



Efficacy and Safety of Tirzepatide Compared with GLP-1 RAs in Patients with Type 2 Diabetes Treated with Basal Insulin: A Network Meta-analysis

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ABSTRACT

Introduction: The relative efficacy and safety of tirzepatide was compared with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in patients with type 2 diabetes mellitus (T2DM) treated with basal insulin using a network meta-analysis (NMA).

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Methods: A systematic literature review was performed to identify randomized controlled trials of GLP-1 RAs in patients with T2DM treated with insulin and an antihyperglycaemic drug. For the NMA, studies included trials with 100% of patients treated with basal insulin background therapy with a titration scheme comparable to the SURPASS-5 trial. The following data were extracted for efficacy and safety assessment at the primary endpoint of each study: changes from baseline in glycated haemoglobin (HbA1c) and body weight and the incidence of nausea, vomiting or diarrhoea, hypoglycaemia, and patients discontinuing treatment because of adverse events. In this study, a comparative analysis of tirzepatide was performed with the GLP-1 RAs dulaglutide, exenatide, and lixisenatide in addition to placebo.

Results: A total of six studies were included across the analyses. Tirzepatide 5, 10, and 15 mg showed statistically significant, greater reductions in HbA1c and body weight at the primary endpoint versus all GLP-1 RA comparators and placebo. Tirzepatide 5, 10, and 15 mg showed a statistically significant, higher likelihood of experiencing nausea compared with those who received placebo or exenatide 2 mg; no statistically significant differences were observed when compared with all other GLP-1 RA comparators. No statistically significant differences were observed in the proportions of patients who discontinued treatment because of adverse events

when tirzepatide 5, 10, and 15 mg were compared with GLP-1 RA comparators, apart from tirzepatide 10 and 15 mg versus placebo.

Conclusion: Tirzepatide demonstrated statistically significantly greater reductions in HbA1c and body weight when compared with selected GLP-1 RAs and placebo in patients with T2DM treated with basal insulin. Overall, the safety profile of tirzepatide was similar to that of GLP-1RAs.

Keywords: Basal insulin; GLP-1 receptor agonists; Glycaemic control; Network meta-analysis; Tirzepatide; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

Currently, there are no comparative data on the efficacy and safety of tirzepatide versus glucagon-like peptide 1 receptor agonists (GLP-1 RAs) added on to basal insulin.

This study sought to assess the relative efficacy and safety of tirzepatide versus GLP-1 RAs added on to basal insulin in patients with type 2 diabetes mellitus (T2DM) using a network meta-analysis.

What was learned from the study?

For change from baseline, tirzepatide 5, 10, and 15 mg demonstrated statistically significantly greater reductions in glycated haemoglobin (HbA1c) and body weight compared with placebo and the GLP-1 RAs dulaglutide, exenatide, and lixisenatide.

Tirzepatide is an efficacious treatment that offers patients with T2DM treated with basal insulin improved outcomes and a similar safety profile when compared with GLP-1 RAs.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease characterised by chronic hyperglycaemia [1]. T2DM is the most common form of diabetes and, as of 2017, has affected 462 million individuals worldwide, corresponding to 6.3% of the global population [2]. T2DM is associated with significant morbidity and premature mortality, and poor management of T2DM increases the risk of developing a range of comorbidities [3]. In addition, T2DM is associated with considerable global burden, exerting an economic strain on both individuals and within-country healthcare systems [4]. Clinical guidelines acknowledge the importance of obesity management and recommend diet and lifestyle interventions for patients with T2DM who are overweight or have obesity; if needed, diet and lifestyle interventions should be supplemented with an antihyperglycaemic agent with proven weight loss benefits [5, 6]. Medications that address the incretin effect and other defective pathophysiological pathways such as glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) are important tools in the treatment of T2DM [7, 8]. Tirzepatide, a long-acting GIP receptor and GLP-1 RA, is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1, and it has been approved for the treatment of T2DM and chronic weight management [9–12].

Tirzepatide has demonstrated significant improvements in glycaemic control compared with placebo for managing glycated haemoglobin (HbA1c) levels, and its efficacy has been shown to depend on both GIP and GLP-1 receptor-mediated actions [13]. Several phase 3 randomized controlled trials (RCTs) for tirzepatide (SURPASS trials) investigated the clinical effectiveness and safety of tirzepatide as a treatment for T2DM [11, 14–21]. The SURPASS trials compared three doses of tirzepatide (5, 10, and 15 mg) with a range of comparators and background antihyperglycaemic agents. In the

SURPASS trials, all three doses of tirzepatide demonstrated superior HbA1c reductions and weight loss in comparison with placebo [14], a GLP-1 RA [15], and insulin [14–21]. A long-term cardiovascular outcomes trial, SURPASS-CVOT, is currently ongoing to assess the efficacy and safety of tirzepatide in people with T2DM and increased cardiovascular risk [22]. While the SURPASS trials provided direct comparative evidence on the efficacy and safety of tirzepatide versus a wide range of comparators, it was not feasible to conduct RCTs versus all relevant comparators in all clinical settings, including all GLP-1 RAs. For this reason, comparative data on the efficacy and safety of tirzepatide versus GLP-1 RAs in basal insulin population is sparse, and consequently, a network meta-analysis (NMA) approach has been employed to assess the relative efficacy and safety of tirzepatide versus additional standard-of-care treatments. An NMA is a method for comparing multiple treatments at the same time in a single analysis by using direct and indirect evidence within a network of RCTs [23]. NMAs can help in evaluating the comparative effectiveness of different treatments used in clinical practice [23]. The objective of this NMA was to compare the efficacy and safety of tirzepatide with GLP-1 RAs in patients with T2DM receiving treatment with basal insulin.

METHODS

Study Design

The NMA was based on evidence from RCTs identified in a systematic literature review (SLR) on the safety and efficacy of tirzepatide and selected GLP-1 RAs in comparison to themselves, basal or premixed insulin, oral antihyperglycaemic drugs (OADs) of interest, or placebo for the treatment of T2DM. Data for tirzepatide were obtained from the SURPASS-5 trial at the time this analysis was conducted. The studies included are described below.

This article is based on previously conducted studies and does not contain any new studies

with human participants or animals performed by any of the authors.

SLR Procedures

The SLR was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24] and the Centre for Reviews and Dissemination (CRD) [25]. The Population, Intervention, Comparison, Outcomes, and Study (PICOS) framework [26] was used to establish several inclusion criteria for studies to be included in this review.

Eligibility Criteria

Eligible studies included RCTs with a duration of ≥ 16 weeks of a single treatment that assessed the efficacy and safety of tirzepatide (5, 10, or 15 mg once weekly [QW]) and GLP-1 RAs in adult patients (≥ 18 years of age) with T2DM.

Information Sources and Searches

At the time of analysis, searches were conducted in Cochrane, Embase, and MEDLINE databases (including e-publications ahead of print) in September 2021. An updated search was done in October 2021 in the same databases, thus resulting in 22 publications that were eligible for this NMA. Relevant clinical study reports and conference abstracts were also assessed when available. The full search strategy and list of databases and other sources are presented in Supplementary Material, Sect. 1 (Table S1.1 to S1.3). The searches were further updated in June 2022, January 2023, and February 2024, but no eligible publications for the NMA were found.

Study Selection

Studies were screened against PICOS eligibility criteria in double and independently by two reviewers who combined their decisions and resolved any disagreements. One researcher extracted the data, and a second reviewer independently reviewed all the data extracted for accuracy and completeness. Studies were assessed for risk of bias using the Cochrane risk of bias assessment

tool and the CRD tool, and responses were consolidated.

NMA Procedures

The NMA was reported in accordance with the PRISMA-NMA, which is an extension statement for reporting systematic reviews incorporating NMAs of healthcare interventions [27].

Inclusion criteria for studies in the NMA included trials with 100% of patients who received basal insulin background therapy with a titration scheme comparable to SURPASS-5 (Table 1). Studies of patients without basal insulin and patients who received other insulins (e.g. bolus insulin) or a combination of basal insulin and other insulins were excluded.

Multiple efficacy and safety outcomes were identified in the SLR and extracted from the studies for inclusion in this NMA. It is anticipated that tirzepatide will be used as an alternative treatment to current GLP-1 RAs in future clinical practice. The reference treatment in the NMA was placebo and the results are presented as treatment relative to tirzepatide 5, 10, and 15 mg. A feasibility assessment was conducted to assess the quality of the studies and to ensure that the study designs, populations, treatments, outcomes, and timepoints were aligned to provide robust analysis and clinically meaningful results.

Efficacy Outcomes

All trials identified in the SLR were examined for data on primary efficacy outcomes, including change from baseline in HbA1c and body weight and the proportion of patients with T2DM achieving HbA1c < 7.0% or ≤ 6.5%. Secondary efficacy outcomes included the proportion of patients with T2DM reaching weight loss of ≥ 5% and change from baseline in low- and high-density lipoprotein cholesterol, triglycerides, total cholesterol, systolic blood pressure (SBP), and diastolic blood pressure.

Safety Outcomes

The safety outcomes assessed in the NMA included the proportion of patients with T2DM

with ≥ 1 episode of hypoglycaemia with blood glucose (BG) < 54 mg/dL (with or without severe hypoglycaemia), the proportion of patients with T2DM experiencing nausea, vomiting, or diarrhoea, and the proportion of patients with treatment discontinuation due to adverse events (AEs).

The definitions for hypoglycaemia varied between trials, including with or without severe hypoglycaemia, BG value of < 54/56 mg/dL, or symptomatic hypoglycaemia. In order to ensure consistency and to facilitate understanding, it was opted to define an episode of hypoglycaemia as “with BG < 54 mg/dL (with or without severe hypoglycaemia)”.

The analysis of AEs allowed for the inclusion of comparator studies with safety windows that ended outside the analysis window (26 ± 4 weeks).

Dose Escalation

The duration of dose escalation employed to reach the target dose of tirzepatide in the SURPASS-5 trial was 0 to 24 weeks [14, 21, 28]. The escalation period for tirzepatide 15 mg was 24 weeks to allow 20 weeks to escalate to 15 mg and an additional 4 weeks to reach a steady state, defined as achieving a stable concentration of the drug (tirzepatide) in the blood [29]. Since most comparator studies had a duration between 22 and 30 weeks (and all comparator studies reported on at least one outcome of interest between 20 and 28 weeks), the endpoints were analysed at 26 ± 4 weeks (weeks 22–30) for comparator data, compared to tirzepatide data at week 40. The time window of 26 ± 4 weeks allowed a balanced approach between data obtained from the dose escalation of tirzepatide and data available from the comparators.

Statistical Analysis

The NMA was conducted in Just Another Gibbs Sampler (JAGS), version 4.2.0, via R. A two-stage analytical approach was used for this NMA: (1) a frequentist meta-analysis was conducted to assess heterogeneity of the data, and (2) an NMA was conducted using Bayesian mixed treatment

Table 1 SURPASS-5 eligibility criteria for background therapy with associated titration scheme

SURPASS-5 basal insulin background therapy with a titration scheme [14]			
1. For visit 1, the patient was required to be taking once-daily IG (at least 0.25 IU/kg/day or 20 IU/day) and metformin (if applicable) for the preceding 3 months	2. When all the insulin doses administered during a particular period remained within the range of $\pm 20\%$, the IG dose was considered stable	3. Metformin doses were stable if they met the prescribed range of ≥ 1500 mg/day to the maximum approved dose as per the locally approved label during the specified period	4. Increases in IG dose at visit 3 were based on SMBG data from the prior week per the treat-to-target algorithm
IG treat-to-target method [14, 232]			
For patients with a FBG ^a of:		IG change if dose < 20 IU	IG change if dose ≥ 20 IU
≤ 3.9 mmol/L		-1 or -2 IU ^{b,c}	-2 to 4 IU ^{b,c}
4.0 to 5.5 mmol/L		No change	No change
5.6 to 6.6 mmol/L		$+1$ IU	$+2$ IU
6.7 to 7.7 mmol/L		$+2$ IU	$+4$ IU
7.8 to 9.9 mmol/L		$+3$ IU	$+6$ IU
≥ 10.0 mmol/L		$+4$ IU	$+8$ IU

IG treat-to-target method created from data from SURPASS-5 [14] and Riddle et al., 2003 [232]

FBG fasting blood glucose, IG insulin glargine, SMBG self-monitored blood glucose, IU international units

^aFBG is the median of the last 3 SMBG values

^bDecrease insulin dose by 1–2 IU or 2–4 IU based on hypoglycaemic episodes or their severity

^cNo insulin dose change is needed if only 1 hypoglycaemic episode with SMBG values between 54 mg/dL and 70 mg/dL was recorded

comparisons as described in the National Institute for Health and Care Excellence Decision Support Unit technical support documents [30].

Sensitivity Analysis

To evaluate the strength of the main analysis findings, a sensitivity analysis that considered outcomes measured at multiple timepoints was planned. The sensitivity analysis was conducted for continuous outcomes such as the change from baseline in HbA1c and weight. These endpoints were chosen because these are critical clinical endpoints in the management of diabetes and disease improvement/progression. A model-based NMA was conducted [31], allowing the inclusion of outcomes at multiple timepoints when studies reported three or more timepoints, on change from baseline in weight.

Presentation of Results

For the continuous endpoints, standardised median differences and 95% credible intervals (CrIs) were estimated for each treatment versus placebo and comparators [26, 27]. Median differences below 0 indicate a greater reduction in the outcome with the treatment (tirzepatide) versus the comparator; values above 0 indicate a lower reduction in the outcome with the treatment (tirzepatide) versus the comparator. For the binary endpoints, odds ratios (ORs) were estimated in each analysis. The OR represents the increase or decrease in the odds of an event occurring in one group compared with another. An $OR > 1$ indicates greater odds for the treatment arm compared to the control arm. Similarly, an OR between 0 and 1 indicates a reduction in odds for the treatment arm compared to the control arm. When both the upper and lower bounds of the CrIs around the OR are either > 1 or < 1 , a statistically significantly greater increase or reduction, respectively, in the odds of the event for the treatment arm compared to the control arm is indicated. When the CrI crosses 1, a lack of a statistically significant difference in the odds between the two arms is indicated. Within the Bayesian framework NMA, the significance of a treatment effect is determined by the 95% CrI, which represents a 95%

probability that the true treatment effect lies within this interval.

RESULTS

Identification of Publications

A PRISMA flow diagram of the SLR is shown in Fig. 1. Overall, 205 original studies were included in this SLR, which were reported in a total of 246 publications. Of the included trials, six trials [14, 32–36] were considered potentially relevant for inclusion in the NMA and 199 were excluded. The rationale for including and excluding these trials is detailed in Tables S2.1 and S2.2 of the Supplementary Material.

In brief, trials were excluded ($n = 199$) if patients were not treated with basal insulin therapy \pm OADs as background therapy ($n = 196$) [11, 15–17, 37–228] or if the study design or insulin titration schemes were not comparable to SURPASS-5 ($n = 2$). For example, the mixed background therapy and insulin titration in the PIONEER 8 study [229] and the insulin titration in SUSTAIN 5 [230] were not comparable to SURPASS-5. Finally, the SIMPLE trial was excluded because liraglutide 1.8 mg was compared with insulin aspart and not basal insulin treatment [231], hence not meeting the NMA criteria.

NMA Results

Overall, six trials [14, 32–36] and eight treatments were considered in the NMA and formed a connected network (Fig. 2). No restrictions were placed on the number of comparators; however, the final comparators were included owing to the feasibility and comparability of the insulin titration schemes in the studies to SURPASS-5. The analysis was completed for the following comparators: dulaglutide 1.50 mg QW, exenatide 10 μ g twice daily (BID) (prefilled pen), exenatide 2.0 mg QW, lixisenatide 20 μ g once-daily (QD), and placebo. The quality assessment indicated a low risk of bias across the studies for elements of bias assessment (Table S3.1).

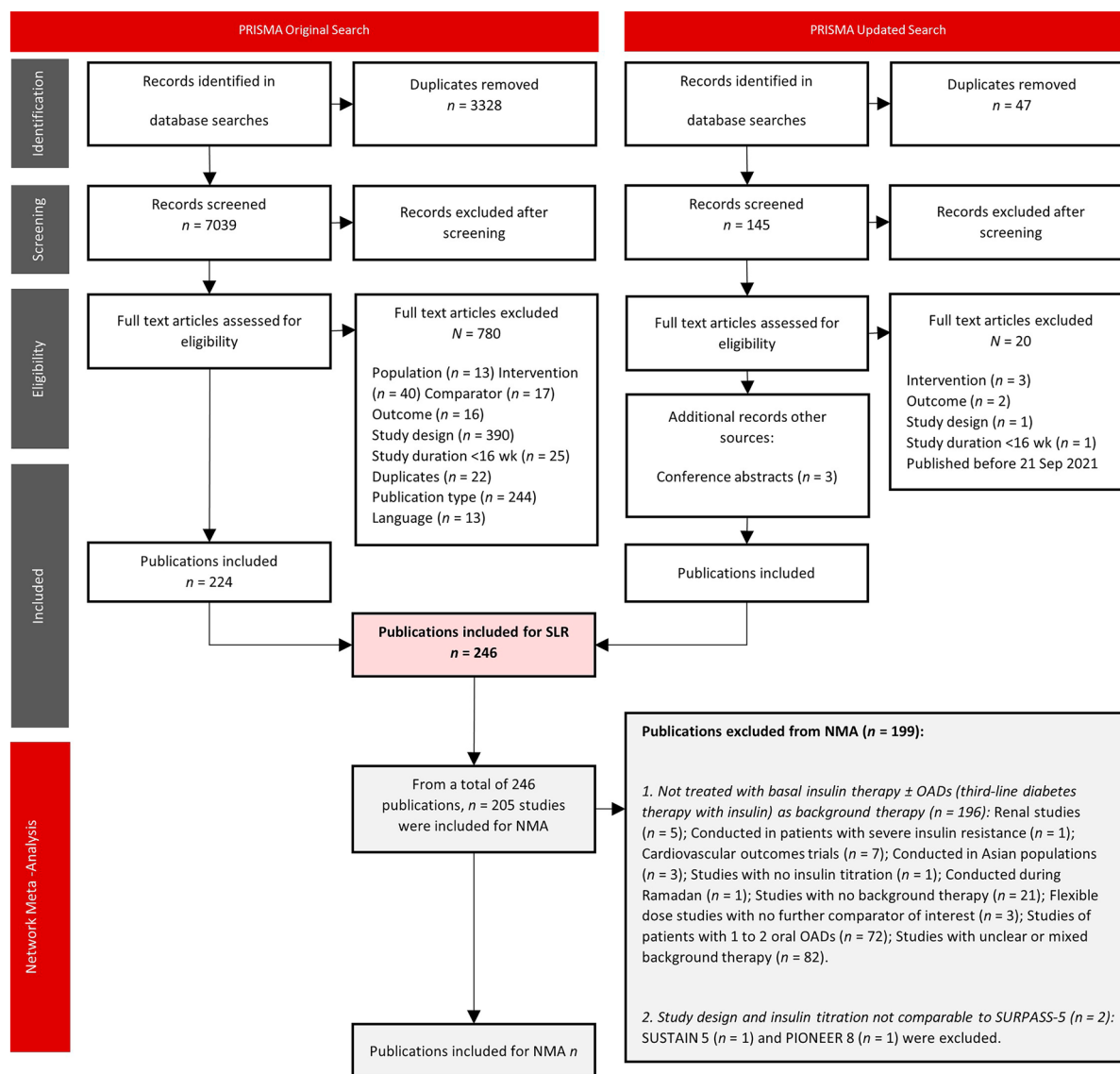


Fig. 1 PRISMA flow diagram of the SLR and NMA. The rationale for including and excluding trials is detailed in Sect. 2 of the Supplementary Material. NMA network meta-analysis, OADs oral antihyperglycaemic

drugs, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *SLR* systematic literature review, *wk* week(s)

Trial Characteristics

The six studies were double-blind trials, and treatment duration ranged from 24 to 40 weeks. No studies had a crossover design, and no studies included patients with comorbidities of interest. The primary efficacy measure was HbA1c for all studies, and secondary

measures included body weight, fasting blood glucose, self-monitored blood glucose, and insulin glargine dose. Safety measures included SBP, treatment-emergent AEs, and hypoglycaemic episodes.

The trial characteristics are summarized in Table 2.

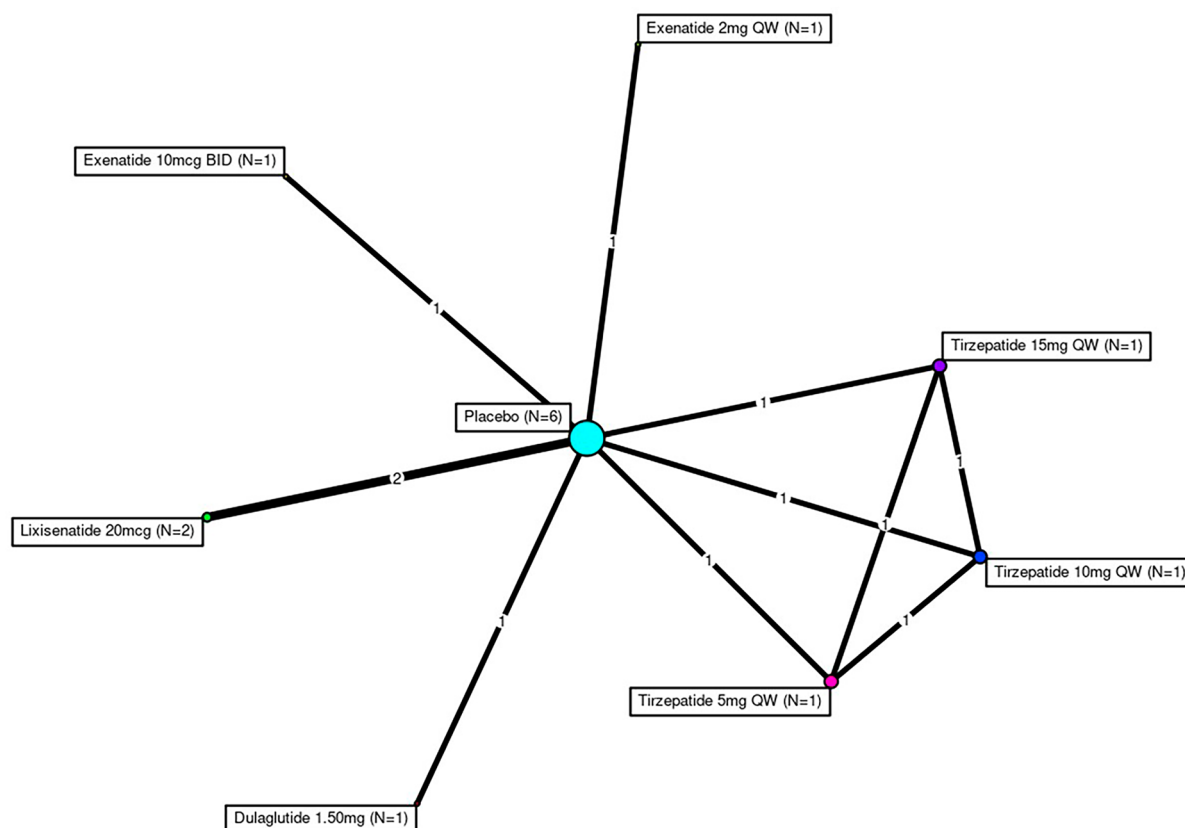


Fig. 2 Evidence network for 6 studies and 8 treatments (nodes) included in the network meta-analysis. The thickness of the lines indicates the number of studies comparing between the interventions, and the radius of the circle shows the number of studies within a given treatment arm. Outcomes included change from baseline in HbA1c; proportion of patients reaching target HbA1c < 7.0%; change

from baseline in weight (kg); proportion of patients experiencing nausea, vomiting, and diarrhoea; proportion of patients with ≥ 1 episode of hypoglycaemia with blood glucose < 54 mg/dL (with or without severe hypoglycaemia); and proportion of patients with treatment discontinuation. *BID* twice daily, *HbA1c* glycated haemoglobin, *QW* once weekly

Participants Characteristics in the Included Trials

A total of 2436 patients with T2DM were included in the analysis (male/men, $n=1256$; female/women, $n=1180$) who received treatment with tirzepatide ($n=355$) or a comparator (lixisenatide, $n=551$; exenatide, $n=368$; dulaglutide, $n=150$; or placebo, $n=1012$). Mean age in the treatment arms across the six included studies ranged from 56 to 62 years. At baseline, mean HbA1c ranged from 7.6% to 8.5%. Mean body weight ranged from 86.8 to 96.3 kg, and mean body mass index (BMI) ranged from 31.7 to 34.1 kg/m². The mean duration of diabetes

ranged from 8.7 to 14.1 years. Background therapy included insulin glargine \pm metformin, basal insulin \pm metformin, insulin glargine + metformin \pm thiazolidinedione, and insulin glargine \pm OADs (Table 3).

Efficacy Outcomes

Glycaemic Control

Change from Baseline in HbA1c

All six trials reported data on change in HbA1c from baseline to week 40 (tirzepatide) and week 26 (± 4 weeks) (comparators). Tirzepatide

Table 2 Trial characteristics

Trial	Author, year	Study design	Duration	Inclusion criteria	Primary efficacy measures	Secondary efficacy measures	Safety measures
SURPASS-5 (tirzepatide 5, 10, 15 mg)	Dahl et al., 2022	Phase 3 RCT Double-blind Parallel group Multicentre Placebo-controlled	40 weeks + 4 weeks safety follow-up	Adults with T2DM Baseline HbA1c of 7.0–10.5% BMI ≥ 23 kg/m ² Stable dose of daily IG ± MET	HbA1c	HbA1c < 7.0%, ≤ 6.5%, and < 5.7% Body weight loss SMBG FSG IG dose	TEAEs Early discontinuation due to AEs Adjudicated pancreatitis Serum calcitonin Allergic and hypersensitivity reactions Blood pressure Hypoglycaemic events Initiation of rescue therapy
GetGoal-L (lixisenatide 20 µg)	Riddle et al., 2013(b)	Phase 3 RCT Double-blind Parallel group Placebo-controlled	24 weeks	Adults with T2DM for ≥ 1 year HbA1c of 7.0–10.0% BMI > 20 kg/m ² Stable dose of basal insulin ± MET	HbA1c	HbA1c < 7.0% or ≤ 6.5% FPG Body weight SMPG 2-h PPG Daily basal insulin dose Rescue therapy	AEs Symptomatic hypoglycaemia Clinical laboratory data

Table 2 continued

Trial	Author, year	Study design	Duration	Inclusion criteria	Primary efficacy measures	Secondary efficacy measures	Safety measures
GetGoal-Duo 1 (lixisenatide 20 µg)	Riddle et al., 2013(a)	Phase 3 RCT Double-blind Parallel group Placebo-controlled	12-week run-in phase + 24-week treatment period	Adults with T2DM for ≥ 1 year HbA1c ≥ 7.0 to ≤ 10.0% BMI > 20 kg/m ² Stable dose of MET 1.5 g/day ± SU/glinide/TZD or combination	HbA1c	2-h PPG Blood glucose SMPG FPG Body weight IG dose HbA1c < 7.0% Rescue therapy	TEAEs Symptomatic hypoglycaemia Injection site reactions Allergic events Clinical laboratory data
DURATION-7 (exenatide 2 mg QW)	Guja et al., 2018	Phase 3 RCT Double-blind Parallel group Placebo-controlled	8-week IG titration phase + 28-week treatment phase + 10-week safety follow-up	Adults (≥ 18 years) with T2DM HbA1c of 7.5%–12.0% at screening and 7.0–10.5% at randomization FPG < 280 mg/dL Stable IG ≥ 20 U/day for ≥ 6 weeks with diet and exercise alone or with stable MET ≥ 1500 mg/day for > 8 weeks ± SU	HbA1c	Body weight 2-h PPG HbA1c < 7.0% IG dose Body weight SBP	TEAEs Hypoglycaemic events Vital signs Injection site-related AEs
Buse et al. (exenatide 10 µg BID)	Buse et al., 2011	Phase 3 RCT Double-blind Parallel group Placebo-controlled	30 weeks	Adults (≥ 18 years) with T2DM HbA1c of 7.1%–10.5% BMI ≤ 45 kg/m ² IG ≥ 20 U/day without any other insulin ± stable MET or pioglitazone for ≥ 3 months	HbA1c	FPG SMBG Vital signs Weight Waist circumference Insulin doses	AEs Hypoglycaemic episodes Vital signs Heart rate Clinical laboratory data

Table 2 continued

Trial	Author, year	Study design	Duration	Inclusion criteria	Primary efficacy measures	Secondary efficacy measures	Safety measures
AWARD-9 (dulaglutide 1.50 mg)	Pozzilli et al., 2017	Phase 3	3 weeks screening + 28 weeks treatment	Adults with T2DM	HbA1c	Body weight	AEs
		RCT		HbA1c $\geq 7.0\%$ to $\leq 10.5\%$		HbA1c $< 7.0\%$	Vital signs
		Double-blind		BMI ≤ 45 kg/m ²		and $\leq 6.5\%$	Hypoglycaemic events
		Parallel arm		Stable dose of		FSG	
		Multicentre		IG \pm MET ≥ 1500 mg/day for ≥ 3 months before visit 1		SMPG	Clinical laboratory values
		Placebo-controlled				IG dose	

AE adverse event, *BID* twice daily, *BMI* body mass index, *FPG* fasting plasma glucose, *FSG* fasting serum glucose, *HbA1c* glycated haemoglobin, *IG* insulin glargine, *MET* metformin, *PPG* postprandial glucose, *QW* once weekly, *RCT* randomized controlled trial, *SBP* systolic blood pressure, *SMBG* self-monitored blood glucose, *SMPG* self-monitored plasma glucose, *SU* sulfonylurea, *T2DM* type 2 diabetes mellitus, *TEAE* treatment-emergent adverse event, *TZD* thiazolidinedione

5, 10, and 15 mg showed significantly greater reductions in HbA1c from baseline compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 µg, and lixisenatide 20 µg (Fig. 3a; Table S4.1).

Proportion of Patients Reaching Target HbA1c < 7.0%

All six trials reported data on the proportion of patients achieving HbA1c < 7.0% from baseline to week 40 (tirzepatide) and week 26 (± 4 weeks) (comparators) (Fig. 3b; Table S4.2). A significantly greater proportion of patients receiving tirzepatide 5, 10, and 15 mg reached a target HbA1c < 7.0% compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 µg, and lixisenatide 20 µg. The likelihood of achieving a target HbA1c < 7.0% ranged from 4.5 times more likely (95% CrI 1.7, 12.7) with tirzepatide 5 mg versus exenatide 2 mg to up to 14.8 times more likely (95% CrI 6.2, 40.4) with tirzepatide 15 mg versus lixisenatide 20 µg. However, the results showed a very large 95% CrI, indicating uncertainty around the estimated treatment difference. Therefore, this estimate should be interpreted with caution.

Proportion of Patients Reaching Target HbA1c $\leq 6.5\%$

Five trials reported data on the proportion of patients reaching HbA1c $\leq 6.5\%$ from baseline to week 40 (tirzepatide) and week 26 (± 4 weeks) (comparators) (Fig. 3c; Table S4.3). A significantly greater proportion of patients receiving tirzepatide 5, 10, and 15 mg reached a target HbA1c $\leq 6.5\%$ compared with placebo, dulaglutide 1.50 mg, exenatide 10 µg, and lixisenatide 20 µg. The likelihood of achieving a target HbA1c $\leq 6.5\%$ ranged from 4.0 times more likely (95% CrI 1.7, 9.6) with tirzepatide 5 mg versus dulaglutide 1.50 mg to up to 23.1 times more likely (95% CrI 9.5, 62.7) with tirzepatide 15 mg versus lixisenatide 20 µg. However, the results showed a very large 95% CrI, indicating uncertainty around the estimated treatment difference. Therefore, this estimate should be interpreted with caution.

Table 3 Patient characteristics

Trial	Sample (N = 2436) ^a	Treatment	Mean (SD) age, years	Baseline		Background therapy			Insulin titration scheme	
				Mean (SD) BMI, kg/ m ²	Mean (SD) weight, kg	Mean (SD) HbA1c, %	Mean (SD) duration of diabetes, years	Baseline	Endpoint	
SUR- PASS-5	116	Tirzepatide 5 mg QW	62 (10)	33.6 (5.9)	95.8 (19.8)	8.3 (0.88)	14.1 (8.1)	IG (100%) ± MET (85%)	Mean IU/ day: 39.1	Week 40 mean IU/ day: 45.5
SUR- PASS-5	119	Tirzepatide 10 mg QW	60 (10)	33.4 (6.2)	94.5 (22.2)	8.36 (0.83)	12.6 (6.2)	IG (100%) ± MET (83%)	Mean IU/ day: 34.7	Week 40 mean IU/ day: 40.7
SUR- PASS-5	120	Tirzepatide 15 mg QW	61 (10)	33.4 (5.9)	96.3 (22.8)	8.23 (0.86)	13.7 (7.5)	IG (100%) ± MET (81%)	Mean IU/ day: 40.5	Week 40 mean IU/ day: 39.8
SUR- PASS-5	120	Placebo	60 (10)	33.2 (6.3)	94.1 (21.8)	8.37 (0.84)	12.9 (7.4)	IG (100%) ± MET (83%)	Mean IU/ day: 36.3	Week 40 mean IU/ day: 63.5
GetGoal-L	328	Lixisenatide 20 µg	57 (10)	31.9 (6.2)	87.1 (20.0)	8.4 (0.9)	12.5 (7.0)	Basal insulin (100%) ± MET (80%)	Mean (SD) units/day: 54 (34)	Week 24 mean (SD) units/day: 50 (28)
GetGoal-L	167	Placebo	57 (10)	32.6 (6.3)	88.9 (20.8)	8.4 (0.8)	12.4 (6.3)	Basal insulin (100%) ± MET (78%)	Mean (SD) units/day: 58 (35)	Week 24 mean (SD) units/day: 57 (35)

Table 3 continued

Trial	Sample (<i>N</i> = 2436) ^a	Treatment	Mean (SD) age, years	Baseline			Background therapy			Insulin titration scheme	
				Mean (SD) BMI, kg/ m ²	Mean (SD) weight, kg	Mean (SD) HbA1c, %	Mean (SD) duration of diabetes, years	IG	(100%) + MET ± TZD (12%)	Baseline	Endpoint
GetGoal- Duo 1	223	Lixisenatide 20 µg	56 (10)	32.0 (6.6)	87.3 (21.8)	7.6 (0.5)	9.6 (6.0)	IG	(100%) + MET ± TZD (12%)	Mean (SD) units/ day: 43.4 (18.9)	Week 24 mean (SD) units/ day: 46.7 (23.8)
GetGoal- Duo 1	223	Placebo	56 (10)	31.7 (6.0)	86.8 (20.4)	7.6 (0.5)	8.7 (5.8)	IG	(100%) + MET ± TZD (12%)	Mean (SD) units/ day: 44.2 (19.9)	Week 24 mean (SD) units/ day: 50.4 (26.4)
DURA- TION-7	231	Exenatide 2 mg QW	58 (9)	33.3 (6.1)	93.3 (20.0)	8.53 (0.91)	11.5 (6.6)	IG (100%) ± MET (84%)		Mean (SD) units/ day: 50.1 (21.4)	Week 28 mean (SD) units/ day: 51.9 (24.3)
DURA- TION-7	230	Placebo	58 (10)	34.1 (6.6)	94.7 (19.8)	8.53 (0.92)	11.1 (6.1)	IG (100%) ± MET (81%)		Mean (SD) units/ day: 52.0 (25.0)	Week 28 mean (SD) units/ day: 54.2 (26.9)

Table 3 continued

Trial	Sample (<i>N</i> = 2436) ^a	Treatment	Mean (SD) age, years	Baseline		Background therapy				Insulin titration scheme	
				Mean (SD) BMI, kg/ m ²	Mean (SD) weight, kg	Mean (SD) HbA1c, %	Mean (SD) duration of diabetes, years	Baseline	Endpoint		
Buse et al.	137	Exenatide 10 µg BID	59 (9)	33.8 (5.8)	95.4 (20.4)	8.32 (0.85)	12 (7)	IG (100%) ± OADs (66% MET alone, 2% TZD alone, 17% MET + TZD)	Mean (SD) units/ day: 49.5 (29.9)	Increase from baseline to week 30 units/day: 13 (9–17)	
Buse et al.	122	Placebo	59 (10)	33.1 (6.2)	93.4 (21.2)	8.5 (0.96)	12 (7)	IG (100%) ± OADs (75% MET alone, 5% TZD alone, 7% MET + TZD)	Mean (SD) units/ day: 47.4 (25.4)	Increase from baseline to week 30 units/ day: 20 (16–24)	
AWARD-9	150	Dulaglutide 1.50 mg	60 (10)	32.8 (4.9)	93.3 (17.5)	8.4 (0.9)	13.0 (7.5)	IG (100%) ± MET (89%)	Mean (SD) units/ day: 40.7 (23.1)	Week 28 mean (SD) units/ day: 54.6 (31.9)	
AWARD-9	150	Placebo	61 (10)	32.6 (4.9)	92.6 (17.1)	8.3 (0.8)	13.3 (7.7)	IG (100%) ± MET (88%)	Mean (SD) units/ day: 36.6 (21.5)	Week 28 mean (SD) units/day: 63.1 (37.3)	

BID twice daily, *BMI* body mass index, *HbA1c* glycated haemoglobin, *IG* insulin glargine, *IU* international units, *MET* metformin, *OAD* oral antihyperglycaemic drug, *QW* once weekly, *SD* standard deviation, *TZD* thiazolidinedione

^aTotal sample: *N* = 2436 (tirzepatide 5, 10 mg, and 15 mg QW; *n* = 355; lixisenatide 20 µg, *n* = 551; exenatide 2 mg QW; *n* = 231; exenatide 10 µg BID, *n* = 137; dulaglutide 1.50 mg, *n* = 150; and placebo, *n* = 1012)

Body Weight

Change from Baseline in Weight

All six trials reported change from baseline in weight to week 40 (tirzepatide) and week 26 \pm 4 weeks (comparators). Tirzepatide 5, 10, and 15 mg showed significantly greater reductions in weight from baseline compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 μ g, and lixisenatide 20 μ g. Differences ranged from 5.2 kg versus exenatide 10 μ g in favour of tirzepatide 5 mg and 11.5 kg versus lixisenatide 20 μ g in favour of tirzepatide 15 mg (Fig. 4; Table S4.4).

Other efficacy outcomes, including the proportion of patients reaching weight loss of \geq 5% and change from baseline in lipoproteins, total cholesterol, triglycerides, and blood pressure, are available in the Supplementary Material, Sect. 5.

Safety Outcomes

Proportion of Patients Experiencing Nausea, Vomiting, and Diarrhoea

All six trials reported the proportion of patients experiencing nausea, vomiting, and diarrhoea (any grade permitted) at week 40 (tirzepatide) and week 26 (\pm 4 weeks) (comparators). A significantly higher proportion of patients receiving tirzepatide 5, 10, and 15 mg experienced nausea compared with placebo and exenatide 2 mg. No significant differences were observed when tirzepatide 5, 10, and 15 mg were compared with dulaglutide 1.50 mg, exenatide 10 μ g, and lixisenatide 20 μ g (Fig. 5a; Table S6.1).

No significant differences were observed in the proportion of patients experiencing vomiting when tirzepatide 5 mg was compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 μ g, and lixisenatide 20 μ g. A higher proportion of patients experienced vomiting with tirzepatide 15 mg compared with placebo (6.1 [95% CrI 1.9, 28.3]) as well as with tirzepatide 10 mg and 15 mg compared with exenatide 2 mg (TZP 10 mg: 14.8 [95% CrI 1.1, 664.8]; TZP 15 mg: 26.3 [95% CrI 1.9, 1144.9]). No significant differences were observed when tirzepatide 15 mg was compared with dulaglutide 1.50 mg,

exenatide 10 μ g, and lixisenatide 20 μ g (Fig. 5b; Table S6.2). Caution must be used when interpreting these estimates as the results showed large 95% CrIs, indicating uncertainty around the estimated treatment difference.

No significant differences were observed in the proportions of patients experiencing diarrhoea when tirzepatide 5 mg or 10 mg was compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 μ g, and lixisenatide 20 μ g. A significantly greater proportion of patients receiving tirzepatide 15 mg experienced diarrhoea compared with placebo. However, no significant differences were observed when tirzepatide 15 mg was compared with dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 μ g, and lixisenatide 20 μ g (Fig. 5c; Table S6.3).

Proportion of Patients with \geq 1 Episode of Hypoglycaemia with BG < 54 mg/dL (with or Without Severe Hypoglycaemia)

All six trials reported the proportion of patients with \geq 1 episode of hypoglycaemia with BG < 54 mg/dL (with or without severe hypoglycaemia) to week 40 (tirzepatide) and week 26 (\pm 4 weeks) (comparators). No significant differences were observed in the proportions of patients experiencing \geq 1 episode of hypoglycaemia with BG < 54 mg/dL (with or without severe hypoglycaemia) when tirzepatide 5, 10, or 15 mg was compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 μ g, and lixisenatide 20 μ g (Fig. 6; Table S6.4).

Proportion of Patients with Treatment Discontinuation Due to AEs

All six trials reported the proportion of patients with treatment discontinuation due to AEs through week 40 (tirzepatide) and week 26 (\pm 4 weeks) (comparators). No significant differences were observed in the proportions of patients discontinuing treatment because of AEs when tirzepatide 5, 10, and 15 mg was compared with placebo, dulaglutide 1.50 mg, exenatide 2 mg, exenatide 10 μ g, and lixisenatide 20 μ g (Fig. 7; Table S6.5).

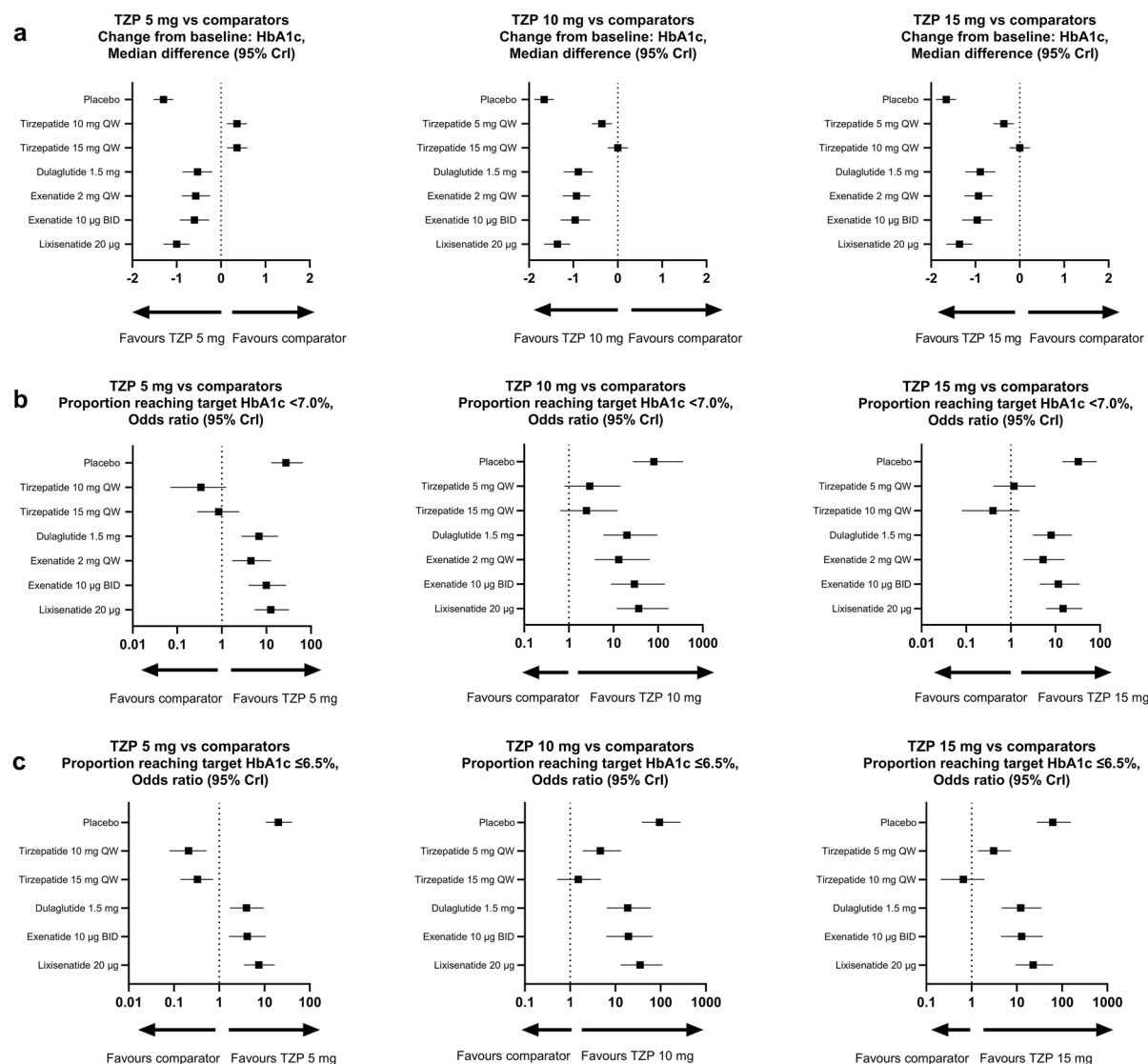


Fig. 3 Forest plots of change in **a** HbA1c, **b** likelihood of patients reaching HbA1c <7.0%, and **c** likelihood of patients reaching HbA1c ≤6.5% from baseline to week 40

(Tizapide) and week 26 ± 4 weeks (comparators). *BID* twice daily, *CrI* credible interval, *HbA1c* glycated haemoglobin, *QW* once weekly, *Tizapide* tirzepatide

Sensitivity Analysis

Conducting a sensitivity analysis for change from baseline in HbA1c (%) at week 40 was not feasible as a result of very few studies reporting at least three timepoints; only four studies reported HbA1c at three or more timepoints. However, the model-based NMA sensitivity analysis included all available timepoints for change from baseline in weight (kg), allowing

for comparisons at week 40, despite most studies concluding at week 26. The sensitivity analysis conducted for change from baseline in weight at week 40 for three or more timepoints for all treatments was consistent in magnitude, although it showed smaller differences from the main analysis versus the model-based NMA approach (Table S4.4).

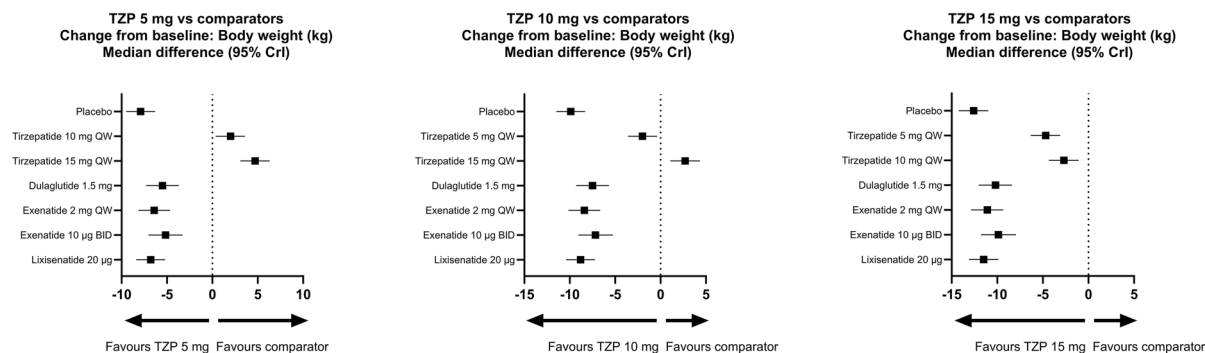


Fig. 4 Forest plots of change in body weight from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *BID* twice daily, *CrI* credible interval, *QW* once weekly, *TZP* tirzepatide

DISCUSSION

The objective of this study was to demonstrate the efficacy and safety of tirzepatide and GLP-1 RAs in patients with T2DM receiving treatment with basal insulin, aligning with the SURPASS-5 trial. Three doses of tirzepatide (5, 10, and 15 mg) were compared with the GLP-1 RAs dulaglutide 1.50 mg, exenatide 2 mg QW, exenatide 10 µg BID, and lixisenatide 20 µg with study designs comparable to SURPASS-5.

The network analyses revealed that all doses of tirzepatide demonstrated a statistically significantly greater reduction in HbA1c and body weight from baseline compared with the selected GLP-1 RAs. All doses of tirzepatide demonstrated statistically significantly greater odds of reaching the HbA1c targets of $\text{HbA1c} < 7.0\%$ and $\text{HbA1c} \leq 6.5\%$ compared with all selected GLP-1 RAs, with all doses of tirzepatide demonstrating significantly greater odds of reaching a target weight loss of $\geq 5\%$ compared with exenatide 2 mg QW. However, exenatide was the only GLP-1 RA in the network for this endpoint. Overall, tirzepatide was similar to most GLP-1 RAs in terms of the odds of experiencing nausea, vomiting, and diarrhoea. However, patients receiving all doses of tirzepatide had statistically significantly higher odds of experiencing nausea compared with exenatide 2 mg QW, and patients receiving tirzepatide 10 and 15 mg had statistically significantly higher odds of experiencing vomiting compared with exenatide 2 mg QW. All doses of tirzepatide were

comparable with all selected GLP-1 RAs in terms of the odds of experiencing at least one episode of hypoglycaemia with $\text{BG} < 54 \text{ mg/dL}$ with or without severe hypoglycaemia and the odds of patients discontinuing treatment because of AEs.

As the analysis of interest required patients to be treated with basal insulin therapy \pm OADs (third-line diabetes therapy with insulin) as background therapy, a limited number of studies were available to include in the network. Hence, the analysis of tirzepatide with comparators such as dulaglutide (0.75 mg, 3.0 mg, 4.5 mg), subcutaneously/orally administered semaglutide, liraglutide and exenatide (5 µg) were not possible as study designs were not comparable to SURPASS-5.

Additionally, patients were required to have basal insulin titration like that of patients enrolled in SURPASS-5 (i.e. increasing dose during the study following the titration scheme in SURPASS-5) to allow comparison of studies with similar designs.

The inclusion of semaglutide in this NMA would have been important, considering that semaglutide is among the most efficacious GLP-1 RAs and represents the current standard-of-care for T2DM [6]. However, comparisons of tirzepatide with subcutaneously administered semaglutide were not feasible because of the different study design of SUSTAIN 5 [230]; insulin titration was very different between SUSTAIN 5 (restricted) and SURPASS-5 (free titration to the target). In SUSTAIN 5, basal insulin therapy was maintained at stable or decreasing doses among patients who received placebo (mean basal

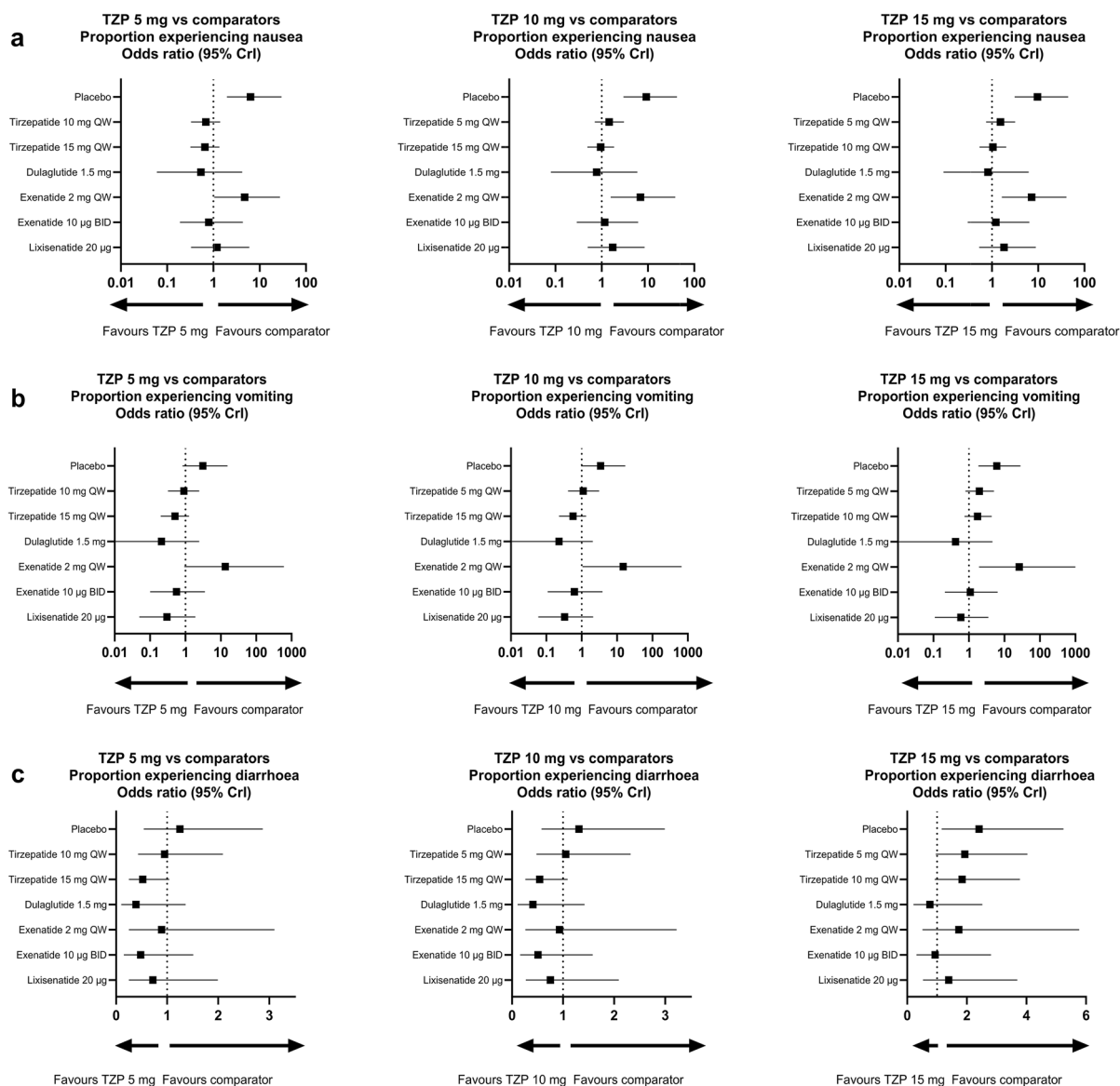


Fig. 5 Forest plots of likelihood of patients experiencing **a** nausea, **b** vomiting, and **c** diarrhoea from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *BID* twice daily, *CrI* credible interval, *QW* once weekly, *TZP* tirzepatide

insulin dose from baseline to endpoint was 37 to 35 IU/day with variations between the several included insulins). In SURPASS-5, basal insulin therapy increased substantially in the placebo arm (mean basal insulin dose from baseline to endpoint, 36 to 64 U/day) [14], leading to clinically significant differences in placebo arm results between SUSTAIN 5 and SURPASS-5 (i.e. HbA1c staying stable in SUSTAIN 5 [mean change from baseline, −0.1%] and decreasing by

0.86% in SURPASS-5). Weight was also impacted in the placebo arm of SUSTAIN 5 (mean weight change from baseline to week 30, −1.4 kg) [230] and in SURPASS-5 (mean weight change from baseline to week 40, +1.6 kg) [14]. As such, it was not suitable to use the placebo arm from SUSTAIN 5 as a common comparator in the context of this NMA, and the study was therefore excluded from the analyses. Similarly, a comparison of orally administered semaglutide was

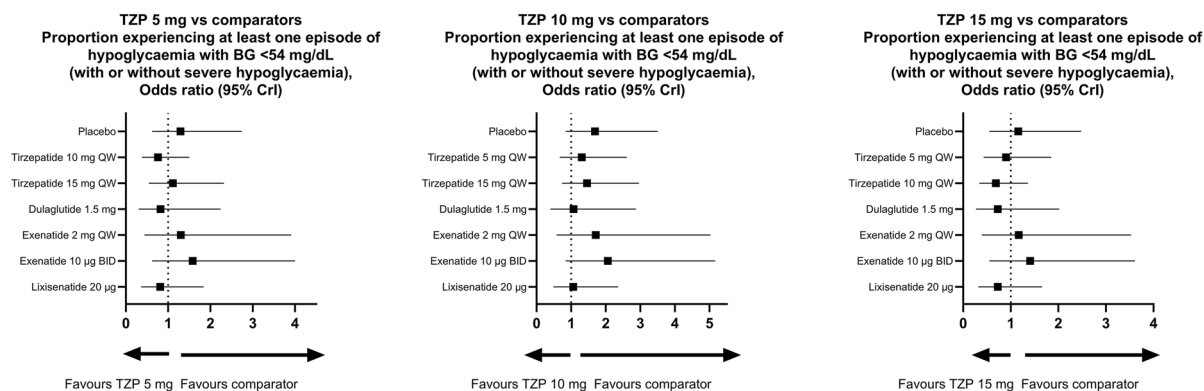


Fig. 6 Forest plots of the likelihood of patients with ≥ 1 episode of hypoglycaemia with BG <54 mg/dL (with or without severe hypoglycaemia) from baseline to week 40

(TZIP) and week 26 ± 4 weeks (comparators). BG blood glucose, BID twice daily, CrI credible interval, QW once weekly, TZIP tirzepatide

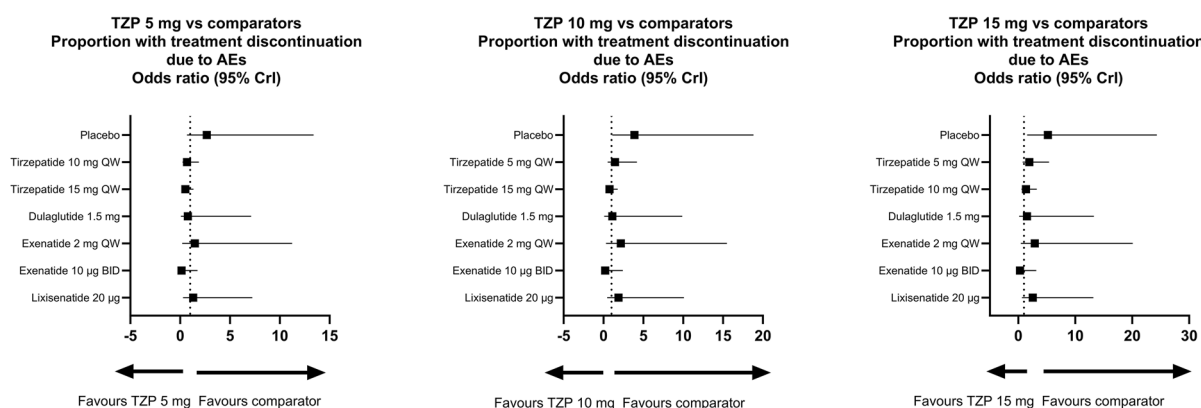


Fig. 7 Forest plots of the likelihood of patients with treatment discontinuation due to AEs from baseline to week 40 (TZIP) and week 26 ± 4 weeks (comparators). AE adverse

event, BID twice daily, CrI credible interval, QW once weekly, TZIP tirzepatide

not feasible and the PIONEER 8 trial had to be excluded [229]. In PIONEER 8, insulin titration remained stable with a maximum 20% reduction in the total daily dose (week 0–8). Unlike SURPASS-5, which used free titration to the target, titration of the insulin dose in PIONEER 8 could not exceed the prerandomization dose during weeks 8–26. This resulted in an HbA1c at week 26 being similar to baseline levels in patients receiving placebo (mean HbA1c at baseline vs. week 26, 8.2% vs. 8.1%); therefore, this study was excluded from the analyses.

Limitations

While the SLR search was originally conducted in September 2021 and updated in October 2021, the searches were further updated in June 2022, January 2023, and February 2024, but no eligible publications for the NMA were found. Data availability for some endpoints (e.g. change from baseline in HbA1c [%] at week 40) was limited, meaning that comparisons between all treatments of interest could not be made for all comparators and endpoints. Although BMI is an important endpoint, this could not be fully analysed because of limited

Declarations

Conflict of Interest. Beatrice Osumili, Kari Ranta, Hélène Sapin, and Jim S. Paik are employees and minor shareholders of Eli Lilly and Company. Zhengyu Yang was an employee and shareholder of Eli Lilly and Company during the development of the NMA and the manuscript and is currently an employee of Amylyx Pharmaceuticals. Matthias Blüher received honoraria as a consultant and speaker for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly and Company, Novartis, Novo Nordisk, Pfizer, and Sanofi.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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