-escalation would need appropriate monitoring. How this was done would need to be considered in the implementation of the wraparound obesity management services for delivering tirzepatide.'* To note, the tirzepatide summary of product characteristics does not include any guidance on dose de-escalation and raises questions around when such a decision should be made, what is appropriate de-escalation and patient education on implications for weight (i.e. weight loss plateau/regain).
7	**Waning of treatment effect post treatment with semaglutide 2.4mg** Current wording: *'They explained that for semaglutide, around two thirds of the weight lost while on treatment is regained within the first year after stopping and that the benefits gained such as reduced blood pressure are also lost by this time.'* Even though the statement related to the blood pressure results in the STEP 1 extension trial is factually correct, the sentence needs to be rephrased because benefits compared to baseline were observed for some endpoints i.e. LDL cholesterol, c-reactive protein, HbA1c and change in glycaemic status category.[2] Novo Nordisk proposes the following amendment: 'They explained that for semaglutide, around two thirds of the weight lost while on treatment is regained within the first year after stopping and that the benefits gained **in some endpoints,** such as reduced blood pressure are also lost by this time.'
8	**Minor wording corrections** • Current wording*: 'Some people may also have semaglutide alongside diet and exercise support if their obesity is managed in a specialist weight management service.'* Liraglutide 3mg is also recommended by NICE as an option for managing overweight and obesity; therefore, Novo Nordisk proposes the following amendment: 'Some people may also have semaglutide 2.4mg **or liraglutide 3mg** alongside diet and exercise support if their obesity is managed in a specialist weight management service.' • Current wording: *'The company proposed that tirzepatide could be used for people with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity.'* We propose the wording is update to 'The company proposed that tirzepatide could be used for **adults** with a BMI of at least 30 kg/m^2 and at least 1 weight-related comorbidity.' • Current wording: *'Consider stopping tirzepatide if less than 5% of the initial weight has been lost after 6 months of treatment.'*

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	Novo Nordisk proposes the following amendment to ensure alignment with the product's label: 'Consider stopping tirzepatide if less than 5% of the initial weight has been lost **6 months after titrating to the highest tolerated dose**'

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.
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- 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.
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References

1. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002.
2. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022;24(8):1553-64.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England (NHSE)

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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.	No disclosures.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures.
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.
1	**NHSE Position Statement** The advent of new pharmacotherapies for use in people living with obesity and weight related comorbidities offers a treatment intervention, with the potential, when delivered along with dietary and exercise lifestyle support, to help improve heath for many people. NHSE recognises the potential benefits of the technology appraisal. However, due to the size of the eligible population and the new recommendation for a setting of care which would enable prescribing within primary care from introduction, there will be financial, capacity, resource and clinical challenges to implementation that will require further work to ensure it is implemented in a safe and effective manner. This will include pathway development, addressing additional workforce requirements, education and training material and development of clinical governance pathways surrounding the multi-disciplinary team with robust data sharing pathways in order to optimise patient care.

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	To ensure correct positioning of Tirzepatide within the wider weight management intervention pathway, NHSE will propose a funding variation and phased implementation approach which will address clinical prioritisation to ensure those will the highest need are treated as priority. It is hoped that such an approach will also mitigate the risk of widening health inequalities. **Eligibility criteria: BMI thresholds** Page 4, 1.1: The recommendation stipulates use for people living with overweight and obesity; however, BMI criteria of ≥ 35 (reduced for specific ethnicities) is classified as obesity according to NICE's definition (obesity class I is defined by BMI ≥ 30, class II by BMI ≥ 35). Further, page 41, 3.31: The guidance recommends lower BMI thresholds for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean ethnic backgrounds, which is states is "usually reduced by 2.5 kg/m^2" but does not explicitly state what the cut-off should be in this instance. NHSE considers that use of 'overweight' and non-specific ethnicity-based reductions in BMI risks confusion amongst clinicians in respect to eligibility and may lead to variation in access to Tirzepatide. NHSE would welcome definitive lower BMI range to be clarified by removal of the term 'overweight' and a clear statement of the lower BMI range based on ethnicity. **Eligibility criteria: Comorbidities** Page 4, 1.1: The proposed recommendation for adults, with a BMI of at least 35 kg/m2, and *at least 1 weight-related comorbidity.* The co-morbidities listed in the marketing authorisation indication provides examples, but this is not positioned as an indicative list for use clinically. Further (page 12 3.7) there is a review of comorbidities in SURMOUNT-1 but no clear conclusion as to which may be included. Given the wide spectrum of clinical conditions that might subjectively be considered to be weight related, this may risk recommendations being subject to judgement and unconscious bias, resulting in inequity and widened health inequalities. Clinical stakeholders have expressed concerns to NHSE about this and we would welcome more detailed clinical guidance regarding the eligibility criteria for Tirzepatide in relation to the term "weight-related" comorbidities. There is variance between the current draft TA for the use of *Tirzepatide for managing overweight and obesity* and the published recommendations for use of Tirzepatide in the management of type 2 diabetes mellitus (T2DM) (TA 924). In TA924 Tirzepatide is recommended for treating T2DM alongside diet and exercise in adults when diabetes is insufficiently controlled. This raises concern that the clinical threshold for use of Tirzepatide in T2DM associated with class II obesity is recommended at a different clinical threshold than for use in obesity management. This risks confusion amongst prescribers and might be interpreted as a more stringent clinical threshold. There is also the clinical of risk of hypoglycaemia when used alongside other glucose lowering medication(s) and this will need to be considered in respect to prescribing and deprescribing threshold to mitigate risk of hypoglycaemia. Hence further clarity in reference to T2DM in draft TA11156 would be welcomed. **Development of clinical guidelines to support changes to weight management service provision** Page 4, 1.1: The draft recommendations support that Tirzepatide therapy should be delivered in conjunction with a reduced calorie diet and increased physical activity. NHSE would welcome the development of an updated clinical guideline from NICE to support the consistent implementation of a clinically effective wrap-around care model, given the current lack of consistent access to existing suitable weight management services. Concern has been raised by clinicians with NHSE that a lack of specific exclusion criteria, compounded by delivery of prescribing by clinicians with limited expertise in the clinical area of obesity, creates a potential risk posed to patient safety in a complex cohort of patients. An updated clinical guideline could also build clinical confidence and support safe prescribing in the community.

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2	**Long term use & stopping guidance** Page 4, 1.2: NHSE feels that greater clarity may be required around guidance for stopping therapy. Guidance states "consider stopping Tirzepatide if less than 5% of the initial weight has been lost after 6 months of treatment". Whilst NHSE understands the difficulty with guidance being too prescriptive, there is a risk that this may lead to continuance of treatment for some individuals with minimal or no response to treatment at which point the side-effects may outweigh clinical benefit. It is understood by NHSE that Semaglutide' s stopping rule was based on cost-effectiveness and NHSE would welcome further clarification around the decision making process for Tirzepatide. Page 17, 3.11: NHSE note the uncertainty around the clinical effectiveness of Tirzepatide beyond the 72-week period observed in the trial. Additionally, (Page 24, 3.17), the TA suggests there is no evidence to suggest the *absolute treatment benefit* of Tirzepatide is lost over time and there is no biological rationale to support that assumption. NHSE recognised that whilst in the short term the outcomes are very promising, data on long-term benefit (and harms) after an extended treatment period will only emerge over time but are not yet established. Page 23, 3.18: Furthermore, there is a lack of direction on tapering or withdrawing Tirzepatide. It is noted that the clinical trials allowed for weight loss therapies to be continued until BMI threshold of ≤ 18.5kg/m^2, with adjustment of hypocaloric deficit at BMI of 22kg/m^2. As further evidence emerges clinicians are likely to welcome updating of guidance particularly around when pharmacotherapy should be tapered or deprescribed particularly where significant weight loss (achievement of a non-obesity BMI or healthy weight) and resolution of weight-related comorbidities is achieved.
3	**Setting of care** Page 4 ("Why the committee made these recommendations"): The guidance suggests Tirzepatide can be used across primary, community and secondary care settings and not confined to use in specialist weight management service. **Definition of primary care** Page 4 ("Why the committee made these recommendations"): NHSE would welcome further clarity around the definition of primary care, used throughout the document. There is concern this could be interpreted to include: General Practice, Community Pharmacy, Dentistry and Optometry services. It is unclear whether all primary care professionals with prescribing skills would necessarily be able to provide safe optimum management for patients due to lack of clinical experience, knowledge and lack of access to wrap-around care and primary healthcare records. It is vital that clinical assessment and prescribing of these therapies is recorded in, and with full sight of, the patient's past medical history to reduce the risk of adverse effects, or inappropriate use for example, where there are established contraindications or cautions, such as eating disorders. **Primary Care: Current service variability & access to workforce** Page 4 ("Why the committee made these recommendations"): NHSE notes the NICE draft guidance acknowledges varying and limited provision of weight management services in general. NHSE would welcome clarity on the definitions used for services outside of NHS commissioned SWMS in secondary care and community; primary care weight management services (i.e. delivered and commissioned by a general practice and community weight management services (i.e., delivered in the community predominantly commissioned by local authority) when describing provision of services. Whilst the inclusion of primary care (presumed to mean general practice) initiation could have a key role in targeted treatment and support to those who need it most in areas of highest deprivation; the availability of primary care pathways and access to specialist dietary and exercise support specifically for weight loss have limited availability. NHSE believe the evidence given by

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	Eli Lilly describing GP access to dietitians and exercise professionals to support weight loss (Page 8, 3.3) does not accurately reflect the provision of current services across all 42 ICBs. Community weight management (Tier 2) services commissioned through local government have better provision in comparison but variability in access across England still exists and many services are not delivered by specialist-trained healthcare professionals (e.g., dietary advice not given by a dietician). Page 14, 3.9: Both the SURMOUNT-1 trial and the NICE EAG highlighted that the trial protocol specified the need for an appropriately trained professional to deliver individualised dietary advice. NHSE notes that the support provided in the trial significantly exceeds current clinical practice across primary and community care for those in need of weight management support. The frequency of contact and consultation with a dietitian or equivalently qualified delegate according to local standards is not common practice - and has been corroborated by the experience of GPs in England. Due to the potential for significant resource impact, NHSE would welcome guidelines, as mentioned above, to include the content and duration of dietary advice to aid consistency in NHSE service planning. Guidelines would also ensure commissioning is aligned to deliver the best outcomes and value for patients and the NHS, by appropriately trained professionals.
4	Multi-disciplinary Team Page 7 3.2: NHSE notes there is a disparity between current guidelines [CG189], which recommend that pharmacotherapy for managing obesity requires access to a MDT (including a dietitian, psychologist and physical activity instructor) as provided in specialist weight management service, whereas the draft recommendation for Tirzepatide treatment is positioned outside of this recommendation suggesting diet and exercise alone is sufficient. There is some concern around the quality of evidence supporting this decision (given organisation and structure in English primary care are very different to countries participating in the relevant trials). There is potential to cause confusion for clinicians around which guidance to follow. Furthermore, (Page 12 3.6) NHSE have concern around generalisability of the clinical effectiveness, as SURMOUNT-1 did not cover the whole population that would potentially be offered Tirzepatide based on NICE recommendations. The SURMOUNT-1 trial excluded people with type 2 diabetes and people with history of severe psychiatric disorders within the last 2 years, but this is not reflected in the recommended patient cohort for Tirzepatide. This further suggests that an MDT may be required to support primary care with management of a complex patient cohort. Page 13 3.7: Due to the potential risk for fragmented care and complex clinical governance if patients psychiatric and physical or functional weight-related health concerns are managed separately, NHSE note NICE's acknowledgement for the need for an MDT to manage this complex cohort of patients. NHSE has provided evidence on the MDT required to support the use of this medicine. For example, we might expect a proportion of patients to require psychological support. Comprehensive reviews of the literature have suggested that between 20-60% of people living with obesity, and extreme obesity in particular, suffer from psychiatric illness. These include depression, eating disorders (particularly binge-eating disorder) and anxiety (Sarwer and Polonsky, 2016). There is concern that by removing access to a MDT, and therefore removing psychological assessment and support that some patients would benefit from, may be a risk to patient safety. *'Confidential information removed'*. It should be noted that there are a small number of GPs with specific expertise or training in obesity who are involved in the delivery of specialist weight management service but these GPs and the services in which they operate, are not representative of usual primary care services in England. Further, the NHS is not responsible for the commissioning of all community services; local authorities hold the commissioning responsibility for Tier 2 community weight management services in England.

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5	**Pharmacotherapy positioning** Page 15, 3.9: NHSE strongly supports NICE's conclusion that tirzepatide should be prescribed with diet and exercise support. The aforementioned need for clinical guidelines, covering wrap around care provision and ensuring that pharmacotherapy is positioned appropriately within the weight management pathway, would add value for commissioners and clinicians.
6	**Inclusion of obesity care in existing general practice capacity** Page 15: Based on the understanding of NHSE that not all weight-related comorbidities are managed exclusively in primary care with comorbidities likely to still require GP time despite being on pharmacotherapy, NHSE are in agreement with the NICE committee conclusion; that following evidence presented by Eli Lilly it was uncertain as to whether diet and exercise support could be incorporated into ongoing care for comorbidities in primary care.
7	**Dose titration** Page 16. "The committee also concluded that dose escalation and de-escalation would need appropriate monitoring. How this was done would need to be considered in the implementation of the wraparound obesity management services for delivering tirzepatide." This statement acknowledges an entirely new care pathway is required for tirzepatide for delivery by the NHS. As set out above, NHSE would welcome the revision of a clinical guideline from NICE as such to avoid unwarranted variation in treatment and care.
8	**Uncertainty** Page 33, 3.25: NHSE acknowledges the committee has considered, 'as well as the high levels of uncertainty, there is also high decision risk given the potential population size eligible for Tirzepatide if it was recommended".

Insert extra rows as needed

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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):	Weight Management Unit (WMU) comments to be considered as part of DHSC response
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.	None from WMU
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None from WMU
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.
1	Primary care weight management services may benefit from definition, as it is unclear if these are NHS primary care services, local authority behavioural (tier 2) services community services, or both. Local authority services are not generally referred to as primary care services.
2	The Committee discussion section makes clear the Committee concluded tirzepatide should be provided alongside diet and exercise support services. However, the recommendation itself says "*Tirzepatide is recommended as an option for managing overweight and obesity, alongside a reduced-calorie diet and increased physical activity, in adults, only if [continues].*" Interpretation and understanding of the recommendations could be made clearer by clarifying that tirzepatide is recommended alongside 'diet and exercise support services' for a reduced calorie-diet and increased physical activity.
3	**Section 3.2: Treatment pathway for overweight and obesity in the NHS** In this section it is unclear if behavioural (tier 2) weight management services provided by local authorities (not the NHS) have been considered. This links to Comment 1, in that local authority services are not generally referred to as primary care services. References to services could be clearer in this section to support the interpretation of the guideline. The section title may also need to be adjusted to reflect the fact that local authority services are also part of the treatment pathway.
4	**3.7 Generalisability of population comorbidities in SURMOUNT-1** It is unclear if the tirzepatide for overweight and obesity guideline applies to people with type 2 diabetes or if they should instead be treated according to the type 2 diabetes guidelines. This could be clarified to support the interpretation of these guidelines.
5	**3.7 Generalisability of population comorbidities in SURMOUNT-1** There is discussion on whether tirzepatide can be used in people with mental health disorders including severe mental illness, as this group were excluded from the clinical trial. In the committee discussion, it is stated 'that populations excluded from SURMOUNT-1 should not be excluded from the recommendations for tirzepatide'. This could be made clearer in the guideline recommendations to support the interpretation of these guidelines.
6	**3.8 BMI in SURMOUNT-1** Discussion on BMI cohort of adults referred to primary care weight management services, appears to cite the final report on the OHID 2021/22 Local Authority Weight Management Services Grant. These are local authority services delivered in the community, not primary care services. This could be clarified in the committee discussion included in the draft guideline. It is important to note that these data are on a subset of local authority commissioned behavioural (tier 2) services, not all services commissioned under the Public Health Grant. Therefore, these data are not representative of all local authority services. We are not currently aware of a comprehensive data set on these services. The report is available here: https://www.gov.uk/government/statistics/adult-tier-2-weight-management-services-provisional-data-for-april-2021-to-december-2022-experimental-statistics
7	**3.9 Diet and exercise support in SURMOUNT-1** It is not clear who should provide the diet and exercise support (a Dietitian or a health care professional) alongside tirzepatide, and the committee discussion section may be confusing because the professionals cited and definitions are unclear or overlapping. It might be helpful to clarify who should provide the diet and exercise support to support the interpretation of the guideline and ensure tirzepatide meets the conditions for effective and cost-effective use.
8	**3.9 Diet and exercise support in SURMOUNT-1** The committee discussion states 'People in all arms of SURMOUNT-1 were advised on diet and exercise, to include a diet with a 500-calorie per day deficit and an increase in physical activity by 150 minutes per week'.

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	The UK CMO guideline recommends 'each week, adults should accumulate at least 150 minutes (2 1/2 hours) of moderate intensity activity'. Unless the committee discussion is quoting the clinical trial protocol or publication, this would be more accurate if it said 'increase in physical activity to 150-minutes' rather than increase 'by 150-minutes'.
9	**3.16 Costs of obesity management services** As in comment 7, it might be helpful to clarify who should provide the diet and exercise support to support the interpretation of the guideline and ensure tirzepatide meets the conditions for effective and cost-effective use.
10	**3.16 Costs of obesity management services** NHSE proposed that psychological support is provided for around a third of people. The EAG 'amended the proportion of people having psychological support to align with the proportion of people in SURMOUNT-1 with current or historic psychiatric problems'. Please can NICE and/or the guidance explain why the EAG made this decision? It is not evident why they would assume the population in SURMOUNT-1 applies to the population that would be eligible if tirzepatide was recommended for use in the NHS.
11	**3.29 Equality** As in comment 5, there is discussion on whether tirzepatide can be used in people with mental health disorders including severe mental illness, as this group were excluded from the clinical trial. In the committee discussion, it is stated 'that populations excluded from SURMOUNT-1 should not be excluded from the recommendations for tirzepatide'. This could be made clearer in the guideline recommendations to support the interpretation of these guidelines.
12	**Cost effectiveness** It is unclear if the cost-effectiveness estimates consider the management of side effects, for example adverse events (i.e. gallstones) or excess skin from significant weight loss.

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- 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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NICE National Institute for Health and Care Excellence

Tirzepatide for managing overweight and obesity [ID6179]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 25 June 2024. 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):	[Insert organisation name]

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NICE National Institute for Health and Care Excellence

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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.	Nothing to disclose
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Prof. Jonathan Pinkney

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	Has all of the relevant evidence been taken into account? Yes

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NICE National Institute for Health and Care Excellence

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2	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes
3	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? I agree with the case presented for clinical need, the proposed target population, and suggestions for stopping rules. The correct evidence base has been reviewed. The interpretations are appropriate. I think the economic model is challenging but not unreasonable as a starting point. Many assumptions have to be made. Overall, I take that view that Tirzepatide is an important advance in the area of weight management, and the closely related area of T2D, offering a valuable new option for many people. I have several specific comments below. My main questions relate to the challenges of real-world implementation in the NHS, although I appreciate that this is not the primary responsibility of NICE (section 6). Indication In my opinion, the conclusion that Tirzepatide would be most appropriately offered within the NHS context for BMI>35 + 1 or more comorbidites appears to make sense. There would less advantage to offer this below BMI 35 or to those without any comorbidity. Although outside the scope of NICE and being considered through the metrics of ICERs and QALYs, for these groups there might be other better uses of public funds, including planning changes, health promotion, legislational changes, more support for lifestyle change, and of course self-pay. Challenge of costs The proposed NHS costs are noted. I agree that the cost assumptions are difficult because service models are so poorly defined. As some indication of the likely challenge of costs, in our service, to treat 100 newly referred patients every year, at the 10mg dose, for 10 years, without allowing for inflation would cost £12.8M. In reality many more than this number will probably be referred for treatment. 10 year running costs for our SWMS, without allowing fo inflation are £4.6M. Therefore, drug costs could soon outstrip existing service provision costs. Beyond the metrics of ICERs and QALYs, It is unclear whether this is affordable. This supports limiting the indication to BMI>35. I agree that the main comparator (phamacological treatment) is Semaglutide (plus behavioual lifestyle intervention). However, long term assumptions can only be tentative. (i) I was not sure about the comparative long term stopping rules for comparing Tirzepatide with Semaglutide (p30). I understand why this is done, but in time it may be that Semaglutide will come to be used long term, as logic would

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	also dictate. (ii) Also, if Semaglutide is simply stopped at 2 years, in my opinion, based on what patients often tell me, many patients are likely to opt for bariatric surgery as the best long term option. Therefore bariatric surgery is another long term comparator option, although there are no data on this comparison yet. (iii) After stopping Semaglutide, Tirzepatide and other new drugs would also become options. (iv) In long term treatment, it may be that intermittent treatment will come to be used, as has commonly been the case with previous weight loss medications. If effective, this would reduce costs. However, this just illustrates the many challenges of the assumptions required for long term cost modelling. Perhaps NICE might acknowledge the tentative nature of the cost modelling and revisit this issue in the future when more real-world data become available? Need for behavioural lifestyle intervention I agree that treatment should be accompanied by behavioural lifestyle treatment, and I believe that this would be a common opinion in the field. Thus, there is a discussion to be had about the suggestion made that the effect of the drug might be the same without any behavioural lifestyle modification (page 15). This is not proven. Previous expert consensus guidance considered behavioural lifestyle treatment the cornerstone of weight management, and it is unclear that the advert of GLP1ras changes that principle. It is reasonable to argue that significant attention is still required to these issues. In the view of many clinicians and researchers, the debate is more around how much is needed, how “light touch” can it be, the intensity, duration, delivery mode and cost. It is possible the NHSE pilot, if it proceeds, might provide some further information about the supporting treatments.
4	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. No.
5	Could have any adverse impact on people with a particular disability or disabilities. No
6	There is a requirement for relevant health bodies to comply with the recommendations in this evaluation within 3 months of the date final guidance is published by NICE (see section 4.1). We are aware there may be system challenges that mean an extension to this normal period may be appropriate because tirzepatide cannot be appropriately administered until: training is in place certain health service infrastructure requirements

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	including goods, materials or other facilities are in place other appropriate health services resources, including staff, are in place. These challenges may include: commissioning arrangements for weight management services how tirzepatide will fit into the current treatment pathway for weight management the provision of counselling, psychological support and concomitant behavioural, dietary and physical activity advice titration of tirzepatide and how a stopping rule based on treatment response at 6 months would be implemented capacity in the system. Please specify any potential challenges with implementing these recommendations and the associated reasons. Please also provide any ways to overcome these potential challenges, any estimate of the time period within which the recommendation can be complied with, and any approaches to phase in funding to manage access to tirzepatide during any potential extended funding variation period. In my opinion, these are the critical issues facing the NHS in bringing in the use of Tirzepatide (and other new weight loss medications). NHS implementation There certainly “may be system challenges that mean an extension to this normal period may be appropriate…”. Based on our discussions with many sites nationally, as a part of research, this is an understatement. While NICE is not responsible for service commissioning, the 2013 expectation of implementation of this guidance within 3 months is already difficult, if not impossible for many services in respect of Semaglutide. This is because (i) obesity BMI>35 is very common, (ii) service provision is patchy and capacity is generally low, (iii) drug costs are relatively high for drugs that are likely to be very widely used, (iv), introducing Tirzepatide or Semaglutide is not like introducing a new diabetes drug into an existing well-developed national diabetes service network, or a new cancer drug with a narrow indication into well-established oncology services, (v) in 2024 the NHS is in a financially and administratively different place from 2013. GLP1ras are landmark treatment advances, but system change is not straightforward. In my experience it is awkward when NICE expects implementation of say Semaglutide within 3 months, and this left many clinicians and commissioners is a difficult position, being asked to divert funds from other budgets, while patient complaints begin to accumulate. Therefore, it would be helpful to avoid stipulating such a deadline, and perhaps make a brief comment, or acknowledgement, that availability will be subject to local considerations and in some places service development. This would cover the many challenges of staff recruitment and training, pathways development, affordability and funding. It might also help to avoid clinical service being blamed for their inability to make the treatment available. Pathway development is also relatively complex and takes time. Primary Care feasibility I agree with the suggested principle that treatment for a common LTC like obesity should become primary care based, at least for less complex patients, although significant numbers will still require referral to specialists for a review. These include some with complex comorbidity, mental and physical health concerns, psychological trauma, eating disorders, those interested in discussions about bariatric surgery, or where specialised

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	diets may be needed for a time. This is often why patients are currently referred to SWMS. I also agree with the manufacturer that the behavioural diet and exercise support provided in the trials "could be" replicated in primary care (page 11 onwards). Whether or not it generally can be replicated at the present time is another matter. Although I understand that a primary care survey was considered to support this, it might be helpful to understand where this was done and number of sites surveyed. Are we confident that the survey is nationality representative of primary care? In many regions, our understanding is that primary care is not in such a state of readiness to take on a new area of treatment without investment for staff and training, because of loss of staff and increasing numbers of unfilled positions. It is possible that areas of greater deprivation, with more stretched primary care services, and competing medical service needs, might find it harder to introduce this treatment. This might also introduce inequalities in some areas. Most LTC management in primary care is undertaken by practice nurses and ANPs, who prescribe. Currently, however, few are trained in complex obesity or its pharmacotherapy. More staff would be required and to trained up in order to provide weight management at scale in primary care. Posts are not necessarily easy to fill. In my opinion the suggestion (Page 21) the health care professional are not needed to deliver support, and that some form of counselling is sufficient, should be treated with some caution. It is unclear to me who else would provide such support. Training would still be required. I think any such support would still have to be within defined pathways that also provided access, where necessary, to expert dietitians, nurse prescribers, psychologists, access to NHS data and records, and medical support. Dose escalation, de-escalation and stopping still have to managed. Therefore, HCPs are still needed for the system. In summary, while these matters are outside the remit of NICE, but it would be helpful for patients, clinicians and commissioners if what NICE advocates is broadly deliverable in clinical practice within a foreseeable timeframe.

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 confidential in turquoise. If confidential information is submitted, please

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- Do not use abbreviations.
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Single Technology Appraisal

Tirzepatide for managing overweight and obesity

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	[redacted]
Location	
Conflict	
Notes	
Comments on the DG:	

Has all of the relevant evidence been taken into account?

No
The cohort used in SURMOUNT-1 is different to that of the real-world population. The evidence for tirzepatide in the highest risks groups is limited and these are patients that should potentially be prioritised for treatment in systems that already have stretched capacity.

There is no evidence of long-term safety and the outcomes of further trials such as SURMOUNT-MAINTAIN are not available. The draft states that ‘it is uncertain what long-term effect tirzepatide would have on morbidity and mortality rates'. It was also ‘uncertain what the effectiveness of tirzepatide is beyond the 72-week period observed in the trial’. However, there appears to be no maximum duration of treatment to reflect this in the draft TA, indicating that use could be indefinite. This is not comparable to other drugs used for weight management within the NHS currently.

The recommendations for semaglutide being restricted to 2 years was due to lack of evidence for longer use as well as restricted time in specialist services. This should be
The recommendations for semaglutide being restricted to 2 years was due to lack of evidence for longer use as well as restricted time in specialist services. This should be

indicating that use could be indefinite. This is not comparable to other drugs used for weight management within the NHS currently.

There is a requirement for relevant health bodies to comply with the recommendations in this evaluation within 3 months of the date final guidance is published by NICE (see section 4.1). We are aware there may be system challenges that mean an extension to this normal period may be appropriate because tirzepatide cannot be appropriately administered until:

- training is in place
- certain health service infrastructure requirements including goods, materials or other facilities are in place
- other appropriate health services resources, including staff, are in place.

These challenges may include:

- commissioning arrangements for weight management services
- how tirzepatide will fit into the current treatment pathway for weight management
- the provision of counselling, psychological support and concomitant behavioural, dietary and physical activity advice
- titration of tirzepatide and how a stopping rule based on treatment response at 6 months would be implemented
- capacity in the system.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No

Weight management is a wider Public Health issue, which should be supported by the NHS.

There are currently long wait times to access NHS specialist services in many areas, which will increase without provision of further support.

Other injectable weight loss drugs, such as liraglutide and semaglutide were not considered for use in primary care. By making tirzepatide available in primary care, this opens up potential challenges from other manufacturers who may seek to follow the same pathway. Specialist weight management services have already struggled to implement these TAs where they already have the wrap around care available, unlike primary care where a whole new service would need to be designed to implement this TA.

The lack of a 2-year period of prescribing would also potentially come under challenge from the other manufacturers of weight loss drugs, as this is not specified in the current proposed TA for tirzepatide despite no acknowledgment of benefit past this point.

Unlike other injectable weight loss drugs, tirzepatide is licensed in the same presentation for both diabetes management and weight management. Therefore, even if tirzepatide were to be supported in specialist weight management services only, it would still create challenges in identifying inappropriate prescribing in primary care for weight management purposes.

There has been no specific modelling of the non-prescribing costs of this service to look at the proposal holistically and decide if this is cost-effective.

These treatments should be prioritised for the patients who are most in need. The draft proposal states that people need ‘at least 1 weight-related comorbity’ to be eligible. However, in the tirzepatide marketing authorisation, there are specific comorbidities listed. These specific comorbidities need to be included in the TA documentation to prevent this becoming open to interpretation.

In the draft proposal, the committee noted that the population in SURMOUNT-1 ‘was different to the population who would be eligible for tirzepatide in clinical practice’. The ‘light touch’ approach to diet and exercise support used in SURMOUNT-1 is not an appropriate model for use in the NHS. Diet and exercise support should be a key intervention before medication is even considered, as well as during treatment with medication. The trial population is not indicative of the likely population to gain most benefit.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

This is currently unclear.

There is a requirement for relevant health bodies to comply with the recommendations in this evaluation within 3 months of the date final guidance is published by NICE (see section 4.1). We are aware there may be system challenges that mean an extension to this normal period may be appropriate because tirzepatide cannot be appropriately administered until:
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- how tirzepatide will fit into the current treatment pathway for weight management
- the provision of counselling, psychological support and concomitant behavioural, dietary and physical activity advice
- titration of tirzepatide and how a stopping rule based on treatment response at 6 months would be implemented
- capacity in the system.

With some services being more developed than others, demand for drugs in these areas will likely increase quickly. With the delays in stock availability seen in the initial introduction of tirzepatide to the UK market, there doesn’t appear to be any evidence of stock assurance or modelling of how demand will be managed in the draft proposal. Many private providers are already supplying tirzepatide for weight management due to increasing demand for this drug. It is important that we avoid a similar situation to the long term

GLP1 shortages seen, that affect other areas of care, such as diabetes management for which tirzepatide is already recommended.
LES provisions are already required in many cases for initiations of GLP1s in primary care. Current service models would need to be completely restructured and there is currently no additional investment funding available to support this.
Primary care may take a similar stance to that of inclisiran if inadequate evidence, resource and support is put in place for this proposal.

Please specify any potential challenges with implementing these recommendations and the associated reasons.
With some services being more developed than others, demand for drugs in these areas will likely increase quickly. With the delays in stock availability seen in the initial introduction of tirzepatide to the UK market, there doesn't appear to be any evidence of stock assurance or modelling of how demand will be managed in the draft proposal. Many private providers are already supplying tirzepatide for weight management due to increasing demand for this drug. It is important that we avoid a similar situation to the long term GLP1 shortages seen, that affect other areas of care, such as diabetes management for which tirzepatide is already recommended.
LES provisions are already required in many cases for initiations of GLP1s in primary care. Current service models would need to be completely restructured and there is currently no additional investment funding available to support this.
Primary care may take a similar stance to that of inclisiran if inadequate evidence, resource and support is put in place for this proposal.

Please also provide any ways to overcome these potential challenges, any estimate of the time period within which the recommendation can be complied with, and any

The use of weight management drugs should form part of a wider Public Health plan which has considered the issues holistically, in the context of systems.
Obesity services need to be defined and developed with appropriate investment in staffing and infrastructure, before guidance is published that mandates the use of a weight management drug in a large cohort of patients.

External Assessment Group's report

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

Produced by	*Warwick Evidence*
Authors	*Dr. Ewen Cummins, McMDC Ltd.* *Dr. Rhona Johnston, McMDC Ltd.* *Rachel Court, Information Specialist, Warwick Evidence* *Mubarak Patel, Research Fellow, Warwick Evidence* *Dr. Lena Al-Khudairy, Associate Professor, Warwick Evidence*
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Date completed	*26 July 2024*

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Declared competing interests of the authors

None.

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Dr Thomas Barber, Associate Clinical Professor, Warwick Medical School, Biomedical Sciences, University of Warwick, provided clinical support and advice throughout the work of this appraisal.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Contributions of authors

Ewen Cummins critiqued the cost-effectiveness evidence, Rhona Johnston reviewed and revised the VBA model implementation and both implemented the revised EAG economic modelling. Mubarak Patel critiqued statistical aspects of the Company submission and provided statistical input. Rachel Court conducted additional EAG searches. Lena Al-Khudairy supported the critique of the clinical effectiveness evidence and coordinated the project. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in [redacted] are '[redacted]. Sections highlighted in [redacted]. Figures that are CIC have been bordered with blue. [redacted] is highlighted in pink.

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1 Executive summary

1.1 *Overview of the EAG's key issues*

Table 1: Summary of key issues

ID 6179	Summary of issue	Section
Issue 1	The recommended cohort may be too large.	3.1
Issue 2	The recommendation includes those with T2DM despite the October 2023 recommendation of TA294 covering these patients. No cost effectiveness estimates for those with T2DM have been submitted for the current assessment.	3.2
Issue 3	The recommendation to consider stopping treatment if there is not at least 5% weight loss at 6 months is not mandatory.	3.3
Issue 4	There is a lack of longer term data. Assuming an indefinite ongoing benefit may be too optimistic. The NICE methods guide requires waning scenarios to be presented.	3.4
Issue 5	The SURMOUNT-1 patient population may not reflect the probable BMI distribution of those who will present for tirzepatide treatment in the NHS.	4.2
Issue 6	Being obese and then losing weight may not return patients to the risks of complications of those who have never been obese.	4.4
Issue 7	The Company thinks that the EAG estimated costs of T2DM are too low.	4.5
Issue 8	The Company thinks that the NHSE MDT costs are too high. The Company also thinks that if no MDT costs are applied in the comparator arm, the comparator arm should have no clinical effects.	4.6

Issue 1	The recommended cohort is too large.
Report section	3.1
Why important	A number of consultees are concerned that the recommended cohort is too large and that it will not be feasible to deliver tirzepatide to these patients. The EAG base case for the recommended target group subset with a BMI ≥ 35 kgm^{-2} is £21,372 per QALY. It increases to £23,109 per QALY if the model overestimates the probable reduction in T2DM which may be reasonable to assume given concerns about whether losing weight completely reverses the risks of complications. It increases to £26,702 per QALY if relatively muted waning of a 2% annual loss in net BMI benefit is applied from year 5. It improves to £17,171 per QALY if the NHSE MDT costs are not applied.
EAG approach	Exploring smaller subsets of the patient group.
Effect on ICER	For those with a BMI ≥ 35 kgm^{-2} and prediabetes the EAG base case ICER is £19,504 per QALY. Its ICERs are around £2,000 per QALY better than the ICER of the corresponding scenario analyses of those with a BMI ≥ 35 kgm^{-2}.
Additional analyses	The EAG thinks that the ICERs for those with a BMI ≥ 35 kgm^{-2} and prediabetes will show little sensitivity to subset specific baseline characteristics and clinical effectiveness estimates. The Company is free to supply these. If Committee is unhappy with the EAG approach a fall back is the smaller subset with a BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk. These ICERs are around £1,000 per QALY worse than the corresponding analyses for those with a BMI ≥ 35 kgm^{-2} and prediabetes.

Issue 2	The recommendation covers those with T2DM
Report section	3.2
Why important	A number of consultees are concerned that SURMOUNT-1 excluded those with T2DM so provides no evidence for these patients and that the recommendation moves tirzepatide use among those with T2DM from after triple OAD therapy up to potentially a first line therapy for T2DM.
EAG approach	The current model is poorly suited to modelling those with T2DM but if this is attempted the Company base case ICER for the target group of £14,726 per QALY worsens to £22,530 per QALY. The current modelling covers those without T2DM. A key driver of the ICER is the avoidance or delay in onset of T2DM which obviously would not apply to those with T2DM. The EAG thinks that the October 2023 TA924 recommendation for those with T2DM considered the clinical and cost effectiveness evidence for those with T2DM. The EAG does not understand what the evidence base is that leads to a recommendation which overturns that of TA294 and moves tirzepatide use among those with T2DM from after triple OAD therapy up to potentially be the first line therapy for T2DM.
Effect on ICER	See TA924.
Additional analyses	None in addition to those presented during TA924.

Issue 3	The recommendation is to consider stopping treatment at 6 months.
Report section	3.3
Why important	A number of consultees have expressed concern that the recommendation is to consider stopping treatment if weight loss at 6 months is less than 5% rather than it being mandatory.
EAG approach	The EAG only notes that a mandatory stopping rule at 6 months is in line with both the Company and the EAG economic modelling.
Effect on ICER	None.
Additional analyses	None.

Issue 4	The lack of long term data and model extrapolation.
Report section	3.4
Why important	A number of consultees have expressed concern about the lack of long term data and by implication the reliability of the model extrapolations that assume an indefinitely increasing net BMI benefit from tirzepatide in the Company base case and an indefinite constant net benefits in the EAG base case.
EAG approach	In line with the NICE methods guide exploring treatment waning scenarios. The company also argues that the scenario of an indefinite constant weight and no natural weight gain while on tirzepatide with ongoing natural weight gain in the comparator arm should be considered.
Effect on ICER	Results are sensitive to a relatively muted treatment waning of an average annual loss of net BMI effect of 2% from year 5. For the target group the EAG base case ICER worsens from £28,697 per QALY to £34,231 per QALY. For the target group subset with a BMI ≥ 35 kgm^{-2} the EAG base case ICER worsens from £21,372 per QALY to £26,702 per QALY. An indefinite constant weight while on tirzepatide improves the EAG base case ICER from £21,372 per QALY to £18,019 per QALY. This scenario with an alternative weight gain estimate for diet and exercise yields £19,428 per QALY.
Additional analyses	The model implementation of treatment waning has errors. These may be Company errors or EAG cut and paste errors. Correcting these would increase confidence in the treatment waning scenarios.

Issue 5	The probable distribution of patient BMI
Report section	4.2
Why important	The SURMOUNT-1 BMI distribution may not reflect the probably NHS patient BMI distribution. Given the Patient Expert comments Committee had a preference for NHS HSE survey BMI data over SURMOUNT-1. The Company notes that the EAG assumption that the HSE data was normally distributed was not evidence based.
EAG approach	The EAG has sourced HSE survey BMI distribution data for 2016-18 which exhibits some rightward skew. The gamma distribution is a poor fit. Over the HSE BMI distribution the normal outperforms the lognormal. Restricting attention to the section for those with a BMI 30 ≥ kgm^{-2} the lognormal outperforms the normal. In the light of the SURMOUNT-1 BMI distribution submitted by the Company the assumed gamma may not be a good fit at the lower end. The EAG base case applies the lognormal. Scenarios applying the normal are provided, as well as sampling from the SURMOUNT-1 distribution and applying the Company assumed gamma distribution.
Effect on ICER	For the target group the EAG base case of £28,697 per QALY worsens to £29,243 per QALY with the normal but improves to £26,013 per QALY sampling from SURMOUNT-1 and to £25,512 per QALY with the gamma. For the target group subset with a BMI ≥ 35 kgm^{-2} the EAG base case of £21,372 per QALY improves to £21,332 per QALY with the normal but worsens to £22,565 per QALY sampling from SURMOUNT-1 and to £21,942 per QALY with the gamma.
Additional analyses	None.

Issue 6	Weight loss may not entirely reverse the effects of obesity
Report section	4.4
Why important	The key model assumption is that for those with weight loss there are no long term effects of having been obese. Their risks of complications are the as if they had never been obese. If this is not the case the model will be biased in favour of tirzepatide, possibly seriously so.
EAG approach	The EAG has previously used the Haase et al paper to justify exploring weight loss not resulting in patients' risk of T2DM falling to as though they had never been obese. This also suggested other risks of complications may remain elevated and that the risks of angina or MI might not be affected at all. The Company has highlighted an additional paper, Khunti et al, which suggests much the same. For some complications of obesity a weight loss of 20% results in the same risk as a weight loss of 10%. For others such as angina and MI there are no measurable effects. The Company highlights the 50% hazard ratio for T2DM from a weight loss of 20% of Khunti et al. This is more than double the 10 year relative risk estimated within the model and suggests a 61% adjustment factor.
Effect on ICER	Applying a 61% adjustment factor to the costs of T2DM worsens the EAG base case ICER for the target group from £28,697 per QALY to £31,181 per QALY. The EAG base case ICER for the target group subset with a BMI ≥ 35 kgm^{-2} worsens from £21,372 per QALY to £23,109 per QALY. Including similar adjustments for OSA, TKA, angina and MI further worsens the ICERs but not by much.
Additional analyses	Given the apparent Company preference for Khunti et al over Haase et al none suggest themselves to the EAG.

Issue 7	The Company thinks that EAG T2DM costs are too low
Report section	4.5
Why important	Cost offsets from avoiding/delaying T2DM are model drivers.
EAG approach	The Company indexes UKPDS68 gross costs of T2DM without complications to 2022/23 prices using the Personal Social Services (PSS) excluding capital costs index. The EAG indexes UKPDS68 gross costs of T2DM without complications to 2021/22 prices using the standard NHS Cost Inflation Index (NHSCII). The Company applies the discounted drug costs estimate of £552 from a modelling exercise among those with a 7 year duration of T2DM sponsored by the manufacturer of semaglutide. The EAG provides an average annual discounted drug cost estimate for those with T2DM of £340. The EAG notes that the UKPDS68 costs are gross costs of T2DM without complications so routine resource use should be subtracted to give a net additional cost. The EAG provides scenario analyses that include a proportion of the estimated costs of the microvascular complications of T2DM from the same source as the Company drug cost estimates.
Effect on ICER	The Company base case ICER of £14,726 per QALY for the target group worsens by 9% to £16,039 per QALY when using the EAG cost estimates. The EAG has not explored the Company T2DM cost estimates within its main analyses due to time constraints.
Additional analyses	None.

Issue 8	The Company thinks that NHSE MDT cost estimates are too high, and if not applied in the comparator arm the comparator arm should have no clinical effects.
Report section	4.6
Why important	The NHSE MDT costs are key model drivers.
EAG approach	The EAG supplies scenario analyses excluding the NHSE MDT costs, and excluding them from the comparator arm while assuming no clinical effects in the comparator arm.
Effect on ICER	The EAG base case ICER for the target group of £28,697 per QALY improves to £23,192 per QALY if NHSE MDT costs are excluded, and to £24,789 per QALY if the comparator arm has no MDT costs and no clinical effects. The EAG base case ICER for the target group subset with a BMI ≥ 35 kgm^{-2} of £21,372 per QALY improves to £17,171 per QALY and to £19,129 per QALY in the corresponding analyses.
Additional analyses	The EAG has not applied any of the other Company resource use scenarios, in part due to time constraints. NHSE is better placed than the EAG to assess the reasonableness of the Company resource use scenarios.

2 Background

After the second Committee meeting NICE circulated a summary of the Committee concerns and analyses it wished to see. The Company responded to this with a range of analyses but which did not address all the analyses requested within the NICE document, not providing estimates for a number of target group subsets.

The EAG subsequently submitted a report dated 5 April 2024 which provided a brief critique of the Company submission and inferred some additional analyses for the target group subsets. It did not provide a full critique or a full set of analyses as it had been informed that this should be provided in response to consultation. It does so now.

The Committee recommendation that went to consultation was to recommend tirzepatide alongside diet and exercise for those with a BMI ≥35 kgm^{-2} and at least 1 weight related comorbidity, and to consider stopping treatment if less than 5% weight has been lost after 6 months of treatment.

In addition to the Company response to consultation there have been a number of other consultation responses. The EAG addresses the issues raised by these Consultees that affect the economic modelling.

- Section 3.1: The recommended cohort is too large
- Section 3.2: The recommendation includes those with T2DM
- Section 3.3: The recommendation to consider stopping treatment
- Section 3.4: The lack of longer term efficacy data
- Section 3.5: The proportion of patients that require psychological support

The Company response to consultation provides ICERs for the target group and for the BMI 30 – 35 kgm^{-2} subset of the target group. It provides these for what it labels the “Committee base case” and also for the Company base case. These differ in three aspects.

1. UKPDS T2DM non-drug costs in the absence of complications of £674, compared to £803 due to the £674 being incorrectly indexed for inflation by the EAG.
2. Natural weight gain while on tirzepatide resulting in a constant net weight loss benefit from tirzepatide vs diet and exercise, compared to no natural weight

gain while on tirzepatide and an ever increasing net weight loss benefit from tirzepatide vs diet and exercise.

3. A normal distribution for BMI based upon Health Survey of England data compared to a gamma distribution based upon the SURMOUNT-1 trial.

The EAG addresses the modelling and concerns of the Company and the concerns of Committee that affect the modelling to the extent that they have not been covered by the other Consultee comments.

- Section 4.1: Relevance of tirzepatide 5mg and 10mg arms
- Section 4.2: The probable patient BMI distribution
- Section 4.3: Natural weight gain by arm
- Section 4.4: Risk reductions from weight loss
- Section 4.5: T2DM costs
- Section 4.6: NHSE MDT resource use

Mechanical technical issues are subsequently addressed.

- Section 5.1: Which model version to use
- Section 5.2: Model convergence
- Section 5.3: Price indexing of UKPDS T2DM 68 costs
- Section 5.4: Price indexing of NHSE MDT professionals' costs

These are followed by the Company results in Section 6 and EAG exploratory modelling and scenario analyses in Section 7.

In common with the Company modelling the EAG modelling does not include any probabilistic sensitivity analyses due to time constraints and the need to ensure model convergence, the latter significantly increasing model run time.

3 Issues arising from Consultee concerns

3.1 *The recommended cohort is too large*

The ICB, HWE and RCP state that the eligible cohort is in effect too large and needs to be tightened. NICE has indicated that if tirzepatide is found to not be cost effective in the target group, subsets of the target population should be explored with a view to an optimized recommendation. NHSE has indicated that if tirzepatide is approved it is likely that a funding variation will be sought. These all suggest that if tirzepatide is not cost effective for the target population, its cost effectiveness in subsets of the target population should be explored with a view to both an optimized recommendation and an optimized roll out of tirzepatide.

NICE previously indicated that Committee wished to explore the target population and two splits of the target population, generating four subsets of the target population.

1. Split 1: (A) Those with a BMI ≥ 35 kgm^{-2} and (B) those not within this group; i.e. with a BMI 30 - 35 kgm^{-2}
2. Split 2: (C) Those within the TA664 patient group, with BMI ≥35 kgm^{-2}, prediabetes and a high risk of CVD, and (D) those not within this group.

The current Company submission only presents cost effectiveness estimates for the target population and subset (B): those with a BMI 30 - 35 kgm^{-2}.

The Company has over the course of the assessment presented baseline characteristics and clinical effectiveness estimates for the target population and subsets (A), (B) and (C). The EAG has inferred baseline characteristics and clinical effect estimates for (D) as presented in its April 2024 report.

The EAG thinks that for current purposes the TA664 split may or may not be optimal. The EAG also notes that the SURMOUNT-1 extension study is limited to those with prediabetes at baseline. There may be a suggestion that the TA664 subset is to an extent arbitrarily restricting the patient population to that of the liraglutide trial. The subset with a BMI ≥ 35 kgm^{-2} and prediabetes may be an equally valid clinical subset. Call this subset (E).

The proportions of the SURMOUNT-1 target group ([redacted]) in each of these subsets is around*:

(A) BMI ≥ 35 kgm^{-2}: [redacted]
(B) BMI 30 – 35 kgm^{-2}: [redacted]
(C) BMI ≥ 35 kgm^{-2}, prediabetes, high CVD risk: [redacted]
(D) Non (C): [redacted]
(E) BMI ≥ 35 kgm^{-2}, prediabetes: [redacted]
(F) Non (E): [redacted]

Restricting those with a BMI ≥ 35 kgm^{-2} to those with a BMI ≥ 35 kgm^{-2} and prediabetes reduces subset (A) by [redacted] within SURMOUNT-1.

Restricting those with a BMI ≥ 35 kgm^{-2} and prediabetes to those with a high CVD risk as well reduces subset (E) by a further [redacted] within SURMOUNT-1.

The previous Company modelling for subset (A) has assumed that the baseline characteristics are the same for those with and those without prediabetes, with the obvious exception of prediabetes status. Similarly, the modelling has applied the same clinical effectiveness estimates to those with and without prediabetes.

The baseline characteristics for subsets (A) and (C) are mostly very similar, as reviewed in greater detail in Section 9. They only differ to any real degree by total cholesterol, HDL cholesterol, the proportion with GERD and the proportion with hyperlipidaemia, but these inputs have very little effect upon cost effectiveness estimates†. The proportions with hypertension and treated hypertension might be viewed as differing slightly.

The clinical effectiveness estimates for subsets (A) and (C) are virtually identical, as reviewed in greater detail in Section 9.

The Company modelling of subset (A) is in effect to:

- assume the same baseline characteristics for subsets (E) and (F) with the exception of (E) all having prediabetes and (F) all having normal glycaemia,

* Numbers are taken from various tables and model inputs and may not have precisely the same denominator but any errors are likely to be minor.
† For example, running the same set of assumptions as the 24 June 2024 Company base case for subset (A) yields an ICER of £12,613 per QALY. This only worsens to £12,681 per QALY when the baseline distributions of total cholesterol, HDL cholesterol, proportion with GERD and proportion with hyperlipidaemia are assumed to be that of subset (C). Also applying the baseline distributions of hypertension and treated hypertension of subset (C) results in an ICER of £12,697 per QALY.

- apply the same clinical effectiveness estimates to subsets (E) and (F), and,
- combine their results 40:60.

In the light of this, the EAG will present cost effectiveness estimates for subset (E) by setting the proportion of subset (A) with prediabetes at baseline to 100%; i.e. to not combine the results for subsets (E) and (F) into subset (A).

3.2 *The recommendation includes those with T2DM*

The HWE notes that those with T2DM were excluded from SURMOUNT-1 and concludes that these patients should not be included in the recommendation. NHSE also notes that T2DM patients were excluded from the evidence base.

Committee previously asked the Company to include modelling of a subset with T2DM. If the model is set to assume that the probability of developing T2DM in the first cycle is 100%‡ the Company base case ICER for tirzepatide 15mg compared to diet and exercise of £14,726 per QALY worsens to £22,530 per QALY. The Company declined to model those with T2DM due to it stating that the model is not suited to modelling those with T2DM. The EAG thinks that the current model is poorly suited to modelling those with T2DM.

The economic modelling was based upon clinical effectiveness estimates from the SURMOUNT-1 trial. This excluded those with T2DM. During the current assessment the Company has not presented any evidence of the cost effectiveness of tirzepatide for those with T2DM.

A key model driver within the current modelling is the avoidance or delay in onset of T2DM. This obviously will not apply to those with T2DM.

The cost effectiveness estimates for tirzepatide presented during the current submission relate only to patients that would fulfil the SURMOUNT-1 inclusion and exclusion criteria. No inference can be made from these cost effectiveness estimates to the cost effectiveness of tirzepatide among those with T2DM.

The EAG thinks that estimates of the cost effectiveness of tirzepatide among those with T2DM can only be made within a T2DM model such as the iQVIA CDM, which has been used for a number of previous NICE assessments. This would preferably apply T2DM specific clinical effect estimates. It can be noted TA924 did just this.

‡ Implemented in the VBA by revising *If rand1 < p_event Then QDiabetes_C = 1 End If* to *QDiabetes_C = 1*.

In October 2023 NICE approved tirzepatide for those with T2DM provided that:

1. Triple therapy metformin plus two other oral antidiabetic drugs (OADs) is ineffective, not tolerated or contraindicated; and,
   a. They have a BMI ≥ 35 kgm^{-2} and specific psychological or other medical problems associated with obesity; or
   b. They have a BMI < 35 kgm^{-2}; and,
      i. Insulin therapy would have significant occupational implications; or
      ii. Weight loss would benefit other significant obesity related complications.

The draft recommendation of the current assessment would overturn the recommendation of TA924 and change the positioning of tirzepatide among those with T2DM from essentially being after triple therapy with OADs to potentially being first line therapy.

Given:

- The October 2023 recommendation of TA924 based upon a full consideration of the clinical evidence and cost effectiveness of tirzepatide for those with T2DM, and
- The absence of any cost effectiveness estimates for those with T2DM during the current assessment,

The EAG does not understand why the current assessment needs to make any recommendation for those with T2DM, and if a recommendation is made for those with T2DM on what evidence base it is being made.

3.3 *The recommendation to consider stopping treatment*

Consultation comments from the ICBs state that rather than the 5% weight loss criterion being considered by clinicians it should be mandatory. The HWE states that a stopping rule recommending only to consider treatment cessation would be impossible to deliver in practice. The NHSE is also concerned that this may be too unprescriptive.

The RCP suggest that the 5% weight loss criterion at 6 months is insufficient, with subsequent weight gain also requiring consideration as a stopping rule with a possible view to switching to bariatric surgery.

A mandatory 5% weight loss criterion is consistent with the economic modelling assumptions.

3.4 *The lack of longer term efficacy data*

HWE, NHSE, ICBs and J. Pinkney express concerns about the lack of data beyond 72 weeks, some also expressing concerns around the lack of long term safety data.

The Company has previously stated that "*There is no evidence that the treatment effect of tirzepatide wanes over time in people who continue to receive therapy. Furthermore, the mechanism of action of tirzepatide (GLP-1/GIP agonism) does not provide a biological rationale for treatment effect waning*".

The EAG undertook a literature search for published longer term randomised controlled follow-up data for tirzepatide, both among those without T2DM and among those with T2DM. 72 week follow-up is the longest duration of randomized controlled follow-up data that has been published for tirzepatide.

SURMOUNT-4 had similar inclusion criteria to SURMOUNT-1 and was comprised of a 36 week open label phase aiming at maximising the tolerated dose up to 15mg followed by a 52 week randomised controlled follow-up phase that examined the effect of treatment withdrawal. During the open label 36 week randomized controlled phase the average weight loss was 20.9%, with this being followed by a further 5.5% weight loss between weeks 36 and 88 among those who remained on tirzepatide. Note that those who had tirzepatide withdrawn experienced a weight gain of 14.0% between weeks 36 and 88, which is further evidence supporting revising the loss of effect upon treatment withdrawal from 3 years to 2 years.

The EAG has previously presented the longer term follow-up data for the liraglutide SCALE trial to week 160. Patient numbers followed up to week 160 were around 50% of baseline numbers. It suggested a decline in net effect at an annual rate of around 11% from week 72. Liraglutide is a GLP-1, though weight loss with it is somewhat less than weight loss with semaglutide and tirzepatide.

During Factually Accuracy Check the company has highlighted that it is not clear whether the liraglutide follow up data relates to those followed up who were in the liraglutide arm so may include some no longer receiving liraglutide or if it is restricted to those on liraglutide. The EAG acknowledges this but thinks that during TA664 the manufacturer submission is unlikely to unnecessarily present liraglutide in a bad light. Including those who have ceased liraglutide treatment would do so, unless the

weight changes for those on liraglutide during follow up were actually worse. The EAG thinks that the most natural assumption is that the TA664 figure is an analysis of those remaining on liraglutide treatment.

The Company 24 Jun 2024 consultation response provides extension phase data from the semaglutide SELECT trial. The EAG has not been able to source the Company figure from the cited reference. It presents follow up data to week 221, or around 4 years. Patient follow-up drops off in a similar manner to the liraglutide SCALE trial follow-up to week 160, and drops further to around 1.5% by week 221. The EAG thinks that a reasonable interpretation of the Company figure is that there is no evidence of either a decline in the absolute effect or an increase in the net effect.

The NICE January 2022 methods guide Section 4.6.20 states "*Alternative scenarios should also be routinely considered to compare the implications of different methods for extrapolation of the results. For example, for duration of treatment effects, scenarios in the extrapolated phase might include: (1) treatment effect stops or diminishes gradually over time, (2) treatment effect is sustained for people who continue to have treatment, and (3) treatment effect (or some effect) is sustained beyond discontinuation for people who stop treatment, when it is clinically plausible for lasting benefit to remain.*" In the opinion of the EAG, given the evidence for semaglutide from the STEP-1 trial and the evidence for tirzepatide from the SURMOUNT-4 trial on treatment cessation, the base case assumption of an ongoing but diminishing effect for 2 years after cessation of treatment covers point (3) of the methods guide.

Committee previously asked the Company to submit treatment waning scenarios, which it supplied. The EAG has had more time to examine its implementation of the original Company treatment waning implementation[§] in the VBA and notes that it appears that only the net effects upon weight and BMI have treatment waning applied to them. It also appears that the treatment waning scenarios somewhat overstated the actual degree of treatment waning that was being applied. For example, for a stated 5% treatment waning from year 5 it appears that the actual

[§] Note that this is within the EAG amended model. The EAG has not checked that these waning scenarios correspond with those of the Company model version that includes treatment waning as an option. The EAG implementation has attempted to replicate the company VBA revisions for treatment waning within the model.

annual waning percentages that the model applies are[**] means (min, max) of 2.05% (0.74%, 3.62%) for the target group, and for the subsets of the target group:

- 1.71% (0.51%, 3.62%) for those with BMI 30 – 35 kgm^{-2}
- 2.26% (1.22%, 3.62%) for those with BMI ≥ 35 kgm^{-2}
- 2.00% (0.73%, 3.62%) for those with BMI 30 – 35 kgm^{-2}, or no prediabetes or not high CVD risk
- 2.17% (1.05%, 3.62%) for those with BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk

The EAG has not been able to identify the error in the VBA but it appears to be a programming error rather than an input value error. The EAG has not revised the VBA code or model inputs. The EAG will provide waning scenarios of with a 5% input value for waning from year 5 but given the above this appears to be best interpreted as an average annual waning of approximately 2% in the net benefit for weight and BMI from year 5 and the EAG will label it as such. In other words, for these scenarios after 15 years an average of approximately 80% of the net weight benefit from tirzepatide is retained and after 25 years an average of approximately 60% of the net weight benefit from tirzepatide is retained.

3.5 *The proportion of patients requiring psychological support*

The WMU notes that the within the NHSE MDT costings the EAG changed the proportion needing psychological support from that assumed by NHSE to the proportion of SURMOUNT-1 with existing or previous psychological problems without justification. It questions why the SURMOUNT-1 proportion would apply to the probable NHS population.

NHSE states that between 20-60% of those with obesity have psychological problems. The RCP states that there is "*little mention about the provision of psychological support which has a significant predominance in people living with obesity and how this might be managed*".

It can also be noted that exclusion criteria for SURMOUNT-1 included "*A history of significant active or unstable MDD or other severe psychiatric disorders within the last 2 years*". As with the consideration of those with T2DM in Section 3.2, the cost effectiveness estimates for tirzepatide presented during the current submission

[**] Based upon examining the first 10 patients across 48 model runs within the EAG revised model labelled as for audit purposes.

relate only to patients that would fulfil the SURMOUNT-1 inclusion and exclusion criteria. It is questionable to what degree the current modelling relates to those with psychiatric disorders.

The EAG amended the proportion requiring psychological support because it appeared that the NHSE proportion has been taken from the assessment of bariatric surgery. The EAG accepts that SURMOUNT-1 may not provide the best estimate for the NHS proportion. This amendment has relatively little effect. The EAG base case will retain the NHSE costing proportion and will provide scenarios of 20% and 60%.

4 Issues arising from Company and Committee Concerns

4.1 *Relevance of tirzepatide 5mg and 10mg arms*

The EAG recollection is that expert opinion suggested the treatment with tirzepatide would aim for the maximum tolerated dose.

The Company presents cost effectiveness estimates for tirzepatide 5mg and tirzepatide 10mg. These use the clinical effectiveness estimates from the SURMOUNT-1 arms of those randomised to receive 5mg and 10mg respectively.

Given experience in the SURMOUNT-1 15mg arm it is likely that most of those in the SURMOUNT-1 10mg arm would have tolerated a higher dose than 10mg if offered it, and likewise in the 5mg arm. While some NHS patients may only tolerate a maximum dose of, say, 10mg, the SURMOUNT-1 10mg arm will not be representative of these patients.

The EAG will only present cost effectiveness estimates for tirzepatide 15mg compared to diet and exercise.

4.2 *The probable patient BMI distribution*

The Company states that the EAG normal distribution based upon Health Survey for England (HSE) data for BMI suggests that those with a lower BMI of, say 32 kgm^{-2}, will vastly outnumber those with a higher BMI, of say 38 kgm^{-2}. The Company argues that this lacks face validity. The EAG does not understand why this lacks face validity.

The EAG recollection is that during the first Committee meeting the patient expert said that given the publicity around new weight loss drugs those eligible for them would use them. This argues for applying HSE BMI distribution, restricting this to those with a BMI ≥30 kgm^{-2}, 30 – 35 kgm^{-2} and 35 kgm^{-2} as required when modelling

the different subsets of the target population. This can be objected to on ground of not all those with a BMI ≥ 30 kgm^{-2} necessarily having an obesity related complication, but as per the EAG 5 April 2024 report Section 3.1.1 applying this restriction to SURMOUNT-1 data had relatively little effect upon the BMI distribution.

The Company is correct that the EAG assumed the HSE BMI data was normally distributed, as was clearly stated in the EAG report. There was no additional evidence within the HSE data set to support a different assumption. The EAG has since undertaken a literature search and has found BMI distributions for 2016-18 HSE BMI data, pooled across age groups but presented separately for men and women.

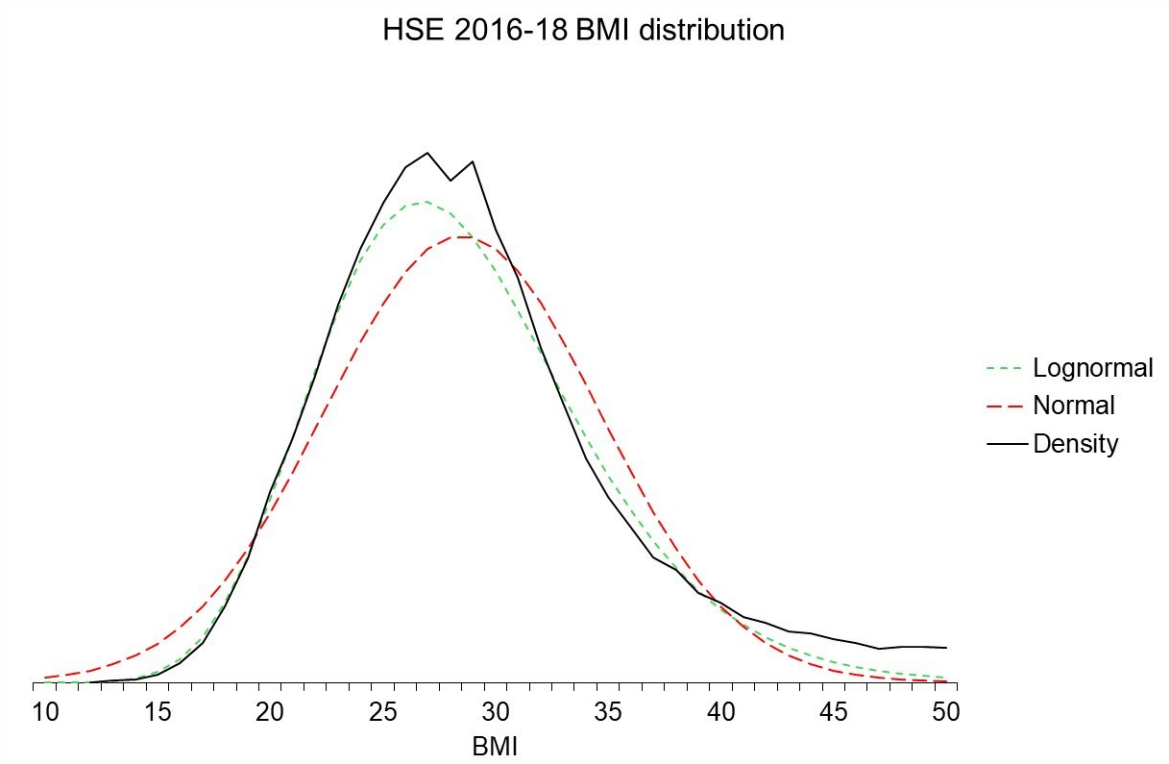

Figure 1: BMI: HSE 2016-18 and fitted curves

The density is not symmetric, it skewing slightly to the right. The dip in the middle of the density function is the result of pooling male and female distributions, the model sampling from a single distribution. The apparent tail of the density at a BMI of 50 kgm^{-2} may be largely the result of digitising what is a rather thick line on a chart. EAG statistical opinion is that it would be equally valid to set this to zero.

The EAG examined fitting a gamma distribution but this performed poorly. Goodness of fits can be examined for the lognormal and the normal over the entire curves. But

the more relevant goodness of fit statistics for current purposes are those limited to the section for those with a BMI ≥ 30 kgm^{-2}.

Table 2: BMI: HSE 2016-18 goodness of fit

	All		BMI ≥ 30 kgm^{-2}	
	LogNormal	Normal	LogNormal	Normal
AIC	1,472.9	1,466.9	924.0	975.3
BIC	1,479.5	1,473.4	922.8	974.1

Despite the slight rightwards skew, the normal out performs the lognormal over the entire density function. But restricting attention to the section those with a BMI ≥ 30 kgm^{-2} the lognormal outperforms the normal. As a consequence, the EAG thinks that it is most reasonable to assume a lognormal distribution for BMI and to provide a scenario of the normal.

The Company has supplied the actual SURMOUNT-1 BMI distribution by BMI point. This suggests a reasonably substantial proportion of patients with a BMI of 30 – 31 kgm^{-2} which in turn suggests that the Company gamma may tend to underestimate the number of patients at the lower end of the distribution.

For the Company modelling run over 1,000 patients the various distributions result in the following ICERs.

Table 3: Company ICERs and BMI distribution

	Target Group (TG)		TG subset: BMI 30-35 kgm^{-2}	
BMI distribution	Company "Committee preferred"	Company preferred	Company "Committee preferred"	Company preferred
Gamma	£17,717	£14,726	£27,410	£23,457
Normal	£19,500	£16,766	£27,545	£23,971
LogNormal	£19,619	£16,752	£28,451	£24,773
SURMOUNT-1	£18,656	£15,543	£29,113	£25,010

Note that the EAG sampling from the SURMOUNT-1 distribution replicates the Company supplied histogram by BMI point. Within each BMI point a uniform distribution is assumed. For the target group subset with a BMI 30-35 kgm^{-2} there are only 5 BMI points. The EAG sampling for this subset may be unduly stepped and may have sampled too many patients towards the very bottom end of the distribution within the BMI 30 – 31 kgm^{-2} frequency.

The EAG base case will apply the lognormal distribution based upon the 2021 HSE data for those with a BMI of 45 – 54 kgm^{-2}: a mean of 28.4 kgm^{-2} and a standard deviation of 5.96 kgm^{-2}. Note that this is not the HSE 2016-18 data depicted in Figure 1 above.

Scenarios that apply the normal distribution, sampling from the actual SURMOUNT-1 distribution and the Company gamma approximation of the SURMOUNT-1 distribution will be supplied.

4.3 *Natural weight gain by arm*

The EAG recollection is that during the first Committee meeting the clinical expert suggested that those on tirzepatide would over time be subject to much the same events that lead to weight gain as those not on tirzepatide; e.g. advancing age and a generally more sedate lifestyle.

The Company suggests that assuming a natural weight gain for those on tirzepatide is to assume that the treatment effect wanes over time. In terms of the net effect from tirzepatide this is incorrect.

- Assuming natural weight gain in both arms maintains a constant net effect from tirzepatide. For the mean BMI of the target group this is a net BMI benefit of [redacted] kgm^{-2}. This is the EAG base case.
- Assuming natural weight gain in only the diet and exercise arm results in an ever increasing net gain from tirzepatide. Assuming the patient remains on treatment and is under 68[††], by year 15 the original net benefit of [redacted] kgm^{-2} has increased by [redacted] to [redacted] kgm^{-2}, and by year 25 has increased by [redacted] to [redacted] kgm^{-2}. This is the Company base case.

Due to previous Committee preferences reducing the importance of the natural weight gain estimate the EAG has not particularly reviewed the model input for this.

[††] The annual increase in BMI is assumed to stop after 68 years of age.

The Company preferred estimates of annual BMI increases to age 68 of 0.447 kgm^{-2} for men and 0.1747 kgm^{-2} for women taken from Ara et al can be contrasted with the TA875 EAG scenario analysis of 0.106 kgm^{-2} taken from Iyen et al. These can further be compared with the implied annual differences in the HSE data between those age

- 35-44 and 45-54 of +0.063 kgm^{-2}
- 45-54 and 45-54 of +0.007 kgm^{-2}
- 55-64 and 45-54 of -0.007 kgm^{-2}
- 65-74 and 75+ of -0.082 kgm^{-2}

It should be noted that the HSE data is cohort data rather than data that follows individuals through time. Unfortunately, time constraints mean that the EAG has not been able to further explore this.

For the scenario that assumes no natural weight gain for tirzepatide but weight gain for diet and exercise, the EAG provides an additional scenario that applies the natural weight gain of 0.106 kgm^{-2} of Iyen et al.

4.4 *Risk reductions from weight loss*

Whether weight loss results in the same risk of complications as never having been obese was explored by Haase et al, sponsored by Novo Nordisk around the time of the semaglutide launch for treatment of obesity. A number of complications are found to have a residual risk from having been obese; i.e. the risk of the complication among those who were obese but have lost weight falls but does not fall to that of those who have never been obese. The EAG recollection is that the clinical expert thought that there would be residual risks.

The Company highlights a newer paper by Khunti et al, also sponsored by Novo Nordisk, which it appears to prefer. This is in some ways a less interesting and more conventional paper than Haase et al. It explores the hazard ratios of complications from weight losses of 10% and 20% compared to remaining at a stable weight. It does not address whether weight loss causes the risks of complications fall to as if the patient had never been obese, the key model assumption.

4.4.1 EAG implementation of residual risks

The Company states that the EAG exploration of residual risks within the model is odd because it does not increase the risks of complications for those with a residual

risk within Haase et al. There is no ready means within the model of correctly implementing the results of Haase et al. The EAG adopts the simpler approach of dialling down the direct effects that complications with residual risks have upon model outputs. For instance, if residual risks suggest that the model overestimates the effects upon T2DM by 100% the EAG simply halves the T2DM direct effects within the model. This in turn halves the net effect of T2DM upon model outputs. This is simple, transparent and in the opinion of the EAG a reasonable means of exploring residual risks.

The Company method of its 24 June 2024 submission is that if the model overestimates the effects upon T2DM by 100% the direct effects of T2DM should be doubled in each arm. This has the undesirable effect of doubling the net impact of T2DM. The ICER for tirzepatide improves as a result, from e.g. £27,699 per QALY for those with a BMI 30 – 35 kgm^{-2} to £25,652 per QALY. This is clearly incorrect and not what is desired.

The Company notes that the EAG approach does not take into account the knock on effects of residual risks. Only the direct effects of residual risks of the complications are explored. The knock on effects of overestimating the risk reductions of, say, T2DM upon heart disease and mortality are not explored. This is correct. The EAG method will for a given stated exploration of residual risks, e.g. a 50% reduction in the modelled direct effects, underestimate the probable total effects had knock on effects been taken into account. The EAG method understates the effects upon the ICER of taking into account residual risks due to not taking into account knock on effects on other complications

Previous model changes have also caused the model to estimate quality of life largely based upon BMI and mortality exclusively based upon BMI. The estimated functions that underlie this reflect general population characteristics. The EAG adjustments do not alter these functions. If there are residual risks or if the model overestimates the effects upon relative risks, the EAG adjustment will understate the effects upon the ICER of not taking these into account.

During Factual Accuracy Check the Company has again objected to the EAG exploration of residual risks. As a consequence, the EAG further explores this in in the context of the model possibly estimating too low a relative risk for tirzepatide compared to diet and exercise for the various complications of obesity in Sections 4.4.2, 4.4.3 and 4.4.4 below.

4.4.2 Haase et al with particular reference to the risk of T2DM

The Company notes some limitations of Haase et al.

Haase et al is based upon a mean weight loss of 13% from a baseline of 35 kgm^{-2} compared to SURMOUNT-1 estimating a weight loss of [redacted] from a mean baseline of 39 kgm^{-2}. The Company made a similar objection during Committee and noted that the larger weight loss would be associated with a larger reduction in the risks of events. But this is not the point addressed by Haase et al. Haase et al address the question of whether weight loss means that it is as if the patient had never been obese or if some residual risks from having been obese remain. It can be argued that very large weight loss among the very obese‡‡ will be less likely to get them to the risks of those who have never been obese than a smaller weight loss among the moderately obese. The EAG agreed that a larger weight loss would typically be associated with a larger absolute risk reduction, but as reviewed in Section 4.4.3 below the results of Khunti et al raise questions about this for a number of complications. Haase et al included a number of arbitrary data cuts, a possible failure to control for comorbidities, differing proportions of male and female in the weight loss group compared to the stable cohort, weight loss interventions not being fully itemised and a number of other concerns. The EAG agrees that there is much within Haase et al that could have been better reported. The EAG previously questioned why mortality had not been examined as an obvious outcome. Whether Haase et al is obviously biased is more difficult to determine. But it should be borne in mind that Haase et al was funded by Novo Nordisk at the same time as Novo Nordisk was launching semaglutide for weight loss. It is possible that Haase et al were incompetent and that their results are biased against the effects of weight loss. But the EAG thinks that this is unlikely and if there were any incentives for Haase et al to bias their results it would be to overestimate the effects of weight loss and not find evidence of residual risks.

The Company notes that the weight loss interventions in Haase et al are not well documented. This is correct but it can also be noted that they will not have included the current crop of weight loss drugs. This may be relevant to the results of Haase et

‡‡ This is to slightly simplify the argument for ease of exposition. The correct comparison would be to ask whether for someone with a BMI of 40 kgm^{-2} a weight loss of 5 kgm^{-2} gets them proportionally closer to the risks of complications of someone who has always had a BMI of 35 kgm^{-2} than a weight loss of 10kgm^{-2} gets them towards the risks of complications of someone who has always had a BMI of 30 kgm^{-2}.

al, as can be illustrated by consideration of their estimated effect of weight loss among those with a BMI ≥ 35 kgm^{-2} upon the risk of T2DM. They estimated that weight loss among this group resulted in a superior T2DM risk than those who had always been stable at the lower weight. A plausible reason for this is that those who lost weight were exercising more and eating more healthily, while those at the lower stable weight required no such changes and remained exercising less and eating less healthily. This begs the question of whether weight loss from tirzepatide use in conjunction with diet and exercise will be associated with the same degree of changes in exercise and healthy eating as occurred among the weight loss group of Haase et al. If not, the effects of weight loss estimated by Haase et al may be too optimistic for tirzepatide use in conjunction with diet and exercise.

The company has highlighted the paper by Khunti et al which it appears to prefer to Haase et al and which the EAG reviews in the Section 4.4.3 below.

If some of the health benefits of the 13% weight loss from diet and exercise within Khunti et al occur for reasons that would not apply or would apply less forcefully to the weight loss associated with tirzerpatide in conjunction with diet and exercise as per SURMOUNT-1, this argument applies equally to the results of Khunti et al. It can also be noted that the weight loss in the diet and exercise arm of SURMOUNT-1 was only [redacted], somewhat less than 13%. The 13% weight loss explored in Haase et al presumably arose from a more effective diet and exercise regime than that of SURMOUNT-1, this presumably applying to both the diet and exercise arm and the tirzepatide arm.

Haase et al present the hazard ratios relative to those who have always been at the lower stable weight for those without weight loss and for those with a weight loss of 13%. The central estimates of the latter two can be used to derive the hazard ratios for a weight loss of 13%. This is useful when considering the results of Khunti et al. The hazard ratios for T2DM by baseline BMI are:

- BMI 35 kgm^{-2} an HR of 0.60
- BMI 40 kgm^{-2} an HR of 0.59
- BMI 45 kgm^{-2} an HR of 0.61

This suggests a reasonably constant hazard ratio for T2DM from a weight loss of 13% of 0.60 across BMI categories. The modelled relative risk for T2DM from a weight loss of 13% using the same method as in Section XX below

Table 4: QDiabetesC relative risks from 13% weight loss

	QDiabetesC relative risks			
	10 year	10 year	1 year	1 year
	Male	Female	Male	Female
White, non-smoker	31%	27%	25%	23%
White, smoker	31%	28%	25%	23%
Pakistani, smoker	41%	34%	26%	24%

The modelled relative risks are somewhat below the 0.60 hazard ratio implied by the central estimates of Haase et al. A simple average of the modelled 10 year relative risks suggests is a relative risk of 32%, though it can be noted that this will over represent men, smokers and those of Pakistani origin so will overestimate the actual average modelled relative risk. The 32% relative risk compares to the 0.60 hazard ratio suggests an adjustment factor of 59%. Similarly, the simple average of the modelled 1 year relative risks of 24% suggests an adjustment factor of 53%.

As noted in Section above at Factual Accuracy Check the Company again objected to the EAG method of exploring the possibility that the model overestimates the reduction in the risks of the complications of diabetes; i.e. the relative risk for tirzepatide compared to diet and exercise is too low.

As an illustration a simple example can be presented. Suppose that the relative risk for T2DM is overestimated by 100%, e.g. a modelled relative risk of 0.50 compared to the true relative risk of 0.75. Assume a baseline risk of 8%. The model estimates:

- An 8% T2DM for placebo and, say, a T2DM cost of £1,000
- A 4% T2DM for tirzepatide and a T2DM cost of £500
- A net saving of £500

But simplistically the model should have estimated:

- An 8% T2DM for placebo and, say, a T2DM cost of £1,000
- A 6% T2DM for tirzepatide and a T2DM cost of £750
- A net saving of £250

The EAG method halves the cost impacts along the following lines:

- For placebo a T2DM cost of £1,000 * 50% = £500
- For tirzepatide a T2DM cost of £500 * 50% = £250
- A net saving of £250

Calculating the ICER only requires the absolute net saving to be correctly estimated. If this is correctly estimated the absolute costs in each arm are irrelevant.

The EAG method is not strictly correct. It fails to take into account the diminishing pool of those without T2DM that the risks apply to. Initial work by the EAG suggests that for the above example the EAG method may actually understate the overestimation of net costs, though not by much.

The EAG cannot correctly implement the required adjustments without considerable revisions to the model VBA. The EAG is not confident that it can correctly revise the model VBA.

The method of the EAG is simple, transparent and in the opinion of the EAG permits a reasonable exploration of the issue.

4.4.3 Khunti et al with particular reference to the risk of T2DM

The Company appears to prefer the paper by Khunti et al over that of Haase et al, and states that among those with a BMI of 40 kgm^{-2} it was found that the risk of T2DM fell by around 25% and 50% for weight losses of 10% and 20% respectively.

Khunti et al used CPRD data, linking this to HES data to capture additional diagnoses and fatal CVD events. Eligible patients were adult, required to have a mean 1st year BMI ≥ 30 kgm-2 and to have had at least two BMI measurements during a 4 year baseline period. Exclusion criteria were similar to Haase et al. The follow-up period began at the end of the 4 year period and ended at the date of the first obesity related complication (ORC), death, transfer out of the data set or last data collection point for the corresponding practice.

13 ORCs were selected:

- Metabolic disorders: T2DM, hypertension, dyslipidaemia and PCOS
- Biomechanical disorders: OSA, asthma, hip or knee osteoarthritis
- Cardiovascular disorders: heart failure, CKD, AF, venous thromboembolisms and a combined angina/MI

- Mental health disorders: depression

Khunti et al estimated hazard ratios for the ORCs for weight losses of 10% and 20% compared to being at a stable weight, the hazard ratio modelling also including patients' baseline BMI as an explanatory variable. They reported their results grouped into the following four main categories of weight loss effects.

1. ORCs where the greatest benefit from weight loss was among those with a low BMI and where there was a greater effect from a 20% weight loss than a 10% weight loss: T2DM, OSA, Hypertension and dyslipidaemia.
2. ORCs with a benefit among those with a low BMI but not a high BMI and a greater effect from a 20% weight loss than a 10% weight loss: asthma, hip/knee osteoarthritis and PCOS.
3. ORCs with a benefit from weight loss but no additional benefit from a 20% weight loss than a 10% weight loss: heart failure, AF, venous thromboembolisms and CKD. Noter that for these ORCs while the confidence intervals for the 10% weight loss and 20% weight loss cross over, at central estimates the 20% weight loss had a slightly greater effect than the 10% weight loss.
4. ORCs with no relationship with weight loss: depression and unstable angina/MI.

Immediately obvious from Khunti et al is that under (1) the risk reductions are less for those with a high baseline BMI than for those with a low baseline BMI. The risks of these ORCs from being severely obese appear to be less reversible than from being moderately obese. The damage may have been done.

Similarly for (2) the risks of ORCs remain more stubbornly for those with a high baseline BMI.

For both (1) and (2) the hazard ratio compared to a stable weight is more affected by weight loss for those with a lower baseline BMI than for those with a higher baseline BMI. This in part runs contrary to the findings of Haase et al, where residual risks were more prevalent among those with a BMI 30 – 35 kgm^{-2} than among those with a BMI ≥ 35 kgm^{-2}.

For (3) the hazard ratio compared to a stable weight is typically less affected by weight loss for those with a lower baseline BMI than for those with a higher baseline BMI. Within (3) there is little to no additional benefit from a weight loss of 20%

compared to a weight loss of 10% for heart failure, AF, venous thromboembolisms and CKD.

The finding for (4) of no relation between weight loss, baseline weight and unstable angina/MI mirrors that of Haase et al and supports the EAG scenario that removes the direct effects of these from the model.

The above raises question about the model assumption that the risk reduction continuously increases as weight loss increases. It suggests that for some ORCs the estimates of Haase et al of whether and the degree to which residual risks remain with a weight loss of 13% may tend to understate whether and the degree to which residual risks remain with a weight loss of [redacted].

The Company cites the 50% hazard ratio for T2DM from a 20% weight loss. This can be compared with the model predictions for a 20% weight loss for the three characteristics previously explored by the EAG:

- Gender: male, female
- Race: white, Pakistani
- Smoking status: none, moderate

This retains the trial effects upon SBP and cholesterol, though the effects of these upon the QDiabetesC risk function are relatively modest. The EAG presents results relative to the baseline risk due to the results of Khunti et al being relative to a stable weight.

Table 5: QDiabetesC relative risks from 20% weight loss

	QDiabetesC relative risks			
	10 year	10 year	1 year	1 year
	Male	Female	Male	Female
White, non-smoker	22%	20%	18%	17%
White, smoker	23%	21%	18%	17%
Pakistani, smoker	30%	26%	18%	18%

The model estimates relative risks for T2DM that are typically less than half the 50% hazard ratio of Khunti et al, averaging 24% for the 10 year risk and 18% for the

inferred 1 year risk. This suggests that the model may overestimate the relative risk reduction from tirzepatide.

It should be noted that there are difference in the definitions and applications of relative risks and hazard ratios. Relative risk compares the probability of an event over a specified period while the hazard ratio compares the instantaneous event rates between treatment and control groups. Over short periods and with small probabilities the two measures are typically similar. With longer follow-up and larger event probabilities the two measures can diverge.

While the model updates risks for changing patient characteristics, for a given set of patient characteristics the risk is constant. EAG statistical opinion notes that this is akin to a constant hazard and a constant hazard ratio. In such scenarios the short term relative risk captures the relative likelihood of the event occurring within a brief period, aligning more closely with the instantaneous nature of the hazard ratio. This suggests concentrating upon the 1 year relative risks when comparing relative risks to the hazard ratios of Khunti et al.

In the light of the Khunti et al result highlighted by the Company and their general consistency with those of Haase et al et al the EAG will provide a scenario analysis that applies an adjustment factor on the effect of T2DM on model outputs by (50% - 1) /(18% - 1) = 61%, this formula[§§] resulting in the "correct" net costs much as per the simple illustrative example in Section 4.4.2 above.It can be argued that this should form part of the base case.

4.4.4 Haase et al and Khunti et al other ORCs

Time constraints have meant that the EAG has not been able to perform as detailed analyses for the other ORCs within Haase et al and Khunti et al. While the other ORCs are individually less important within the modelling than T2DM, when adjusted for the results of Khunti et al their collective effect may not be minor.

The hazard ratios for a weight loss of 13% compared to no weight loss from Khnuti et al for ORC within the model are presented in Table 6, this presenting the hazard ratios for osteo-arthritis of the hip or knee as a proxy for total knee replacement.

[§§] Simplifying to a single period, if the cost of the ORC is £ and the baseline risk r then the cost in the control arm is r.£. If the modelled relative risk for the active treatment is RR_M the modelled cost in the active treatment arm is RR_M.r.£. This leads to a modelled net cost of RR_M.r.£ - r.£ = r.£.(RR_M-1). Similarly, if the true relative risk is RR_T the net cost should be r.£.(RR_T-1). The adjustment factor that needs to be applied to the modelled cost is r.£.(RR_T-1) / r.£.(RR_M-1) = (RR_T-1) / (RR_M-1).

Table 6: Haase et al hazard ratios from a 13% weight loss

	OSA	Joint OA	Angina/MI
BMI 35	0.573	0.869	0.934
BMI 40	0.607	0.914	1.019
BMI 45	0.663	0.983	1.131

The company highlights the results of OSA within Khunti et al. The hazard ratios of Khunti et al are only graphed and the vertical scales are not obviously linear or logarithmic. As a consequence, the EAG inferred values have an unavoidable degree of uncertainty about them.

Table 7: Khunti et al hazard ratios from a 20% weight loss

	OSA	Joint OA	Angina/MI
BMI 35	0.333	0.731	0.934
BMI 40	0.389	0.769	0.947
BMI 45	0.472	0.808	0.974

The modelled relative risks for the SURMOUNT-1 baseline BMI of 38.8 kgm^{-2} can be presented for weight losses of 13% and 20%. The relative risk for OSA needs to be treated with some caution*** as there is a step change in the function at BMIs of 35 kgm^{-2} and 40 kgm^{-2}. Given the baseline BMI 38.8 kgm^{-2} the weight losses of both 13% and 20% cause the patient weight to fall below this, so resulting in the same relative risks.

Race does not enter the OSA risk function so the relative risks reported are simple averages across equally weighted male and female non-smokers and smokers. The osteoarthritis relative risk is also for those below the age of 65, the function changing for those above 65.

*** The EAG is also concerned by its implementation of the OSA risk function which results in quite high 5 year risks. There is no obvious discrepancy with the Company model implementation but the EAG urges the Company to cross check this within the EAG derivation of the relative risks.

Table 8: Modelled relative risks from a 13% and a 20% weight loss

	OSA		TKR	Angina/MI	
	5 Year RR	1 Year RR	1 year RR	10 year RR	1 year RR
13% loss	24.5%	22.4%	57.1%	87.3%	86.9%
20% loss	24.5%	22.4%	39.4%	84.3%	83.9%

The relative risks all lie somewhat below the hazard ratios of both Haase et al and Khunti et al.

The EAG will provide additional scenario analyses that apply adjustment factors of 79% for OSA, 38% for TKR and 33% for Angina/MI within the model, these again being based upon $(HR_{Khunti} – 1)/(RR_{Model} – 1)$ using the HRs for a 40 year old and the 1 year relative risks.

4.5 *T2DM costs*

The Company base case applies:

- A net cost of T2DM without complications of £803 based upon the EAG UKPDS68 cost but with different price indexing
- An annual drug cost of £552 sourced from Capehorn et al

The EAG thinks that what is required are:

- The net costs of managing T2DM in the absence of complications
- The direct drug costs of T2DM
- The costs of the complications of T2DM that are not modelled

4.5.1 Gross versus net cost of T2DM without complications

The EAG UKPDS £683 estimate is the gross cost of non-inpatient care for those with T2DM and without complications, excluding direct drug costs. The model supplies an estimate of £233 for the ongoing cost of those with obesity and no complications, this being applied to all patients in both arms throughout the model, whether they are on or off treatment. The EAG applies a net cost of £683 minus £233, or £450, for the net additional routine management costs of T2DM in the absence of complications and excluding T2DM direct drug costs. EAG opinion is that T2DM without complications

is largely managed in primary care. The EAG net cost estimate of £450 is sufficient for an additional annual 11 visits to a GP[†††]. This may be an over estimate.

Price indexing of these costs is addressed in Section 5.3.

4.5.2 Direct drug costs of T2DM

The Company direct drug costs of T2DM of £552 are sourced from Capehorn et al. Capehorn et al is a Novo Nordisk funded study of the cost effectiveness of semaglutide versus empagliflozin for the treatment of T2DM. Those in the comparator arm had been diagnosed with T2DM for 7 years and were receiving empagliflozin. As a consequence, the discounted annual average direct drug costs of Capehorn et al are not applicable to those newly diagnosed with T2DM.

As reviewed in greater detail in EAG 05 April 2024 Section 2.1.8, the direct drug costs for newly diagnosed patients can be modelled using the UKPDS HbA1c evolution function to simulate the timing of treatment intensification while on OADs and the intensification to insulin. This can then be coupled with UK life tables and the Company T2DM mortality multiplier to provide discounted annual average lifetime drug costs. The EAG has also allowed for 32% of patients having a high CVD risk so requiring an SGLT2 from diagnosis of T2DM. This results in an average discounted T2DM drug cost estimate of £340.

4.5.3 Costs of T2DM complications

As mentioned in the original EAG report both the EAG base case and the Company results of its 24 June 2024 submission do no include any costs for the microvascular complications of T2DM.

The Company has previously applied the discounted annual average costs of microvascular complications of Capehorn et al. As previously reviewed by the EAG there are concerns that the gross costs rather than the net costs of these complications are applied by Capehorn et al. There may also be concerns around model estimates based upon the iQVIA Core Diabetes Model but the EAG has not had time to review the model validation exercises of the Mt Hood challenges.

[†††] GP 9.22 minute cost including direct care staff and qualification costs, PSSRU 2021/22 costings

The EAG will supply scenario analyses that apply proportions of the Capehorn et al modelled discounted annual average costs of microvascular complications of T2DM. These are subject to the caveats of this section and Section 4.4 above.

4.6 *NHSE MDT resource use*

The Company thinks that MDT resource use should be applied for those on diet and exercise and that if this resource use is removed it should affect net efficacy estimates.

The EAG base case applies MDT resource use for diet and exercise for the first two years of the model, regardless of response status at 6 months. This is in line with the modelled treatment effects for diet and exercise and NHSE advice that the maximum duration of diet and exercise should be two years.

The EAG will provide a scenario that for the diet and exercise arm assumes no MDT costs and no clinical effect.

5 Mechanical issues

5.1 *Which model version to use*

During the course of the assessment the original EAG revised model was further revised by the Company, these further revisions introducing a type mismatch error that caused the EAG model change functionality to no longer work. The EAG consequently fell back on the original EAG revised model and has made all its changes to this model in a sequential manner in the light of the various submissions and required EAG reports. This includes the EAG replicating Company model changes to other model versions within this model. The latest EAG model version has been through a formal Factual Accuracy Check with the Company, which did not identify any errors.

But it means that the EAG and the Company are using different model versions. Provided they result in the same or very similar estimates this is not a concern and may actually provide some additional assurance as an informal cross check of the implementation of model changes

The current Company model version of 24 June 2024 results in a Company base case ICER for the target population of £14,735 per QALY. The EAG model version also results in an ICER of £14,735 per QALY.

The Company model version results in an ICER for the BMI 30 – 35 kgm^{-2} subgroup of the target population of £23,425 per QALY. The EAG model version estimate is £23,457 per QALY. The models' inputs for baseline characteristics and clinical efficacy appear identical and the EAG has not been able to trace the source of the discrepancy. But the discrepancy is small and the EAG thinks inconsequential.

The EAG uses the model version that takes the original Company submitted model and makes all subsequent model revisions to it in a sequential manner.

5.2 *Model convergence*

The original Company model chose a random number seed of 2,000 and a cohort of 1,000 patients. Convergence graphs presented in the model suggested that the model had converged. The EAG did not check this.

Given the additional time available, the EAG has rerun the original model using different random number seeds and different cohort sizes. The effect upon the original Company ICER of £12,792 per QALY‡‡‡ for tirzepatide 15mg without a stopping rule compared to diet and exercise is presented in Table 9. The choice of using the original model is due to the time taken to run the larger cohort sizes and this work having to be completed prior to the current Company submission.

Table 9: Random number seed and cohort size effect upon ICER

Random Seed	Cohort size			
	1,000	5,000	10,000	20,000
1,000	£14,650 (+15%)	£13,912 (+9%)	£13,494 (+5%)	£13,790 (+8%)
1,500	£14,953 (+17%)	£13,999 (+9%)	£14,021 (+10%)	£13,827 (+8%)
1,900	£13,836 (+8%)	£14,090 (+10%)	£14,213 (+11%)	£13,582 (+6%)
2,000	£12,792 ..	£14,174 (+11%)	£14,368 (+12%)	£13,814 (+8%)
2,100	£13,463 (+5%)	£13,931 (+9%)	£13,529 (+6%)	£13,843 (+8%)
2,500	£13,332 (+4%)	£14,148 (+11%)	£13,471 (+5%)	£13,851 (+8%)
3,000	£11,995 (-6%)	£13,301 (+4%)	£13,396 (+5%)	£13,597 (+6%)

‡‡‡ Model run with only Tirzepatide 15mg and diet and exercise as comparators

Table 9 shows that the model has not converged when run with a cohort of 1,000 patients. The Company chosen random number seed of 2,000 typically results in a better ICER than the other random number seeds arbitrarily selected by the EAG. Results are somewhat more consistent with a patient cohort of 5,000, these ICERs typically being around 10% worse than the Company base case. Some variability remains with a cohort of 10,000, and it appears that the model does not fully converge until the cohort is increased to 20,000. The ICERs are typically 8% worse than the Company submitted base case.

Turning to the Company 24 Jun 2024 submission, running the model with a cohort of 1,000 and 20,000 results in the following Company ICERs. Note that these ICERs are the taken from EAG runs of the Company submitted 24 June 2024 model and differ marginally from those stated in the written Company submission.

Table 10: Company ICERs and model convergence

	Target Group (TG)		TG subset: BMI 30-35 kgm^{-2}	
Cohort size	Company "Committee preferred"	Company preferred	Company "Committee preferred"	Company preferred
1,000	£19,500	£14,726	£27,673	£23,457
20,000	£21,919	£15,965	£28,626	£23,782

The ICERs for the target group worsen most, being 12% worse for the Company "Committee Preferred" assumptions and 8% worse for the Company base case. The Company "Committee Preferred" ICER for the target group rises above £20,000 per QALY.

The ICERs for the BMI 30 – 35 kgm^{-2} subset of the target group are less affected, worsening by 2-3%.

The EAG will run the model with a cohort of 20,000 to achieve convergence.

5.3 *Price indexing of UKPDS 68 T2DM costs*

The Company states that "*standard practice for inflating costs is to use the P&P* [pay and prices] *index as reported in the PSSRU*" and that "*Using the P&P Index excluding capital results in a calculated value of £803*". It is unclear why the Company chooses to exclude capital costs.

The UKPDS 68 cost calculations are in 2012/13 prices, the Company model also stating this to be the case. Other costs within the model[§§§] are typically in 2021/22 prices.

The Company adjusts the UKPDS costs for inflation using the Personal Social Services pay and prices (PSS) excluding capital costs index. The Company inflates to 2022/23 prices with a 36% increase. Inflating to 2022/23 prices also results in misalignment with the other costs in the model due to the Company using 2021/22 costs for these.

[§§§] See for example the *Resource Use* worksheet

The EAG thinks that the PSS index is not appropriate and prefers the more general NHS Cost Inflation Index[****]. The PSSRU states that "*The NHSCII identifies an appropriate inflation measure for each item of spend in four broad categories: NHS providers, general practice, prescribing and dentistry to create an overall inflation measure for the NHS*" which the EAG thinks makes it the appropriate index to use[††††]. Note that over the relevant period the NHSCII results in 15.5% cost inflation compared to 26.4% for the PSS index.

The EAG previously incorrectly inflated from 2013/14 prices due to the UKPDS cost calculator describing itself as "*UKPDS Diabetes Complications Cost Calculator 2013*", only inflating costs by 14%.

The UKPDS 68 non-inpatient costs for those with T2DM, age 48 and no complications in 2012/13 prices are £484 for men and £647 for women resulting in a weighted average cost of £592. Inflating this by 15.5% results in an average cost of £683. This is marginally higher than the £674 previously applied by the EAG. The EAG will apply the revised £683.

5.4 *Price indexing of NHSE MDT professionals' costs*

The NHSE MDT costs have two main sources.

Primary care costs are reported as being sourced from the PSSRU Unit Costs of Health and Social Care and are in 2021/22 prices.

Other professional costs are based upon 2023/24 pay scales. To align these with the other costs in the model these can be deflated by the NHSII Pay Index. The index rose by 7.03% in 2022/23. The 2023/24 index is not available but it appears that the general pay award was 5%[‡‡‡‡]. This suggests an overall deflator of 89% for the other professional costs within the NHSE MDT costs to bring them into line with the other costs in the model. The EAG will apply this deflator.

[****] The precursor to the NHSCII was the Hospital and Community Health Services Pay and Prices Index

[††††] The PSSRU notes for the PSS index "*The Adult PSS Pay & Prices Index is calculated by the Department of Health and Social Care (DHSC). Skills for Care (SfC) data have been used to calculate the pay percentages from 2019/20 onwards, in place of the Annual Survey of Hours and Earnings (ASHE) data used for previous years. Skills for Care data are taken from the Adult Social Care Workforce Data Set (ASC-WDS) which consists of non-mandatory returns from the independent sector (covering 51% of all CQC regulated locations) and mandatory returns from all local authorities in England. Skills for Care weight the independent sector returns to remove any geographical, service type and sector biases*."

[‡‡‡‡] https://www.nhsemployers.org/payofferFAQs

6 Company cost effectiveness results

The EAG has only cross checked the Company base cases. It reports the Company scenario analyses for completeness.

- CSA01: NHSE MDT resource use for tirzepatide but not diet and exercise
- CSA02: NHSE MDT resource use for tirzepatide but not diet and exercise, and no efficacy for diet and exercise
- CSA03: NHSE MDT resource use for tirzepatide without appointments specific to tirzepatide
- CSA04: Light touch SURMOUNT-1 HCRU
- CSA05: Gamma sampling of BMI distribution
- CSA06: BMI sampling based upon IMPACT-O data
- CSA07: No natural increase in weight while on tirzepatide
- CSA08: Natural increase in weight while on tirzepatide from year 10
- CSA09: Natural increase in weight while on tirzepatide from year 20

The values of Table 11 are taken from the Company word document and relate to model runs with a cohort of 1,000.

Table 11: Company ICERs and scenario analyses

	Target Group (TG)		TG subset: BMI 30-35 kgm^{-2}	
	Company "Committee preferred"	Company preferred	Company "Committee preferred"	Company preferred
Base case	£19,514	£14,735	£27,699	£23,425
CSA01	£24,170	£18,381	£34,191	£29,098
CSA02	£18,706	£14,289	£23,474	£20,177
CSA03	£19,774	£14,943	£28,064	£23,744
CSA04	£20,071	£15,144	£28,535	£24,148
CSA05	£17,729	..	£27,295	..

CSA06	£18,273	£19,717	£26,758	£22,831
CSA07	£17,143	..	£24,511	..
CSA08	£18,008	£15,691	£25,178	£24,274
CSA09	£17,335	£15,001	£24,395	£23,668

7 EAG exploratory cost effectiveness results

Given the Committee preferences and requested analyses, and time constraints, the EAG focusses upon the comparison of tirzepatide 15mg with diet and exercise in the primary care setting.

The EAG largely retains the changes it made in its exploratory revised base case of its original report, with some additional assumptions as directed by Committee and applied in the Company preferred base case.

- Assuming no stopping rule for tirzepatide other than the 6 month 5% weight loss responder rule
- Only applying the BMI mortality multipliers
- Mainly applying the adverse event discontinuation rates in the first year, with a common 1% annual rate thereafter
- An annual NAFLD rate of 0.06/1,000 patient years
- A 5 year OSA risk of 2.85%
- Revising the quality of life function intercepts to align with SURMOUNT-1 quality of life data and align the two quality of life functions at 35 kgm^{-2}
- Only applying the QoL coefficients of the main BMI quality of life function
- Various minor revision detailed in the original EAG report Section 5.5.7
- Applying the subgroup specific baseline characteristics and clinical effect estimates as supplied by the Company.
- Assuming that reversal of prediabetes is lost when the patient returns to their original weight
- Assumes a 2 year loss of effect after treatment cessation
- Applies the 48 week 5% weight loss proportions

- Applies the Company revision to include the baseline prevalences of the comorbidities whose subsequent incidence is modelled

For the current report the EAG makes the following changes to its exploratory base case.

- Applying the constant annual natural increase in BMI as implemented through the Company model revision to both diet and exercise and tirzepatide.
- Assuming the 2021 HSE lognormal distribution for BMI.
- Applying an annual net cost for T2DM without complications of £789, this including £340 medication costs and netting out the £234 routine management costs in the absence of complications that patient incur both with and without T2DM.
- Changing the SWMS costs to be the NHSE MDT costs, assuming a two year duration of MDT costs for diet and exercise regardless of response status at 6 months. Professional costs are deflated from 2022/23 costs to be in 2020/21 costs so as to be aligned with the other Company model inputs.
- Applying a patient cohort of 20,000 to ensure model convergence.

Note that during Factual Accuracy Check the Company stated that within the NHSE MDT costs only 135 minutes of GP time related to tirzepatide titration rather than the 140 minutes applied by the EAG. This improves the EAG base case for the target group from £28,697 per QALY to £28,675 per QALY. The EAG thinks that this is inconsequential for decision making. The Company describes it as a minor error. As a consequence, due to time constraints the EAG has not rerun the analyses of Table 12 below which retain the 140 minutes of GP time for tirzepatide titration.

The EAG presents the costs effectiveness estimates for the target group, and for the target group split into the subsets of those with a BMI of 30 – 35 kgm^{-2} and those with a BMI 35 kgm^{-2}.

Given Consultee comments and the uncertainty around the cost effectiveness of tirzepatide for the target group subset of those with a BMI 35 kgm^{-2}, the EAG progressively restricts the target group subset of those with a BMI 35 kgm^{-2} to:

- The subset with a BMI 35 kgm^{-2} and prediabetes:
- The subset with a BMI 35 kgm^{-2}, prediabetes and a high CVD risk:

The EAG supplies the following scenario analyses.

- SA01: BMI distributions of 2021 HSE normal, gamma fit of the SURMOUNT-1 distribution, and, sampling from the SURMOUNT-1 BMI distribution.
- SA02: A waning of the BMI effect of 2% annually from year 5 onwards, and a waning of the BMI effect of 2% annually from year 5 onwards with a tirzepatide stopping rule of 15 years when 80% of the net benefit is retained and of 25 years when 60% of the BMI net benefit is retained.
- SA03: Adjusting model outputs to reflect the possible overestimation of the effect of weight loss upon the reduction in the risks of obesity related complications based upon the results of the Company preferred source of Khunti et al: (a) an adjustment factor of 61% for T2DM, (b) point (a) coupled with adjustment factors of 79% for OSA and 38% for TKR, and (c) point (b) coupled with an adjustment factor for angina, MI and stroke of 33%,
- SA04: For both arms no MDT costs
- SA05: For diet and exercise no MDT costs and no clinical effects
- SA06: No annual weight gain while receiving tirzepatide, also coupling this with the natural weight gain estimate of Iyen et al for diet and exercise
- SA07: Including 25%, 50%, 75% and 100% of the microvascular complication costs of T2DM as reported in Capehorn et al.
- SA08: 20% and 60% require psychological support.
- SA09: 0% of those in the BMI 30 – 35 kgm^{-2} target group subset require an SGLT2 from diagnosis of T2DM, and 100% of those in the BMI ≥ 35 kgm-2, prediabetic and high CVD risk target group subset require an SGLT2 from diagnosis of T2DM.
- SA10: Applying the weight gain parameter of Iyen et al in both arms.

Table 12: EAG exploratory ICERs

	Target Group	BMI 30 - 35	BMI ≥ 35	BMI ≥ 35, prediabetic	BMI ≥ 35, prediab, high CVD risk
Base case	£28,697	£37,151	£21,372	£19,504	£20,689
SA01a: BMI normal	£29,243	£36,864	£21,332	£19,481	£20,708
SA01b: BMI gamma	£25,512	£35,542	£21,942	£19,993	£21,457
SA01c: BMI SURMOUNT-1	£26,013	£35,689	£22,565	£20,603	£21,919
SA02a: 2% waning years 5+	£34,231	£43,097	£26,702	£24,167	£25,256
SA02b: SA02a + Tx stop 15 yr	£32,489	£42,806	£23,935	£21,562	£22,802
SA02c: SA02a + Tx stop 25 yr	£33,178	£42,716	£25,298	£22,735	£23,877
SA03a: Khunti T2DM	£31,181	£40,188	£23,109	£21,837	£23,035
SA03b: SA03a + OSA +TKR	£31,904	£40,778	£23,899	£22,579	£23,800
SA03c: SA03b + Angina/MI	£31,963	£40,840	£23,926	£22,636	£23,855
SA04: No MDT costs	£23,173	£30,197	£17,171	£15,478	£16,457
SA05: No D&E MDT cost/effect	£24,789	£29,804	£19,129	£16,962	£17,251
SA06a: No weight gain TIRZ	£25,011	£33,359	£18,019	£16,555	£17,444
SA06b: SA06a + Iyen param	£27,877	£38,035	£19,428	£17,961	£18,982
SA07a: T2DM Capehorn 25%	£28,118	£36,551	£20,890	£18,838	£20,038
SA07b: T2DM Capehorn 50%	£27,539	£35,951	£20,409	£18,172	£19,387
SA07c: T2DM Capehorn 75%	£26,960	£35,351	£19,928	£17,506	£18,737
SA07d: T2DM Capehorn 100%	£26,381	£34,750	£19,447	£16,840	£18,086
SA08a: 20% psych support	£28,519	£36,928	£21,237	£19,374	£20,553
SA08b: 60% psych support	£29,052	£37,596	£21,642	£19,763	£20,960
SA09: T2DM SGLT2 use	..	£37,576	..	..	£19,659
SA10: Iyen et al param	£30,320	£40,094	£21,701	£19,982	£21,342

Target group

For the target group the EAG base case ICER is £28,697 per QALY.

Assuming that the HSE BMI distribution is normally distributed slightly worsens this to £29,243 per QALY, while applying the distributions derived from SURMOUNT-1 improves the ICER to around £26,000 per QALY.

Relative minor waning from year 5 in the net BMI effect of an annual average of around 2% significantly worsens the cost effectiveness estimate to £34,231 per QALY. This is relatively insensitive to whether patients cease treatment after having lost around 20% of the net effect at 15 years, or stop treatment after having lost around 40% of the net effect at 25 years.

Given the results of both Khunti et al and Haase et al the EAG thinks that reducing the impact of T2DM on the model to 61% of the base case should be considered for inclusion in the base case. It significantly worsens the ICER to £31,181 per QALY.

Results are sensitive to the NHSE MDT costs. Excluding these significantly improves the ICER to £23,192 per QALY. If they are excluded from the diet and exercise arm along with an assumption of no clinical effect in the diet and exercise arm the ICER improves to £24,789 per QALY.

No natural weight gain for tirzepatide improves the ICER to £25,011 per QALY. Applying the weight gain parameter of Iyen et al yields £27,877 per QALY.

Including the Capehorn et al estimates for the microvascular complications of T2DM improves the ICER but the effect is not dramatic. It can also be noted that if these scenarios were combined with the 61% T2DM qualifier derived from Khunti et al the effect of these scenarios would be similarly reduced.

The effect of varying the proportion requiring psychological support while receiving treatment is relatively muted.

There is also a reasonable sensitivity to applying the weight gain parameter of Iyen et al in both arms, rather than that of Ara et al.

Target group subset with BMI 30 – 35 kgm^{-2}

The cost effectiveness estimates for the target group subset with a BMI 30 – 35 kgm^{-2} are typically poor. Only removing the NHSE MDT costs or removing these from the diet and exercise arm moves them towards the NICE WTP upper threshold of £30,000

per QALY, but given the uncertainty around the topic it appears that Committee has adopted the £20,000 per QALY WTP threshold.

Results worsen somewhat with only a mild treatment waning of 2% annually, to over £40,000 per QALY.

No natural weight gain for tirzepatide improves the ICER to £18,019 per QALY. Applying the weight gain parameter of Iyen et al yields £38,035 per QALY. This estimate initially appears counterintuitive as it is worse than the EAG base case for this subgroup.

It can be noted that the base case for this subset of £37,151 per QALY worsens to £40,094 when only the weight gain parameter of Iyen is changed. Even when natural weight gain is assumed in both arms with their BMI moving in parallel results for this subset are sensitive to the assumed common annual weight gain.

Target group subset with BMI ≥ 35 kgm^{-2}

For the target group subset with a BMI ≥ 35 kgm^{-2} the EAG base case ICER is £21,372 per QALY. Sampling using the SURMOUNT-1 derived distributions worsens this slightly to between £21,942 and £22,565 per QALY.

Results are again sensitive to relatively muted waning of 2% annually in the BMI net effect, the ICERs increasing to between £23,395 and £26,702 per QALY.

Moderating the effects of T2DM upon model outputs to 47% worsens the base case to £24,369 per QALY. The effects of applying the Haase et al scenarios are more mixed due to Haase et al estimating a superior performance in the weight loss group for the risk of T2DM.

Results are also sensitive to not applying the NHSE MDT costs, this improving the ICER to £17,171 per QALY. Not applying MDT costs or clinical effects in the diet and exercise arm improves the ICER to £19,129 per QALY.

No natural weight gain for tirzepatide improves the ICER to £18,019 per QALY. Applying the weight gain parameter of Iyen et al yields £19,428 per QALY.

There is some sensitivity to the costs of T2DM, but again with the 61% adjustment derived from Khunti et al these scenarios would be similarly affected.

Target group subset with BMI ≥ 35 kgm^{-2} and prediabetes

For the target group subset with a BMI ≥ 35 kgm^{-2} and prediabetes the EAG base case ICER is £19,504 per QALY.

Results broadly move in parallel with those of the subset with a BMI ≥ 35 kgm^{-2}. But the restriction to those with prediabetes typically improves the ICER by between £1,000 and £2,000 per QALY and in some cases a little more compared to the corresponding ICER for the subset with a BMI ≥ 35 kgm^{-2}.

Target group subset with BMI ≥ 35 kgm^{-2}, prediabetes and high CVD risk

For the target group subset with a BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk the EAG base case ICER is £20,689 per QALY.

Results broadly move in parallel with those of the subset with a BMI ≥ 35 kgm^{-2} and prediabetes. But the restriction to those with a high CVD risk typically worsens the ICER by around £1,000 compared to the corresponding ICER for the subset with a BMI ≥ 35 kgm^{-2} and prediabetes.

Additional scenario analyses

Committee or the Chair may wish to review combinations of the EAG scenario analyses. The EAG can turn this around fairly quickly but notes there may be issues around Factual Accuracy Check and the need to ensure that the Company has had sufficient sight of any additional analyses before the next Committee meeting.

8 REFERENCES

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Haase, C.L. et al Weight loss and risk reduction of obesity-related outcomes in 0.5 million people: evidence from a UK primary care database, Int J Obes (Lond), 2021, Jun;45(6):1249-1258

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Khunti, et al Weight change and risk of obesity-related complications: A retrospective population-based cohort study of a UK primary care database, Diabetes Obes Metab, 2023, 25:2669-2679

9 Appendix 01: Patient baseline characteristics and clinical effects

The baseline patient characteristics in SURMOUNT-1 for the target group and the three subsets of those with:

- a BMI of 30 – 35 kgm^{-2}
- a BMI ≥ 35 kgm^{-2}
- a BMI ≥ 35 kgm^{-2}, prediabetes and a high CVD risk, labelled as TA664

are presented in Table 13.

Table 13: SURMOUNT-1 baseline patient characteristics by subset

	All	BMI 30-35	BMI 35+	TA664
Age (Years)	47	50	46	47
Sex (% Female)	66%	65%	67%	66%
Weight (kg)	107	90	117	118
Height (m)	1.66	1.66	1.66	1.66
BMI (kg/m2)	38.8	32.6	42.1	42.6
SBP (mmHg)	125	124	125	126
Total Chol (mg/dL)	194	197	186	159
HDL (mg/dL)	49	48	47	45
% Hypertension	44%	40%	46%	41%
eGFR (ml/min/1.73 m2)	95	92	97	97
Triglycerides (mg/dL)	134	140	131	144
% Female with PCOS	2%	1%	3%	1%
FPG (mmol/L)	5.41	5.34	5.46	5.69
% Treated HT	40%	38%	44%	38%
% COPD	1%	2%	1%	1%
% Hypothyroidism	12%	12%	13%	12%
% Gestational Diabetes	1%	1%	1%	2%
% SLE	0%	0%	0%	0%
% of Male with ED	6%	7%	5%	4%
% CKD (3, 4 or 5)	0%	2%	1%	0%
% Rheumatoid Arthritis	1%	0%	0%	1%
% Atrial Fibrillation	0%	1%	1%	0%
% Migraine	5%	7%	7%	5%
% PVD	0%	0%	0%	0%
% Hyperlipidaemia	24%	13%	9%	24%
% GERD	38%	17%	15%	38%
% using Corticosteroids	2%	3%	1%	2%
% using Statins	18%	22%	16%	13%
% Prediabetes	[redacted]	[redacted]	[redacted]	[redacted]

The target group subsets of BMI ≥ 35 kgm^{-2} and TA664 have very similar baseline characteristics. The main differences between them are total cholesterol, the proportion with hyperlipidaemia and the proportion with GERD. This implies that the

target group subset of BMI ≥ 35 kgm^{-2} with prediabetes will have very similar baseline characteristics to the target group subsets of BMI ≥ 35 kgm^{-2} and TA664.

Table 14: SURMOUNT-1 clinical effectiveness estimates by subset

	Weight (%)	SBP (mmHg)	HDL (%)	TC (%)	Prediabetes reversal
Target group Diet and exercise Tirzepatide 15mg					
BMI 30-35 Diet and exercise Tirzepatide 15mg					
BMI 35+ Diet and exercise Tirzepatide 15mg					
TA664 Diet and exercise Tirzepatide 15mg					

The target group subsets of BMI ≥ 35 kgm-2 and TA664 have very similar clinical effectiveness estimates. This implies that the target group subset of BMI ≥ 35 kgm^{-2} with prediabetes will very similar clinical effectiveness estimates to the target group subsets of BMI ≥ 35 kgm^{-2} and TA664.

External Assessment Group's Addendum to 26 July 2024 report

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

Produced by	*Warwick Evidence*
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None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Contributions of authors

Ewen Cummins critiqued the cost-effectiveness evidence, Rhona Johnston reviewed and revised the VBA model implementation and both implemented the revised EAG economic modelling. Mubarak Patel critiqued statistical aspects of the Company submission and provided statistical input. Rachel Court conducted additional EAG searches. Lena Al-Khudairy supported the critique of the clinical effectiveness evidence and coordinated the project. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

1 Ara et al and Iyen et al weight gain parameters

The EAG exploratory ICERs of the original EAG report removed the natural weight gain parameter to avoid an ever increasing net BMI benefit for tirzepatide over diet and exercise. As a consequence, the EAG did not particularly review the weight gain parameter in its original report.

Committee also preferred that there was not an ever increasing net BMI benefit for tirzepatide over diet and exercise, but that this should be implemented by applying the natural weight gain parameter equally in both arms.

During Factual Accuracy Check the Company stressed that a scenario of no weight change while receiving tirzepatide while assuming natural weight gain in the diet and exercise arm should be considered, the EAG supplying this in its 26 July 2024 report. This causes there to be an ever increasing net BMI benefit for tirzepatide over diet and exercise, increasing the importance of the natural weight gain parameters within the modelling. This also led the EAG to review the natural weight gain parameters within the model in more detail.

Ara et al (2012) analysed the GPRD data of 100,000 randomly selected UK primary care patients, removing all data prior to 1980. Ara et al explicitly modelled BMI trajectories in quite sophisticated multivariate analyses. These analyses were conducted with a view to populating an economic model to estimate the cost effectiveness of using drugs to treat obesity in UK primary care.

Iyen et al (2021) analysed the CPRD data of 264,230 UK patients in primary care with a mean BMI of 33.8 kgm^{-2}. Over a median follow up of 10.9 years there was a mean BMI increase of 1.06 kgm^{-2}. The EAG of TA875 derived an annual BMI increase of 0.106 kgm^{-2} from this data and preferred this to the estimates of Ara et al, in part it seems due to Iyen et al analysing more recent data.

The FAC of TA875 notes the differences between the Company preference for the Ara et al estimates and the EAG preference for Iyen et al but does not appear to express a Committee preference for either.

Perhaps more important is that the weight gain parameters of Ara et al that are applied in the model are for non-diabetic patients. Ara et al also supply a separate parameter for those with diabetes though this is not differentiated by sex.

Table 1: Weight gain parameters

	Ara et al		
	Non-diabetic	Diabetic	Iyen et al
Male	0.1447	0.0398	0.1060
Female	0.1747		

The above may in part account for the differences in the parameter estimates of Ara et al and Iyen et al, as the parameter estimates derived from Iyen et al do not separately analyse diabetic and non-diabetic patients.

The analysis of Ara et al is somewhat more sophisticated that the annual BMI change derived from Iyen et al. It can also be noted the Ara et al supply separate estimates for men and women which is another possible reason to prefer it. But the parameter derived from Iyen et al should not be entirely dismissed.

The EAG thinks that reasons for preferring Ara et al are the sophistication of and motivation behind their analyses. The EAG agrees with the TA875 EAG that a reason for preferring Iyen et al is that it uses more recent data.

Another reason for preferring Iyen et al is that if the model does not differentiate between the non-diabetic and the diabetic in terms of natural weight gain, a parameter pooled across these groups rather than a parameter specific to the non-diabetic may be most reasonable to apply.

In short, if the model can be sensibly adapted to incorporate the diabetic weight gain parameter of Ara et al this would be the EAG preference. If not, the pooled weight gain parameter estimated from Iyen et al may be more reasonable.

The EAG has tried to incorporate the diabetic weight gain parameter of Ara et al in the model. This requires a reasonable amount of VBA programming within what is a reasonably involved VBA model. The EAG would be grateful if the Company could error check the EAG implementation of this and supply any required corrections.

The EAG exploratory ICERs that apply the EAG implementation of the Ara et al non-diabetic and diabetic natural weight gain parameters are presented in Table 2 below. The EAG exploratory ICERs of its 26 July 2024 report that do not apply this are presented in Table 3 for ease of reference.

These present the same set of scenario analyses as the EAG 26 July 2024 report.

- SA01: BMI distributions of 2021 HSE normal, gamma fit of the SURMOUNT-1 distribution, and, sampling from the SURMOUNT-1 BMI distribution.
- SA02: A waning of the BMI effect of 2% annually from year 5 onwards, and a waning of the BMI effect of 2% annually from year 5 onwards with a tirzepatide stopping rule of 15 years when 80% of the net benefit is retained and of 25 years when 60% of the BMI net benefit is retained.
- SA03: Adjusting model outputs to reflect the possible overestimation of the effect of weight loss upon the reduction in the risks of obesity related complications based upon the results of the Company preferred source of Khunti et al: (a) an adjustment factor of 61% for T2DM, (b) point (a) coupled with adjustment factors of 79% for OSA and 38% for TKR, and (c) point (b) coupled with an adjustment factor for angina, MI and stroke of 33%,
- SA04: For both arms no MDT costs
- SA05: For diet and exercise no MDT costs and no clinical effects
- SA06: No annual weight gain while receiving tirzepatide, also coupling this with the natural weight gain estimate of Iyen et al for diet and exercise
- SA07: Including 25%, 50%, 75% and 100% of the microvascular complication costs of T2DM as reported in Capehorn et al.
- SA08: 20% and 60% require psychological support.
- SA09: 0% of those in the BMI 30 – 35 kgm^{-2} target group subset require an SGLT2 from diagnosis of T2DM, and 100% of those in the BMI ≥ 35 kgm-2, prediabetic and high CVD risk target group subset require an SGLT2 from diagnosis of T2DM.
- SA10: Applying the weight gain parameter of Iyen et al in both arms.

Including the Ara et al diabetic weight gain parameter typically worsens the ICERs by around £1,000, though the treatment waning scenarios worsen a by a bit more.

Table 2: EAG ICERs: with Ara et al diabetic weight gain parameter

	Target Group	BMI 30 - 35	BMI ≥ 35	BMI ≥ 35, prediabetic	BMI ≥ 35, prediab, high CVD risk
Base case	£29,810	£38,601	£22,076	£20,398	£21,553
SA01a: BMI normal	£30,529	£38,290	£22,115	£20,518	£21,755
SA01b: BMI gamma	£26,233	£36,984	£22,470	£20,707	£22,074
SA01c: BMI SURMOUNT-1	£26,723	£37,014	£23,005	£21,266	£22,555
SA02a: 2% waning years 5+	£36,228	£45,293	£28,202	£25,908	£26,967
SA02b: SA02a + Tx stop 15 yr	£34,013	£44,819	£24,986	£22,895	£24,086
SA02c: SA02a + Tx stop 25 yr	£34,715	£44,429	£26,312	£24,050	£25,084
SA03a: Khunti T2DM	£32,486	£41,879	£23,938	£22,925	£24,078
SA03b: SA03a + OSA +TKR	£33,220	£42,478	£24,703	£23,676	£24,848
SA03c: SA03b + Angina/MI	£33,283	£42,544	£24,747	£23,737	£24,907
SA04: No MDT costs	£24,068	£31,372	£17,735	£16,185	£17,161
SA05: No D&E MDT cost/effect	£25,972	£31,265	£19,904	£17,964	£18,247
SA06a: No weight gain TIRZ	£26,113	£34,743	£18,719	£17,378	£18,177
SA06b: SA06a + Iyen param	£27,877	£38,035	£19,428	£17,961	£18,982
SA07a: T2DM Capehorn 25%	£29,201	£37,971	£21,574	£19,695	£20,870
SA07b: T2DM Capehorn 50%	£28,593	£37,342	£21,072	£18,991	£20,186
SA07c: T2DM Capehorn 75%	£27,985	£36,712	£20,570	£18,288	£19,503
SA07d: T2DM Capehorn 100%	£27,377	£36,082	£20,068	£17,585	£18,819
SA08a: 20% psych support	£29,625	£38,370	£21,937	£20,262	£21,412
SA08b: 60% psych support	£30,179	£39,064	£22,356	£20,669	£21,836
SA09: T2DM SGLT2 use	..	£39,048	..	..	£20,472
SA10: Iyen et al param	£30,320	£40,094	£21,701	£19,982	£21,342

Table 3: EAG ICERs: without Ara et al diabetic weight gain parameter

	Target Group	BMI 30 - 35	BMI ≥ 35	BMI ≥ 35, prediabetic	BMI ≥ 35, prediab, high CVD risk
Base case	£28,697	£37,151	£21,372	£19,504	£20,689
SA01a: BMI normal	£29,243	£36,864	£21,332	£19,481	£20,708
SA01b: BMI gamma	£25,512	£35,542	£21,942	£19,993	£21,457
SA01c: BMI SURMOUNT-1	£26,013	£35,689	£22,565	£20,603	£21,919
SA02a: 2% waning years 5+	£34,231	£43,097	£26,702	£24,167	£25,256
SA02b: SA02a + Tx stop 15 yr	£32,489	£42,806	£23,935	£21,562	£22,802
SA02c: SA02a + Tx stop 25 yr	£33,178	£42,716	£25,298	£22,735	£23,877
SA03a: Khunti T2DM	£31,181	£40,188	£23,109	£21,837	£23,035
SA03b: SA03a + OSA +TKR	£31,904	£40,778	£23,899	£22,579	£23,800
SA03c: SA03b + Angina/MI	£31,963	£40,840	£23,926	£22,636	£23,855
SA04: No MDT costs	£23,173	£30,197	£17,171	£15,478	£16,457
SA05: No D&E MDT cost/effect	£24,789	£29,804	£19,129	£16,962	£17,251
SA06a: No weight gain TIRZ	£25,011	£33,359	£18,019	£16,555	£17,444
SA06b: SA06a + Iyen param	£27,877	£38,035	£19,428	£17,961	£18,982
SA07a: T2DM Capehorn 25%	£28,118	£36,551	£20,890	£18,838	£20,038
SA07b: T2DM Capehorn 50%	£27,539	£35,951	£20,409	£18,172	£19,387
SA07c: T2DM Capehorn 75%	£26,960	£35,351	£19,928	£17,506	£18,737
SA07d: T2DM Capehorn 100%	£26,381	£34,750	£19,447	£16,840	£18,086
SA08a: 20% psych support	£28,519	£36,928	£21,237	£19,374	£20,553
SA08b: 60% psych support	£29,052	£37,596	£21,642	£19,763	£20,960
SA09: T2DM SGLT2 use	..	£37,576	..	..	£19,659
SA10: Iyen et al param	£30,320	£40,094	£21,701	£19,982	£21,342

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External Assessment Group's FAC report: Addendum 2

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

Produced by	*Warwick Evidence*
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Declared competing interests of the authors

None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the authors'.

Contributions of authors

Ewen Cummins provided the additional cost-effectiveness modelling. Lena Al-Khudairy coordinated the project.

Background

At the PMB NICE asked the EAG to provide a table that applies the EAG changes individually to the company base case for the Target Group. It also asked the EAG to apply the Company supplied baseline characteristics and clinical effect estimates for the BMI ≥ 35 kgm^{-2} subset of the Target Group, and then similarly explore the EAG changes.

Due to the EAG report concluding that the model had not converged with a cohort of 1,000 patients NICE asked the EAG to initially revise the Company base case to be run with a cohort of 20,000 patients. The EAG applies its changes individually to the model run with

The EAG 2024-07-26 report highlighted the Company position that diet and exercise be associated with natural weight gain while tirzepatide be associated with no weight gain for the duration of treatment. This led the EAG to reappraise the estimates of Ara et al and Iyen et al, during which it noted that the Ara et al coefficients of the model are for non-diabetic patients. Ara et al provide a separate weight gain coefficient for those with diabetes. Correcting the model to apply the on-diabetic and diabetic coefficients resulted in the EAG 2024-07-27 Addendum 1.

Table 1: ICERs from Company assumptions and effects of EAG changes

Cohort size	Target group	BMI ≥ 35 kgm^{-2}
A) 1,000	£14,726	£12,606
B) 20,000	£15,965	£13,375
All results below are run for (B) so with a cohort of 20,000 patients		
1) Lognormal BMI distribution	£18,305	£13,087
2) Natural weight gain for tirzepatide	£18,912	£16,138
3) Exclude CVD and NAFLD SMRs	£16,041	£13,391
5) NHSE MDT costs	£20,165	£16,983
6) T2DM Costs	£17,351	£14,624
7) Ara diabetic weight gain coef for T2DM	£16,506	£13,782
(B) + (1) through (6): 2024-07-26 EAG	£28,697	£21,372
(B) + (1) through (7): 2024-07-27 EAG	£29,810	£22,076

Reference

Ara et el What is the clinical and cost effectiveness of using drugs in treating obese patients in primary care? A systematic review, Feb 2012, Health Tech Ass: 2012, 16, 5

External Assessment Group's addendum to 26 July 2024 report

Title: ***Tirzepatide for managing overweight and obesity [ID6179]***

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None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Contributions of authors

Ewen Cummins critiqued the cost-effectiveness evidence. Lena Al-Khudairy coordinated the project. All authors contributed to the writing and editing of the report.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

Background

NICE has requested further analyses in the light of the third Committee meeting. Four main analyses of:

1. The EAG base case, including natural weight gain in both arms
2. (1), but not including natural weight gain in either arm
3. (1) but sampling BMI using the IMPACT-O histogram
4. (2) but sampling BMI using the IMPACT-O histogram

For each of these main analyses NICE requested that the EAG provide scenarios of:

A. No treatment effect and no MDT costs for diet and exercise
B. Netting out routine obesity management costs from the NHSE MDT costs

NICE did not request combining A and B in a joint scenario. The EAG supplies this for completeness.

Table 1: NICE requested cost effectiveness estimates

	Target Group	BMI ≥ 35	BMI ≥ 35, prediabetic	BMI ≥ 35, prediab, high CVD risk
Main analyses				
1. EAG base case	£29,810	£22,076	£20,398	£21,553
2. No natural weight gain	£35,325	£23,212	£21,961	£23,323
3. (1) with IMPACT-O BMI	£29,583	£22,501	£20,849	£22,062
4. (2) with IMPACT-O BMI	£33,857	£23,042	£21,790	£23,192
(A) No effect or NHSE MDT costs diet and exercise				
1. EAG base case	£25,972	£19,904	£17,964	£18,247
2. No natural weight gain	£27,583	£19,143	£16,938	£17,219
3. (1) with IMPACT-O BMI	£25,805	£20,192	£18,215	£18,558
4. (2) with IMPACT-O BMI	£28,876	£19,181	£17,006	£17,290
(B) Net out routine management costs from NHSE MDT costs				
1. EAG base case	£26,230	£19,366	£17,768	£18,813
2. No natural weight gain	£31,183	£20,430	£19,255	£20,480
3. (1) with IMPACT-O BMI	£26,034	£19,741	£18,169	£19,264
4. (2) with IMPACT-O BMI	£29,899	£20,289	£19,112	£20,374
(A+B) No effect or MDT costs for D&E and net out routine management costs				
1. EAG base case	£22,247	£17,123	£15,278	£15,528
2. No natural weight gain	£23,816	£16,459	£14,395	£14,643
3. (1) with IMPACT-O BMI	£22,280	£17,377	£15,499	£15,798
4. (2) with IMPACT-O BMI	£23,208	£16,499	£14,463	£14,714

With regards sampling from the IMPACT-O histogram the EAG notes its stepped nature by BMI point. Given the patient numbers involved a finer gradation is very likely to increase the number sampled towards the bottom of each BMI point and reduce it towards the top. This would probably worsen the ICER for the Target Group.

Tirzepatide for managing overweight and obesity [ID6179]

Committee Requests Post-ACM3

Introduction

Lilly would like to thank NICE for sharing the Committee requests following the third Appraisal Committee meeting (ACM3), and for providing the opportunity to present a final set of scenarios to support their decision regarding a recommendation for the use of tirzepatide in patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity.

This response has two key sections. First, Lilly have presented the post-ACM3 Committee-requested scenarios for patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity (Section 1). Next, Lilly have presented a set of additional scenarios for this population incorporating the costs of T2DM accepted in TA875 (semaglutide), in light of the question by the Chair during ACM3 about which appraisal the Company referred to regarding the inconsistency of T2DM costs (Section 2). Further information of the implementation of these scenarios (including IMPACT-O and no natural weight regain) is provided in the Appendix.

Importantly, whilst Lilly have provided all of the Committee-requested scenarios, the cost-effectiveness results presented in the following sections should be considered **highly conservative** for the following key reasons:

- All scenarios assume that patients receiving no healthcare resource use (HCRU) (i.e. no intervention) in the diet and exercise arm after 2 years have the same weight trajectory as those who are receiving tirzepatide, which is a disease-modifying treatment
- It is well-established in the clinical community and in the literature that patients not receiving any intervention for their obesity naturally put on weight over time – assuming no weight regain in the diet and exercise arm after 2 years is therefore implausible
- The T2DM costs included in the EAG ACM3 base case (£789) are less than half what has previously been accepted by the Committee in TA875 (£1,770; see Table 43 of the Company Submission), despite both appraisals being in the same indication and the ever-increasing economic burden associated with T2DM in the UK[1-5]
- Clinicians in ACM3 stated that they would expect those with more severe disease to represent a substantial proportion of patients who would seek treatment for their obesity, contradicting the use of a lognormal BMI distribution (informed by HSE data) in the EAG ACM3 base case (versus the use of gamma distribution)
- Whilst not incorporated into any scenarios due to NICE processes, newly available evidence from SURMOUNT-1 (see Appendix) indicates that patients who remain on tirzepatide treatment would maintain their absolute weight loss for at least 176 weeks, demonstrating that the application of natural weight regain in the tirzepatide arm from Week 72 in the EAG ACM3 is overly pessimistic.[6]

Model version and cohort size

All scenarios presented in this document have been run on the model used to generate the ICERs in ACM3 (Model name: ID6179 Tirzepatide - EAG revised model post ACM3 - 150824 [CON]) with the EAG-preferred cohort size of 20,000 and starting from the EAG ACM3 base case ICER of £29,810.

Summary

This response provides a range of ICERs that, taking into consideration the highly conservative assumptions included, provide confidence that tirzepatide represents a cost-effective use of NHS resources in patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity.

Section 1. Committee Requests

Table 1 presents the cost-effectiveness results for tirzepatide versus diet and exercise for 15 mg tirzepatide.

Table 1. Committee requested cost-effectiveness results for tirzepatide versus diet and exercise in patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity

	EAG ACM3 base case (1)	EAG ACM3 base case + IMPACT-O sampling (2)	EAG ACM3 base case with no natural weight regain in either arm (3)	EAG ACM3 base case with no natural weight regain in either arm + IMPACT-O sampling (4)
Base case	£29,810	£29,583	£29,151	£27,865
Scenario A: no effect and no MDT costs for diet and exercise	£25,972	£25,805	£22,069	£21,468
Scenario B: MDT costs for Y1 and Y2+ having routine costs of £233 netted out	£26,230	£26,034	£25,710	£24,590
Scenario A + B: no effect and no MDT costs for diet and exercise + MDT costs for Y1 and Y2+ having routine costs of £233 netted out	£22,427	£22,280	£18,982	£18,471

Section 2. Additional Scenarios

Table 2 presents the cost-effectiveness results for tirzepatide versus diet and exercise for 15 mg tirzepatide, when incorporating the TA875 T2DM costs.[1]

Table 2. Scenario analyses results for tirzepatide versus diet and exercise in patients with a BMI ≥30 kg/m^2 with at least one weight-related comorbidity with TA875 T2DM costs

	EAG ACM3 base case (1) + TA875 T2DM costs	EAG ACM3 base case + IMPACT-O sampling (2) + TA875 T2DM costs	EAG ACM3 base case with no natural weight regain in either arm (3) + TA875 T2DM costs	EAG ACM3 base case with no natural weight regain in either arm + IMPACT-O sampling (4) + TA875 T2DM costs
Base case	£26,554	£26,354	£26,631	£25,547
Scenario A: no effect and no MDT costs for diet and exercise	£22,284	£22,139	£18,253	£17,812
Scenario B: MDT costs for Y1 and Y2+ having routine costs of £233 netted out	£22,974	£22,805	£23,190	£22,273
Scenario A + B: no effect and no MDT costs for diet and exercise + MDT costs for Y1 and Y2+ having routine costs of £233 netted out	£18,739	£18,614	£15,166	£14,815

Appendix

SURMOUNT-1 Week 176 extension data

As per NICE processes, Lilly acknowledge that the presentation and incorporation of new evidence at this stage of the appraisal is not permitted. However, Lilly wishes to note that extension data for SURMOUNT-1 became available publicly on Tuesday 20th August (two days prior to this response submission).[6] These data have not been incorporated into any analyses to adhere to the NICE processes, however, Lilly wish to highlight that these data demonstrate that patients who remain on tirzepatide treatment maintain their absolute weight loss until at least Week 176 (Figure 1).[6] Whilst a plateau in weight loss is also observed in the diet and exercise arm, these patients continued to receive diet and exercise support until 176 weeks – this is not in line with the modelled comparator for this appraisal, where HCRU costs are only applied for 2 years in the diet and exercise arm. The observations of no natural weight regain in the diet and exercise arm cannot therefore be considered applicable to the model underpinning this appraisal.

Figure 1: Percentage change from randomisation in body weight over time to Week 176 in the SURMOUNT trial

IMPACT-O implementation

As per the Committee request, Lilly have reviewed the implementation of the new EAG IMPACT-O sampling method and have no concerns. Lilly have also noted the Committee's request to replace the IMPACT-O patient numbers derived by the EAG with the actual patient numbers. Unfortunately, it was not possible for Lilly to obtain these data. As such, all analyses including IMPACT-O sampling use the same patient numbers as the EAG in their post-ACM3 model.

Implementation of scenarios that include 'no natural weight regain in either arm'

Various scenarios requested by the Committee include an assumption in which there is no natural weight gain in either the diet and exercise or the tirzepatide arm of the model. Lilly understand that these scenarios are intended to reflect the discussions at ACM3, where the Committee expressed a preference for maintaining the net effect between the tirzepatide arm and the diet and exercise arm over the modelled time horizon, whilst also considering the possibility that there may be no natural weight regain in either arm. It is understood the latter concept was informed by the SELECT trial data presented and discussed during the Committee meeting.[7]

In line with these ACM3 discussions and the post-ACM3 Committee requests, Lilly have therefore provided the requested analyses in which no natural weight regain is modelled in either arm. However, Lilly wish to highlight that the suggested implementation by the Committee (to set the Ara *et al.* coefficients that inform

natural weight regain for diabetic and non-diabetic patients to zero) did not produce the requested effect of maintaining the net benefit between tirzepatide and diet and exercise.[8]

Therefore, Lilly have run these scenarios using an adjusted method, which reflects the requested modelled scenario, in which weight loss for the diet and exercise arm is held constant (reflecting the SELECT data) whilst also modelling a constant net weight loss benefit for tirzepatide versus diet and exercise over time. Figure 2 presents the modelled impact on weight (kg) for both the tirzepatide and diet and exercise arm when this scenario is implemented, as a means of illustrating the impact of this scenario on the model outputs.

As such, please note that in this response, all results for scenarios which include no weight regain in either arm include the Company-adjusted method.

Figure 2. Modelled impact on weight (kg) in the diet and exercise and tirzepatide arms using Company-adjusted method of 'no natural weight regain in either arm'

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