Tirzepatide for the treatment of patients with type 2 diabetes

Slides for the public – contains no ACIC or CPAS information

Technology appraisal committee A [6th June 2023]

Chair: Radha Todd

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External assessment group: Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University Medical Center (UMC+)

Technical team: Janet Boadu, Ewa Rupniewska, Janet Robertson

Company: Eli Lilly

Key issues (1)

Submissions

- Company (Eli Lilly)
- Diabetes UK

No technical engagement
(but ACM delayed by 1 month to allow company to address issues raised by EAG)

Decision problem and clinical effectiveness evidence

Issues
Mismatch between scope and decision problem: line of therapy and comparators
Network meta-analysis at high risk of bias due to lack of feasibility assessment, assessment of trial comparability and insufficient sensitivity analyses
Mismatch between decision problem and evidence: line of therapy + prior oral antidiabetic drug intensity
Mismatch between tirzepatide administration in clinical practice (by titration) and in the trials, network meta-analysis and cost-effectiveness analyses (according to maintenance dose strata)

Key issues (2)

Cost effectiveness evidence

Issues
Company's modelling approach not adequately justified
Technical verification of company model insufficient
No comparative evidence on treatment effects on macro- and micro-vascular complications - modelling used. Selection and use of risk models to estimate complications not adequately justified
No justification for no treatment effect waning when extrapolating treatment effectiveness data
Only one criterion (HbA1c threshold) for treatment discontinuation/intensification applied in model
Not all adverse events incorporated for all treatments
Potentially inappropriate probabilistic sensitivity analyses
No full deterministic one-way sensitivity analyses

Background on type 2 diabetes mellitus

Type 2 diabetes mellitus:

- Chronic metabolic disorder: reduced tissue sensitivity to insulin (known as insulin resistance) → loss of endogenous insulin production → elevated blood glucose levels (hyperglycaemia)

Epidemiology: UK prevalence of type 2 diabetes is rising

- Around 3 million diagnosed in England in 2019; plus estimated 1 million undiagnosed in the UK
- UK prevalence is rising due to increasing prevalence of obesity
- People from Black African, African Caribbean and South Asian family backgrounds at a higher risk, and from a younger age

Complications, if not managed effectively, include:

- kidney disease (including failure)
- eye problems (including blindness)
- foot problems (can lead to amputation)
- nerve damage
- cardiovascular disease (including heart attack and stroke)
- treatment-related: low blood glucose (hypoglycaemia)

Treatment pathway: summary

Depends on HbA1c level, cardiovascular risk, kidney function and other factors
Treatment intensified when HbA1c not controlled or change in cardiovascular risk/status

1st line	Chosen individually, based on multiple factors and patients circumstances, including HbA1c level, cardiovascular risk and kidney function; generally includes: • metformin (not at high CVD risk) • metformin plus SGLT2 inhibitor (chronic heart failure or established atherosclerotic CVD*) • DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor (if metformin contraindicated)	Tirzepatide's marketing authorisation spans entire treatment pathway- discussed later
2nd line	Treatment intensified when: • person's HbA1c not controlled below individually agreed threshold: switching to or adding DPP-4 inhibitor, pioglitazone, sulfonylurea or SGLT2 inhibitor • person develops CVD or a high risk of CVD (switching to or adding SGLT2 inhibitor)	

3rd & further lines	• Insulin-based therapy (with or without other drugs): when dual therapy has not continued to control HbA1c to below the person's individually agreed threshold
	• GLP-1 mimetic treatments: if triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated[c]; for adults with type 2 diabetes who have:
	  • BMI of ≥35[b] kg/m^2 and specific psychological or other medical problems associated with obesity
	  • BMI <35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities.
		Company positions tirzepatide as alternative to GLP-1 mimetics

[a] SGLT2 inhibitor can also be considered for people at high risk of CVD (QRISK2 of 10% or higher or elevated lifetime risk); [b] adjusted accordingly for people from Black, Asian and other minority ethnic groups; [c] switching one of the drugs to a GLP-1 mimetic.
Source: NICE guideline 28. Abbreviations: CVD, cardiovascular disease; DPP-4, Dipeptidyl-Peptidase 4; GLP-1, glucagon-like peptide-1; HbA1c, Glycated Haemoglobin; QRISK2, cardiovascular risk score; SGLT2, Sodium-Glucose Co-Transporter-2.

Patient perspectives

People feel overwhelmed by the pressures of having the condition over a long period of time

Submissions from Diabetes UK

- Serious and sometimes progressive condition that deeply impacts health and wellbeing; can cause devasting, life-changing complications
- Estimated 90% of adults with type 2 diabetes are living with overweight or obesity at diagnosis. Carrying excess weight strongly tied to difficulties managing blood glucose levels and to increased risk of complications
- Reducing blood glucose levels and weight loss are proven ways to improve condition and reduce risk of complications so an additional treatment with these benefits is very important for many people living with type 2 diabetes
- Tirzepatide offers another welcome option for people with type 2 diabetes when developing an individualised treatment plan with their healthcare team

"There is an unmet need given the increasing prevalence of type 2 diabetes in the population"

"[Tirzepatide] would offer patients more choice for their care, reduce the risk of people feeling a sense of hopelessness and could encourage a shared-decision making approach where a full range of options are discussed"

Clinical perspectives

Submissions from clinical experts: Association of British Clinical Diabetologists and Portsmouth Hospitals University Trust (Diabetes and Endocrinology)

- Aims of therapy: reversal of symptoms of high glucose level, avoiding negative effects of therapy, and reducing the risk of micro- and macrovascular complications
- International guidelines[a] now cite reduction of obesity as a major aim of therapy; over 90% people with T2D have excess weight which is associated with insulin resistance and health issues per se
- Unmet need: despite availability of 8 different classes of glucose lowering therapies (in addition to lifestyle interventions), less than 2/3rds of people with T2D in the UK achieve an HbA1c <53 mmol/mol (<7%)

Tirzepatide:

- First in class glucose lowering therapy which stimulates GLP-1 and GIP receptors
- Expected to be positioned as alternative to GLP-1 RAs (although current BMI threshold for GLP-1 RAs use is too restrictive and not based on clinical evidence)
- Gives better reduction of HbA1c, weight and BMI than placebo and other active glucose lowering therapies (shown in SURPASS trials)
- Has similar safety and side-effect profile to GLP-1 RAs

"Additional glucose lowering therapies are warranted to assist individuals and populations to achieve optimal glycaemic control"

"Tirzepatide is a once weekly injectable glucose lowering therapy that offers a unique approach to improve glycaemic control and is associated with weight loss"

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[a] American (ADA) and European (EASD) guidelines, updated September 2022; Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; RA; receptor agonist; T2D, type 2 diabetes.

Equality considerations

Equality considerations (patient organisation)

- Higher risk of being diagnosed with type 2 diabetes, and at a younger age, for people of South Asian, Black Caribbean and Black African ethnic background
- Higher prevalence of the condition amongst those in more deprived areas and they receive poorer care which is borne out in consistently poorer achievement of care processes and treatment targets. Obesity also disproportionately impacts these groups
- People with type 2 diabetes who experience weight stigma are less likely to receive good care and seek help from a healthcare professional to support weight loss

Tirzepatide (Mounjaro, Eli Lilly)

Technology details

Marketing authorisation	treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications • in addition to other medicinal products for the treatment of diabetes
Mechanism of action	• Dual receptor agonist of the GIP and GLP-1 hormones which act to stimulate insulin secretion
Administration	• Weekly subcutaneous injection
Price	• Proposed list price per pack of 4 pre-filled single-dose autoinjector pen devices disposable injection 5 mg, 10 mg and 15 mg: £[redacted], respectively • Proposed list price for 12 months of treatment 5 mg, 10 mg and 15 mg: £[redacted] • [redacted], respectively • Note: price will be disclosed when guidance is published

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Note: Marketing authorisation granted by MHRA in September 2022.
Abbreviations: GIP, Glucose-Dependent Insulinotropic Polypeptide; GLP-1, Glucagon-Like Peptide-1.

Decision problem: company submission deviates from scope

	Final scope	Company submission	EAG comments
Population	Tirzepatide monotherapy: • Adults with T2D, inadequately controlled with diet & exercise alone & metformin considered inappropriate Tirzepatide with other antidiabetic agents: • Adults with T2D, inadequately controlled with one or more antidiabetic agents	People with T2D, inadequately controlled with 3 or more antidiabetic agents, as an option whenever GLP-1 RAs would otherwise be considered	Company target population narrower than NICE scope
Intervention	Tirzepatide alone or with other antidiabetic agents	Tirzepatide with other antidiabetic agents	Company submission limited to combination therapy
Comparators	Sulfonylureas, DPP-4 inhibitors, pioglitazone, GLP-1 RAs, SGLT-2 inhibitors, insulin (all as monotherapy or in combination)	GLP-1 RAs	Company have not presented a convincing argument for restricting to GLP-1 RAs
Outcomes	HbA1c/glycaemic control, complications of diabetes, including CV, renal and eye, mortality, BMI, frequency and severity of hypoglycaemia, changes in CV risk factors, adverse effects of treatment, HRQoL	Aligned with final NICE scope	Some outcomes are modelled (details later)

Abbreviations: GLP-1, glucagon-like peptide-1; HRQoL, health-related quality of life; OAD, oral antidiabetic drug; RA, receptor agonist; T2D, type 2 diabetes.

Key issue: Mismatch between scope and decision problem: line of therapy and comparators

Line of therapy – EAG comments:

- Company target population narrower than NICE scope
- No evidence to assess tirzepatide in wider population
- Use of GLP-1 RAs more precise than only according to treatment experience (NICE guideline 28)

Company: Population narrower as expected tirzepatide would be used as alternative to GLP-1 RAs in clinical practice (both in combination with 2 OADs) + this population has highest unmet need

"If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with type 2 diabetes who:

- have a body mass index (BMI) of 35 kg/m^2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
- have a BMI lower than 35 kg/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities."

Comparators – EAG comments:

- Company included only GLP-1 RAs: dulaglutide, liraglutide, oral semaglutide, injectable semaglutide
- Some GLP-1 RAs (lixisenatide, standard & modified-release exenatide) excluded due to limited market share

Company: comparators dictated by proposed positioning

Is company positioning clinically appropriate?
Would we expect people at third line to respond as well as those at earlier stage in disease?
If alternative to GLP-1 RAs, should the same criteria for use apply?
Are all relevant comparators included?

NICE Abbreviations: GLP-1, Glucagon-Like Peptide-1; RA, receptor agonist

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trials: SURPASS-2 to 5 (1)

Clinical trial designs and outcomes

	SURPASS-2	SURPASS-3	SURPASS-4	SURPASS-5
Design	Randomised, multicentre phase 3			
	Open-label			Double-blind
Population	People with T2D, stable treatment, unchanged dose of metformin >1500 mg/day for ≥3 months before screening	People with T2D, stable treatment, unchanged dose of metformin/ metformin plus an SGLT-2 inhibitor for ≥3 months before screening	People with T2D with high CV disease risk, stable treatment, unchanged dose of at least 1 and no more than 3 types of oral antihyperglycemic drugs, (only include metformin, SGLT-2 inhibitors, and/or sulfonylureas) for ≥3 months before screening	People with T2D, stable dose of insulin glargine (U100) once daily, with/ without metformin ≥3 months before screening
Key inclusion criteria	HbA1c of ≥7.0% (≥7.5% in SURPASS-4) to ≤10.5% Stable weight for 3 months and BMI ≥25 kg/m² (≥23 kg/m² in SURPASS-5)			
Key exclusion criteria	Prior history of proliferative diabetic retinopathy, diabetic maculopathy, or non-proliferative diabetic retinopathy that requires acute treatment			

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Note: SURPASS-1 population and treatment not relevant to submission

Abbreviations: CV, cardiovascular; HbA1c, glycated haemoglobin; SGLT2, Sodium-Glucose Co-Transporter-2; T2D, type 2 diabetes.

Key clinical trials: SURPASS-2 to 5 (2)

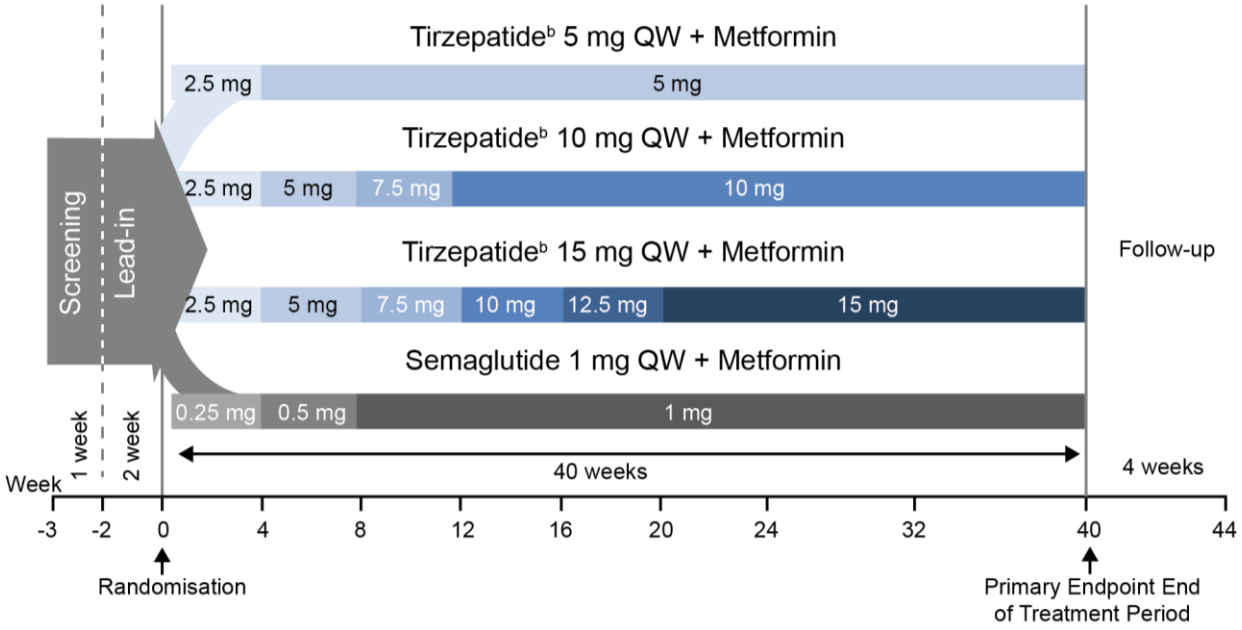
Clinical trial designs and outcomes

	SURPASS-2*	SURPASS-3	SURPASS-4	SURPASS-5
Intervention	Tirzepatide 5 mg, 10 mg, 15 mg			
Comparator	Semaglutide	Insulin degludec	Insulin glargine	Placebo
Duration	40 weeks	52 weeks	52 weeks	40 weeks
Primary outcome	Mean change from baseline in HbA1c (10 mg and 15 mg)			
Key secondary outcomes	Mean change from baseline in HbA1c (tirzepatide 5 mg) Mean change from baseline in body weight (all tirzepatide doses) Proportion of patients achieving HbA1c <7% (53 mmol/mol; all tirzepatide doses) Proportion of patients achieving HbA1c <5.7% (39 mmol/mol; tirzepatide 10 mg and 15 mg)			
Locations	128 centres across 8 countries	121 sites across 12 countries	187 sites in 14 countries	45 sites in 8 countries

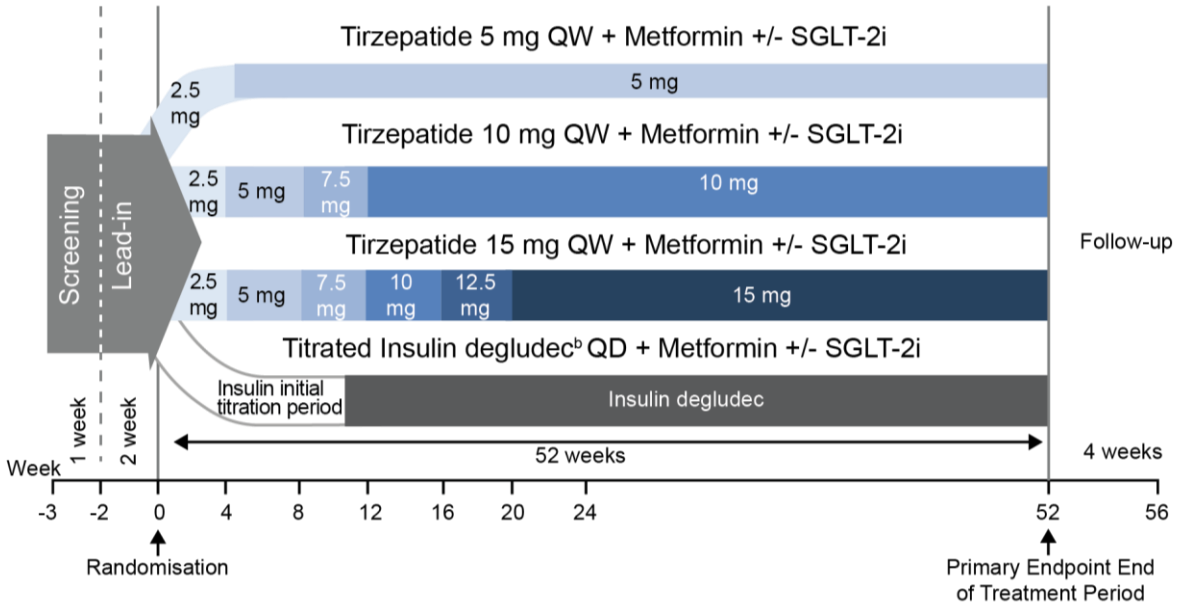
NICE Abbreviations: HbA1c, glycated haemoglobin.

SURPASS trials study design (1)

SURPASS-2



SURPASS-3

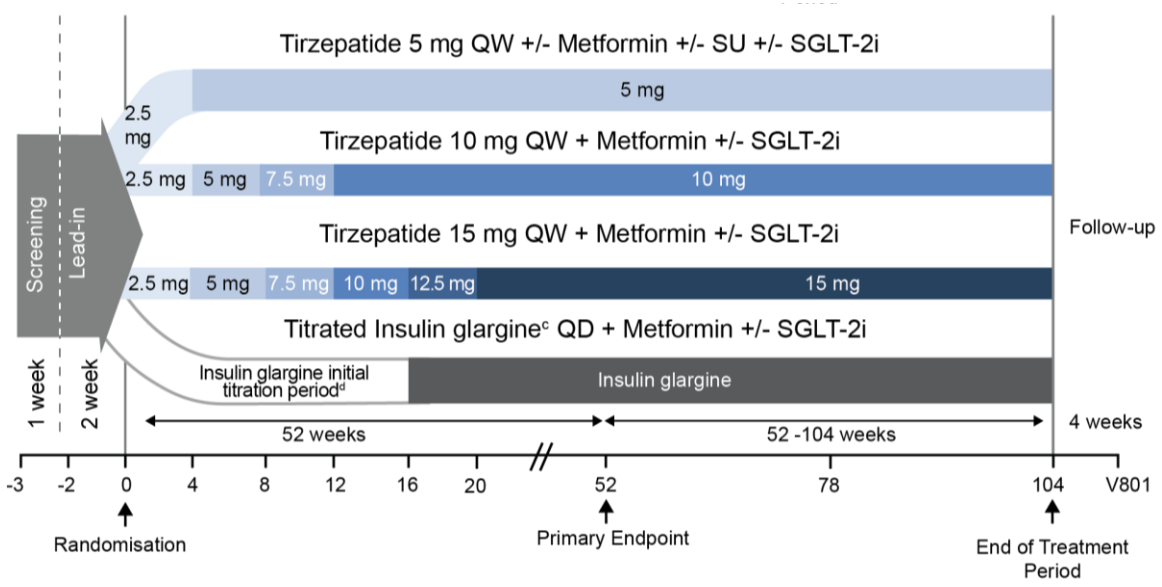


Is this dose escalation schedule representative of how tirzepatide will be dosed in clinical practice? Does this matter?

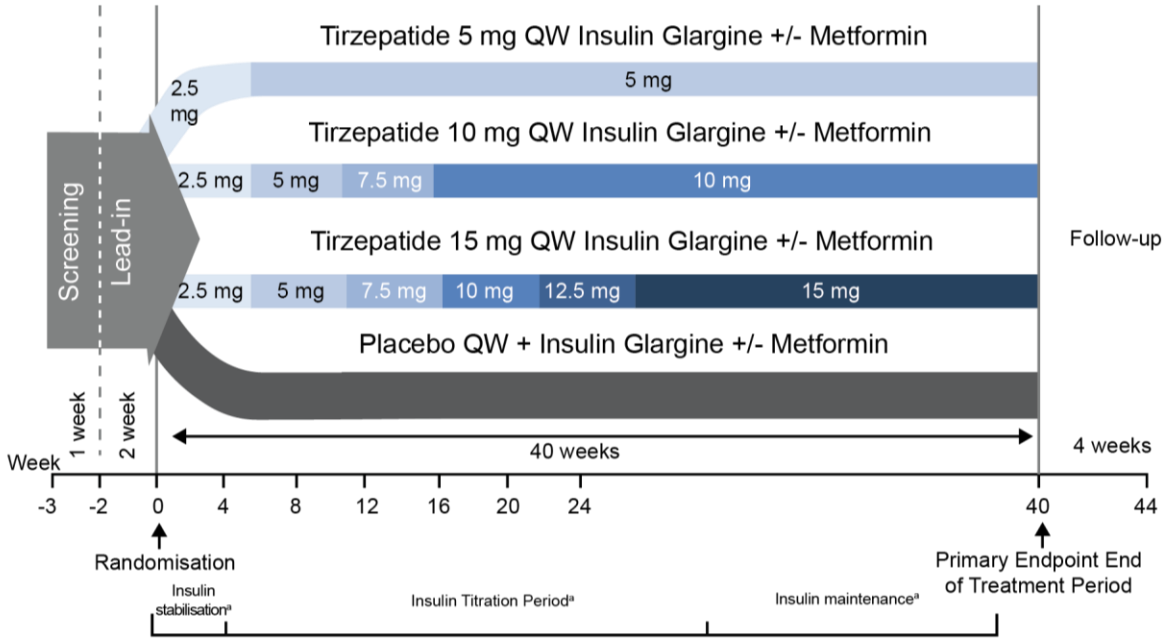
Abbreviations: QD, once a day; QW, once weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

SURPASS trials study design (2)

SURPASS-4



SURPASS-5



Abbreviations: QD, once a day; QW, once weekly; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonylurea.

Clinical trials baseline characteristics (overall population)

SURPASS trial, N	2 (N=1,878)	3 (N= 1,437)	4 (N=1,995)	5 (N= 475)
Age (years), mean ± SD	56.6 ± 10.4	57.4 ± 10.0	63.6 ± 8.6	60.6 ± 9.9
Female, n (%)	996 (53.0)	635 (44.2)	749 (37.5)	211 (44.4)
White, n (%)	1551 (82.6)	1307 (91.0)	1629 (81.8)	380 (80.0)
Weight (kg), mean ± SD	93.7 ± 21.9	94.28 ± 20.06	90.3 ± 18.7	95.2 ± 21.6
BMI (kg/m²), mean ± SD	34.2 ± 6.9	33.52 ± 6.06	32.6 ± 5.5	33.4 ± 6.1
BMI category, n (%)				
<30	[redacted]	446 (31.0)	[redacted]	[redacted]
30 to <35	[redacted]	496 (34.5)	[redacted]	[redacted]
≥35	[redacted]	495 (34.4)	[redacted]	[redacted]
Duration of diabetes (years), mean ± SD	8.6 ± 6.5	8.38 ± 6.24	11.78 ± 7.51	13.3 ± 7.3
HbA1c (%), mean ± SD	8.28 ± 1.03	8.17 ± 0.91	8.52 ± 0.88	8.31 ± 0.85
HbA1c (mmol/mol), mean ± SD	67.03 ± 11.25	65.78 ± 9.99	69.65 ± 9.65	[redacted]
HbA1c category, n (%)				
≤8.5% (69 mmol/mol)	1192 (63.5)	1005 (69.9)	[redacted]	[redacted]
>8.5% (69 mmol/mol)	686 (36.5)	432 (30.1)	[redacted]	[redacted]
History of CV disease	[redacted]	[redacted]	1738 (86.8)	[redacted]

Generalisable to NHS practice?

NICE Abbreviations: BMI, body mass index; CV, cardiovascular; HbA1c, glycated haemoglobin; SD, standard deviation.

Clinical trials (concomitant treatments at baseline)

Characteristics	TZP 5 mg	TZP 10 mg	TZP 15 mg	Comparator	Overall population
SURPASS-2					
Metformin	100%				
SURPASS-3					
Metformin alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin + SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	458 (31.9)
Metformin dose (mg/day), mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURPASS-4					
Metformin alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin + SU, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin + SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metformin + SU + SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SU alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SGLT-2i alone, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SU + SGLT-2i, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SURPASS-5					
Insulin dose mean ± SD	39.1 ± 25.4	34.7 ± 15.4	40.5 ± 29.1	36.3 ± 18.0	37.6 ± 22.7
Metformin, n (%)	99 (85.3)	99 (83.2)	97 (80.8)	99 (82.5)	394 (82.9)

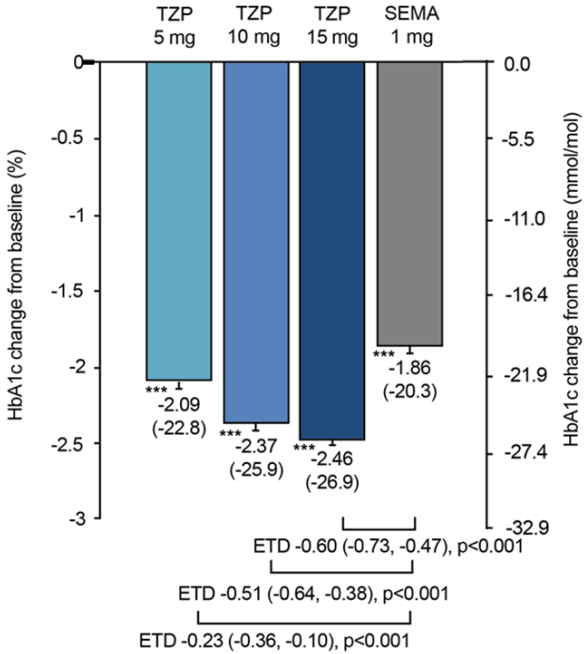
Triple therapy

NICE Abbreviations: SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZP, tirzepatide.

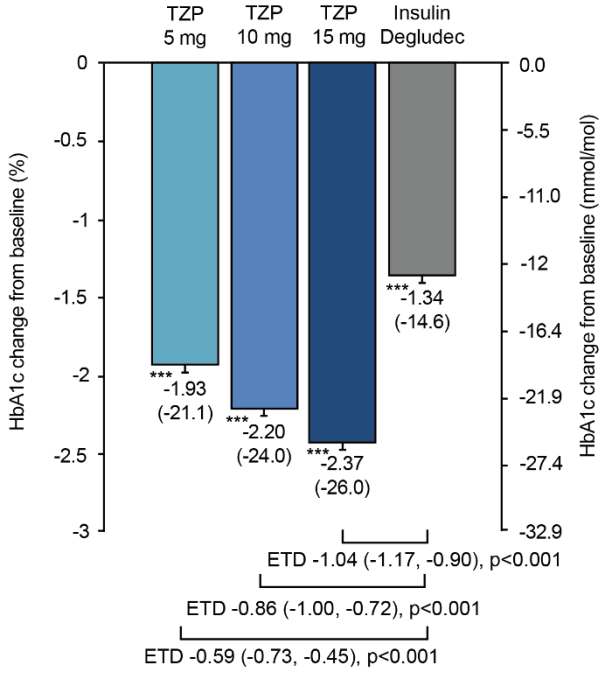
Results: change from baseline in HbA1c (primary endpoint)

Tirzepatide showed statistically significant reductions in HbA1c vs comparator (all doses)

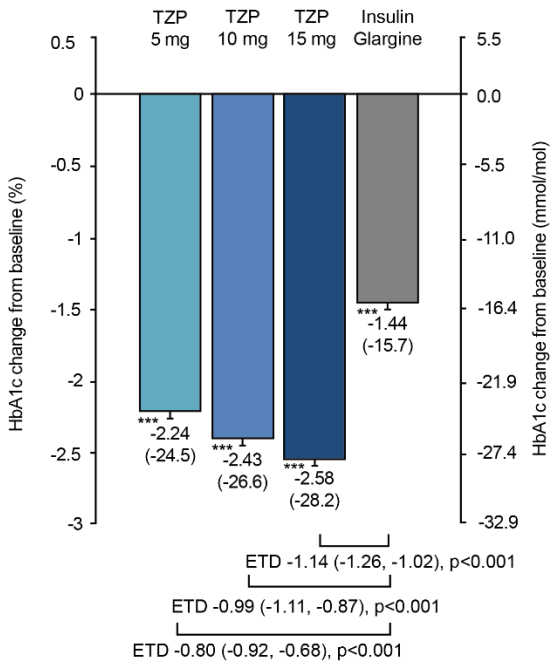
SURPASS-2 (baseline to 40 weeks)



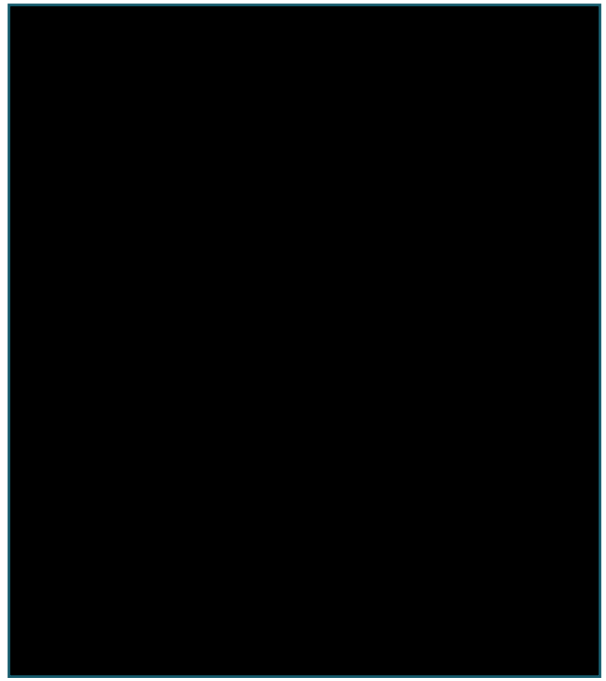
SURPASS-3 (baseline to 52 weeks)



SURPASS-4 (baseline to 52 weeks)



SURPASS-5 (baseline to 40 weeks)



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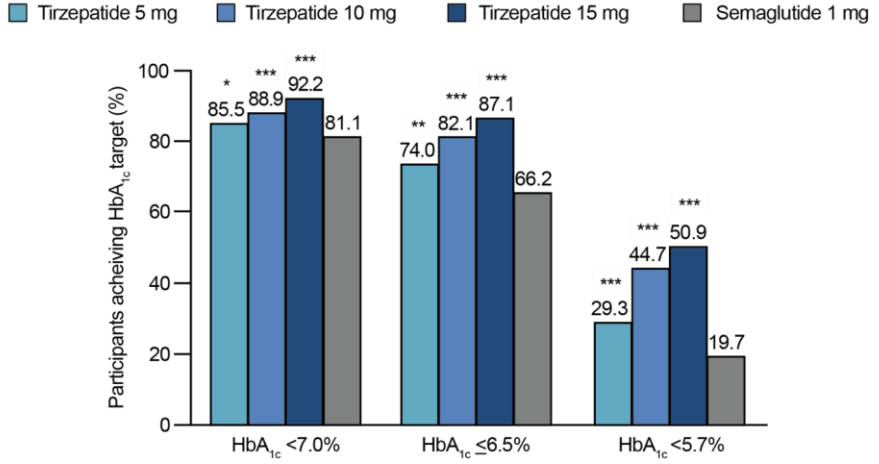
Note: efficacy estimand presented (assesses on-treatment efficacy using data up to the time of initiating rescue therapy); ***p<0.001 versus baseline
Abbreviations: ETD, estimated treatment difference; HbA1c, glycated haemoglobin; PBO, placebo; SEMA, semaglutide; TZP, tirzepatide.

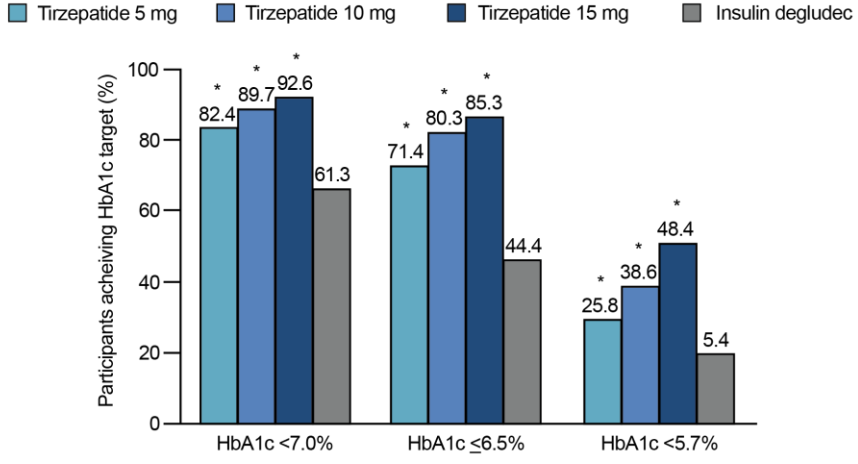
Trial results: % patients who reached HbA1c targets

Tirzepatide: statistically significantly more people met their HbA1c targets

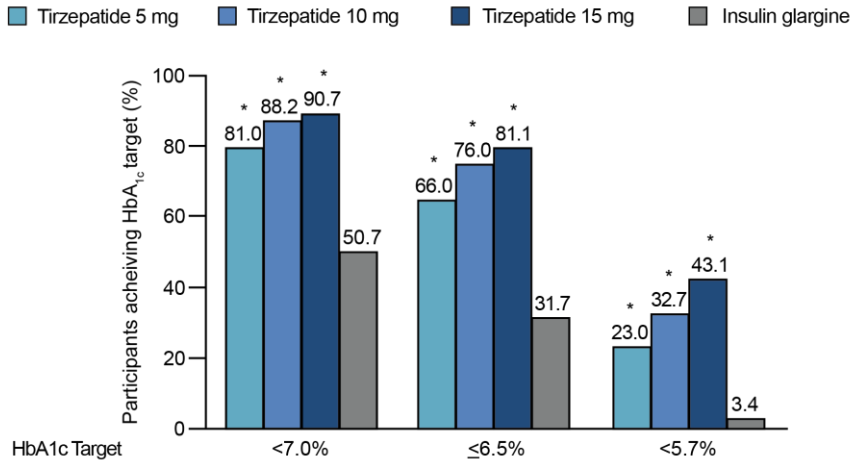
SURPASS-2 (at 40 weeks)



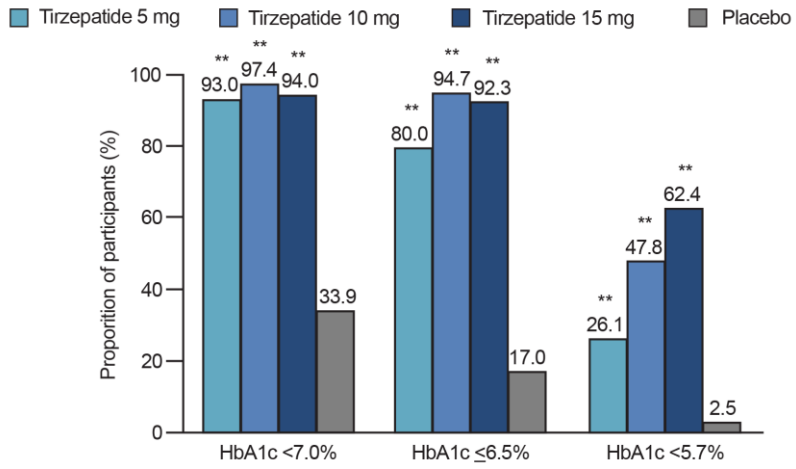
SURPASS-3 (at 52 weeks)



SURPASS-4 (at 52 weeks)



SURPASS-5 (at 40 weeks)



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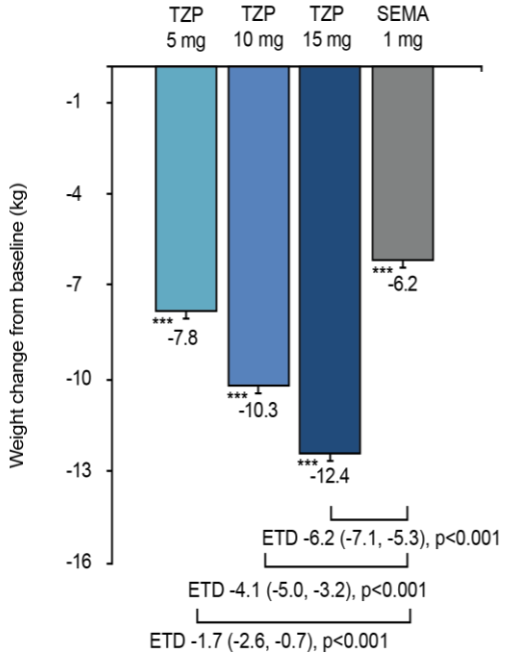
*p<0.05 vs comparator; **p<0.01 vs comparator; ***p<0.001 vs comparator. Note: HbA1c ≤6.5% comparisons not controlled for type 1 error for any doses of tirzepatide. HbA1c <5.7% comparisons not controlled for type 1 error for tirzepatide 5 mg [SURPASS-2 and -5] or all doses [SURPASS-2 and-3].

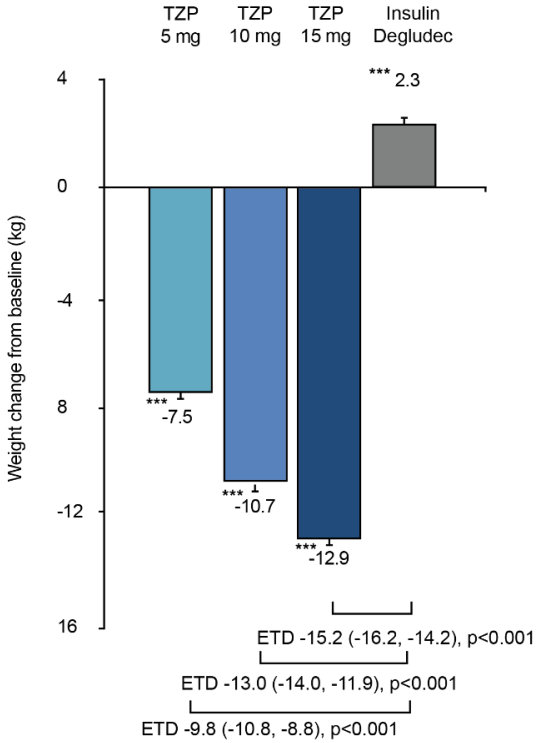
Trial results: change in body weight from baseline

Tirzepatide showed statistically significant reductions in body weight vs comparators (all doses)

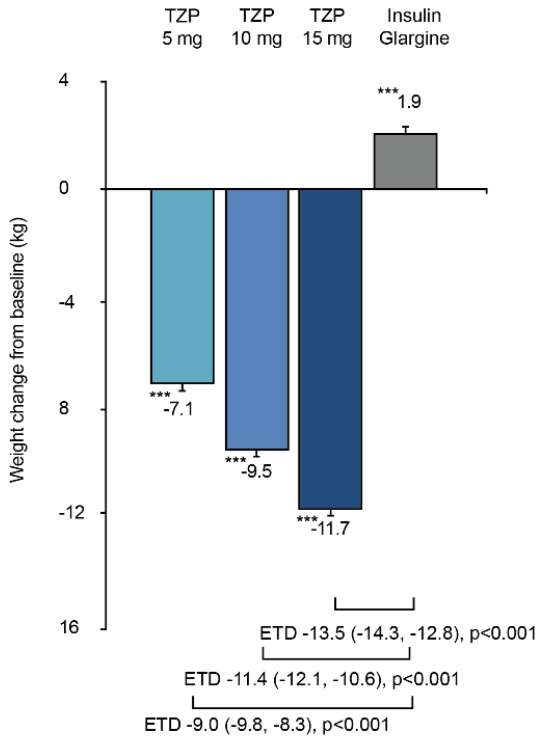
SURPASS-2 (baseline to 40 weeks)



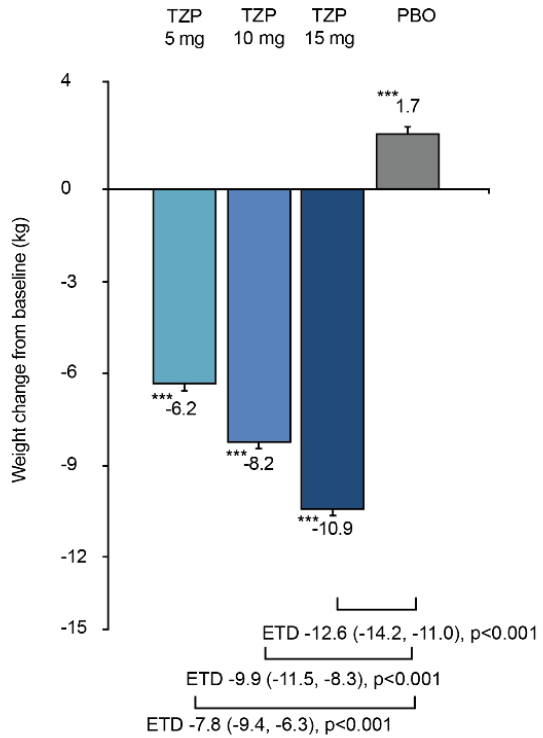
SURPASS-3 (baseline to 52 weeks)



SURPASS-4 (baseline to 52 weeks)



SURPASS-5 (baseline to 40 weeks)



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***p<0.001 versus baseline; Abbreviations: ETD, estimated treatment difference; TZP, tirzepatide

Adverse events

Most common treatment-emergent adverse events occurring in at least 5% of patients in any treatment group (placebo-controlled analysis set; tirzepatide all doses [N=718] vs placebo [N=235]):

- Nausea ([redacted] vs [redacted]
- Diarrhoea ([redacted] vs [redacted]
- Nasopharyngitis ([redacted] vs [redacted]
- Decreased appetite ([redacted] vs [redacted]
- Dyspepsia ([redacted] vs [redacted]
- Vomiting ([redacted] vs [redacted]
- Constipation ([redacted] vs [redacted]
- Hyperglycaemia ([redacted] vs [redacted]

Network meta-analysis (methods)

- Done to assess relative efficacy and safety of tirzepatide vs GLP-1 RAs available in NHS practice
- Network defined to align with SURPASS-2 and 3 trials → included RCTs in people on 1-2 oral antidiabetic drugs:
    - 53 studies in the main analysis
    - 72 studies in sensitivity analyses

Two-stage analytical approach

- Frequentist meta-analysis to assess heterogeneity and understand the data
- NMA conducted using Bayesian Mixed Treatment Comparisons as described in NICE DSU

Analysis time window

- Dose escalation in SURPASS trials longer than in comparator trials: 0-20[a] weeks compared to 0-12 weeks
- Comparator data analysed at 26 ± 4 (22–30) weeks
- Tirzepatide data analysed at 40 weeks (42 for SURPASS4)

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[a] 5 weeks for tirzepatide 5 mg, 13 weeks for tirzepatide 10 mg and 21 weeks for tirzepatide 15 mg dose.
Abbreviations: NMA, network meta-analysis; RCTs, randomised controlled trials.

Network meta-analysis results

TZP: significantly greater reductions in HbA1c and BMI from baseline compared to GLP-1 RAs

Tirzepatide 10 mg vs comparators (example)
Forest plots (median difference [95% CrI]; random effects model) for change from baseline in:

HbA1c (%)

Body mass index (kg/m^2)

Note: Semaglutide 2.0 mg not currently available in NHS but included for completeness. Degludec, glargine, sitagliptin 100 mg and glimepiride used as nodes to connect other treatments and not included in PICOTS, results for these treatments should not be interpreted. Abbreviations: BMI, body mass index; CrI, credible interval; GLP-1, Glucagon-Like Peptide-1; HbA1c, glycated haemoglobin; RA, receptor agonist; TZP, tirzepatide.

Key issue: Lack of feasibility assessment/assessment of comparability in the NMA (1)

Company

- NMA provides robust results that are generalisable to UK clinical practice
- Studies with extreme values of baseline characteristics, such as BMI and diabetes duration were excluded from NMA
- Acknowledges heterogeneity identified for some outcomes but adequate feasibility assessment done, and heterogeneity thoroughly tested – limited concerns identified
- Meta-regression analysis on treatment effect modifiers gives similar results to main analysis, supporting that treatment effect is not influenced by differences between baseline characteristics
- Additional sensitivity analyses on HbA1c, body weight and BMI[a] in which studies that contributed to increased heterogeneity were removed → results similar to main NMA for HbA1c and body weight (BMI analysis had sigma convergence issues and should be interpreted with caution)

[a] Company response to EAG report May 2023.

Abbreviations: NMA, network meta-analysis.

Key issue: Lack of feasibility assessment/assessment of comparability in the NMA (2)

EAG comments

- NMA criteria (1-2 OADs) don't match company's target population
- External and internal validity of NMA in question → high risk of bias
- Validity of NMA based on assumption that all the studies included in network are similar in all factors that may affect the relative effects (i.e. disease and patient characteristics that are potentially effect modifiers), but:
  - No analysis of degree of variation between trials included, which appeared large, e.g. mean baseline HbA1c values varied from 7.4% to 10.3% and baseline diabetes duration from 0.6 - 10.1 years
  - Substantial/considerable heterogeneity (I^2 results > 60%) identified in 21 of 91 pairwise comparisons across 7 characteristics[a]
- Concerns about meta-regression and sensitivity analyses presented by company:
  - Meta-regression results limited to only one factor (i.e. number of prior OADs: 1 vs 2)
  - Sensitivity analysis around background therapy mixed 2 unrelated populations: trials with unclear proportion of people receiving metformin (n=1 study), and trials including people on 3 OADs (n=6 studies) + does not address heterogeneity in background OADs (i.e. type rather than number of OADs)
- Notes company's additional sensitivity analyses, in which all trials making the same direct comparison with high heterogeneity between them are excluded, seem to show little difference to the main analysis
- Tirzepatide and GLP-1 RA: precise treatment effect that would be observed in clinical practice unknown, as treatments would be titrated in NHS, not given as fixed maintenance doses (discussed in next slides)

How applicable is company NMA to decision problem? Is it suitable for decision-making?

[a] BMI, body weight, eGFR, HbA1c, HDL, nausea and SBP. Abbreviations: NMA, network meta-analysis.

Key issue: Mismatch between decision problem and evidence: line of therapy and prior oral antidiabetic drug therapy intensity

Company decision problem: 3 or more prior OADs (as alternative to GLP-1 RAs)

Source	Prior antidiabetic drug therapy allowed
SURPASS-2	Metformin
SURPASS-3	Metformin or metformin plus SGLT-2i
SURPASS-4	Triple OADs, which could only include metformin, SGLT2i, and/or sulfonylurea inhibitor
SURPASS-5	Insulin glargine with/without metformin
NMA	Aligned with SURPASS-2 and 3 trials: 1-2 OADs

Company

- Trials designed to meet global regulatory evidence requirements
- Similar mismatch between GLP-1 RA trials and their use in NHS
- Following analyses support generalisability of tirzepatide results:
  - SURPASS-4 subgroup analyses of baseline OADs for change from baseline in HbA1c, weight and BMI → in line with main analyses
  - NMA meta-regression analysis[a] → results adjusted for number of background OADs similar to unadjusted results
  - NMA sensitivity analysis including studies including patients on 3 OADs → aligned with main analysis

EAG comments

- SURPASS trial evidence generally at earlier line of therapy than company decision problem - more aligned with broader population in NICE scope
- Only SURPASS-4 allowed prior triple therapy (but only ~[redacted] people had it)
- SURPASS subgroup analysis: showed significant effect on HbA1c; had limited ability to test hypothesis of baseline OAD independence as so few people had 3 OADs at baseline
- Critique of NMA-related analyses on previous slide

[a] for change from baseline in HbA1c and weight. Abbreviations: OADs, oral antidiabetic drugs; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

Key issue: Mismatch between tirzepatide administration in clinical practice and in trials, NMA and cost-effectiveness analyses

Background

- Tirzepatide MA: titrated as needed to recommended maintenance doses of 5 mg, 10 mg, or 15 mg
- Company's analyses stratified by maximum maintenance dose into 5 mg, 10 mg and 15 mg groups, without titration permitted between maintenance doses

Company

- Accepts an issue – but notes it applies to all relevant comparator trials
- Clinical practice: patients titrate to maintenance doses of GLP-1 RAs; few patients de-escalate to lower doses
- Most important comparisons are within each recommended maintenance dose step, rather than between them (but all analyses provided) – because GLP-1 RAs and tirzepatide exhibit dose-response relationship in terms of efficacy and GI side-effects; patients unable to tolerate higher doses of one GLP-1 RA not expected to tolerate higher doses of another GLP-1 RA or tirzepatide

EAG comments

- Concerned lack of applicability to clinical practice where titration is permitted
- Mismatch applies even if there is no de-escalation as comparison between treatments depend both on relative effectiveness between two maintenance doses and proportion of patients who escalate (which may vary)
- In the absence of titrated treatment evidence, comparison in tirzepatide 10 mg stratum might be closest approximation: efficacy likely underestimated for 5 mg and overestimated for 15 mg strata

How is an individual's optimal dose determined in clinical practice?

NICE

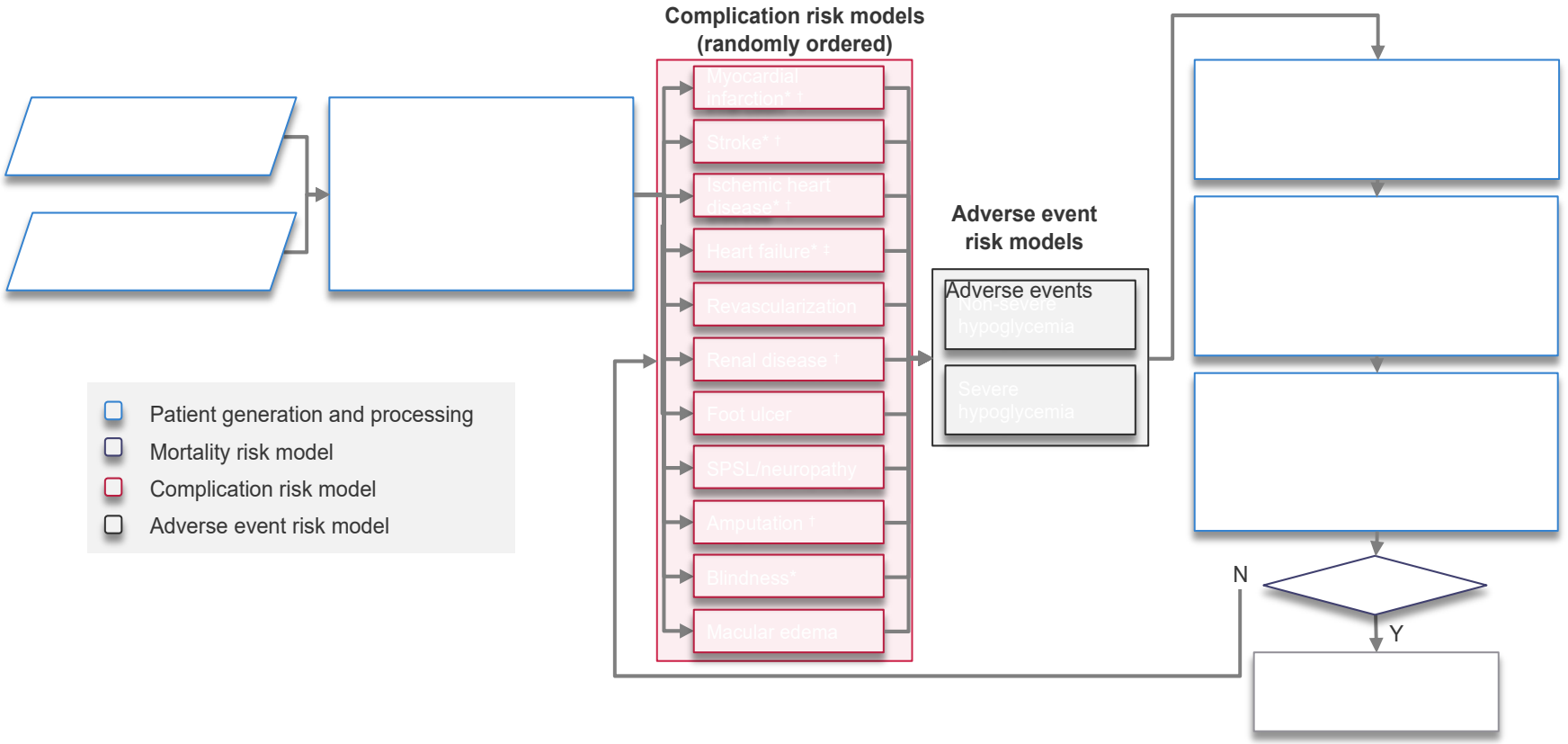
[a] Company response to EAG report May 2023. Abbreviations: CEA, cost effectiveness analysis; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; MA, marketing authorisation; NMA, network meta-analysis; RA, receptor agonist

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

PRIME T2D model structure[a]



Technology affects **costs** by:

- Additional treatment costs
- Reductions in diabetes-related complication costs (especially cardiovascular events avoided)

Technology affects **QALYs** by:

- Reductions in diabetes-related complications
- Reductions in BMI

[a] source: Company response to EAG report, May 2023

*Model averaging used in controller; †,complications with increased risk of mortality in year of complication onset and subsequent years; ‡, complications with increased risk of mortality associated with history of this complication

Abbreviations: QALYs, quality-adjusted life years; QoL, quality of life; RNG, random number generator; SPSL, severe pressure sensation loss.

How company incorporated evidence into model

Company agreed with some EAG assumptions (marked with*) but discrepancy remains

Input	Assumption and evidence source (revised base case)	EAG concerns
Baseline characteristics	THIN second intensification cohort and SURPASS-2 clinical trial cohort (if data from THIN missing)	Some: scenario using SURPASS-2 characteristics
Efficacy	NMA (1-2 OADs) (BMI directly from NMA when available*)	Yes: NMA high risk of bias + mismatch with decision problem
Long-term risk factor progression	Model averaging for macrovascular complications and blindness risks; based on UKPDS OM2 for all other risk factors* (except SBP and BMI while on treatment)	Yes: about model averaging
Discontinuation	Switch to basal insulin therapy when HbA1c rise above 7.5%	Yes: include further reasons for discontinuation
Utilities	Literature review; disutility for complications, adverse events and overweight (additive method); no utility benefit for weight loss and administration*; adjusted for ageing*	Yes: multiplicative preferred; baseline utility value seems high
Adverse events	Only nausea included (from NMA)	Yes: include also vomiting
Intervention and comparators costs and resource use	NHS Electronic Drug Tariff, NICE NG28 2022 model, PSSRU Unit Costs of Health and Social Care (all inflated to 2022*; errors fixed*)	-

Abbreviations: AEs, adverse events; eGFR, estimated Glomerular Filtration Rate; NMA, network meta-analysis; PSSRU, Personal Social Services Research Unit.

Key issue: Model approach adopted by the company

EAG: Technical implementation of company's model unclear

Company

- Developed PRIME T2D model (in JAVA): discrete time event, patient-level simulation
  - Uses data exclusively from populations with type 2 diabetes
  - Meets ISPOR good modelling practice guidelines, underwent PRIMA review
  - Shown to project long-term patient outcomes consistent with those reported for several long-term studies, including cardiovascular outcome trials, during validation analyses
- Models developed before 2016 performed poorly in validations against cardiovascular outcomes trials at the Ninth Mount Hood Challenge Meeting; need calibration with hazard ratios from CVOTs → complex due to heterogeneity of trials; can lead to misleading results (Evans et al. 2023)
- PRIME T2D Model includes a revascularization endpoint (CORE Diabetes Model and UKPDS OM2 don't) – shown important to predict cardiovascular risk in a modern UK population (Keng et al. 2022)
- 'Discrete time event model' misunderstood by EAG - term analogous to 'discrete-time illness-death' description of UKPDS Outcomes Model

EAG comments

- No comparison of Ninth Mount Hood Diabetes Challenge results and current implementation of PRIME T2D Model – not clear it better predicts cardiovascular complications than existing diabetes models
- Prefers CORE Diabetes model
- Prefers discrete event simulation or individual-patient state transition model

NICE

Abbreviations: CVOTs, cardiovascular outcomes trials; PRIMA, Preliminary Independent Model Advice; T2D, type 2 diabetes; UKPDS, UK Prospective Diabetes Study.

Key issue: Technical verification insufficient/model results not reproducible

Background

- EAG had issues to run the model locally (without using the online version of the model). Requested description of how BMI-related utility is implemented in model & full overview of all input parameters

Company

- Notes it explained how to implement BMI-related utilities at clarification stage
- EAG given full access to base case simulations and settings via model interface in August 2022
- All model inputs for base case analysis given in JSON files to run model off-line

EAG comments

- EAG able to run model locally, reproducing company's base-case results. But this is typically only starting point of EAG model assessment. Validating and scrutinizing model via online interface is challenging: e.g., not all input parameters can be adjusted, and model implementation/assumptions difficult to examine
- Still unclear how BMI related utility implemented in model
- No complete overview of all model inputs → face, internal and external validity checks likely incomplete

Is company model suitable for decision making?

NICE

Abbreviations: BMI, body mass index; JSON, JavaScript Object Notation

Key issue: Lack of comparative evidence on micro and macrovascular complications

Background

- No comparative data on micro- and macrovascular complications of diabetes, including CV outcomes
- Company estimated rates of micro- and macrovascular complications using risk models instead (next slide)

Company

- Further data on CV outcomes expected from SURPASS-CVOT trial in 2025
- Ongoing addendum study to SURPASS-CVOT will assess impact on diabetic retinopathy progression
- No excess risk for CV events with tirzepatide[a]

EAG comments

- Risk models based on surrogate outpoints such as HbA1c → treatment effect on final endpoints uncertain

NICE

[a] as per meta-analysis of positively adjudicated major adverse cardiovascular events (MACE) in SURPASS trials.
Abbreviations: CV, cardiovascular; CVOT, Cardiovascular Outcomes Trial.

Key issue: Selection and use of risk models to estimate complications

Background

- PRIME T2D Model uses model averaging approach to estimate risk of macrovascular complications

Company

- Establishing which model is "best match" to decision problem is challenging → averaging allows model to draw on data derived from populations with diverse risk profiles
- Approach to model averaging documented in Pollock et al. 2022; risk equations from:
  - UKPDS OM2 → for patients with a low risk profile and short duration of disease
  - BRAVO Model → better suited to patients with more advanced disease and higher risk profile (derived from the ACCORD trial population which was at high risk of cardiovascular complications)
  - Hong Kong Diabetes Registry → applicable to South East Asian populations (not influential)
- PRIME T2D Model, using the model averaging approach, shown to compare well to published outcomes

EAG comments

- Justification for model averaging approach not compelling, justification for selection of individual predictive models is limited
- Company did not provide any scenario analyses examining impact of approach (e.g. selecting a single predictive model based on the best match of derivation cohort to decision problem)

What is the best approach to estimate risk of micro- and macrovascular complications? Should sensitivity analyses be presented?

NICE

Abbreviations: T2D, type 2 diabetes; UKPDS, UK Prospective Diabetes Study.

Key issue: Extrapolation of treatment effectiveness

Revised base case follows UKPDS OM2 risk factor progression for all risk factors except SBP and BMI

Background

- QALY gains mainly after the first year (beyond trial time horizon) and mostly likely related to utilities for weight

Company

- For most risk factors other than HbA1c, only modest changes over time
- HbA1c key driver of cost-effectiveness; progression based on UKPDS data that leads to relative reduction in treatment benefit whilst on treatment
- Agreed with EAG suggestion - UKPDS OM2 progression assumed for:
  - all risk factors while on insulin therapy
  - HbA1c, LDL, HDL, eGFR, white blood cells count, heart rate and haemoglobin levels while on tirzepatide or GLP-1 RAs
- For SBP and BMI, no change assumed while on tirzepatide or GLP-1 RAs:
  - in line with published data for GLP-1 RAs showing maintained benefit while on treatment – if UKPDS OM2 progression applied, levels would return to baseline in 5 years (at odds with published data)

EAG comments

- Risk factor progression follows EAG's suggestion
- Notes company's justification for assuming no treatment waning for SBP and BMI while on treatment

Company approach appropriate?

Note: After switching to basal insulin, BMI assumed to return to baseline levels in first year, all other risk factors assumed to return to baseline levels immediately. Company considers these to be conservative assumptions as no data were available to inform BMI, and due to absence of evidence to support continued benefit (other risk factors).

Abbreviations: BMI, body mass index; eGFR, estimated Glomerular Filtration Rate; HbA1c, Glycated Haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; UKPDS, UK Prospective Diabetes Study.

Key issue: Treatment discontinuation/intensification

EAG: prefers including other causes for treatment discontinuation

Background

- Patients assumed to intensify therapy, that is, discontinue initial treatment and switch to basal insulin therapy when HbA1c rose above 7.5%. No other causes for treatment discontinuation were included

Company

- This approach taken to avoid potential for rescue medication influencing outcomes
- Patients who do not tolerate the interventions well are likely to miss doses, leading to poorer glycaemic control and meeting the criterion for intensification
- Aligned with NG28 evaluation approach and NICE Guidance
- Changing intensification criteria has modest effect on ICERs

EAG comments

- Disagrees as changing intensification criteria increases ICERs by ~£9,000 and ~£15,000 when HbA1c threshold increased to 8.5% and 9.5%, accordingly (for tirzepatide 10 mg vs semaglutide 1.0 mg)[a]
- EAG prefers to include other causes for treatment discontinuation

When would treatment be discontinued/ intensified in clinical practice?

NICE

[a] compared with revised company base case. Source: Additional sensitivity analyses, May 2023.
Abbreviations: HbA1c, Glycated Haemoglobin; ICER, incremental-cost effectiveness ratio.

Key issue: Adverse events: not all incorporated for all treatments

EAG concerned only nausea included in the model

Background

- Base-case included only nausea rates for tirzepatide and comparators (hypoglycaemia rates set to zero)
- Severe and non-severe hypoglycaemic rates included for basal insulin therapy only (NG28 2022 report)

Company

- Rates of hypoglycaemia were not reported in NMA as many studies reported zero events. Assuming zero events reasonable considering low rates of hypoglycaemia in SURPASS and GLP-1 RAs trials
  - Included in SURPASS-2 scenario analysis → negligible impact on projected outcomes
- Incorporating rates of diarrhoea from NMA showed modest QALY differences from base case analysis[a]
- Including both nausea and vomiting rates from NMA would create risk of double-counting events; conservative approach used: 1) assumed NMA rate of nausea represents combined nausea and vomiting endpoint, and 2) applied disutility of more severe health state of nausea and vomiting to this rate

EAG comments

- Agrees hypoglycaemia likely not influential due to very low number of events
- Prefers to include both nausea and vomiting

Which AEs should be included in the model?

[a] Source: company clarification response; compared to initial company base case. Abbreviations: AEs, adverse events; GI, gastrointestinal; ICER, incremental-cost effectiveness ratio; NMA, network meta- analysis; QALYs, quality-adjusted life years.

Health state utility values

EAG prefers multiplicative method of combining utility values in base case

Background

- Base utility score of 0.815, per NG28 2022 model
- Disutility applied for complications, adverse events and overweight (combined using additive method)
- No utility benefit for weight loss in first year and administration in revised base case per EAG suggestion
- Utilities adjusted for ageing (Ara and Brazier 2010) in revised base case per EAG suggestion

Company

- Additive approach aligns with previous health economic evaluations, including NG28, TA288, TA418, TA390[a], and TA336[a] modelling

EAG comments

- Base utility score of 0.815 seems high:
  - utility score of 0.804 for general population at the same age
  - average utility of 0.772 in recent meta-analysis (n=19 studies; 0.037 reduction compared to general population)
- Prefers multiplicative approach: considered best approach overall and more conservative than additive method (although best method to combine multiple disutility values still debated)
- Using multiplicative methods increases ICER by almost £7,000 (compared with revised company base case)[b]

NICE health technology evaluations: the manual (2022)

"4.3.7. In some circumstances adjustments to utility values may be needed, for example for age or comorbidities. […] A multiplicative approach is generally preferred."

What is the best method to model health state utility values in type 2 diabetes?

NICE

[a] Approach not reported (assumed additive based on data presented). [b] Additional sensitivity analyses May 2023.
Abbreviations: ICER, incremental-cost effectiveness ratio.

Key issue: Potentially inappropriate probabilistic sensitivity analysis (PSA)

Company - PSA includes bootstrapping

- PSA in PRIME T2D Model aims to capture uncertainty around all aspects of simulation, not only uncertainty around model parameters/coefficients (but every class of uncertainty can be separated out in model)
- Patient characteristics, sub-model execution order, sub-model coefficients treatment effects, costs and utilities are all sampled or randomised
- Then, uncertainty around outcomes evaluated using non-parametric bootstrapping
- Unclear why EAG suggests Corro-Ramos et al 2020: impossible to implement as not transparent enough, and not feasible with PRIME T2D model.
- PSA in Corro-Ramos simulated 100 patients over 300 PSA iterations, versus 300,000 patients over 1,000 bootstrap iterations in PRIME T2D Model

EAG comments

- Company's approach not standard in PSAs - NICE TSD 15: "*it is usually necessary to run two nested simulation loops*" in patient-level simulation using PSA
- Literature: combining first and second order uncertainty (like in company model) can deliver expected value (e.g. estimate of ICER), but nested simulations needed to get distribution of expected outcomes (reflecting parameter uncertainty)
- Potential implications: estimated mean results might be correct but distribution around results distorted; likely underestimates uncertainty
- Suggests PSA implemented considering recommendations by Corro-Ramos et al 2020

Is company's probabilistic sensitivity analysis appropriate for decision-making?

Key issue: No full deterministic one-way sensitivity analyses provided

Background

- Company performed some deterministic sensitivity analyses and scenario analyses

Company

- Providing sensitivity analysis for all input parameters impracticable (over 185 inputs; 1,110 simulations needed) → all key model inputs that influence cost-effectiveness were explored in sensitivity analyses
- Tornado diagrams provided for these key inputs at clarification stage

EAG comments

- Initially, sensitivity and scenario analyses provided only for tirzepatide 10 mg against semaglutide analysis[a]
- No deterministic one-way sensitivity analyses exploring impact of all input parameters individually → needed to identify all potentially influential parameters (presented in tornado diagrams; for all doses of tirzepatide)
- One-way sensitivity analyses also very informative to validate that model behaves as you would expect/to increase model understanding

Are sensitivity analyses provided sufficient for decision-making?

[a] Additional scenario analyses reported in company response to EAG report, May 2023 included all comparisons.

Summary of company and EAG base case assumptions (1)

Assumptions in company and EAG base case

Assumption	Company initial base case	EAG base case	Revised base case
Comparators	GLP-1 RAs only	Including all comparators described in scope	No changes
Treatment strategies	Comparisons made within each recommended maintenance dose step (titration not allowed)	Comparisons made between all maintenance doses (titration allowed)	All comparisons reported[a] (titration not allowed)
Costs	2022 and 2021 values (treatment costs and complication costs respectively)	Inflating all costs to the same price year, preferably 2022	✓ EAG
BMI inputs	BMI changes calculated from body weight changes[b] (from NMA)	BMI directly from NMA when available (calculated from body weight otherwise)	✓ EAG
Device utility	Device utility added for tirzepatide and dulaglutide (except for comparison with oral semaglutide)	No device utility associated with tirzepatide or dulaglutide	✓ EAG

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[a] Company maintains 'within dose step' comparisons most relevant. [b] Assuming average height of 1.68cm reported for THIN population.
Abbreviations: BMI, body mass index; GLP-1, Glucagon-Like Peptide-1; NMA, network meta-analysis; RA, receptor agonist.

Summary of company and EAG base case assumptions (2)

Assumption	Company base case	EAG base case	Revised base case
Combining multiple disutility values	Additive method	Multiplicative approach preferred	No changes
Risk factor progression	Assumed constant for SBP, HDL, LDL and BMI after a year up to treatment intensification	Assuming UKPDS OM2 risk factor progression for all risk factors	✓ EAG (constant for SBP and BMI but justification given)
Treatment discontinuation/ intensification	When 7.5% HbA1c threshold reached (no other causes included)	Including additional causes for treatment discontinuation (than reaching the HbA1c threshold)	No changes
Adverse events	Only nausea included (hypoglycaemia only for basal insulin therapy)	Including all relevant adverse events (also vomiting)	No changes
Age adjustment	No age-adjustment	Including age-adjustment*	✓ EAG (higher than general population at the same age)

*EAG notes company's high baseline utility for T2D (higher than general population and higher than in identified review)

Abbreviations: BMI, body mass index; T2D, type 2 diabtes; HbA1c, Glycated Haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; UKPDS, UK Prospective Diabetes Study.

Company revised base case results

Tirzepatide 5 mg: Deterministic incremental revised base case results

	Total costs (£)	Total QALYs	Incremental costs (£)[a]	Incremental QALYs[a]	ICER[a] (£/ QALY)	NHB[a] (QALYs)
Tirzepatide 5 mg	[redacted]	8.715	--	--	--	--
Dulaglutide 1.5 mg*	[redacted]	8.615	705	0.100	7,073	0.064
Dulaglutide 3.0 mg	[redacted]	8.636	644	0.079	8,182	0.047
Dulaglutide 4.5 mg	[redacted]	8.657	628	0.058	10,891	0.026
Semaglutide 0.5 mg*	[redacted]	8.634	682	0.081	8,401	0.047
Semaglutide 1.0 mg	[redacted]	8.673	708	0.042	16,817	0.007
Oral semaglutide 7 mg*	[redacted]	8.595	742	0.120	6,202	0.083
Oral semaglutide 14 mg	[redacted]	8.642	719	0.073	9,873	0.037
Liraglutide 1.2 mg*	[redacted]	8.581	672	0.134	5,021	0.100
Liraglutide 1.8 mg	[redacted]	8.600	-409	0.115	Dominant	0.135

[a] tirzepatide versus comparator; *comparisons considered most relevant by company.
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

Company revised base case results

Tirzepatide 10 mg: Deterministic incremental revised base case results

	Total costs (£)	Total QALYs	Incremental costs[a] (£)	Incremental QALYs[a]	ICER[a] (£/ QALY)	NHB[a] (QALYs)
Tirzepatide 10 mg	[redacted]	8.768	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	8.615	1,723	0.153	11,272	0.067
Dulaglutide 3.0 mg*	[redacted]	8.636	1,662	0.132	12,599	0.049
Dulaglutide 4.5 mg	[redacted]	8.657	1,646	0.111	14,851	0.029
Semaglutide 0.5 mg	[redacted]	8.634	1,700	0.134	12,651	0.049
Semaglutide 1.0 mg*	[redacted]	8.673	1,726	0.095	18,115	0.009
Oral semaglutide 7 mg	[redacted]	8.595	1,760	0.173	10,183	0.085
Oral semaglutide 14 mg*	[redacted]	8.642	1,737	0.126	13,786	0.039
Liraglutide 1.2 mg	[redacted]	8.581	1,690	0.187	9,038	0.102
Liraglutide 1.8 mg*	[redacted]	8.600	609	0.168	3,625	0.138

[a] tirzepatide versus comparator; *comparisons considered most relevant by company.
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

Company revised base case results

Tirzepatide 15 mg: Deterministic incremental revised base case results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs[a]	ICER[a] (£/ QALY)	NHB[a] (QALYs)
Tirzepatide 15 mg	[redacted]	8.808	--	--	--	--
Dulaglutide 1.5 mg	[redacted]	8.615	2,047	0.192	10,642	0.090
Dulaglutide 3.0 mg	[redacted]	8.636	1,987	0.171	11,586	0.072
Dulaglutide 4.5 mg*	[redacted]	8.657	1,970	0.150	13,104	0.052
Semaglutide 0.5 mg	[redacted]	8.634	2,025	0.174	11,641	0.073
Semaglutide 1.0 mg*	[redacted]	8.673	2,051	0.135	15,209	0.032
Oral semaglutide 7 mg	[redacted]	8.595	2,085	0.212	9,815	0.108
Oral semaglutide 14 mg*	[redacted]	8.642	2,061	0.166	12,453	0.062
Liraglutide 1.2 mg	[redacted]	8.581	2,014	0.227	8,893	0.126
Liraglutide 1.8 mg*	[redacted]	8.600	934	0.208	4,498	0.161

[a] tirzepatide versus comparator; *comparisons considered most relevant by company.
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years.

Company revised base case results

Probabilistic revised base case results (tirzepatide vs comparator)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/ QALY)	Probability of tirzepatide being cost-effective[a]
Tirzepatide 5 mg	[redacted]	7.224				
Semaglutide 0.5 mg	[redacted]	7.138	707	0.087	8,149	70.6%
Tirzepatide 10 mg	[redacted]	7.286				
Semaglutide 1.0 mg	[redacted]	7.174	1,585	0.112	14,137	65.3%
Tirzepatide 15 mg	[redacted]	7.331				
Semaglutide 1.0 mg	[redacted]	7.174	1,801	0.157	11,506	77.3%

[a] assuming a willingness to pay threshold of £20,000 per QALY gained.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Deterministic scenario analyses

Clinical drivers and duration of therapy: tirzepatide 10 mg vs semaglutide 1.0 mg[a]

No.	Scenario*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
	Company revised base case	1,726	0.095	18,115
1	No HbA1c difference	[redacted]	[redacted]	39,085
2	No SBP difference	[redacted]	[redacted]	19,474
3	No serum lipids difference	[redacted]	[redacted]	18,433
4	No BMI difference	[redacted]	[redacted]	30,878
5	HDL and LDL changes for tirzepatide matched to dulaglutide	1,745	0.088	19,724
6	Only HbA1c difference between treatments	[redacted]	[redacted]	35,059
7	Intensification to insulin after 3 years	[redacted]	[redacted]	17,512
8	Intensification to insulin after 5 years	[redacted]	[redacted]	23,939
9	Second intensification to basal-bolus therapy	[redacted]	[redacted]	15,845
10	Intensification at HbA1c 8.5% threshold	[redacted]	[redacted]	27,251
11	Intensification at HbA1c 9.5% threshold	[redacted]	[redacted]	33,008

*Sources: Scenario 5: company response to EAG report, May 2023; Scenarios 1-4, 6-11: additional sensitivity analyses, May 2023.
Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; ICER, incremental cost-effectiveness ratio; LDL, low-density lipoprotein; QALYs, quality-adjusted life years; SBP, systolic blood pressure.

Deterministic scenario analyses

Other clinical assumptions: tirzepatide 10 mg vs semaglutide 1.0 mg

No.	Scenario*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
	Company revised base case	1,726	0.095	18,115
1	SURPASS-2 population characteristics	1,286	0.090	14,236
2	Sulfonylurea added to background therapy	[redacted]	[redacted]	18,416
3	BMI changes estimated from body weight changes	[redacted]	[redacted]	18,846
4	UKPDS OM2 renal failure estimation	[redacted]	[redacted]	17,939
5	UKPDS OM2 mortality risk estimation	[redacted]	[redacted]	18,157
6	Cause-subtracted life tables for mortality risk	[redacted]	[redacted]	14,278

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*Sources: Scenario 1: company response to EAG report, May 2023; Scenarios 2-6: additional sensitivity analyses, May 2023.
Abbreviations: BMI, body mass index; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Deterministic scenario analyses

Health state utility values: tirzepatide 10 mg vs semaglutide 1.0 mg

No.	Scenario*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
	Company revised base case	1,726	0.095	18,115
1	Weight loss utilities included in year 1	1,726	0.106	16,337
2	No weight/BMI utilities	[redacted]	[redacted]	27,997
3	Device utility included	[redacted]	[redacted]	16,893
4	No nausea utilities	[redacted]	[redacted]	17,577
5	No hypoglycaemia utilities	[redacted]	[redacted]	21,224
6	No age-adjustment on utilities	[redacted]	[redacted]	16,938
7	Multiplicative approach to combining utilities (with age-adjustment)	[redacted]	[redacted]	24,911

*Sources: Scenario 1: company response to EAG report, May 2023; Scenarios 2-7: additional sensitivity analyses, May 2023.
Abbreviations: BMI, body mass index; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Deterministic scenario analyses

Costs, time horizon and discounting: tirzepatide 10 mg vs semaglutide 1.0 mg

No.	Scenario*	Incremental costs (£)	Incremental QALYs	ICER (£/QALY gained)
	Company revised base case	1,726	0.095	18,115
1	Costs associated with nausea included	1,735	0.095	18,205
2	Health state costs associated with T2D included	1,791	0.095	18,792
3	Complication costs taken from alternative sources (lit. review)	[redacted]	[redacted]	17,685
4	5-year time horizon	[redacted]	[redacted]	33,518
5	10-year time horizon	[redacted]	[redacted]	24,853
6	15-year time horizon	[redacted]	[redacted]	20,693
7	20-year time horizon	[redacted]	[redacted]	19,331
8	0% discount rate (costs and clinical benefits)	[redacted]	[redacted]	14,602
9	6% discount rate (costs and clinical benefits)	[redacted]	[redacted]	20,391

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*Sources: Scenarios 1-2: company response to EAG report, May 2023; Scenarios 3-9: additional sensitivity analyses, May 2023.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; T2D, type 2 diabetes.

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Thank you.

Back-up slides

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Adverse events

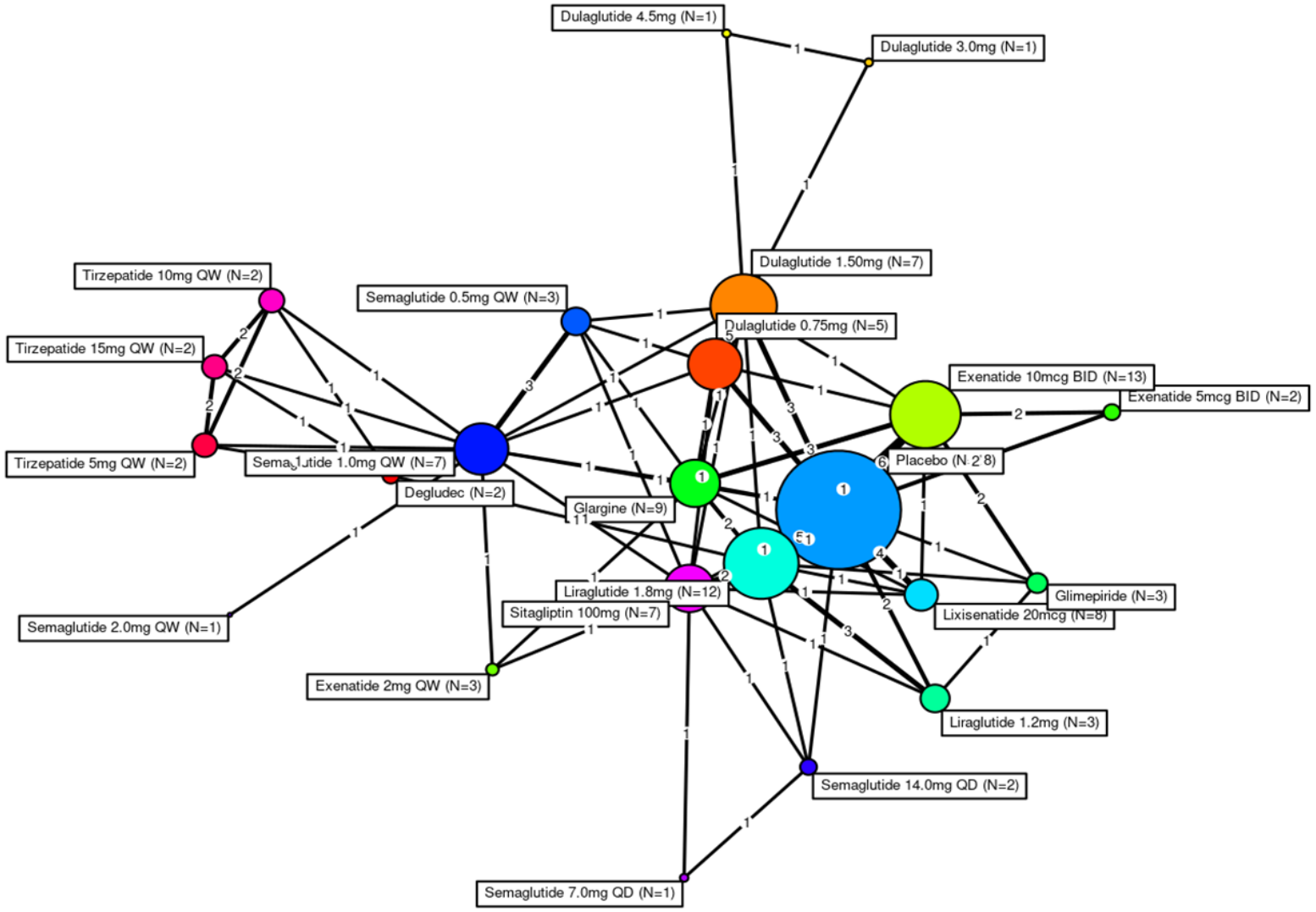
Category[a] Placebo-controlled analysis set n (%)	TZP all doses (N=718)	Placebo (N=235)	TZP all doses vs placebo p-value
Deaths[b]	[redacted]	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]	[redacted]
Discontinuation from study due to AE	[redacted]	[redacted]	[redacted]
Discontinuation from study drug due to AE[c]	[redacted]	[redacted]	[redacted]
TEAEs	[redacted]	[redacted]	[redacted]
TEAEs occurring in at least 5% of patients in any treatment group			
Nausea	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]

a Patients may be counted in more than one category; b Deaths also included as SAEs and discontinuations due to AEs; c Patients remained in study after permanent discontinuation of study drug and initiation of an alternative antihyperglycaemic medication so additional data could be collected; such patients may have subsequently discontinued study for same or a different reason

Abbreviations: AE, adverse event; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TZP, tirzepatide

NMA/ITC network diagram

Main analysis network for HbA1c (%) change from baseline



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Abbreviations: BID, twice a day; CS, company submission; Hb1Ac, glycated haemoglobin; QD, once a day; QW, once weekly

NMA/ITC results: Pairwise results- HbA1c (%) change from baseline

Column versus row	TZP 5 mg	TZP 10 mg	TZP 15 mg
Placebo	[redacted]	[redacted]	[redacted]
Tirzepatide 5 mg QW	-	[redacted]	[redacted]
Tirzepatide 10 mg QW	[redacted]	-	[redacted]
Tirzepatide 15 mg QW	[redacted]	[redacted]	-
Semaglutide 0.5 mg QW	[redacted]	[redacted]	[redacted]
Semaglutide 1.0 mg QW	[redacted]	[redacted]	[redacted]
Liraglutide 1.2 mg	[redacted]	[redacted]	[redacted]
Liraglutide 1.8 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 0.75 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 1.5 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 3.0 mg	[redacted]	[redacted]	[redacted]
Dulaglutide 4.5 mg	[redacted]	[redacted]	[redacted]
Semaglutide 7.0 mg QD	[redacted]	[redacted]	[redacted]
Semaglutide 14.0 mg QD	[redacted]	[redacted]	[redacted]
Exenatide 2 mg QW	[redacted]	[redacted]	[redacted]
Exenatide 5 mcg BID	[redacted]	[redacted]	[redacted]
Exenatide 10 mcg BID	[redacted]	[redacted]	[redacted]
Lixisenatide 20 mcg	[redacted]	[redacted]	[redacted]

Abbreviations: BID, twice a day; CrI, credible interval; HbA1c, glycated haemoglobin; QD, once a day; QW, once weekly; TZP, tirzepatide

Key issue: Age-adjustment for utility values: none for older age

EAG: Prefers base case utility score to include age-adjustment

Background

- Company use base utility score of 0.815 for patients for each year they were alive in the simulation
- No age-adjustment used in base-case analysis but explored in sensitivity analyses (Ara and Brazier 2010)
- NICE methods guide: If baseline utility values are extrapolated over long time horizons, they should be adjusted so they don't exceed general population values at a given age

Company - adjusting utilities for age:

- Poses risk of double-counting the effect of age on QoL, as unadjusted utilities already reflect impact of complications on aging population
- Not included to align with NG28 economic modelling
- Explored in sensitivity analysis → little impact on cost-effectiveness

EAG comments

- Base-case utility score is relatively high, and overtime potential overestimation will likely increase due to lack of age-adjustment
- Prefers base-case scenario to include age-adjustment (ensuring that utility does not exceed the age-matched general population utility as these estimates will provide a more conservative ICER estimate

	Utility value
Company base case	0.815
UK general population utility (64 years old)	0.804
UK general population utility (65-74 years old)	0.785

Should utilities be adjusted for age?

Abbreviations: ICER, incremental-cost effectiveness ratio, QoL, quality of life