Diabetes Ther
https://doi.org/10.1007/s13300-025-01728-5

ORIGINAL RESEARCH

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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Received: November 18, 2024 / Accepted: March 12, 2025

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).

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

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-025-01728-5.

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Published online: 11 April 2025

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 ± 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	≤ 70 mg/dL	− 1 or − 2 IU[b,c]	− 2 to 4 IU[b,c]
4.0 to 5.5 mmol/L	71 to 100 mg/dL	No change	No change
5.6 to 6.6 mmol/L	101 to 119 mg/dL	+ 1 IU	+ 2 IU
6.7 to 7.7 mmol/L	120 to 139 mg/dL	+ 2 IU	+ 4 IU
7.8 to 9.9 mmol/L	140 to 179 mg/dL	+ 3 IU	+ 6 IU
≥ 10.0 mmol/L	≥ 180 mg/dL	+ 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

[a]FBG is the median of the last 3 SMBG values

[b]Decrease insulin dose by 1–2 IU or 2–4 IU based on hypoglycaemic episodes or their severity

[c]No 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 ± 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 µg twice daily (BID) (prefilled pen), exenatide 2.0 mg QW, lixisenatide 20 µg 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).

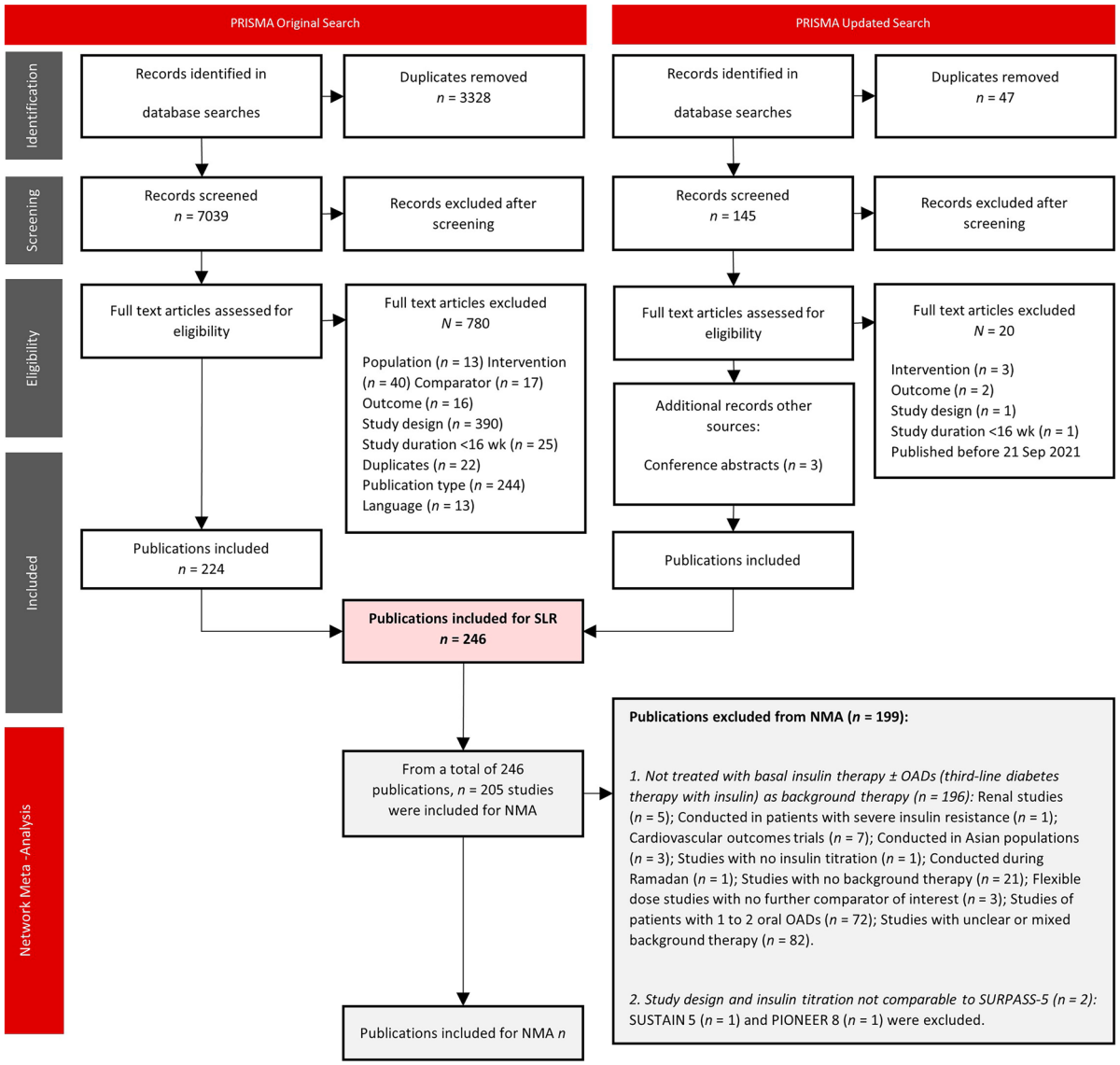

Fig. 1 PRISMA flow diagram of the SLR and NMA. The rationale for including and excluding trials is detailed in Sect. 2 of the Supplementary Material. NMA network meta-analysis, *OADs* oral antihyperglycaemic drugs, *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *SLR* systematic 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.

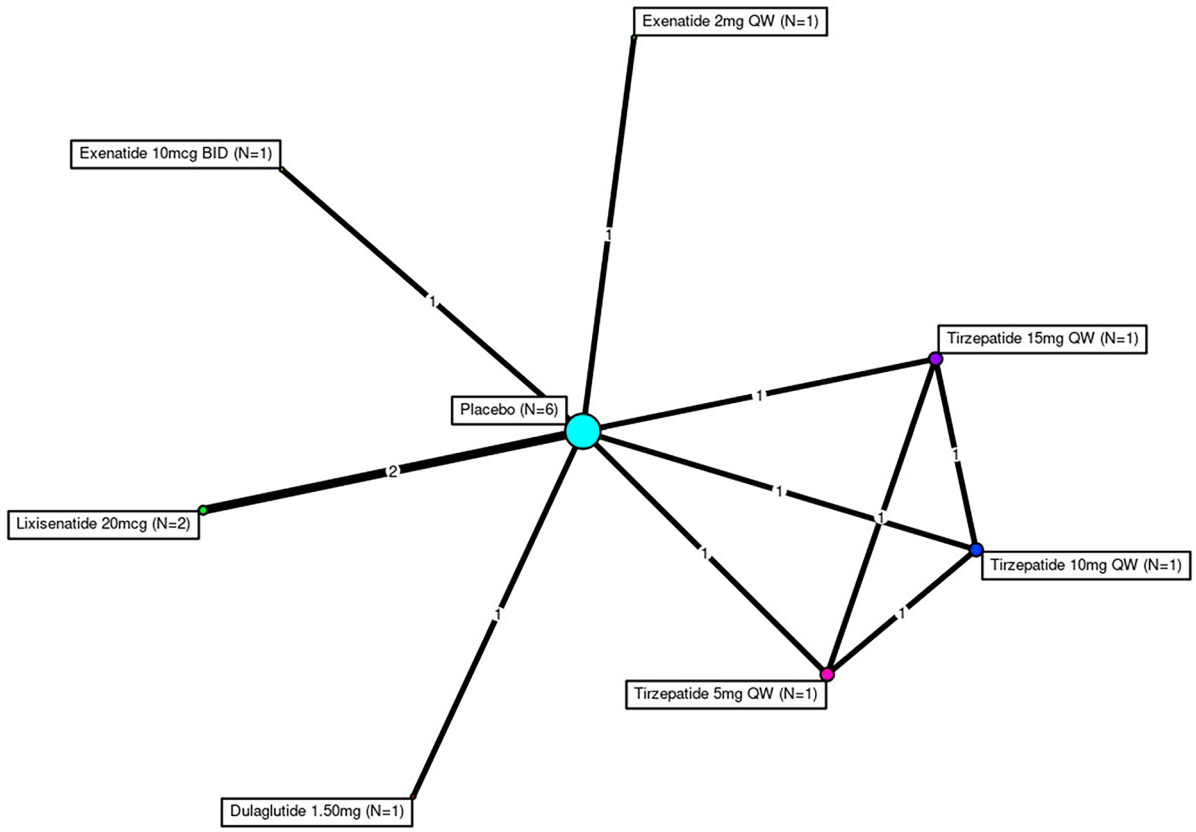

Fig. 2 Evidence network for 6 studies and 8 treatments (nodes) included in the network meta-analysis. The thickness of the lines indicates the number of studies comparing between the interventions, and the radius of the circle shows the number of studies within a given treatment arm. Outcomes included 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/m^2. The mean duration of diabetes ranged from 8.7 to 14.1 years. Background therapy included insulin glargine ± metformin, basal insulin ± metformin, insulin glargine + metformin ± thiazolidinedione, and insulin glargine ± 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% or ≤ 6.5% 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 RCT Double-blind Parallel arm Multicentre Placebo-controlled	3 weeks screening + 28 weeks treatment	Adults with T2DM HbA1c ≥ 7.0% to ≤ 10.5% BMI ≤ 45 kg/m^2 Stable dose of IG ± MET ≥ 1500 mg/day for ≥ 3 months before visit 1	HbA1c	Body weight HbA1c < 7.0% and ≤ 6.5% FSG SMPG IG dose	AEs Vital signs Hypoglycaemic events Clinical laboratory values

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 ≤ 6.5%

Five trials reported data on the proportion of patients reaching HbA1c ≤ 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 ≤ 6.5% compared with placebo, dulaglutide 1.50 mg, exenatide 10 µg, and lixisenatide 20 µg. The likelihood of achieving a target HbA1c ≤ 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
SURPASS-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
SURPASS-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
SURPASS-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
SURPASS-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 ($N = 2436$)[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
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)
DURATION-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)
DURATION-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 ($N = 2436$)[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
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

[a]Total 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 ± 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 µg, and lixisenatide 20 µg. Differences ranged from 5.2 kg versus exenatide 10 µg in favour of tirzepatide 5 mg and 11.5 kg versus lixisenatide 20 µg in favour of tirzepatide 15 mg (Fig. 4; Table S4.4).

Other efficacy outcomes, including the proportion of patients reaching weight loss of ≥ 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 (± 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 µg, and lixisenatide 20 µg (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 µg, and lixisenatide 20 µg. 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 µg, and lixisenatide 20 µg (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 µg, and lixisenatide 20 µg. 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 µg, and lixisenatide 20 µg (Fig. 5c; Table S6.3).

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

All six trials reported the proportion of patients with ≥ 1 episode of hypoglycaemia with BG < 54 mg/dL (with or without severe hypoglycaemia) to week 40 (tirzepatide) and week 26 (± 4 weeks) (comparators). No significant differences were observed in the proportions of patients experiencing ≥ 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 µg, and lixisenatide 20 µg (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 (± 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 µg, and lixisenatide 20 µg (Fig. 7; Table S6.5).

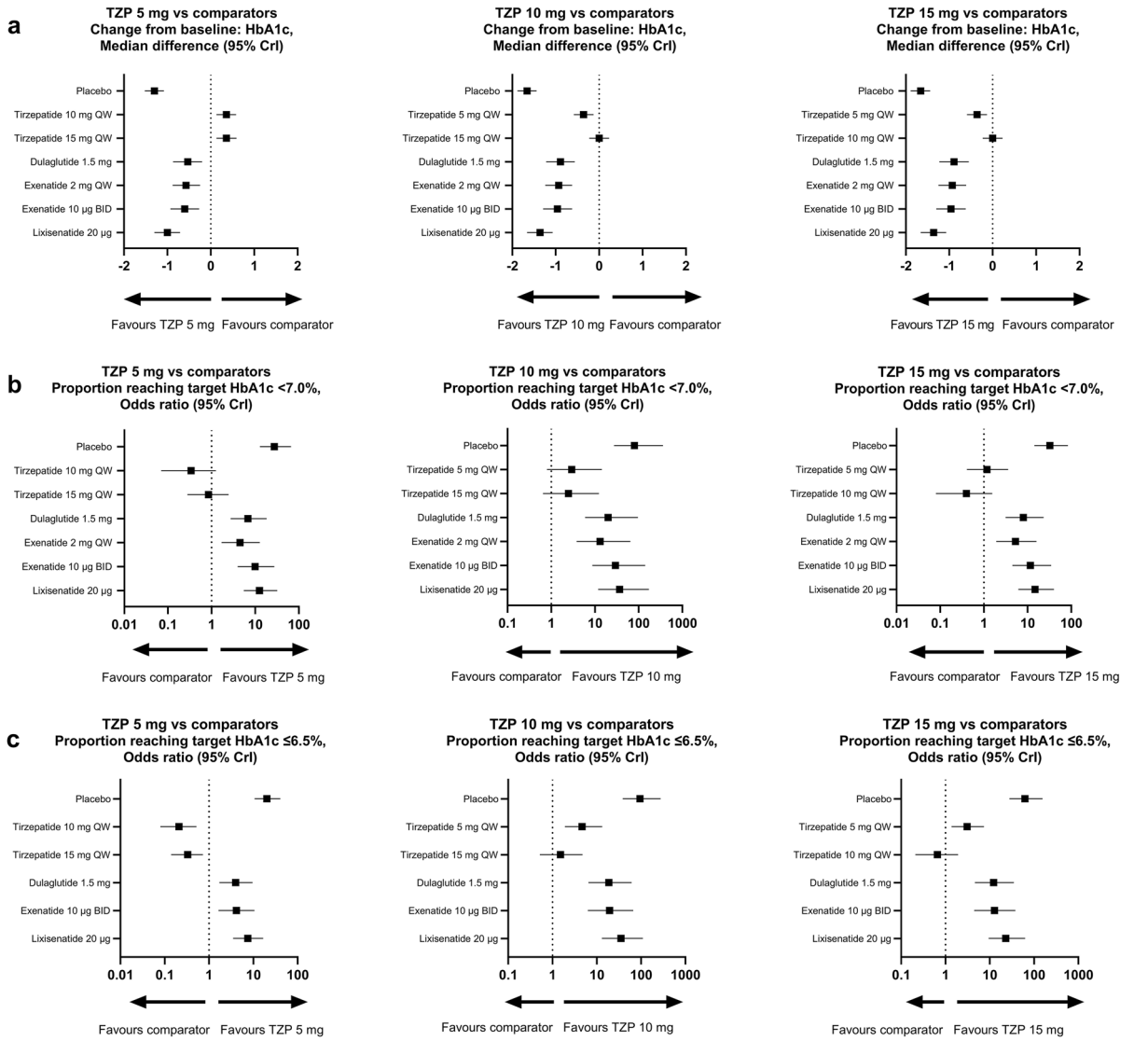

Fig. 3 Forest plots of change in **a** HbA1c, **b** likelihood of patients reaching HbA1c < 7.0%, and **c** likelihood of patients reaching HbA1c ≤ 6.5% from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *BID* twice daily, *CrI* credible interval, *HbA1c* glycated haemoglobin, *QW* once weekly, *TZP* 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).

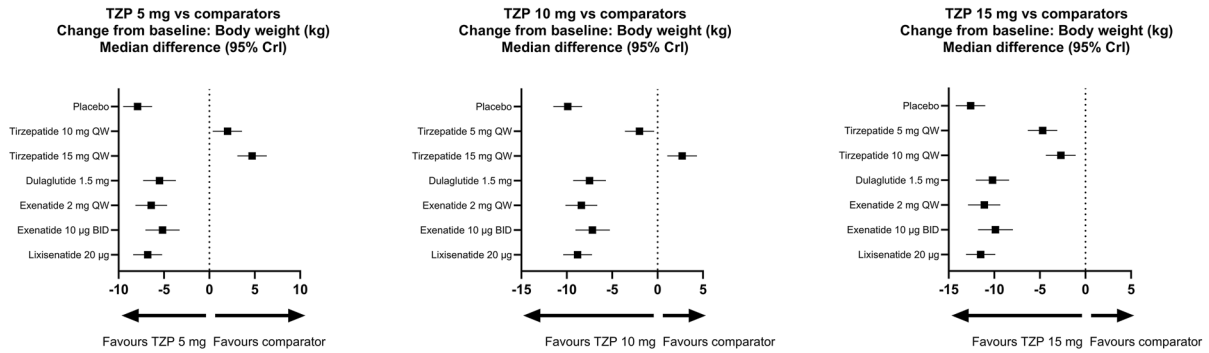

Fig. 4 Forest plots of change in body weight from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *BID* twice daily, *CrI* credible interval, *QW* once weekly, *TZP* tirzepatide

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 HbA1c < 7.0% and HbA1c ≤ 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 ≥ 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 BG < 54 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 ± 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

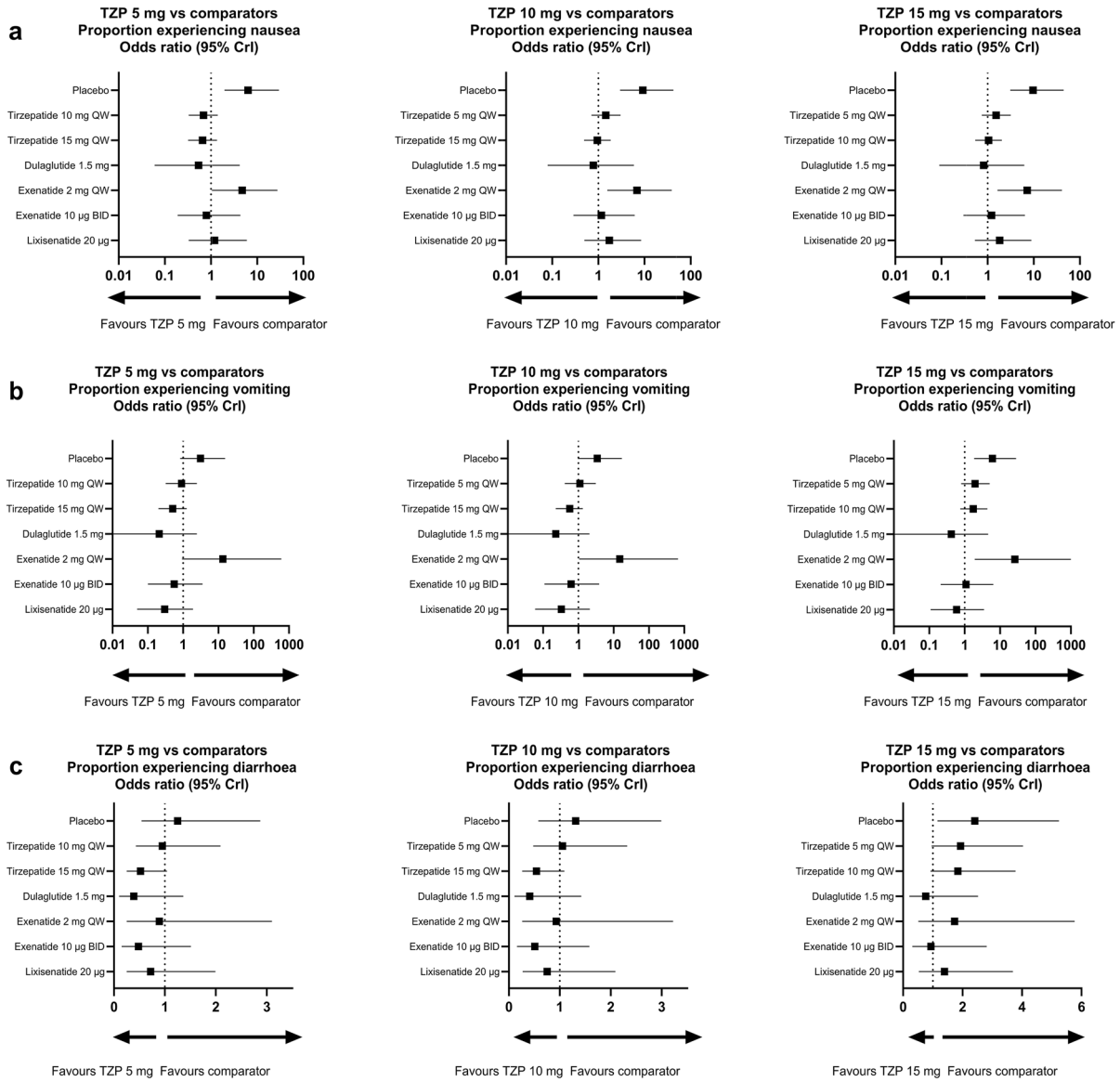

Fig. 5 Forest plots of likelihood of patients experiencing **a** nausea, **b** vomiting, and **c** diarrhoea from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *BID* twice daily, *CrI* credible interval, *QW* once weekly, *TZP* tirzepatide

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

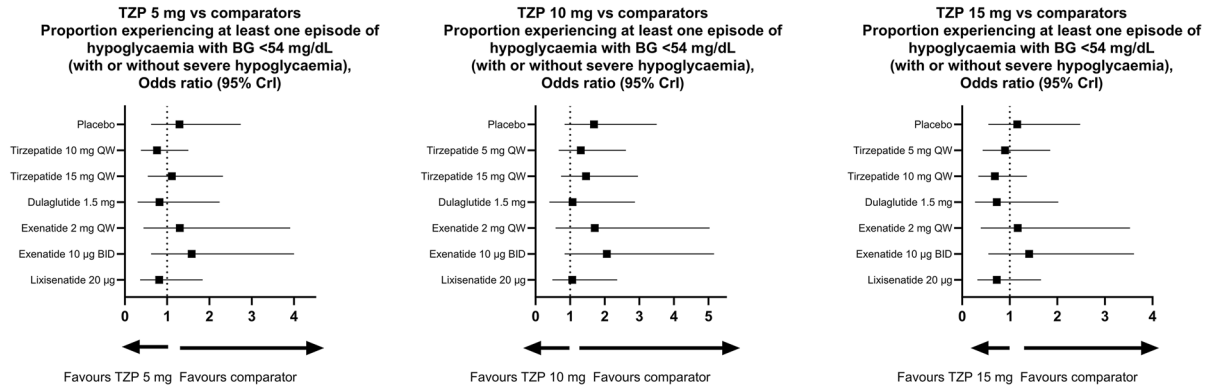

Fig. 6 Forest plots of the likelihood of patients with ≥ 1 episode of hypoglycaemia with BG < 54 mg/dL (with or without severe hypoglycaemia) from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *BG* blood glucose, *BID* twice daily, *CrI* credible interval, *QW* once weekly, *TZP* tirzepatide

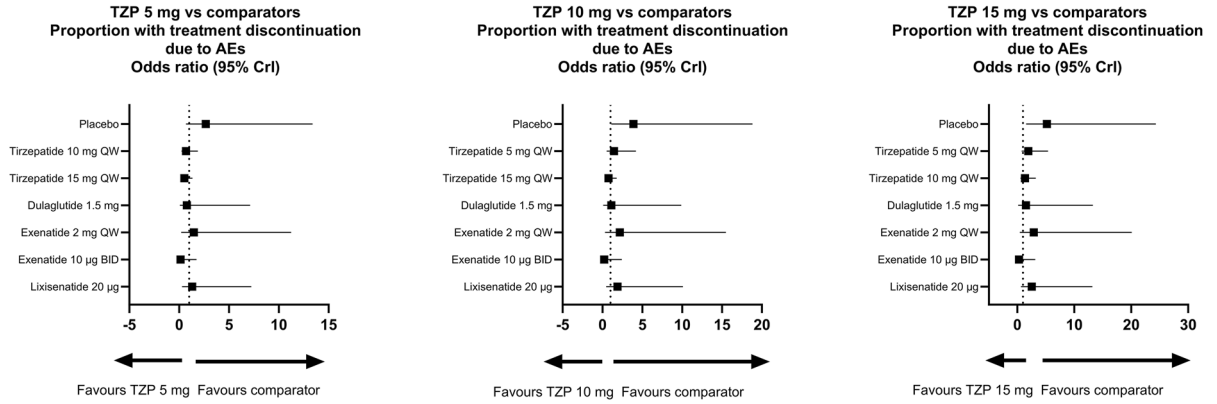

Fig. 7 Forest plots of the likelihood of patients with treatment discontinuation due to AEs from baseline to week 40 (TZP) and week 26 ± 4 weeks (comparators). *AE* adverse event, *BID* twice daily, *CrI* credible interval, *QW* once weekly, *TZP* tirzepatide

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

data availability across trials. Heterogeneity across studies in follow-up time was another limitation of the analyses, with data input for tirzepatide based on week 40 contrasting with the week 26 (±4 weeks) data of the comparator trials. The duration of dose escalation employed to reach the target dose of tirzepatide in the SURPASS trial was longer (0–20 weeks) than the corresponding durations used for the comparators in the comparator studies (0–8 weeks), contributing to a source of heterogeneity between trials. This is not expected to impact HbA1c as the maximum effect in comparators was generally around 26 weeks while the tirzepatide dose was still being escalated. Follow-up time may have impacted weight; however, the sensitivity analysis conducted provides confidence in the analysis. Additionally, the exclusion of semaglutide from the NMA, due to differences in insulin titration scheme not comparable to SURPASS-5, limits the comparative scope of the study, potentially making the findings less generalizable to all GLP-1 RAs. Lastly, the authors acknowledge that head-to-head results from RCTs should be generally preferred but considering that they are not available for several treatment comparisons, the results of this analysis are from mixed treatment comparisons consisting of both direct and indirect evidence.

CONCLUSIONS

Overall, tirzepatide demonstrated statistically significantly improved efficacy outcomes when compared with several relevant GLP-1 RAs dulaglutide, exenatide, and lixisenatide in patients with T2DM receiving treatment with basal insulin and a generally comparable safety profile in terms of cardiovascular biomarkers and AEs (with some exceptions such as nausea and vomiting). For change from baseline in HbA1c and weight, all three doses of tirzepatide demonstrated statistically significantly greater reductions in HbA1c and weight from baseline compared with several relevant GLP-1 RAs.

Medical Writing/Editorial Assistance. The authors would like to acknowledge Caragh Flannery, PhD, of Eli Lilly and Company for project management support, writing, and strategic communication expertise. Quality review and editorial support were provided by Adrienne Schreiber and Raena Fernandes of Syneos Health, funded by Eli Lilly and Company. Editorial support was provided by John Downey of Eli Lilly and Company.

Author Contribution. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Beatrice Osumili contributed to the conception and design of the work, acquisition and analysis of data for the work, and critical revision of work for important intellectual content. Hélène Sapin contributed to the analysis and interpretation of data for the work, and critical revision of work for important intellectual content. Zhengyu Yang contributed to the analysis and interpretation of data for the work, and drafting the article. Kari Ranta contributed to the conception and design of the work, interpretation of data for the work, and critical revision of the work for important intellectual content. Jim S. Paik contributed to the conception of the work, interpretation of data for the work, and critical revision of work for important intellectual content. Matthias Blüher contributed to the interpretation of data and critical revision of work for important intellectual content.

Funding. This study was sponsored by Eli Lilly and Company (Indianapolis, IN, USA). All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. The journal's Rapid Service Fee was funded by Eli Lilly and Company (Indianapolis, IN, USA).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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.

REFERENCES

1. Nasykhova YA, Tonyan ZN, Mikhailova AA, Danilova MM, Glotov AS. Pharmacogenetics of type 2 diabetes-progress and prospects. Int J Mol Sci. 2020;21(18):6842.
2. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al KJ. Epidemiology of type 2 diabetes–global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020;10(1):107–11.
3. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322–35.
4. Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. Pharmacoeconomics. 2015;33(8):811–31.
5. Landgraf R, Aberle J, Birkenfeld AL, et al. Therapy of type 2 diabetes. Exp Clin Endocrinol Diabetes. 2019;127(Suppl 1):S73–92.
6. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753–86.
7. Holst JJ, Gasbjerg LS, Rosenkilde MM. The role of incretins on insulin function and glucose homeostasis. Endocrinology. 2021;162(7):bqab065.
8. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig. 2010;1(1–2):8–23.
9. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. Mol Metab. 2018;18:3–14.
10. Tall Bull S, Nuffer W, Trujillo JM. Tirzepatide: a novel, first-in-class, dual GIP/GLP-1 receptor agonist. J Diabetes Complicat. 2022;36(12):108332.
11. Rosenstock J, Wysham C, Frías JP, et al. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021;398(10295):143–55.
12. European Medicines Agency. Mounjaro™. https://www.ema.europa.eu/en/medicines/human/EPAR/mounjaro. Accessed 04 Feb 2024.
13. Forzano I, Varzideh F, Avvisato R, Jankauskas SS, Mone P, Santulli G. Tirzepatide: a systematic update. Int J Mol Sci. 2022;23(23):14631.
14. Dahl D, Onishi Y, Norwood P, et al. Effect of subcutaneous tirzepatide vs placebo added to titrated insulin glargine on glycemic control in patients with type 2 diabetes: the SURPASS-5 randomized clinical trial. JAMA. 2022;327(6):534–45.

15. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503–15.

16. Ludvik B, Giorgino F, Jódar E, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. Lancet. 2021;398(10300):583–98.

17. Del Prato S, Kahn SE, Pavo I, et al. Tirzepatide versus insulin glargine in type 2 diabetes and increased cardiovascular risk (SURPASS-4): a randomised, open-label, parallel-group, multicentre, phase 3 trial. Lancet. 2021;398(10313):1811–24.

18. Eli Lilly and Company. Tirzepatide results published in The Lancet show superior A1C and body weight reductions compared to insulin glargine in adults with type 2 diabetes with increased cardiovascular risk [press release]. 2021. https://investor.lilly.com/news-releases/news-release-details/tirzepatide-results-published-lancet-show-superior-a1c-and-body#:~:text=At%2052%20weeks%2C%20the%20highest%20dose%20of%20tirzepatide,percent%20and%20weight%20gain%20of%201.9%20kg%20. Accessed 4 Feb 2025.

19. PR Newswire. Latest data from SURPASS trials demonstrate tirzepatide provided meaningful blood sugar reductions [press release]. 2021. Latest Data From SURPASS Trials Demonstrate Tirzepatide Provided Meaningful Blood Sugar Reductions And Weight Loss. https://www.prnewswire.com/news-releases/latest-data-from-surpass-trials-demonstrate-tirzepatide-provided-meaningful-blood-sugar-reductions-and-weight-loss-301322048.html. Accessed 4 Feb 2025.

20. PR Newswire. Tirzepatide achieved superior A1C and body weight reductions across all three doses compared to injectable semaglutide in adults with type 2 diabetes [press release]. 2021. Tirzepatide achieved superior A1C and body weight reductions across all three doses compared to injectable semaglutide in adults with type 2 diabetes. https://www.prnewswire.com/news-releases/tirzepatide-achieved-superior-a1c-and-body-weight-reductions-across-all-three-doses-compared-to-injectable-semaglutide-in-adults-with-type-2-diabetes-301239948.html. Accessed 4 Feb 2025.

21. ClinicalTrials.gov. A study of tirzepatide (LY3298176) versus insulin lispro (U100) in participants with type 2 diabetes inadequately controlled on insulin glargine (U100) with or without metformin (SURPASS-6) (NCT04537923). 2022. https://clinicaltrials.gov/study/NCT04537923. Accessed 04 Feb 2024.

22. ClinicalTrials.gov. A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT) (NCT04255433). 2023. https://clinicaltrials.gov/study/NCT04255433. Accessed 04 Feb 2024.

23. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. Intern Emerg Med. 2017;12(1):103–11.

24. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9.

25. Booth AM, Wright KE, Outhwaite H. Centre for Reviews and Dissemination databases: value, content, and developments. Int J Technol Assess Health Care. 2010;26(4):470–2.

26. Higgins JP, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. Wiley; 2019. https://doi.org/10.1002/9781119536604.

27. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777–84.

28. Dahl D, Onishi Y, Norwood P, Huh R, Patel H, Rodriguez A. Tirzepatide, a dual GIP/GLP-1 receptor agonist, is effective and safe when added to basal insulin for treatment of type 2 diabetes (SURPASS-5). Diabetol Stoffwechs. 2022;17(Suppl 1):S23.

29. Wadhwa RR, Cascella M. Steady state concentration. Treasure Island (FL): StatPearls. 2023. https://www.ncbi.nlm.nih.gov/books/NBK553132/.

30. Dias S, Welton NJ, Sutton AJ, Ades A. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. National Institute for Health and Care Excellence (NICE). 2014. https://www.ncbi.nlm.nih.gov/books/NBK310366/.

31. Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Modelling time-course relationships with multiple treatments: model-based network meta-analysis for continuous summary outcomes. Res Synth Methods. 2019;10(2):267–86.

32. Pozzilli P, Norwood P, Jódar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in

patients with type 2 diabetes (AWARD-9). Diabetes Obes Metab. 2017;19(7):1024–31.

33. Buse JB, Bergenstal RM, Glass LC, et al. Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. Ann Intern Med. 2011;154(2):103–12.

34. Guja C, Frías JP, Somogyi A, et al. Effect of exenatide QW or placebo, both added to titrated insulin glargine, in uncontrolled type 2 diabetes: the DURATION-7 randomized study. Diabetes Obes Metab. 2018;20(7):1602–14.

35. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care. 2013;36(9):2497–503.

36. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care. 2013;36(9):2489–96.

37. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol. 2018;6(8):605–17.

38. Hiramatsu T, Asano Y, Mabuchi M, Imai K, Iguchi D, Furuta S. Liraglutide relieves cardiac dilated function than DPP-4 inhibitors. Eur J Clin Investig. 2018;48(10):e13007.

39. Davies MJ, Bain SC, Atkin SL, et al. Efficacy and safety of liraglutide versus placebo as add-on to glucose-lowering therapy in patients with type 2 diabetes and moderate renal impairment (LIRA-RENAL): a randomized clinical trial. Diabetes Care. 2016;39(2):222–30.

40. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):515–27.

41. Wang X, Zhang H, Zhang Q, et al. Exenatide and renal outcomes in patients with type 2 diabetes and diabetic kidney disease. Am J Nephrol. 2020;51(10):806–14.

42. Distiller LA, Nortje H, Wellmann H, Amod A, Lombard L. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U-500 regular insulin plus metformin. Endocr Pract. 2014;20(11):1143–50.

43. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247–57.

44. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39.

45. Hernandez A, Green J, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. Lancet. 2018;392(10157):1519–29.

46. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22.

47. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841–51.

48. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121–30.

49. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44.

50. Seino Y, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab. 2012;14(10):910–7.

51. Yang W, Min K, Zhou Z, et al. Efficacy and safety of lixisenatide in a predominantly Asian population with type 2 diabetes insufficiently controlled with basal insulin: the GetGoal-L-C randomized trial. Diabetes Obes Metab. 2018;20(2):335–43.

52. Jiang J, Lin L, Chen P. Comparison of dapaglifozin and liraglutide in patients with poorly controlled type 2 diabetes mellitus: a 24-week, open, double-centered, head to head trial. Endocr Metab Immune Disord Drug Targets. 2021;21(7):1366–74.

53. Azar ST, Echtay A, Wan Bebakar WM, et al. Efficacy and safety of liraglutide compared to sulphonylurea

during Ramadan in patients with type 2 diabetes (LIRA-Ramadan): a randomized trial. Diabetes Obes Metab. 2016;18(10):1025–33.

54. Umpierrez G, Tofé Povedano S, Pérez Manghi F, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). Diabetes Care. 2014;37(8):2168–76.

55. Chen YH, Huang CN, Cho YM, et al. Efficacy and safety of dulaglutide monotherapy compared with glimepiride in East-Asian patients with type 2 diabetes in a multicentre, double-blind, randomized, parallel-arm, active comparator, phase III trial. Diabetes Obes Metab. 2018;20(9):2121–30.

56. Xu W, Bi Y, Sun Z, et al. Comparison of the effects on glycaemic control and β-cell function in newly diagnosed type 2 diabetes patients of treatment with exenatide, insulin or pioglitazone: a multicentre randomized parallel-group trial (the CONFIDENCE study). J Intern Med. 2015;277(1):137–50.

57. Russell-Jones D, Cuddihy RM, Hanefeld M, et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care. 2012;35(2):252–8.

58. Feng WH, Bi Y, Li P, et al. Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: a randomized trial. J Diabetes Investig. 2019;10(2):399–407.

59. Lambadiari V, Pavlidis G, Kousathana F, et al. Effects of 6-month treatment with the glucagon like peptide-1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes. Cardiovasc Diabetol. 2018;17(1):8.

60. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373(9662):473–81.

61. Li R, Xu W, Luo S, et al. Effect of exenatide, insulin and pioglitazone on bone metabolism in patients with newly diagnosed type 2 diabetes. Acta Diabetol. 2015;52(6):1083–91.

62. Liu L, Yan H, Xia M, et al. Efficacy of exenatide and insulin glargine on nonalcoholic fatty liver disease in patients with type 2 diabetes. Diabetes Metab Res Rev. 2020;36(5):e3292.

63. Liu Y, Jiang X, Chen X. Liraglutide and metformin alone or combined therapy for type 2 diabetes patients complicated with coronary artery disease. Lipids Health Dis. 2017;16(1):227.

64. Miyagawa J, Odawara M, Takamura T, Iwamoto N, Takita Y, Imaoka T. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: a 26-week randomized phase III study. Diabetes Obes Metab. 2015;17(10):974–83.

65. Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2008;30(8):1448–60.

66. Inagaki N, Takeuchi M, Oura T, Imaoka T, Seino Y. Efficacy and safety of tirzepatide monotherapy compared with dulaglutide in Japanese patients with type 2 diabetes (SURPASS J-mono): a double-blind, multicentre, randomised, phase 3 trial. Lancet Diabetes Endocrinol. 2022;10(9):623–33.

67. Yamamoto S, Hayashi T, Ohara M, et al. Comparison of liraglutide plus basal insulin and basal-bolus insulin therapy (BBIT) for glycemic control, body weight stability, and treatment satisfaction in patients treated using BBIT for type 2 diabetes without severe insulin deficiency: a randomized prospective pilot study. Diabetes Res Clin Pract. 2018;140:339–46.

68. Yuan GH, Song WL, Huang YY, Guo XH, Gao Y. Efficacy and tolerability of exenatide monotherapy in obese patients with newly diagnosed type 2 diabetes: a randomized, 26 weeks metformin-controlled, parallel-group study. Chin Med J (Engl). 2012;125(15):2677–81.

69. Zhang LY, Qu XN, Sun ZY, Zhang Y. Effect of liraglutide therapy on serum fetuin A in patients with type 2 diabetes and non-alcoholic fatty liver disease. Clin Res Hepatol Gastroenterol. 2020;44(5):674–80.

70. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. Diabetes Care. 2019;42(9):1724–32.

71. Yamada Y, Katagiri H, Hamamoto Y, et al. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. Lancet Diabetes Endocrinol. 2020;8(5):377–91.

72. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide

monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(4):251–60.

73. Seino Y, Terauchi Y, Osonoi T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes. Diabetes Obes Metab. 2018;20(2):378–88.

74. Charbonnel B, Steinberg H, Eymard E, et al. Efficacy and safety over 26 weeks of an oral treatment strategy including sitagliptin compared with an injectable treatment strategy with liraglutide in patients with type 2 diabetes mellitus inadequately controlled on metformin: a randomised clinical trial. Diabetologia. 2013;56(7):1503–11.

75. Yang J, Xiao W, Guo L, et al. Efficacy and safety of generic exenatide injection in Chinese patients with type 2 diabetes: a multicenter, randomized, controlled, non-inferiority trial. Acta Diabetol. 2020;57(8):991–1000.

76. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):528–39.

77. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010;375(9724):1447–56.

78. Apovian CM, Bergenstal RM, Cuddihy RM, et al. Effects of exenatide combined with lifestyle modification in patients with type 2 diabetes. Am J Med. 2010;123(5):468.e9-17.

79. Araki E, Inagaki N, Tanizawa Y, Oura T, Takeuchi M, Imaoka T. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open-label, phase III, non-inferiority study. Diabetes Obes Metab. 2015;17(10):994–1002.

80. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). Diabetes Care. 2014;37(8):2159–67.

81. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2018;6(5):370–81.

82. Frias JP, Bonora E, Nevarez Ruiz L, et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). Diabetes Care. 2021;44(3):765–73.

83. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). Diabetes Care. 2015;38(12):2241–9.

84. Weinstock RS, Guerci B, Umpierrez G, Nauck MA, Skrivanek Z, Milicevic Z. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. Diabetes Obes Metab. 2015;17(9):849–58.

85. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384(9951):1349–57.

86. Bergenstal R, Lewin A, Bailey T, Chang D, Gylvin T, Roberts V. Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Curr Med Res Opin. 2009;25(1):65–75.

87. Bunck MC, Eliasson B, Cornér A, et al. Exenatide treatment did not affect bone mineral density despite body weight reduction in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13(4):374–7.

88. Davies M, Heller S, Sreenan S, et al. Once-weekly exenatide versus once- or twice-daily insulin detemir: randomized, open-label, clinical trial of efficacy and safety in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylureas. Diabetes Care. 2013;36(5):1368–76.

89. DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care. 2005;28(5):1092–100.

90. Derosa G, Maffioli P, Salvadeo SA, et al. Exenatide versus glibenclamide in patients with diabetes. Diabetes Technol Ther. 2010;12(3):233–40.

91. Derosa G, Putignano P, Bossi AC, et al. Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. Eur J Pharmacol. 2011;666(1–3):251–6.

92. Derosa G, Franzetti IG, Querci F, et al. Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: a randomized placebo-controlled trial. Pharmacotherapy. 2013;33(8):817–26.

93. Gough SCL, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2(11):885–93.

94. Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010;376(9739):431–9.

95. Diamant M, Van Gaal L, Guerci B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial. Lancet Diabetes Endocrinol. 2014;2(6):464–73.

96. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. Lancet. 2013;381(9861):117–24.

97. Jabbour SA, Frías JP, Ahmed A, et al. Efficacy and safety over 2 years of exenatide plus dapagliflozin in the DURATION-8 study: a multicenter, double-blind, phase 3, randomized controlled trial. Diabetes Care. 2020;43(10):2528–36.

98. D'Alessio D, Häring HU, Charbonnel B, et al. Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes. Diabetes Obes Metab. 2015;17(2):170–8.

99. Simó R, Guerci B, Schernthaner G, et al. Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study. Cardiovasc Diabetol. 2015;14:116.

100. Ferdinand KC, White WB, Calhoun DA, et al. Effects of the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide on ambulatory blood pressure and heart rate in patients with type 2 diabetes mellitus. Hypertension. 2014;64(4):731–7.

101. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet. 2018;392(10160):2180–93.

102. Gallwitz B, Böhmer M, Segiet T, et al. Exenatide twice daily versus premixed insulin aspart 70/30 in metformin-treated patients with type 2 diabetes: a randomized 26-week study on glycemic control and hypoglycemia. Diabetes Care. 2011;34(3):604–6.

103. Bolli GB, Munteanu M, Dotsenko S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with type 2 diabetes insufficiently controlled on metformin (GetGoal-F1). Diabet Med. 2014;31(2):176–84.

104. Ahrén B, Leguizamo Dimas A, Miossec P, Saubadu S, Aronson R. Efficacy and safety of lixisenatide once-daily morning or evening injections in type 2 diabetes inadequately controlled on metformin (GetGoal-M). Diabetes Care. 2013;36(9):2543–50.

105. Yu Pan C, Han P, Liu X, et al. Lixisenatide treatment improves glycaemic control in Asian patients with type 2 diabetes mellitus inadequately controlled on metformin with or without sulfonylurea: a randomized, double-blind, placebo-controlled, 24-week trial (GetGoal-M-Asia). Diabetes Metab Res Rev. 2014;30(8):726–35.

106. Pinget M, Goldenberg R, Niemoeller E, Muehlen-Bartmer I, Guo H, Aronson R. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P). Diabetes Obes Metab. 2013;15(11):1000–7.

107. Rosenstock J, Hanefeld M, Shamanna P, et al. Beneficial effects of once-daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal-S). J Diabetes Complicat. 2014;28(3):386–92.

108. Rosenstock J, Raccah D, Korányi L, et al. Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care. 2013;36(10):2945–51.

109. Guo W, Tian W, Lin L, Xu X. Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and nonalcoholic fatty liver disease in twenty-six weeks: a randomized placebo-controlled trial. Diabetes Res Clin Pract. 2020;170: 108487.

110. Gürkan E, Tarkun I, Şahin T. Effect of exenatide on aortic stiffness and blood pressure parameters. Turk J Endocrinol Metab. 2017;21:97–103.

111. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2005;143(8):559–69.

112. Pratley RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): a randomised, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol. 2014;2(4):289–97.

113. Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C, Kilcoyne A. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: results of the Helping Evaluate Exenatide in patients with diabetes compared with Long-Acting insulin (HEELA) study. Diabetes Obes Metab. 2009;11(12):1153–62.

114. Inagaki N, Atsumi Y, Oura T, Saito H, Imaoka T. Efficacy and safety profile of exenatide once weekly compared with insulin once daily in Japanese patients with type 2 diabetes treated with oral antidiabetes drug(s): results from a 26-week, randomized, open-label, parallel-group, multicenter, noninferiority study. Clin Ther. 2012;34(9):1892-908.e1.

115. Ji L, Onishi Y, Ahn CW, et al. Efficacy and safety of exenatide once-weekly vs exenatide twice-daily in Asian patients with type 2 diabetes mellitus. J Diabetes Investig. 2013;4(1):53–61.

116. Kadowaki T, Namba M, Imaoka T, et al. Improved glycemic control and reduced bodyweight with exenatide: a double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks. J Diabetes Investig. 2011;2(3):210–7.

117. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care. 2005;28(5):1083–91.

118. Nauck M, Frid A, Hermansen K, et al. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. Diabetes Obes Metab. 2013;15(3):204–12.

119. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care. 2009;32(7):1224–30.

120. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia. 2009;52(10):2046–55.

121. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet. 2009;374(9683):39–47.

122. Li CJ, Yu Q, Yu P, et al. Efficacy and safety comparison of add-on therapy with liraglutide, saxagliptin and vildagliptin, all in combination with current conventional oral hypoglycemic agents therapy in poorly controlled Chinese type 2 diabetes. Exp Clin Endocrinol Diabetes. 2014;122(8):469–76.

123. Yan J, Yao B, Kuang H, et al. Liraglutide, sitagliptin, and insulin glargine added to metformin: the effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Hepatology. 2019;69(6):2414–26.

124. Blonde L, Fainberg U, Kaltoft MS, Mosenzon O, Ramesh C, Rea R. Efficacy of liraglutide added to sodium-glucose cotransporter-2 inhibitors in type 2 diabetes, stratified by baseline characteristics: Post-hoc analysis of LIRA-ADD2SGLT2i. Diabetes Obes Metab. 2021;23(10):2234–41.

125. Bailey TS, Takács R, Tinahones FJ, et al. Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial. Diabetes Obes Metab. 2016;18(12):1191–8.

126. Rosenstock J, Aronson R, Grunberger G, et al. Benefits of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide, versus insulin glargine and lixisenatide monocomponents in type 2 diabetes inadequately controlled on oral agents: the LixiLan-O randomized trial. Diabetes Care. 2016;39(11):2026–35.

127. Liutkus J, Rosas Guzman J, Norwood P, et al. A placebo-controlled trial of exenatide twice-daily added to thiazolidinediones alone or in combination with metformin. Diabetes Obes Metab. 2010;12(12):1058–65.

128. Webb DR, Htike ZZ, Swarbrick DJ, et al. A randomized, open-label, active comparator trial assessing the effects of 26 weeks of liraglutide or sitagliptin on cardiovascular function in young obese adults with type 2 diabetes. Diabetes Obes Metab. 2020;22(7):1187–96.

129. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia. 2007;50(2):259–67.

130. Nauck M, Rizzo M, Johnson A, Bosch-Traberg H, Madsen J, Cariou B. Once-daily liraglutide versus lixisenatide as add-on to metformin in type 2 diabetes: a 26-week randomized controlled clinical trial. Diabetes Care. 2016;39(9):1501–9.

131. Van Gaal L, Souhami E, Zhou T, Aronson R. Efficacy and safety of the glucagon-like peptide-1 receptor agonist lixisenatide versus the dipeptidyl peptidase-4 inhibitor sitagliptin in young (<50 years) obese patients with type 2 diabetes mellitus. J Clin Transl Endocrinol. 2014;1(2):31–7.

132. Wang W, Nevárez L, Filippova E, et al. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in mainly Asian patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea: a 52-week open-label, randomized phase III trial. Diabetes Obes Metab. 2019;21(2):234–43.

133. Zang L, Liu Y, Geng J, et al. Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial. Diabetes Obes Metab. 2016;18(8):803–11.

134. Rodbard HW, Rosenstock J, Canani LH, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019;42(12):2272–81.

135. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. JAMA. 2019;321(15):1466–80.

136. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019;394(10192):39–50.

137. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020;46(2):100–9.

138. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. Lancet Diabetes Endocrinol. 2017;5(5):341–54.

139. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. Diabetes Care. 2018;41(2):258–66.

140. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017;5(5):355–66.

141. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6(4):275–86.

142. Lingvay I, Catarig AM, Frias JP, et al. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. Lancet Diabetes Endocrinol. 2019;7(11):834–44.

143. Zinman B, Bhosekar V, Busch R, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(5):356–67.

144. Ji L, Dong X, Li Y, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as add-on to metformin in patients with type 2 diabetes in SUSTAIN China: a 30-week, double-blind, phase 3a, randomized trial. Diabetes Obes Metab. 2021;23(2):404–14.

145. Frías JP, Auerbach P, Bajaj HS, et al. Efficacy and safety of once-weekly semaglutide 2·0 mg versus 1·0 mg in patients with type 2 diabetes (SUSTAIN FORTE): a double-blind, randomised, phase 3B trial. Lancet Diabetes Endocrinol. 2021;9(9):563–74.

146. Abdul-Ghani M, Ali AM, Martinez RA, et al. Effect of combination therapy with liraglutide

plus canagliflozin on HGP and HbA1c vs. each therapy alone in T2DM. Diabetes. 2018;67(Suppl 1):109-OR.

147. Ali AM, Martinez R, Al-Jobori H, et al. Combination therapy with canagliflozin plus liraglutide exerts additive effect on weight loss, but not on HbA_{1c}, in patients with type 2 diabetes. Diabetes Care. 2020;43(6):1234–41.

148. Ando Y, Shigiyama F, Hirose T, Kumashiro N. Simplification of complex insulin regimens using canagliflozin or liraglutide in patients with well-controlled type 2 diabetes: a 24-week randomized controlled trial. J Diabetes Investig. 2021;12(10):1816–26.

149. Arturi F, Succurro E, Miceli S, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. Endocrine. 2017;57(3):464–73.

150. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. Lancet. 2015;385(9982):2057–66.

151. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). Diabetes Obes Metab. 2016;18(5):475–82.

152. Barnett AH, Burger J, Johns D, et al. Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: a multinational, randomized, open-label, two-period, crossover noninferiority trial. Clin Ther. 2007;29(11):2333–48.

153. Bojer AS, Sørensen MH, Bjerre J, Gaede P, Vejlstrup N, Madsen PL. Metabolic improvement with short-term, glucagon-like peptide-1 receptor agonist treatment does not improve cardiac diastolic dysfunction in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2021;23(10):2374–84.

154. Bouchi R, Nakano Y, Fukuda T, et al. Reduction of visceral fat by liraglutide is associated with ameliorations of hepatic steatosis, albuminuria, and micro-inflammation in type 2 diabetic patients with insulin treatment: a randomized control trial. Endocr J. 2017;64(3):269–81.

155. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care. 2004;27(11):2628–35.

156. Carlson AL, Mullen DM, Mazze R, Strock E, Richter S, Bergenstal RM. Evaluation of insulin glargine and exenatide alone and in combination: a randomized clinical trial with continuous glucose monitoring and ambulatory glucose profile analysis. Endocr Pract. 2019;25(4):306–14.

157. Davis SN, Johns D, Maggs D, Xu H, Northrup JH, Brodows RG. Exploring the substitution of exenatide for insulin in patients with type 2 diabetes treated with insulin in combination with oral antidiabetes agents. Diabetes Care. 2007;30(11):2767–72.

158. Diamant M, Nauck MA, Shaginian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care. 2014;37(10):2763–73.

159. Kaku K, Araki E, Tanizawa Y, et al. Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naïve Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial. Diabetes Obes Metab. 2019;21(12):2674–83.

160. Wysham CH, Rosenstock J, Vetter ML, Dong F, Öhman P, Iqbal N. Efficacy and tolerability of the new autoinjected suspension of exenatide once weekly versus exenatide twice daily in patients with type 2 diabetes. Diabetes Obes Metab. 2018;20(1):165–72.

161. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. Lancet. 2008;372(9645):1240–50.

162. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96(5):1301–10.

163. de Wit HM, Vervoort GM, Jansen HJ, de Galan BE, Tack CJ. Durable efficacy of liraglutide in patients with type 2 diabetes and pronounced insulin-associated weight gain: 52-week results from the Effect of Liraglutide on insulin-associated wEight GAiN in patients with Type 2 diabetes' (ELEGANT) randomized controlled trial. J Intern Med. 2016;279(3):283–92.

164. Harreiter J, Just I, Leutner M, et al. Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with

type 2 diabetes mellitus treated with metformin: EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial. Diabetes Obes Metab. 2021;23(5):1129–39.

165. Frias JP, Wynne AG, Matyjaszek-Matuszek B, et al. Efficacy and safety of an expanded dulaglutide dose range: a phase 2, placebo-controlled trial in patients with type 2 diabetes using metformin. Diabetes Obes Metab. 2019;21(9):2048–57.

166. Gao Y, Yoon KH, Chuang LM, et al. Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. Diabetes Res Clin Pract. 2009;83(1):69–76.

167. Gao F, Lv X, Mo Z, et al. Efficacy and safety of polyethylene glycol loxenatide as add-on to metformin in patients with type 2 diabetes: a multicentre, randomized, double-blind, placebo-controlled, phase 3b trial. Diabetes Obes Metab. 2020;22(12):2375–83.

168. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 Trial. Diabetes Care. 2016;39(8):1318–28.

169. Meneilly GS, Roy-Duval C, Alawi H, et al. Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: the GetGoal-O randomized trial. Diabetes Care. 2017;40(4):485–93.

170. Miras AD, Pérez-Pevida B, Aldhwayan M, et al. Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(7):549–59.

171. Leiter LA, Gross JL, Chow F, Miller D, Johnson S, Ahrén B. Once weekly glucagon-like peptide-1 receptor agonist albiglutide vs. prandial insulin added to basal insulin in patients with type 2 diabetes mellitus: results over 52 weeks. J Diabetes Complicat. 2017;31(8):1283–5.

172. Leiter LA, Carr MC, Stewart M, et al. Efficacy and safety of the once-weekly GLP-1 receptor agonist albiglutide versus sitagliptin in patients with type 2 diabetes and renal impairment: a randomized phase III study. Diabetes Care. 2014;37(10):2723–30.

173. Reusch J, Stewart MW, Perkins CM, et al. Efficacy and safety of once-weekly glucagon-like peptide 1 receptor agonist albiglutide (HARMONY 1 trial): 52-week primary endpoint results from a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes mellitus not controlled on pioglitazone, with or without metformin. Diabetes Obes Metab. 2014;16(12):1257–64.

174. Nauck MA, Stewart MW, Perkins C, et al. Efficacy and safety of once-weekly GLP-1 receptor agonist albiglutide (HARMONY 2): 52 week primary endpoint results from a randomised, placebo-controlled trial in patients with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetologia. 2016;59(2):266–74.

175. Ahrén B, Johnson SL, Stewart M, et al. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care. 2014;37(8):2141–8.

176. Weissman PN, Carr MC, Ye J, et al. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia. 2014;57(12):2475–84.

177. Home PD, Shamanna P, Stewart M, et al. Efficacy and tolerability of albiglutide versus placebo or pioglitazone over 1 year in people with type 2 diabetes currently taking metformin and glimepiride: HARMONY 5. Diabetes Obes Metab. 2015;17(2):179–87.

178. Hygum K, Harsløf T, Jørgensen NR, Rungby J, Pedersen SB, Langdahl BL. Bone resorption is unchanged by liraglutide in type 2 diabetes patients: a randomised controlled trial. Bone. 2020;132: 115197.

179. Ikonomidis I, Pavlidis G, Thymis J, et al. Effects of glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, and their combination on endothelial glycocalyx, arterial function, and myocardial work index in patients with type 2 diabetes mellitus after 12-month treatment. J Am Heart Assoc. 2020;9(9):e015716.

180. Ishii H, Onishi Y, Oura T, Takeuchi M. Once-weekly dulaglutide with insulin therapy for type 2 diabetes: efficacy and safety results from a phase 4, randomized, placebo-controlled study. Diabetes Ther. 2020;11(1):133–45.

181. Jaiswal M, Martin CL, Brown MB, et al. Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study. J Diabetes Complicat. 2015;29(8):1287–94.

182. Yokoyama H, Hirao K, Yamaguchi K, et al. Liraglutide versus sitagliptin in a 24-week, multicenter, open-label, randomized, parallel-group study in Japanese type 2 diabetes mellitus patients responding inadequately to a sulfonylurea and/or one or two other oral antidiabetic drugs (JDDM 33). Jpn Clin Med. 2014;5:33–41.

183. Joubert M, Opigez V, Pavlikova B, et al. Efficacy and safety of exenatide as add-on therapy for patients with type 2 diabetes with an intensive insulin regimen: a randomized double-blind trial. Diabetes Obes Metab. 2021;23(2):374–81.

184. Seino Y, Rasmussen MF, Nishida T, Kaku K. Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in Japanese patients with type 2 diabetes: Results of a 52-week, randomized, multicenter trial. J Diabetes Investig. 2011;2(4):280–6.

185. Tanaka K, Saisho Y, Manesso E, et al. Effects of liraglutide monotherapy on beta cell function and pancreatic enzymes compared with metformin in japanese overweight/obese patients with type 2 diabetes mellitus: a subpopulation analysis of the KIND-LM randomized trial. Clin Drug Investig. 2015;35(10):675–84.

186. Koska J, Migrino RQ, Chan KC, Cooper-Cox K, Reaven PD. The effect of exenatide once weekly on carotid atherosclerosis in individuals with type 2 diabetes: an 18-month randomized placebo-controlled study. Diabetes Care. 2021;44(6):1385–92.

187. Garber A, Henry RR, Ratner R, Hale P, Chang CT, Bode B. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13(4):348–56.

188. Retnakaran R, Kramer CK, Choi H, Swaminathan B, Zinman B. Liraglutide and the preservation of pancreatic β-cell function in early type 2 diabetes: the LIBRA trial. Diabetes Care. 2014;37(12):3270–8.

189. Wägner AM, Miranda-Calderín G, Ugarte-Lopetegui MA, et al. Effect of liraglutide on physical performance in type 2 diabetes: results of a randomized, double-blind, controlled trial (LIPER2). Diabetes Metab. 2019;45(3):268–75.

190. Rasmussen IKB, Zobel EH, Ripa RS, et al. Liraglutide reduces cardiac adipose tissue in type 2 diabetes: a secondary analysis of the LIRAFLAME randomized placebo-controlled trial. Diabetes Obes Metab. 2021;23(12):2651–9.

191. Lou N, Wu X, Wang Y, Lou D. Liraglutide improves postprandial blood glucose, blood glucose levels, insulin resistance and physical distribution of T2DM patients with MS. Int J Clin Exp Med. 2020;13(2):518–24.

192. Bizino MB, Jazet IM, Westenberg JJM, et al. Effect of liraglutide on cardiac function in patients with type 2 diabetes mellitus: randomized placebo-controlled trial. Cardiovasc Diabetol. 2019;18(1):55.

193. Martinez R, Al-Jobory H, Adams J, et al. Glycaemic control and beta cell function in type 2 diabetes on SGLT2i and GLP-1RA combination therapy [abstract]. Diabetologia. 2017;60:S408–9.

194. Matikainen N, Söderlund S, Björnson E, et al. Liraglutide treatment improves postprandial lipid metabolism and cardiometabolic risk factors in humans with adequately controlled type 2 diabetes: a single-centre randomized controlled study. Diabetes Obes Metab. 2019;21(1):84–94.

195. Lind M, Hirsch IB, Tuomilehto J, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). BMJ. 2015;351:h5364.

196. Mensberg P, Nyby S, Jørgensen PG, et al. Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes. Diabetes Obes Metab. 2017;19(2):172–80.

197. Nagaike H, Ohara M, Kohata Y, et al. Effect of dulaglutide versus liraglutide on glucose variability, oxidative stress, and endothelial function in type 2 diabetes: a prospective study. Diabetes Ther. 2019;10(1):215–28.

198. Nakaguchi H, Kondo Y, Kyohara M, Konishi H, Oiwa K, Terauchi Y. Effects of liraglutide and empagliflozin added to insulin therapy in patients with type 2 diabetes: a randomized controlled study. J Diabetes Investig. 2020;11(6):1542–50.

199. Nino A, Okuda I, Wilson TH, et al. Weekly glucagon-like peptide-1 receptor agonist albiglutide as monotherapy improves glycemic parameters in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study. J Diabetes Investig. 2017;9(3):558–66.

200. Nyström T, Santos-Pardo I, Hedberg F, et al. Effects on subclinical heart failure in type 2 diabetic subjects on liraglutide treatment vs. glimepiride both in combination with metformin: a randomized open Parallel-Group Study. Front Endocrinol (Lausanne). 2017;8:325.

201. Pasquel FJ, Urrutia MA, Cardona S, et al. Liraglutide hospital discharge trial: a randomized controlled trial comparing the safety and efficacy of liraglutide versus insulin glargine for the management of patients with type 2 diabetes after hospital discharge. Diabetes Obes Metab. 2021;23(6):1351–60.

202. Ripa RS, Zobel EH, Von Scholten BJ, et al. Liraglutide and vascular inflammation in type 2 diabetes as assessed by FDG-PET/CT: the LiraFlame study. Diabetologia. 2021;63(Suppl 1):S51.

203. Rosenstock J, Reusch J, Bush M, Yang F, Stewart M. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: a randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care. 2009;32(10):1880–6.

204. Rosenstock J, Nino AJ, Soffer J, et al. Near-normoglycemia, with meaningful discontinuations of prandial insulin, by adding weekly albiglutide (Albi) to uncontrolled basal/bolus insulin-treated type 2 diabetes (T2DM). Diabetes. 2018;67(Suppl 1):1073-P.

205. Savvidou S, Karatzidou K, Tsakiri K, Gagalis A, Hytiroglou P, Goulis J. Circulating adiponectin levels in type 2 diabetes mellitus patients with or without non-alcoholic fatty liver disease: results of a small, open-label, randomized controlled intervention trial in a subgroup receiving short-term exenatide. Diabetes Res Clin Pract. 2016;113:125–34.

206. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA. 2015;314(7):687–99.

207. Seino Y, Inagaki N, Miyahara H, et al. A randomized dose-finding study demonstrating the efficacy and tolerability of albiglutide in Japanese patients with type 2 diabetes mellitus. Curr Med Res Opin. 2014;30(6):1095–106.

208. Kaku K, Rasmussen MF, Nishida T, Seino Y. Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes. J Diabetes Investig. 2011;2(6):441–7.

209. Seino Y, Kaneko S, Fukuda S, et al. Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: a 36-week, randomized, double-blind, parallel-group trial. J Diabetes Investig. 2016;7(4):565–73.

210. Shuai Y, Yang G, Zhang Q, et al. Efficacy and safety of polyethylene glycol loxenatide monotherapy in type 2 diabetes patients: a multicentre, randomized, double-blind, placebo-controlled phase 3a clinical trial. Diabetes Obes Metab. 2021;23(1):116–24.

211. van Eyk HJ, Paiman EHM, Bizino MB, et al. A double-blind, placebo-controlled, randomised trial to assess the effect of liraglutide on ectopic fat accumulation in South Asian type 2 diabetes patients. Cardiovasc Diabetol. 2019;18(1):87.

212. Vanderheiden A, Harrison L, Warshauer J, Li X, Adams-Huet B, Lingvay I. Effect of adding liraglutide vs placebo to a high-dose insulin regimen in patients with type 2 diabetes: a randomized clinical trial. JAMA Intern Med. 2016;176(7):939–47.

213. Wang L, Liu X, Yang W, et al. Comparison of blood glucose variability between exenatide and biphasic insulin aspart 30 in chinese participants with type 2 diabetes inadequately controlled with metformin monotherapy: a multicenter, open-label. Randomized Trial Diabetes Ther. 2020;11(10):2313–28.

214. Wang Q, Wang D, Cheng A, Sun FY, Li Z-J. Comparison between the effects of sitagliptin and liraglutide on blood glucose and cognitive function of patients with both type 2 diabetes mellitus and post-stroke mild cognitive impairment. Int J Clin Exp Med. 2020;13(2):1219–27.

215. Wu JD, Xu XH, Zhu J, et al. Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. Diabetes Technol Ther. 2011;13(2):143–8.

216. Yang W, Chen L, Ji Q, et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial. Diabetes Obes Metab. 2011;13(1):81–8.

217. Yin TT, Bi Y, Li P, et al. Comparison of glycemic variability in Chinese T2DM patients treated with exenatide or insulin glargine: a randomized controlled trial. Diabetes Ther. 2018;9(3):1253–67.

218. Zhang H, Zhang X, Hu C, Lu W. Exenatide reduces urinary transforming growth factor-β1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria. Kidney Blood Press Res. 2012;35(6):483–8.

219. Zhang J, Xian TZ, Wu MX, Li C, Pan Q, Guo LX. Comparison of the effects of twice-daily exenatide and insulin on carotid intima-media thickness in type 2 diabetes mellitus patients: a 52-week randomized, open-label, controlled trial. Cardiovasc Diabetol. 2020;19(1):48.

220. Zinman B, Hoogwerf BJ, Durán García S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med. 2007;146(7):477–85.

221. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. JAMA. 2017;318(15):1460–70.

222. Kaku K, Yamada Y, Watada H, et al. Safety and efficacy of once-weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: a randomized trial. Diabetes Obes Metab. 2018;20(5):1202–12.

223. Lingvay I, Desouza CV, Lalic KS, et al. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin. Diabetes Care. 2018;41(9):1926–37.

224. Yabe D, Nakamura J, Kaneto H, et al. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2020;8(5):392–406.

225. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971–84.

226. Kadowaki T, Chin R, Ozeki A, Imaoka T, Ogawa Y. Safety and efficacy of tirzepatide as an add-on to single oral antihyperglycaemic medication in patients with type 2 diabetes in Japan (SURPASS J-combo): a multicentre, randomised, open-label, parallel-group, phase 3 trial. Lancet Diabetes Endocrinol. 2022;10(9):634–44.

227. Kunihiro S, Seiichi T, Chie A, Kanako K, Teruo J, Yoshimasa A. Greater efficacy and improved endothelial dysfunction in untreated type 2 diabetes with liraglutide versus sitagliptin. Dokkyo J Med Sci. 2014;41(3):211–20.

228. Ahmann A, Rodbard HW, Rosenstock J, et al. Efficacy and safety of liraglutide versus placebo added to basal insulin analogues (with or without metformin) in patients with type 2 diabetes: a randomized, placebo-controlled trial. Diabetes Obes Metab. 2015;17(11):1056–64.

229. Zinman B, Aroda VR, Buse JB, et al. Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: the PIONEER 8 trial. Diabetes Care. 2019;42(12):2262–71.

230. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized controlled trial. J Clin Endocrinol Metab. 2018;103(6):2291–301.

231. Abreu M, Tumyan A, Elhassan A, et al. A randomized trial comparing the efficacy and safety of treating patients with type 2 diabetes and highly elevated HbA1c levels with basal-bolus insulin or a glucagon-like peptide-1 receptor agonist plus basal insulin: the SIMPLE study. Diabetes Obes Metab. 2019;21(9):2133–41.

232. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003;26(11):3080–6.