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Tirzepatide for managing overweight and obesity

Technology appraisal committee A - 16 January 2024

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Current management – overview

See appendix – slides 40 and 41

Care for overweight and obesity is in community or in specialist weight management services

- **Tier 2 (or lifestyle weight management services):** delivered in community, for approximately 12 weeks (for people with BMI ≥30†)
- **Specialist weight management services (SWMS)** - including but not limited to **tier 3** and **tier 4:** specialist MDT intervention, including access to liraglutide (TA664) and semaglutide (TA875)**;** accessed for up to 2 years (for people with BMI ≥35 plus weight related comorbidities†)

NICE CG189:
SWMS can be accessed if (not exhaustive):

- underlying causes of overweight or obesity need to be assessed
- there are complex needs
- conventional treatment has been unsuccessful
- specialist interventions or surgery are considered

NICE PH53:
Lifestyle weight management services should be:

- multi-component
- delivered by an MDT
- delivered at least fortnightly, for minimum 12 weeks

Company positioning: tirzepatide could be delivered in both primary or secondary care for people with BMI ≥30 and ≥1 weight-related comorbidity

Is the company's proposed positioning appropriate?

† regional variation

Patient organisation perspectives

Submissions from All About Obesity and Diabetes UK:

- Living with obesity means fighting against stigma and discrimination daily
- Access to SWMS is not equitable – availability is a postcode lottery – for example, only 1% of those eligible receive bariatric surgery on average, but there is regional variation
- Limited access to semaglutide and liraglutide due to availability in SWMS only and due to national shortages and supply issues
- Options available are limited – long term treatment options would be welcomed
- Peer and person-centred support and attention to psychological needs is key for successful weight management

Professional organisation perspectives

Submissions from The Associations for the Study of Obesity and British Obesity Metabolic Surgery Society:

- Current evidence suggests tirzepatide could be used in place of semaglutide and liraglutide; expects it would deliver significant improvement in QoL and reduce obesity complications
- Should be prescribed within an MDT managing complex obesity (could be in primary care)
- Provision of obesity services is suboptimal and variable
- Should target tirzepatide at people with high BMI but not routinely BMI>45 (best served by surgery)
- Longer term data on impact of stopping and appropriate length of treatment needed – stopping at 2 years for responders not appropriate
- Considered innovative due to improved efficacy in weight loss

Equality considerations

- People with mental health disorders (especially those receiving atypical antipsychotics) may have increased risk of developing obesity but ability to access tirzepatide may be hindered by their mental health condition
- People with disabilities are disproportionately affected by obesity but ability to access treatment may be adversely impacted by their disability
- Tirzepatide may be suitable for people with disabilities who are unable to provide consent or be eligible for bariatric surgery
- Cardiometabolic risk occurs at a lower BMI for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds, so lower BMI thresholds are a practical measure of overweight and obesity (thresholds are usually reduced by 2.5 to identify obesity status; NICE Clinical Guideline 189)

Inequity in treatment access

- Access to SWMS is inequitable across the country
- Office for Health Improvement and Disparities data (2022) suggests that tier 2 services are also not equitably distributed across the country or according to local need (see appendix slide 42)

Decision problem: Population

**in line with marketing authorisation*

Summary qs

	Final scope	Company
Population	Adults with BMI: • ≥30 (obese) or • ≥27 to <30 (overweight) and with at least 1 weight-related comorbidity	**Target population**: **Adults with BMI ≥30 (obesity) and at least 1 weight-related comorbidity** • Subgroups included liraglutide eligible population
Intervention	Tirzepatide	Tirzepatide ***as adjunct to reduced-calorie diet and increased physical activity****
Outcomes	BMI; weight loss; waist circumference; T2DM incidence; glycaemic status; CV events; mortality; adverse effects of treatment; HRQoL	All other than cardiovascular events and mortality (covered by risk equations in model)

EAG:

- Company targets a smaller population than trial and scope: people with BMI ≥27 to <30 + comorbidity (recruited into informing trial) not included in target population; target population also includes some who are not eligible for semaglutide (people not eligible for SWMS)
- Unclear which weight-related comorbidities included in target population; trial excludes people with T2DM
- Could consider subgroups according to risk, i.e. target population includes non-liraglutide eligible (BMI ≥30 to <35 + 1 weight related comorbidity or ≥35 without high CVD risk or prediabetes) and liraglutide eligible (BMI ≥35 + high CVD risk and pre-diabetes) populations

- Is the company's restriction to the target population appropriate?
- Should subgroups according to liraglutide eligibility be considered?

Decision problem: comparators

See appendix – slide 45 Summary qs

Final scope	Company submission
• Standard management without tirzepatide (reduced calorie diet and increased physical activity) • Semaglutide (for population recommended in TA875) • Liraglutide (for population recommended in TA664) • Orlistat (prescription dose)	For people with BMI ≥30 and at least 1 weight-related comorbidity (target population): • semaglutide plus diet and exercise • diet and exercise For population recommended in TA664: • semaglutide plus diet and exercise • liraglutide plus diet and exercise • diet and exercise

Company:
- Orlistat not widely used in practice (exclusion aligns with previous appraisals)
- No data for specific population recommended in TA875 (semaglutide)

EAG: modelled position for comparison with semaglutide reasonable provided any recommendation limits tirzepatide to the same population recommended for semaglutide

- Is semaglutide the appropriate comparator for all people with BMI ≥30 and ≥1 weight-related comorbidity, given semaglutide is only recommended for people *within SWMS* with BMI ≥30 and ≥1 weight-related comorbidity?
- Is liraglutide a relevant comparator for people with BMI ≥35, prediabetes and high CVD risk?

Key issues - overview

See from slide 18 for details of key issues

Key issues (clinical)	ICER impact
Generalisability of trial population	Cannot be quantified
Key issues (economic modelling)	
Treatment setting (and relevant costs)	Large
Tirzepatide 2-year stopping rule	Large
Net increase in tirzepatide treatment effect over time	Large
Treatment effect waning on maintenance treatment in the long term	Not currently quantified
Weight regain after stopping treatment	Moderate
Prediabetes reversal rates	Not currently quantified (other changes to demonstrate suggest large impact)
Responder rates	Large
Annualisation of multi-year event risks	Cannot be quantified
Other issues (see appendix slide 55 and from slide 65)	
NMA heterogeneity (statistical and methodological)	Cannot be quantified
Cost of diabetes	Large
BMI mortality multipliers (age specific and pooling for all BMI >40)	Not currently quantified
Patients had no other complications at baseline	Not currently quantified
Same treatment effect for responders and non-responders	Not currently quantified

Clinical effectiveness

For clinical trial design: see appendix slide 46

For detailed clinical trial results: see slides 47 to 52

For NMA methodology: see slides 54 and 55

For detailed NMA results: see slides 56 to 63

Key clinical trial: SURMOUNT-1

Summary qs

	SURMOUNT-1
Design	Placebo-controlled double blind RCT
Population	• Adults with obesity (BMI ≥30), or overweight (BMI ≥27) plus 1 weight related co-morbidity (hypertension, dyslipidaemia, OSA, CVD) • Excluded people with T2DM and history of severe psychiatric disorders in last 2 years
Baseline characteristics	• Average BMI: 38.0 (SD 6.8) • % with prediabetes: 40.6% • % Asian: 10.9; % Black or African American: 7.9; % White: 70.6
Intervention	Tirzepatide 5mg (n=630), 10mg (n=636) or 15mg (n=630), once weekly, adjunct to reduced-calorie diet and increased physical activity
Comparator	Placebo (n=643) plus reduced-calorie diet and increased physical activity*
Duration	72-week treatment period + 4-week safety follow up; longer-term study ongoing for people with prediabetes at baseline
Primary outcomes	• % change in weight from baseline to week 72 (10 and 15mg) • % achieving ≥5% weight reduction from baseline to week 72 (10 and 15mg)

***Lifestyle modifications during SURMOUNT-1*:**
All participants consulted with a dietician, or equivalent qualified delegate to receive lifestyle management counselling on diet and exercise at weeks 0, 4, 8, 12, 24 and every 12 weeks thereafter. Could be delivered by phone from week 8

Generalisability of SURMOUNT-1 to clinical practice

Summary qs

EAG:

Population

- Target population of BMI ≥30 + ≥1 weight-related comorbidity narrower than trial
- Excludes people with T2DM and psychiatric history
- Most common baseline comorbidities across whole trial population included hypertension, dyslipidaemia, depression and osteoarthritis – but unclear which comorbidities present for population of interest
- No UK study sites
- Baseline characteristics well matched across treatment arms

Dose

- Trial included 3 tirzepatide doses, each modelled separately - no guidance in SmPC on amount of weight loss needed for decision to stay on lower dose
- EAG clinical advice that tirzepatide dose would increase as long as tolerable

Dose escalation and de-escalation

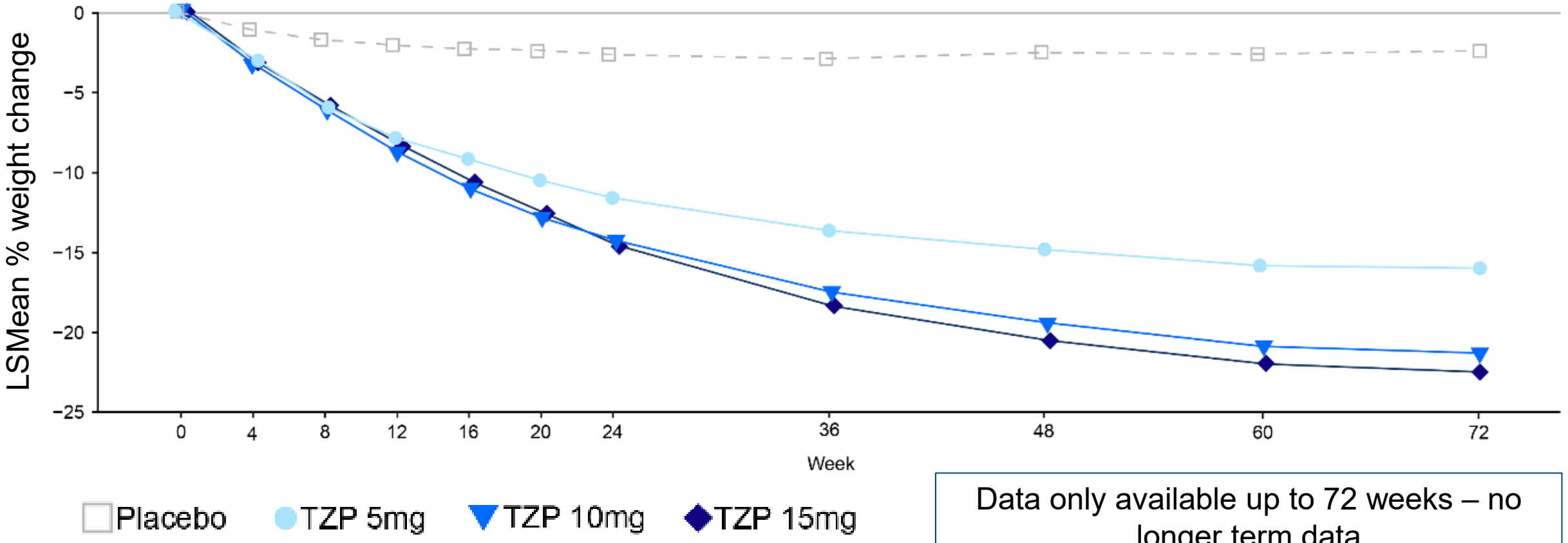
- In SURMOUNT-1, participants titrated up from 2.5mg to maintenance dose they were randomly allocated to; 1 chance for de-escalation in trial due to intolerable GI symptoms
- No data to show impact of escalation (during titration) and de-escalation on relative effectiveness of doses or on adverse events – direction of impact unclear
- SURMOUNT-1 de-escalation rates: placebo: [redacted] 5mg: [redacted] 10mg: [redacted] 15mg: [redacted]
- In SURMOUNT-4, 92.5% able to tolerate 15mg tirzepatide

- Is the trial generalisable to the NHS for the target population?
- Would the highest tolerated dose of tirzepatide be used in clinical practice?
- What proportion of people would be expected to be on 5, 10 and 15 mg doses in practice?
- Is the dose escalation and de-escalation used in the trial generalisable to clinical practice?

Clinical results: SURMOUNT 1, people with BMI ≥30 with ≥1 comorbidity (1)*

* Company's targeted and modelled population

Tirzepatide more effective than placebo at 5, 10 and 15mg doses in target population for percentage change in body weight from baseline to week 72



Data only available up to 72 weeks – no longer term data

Clinical results: SURMOUNT 1, people with BMI ≥30 with ≥1 comorbidity (2)*

* Company's targeted and modelled population

Summary qs

At 72 weeks follow up:

- Tirzepatide more effective than placebo for % responders (≥5% body weight reduction)
- Tirzepatide more effective than placebo for % prediabetes
- Tirzepatide associated with fewer serious adverse events but placebo associated with fewer treatment emergent adverse events

Outcome (at 72 weeks)	Placebo	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
% achieving ≥5% body weight reduction	[redacted]	[redacted]	[redacted]	[redacted]
Prediabetes at baseline to normoglycaemia at 72 weeks, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment emergent adverse events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Incidence of clinical events and comorbidities in model determined via risk equations using surrogate endpoints of CfB in: weight, SBP, HDL and total cholesterol (NMA results used in model)

Tirzepatide data available for 72 weeks treatment and follow up - what assumptions can be made about long-term effectiveness of tirzepatide?

NMA results overview

Company NMAs (change from baseline in target population):

- Semaglutide and tirzepatide 5, 10 and 15mg all statistically superior to diet and exercise for all outcomes
- **Weight:** tirzepatide 15 mg statistically superior to all other treatments; tirzepatide 10 mg statistically superior to tirzepatide 5 mg and semaglutide
- **HDL:** tirzepatide 5, 10 and 15 mg statistically superior to semaglutide, tirzepatide 15 mg only numerically superior to the other tirzepatide doses
- **Total cholesterol:** tirzepatide 15 mg statistically superior to other tirzepatide doses but only numerically superior to semaglutide; tirzepatide 5 and 10 mg numerically inferior to semaglutide
- **SBP:** tirzepatide 10 and 15 mg numerically superior to semaglutide, 5mg numerically inferior to semaglutide; tirzepatide 10 mg numerically superior to 5 and 15 mg

EAG NMAs (change from baseline):

- **Prediabetes reversal (target population):** semaglutide statistically superior to all tirzepatide doses
- **Minimum 5% weight loss (whole trial population):** tirzepatide 15 and 10 mg statistically superior to semaglutide

EAG:
No NMA conducted for adverse events, but adverse event rates in SURMOUNT-1 broadly in line with studies in semaglutide and liraglutide

Company’s model

NICE National Institute for Health and Care Excellence

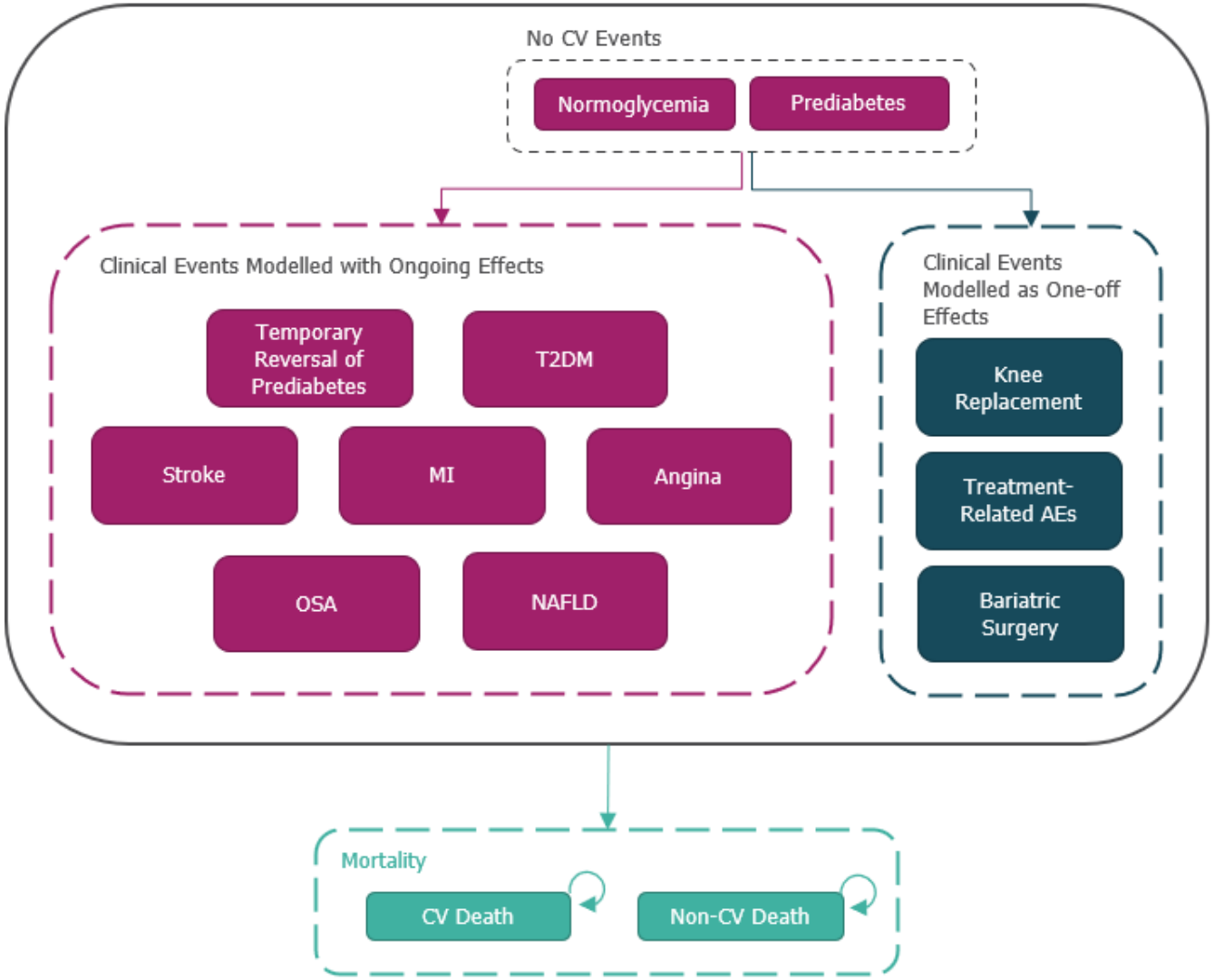
Company's model overview

Individual patient simulation, 4 weekly cycle

See appendix – slide 64

Summary qs

- Population: BMI ≥30 + ≥1 weight-related comorbidity
- Patient characteristics used as inputs for risk equations which determine per-cycle risk of experiencing clinical events
- Events associated with costs, disutilities and changes in risk of future events
- Patients enter model without complications or comorbidities which are modelled outcomes
- Proportion entering model with pre-diabetes based on baseline data from SURMOUNT-1 for tirzepatide and diet and exercise, STEP-1 for semaglutide and SCALE for liraglutide
- Treatment discontinuation occurs due to SWMS time limits (2 years), treatment failure (<5% weight loss after 6 months) or adverse events



EAG: not including baseline model complications and comorbidities likely to bias cost effectiveness results in favour of tirzepatide

Key issues

See supplementary appendix for details of other issues:

- BMI mortality modifiers – slide 70
- Stopping treatment due to adverse events – slide 71

See slide 8 for overview of key issues

NICE National Institute for Health and Care Excellence

Key issue: Treatment setting (1)

Company: SURMOUNT-1 is generalisable to tier 2 obesity services

Summary qs

Model driver

Company

- Pilots ongoing for expansion of SWMS, including delivery of pharmacological treatments outside hospital
- Support could be provided outside SWMSs and still align with indication ('as an adjunct to diet and exercise') – **NICE PH53** recommends tier 2 services provide MDT support and run at least fortnightly for at least 3 months; **SURMOUNT-1** included lifestyle management counselling every 4 weeks until week 12, and continued every 12 weeks thereafter (until end of trial)

EAG and NICE technical team:

- SURMOUNT-1 included dietician (or equivalent) led lifestyle management counselling at regular intervals (at least every 12 weeks for 72 weeks) (see slide 10)
- SURMOUNT-1 participants required to have history of at least 1 unsuccessful dietary effort to lose weight – may reflect a population more likely to be eligible for SWMS
- Tier 2 community services usually accessible for 12 weeks - dose escalation to 15mg takes 20 weeks
- TA875 conclusion: clinical trial (for semaglutide) included behaviour change interventions similar to treatment in SWMS – a reason semaglutide only recommended in SWMS
- EAG base case applies SWMS costs (3 consultant, 8 dietician and 3 psychologist visits in year 1; 2 consultant and 4 dietician visits annually thereafter) to all active treatments – these are uncertain and based on a single expert opinion (see appendix slide 66 for cost details)
- In scenarios which remove SWMS costs, appropriate tier 2 or other community monitoring or follow up costs are not included

Summary qs

Key issue: Treatment setting (2)

- Which treatment setting is SURMOUNT-1 most generalisable to?
- What is the appropriate setting for tirzepatide use and therefore which treatment setting associated costs should be included?
- What is the appropriate comparator for tirzepatide, given the treatment setting?

Key issue: 2-year stopping rules

Summary qs

Company assumes no stopping rule for tirzepatide; EAG presents scenarios with no stopping rules and with 2-year stopping rules for all treatments

Background:

- SWMS are normally accessed for up to 2 years
- Company base case assumes no stopping rule for tirzepatide and a 2-year stopping rule for liraglutide and semaglutide (in line with NICE recommendations/ SWMS limitations within NICE recommendation)

EAG:

- Semaglutide clinical trial data shows weight is regained rapidly after withdrawal of treatment; clinicians therefore suggest semaglutide stopping rule might not be adhered to
- Relaxing the 2-year stopping rule has less impact if SWMS costs are not applied

Company:

- Not appropriate to apply a stopping rule for tirzepatide as discontinuation expected to result in weight regain, potentially limiting long-term benefits of treatment
- Tirzepatide should be used outside SWMS, so not limited by 2-year service provision

Professional organisation:

- Uncommon to treat chronic disease for 2 years and stop – stopping will lead to relapse, so should be continued long term

- Would patients and clinicians want to use tirzepatide long-term and if so, for how long?
- Is it appropriate to apply a 2-year stopping rule?

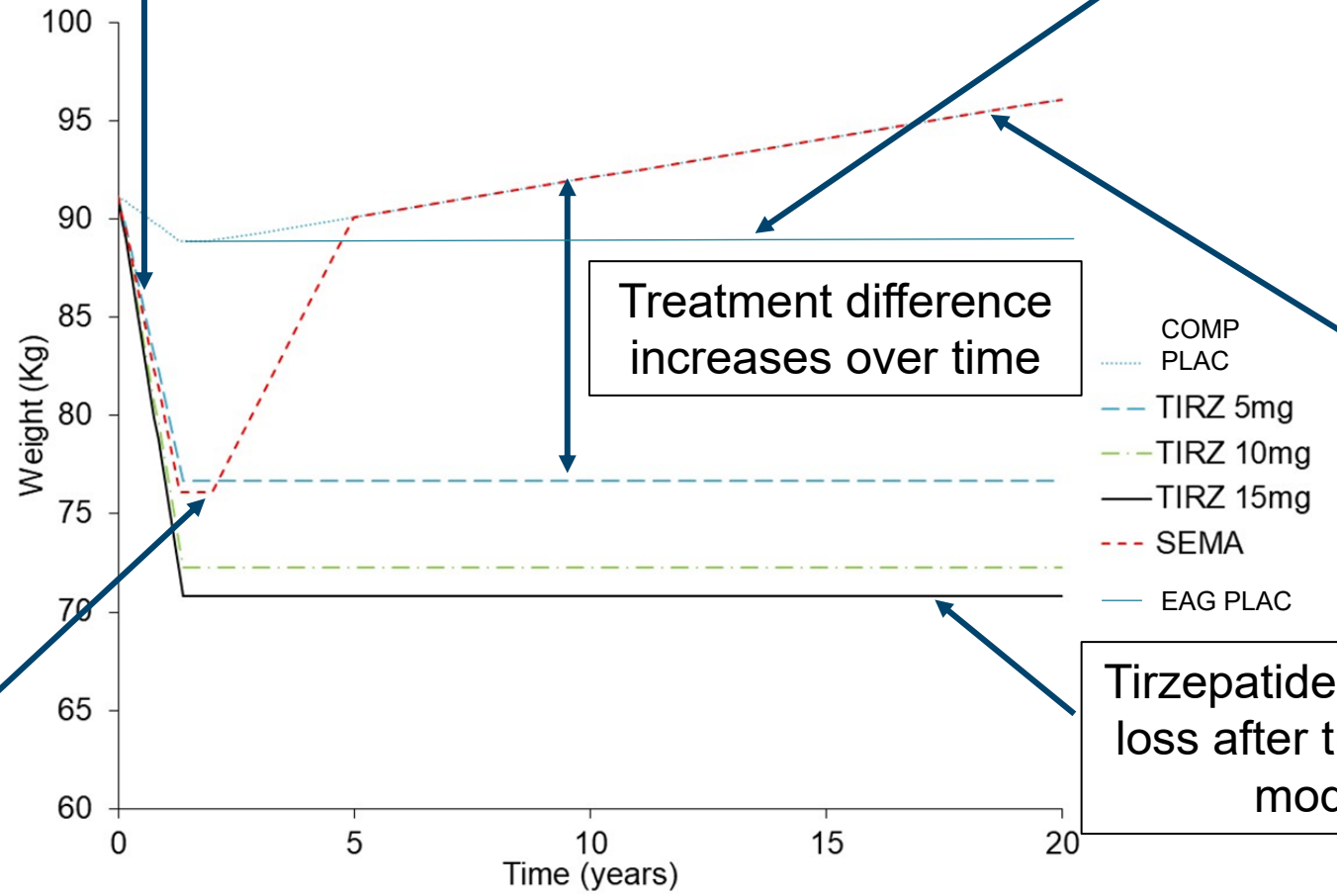
Key issue: Net increase in tirzepatide treatment effect over time

Summary qs

20-year treatment effect modelled in company base case and EAG base case:

Semaglutide and tirzepatide weight loss during trial treatment period

EAG: prefer to remove the net increase in weight between arms over time horizon by removing the annual BMI increase for diet and exercise arm



Treatment difference increases over time

Diet and exercise arm weight increases every year after trial period

Semaglutide weight loss maintained while on treatment and regained over 3 years after stopping and increases in line with diet and exercise arm

Tirzepatide (no stopping rule) weight loss after trial period maintained for modelled time horizon

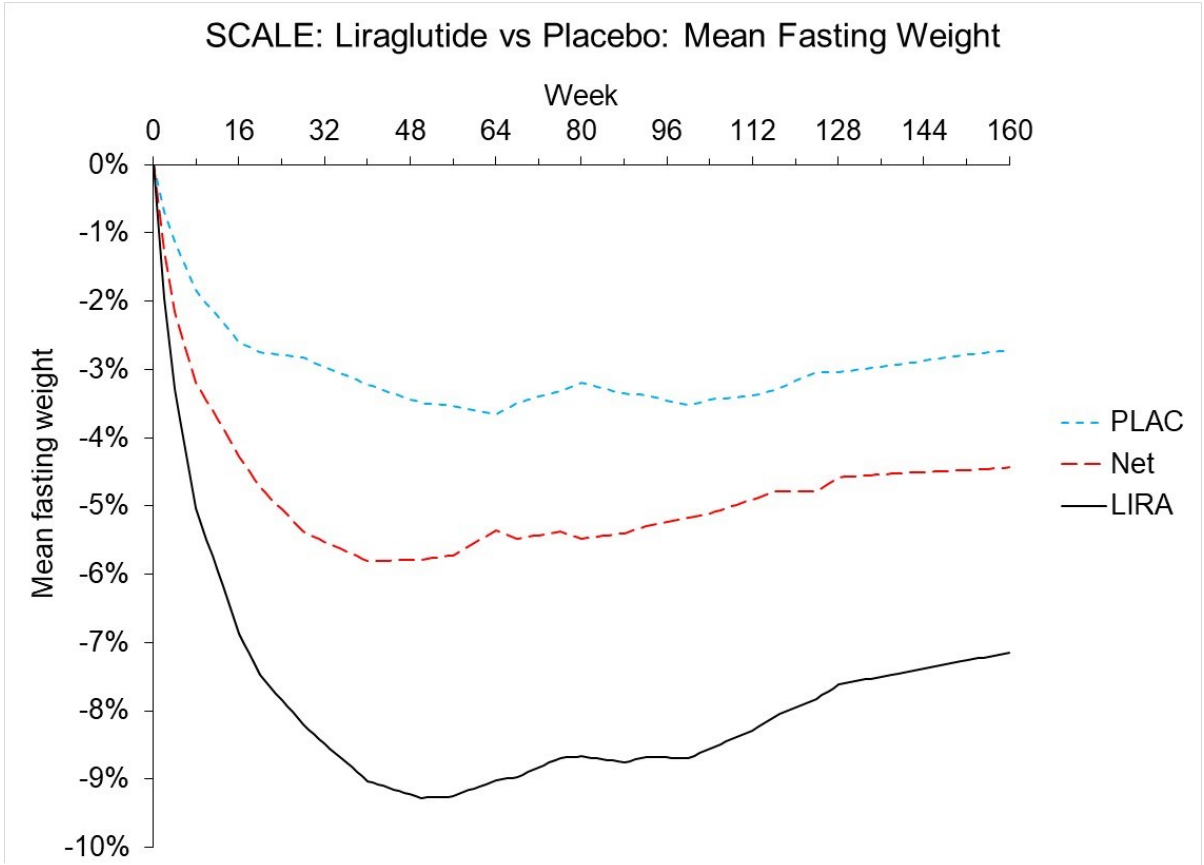
- Does the committee agree with EAG's approach of removing the net increase in weight between arms by removing the annual increase in BMI for people in the diet and exercise arm?

Key issue: Treatment effect waning in the longer term

Summary qs

EAG

- Medium term data (160 weeks) for liraglutide in a population with overweight or obesity and prediabetes indicates loss of treatment effect over time, while still on liraglutide – suggests it's possible that in this treatment class, treatment effect will wane in long term
- Given model limitations, unable to model scenarios where tirzepatide treatment effect wanes



Week	0	28	56	80	104	124	160
LIRA (N)	1,467	1,223	1,100	971	885	833	747
PLAC (N)	734	576	508	436	375	355	322

- Would long-term maintenance of weight be expected while on tirzepatide treatment?
- What is the committee's view on treatment effect waning of tirzepatide treatment?
- Should treatment effect waning be accounted for in the model?

Key issue: Weight regain after stopping treatment

Summary qs

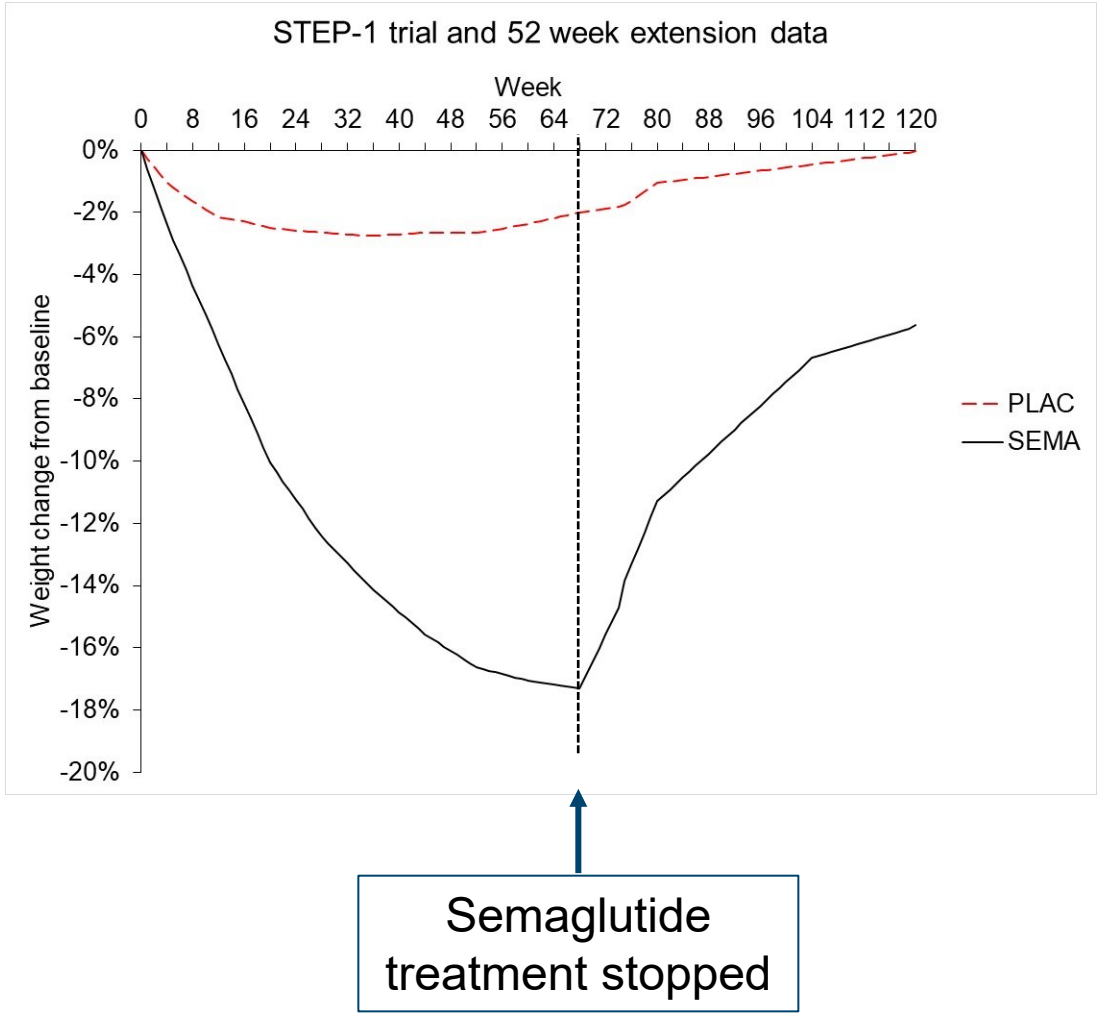
Time to weight regain is an uncertain assumption

Company

- Assumes that after tirzepatide discontinuation, weight is regained over 3 years, to equal weight in diet and exercise arm (more than baseline weight)

EAG

- SURMOUNT-4 shows stopping tirzepatide treatment after 36 weeks on treatment is associated with weight increase
- Also seen in semaglutide STEP-1 extension trial which suggests time to loss of effect after stopping treatment might be closer to 2 years
- Presents scenarios to show impact of weight regained over 2 and 4 years



- Which assumption around time to regaining weight after stopping tirzepatide is most appropriate: 2, 3 or 4 years (or other)?

Key issue: Prediabetes reversal rates

Summary qs
See appendix – slide 68

Company model assumptions:

- For active treatment arms, prediabetes reversal achieved while on treatment is lost after stopping **at end of treatment waning period (3 years after stopping)**
- For diet and exercise arm, prediabetes reversal achieved while on treatment is lost after 2 years
- Uses prediabetes reversal rates from SURMOUNT-1 (tirzepatide and diet and exercise) and TA875 (semaglutide and liraglutide)

EAG

- Different handling of prediabetes reversal for active treatments and diet and exercise arms may bias analysis favouring active treatments as active treatment arms spend longer with prediabetes reversed
- EAG cannot adjust model to retain diet and exercise arm prediabetes reversal to align with active treatment arms – instead applies net effect estimates for all parameters, so diet and exercise has no effect on weight, SBP, HDL, total cholesterol or prediabetes – indicates could be model driver if prediabetes reversal was retained in diet and exercise arm
- Placebo prediabetes reversal rates differ between tirzepatide, semaglutide and liraglutide trials – company does not adjust for placebo effect
- Conducts NMAs to take into account the placebo effect in the trials – used in scenario
  - Has limited impact on ICER when 2 year stopping rules for semaglutide and liraglutide are applied

- Is it appropriate to use EAG scenario analysis for estimating retaining pre-diabetes reversal in the model?
- Should prediabetes reversal be explicitly modelled so diet and exercise and active treatment arms are treated the same?

Key issue: Responder (>5% weight loss) rates

Summary qs

% stopping due to non-response at 6 months:

	Discontinuations	Source
LIRA	17.00%	TA875
SEMA	10.00%	Expert opinion
TIRZ 5mg	9.65%	SURMOUNT-1, 72 weeks
TIRZ 10mg	3.77%	SURMOUNT-1, 72 weeks
TIRZ 15mg	3.74%	SURMOUNT-1, 72 weeks

Which data should inform responder rates in the model for all active treatments?

EAG

- Tirzepatide responder rates based on SURMOUNT-1 72-week data applied at week 26 in the model (leading to a % discontinuing treatment). Trial shows additional gains in treatment effect between 26 and 72 weeks
- Data used from whole trial population (not target population)
- Placebo rates differ between tirzepatide, semaglutide and liraglutide trials – company does not adjust for placebo effect
- Presents scenarios using responder rates from earlier in SURMOUNT-1, responder rates from its NMA and equating semaglutide responder rate with tirzepatide 15mg in SURMOUNT-1
- Suggests exploring estimates for treatment response from earlier in SURMOUNT-1 for comparisons of tirzepatide and diet and exercise arms

Key issue: Annualisation of multi-year event risks

Summary qs

Annualising multi-year event risks adds uncertainty to the model

Company model assumptions

- 10-year risk of an event is annualised assuming a constant event rate
- Annual risks of events updated each year – as people progress, the annualised event risk increases

EAG

- After 10 years in model, the annualised 10-year risk is likely to be greater than at beginning of those 10 years – compounding annualised risks likely to result in higher 10-year risk than estimated at start of time period
- Risk of an event over 10 years is unlikely to be linear and more likely to be back-ended due to worsening health over time and development of comorbidities
- Model may estimate that events occur too early – will bias model due to patients being modelled as having events for too long and due to effects of discounting
- Model will overestimate incidence of events
- Not possible to quantify the extent of issue – but uncertainty could be explored through comparison of initial multi-year risk with modelled annualised risk for people with different baseline characteristics and people with different incidence of development of comorbidities

Would further analysis to demonstrate the level of uncertainty introduced from annualisation of multi-year event risks help inform decision making?

Summary of company and EAG base case assumption differences (1)

Assumption	Company base case	EAG base case
SWMS costs (treatment setting)	No SWMS costs; costs for GP and nurse visits and blood tests	Applies SWMS costs: £1,645 for 1st year and £698 ongoing annual cost
BMI long-term net effect difference	Long-term constant BMI on tirzepatide + increasing BMI on diet and exercise	Removes net treatment effect increase (assumes constant BMI on diet and exercise arm)
T2DM costs	£1,771 from average costs of ~74,000 NHS admissions	£674 from UK Prospective Diabetes study (representative of average of ~4 million with T2DM)
BMI mortality multiplier	Mortality multipliers for BMI + history of angina, MI and stroke	Only mortality modifiers for BMI – others covered by BMI modifier
Adverse event discontinuation	Applies ongoing annual discontinuation due to adverse events calculated from 72-week data	Mainly applying adverse event discontinuation in 1st year followed by annual 1% discontinuation rate

EAG provides 2 base cases with and without 2 year stopping rule for all treatments

= large impact on ICER (other changes have relatively minor impact on ICER individually)

Summary of company and EAG base case assumption differences (2)

Assumption	Company base case	EAG base case
NAFLD hazard ratio and incidence rate	Uses NAFLD incidence rate and hazard ratio from different literature sources with different hazard ratios	Halves NAFLD incidence rate to adjust for differences in hazard ratio across studies
OSA 5-year risk	Assumes risk of OSA for people with BMI 30 to 35 equal to general population	OSA prevalence for BMI 30 to 35 increased to reflect risk of OSA in this group
QoL functions	Soltøft et al. QoL functions to derive utilities for BMI >35 and BMI ≤35	Aligns adjusted QoL functions to avoid discontinuity in QoL function
Disutilities	Disutilities applied for obesity related complications	Removes disutilities for obesity related complications as covered by Soltøft QoL function

Plus, EAG minor changes (minor cumulative impact on ICER, see appendix - slide 74)

EAG: issues contributing to uncertainty

Assumption	Company base case	EAG comment
Issues not unquantifiable but may have impact on ICER		
Treatment effect waning	Assumes constant treatment effect over whole time horizon while on tirzepatide	Cannot adjust model to take into account long-term treatment effect waning – removes annual BMI increase for diet and exercise arm in base case
Prediabetes reversal	Assumes all diet and exercise prediabetes reversal lost between years 2 and 3	Favours active treatments. Cannot adjust model to retain prediabetes reversal - scenario applying net effect estimates for all parameters
Annualisation of multi-year event risks	10-year risk of events annualised assuming a constant rate and updated yearly	Causes model to estimate events to occur too early and therefore events last longer in model than expected
BMI mortality multipliers **(see appendix slide 70)**	As BMI increases, risk of death increases; effect doesn't change with age	Applying same mortality multiplier has greater impact for older people who are at higher risk of death
Uncertainties explored in scenario analyses		
Weight regain after stopping treatment	Weight regained over 3 years after stopping treatment	Highly uncertain how long it takes to regain weight; scenarios show moderate impact on ICER
Responder rates	72-week SURMOUNT-1 tirzepatide responder rates applied at week 26	Company doesn't adjust for placebo effect; scenarios using EAG NMA results, earlier trial results + adjusting for semaglutide responder rates

Cost-effectiveness results

vs diet and exercise

Company and EAG base case results *vs diet and exercise*

Target population: BMI ≥30 with ≥1 comorbidity

Deterministic results: EAG and company

	ICER vs diet and exercise (£/QALY)		
Technology	**Company base case**	**EAG base case including 2 year stopping rules**	**EAG base case excluding 2 year stopping rules (all active treatments)**
Tirzepatide 5 mg	11,510	21,058	33,473
Tirzepatide 10 mg	11,777	19,690	29,310
Tirzepatide 15 mg	12,792	19,563	30,570

Probabilistic results: company

	ICER vs diet and exercise (£/QALY)
Technology	**Company base case**
Tirzepatide 5 mg	11,684
Tirzepatide 10 mg	11,813
Tirzepatide 15 mg	13,203

Specialist Weight Management Service costs: EAG scenario analyses vs *diet and exercise*, with and without stopping rules

	Target population: BMI ≥30 with ≥1 comorbidity (deterministic)	ICER vs diet and exercise (£/QALY)		
SA No.	**Scenario**	**Tirzepatide 5mg**	**Tirzepatide 10mg**	**Tirzepatide 15mg**
EAG base case 1 (with stopping rules for all active treatments)		21,058	19,690	19,563
SA10a	Removing all SWMS costs	12,946	12,766	13,228
SA10b	Removing SWMS costs for diet and exercise	30,321	26,994	26,267
SA10c	Removing SWMS costs for tirzepatide and diet and exercise	12,907	12,735	13,200
EAG base case 2 (with no stopping rules)		33,473	29,310	30,570
SA10a	Removing all SWMS costs	20,022	18,599	20,361
SA10b	Removing SWMS costs for diet and exercise	35,196	30,582	31,788
SA10c	Removing SWMS costs for tirzepatide and diet and exercise	20,014	18,593	20,356

Dom = dominant

Cost-effectiveness results

ICERs including confidential discounts for comparators are included in part 2 slides, including:

Company target population:

- Company base case (vs semaglutide)
- EAG base case with and without stopping rules for all treatments (fully incremental and vs semaglutide)
- EAG scenario analyses on ‘no stopping rules’ base case (vs semaglutide)
- EAG scenario analyses on ‘with stopping rules’ base case (vs semaglutide)
  - See appendix slide 75 for list of scenarios

Liraglutide eligible population:

- Company base case (vs semaglutide and vs liraglutide)
- EAG base case with and without stopping rules for all treatments (fully incremental, vs semaglutide and vs liraglutide)

Summary of questions for committee (1)

Population

- Is the restriction to the company's target population appropriate (BMI ≥30 + ≥1 weight-related comorbidity)?
  - Which comorbidities are appropriate to include within this definition?
- Should subgroups according to risk be considered (i.e. liraglutide eligible population = higher risk subgroup)?

Setting

- Which treatment setting is SURMOUNT-1 generalisable to?
- What is the appropriate setting for tirzepatide use and therefore which treatment setting associated costs should be included?

Comparators

- What is the appropriate comparator for tirzepatide given the treatment setting?

SURMOUNT-1 tirzepatide dose generalisability

- Would the highest tolerated dose of tirzepatide be used in clinical practice?
- Is the dose escalation and de-escalation used in the trial generalisable to clinical practice?

Summary of questions for committee (2)

Initial model baseline characteristics

- How would the ICER be impacted if comorbidities and complications which were model events were included for the population entering the model?

Stopping rules

- Would patients and clinicians want to use tirzepatide long-term, and if so, how long?
- Is it appropriate to apply a 2-year stopping rule for tirzepatide, semaglutide and liraglutide treatment?

Adjusting for net increase in tirzepatide treatment effect over time

- Is the EAG' approach to removing the net increase in weight between arms by adjusting the diet and exercise arm appropriate?

Treatment effect waning

- Efficacy data only available for 72 weeks
  - Would long-term maintenance of weight be expected while on tirzepatide treatment?

Time to weight regain after stopping treatment

- What assumption around time to regaining weight after stopping treatment is appropriate?

Prediabetes reversal

- How should uncertainties around prediabetes reversal timings across arms be addressed?

Responder rates (>5% weight loss after 6 months) and subsequent stopping for non-responders

- Which data should inform responder rates in the model?

Annualisation of multi-year event risks

- Would further analysis to demonstrate the level of uncertainty introduced from annualisation of multi-year event risks help inform decision making?

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Thank you.

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Supplementary appendix

Abbreviations and units

ASCVD: atherosclerotic cardiovascular disease

BMI: body mass index

CfB: change from baseline

CV(D): cardiovascular (disease)

GI: gastrointestinal

HDL: high-density lipoprotein

HRQoL: health-related quality of life

ICER: incremental cost effectiveness ratio

MDT: multi-disciplinary team

MI: myocardial infarction

NAFLD: non-alcoholic fatty liver disease

NMA: network meta-analysis

OSA: obstructive sleep apnoea

QoL: quality of life

QW: once weekly

RCT: randomised controlled trial

SBP: systolic blood pressure

SD: standard deviation

SE: standard error

SmPC: summary of product characteristics

SWMS: specialist weight management service

T2DM: type 2 diabetes mellitus

TEAE: treatment emergent adverse events

UKPDS: UK Prospective Diabetes Study

All BMI measures are in mg/kg^2

= model driver

= impact on model not quantified

Background on overweight and obesity

Other NICE guidance (not exhaustive):

- Clinical guideline:
  - Obesity: identification, assessment and management (CG189)
- Technology appraisals:
  - Liraglutide for managing overweight and obesity (TA664)
  - Semaglutide for managing overweight and obesity (TA875)

Diagnosis and classification

- CG189 defines overweight and obesity according to BMI:
  - Overweight: BMI 25 kg/m^2 to 29.9 kg/m^2
  - Obesity class 1: BMI 30 kg/m^2 to 34.9 kg/m^2
  - Obesity class 2: BMI 35 kg/m^2 to 39.9 kg/m^2
  - Obesity class 3: BMI 40 kg/m^2 or more

Current management

Care for overweight and obesity is through a tier-based system

- **Tier 1:** universal services – population level health promotion and advice
- **Tier 2:** community-based diet, nutrition, lifestyle and behaviour change advice (for 12 weeks)
- **Specialist weight management services** - including but not limited to **tier 3** and **tier 4:** specialist primary, community or secondary care-based multidisciplinary team offering a combination of surgical, dietetic, pharmacological (such as semaglutide and liraglutide) and psychological obesity management interventions; accessed for up to 2 years

NICE clinical guideline 189 recommends referral to tier 3 services if:

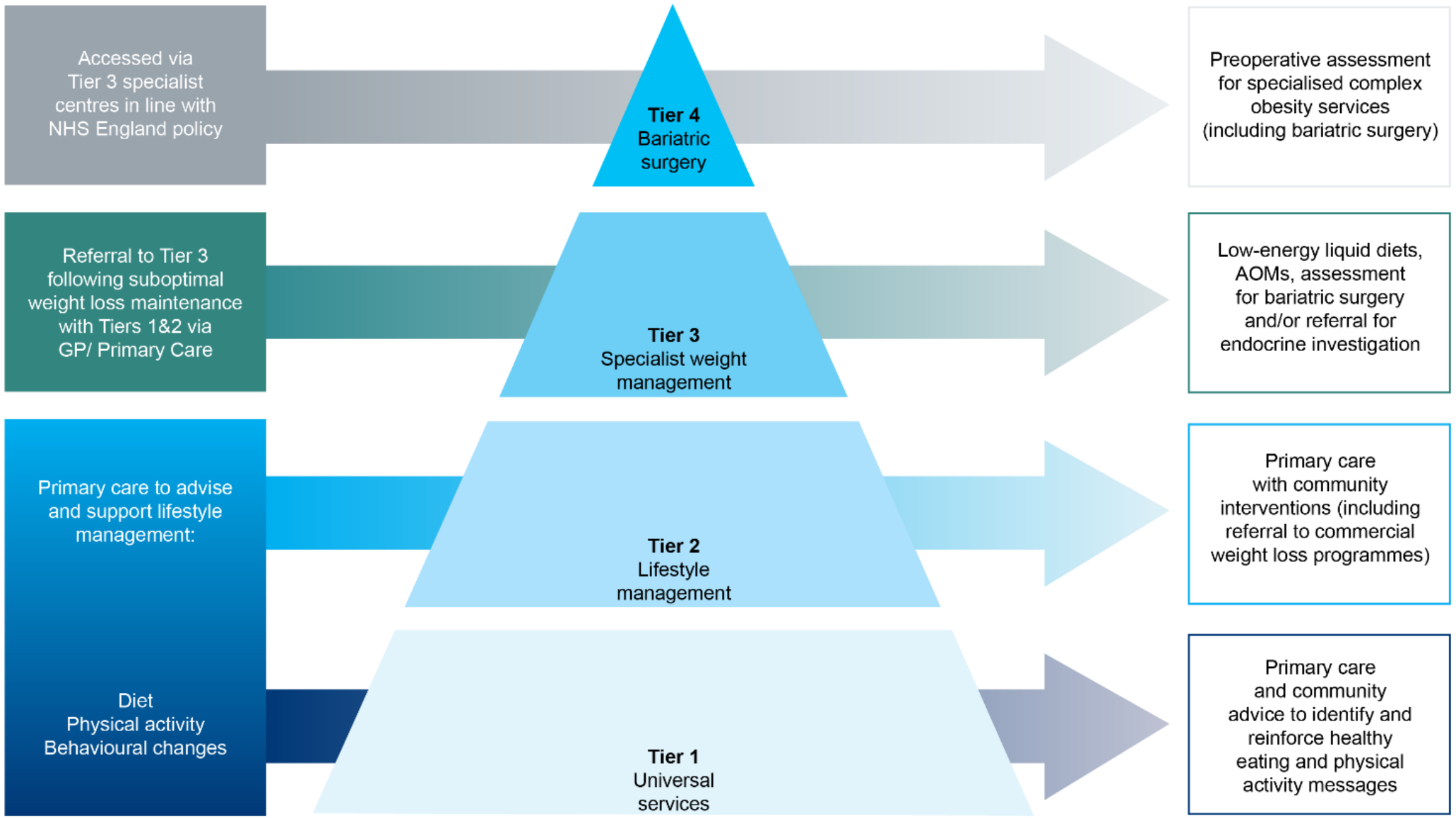
- the underlying causes of overweight or obesity need to be assessed
- the person has complex disease states or needs that cannot be managed adequately in tier 2 (for example, the additional support needs of people with learning disabilities)
- conventional treatment has been unsuccessful
- drug treatment is being considered for a person with a BMI of more than 50
- specialist interventions (such as a very-low-calorie diet) may be needed
- surgery is being considered

NICE public health guideline 53 recommends that lifestyle weight management services (‘usually called tier 2 services’) are commissioned so that they are:

- Multi-component (diet, exercise and behaviour change)
- Developed by a MDT including dietician, psychologist and physical activity instructor
- Last at least 3 months, with sessions offered at least weekly or fortnightly

Current management

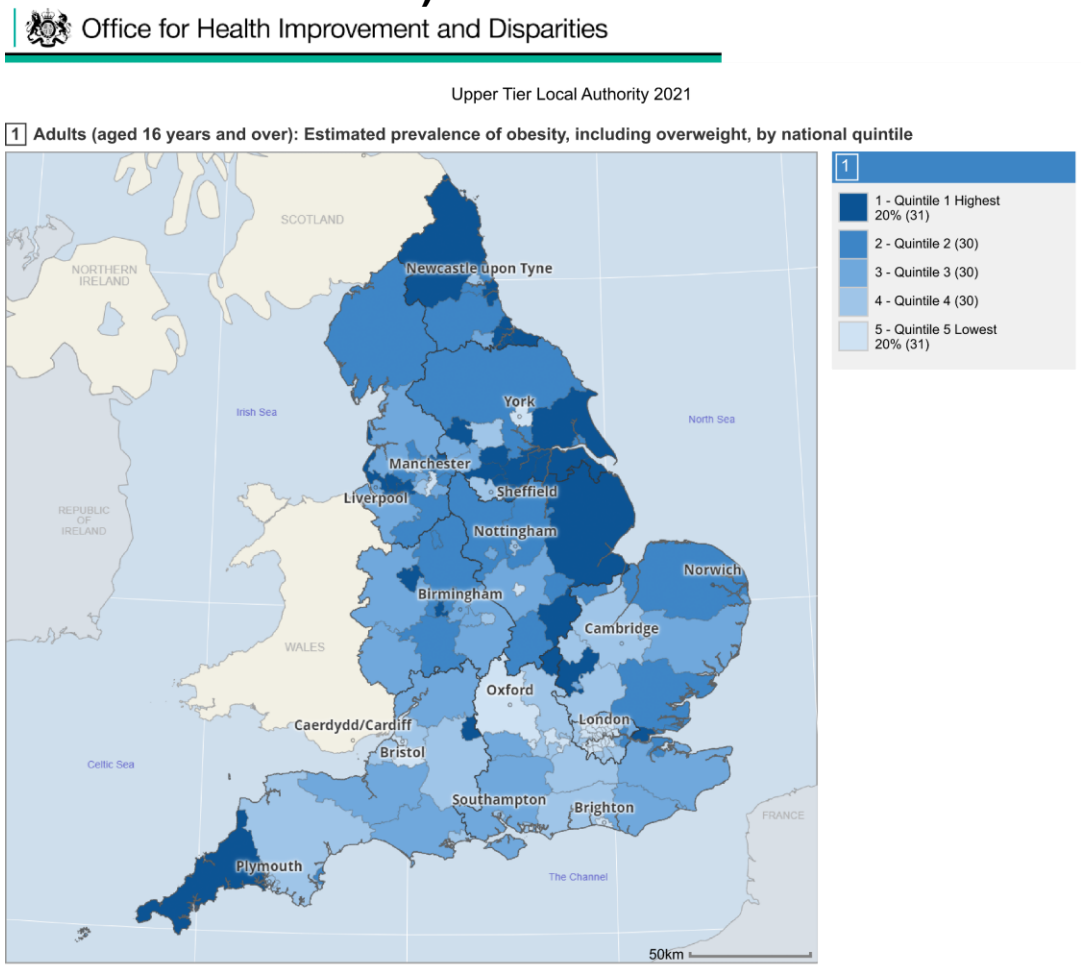
Care for overweight and obesity is through a tier-based system

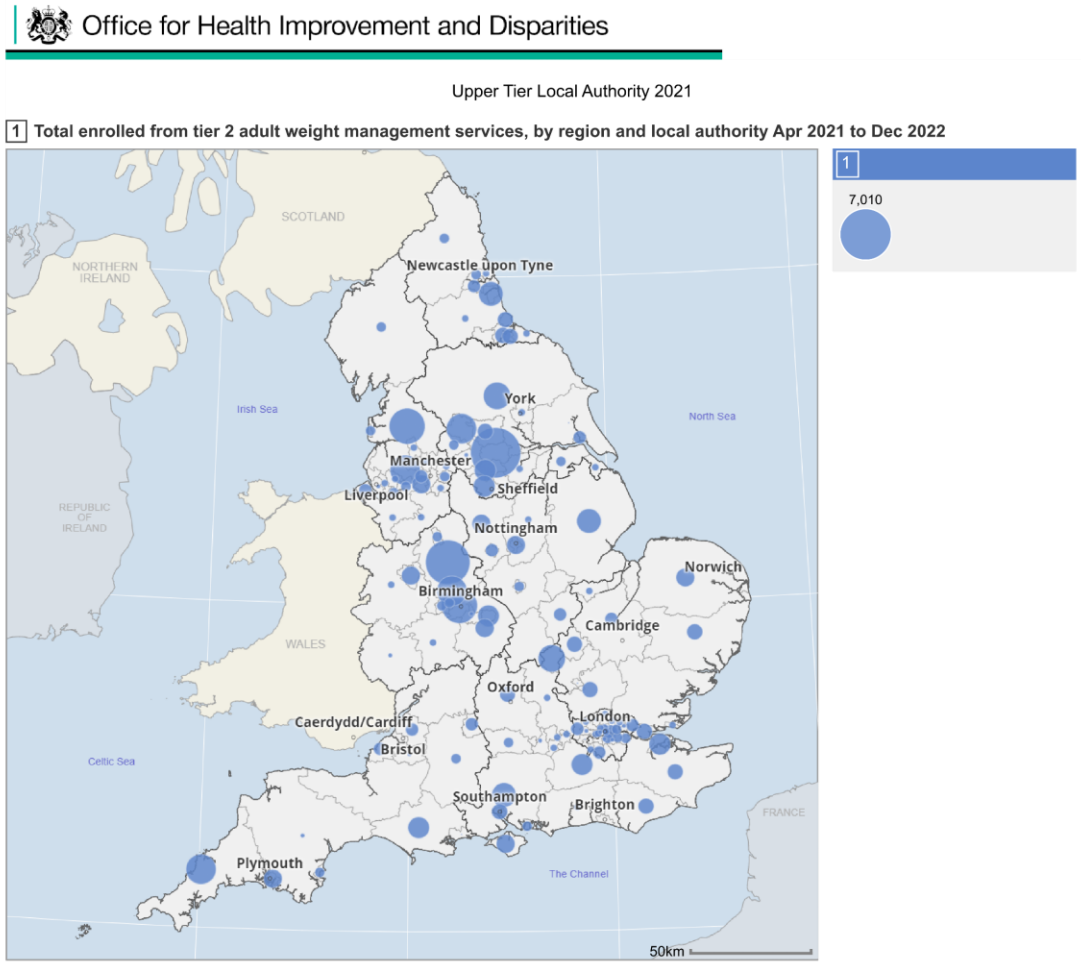


Inequity in treatment access

Distribution of tier 2 services by region and prevalence of overweight and obesity by region

Office for Health Improvement and disparities: estimated prevalence of overweight and obesity by national quantile, 2014 and adult tier 2 weight management services final data for April 2021 to December 2022 (experimental statistics):





Tirzepatide (Mounjaro, Eli Lilly)

Technology details

Marketing authorisation (November 2023)	For weight management, including weight loss and weight maintenance, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial BMI of: • ≥30 (obesity), or • ≥27 to <30 (overweight) in presence of at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidaemia, OSA, CVD, prediabetes, or T2DM)
Related indication (NICE TA924)	Treatment of adults with insufficiently controlled T2DM: • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes
Administration	Subcutaneous injection once weekly, using a pre-filled pen device Initiation: 2.5 mg once weekly; maintenance (after 4 weeks): 5mg once weekly; if needed, dose can be increased in 2.5 mg increments every 4 weeks up to 15 mg
Price	List price for 4-week supply: • 5 mg: £92.00 • 10 mg: £107.00 • 15 mg: £122.00

Mechanism of action

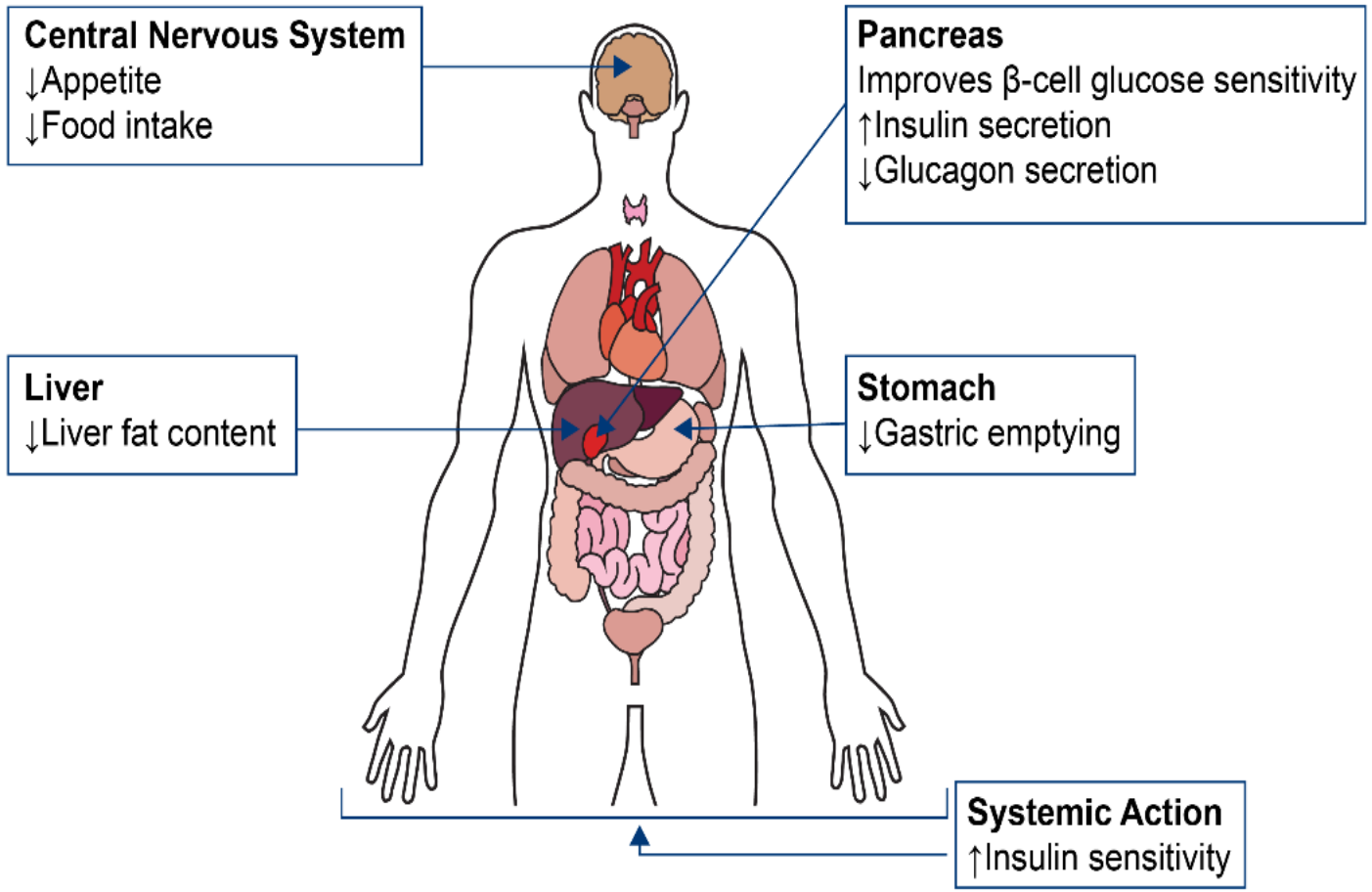
Tirzepatide has an additional mechanism of action to semaglutide

Both tirzepatide and semaglutide:

- act in brain to reduce appetite
- delay gastric emptying
- stimulate insulin secretion
- controls glucagon secretion

- **Tirzepatide** is a GLP-1 **and** GIP receptor (dual) agonist
- **Semaglutide** is a GLP-1 receptor agonist

Tirzepatide mechanism of action:



Comparators

NICE technology appraisals recommend semaglutide and liraglutide

Drug	Recommended alongside reduced-calorie diet and increased physical activity, only if:

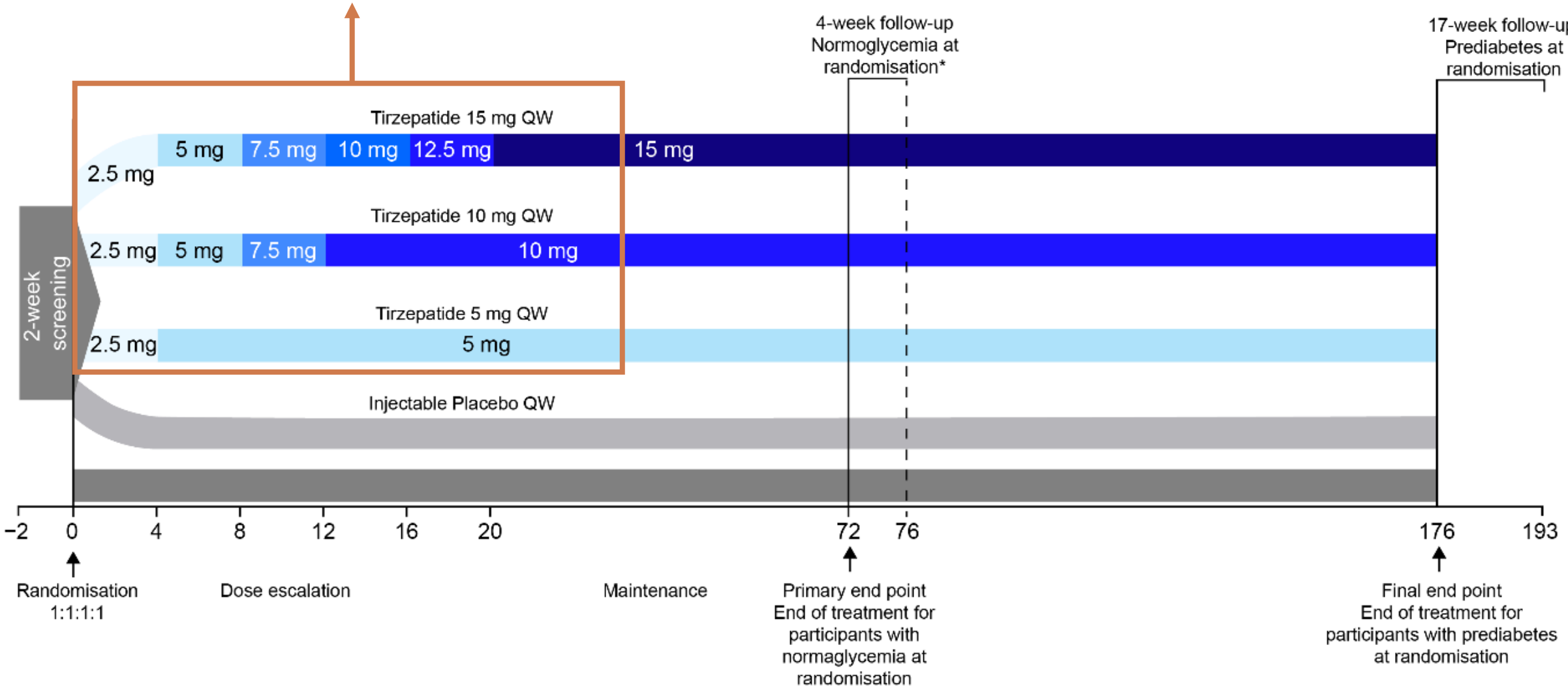
Semaglutide (TA875)	• used for a maximum of 2 years, and within a specialist weight management service providing multidisciplinary management of overweight or obesity (including but not limited to tiers 3 and 4) and
	• they have at least 1 weight-related comorbidity and:
	  • BMI of at least 35.0, or
	  • BMI of 30.0 to 34.9 and meet the criteria for referral to specialist weight management services in NICE's guideline on obesity: identification, assessment and management (CG189)

Liraglutide (TA664)	• they have a BMI of at least 35 and, • have non-diabetic hyperglycaemia and, • have high risk of cardiovascular disease based on risk factors such as hypertension and dyslipidaemia and, • it is prescribed in secondary care by a specialist multidisciplinary tier 3 weight management service

Lower BMI thresholds used for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds

SURMOUNT-1 study design

Different dose escalation periods across arms



Clinical results: SURMOUNT 1, people with BMI ≥30 with ≥1 comorbidity*

* Company's targeted and modelled population

Tirzepatide more effective than placebo at 5, 10 and 15mg doses in target population at 72 weeks

Outcome (at 72 weeks)	Placebo (n= [redacted] †)	Tirzepatide 5mg (n= [redacted] †)	Tirzepatide 10mg (n= [redacted] †)	Tirzepatide 15mg (n= [redacted] †)
Mean % change in body weight from baseline at 72 weeks (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Change in BMI from placebo (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in total cholesterol from baseline at 72 weeks, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in systolic blood pressure from baseline at 72 weeks, mmHg (SE)	[redacted]	[redacted]	[redacted]	[redacted]

† unless otherwise stated

Clinical results: SURMOUNT 1, people with BMI ≥30 with ≥1 comorbidity*

* Company's targeted and modelled population

Patient Global Impression of Severity (PGIS) Physical Activity pre- and post-baseline, excluding people lost to follow up

Clinical results: SURMOUNT 1, people with BMI ≥30 with ≥1 comorbidity*

* Company's targeted and modelled population

Patient Global Impression of Severity (PGIS) Physical Activity pre- and post-baseline, excluding people lost to follow up

SURMOUNT 1 clinical effectiveness results (population: BMI ≥35 with prediabetes and high CVD risk)

Tirzepatide more effective than placebo at 5, 10 and 15mg doses in population currently offered liraglutide

Outcome	Placebo (n=[redacted])	Tirzepatide 5mg (n=[redacted])	Tirzepatide 10mg (n=[redacted])	Tirzepatide 15mg (n=[redacted])
Mean % change in body weight from baseline at 72 weeks (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in HDL cholesterol from baseline at 72 weeks, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in total cholesterol from baseline at 72 weeks, mg/dL (SE)	[redacted]	[redacted]	[redacted]	[redacted]
Mean change in systolic blood pressure from baseline at 72 weeks, mmHg (SE)	[redacted]	[redacted]	[redacted]	[redacted]

SURMOUNT 1 adverse events results (full trial population)

Tirzepatide is associated with more adverse events than placebo – most related to gastrointestinal system

Outcome	Placebo (n=643)	Tirzepatide 5mg (n=630)	Tirzepatide 10mg (n=636)	Tirzepatide 15mg (n=630)
Number (%) with ≥1 GI related TEAE	195 (30.3)	350 (55.6)	387 (60.8)	373 (59.2)
Number (%) with nausea	61 (9.5)	155 (24.6)	212 (33.3)	195 (31.0)
Number (%) with diarrhoea	47 (7.3)	118 (18.7)	135 (21.2)	145 (23.0)
Number (%) with adverse event leading to discontinuation	21 (3.3)	30 (4.8)	46 (7.2)	40 (6.3)

Most treatment emergent adverse events (7/13) were related to GI system (nausea and diarrhoea most common) - more common in tirzepatide groups than placebo

SURMOUNT 1 EQ-5D-5L: full trial population

Outcome	Placebo (n=473)	Tirzepatide 5mg (n=537)	Tirzepatide 10mg (n=532)	Tirzepatide 15mg (n=523)
Baseline	0.85	0.85	0.84	0.85
Change from baseline at 72 weeks	0.02	0.04	0.05	0.07
Change difference from placebo at 72 weeks (95% CI)	N/A	0.03 (0.01, 0.04)	0.03 (0.01, 0.05)	0.05 (0.03, 0.06)

Comparator key clinical trials

	STEP-1	SCALE Obesity and Prediabetes
Design	Placebo-controlled double blind RCT	
Population	Adults with obesity (BMI ≥30), or overweight (BMI ≥27) plus 1 weight related co-morbidity (hypertension, dyslipidaemia, OSA, CVD)	Adults with obesity (BMI ≥30), or overweight (BMI ≥27) plus dyslipidaemia or hypertension
	Excluded people with T2DM	
Intervention	Semaglutide once weekly, adjunct to reduced-calorie diet and increased physical activity*	Liraglutide once daily, adjunct to reduced-calorie diet and increased physical activity
Comparator	Placebo plus reduced-calorie diet and increased physical activity	
Duration	68 weeks	56 weeks
Primary outcomes	• % change in weight from baseline to end of study • % achieving ≥5% weight reduction from baseline to end of study	

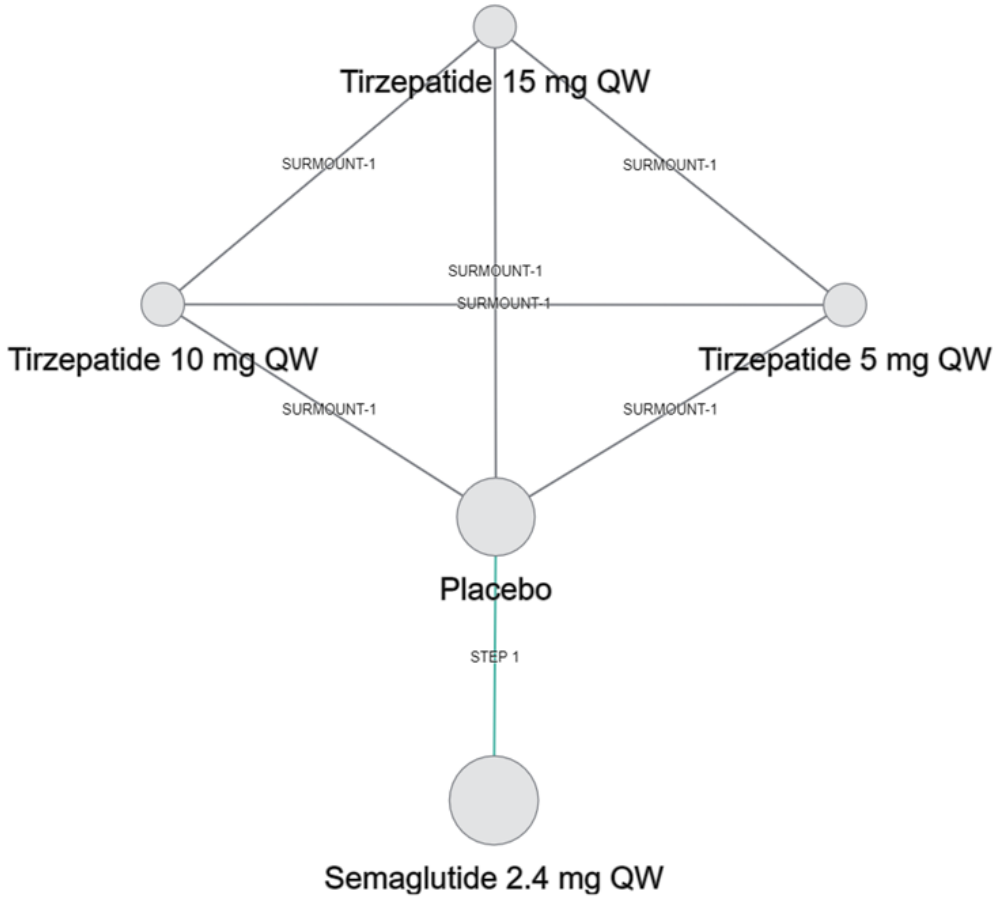
*lifestyle intervention included counselling throughout 52-week trial period

NMA details

NMA details	
Methods	Bayesian approach; fixed effect unadjusted model results used in economic model
Population*	• Target population: BMI ≥30 + ≥1 weight-related comorbidity (**used in economic model**; 2 RCTs) • Whole trial population (6 RCTs) • Liraglutide eligible population: BMI ≥35, prediabetes + high CVD risk • All participants ≥18 years with no diabetes
Outcomes	Mean % change from baseline in: weight, HDL, SBP, and total cholesterol

*NMAs for BMI ≥35 and BMI ≥30 (irrespective of comorbidities) not conducted as only head-to-head evidence for these comparisons were from SURMOUNT-1

NMA network diagram for target population: BMI ≥30 + ≥1 weight-related comorbidity



EAG:
- Additionally conducted NMAs for reversal of prediabetes (whole trial and target population) and achieving a minimum of 5% weight loss at 6 months (whole trial population)

NMA methodology:

NMA shows heterogeneity which impacts certainty in clinical effectiveness results used in the model

EAG

- Company's overall approach for assessing feasibility appropriate
- I^2 values (45 to 72%) for the whole trial population indicate moderate to substantial heterogeneity; but about 20% across 4 NMAs based on targeted subgroup
- Heterogeneity may stem from differences in outcome definitions (change in HDL and total cholesterol reported either as absolute, percentage or ratio change) and diversity in geographic region within and between studies
- Particular uncertainty around HDL and total cholesterol (used in risk equations)

Company NMA results overview: BMI ≥30 with ≥1 comorbidity (1)

Change from baseline in weight (%) for tirzepatide 15mg (reference) compared with other active treatments and diet and exercise alone:

Change from baseline in HDL (%) for tirzepatide 15mg (reference) compared with other active treatments and diet and exercise alone:

Company NMA results overview: BMI ≥30 with ≥1 comorbidity (2)

Change from baseline in total cholesterol for tirzepatide 15mg (reference) compared with other active treatments and diet and exercise alone:

Change from baseline in systolic blood pressure for tirzepatide 15mg (reference) compared with other active treatments and diet and exercise alone:

EAG NMA results overview: BMI ≥30 with ≥1 comorbidity (2)

% difference in prediabetes reversal compared with diet and exercise alone:

% difference in minimum 5% weight loss after 6 months compared with diet and exercise alone:

NMA results: change from baseline vs placebo

Results indicate statically significant improvement in treatment effect for all active treatments compared with placebo in BMI ≥30 + ≥1 weight-related comorbidity population

Outcome (mean difference)	N trials	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 2.4 mg
% CfB in weight (95% CrI)	2	[redacted]	[redacted]	[redacted]	[redacted]
% CfB in HDL (95% CrI)	2	[redacted]	[redacted]	[redacted]	[redacted]
% CfB in total cholesterol (95% CrI)	2	[redacted]	[redacted]	[redacted]	[redacted]
% CfB in SBP, mmHg (95% CrI)	2	[redacted]	[redacted]	[redacted]	[redacted]
Reference treatment = placebo					

EAG

- Statistical and outcome heterogeneity across studies present – particularly for change in HDL and total cholesterol (used in risk equations) – adds uncertainty to model inputs for these outcomes

NMA results: BMI ≥30 with ≥1 weight-related comorbidity

Tirzepatide 10 and 15mg more effective than semaglutide for weight loss

Mean % weight change from baseline weight loss

		Comparator				Absolute CfB in Weight (%)
		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 2.4 mg	
Reference	Tirzepatide 5 mg					[redacted]
	Tirzepatide 10 mg	[redacted]				[redacted]
	Tirzepatide 15 mg	[redacted]	[redacted]			[redacted]
	Semaglutide 2.4 mg	[redacted]	[redacted]	[redacted]		[redacted]
	Diet and exercise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Lower doses of tirzepatide statistically significantly less effective than higher doses
- Tirzepatide 5mg less effective than semaglutide (no statistically significant difference)
- 10mg and 15mg tirzepatide statistically significantly more effective than semaglutide; all doses of tirzepatide and semaglutide statistically significantly more effective than diet and exercise

NMA results: BMI ≥30 with ≥1 weight-related comorbidity

Tirzepatide (all doses) more effective than semaglutide for HDL increase

Mean % change from baseline HDL level

		Comparator				Absolute CfB in HDL (%)
		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 2.4 mg	
Reference	Tirzepatide 5 mg					[redacted]
	Tirzepatide 10 mg	[redacted]				[redacted]
	Tirzepatide 15 mg	[redacted]	[redacted]			[redacted]
	Semaglutide 2.4 mg	[redacted]	[redacted]	[redacted]		[redacted]
	Diet and exercise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Lower doses of tirzepatide less effective than higher doses (no statistically significant difference)
- All tirzepatide doses statistically significantly more effective than semaglutide; all doses of tirzepatide and semaglutide statistically significantly more effective than diet and exercise

NMA results: BMI ≥30 with ≥1 weight-related comorbidity

No significant difference in change in total cholesterol between tirzepatide and semaglutide

Mean % change from baseline total cholesterol

		Comparator				Absolute CfB in Total Cholesterol (%)
		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 2.4 mg	
Reference	Tirzepatide 5 mg					[redacted]
	Tirzepatide 10 mg	[redacted]				[redacted]
	Tirzepatide 15 mg	[redacted]	[redacted]			[redacted]
	Semaglutide 2.4 mg	[redacted]	[redacted]	[redacted]		[redacted]
	Diet and exercise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Tirzepatide 5mg less effective than tirzepatide 10mg (no statistically significant difference)
- Tirzepatide 5 and 10mg less effective than tirzepatide 15mg
- Tirzepatide 5 and 10mg less effective than semaglutide (no statistically significant difference)
- Tirzepatide 15mg more effective than semaglutide (no statistically significant difference)
- All doses of tirzepatide and semaglutide statistically significantly more effective than diet and exercise

NMA results: BMI ≥30 with ≥1 weight-related comorbidity

No significant difference in change in SBP between tirzepatide and semaglutide

Mean change from baseline systolic blood pressure

		Comparator				Absolute CfB in SBP (mmHg)
		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 2.4 mg	
Reference	Tirzepatide 5 mg					[redacted]
	Tirzepatide 10 mg	[redacted]				[redacted]
	Tirzepatide 15 mg	[redacted]	[redacted]			[redacted]
	Semaglutide 2.4 mg	[redacted]	[redacted]	[redacted]		[redacted]
	Diet and exercise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- Tirzepatide 5mg less effective than semaglutide (no statistically significant difference)
- Tirzepatide 10 and 15mg more effective than semaglutide (no statistically significant difference)
- All doses of tirzepatide and semaglutide statistically significantly more effective than diet and exercise

How company incorporated evidence into model

Input	Assumption and evidence source
Intervention + comparator efficacy	• CfB in weight, SBP, HDL, total cholesterol informed by NMA - used in risk equations to determine incidence of clinical events and comorbidities • Reversal of pre-diabetes from SUMOUNT-1 for placebo and tirzepatide and TA875 for semaglutide and liraglutide • Beyond trial data, assumed that on treatment endpoints remain constant until discontinuation
Utilities	• Health Survey for England EQ5D data reporting QoL according to BMI from Soltøft et al. (BMI ≤35); logarithmic function to derive utilities for people with BMI >35 • Adverse events disutility of -0.04 applied • Clinical comorbidity and event disutilities applied

Discontinuation	• Diet and exercise arm: weight loss and clinical effects reversed at week 72
	• Active treatments:
	  • discontinuation after 6 months due to lack of response - from trial data or expert opinion
	  • discontinuation due to adverse events - from trial data
	  • discontinuation due to stopping rule: 2 years for semaglutide and liraglutide; none for tirzepatide
	• Loss of treatment effect assumed 3 years after discontinuation

Further detail on key issues

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EAG applied specialist weight management service costs

EAG

- Applies SWMS costs in base case, as shown below
- Difficult to have precise results given varied nature of individuals in SWMS
- Resource use based on single clinical expert opinion

Breakdown of EAG SWMS costs			
Resource	**Visits year 1**	**Visits year 2+**	**Cost per visit**
Consultant	3	2	Consultant led Dietetics Service non-admitted face-to-face OP cost: £152.14
Psychologist	3	0	
Dietician	8	4	Non-consultant led Dietetics Service non-admitted face-to-face OP cost: £98.43
Total cost	£1,645	£698	

Cost of diabetes

Avoiding diabetes and associated costs is one of the main cost offsets in the model

Company model assumptions

- Annual cost of T2DM without complications is £1,771
- Uses average NHS reference costs for diabetes with hypoglycaemic disorders from ~74,000 hospital attendees - includes elective/non-elective long stay, non-elective short stay, day case, regular admissions

EAG

- Company costs only taken from ~74,000 people when UK prevalence of T2DM ~4 million – over-estimates average costs
- Prefers to take annual cost of T2DM from UKPDS (Alva et al. 2014): £674 per year
- Doesn't account for more expensive care for end-stage renal disease, dialysis and transplant – but in model, patients are recently diagnosed T2DM and complications are modelled separately
- Annual inpatient and non-hospital cost for T2DM and no comorbidities is £1,064 – but not net cost compared with person with obesity. EAG assumes inpatient costs similar for obesity and T2DM without comorbidities and uses UKPDS estimate (£674) in base case
- Provides scenarios using cost of £1,064 and £1,612 (including direct drug treatment costs)
- Avoidance of dialysis not included in model, which may be uncaptured benefit

Prediabetes reversal

EAG: prediabetes reversed at 2 years in diet and exercise arm and at end of 3-year loss of treatment effect after stopping in active treatment arms

Minor issues & issues not quantified but may have impact on cost-effectiveness

- BMI mortality modifiers – slide 56
- Stopping treatment due to adverse events – slide 57

BMI mortality multipliers

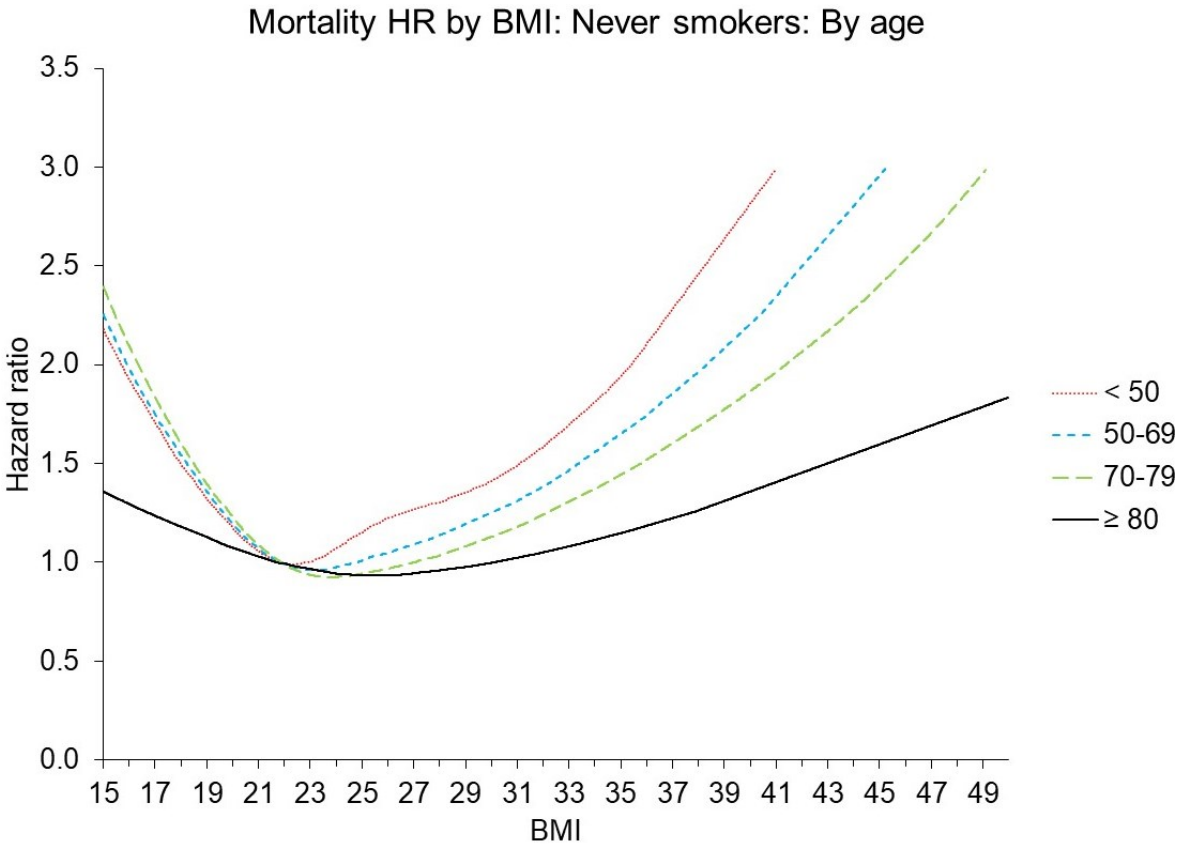
Lack of age specific BMI mortality multipliers adds to model uncertainty

Company model assumption

- Mortality multiplier: as BMI increases (above ~25), the risk of death increases
- Multiplicative effect of BMI upon mortality does not change with age

EAG

- Evidence that association between BMI and mortality stronger when younger
- General population mortality risk increases strongly with age – so applying same mortality multiplier has greater impact for older people
- Increases model uncertainty – unable to quantify effect without age specific BMI mortality multiplier



Bhaskaran et al. 2018

Stopping treatment due to adverse events

N (%)	Placebo	Tirzepatide 5mg	Tirzepatide 10mg	Tirzepatide 15mg
Discontinuation from SURMOUNT-1 due to adverse events	21 (3.3)	30 (4.8)	46 (7.2)	40 (6.3)

EAG

- Company applies ongoing annual discontinuation due to adverse events probabilities calculated from the 72-week data on discontinuation due to adverse events from SURMOUNT-1
- But data shows that adverse event rates fall as time progresses - so not appropriate to apply annualised 72-week data to each subsequent year in the model
- Uncertainty in whether adverse events ongoing or largely occurred the first year with few thereafter
- Issue not important when 2-year stopping rule included – but is if treatment continues for longer in model
- EAG cannot apply 1 year discontinuation rates followed by annual 1% discontinuation rates for all treatments due to model limitations
  - Instead, EAG adds the 1-year discontinuation rates for tirzepatide to primary treatment failure rates, assumes semaglutide has same discontinuation rate as tirzepatide 15 mg, add 9% discontinuation rate to primary treatment failure for liraglutide and assume a common 1% annual discontinuation rate for all treatments thereafter

Other issues arising from EAG report which contribute to model uncertainty

- BMI mortality multipliers pooled for those with BMI ≥40 – people who stay above BMI 40 throughout the model experience no changes in mortality effects from changes in BMI
- SURMOUNT-1 baseline prevalence of ASCVD, OSA and NAFLD not reflected in baseline population entering model – likely to bias in favour of more effective treatments
- Mean trial weight loss (including outcomes for responders and non-responders) assumed for all responders – underestimates effect for responders - the higher the rate of non-responders, the higher the bias – so likely to bias in favour of higher doses of tirzepatide

Further (minor) questions for committee

- Double counting of mortality multipliers – additional mortality multipliers not required if BMI mortality multipliers reliable: EAG only applies BMI mortality multipliers in base case
    - **Is EAG's approach to using only BMI mortality multiplier and removing history of angina, MI and stroke mortality multiplier appropriate?**
- Annualised adverse events data from up to week 72 in clinical trial used as annual adverse event rate in subsequent years – EAG amends model to account for fewer adverse events in later years
    - **Is EAG's approach using 1% discontinuation rate due to adverse events after year 1 appropriate?**
- Company used NAFLD incidence data and hazard ratio from different literature sources – EAG prefers to use same source due to differences between reported hazard functions
    - **Is EAG's approach to account for differences in hazards (adjusting NAFLD incidence rate) appropriate?**
- Company assumes risk of OSA for people with BMI 30 to 35 is in line with general population – EAG uses a prevalence of OSA of 2.85% (from UK CPRD) for people with BMI 30 to 35
    - **Is EAG's approach to increasing the rate of OSA in people with BMI 30 to 35 appropriate?**
- Company uses functions from Soltøft et al. to estimate utilities for those with BMI <35 and BMI ≥35. Functions suggest better QoL as BMI increases beyond 39 for men and 46.5 for women and worse QoL when BMI falls from 35 to below 32.2 (men) and 33 (women) – biases analysis against more effective treatment
    - **Is EAG's approach to reduce QoL functions to align with SURMOUNT-1 EQ5D data appropriate?**
- Company applies disutilities for obesity related complications; EAG removes as included in Soltøft QoL function
    - **Is EAG's approach to removing these appropriate?**

EAG minor amendments

EAG minor amendments to model
Correcting T2DM disutility during initial 4 weekly cycles
Correcting model error identified by company at clarification
Revising NAFLD mortality hazard ratio to 1.71
Equalising semaglutide rate of severe and serious GI events to tirzepatide 15mg
Only applying severe and serious GI rates once
Revising annual NAFLD cost to £952
Semaglutide response assessment at 42 weeks

Total cumulative impact on pairwise ICER:		
	vs semaglutide	**vs diet and exercise**
Tirzepatide 15mg	+129	+£223
Tirzepatide 10mg	-£46	+109
Tirzepatide 5mg	+12	+123

List of EAG scenarios on EAG base cases

EAG scenarios	
2-year stopping rule for semaglutide and liraglutide only (none for tirzepatide)	Plus, combined scenarios to reflect if semaglutide and liraglutide used in SWMS for 2-years and tirzepatide used outside SWMS long-term
Removing SWMS costs for tirzepatide but not for semaglutide or liraglutide	
Removing SWMS costs for: (1) all arms; (2) for diet and exercise arm only; (3) for diet and exercise and tirzepatide arm	
Re-applying company mortality multipliers for history of angina, MI + stroke	
Alternative source of BMI mortality multiplier (Aune et al)	
Tirzepatide responder rates taken from trial at ~6 months of treatment	
EAG NMA results for responder rates	Plus, combined scenario
EAG NMA results for prediabetes reversal	
Semaglutide down titration equal to tirzepatide 15 mg	
Net effects relative to placebo (to mimic retaining prediabetes reversal in diet and exercise arm after 72 weeks)	
Re-applying company NAFLD incidence assumption	
Different costs for (1) T2DM and (2) NAFLD	
Loss of effect after stopping tirzepatide over (1) 2 years and (2) over 4 years	