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ORIGINAL RESEARCH

Tirzepatide Improved Health-Related Quality of Life Compared with Insulin Lispro in Basal Insulin-Treated Adults with Type 2 Diabetes and Inadequate Glycaemic Control: A Randomised Controlled Phase 3b Trial (SURPASS-6)

Kristina Secnik Boye · Jiat Ling Poon · Laura Fernández Landó · Hélène Sapin · Ruth Huh · Mianbo Wang · Suzanne Williamson · Hiren Patel

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ABSTRACT

Introduction: Patients with type 2 diabetes (T2D) who require intensification of basal insulin therapy need treatment options that can improve their health-related quality of life (HRQoL) and translate into better outcomes. These analyses compared patient-reported outcomes (PROs) in patients with T2D receiving tirzepatide or insulin lispro.

Methods: The randomised, open-label, multinational, phase 3b SURPASS-6 trial (NCT04537923) was conducted at 135 medical research centres and hospitals in 15 countries and compared two recommended treatment intensification strategies in people with T2D and inadequate glycaemic control on basal insulin: addition of once-weekly tirzepatide versus addition of prandial insulin lispro. Randomisation was stratified by country, baseline glycated haemoglobin level and metformin use. PROs were measured using the Short Form-36 Health Survey version 2 (SF-36v2) acute form (secondary outcome), EQ-5D-5L, Ability to Perform Physical Activities of Daily Living (APPADL) questionnaire and Impact of Weight on Self-Perceptions (IW-SP) questionnaire (tertiary/exploratory outcomes). PROs were compared for the tirzepatide-pooled dose group (5, 10 and 15 mg) and each tirzepatide dose group versus insulin lispro at 52 weeks using the modified intention-to-treat efficacy analysis set.

Prior Presentation: This manuscript is based on work that has previously been presented in a poster at The American Diabetes Association 83rd Annual Scientific Sessions, 23–26 June 2023 in San Diego, California, USA, with encores at the 59th Annual Meeting of the European Association for the Study of Diabetes, 2–6 October 2023 in Hamburg, Germany; the Schweizerischen Gesellschaft für Endokrinologie und Diabetologie/Société Suisse d'Endocrinologie et de Diabétologie, 17–18 November 2023 in Bern, Switzerland; and the Deutsche Diabetes Gesellschaft – 58th Jahrestagung, 8–11 May 2024 in Berlin, Germany.

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K. S. Boye · J. L. Poon · L. F. Landó · H. Sapin · R. Huh · H. Patel
Eli Lilly and Company, Indianapolis, IN, USA

K. S. Boye (✉)
Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
e-mail: boye_kristina_secnik@lilly.com

M. Wang
Syneos Health, Morrisville, NC, USA

S. Williamson
Greenwich HE&OR Ltd., London, UK

Results: Between 19 October 2020 and 01 November 2022, 2267 people were assessed and 1428 participants with T2D were randomised. At 52 weeks, participants in the tirzepatide-pooled group had statistically significant improved scores across all SF-36v2 domains and both component summary scores compared with insulin lispro-treated participants ($p<0.05$), with the largest differences observed in the general health, vitality and mental health domains. Statistically significant improved APPADL and IW-SP total scores, as well as EQ visual analogue scale and EQ-5D-5L index scores (after adjustment for baseline scores), were observed in tirzepatide-pooled participants compared with insulin lispro-treated participants.

Conclusions: In adult patients with T2D and inadequate glycaemic control with basal insulin, tirzepatide treatment was associated with greater improvements in HRQoL than prandial insulin therapy in addition to clinically significant improvements in glycaemic and body weight-related parameters.

PLAIN LANGUAGE SUMMARY

Basal insulin, which controls blood sugar at times when not eating but when the body still needs energy, may not provide sufficient glycaemic control for some people with type 2 diabetes (T2D). These people require additional therapy to improve their health-related quality of life (HRQoL) and achieve better outcomes. This phase 3 study (SURPASS-6) compared patient-reported outcomes, including HRQoL, between people with T2D on basal insulin receiving additional therapy with tirzepatide or insulin lispro (a fast-acting insulin analogue mealtime injection). Patient-reported outcomes were assessed using several validated measures – the Short Form-36 Health Survey version 2 (SF-36v2) acute form (a measure of HRQoL), the EQ-5D-5L (a measure of overall health status), the Ability to Perform Physical Activities of Daily Living (APPADL) questionnaire and the Impact of Weight on Self-Perceptions (IW-SP) questionnaire. The results in the two treatment groups were compared at the end of the treatment period (52 weeks). At 52 weeks, participants in the tirzepatide group had statistically significant improved scores across all HRQoL aspects measured by the SF-36v2 compared with participants in the insulin lispro group, with the largest differences observed in general health, vitality and bodily pain. Statistically significant improved EQ-5D-5L, APPADL and IW-SP scores were also observed in participants in the tirzepatide group compared with the insulin lispro group. In adults with T2D who require therapy in addition to basal insulin, tirzepatide treatment was associated with greater improvements in HRQoL than mealtime insulin therapy, as well as clinically significant improvements in blood sugar and body weight control.

Keywords: Basal insulin; Health-related quality of life; Insulin lispro; Patient-reported outcomes; SURPASS-6; Tirzepatide; Type 2 diabetes

Key Summary Points

Why carry out this study?

In the phase 3b SURPASS-6 trial, for the first time, the effects of two recommended treatment intensification strategies (addition of once-weekly tirzepatide versus addition of prandial insulin lispro) on the health-related quality of life of people with type 2 diabetes (T2D) and inadequate glycaemic control on basal insulin was evaluated using the Short Form-36 Health Survey version 2 acute form (SF-36v2).

We hypothesised that tirzepatide would be superior to insulin lispro for improving SF-36v2 domain and summary scores and compared the effects of these treatments on EQ-5D-5L, Ability to Perform Physical Activities of Daily Living (APPADL) and Impact of Weight on Self-Perception (IW-SP) outcomes.

What was learned from the study?

The phase 3b SURPASS-6 trial showed that the recommended treatment intensification strategy of adding tirzepatide to basal insulin statistically significantly improved patient-reported outcomes assessed compared with intensification with insulin lispro, including health-related quality of life as assessed by the SF-36v2 acute form, the EQ visual analogue scale and EQ-5D-5L index, the APPADL questionnaire and the IW-SP questionnaire.

Tirzepatide has demonstrated significant improvements in not just clinical outcomes but also health-related quality of life in basal insulin-treated patients with T2D and inadequate glycaemic control compared with prandial insulin therapy.

INTRODUCTION

Type 2 diabetes (T2D) is characterised by insulin resistance and progressive loss of beta cell function [1]. Patients with long-standing inadequately controlled diabetes often require initiation of insulin therapy, usually with basal insulin. Over time, as the disease progresses, intensification of insulin therapy with prandial insulin is often needed to improve glycaemic control [2, 3]. However, weight gain, fear of hypoglycaemia and treatment complexity are recognised barriers to therapy intensification in real-world clinical practice [4, 5]. Furthermore, the greater treatment burden, lower adherence and greater healthcare costs associated with basal-bolus insulin therapy present additional challenges [6–8]. A number of these factors may contribute to the general lack of positive effect seen with basal-bolus insulin therapy on patient-reported outcomes (PROs) measuring overall health-related quality of life (HRQoL) or health state (Short Form-36 Health Survey version 2 [SF-36v2], EQ-5D-5L, World Health Organization-5 Well-Being Index and Diabetes Quality of Life) [9–12].

Selective glucagon-like peptide-1 (GLP-1) receptor agonists are now recommended for patients already on basal insulin before prandial insulin is initiated [13]. The addition of selective GLP-1 receptor agonists to basal insulin reduces insulin requirements while improving glycaemic control and resulting in body weight reduction without increasing the risk of hypoglycaemia [14–18]. However, these agents have shown positive but limited effects on PROs measuring overall HRQoL or health state (SF-36v2, EQ-5D-5L) in some studies [14, 18–20]. Identifying treatment options that can not only simplify insulin regimens and lower insulin use but also improve patients' HRQoL and translate into improved outcomes for patients, is important.

Tirzepatide is a first-in-class once-weekly glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist approved as an adjunct to diet and exercise for the treatment of adults with T2D and as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of ≥ 30 kg/m^2 (obesity) or with BMI ≥ 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition [21, 22]. The SURPASS-1 to SURPASS-5 clinical trials [23–27] have reported improvements in a range of PROs, including the EQ-5D-5L measuring health status, across the dose range for tirzepatide [28]. In SURPASS-5, participants receiving tirzepatide 10 or 15 mg (in addition to background treatment with insulin glargine ± metformin) reported significantly improved overall health, body weight-related self-perceptions and physical well-being, compared with placebo (in addition to background treatment) [28]. These results are encouraging, but there are currently no data available comparing PROs for patients treated with tirzepatide plus basal insulin versus intensification with prandial insulin.

Since all treatments have the potential to impact the patient's HRQoL, inclusion of PRO measures in clinical trials is important and should be considered as routine when new trials are designed [29, 30]; findings, combined with use of PRO measures in routine practice,

can be used to support clinical decision making [30]. The American Diabetes Association and the European Association for the Study of Diabetes recommend that patient preference and experience play a major role in decisions made by healthcare providers, forming part of the discussion when choosing a treatment to optimise glycaemic control and weight management for the individual patient [2, 31]. Patient experience is now also a consideration for regulatory and health technology assessment bodies when assessing new drug candidates [32–35]. A selection of PRO measures has been used in T2D clinical trials [28, 36, 37], allowing for the most appropriate measures to be selected for each individual trial based on their relevance to the study design and the participants being treated, reflecting their assessment of the treatment, disease state and burden. A review of PRO measures used in phase 3 clinical trials of GLP-1 receptor agonists, novel insulins, sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors for T2D published in 2016 identified five important PRO concepts measured using 20 different questionnaires: symptoms, HRQoL, psychological well-being, satisfaction with treatment/health and impact of weight [38].

The phase 3b SURPASS-6 trial compared two recommended treatment intensification strategies in people with T2D and inadequate glycaemic control on basal insulin: addition of tirzepatide versus addition of prandial insulin lispro. Clinical outcomes, including improvements in glycaemic control and reductions in body weight, showed significant advantages for tirzepatide [39], supporting previous studies showing reductions in glycated hemoglobin (HbA1c) levels and body weight with tirzepatide [23–27]. We now report PROs from SURPASS-6, including, for the first time, the effects of tirzepatide compared to intensification with prandial insulin on HRQoL using the SF-36v2. We hypothesised that tirzepatide would be superior to insulin lispro for improving SF-36v2 domain and summary scores and compared the effects of these treatments on EQ-5D-5L, Ability to Perform Physical Activities of Daily Living (APPADL) and Impact of Weight on Self-Perception (IW-SP) outcomes.

METHODS

Study Design

SURPASS-6 (NCT04537923) was a randomised, open-label, multicentre, parallel-arm, phase 3b study that compared the effect of the addition of tirzepatide once weekly or insulin lispro three times a day in adults with T2D and inadequate glycaemic control despite insulin glargine, with or without metformin. The primary results of SURPASS-6 have been presented elsewhere [39].

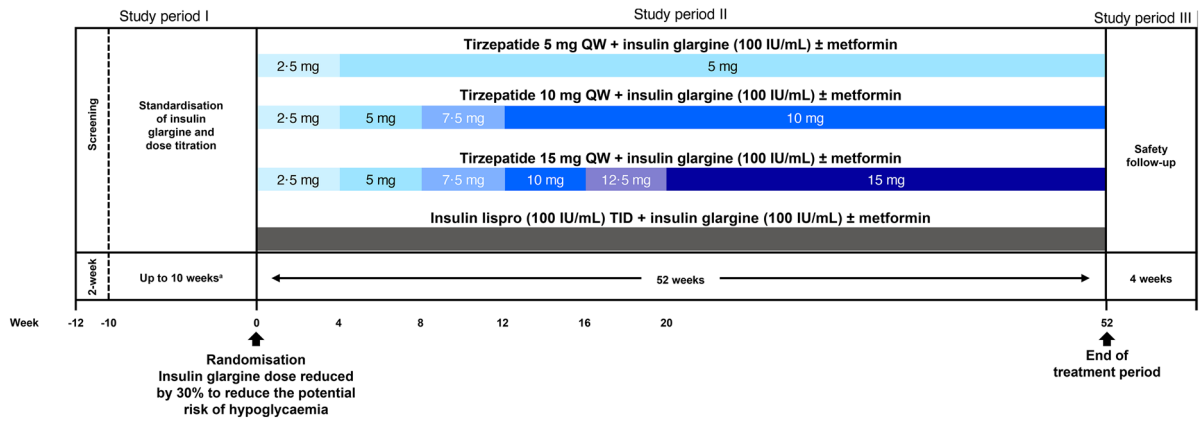


Fig. 1 SURPASS-6 study design. [a]The screening/insulin standardisation period was a total of 12 weeks for participants who needed insulin glargine optimisation and 5 weeks for those who did not need insulin glargine optimisation. *IU* international units, *QW* once weekly, *TID* three times a day

The following is an overview of the SURPASS-6 study design (Fig. 1).

The study was conducted at 135 medical research centres and hospitals in 15 countries (Argentina, Belgium, Brazil, Czech Republic, Germany, Spain, Greece, Hungary, Italy, Mexico, Romania, Russia, Slovakia, Turkey and the USA). The study protocol was approved by the ethical review board at each site (Supplementary Material Table 1), including the ethical review board at the principal investigator site (Advarra Inc., Columbia, MD). This study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki of 1964 and its later amendments, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice guidelines and applicable local laws and regulations. All participants provided written informed consent. This article is based on a previously conducted study and does not contain any new studies with human participants or animals performed by any of the authors.

Participants

Eligible patients were adults with T2D, baseline HbA1c of ≥ 7.5% to ≤ 11.0% (58–97 mmol/mol), BMI from ≥ 23 kg/m^2 to ≤ 45 kg/m^2 and stable weight (± 5%) who agreed not to initiate an intensive diet and/or exercise programme during the study other than the lifestyle and dietary measures for diabetes treatment. Patients were receiving stable doses of once or twice daily basal insulin (with doses of ≥ 30 IU/day and between ≥ 0.3 and ≤ 1.0 IU/kg/day within 90 days prior to screening considered stable). Patients could also be receiving oral glucose-lowering agents in any combination of up to two of the following: stable daily dose of metformin ≥ 1500 mg/day up to maximum approved dose per country-specific approved label, sulfonylureas or dipeptidyl peptidase-4 inhibitors.

Key exclusion criteria included the presence of type 1 diabetes, history of pancreatitis, proliferative diabetic retinopathy, non-proliferative diabetic retinopathy requiring acute treatment, severe hypoglycaemia and established cardiovascular disease. All patients provided written informed consent before participation in the study.

Randomisation and Masking

Eligible participants were randomised (1:1:1:3) to receive tirzepatide 5, 10 or 15 mg once weekly or insulin lispro (100 IU/mL) three times a day, as subcutaneously administered add-on to standardised insulin glargine (100 IU/mL), with or without metformin (≥ 1500 mg/day), for 52 weeks determined by a computer-generated random sequence using an interactive web response system. Randomisation was stratified by country, pre-randomisation HbA1c level (≤ 8.5%, > 8.5% [≤ 69, > 69 mmol/mol]) and baseline metformin use (yes, no).

SURPASS-6 was an open-label study due to the different method of administration, frequency and dosing requirements of tirzepatide and insulin lispro. However, the study team made every effort to remain blinded to the doses of tirzepatide received by participants.

Procedures

All participants discontinued oral glucose-lowering agents except metformin (≥ 1500 mg/day) and switched their pre-study basal insulin regimen to insulin glargine once daily at bedtime during insulin standardisation period (Fig. 1). Insulin glargine was administered via subcutaneous injection and titrated to target fasting blood glucose of 100 to 125 mg/dL as per investigator's clinical discretion.

Participants with HbA1c of ≥ 7.5% (58 mmol/mol) at the end of the insulin standardisation period of up to 10 weeks were randomised to the 52-week treatment period (Fig. 1). Tirzepatide was administered via subcutaneous injection once weekly using single-dose pens, and doses were escalated gradually to improve gastrointestinal tolerability. Insulin lispro was

administered via subcutaneous injection three times a day using prefilled pens and titrated to a target pre-meal/bedtime blood glucose of 100 to 125 mg/dL (5.6 to 6.9 mmol/L).

Clinical and safety data were collected throughout the study. PROs were assessed at baseline, endpoint (week 52) and any early discontinuation visit using the instruments described below.

Outcomes

The primary outcome, change in HbA1c from baseline, and secondary clinical outcomes, including changes from baseline in fasting serum glucose and body weight, as well as proportions of participants at HbA1c and body weight reduction goals, for tirzepatide pooled versus insulin lispro at 52 weeks have been reported elsewhere [39]. PROs were measured at baseline and 52 weeks using the SF-36v2 acute form (secondary outcome), EQ-5D-5L, APPADL questionnaire and IW-SP questionnaire (tertiary/exploratory outcomes) and were compared for the tirzepatide-pooled dose group and for each dose of tirzepatide versus insulin lispro at 52 weeks. An overview of the PRO measures included in SURPASS-6 is presented in Table 1. Safety endpoints included the occurrence of hypoglycaemic events. Safety and tolerability data have been disclosed reported elsewhere [39].

The SF-36v2 acute form is a generic, validated, patient-completed measure designed to assess eight domains of functioning and health that are also combined to obtain two component summary scores (physical and mental) (Fig. 2) [40].

The EQ-5D-5L is a generic instrument commonly used to measure overall health status [41]. The EQ visual analogue scale (EQ VAS) allows the patient to self-rate their overall health status. The EQ-5D-5L index score is based on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with each dimension having five response levels. EQ-5D-5L index scores were based on the UK value set [42].

The APPADL questionnaire contains seven items that assess how difficult it is for patients to engage in certain activities considered to be integral to normal daily life, such as walking, standing and climbing stairs [43].

The IW-SP has three items and is designed to assess how self-perceptions of individuals with T2D and obesity are affected by their body weight [44].

Higher scores indicate better outcomes across all PRO measures included in SURPASS-6.

Statistical Analysis

Sample size selection was guided by establishing non-inferiority of each tirzepatide dose and tested against insulin lispro, relative to the primary endpoint [39]. The tirzepatide-pooled treatment group included participants randomised to tirzepatide 5, 10 or 15 mg.

Guided by the efficacy estimand, defined as the average treatment effect of tirzepatide versus insulin lispro had participants taken treatment as intended, analyses were conducted on the modified intention-to-treat efficacy analysis set. This dataset composed of randomised participants exposed to ≥ 1 dose of study drug (tirzepatide or insulin lispro) who did not discontinue the study drug due to inadvertent enrolment, and observations occurring after the start of rescue therapy with another glucose-lowering agent or early treatment discontinuation were excluded. Baseline demographic and clinical characteristics were described only for participants with a non-missing baseline score and at least one non-missing post-baseline score for at least one of the PRO measures analysed. For PROs, the main comparative analyses were the change from baseline to 52 weeks in individual PRO measures for tirzepatide pooled and each dose of tirzepatide versus insulin lispro. Only participants with a non-missing baseline score and at least one non-missing post-baseline score for the response variable were included in the analysis for that PRO measure. Responses were analysed using analysis of covariance (ANCOVA) models for endpoint measures with last observation carried forward imputation, with model terms treatment, pooled country, baseline

Table 1 Overview of the patient-reported outcome measures administered in SURPASS-6

Name	SF-36v2 acute form [40]	EQ-5D-5L [41]	APPADL [43]	IW-SP [44]
Description of tool	A 36-item, validated, patient-completed questionnaire designed to assess multiple domains of functioning and health asks about the respondent's views about their health, how they feel and how well they are able to do their usual activities	A non-disease-specific instrument commonly used to measure overall health status A two-part questionnaire: EQ VAS: a quantitative measure of health outcome that reflects the patient's own judgement EQ-5D-5L: a descriptive system of the respondent's health state	A seven-item measure of self-reported ability of respondents with T2D and overweight/obesity to perform daily physical activities	A three-item questionnaire assessing the impact of body weight on self-perceptions in respondents with T2D and overweight/obesity
Details	Questions assess eight health domains: physical functioning, role – physical, bodily pain, general health, vitality, social functioning, role – emotional and mental health, which can also be summarised into two component summary scores (Fig. 2) The physical functioning domain assesses limitations due to health 'now', while the remaining seven domains assess functioning 'in the past week' Questions (items) are answered on Likert scales of varying lengths (3-, 5- or 6-point scales) Scoring of each domain and both Component Summary scores are US norm-based and presented in the form of *T*-scores, with a mean of 50 and SD of 10. Per copyright owner, QualityMetric Health Outcomes Scoring Software 4.5 is used to derive domain and Component Summary scores from raw scores Higher scores indicate better functioning and health/well-being	The EQ VAS records the patient's self-rated health on a vertical VAS, with endpoints 'the best health you can imagine' (100) and 'the worst health you can imagine' (0) Higher scores indicate better health utility The EQ-5D-5L descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression Each dimension has five levels: a score of one indicates perfect health, zero indicates death and negative scores represent values worse than death EQ-5D-5L health states may be converted into a single index value that is presented in country-specific value sets to describe the respondent's health state; for these analyses, a UK-based utility index score was calculated [42] UK-based index scores range in value from −0.59 to 1.0 Higher scores indicate better health states	Items assess how difficult it is to engage in certain activities common in daily life: e.g. getting up from floor/ground, getting down to floor/ground, standing, climbing stairs, household chores/yard work, moderate physical activity and strenuous physical activity Items are scored on a 5-point numeric scale from 5 (not at all difficult) to 1 (unable to do); scores are transformed to 0–100 Higher scores indicate better self-reported ability to perform physical activities of daily living	Items relate to the impact of weight on how happy the respondent is with their appearance, how self-conscious they feel in public and how they feel comparing their weight with others Items are scored on a 5-point numeric scale from 1 (always) to 5 (never); scores are transformed to 0–100 Higher scores indicate better self-perception in relation to weight

APPADL Ability to Perform Physical Activities of Daily Living, *IW-SP* Impact of Weight on Self-Perception Questionnaire, *SD* standard deviation, *SF-36v2* Short Form-36 Health Survey version 2, *T2D* type 2 diabetes, *UK* United Kingdom, *US* United States, *VAS* visual analogue scale

HbA1c (≤8.5%, >8.5% [≤69, >69 mmol/mol]), and baseline metformin use (yes, no) as fixed effects, and baseline PRO score as a covariate. *P* values<0.05 were considered statistically significant, and the values were not adjusted for multiplicity.

Exploratory post hoc analyses, conducted for SF-36v2 acute form Physical and Mental Component Summary scores and EQ VAS in the tirzepatide-pooled population only, modelled six baseline characteristics and/or factors changing over time (percentage of body weight change from baseline; HbA1c change from baseline; and baseline weight, age, sex and geographic region) identified as being correlated to the PRO scores based on Akaike information criterion (AIC) using a stepwise linear regression model.

Additional exploratory post hoc analyses were conducted to explore the relationship between weight reduction and PROs using ANCOVA models with model terms treatment, weight change category, treatment-by-weight-change-category interaction and pooled country as fixed effects and baseline PRO score and baseline weight as covariates. Analyses of all PROs by weight reduction category (≥0% to <5%, ≥5% to <10%, ≥10% to <15% and ≥15%) were performed in the tirzepatide-pooled population only. All analyses were carried out using SAS® version 9.4 (SAS Institute Inc., Cary, NC). There was no data monitoring committee.

Role of the Funding Source

The funder of the study, Eli Lilly and Company, had a role in the study design, data collection, data analysis, data interpretation and writing of the report.

RESULTS

Overall, 2267 participants were assessed for eligibility for SURPASS-6 between 19 October 2020 and 01 November 2022; 1428 participants with T2D were randomised (1:1:1:3) to tirzepatide (5, 10 or 15 mg) or insulin lispro. The disposition of the study participants is presented in Supplementary Material Fig. 1.

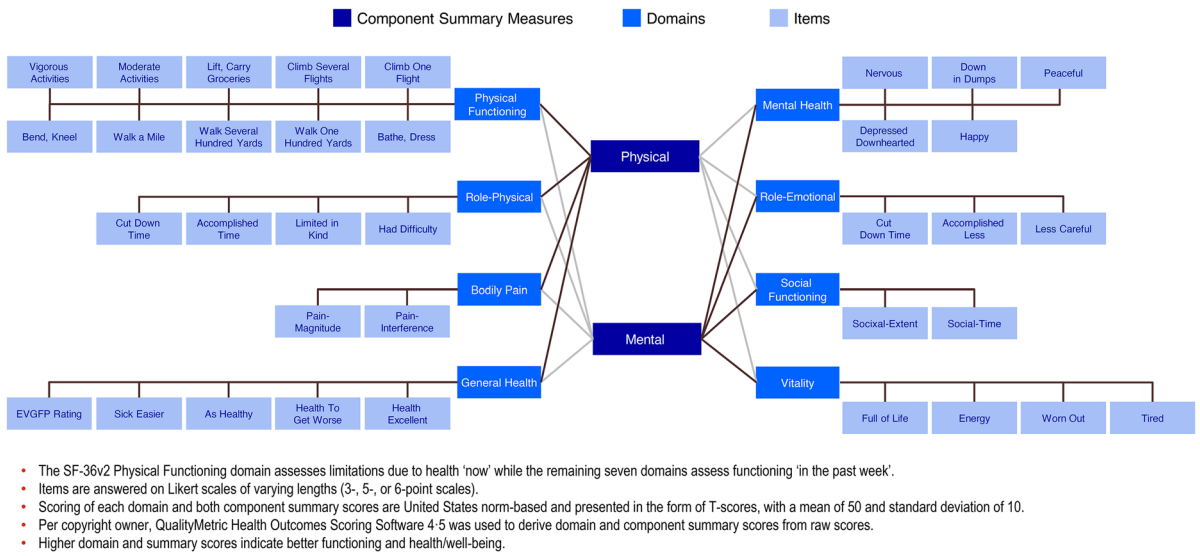
Clinical Outcomes in the Total Study Population

At 52 weeks, tirzepatide pooled was superior versus insulin lispro in change from baseline in HbA1c (least squares [LS] mean difference vs insulin lispro [95% confidence interval (CI)] −1.0% [−1.2 to −0.8], $p<0.001$) with substantially less insulin use (median insulin glargine dose 13 IU/day versus 42 IU/day [and insulin lispro 62 IU/day in basal-bolus arm]) (Supplementary Material Table 2) [39]. At week 52, 67.5% of tirzepatide-pooled participants met HbA1c target<7.0% compared with 36.2% of participants receiving insulin lispro. Tirzepatide pooled was superior versus insulin lispro in change from baseline in body weight at 52 weeks (LS mean difference vs insulin lispro [95% CI] −12.2 [−13.4 to −10.9] kg, $p<0.001$) [39].

Safety and Tolerability in the Total Study Population

At safety follow-up 4 weeks after end of study treatment period, 43 tirzepatide-pooled participants (6.0%) had ≥1 adverse event (AE) leading to study treatment discontinuation compared with 17 participants (2.4%) receiving insulin lispro (Supplementary Material Table 3) [39]. The most frequently reported adverse events with tirzepatide were gastrointestinal (including nausea [13.6–25.8%], diarrhoea [11.0–15.1%] and vomiting [4.5–12.7%]) [39].

Severe hypoglycaemia was reported in three participants (0.4%) treated with tirzepatide (all doses pooled), compared with 30 participants (4.2%) treated with insulin lispro (Supplementary Material Table 4) [39]. Blood glucose level less than 54 mg/dL or severe hypoglycaemia was reported in 76 participants (10.6%) treated with tirzepatide pooled, compared with 340 participants (48.0%) with insulin lispro [39].



- The SF-36v2 Physical Functioning domain assesses limitations due to health 'now' while the remaining seven domains assess functioning 'in the past week'.
- Items are answered on Likert scales of varying lengths (3-, 5-, or 6-point scales).
- Scoring of each domain and both component summary scores are United States norm-based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10.
- Per copyright owner, QualityMetric Health Outcomes Scoring Software 4·5 was used to derive domain and component summary scores from raw scores.
- Higher domain and summary scores indicate better functioning and health/well-being.

Fig. 2 Short Form-36 Health Survey version 2 (SF-36v2) acute form component summary measures, domains and items. All health domains contribute to the scoring of both the Physical and Mental Component summaries. Domains contributing most to the scoring of the component summaries are represented by black lines; domains contributing to a lesser degree are represented by grey lines. *EVGFP* excellent–very good–good–fair–poor health

Baseline Demographic and Clinical Characteristics

The baseline demographics and clinical characteristics of participants with a non-missing baseline score and at least one non-missing post-baseline score for at least one of the PRO measures analysed were well balanced across the treatment groups (Table 2). Overall mean age was 58.6 years, duration of diabetes was 13.7 years, HbA1c was 8.8%, body weight was 90.8 kg, BMI was 33.2 kg/m^2, median insulin glargine dose was 46.0 IU/day (0.53 IU/kg/day) and 85.6% of participants were using metformin.

SF-36v2 Acute Form Outcomes

At 52 weeks, tirzepatide-pooled participants had statistically significant improved scores across all SF-36v2 domains (Fig. 3a, b) and both component summary scores (Fig. 3c) compared with insulin lispro-treated participants after adjustment for baseline PRO scores. The largest statistically significant differences between tirzepatide-pooled and insulin lispro participants were observed in the general health (3.0 versus –0.1, respectively), vitality (1.5 versus –1.1) and mental health (0.9 versus –1.6) domains, followed by the bodily pain (1.3 versus –0.8) and role – emotional (0.8 versus –1.1) domains (all $p<0.05$).

All SF-36v2 domains and both component summary scores improved numerically from baseline to 52 weeks in all individual tirzepatide dose groups, except the social functioning domain for the tirzepatide 5 mg group, whereas all SF-36v2 domain scores worsened in insulin lispro-treated participants. The largest measurable differences between baseline and 52 weeks in the individual tirzepatide dose groups were observed in the general health (5 mg, 2.3; 10 mg, 3.5; 15 mg 3.2; all $p<0.001$) and vitality (5 mg, 1.3; 10 mg, 2.0; 15 mg, 1.3; all $p<0.05$) domain scores.

Other PROs – EQ-5D-5L, APPADL and IW-SP

At 52 weeks, statistically significant improved EQ VAS and EQ-5D-5L index scores were observed in tirzepatide-pooled participants and in participants in each individual tirzepatide dose group compared with insulin lispro-treated participants after adjustment for baseline scores

(Fig. 4a, b). EQ VAS showed statistically significant improvements from baseline to week 52 in all tirzepatide dose groups (5 mg, 4.5; 10 mg, 4.5; 15 mg, 6.6; all $p<0.001$), and EQ-5D-5L index scores showed statistically significant improvements in tirzepatide-pooled participants (0.03; $p<0.001$) and in the tirzepatide 5 mg dose group (0.03; $p<0.05$), whereas EQ VAS remained stable and EQ-5D-5L index scores worsened (–0.02; $p<0.05$) in insulin lispro-treated participants.

At 52 weeks, tirzepatide-pooled participants, as well as participants in each individual tirzepatide dose group, had statistically significant improved transformed APPADL (Fig. 4c) and IW-SP total scores (Fig. 4d) compared with insulin lispro-treated participants after adjustment for baseline scores. Transformed APPADL total scores also showed statistically significant improvements from baseline to week 52 in all tirzepatide dose groups (5 mg, 4.5; 10 mg, 5.0; 15 mg, 4.2; all $p\leq0.001$), whereas this score worsened in insulin lispro-treated participants (–2.7; $p<0.001$). IW-SP transformed total scores also showed statistically significant improvements from baseline to week 52 in all tirzepatide dose groups (5 mg, 7.9; 10 mg, 10.5; 15 mg 10.4; all $p<0.001$), with no statistically significant change in this score in insulin lispro-treated participants.

Impact of Factors Correlated to PROs

Results of the exploratory post hoc analyses that modelled six baseline characteristics and/or factors changing over time identified as being associated with the PRO scores in the tirzepatide-pooled population based on AIC using a stepwise linear regression model are included in Supplementary Material Table 5. Percentage change in body weight was consistently significantly associated with PROs, with age and baseline weight showing less consistent associations.

Association Between Weight Reduction and PROs

Although statistical tests were not conducted, results of these additional exploratory post hoc analyses showed that there was a numerical trend towards improved SF-36v2 Physical and Mental Component Summary scores in participants treated with tirzepatide achieving greater percentage reductions in weight, with participants achieving ≥ 15% weight reduction reporting the greatest improvements in component summary scores (after adjustment for baseline PRO scores) (Fig. 5a). Changes from baseline SF-36v2 acute form domain scores at 52 weeks by weight reduction category for tirzepatide-treated participants are presented in Supplementary Material Fig. 2a, b.

In the absence of statistical tests, similar numerical trends were observed among tirzepatide-treated participants with respect to the EQ VAS and EQ-5D-5L index scores, with participants achieving ≥ 15% weight reduction also reporting the greatest improvements in these scores (after adjustment for baseline scores) (Fig. 5b, c). These trends were also visible in the transformed APPADL and IW-SP total scores, with participants treated with tirzepatide achieving greater percentage reductions in weight generally reporting numerically greater improvements in these scores (Fig. 5d, e).

DISCUSSION

SURPASS-6 showed that, in comparison with basal-bolus insulin therapy, treatment with tirzepatide as an add on to basal insulin in adults with long-standing T2D provided superior and clinically meaningful glycaemic control and had the additional benefits of reducing body weight and being associated with substantially less hypoglycaemia and insulin use [39]. Results of the current analyses build on these findings and reveal that greater improvements across multiple domains of HRQoL were observed for basal-tirzepatide treatment compared with basal-bolus insulin therapy in this population. In addition, improvements in HRQoL were numerically larger with tirzepatide in participants achieving greater percentage reductions in weight.

These PRO findings from SURPASS-6 add to the existing PRO data for tirzepatide obtained from analyses of tirzepatide-pooled (5, 10 and

Table 2 Baseline demographic and clinical characteristics of adults with type 2 diabetes in SURPASS-6 with a non-missing baseline score and at least one non-missing post-baseline score for at least one patient-reported outcome measure

Characteristic	Tirzepatide 5 mg (*N* = 224)	Tirzepatide 10 mg (*N* = 219)	Tirzepatide 15 mg (*N* = 206)	Tirzepatide pooled (*N* = 649)	Insulin lispro (*N* = 606)
Age (years)	57.5 (10.1)	59.6 (9.2)	57.5 (9.2)	58.2 (9.6)	58.9 (9.5)
Female, *n* (%)	132 (58.9)	136 (62.1)	117 (56.8)	385 (59.3)	342 (56.4)
HbA1c (%)	8.9 (1.0)	8.7 (1.0)	8.7 (1.0)	8.8 (1.0)	8.8 (1.0)
HbA1c (mmol/mol)	73 (10	72 (11)	72 (11)	72 (11)	72 (10)
Weight (kg)	91.9 (17.8)	89.6 (18.3)	92.1 (19.0)	91.2 (18.4)	90.3 (17.5)
BMI (kg/m^2)	33.6 (5.3)	33.5 (5.4)	33.3 (5.3)	33.5 (5.3)	33.0 (5.1)
Duration of T2D (years)	13.2 (6.7)	13.9 (6.9)	12.8 (7.3)	13.3 (7.0)	14.0 (7.2)
Insulin glargine dose (IU/day), median (Q1, Q3)	46 (37, 62)	46 (34, 62)	48 (36, 60)	46 (36, 62)	46 (36, 60)
Baseline metformin use (yes), *n* (%)	191 (85.3)	183 (83.6)	177 (85.9)	551 (84.9)	523 (86.3)

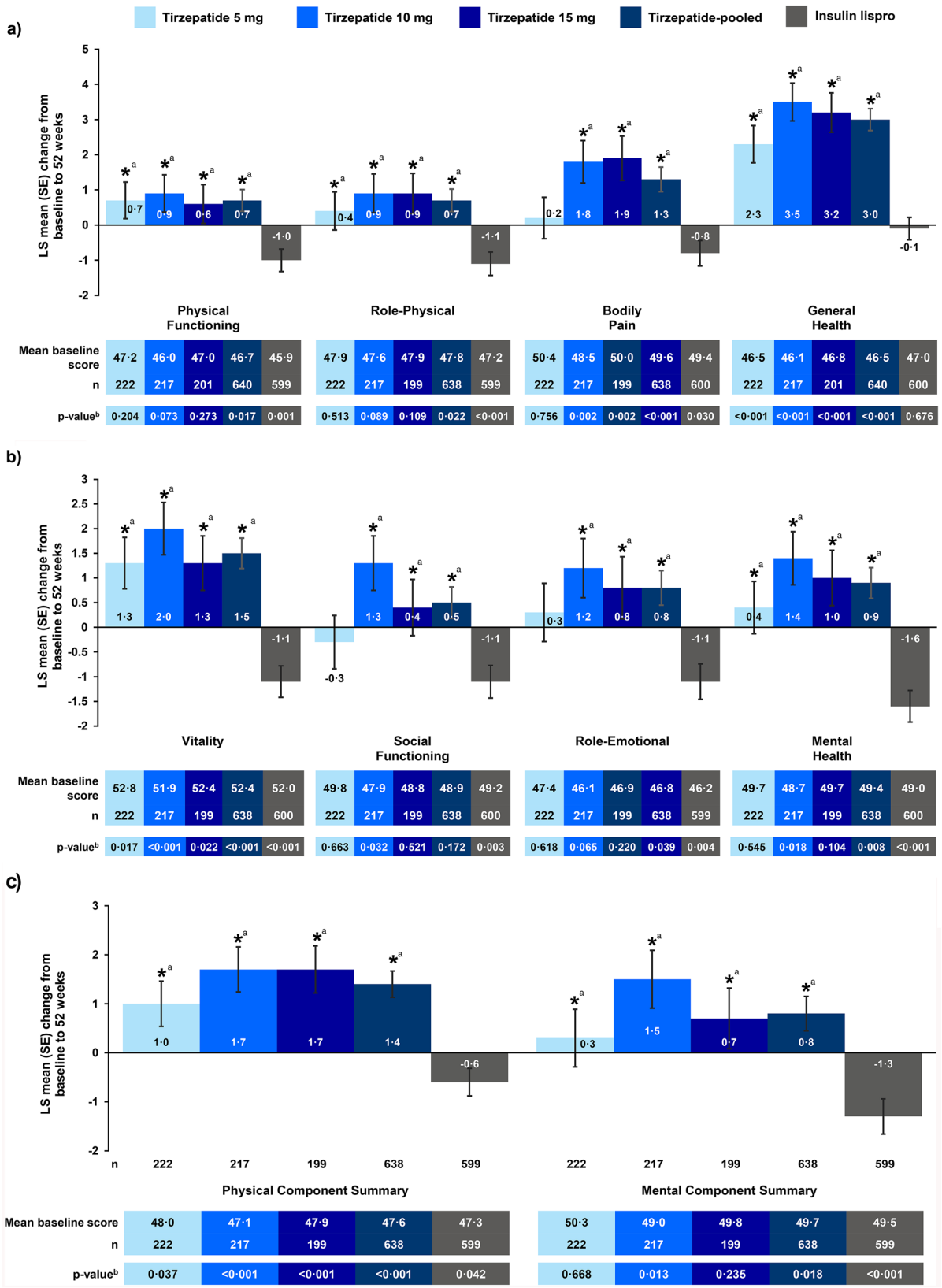
Data reported are mean (standard deviation [SD]) unless otherwise indicated

BMI body mass index, *HbA1c* glycated haemoglobin, *IU* international units, *Q* quartile, *SD* standard deviation, *T2D* type 2 diabetes

15 mg) and pooled comparator data from the SURPASS-1 to SURPASS-5 trials [28, 45]. Tirzepatide produced significant HRQoL improvements versus pooled comparators [28], with those patients achieving higher levels of weight reduction reporting greater improvement in HRQoL [45]. Furthermore, these SURPASS-6 PRO data support the earlier finding of Matza et al. (2022) that treatment benefits observed in clinical trials of tirzepatide are important to patients [46].

Some improvements in PROs have also been reported with GLP-1 receptor agonists. In the AWARD clinical trial programme, dulaglutide-treated patients had greater improvements in IW-SP and APPADL measures compared with insulin glargine-treated patients [36]. Furthermore, in AWARD-9, combined therapy with dulaglutide and insulin glargine resulted in greater improvements in the IW-SP and Disinhibited Eating domain of the 18-item Diabetes Health Profile compared with placebo plus insulin glargine, but EQ-5D-5L index score and EQ VAS results were similar between the two strategies [19]. In SUSTAIN 11, addition of semaglutide was compared with addition of insulin aspart in patients with T2D receiving standardised insulin glargine and metformin therapy; improvements in the SF-36v2 were similar or larger with the semaglutide regimen [20]. Furthermore, in the PIONEER 2 study, which compared oral semaglutide with the sodium-glucose co-transporter 2 inhibitor, empagliflozin, in patients with uncontrolled T2D, observations for the majority of components on the SF-36v2 were similar in both treatment groups [47].

T2D is associated with impairment in all aspects of the HRQoL of those affected, and comorbidities, commonly obesity, can have a further adverse impact [48]. Notably, 90% of people with T2D have been classified as living with overweight or obesity [49], and weight reduction is recognised as an important aspect of T2D management [2, 50]. It is, therefore, important that treatments that can effectively assist people with T2D to achieve


a)
Tirzepatide 5 mg
Tirzepatide 10 mg
Tirzepatide 15 mg
Tirzepatide-pooled
Insulin lispro
LS mean (SE) change from baseline to 52 weeks
Physical Functioning
Role-Physical
Bodily Pain
General Health
Mean baseline score
n
p-value[b]
b)
Vitality
Social Functioning
Role-Emotional
Mental Health
c)
Physical Component Summary
Mental Component Summary

◂**Fig. 3** Changes from baseline in Short Form-36 Health Survey version 2 (SF-36v2) acute form domain and component summary norm-based scores at 52 weeks in SURPASS-6: efficacy estimated. **a** Physical functioning, role – physical, bodily pain and general health domain norm-based scores. **b** Vitality, social functioning, role – emotional and mental health domain norm-based scores. **c** Physical and mental component summary norm-based scores. $^{*}P < 0.05$. ^{a}P value for pairwise treatment comparison (tirzepatide pooled versus insulin lispro). ^{b}P value for within-group change from baseline to endpoint. *LS* least squares, *SE* standard error

glycaemic control and weight reduction are available, as they may result in improved HRQoL [51]. Such options may help people to be more engaged in the recommended patient-centric collaborative approach to T2D management [2, 31]. To help measure patient-perceived benefits of treatment, PROs are increasingly recognised as important [29, 30] and are being integrated into the clinical trial programmes of antihyperglycaemic treatments [20, 28, 36, 37]. In this analysis of the SURPASS-6 trial, tirzepatide treatment was associated with improvements in participant's HRQoL. This may be, at least in part, related to weight reduction, but other factors may also have a role. For example, it is possible that the convenience of a once-weekly medication, in contrast to a basal-bolus insulin regimen, which is intensive and requires regular blood glucose monitoring and multiple injections, may have contributed to the relative improvement in HRQoL. In fact, a recent examination of patient perspectives of injectable treatments currently available for the treatment of T2D identified several characteristics of these treatments that are most important to patients, namely confidence in delivering the correct dose, ease of administering the correct dose, ease of using the injection device, and dose frequency [52].

SURPASS-6 has a number of strengths. Basal insulin doses were standardised before initiation of tirzepatide or insulin lispro, and insulin titration was then monitored to ensure suitable doses of both insulin glargine and insulin lispro were used, as shown by the levels of glycaemic control achieved. In addition, this was a multinational trial, with representation of a range of races and ethnic groups from across the globe. Limitations include that the SF-36v2 was administered in a clinical trial setting so results may not reflect those that may be observed in a real-world setting, where people with T2D may have less contact with or support from healthcare professionals. Only participants with a baseline score and at least one post-baseline score were included in the analysis for each PRO measure, and the open-label study design of SURPASS-6 may have influenced participants to overestimate or underestimate their treatment assessments based on their beliefs regarding their assigned treatment. Furthermore, the EQ VAS results, which capture broad health utility, may have been impacted by differences in the treatment administration regimens. Additionally, exploratory pre-specified weight reduction category analyses were not controlled for multiplicity, and wide CIs in these analyses, due to small sample sizes, suggest that caution is needed when interpreting results. Finally, it was not possible to include insulin lispro in the exploratory weight reduction category analyses as insufficient numbers of patients lost weight in this treatment group (most gained weight).

Our findings also suggest a number of future research possibilities. The link between the weight reduction and improved HRQoL we observed could be further developed by investigations into the reasons for weight reduction (e.g. whether it was related to changes in cravings or satiety or other GIP/GLP-1-related mechanisms). It would also be of interest to determine whether patients' emotions, attitudes and levels of satisfaction are affected by the ability of the patient to achieve HbA1c and weight control, by the ease of use of the administration device employed to administer treatment for T2D and by the potential to simplify treatment regimens by reducing or discontinuing insulin use. Weight reduction had not plateaued in SURPASS-6, so longer follow-up could determine whether further reductions/withdrawals of insulin therapy are possible and whether additional benefits in terms of HRQoL can be achieved. Finally, real-world studies are needed to determine how PRO findings from clinical trials translate into clinical practice.

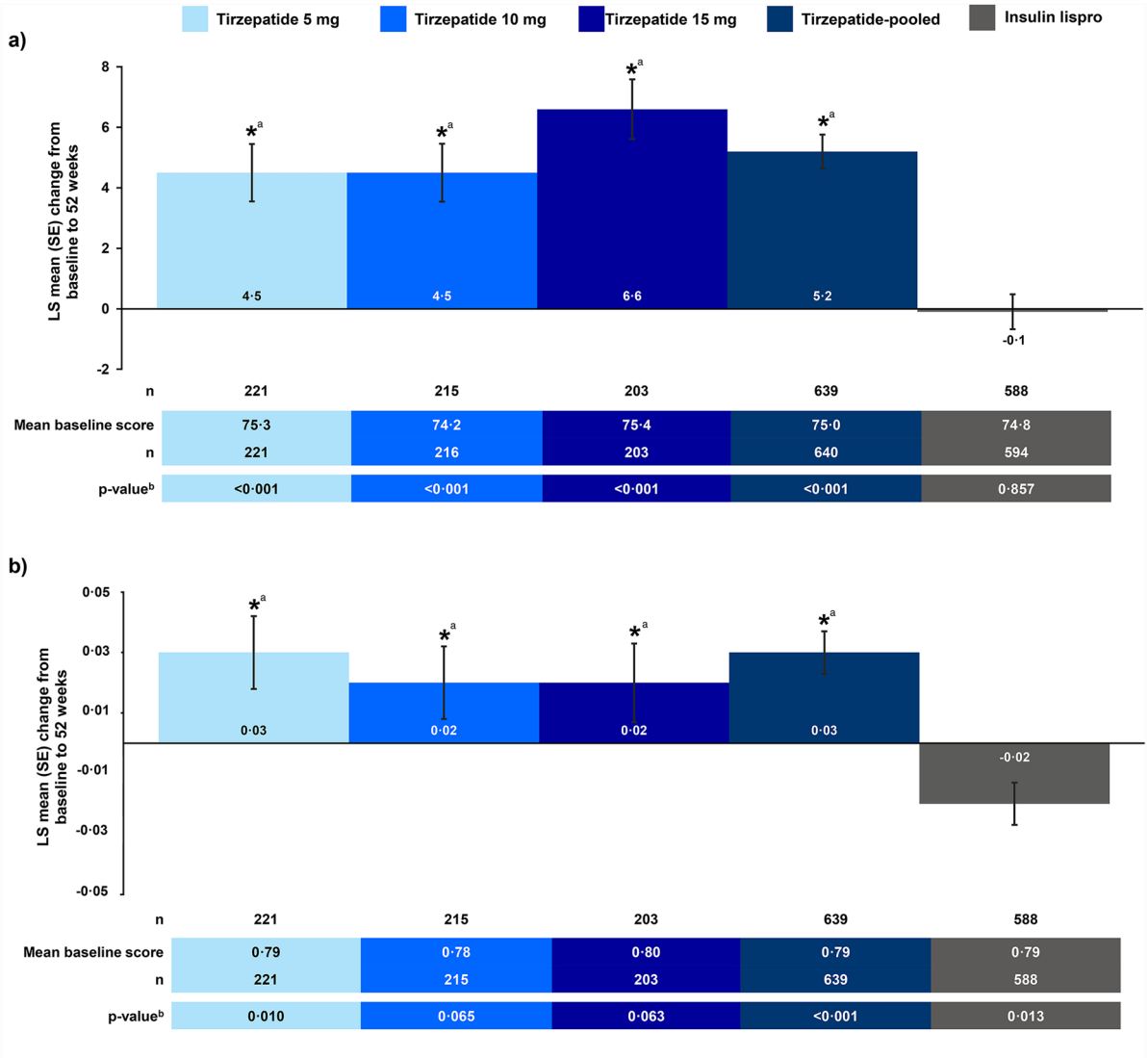


Fig. 4 Changes from baseline in EQ visual analogue scale (VAS), EQ-5D-5L index score, Ability to Perform Physical Activities of Daily Living (APPADL) total score and Impact of Weight on Self-Perception Questionnaire (IW-SP) total score at 52 weeks in SURPASS-6: efficacy estimated. **a** EQ VAS. **b** EQ-5D-5L index score. **c** APPADL total score (transformed). **d** IW-SP total score (transformed). $^{*}P < 0.05$. ^{a}P value for pairwise treatment comparison (tirzepatide pooled versus insulin lispro). ^{b}P value for within-group change from baseline to endpoint. *APPADL* Ability to Perform Physical Activities of Daily Living, *IW-SP* Impact of Weight on Self-Perception Questionnaire, *LS* least squares, *SE* standard error, *VAS* visual analogue scale

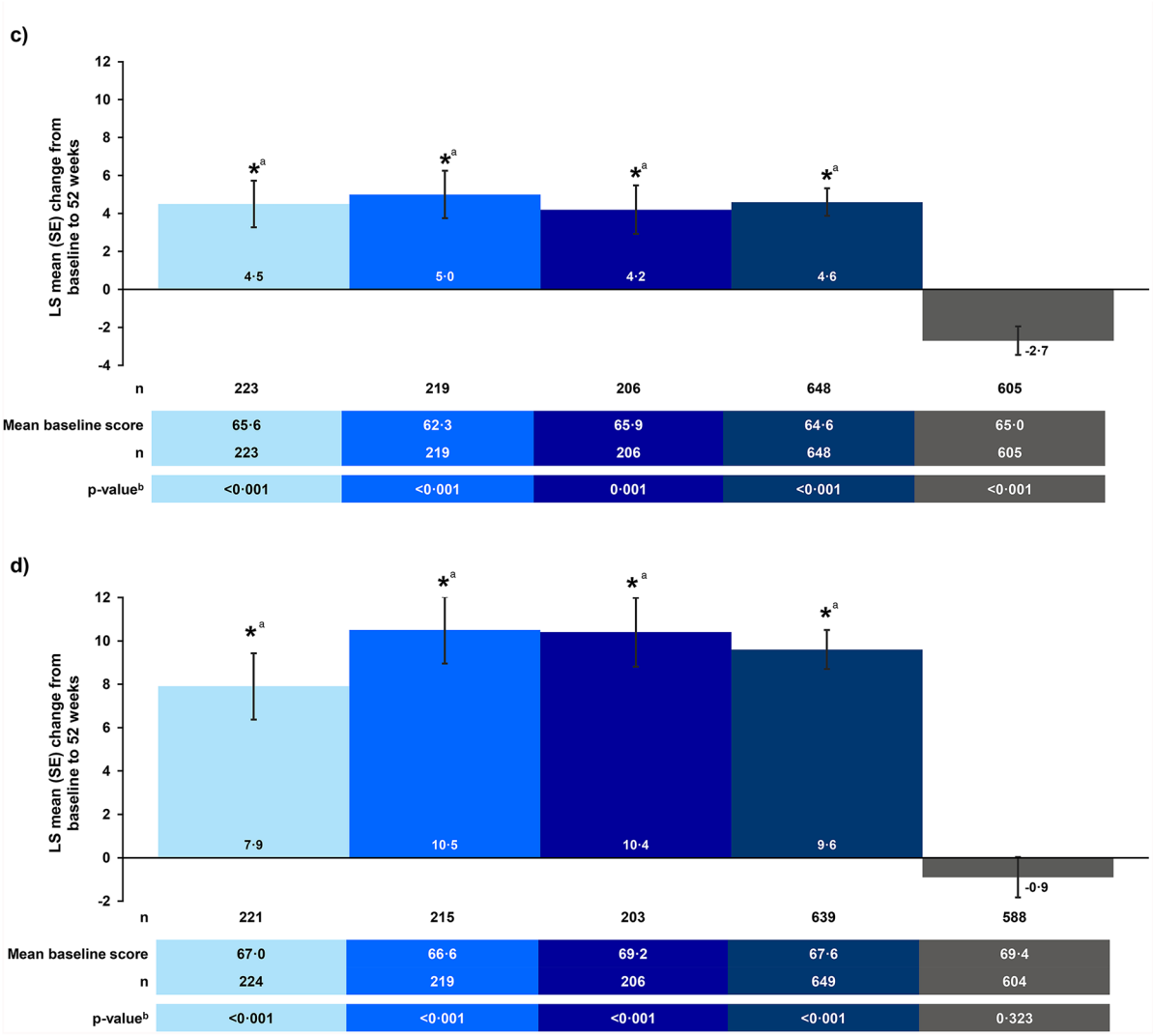


Fig. 4 continued

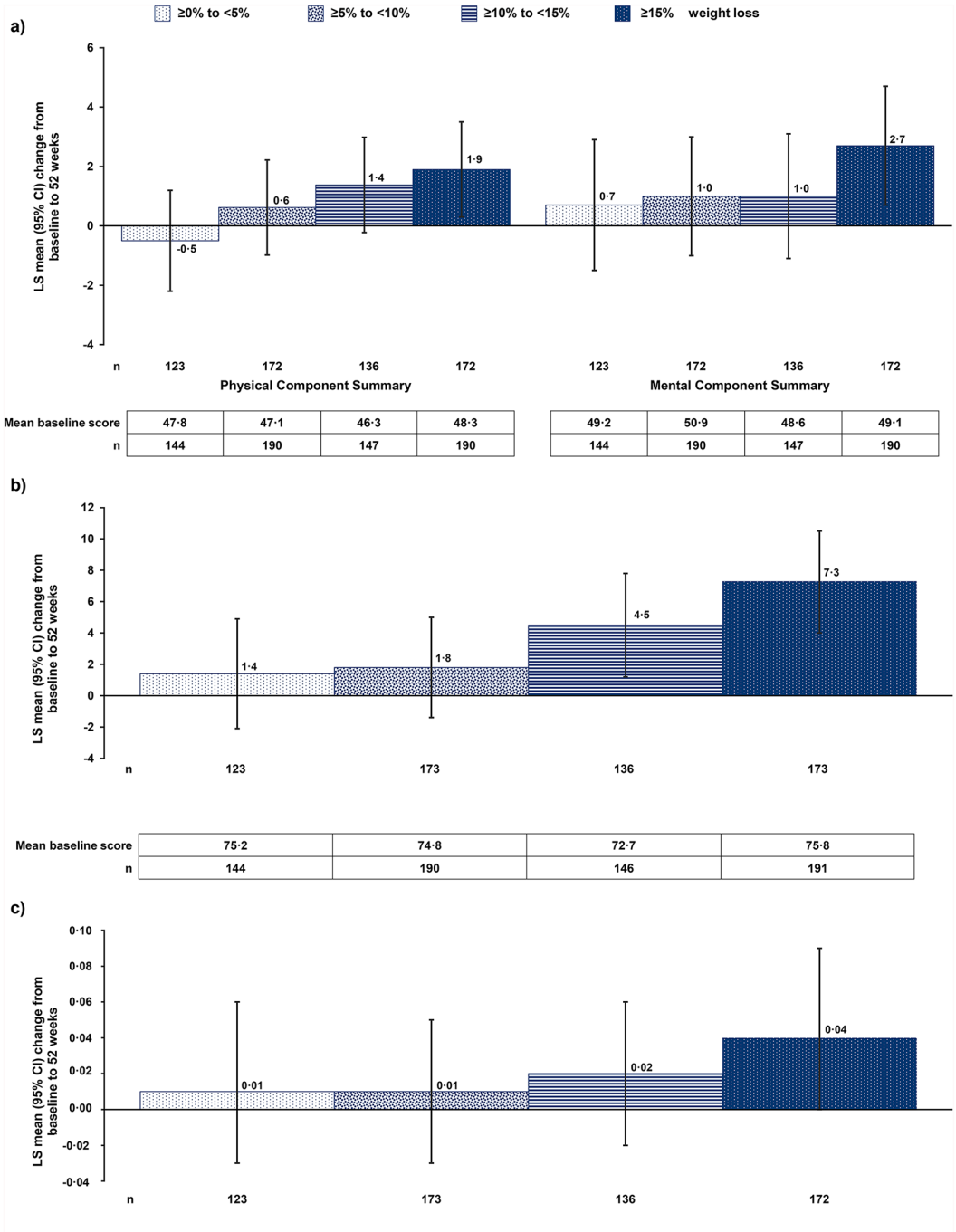


Fig. 5 Changes from baseline in Short Form-36 Health Survey version 2 (SF-36v2) acute form component summary norm-based scores, EQ visual analogue scale (VAS), EQ-5D-5L index score, Ability to Perform Physical Activities of Daily Living (APPADL) total score and Impact of Weight on Self-Perception Questionnaire (IW-SP) total score at 52 weeks by weight reduction category at 52 weeks in the tirzepatide-pooled population in SURPASS-6: Efficacy estimated. **a** SF-36v2 Physical and Mental Component Summary norm-based scores. **b** EQ VAS. **c** EQ-5D-5L index score. **d** APPADL total score (transformed). **e** IW-SP total score (transformed). *APPADL* Ability to Perform Physical Activities of Daily Living, *CI* confidence interval, *IW-SP* Impact of Weight on Self-Perception Questionnaire, *LS* least squares, *SF-36v2* Short Form-36 Health Survey version 2, *VAS* visual analogue scale

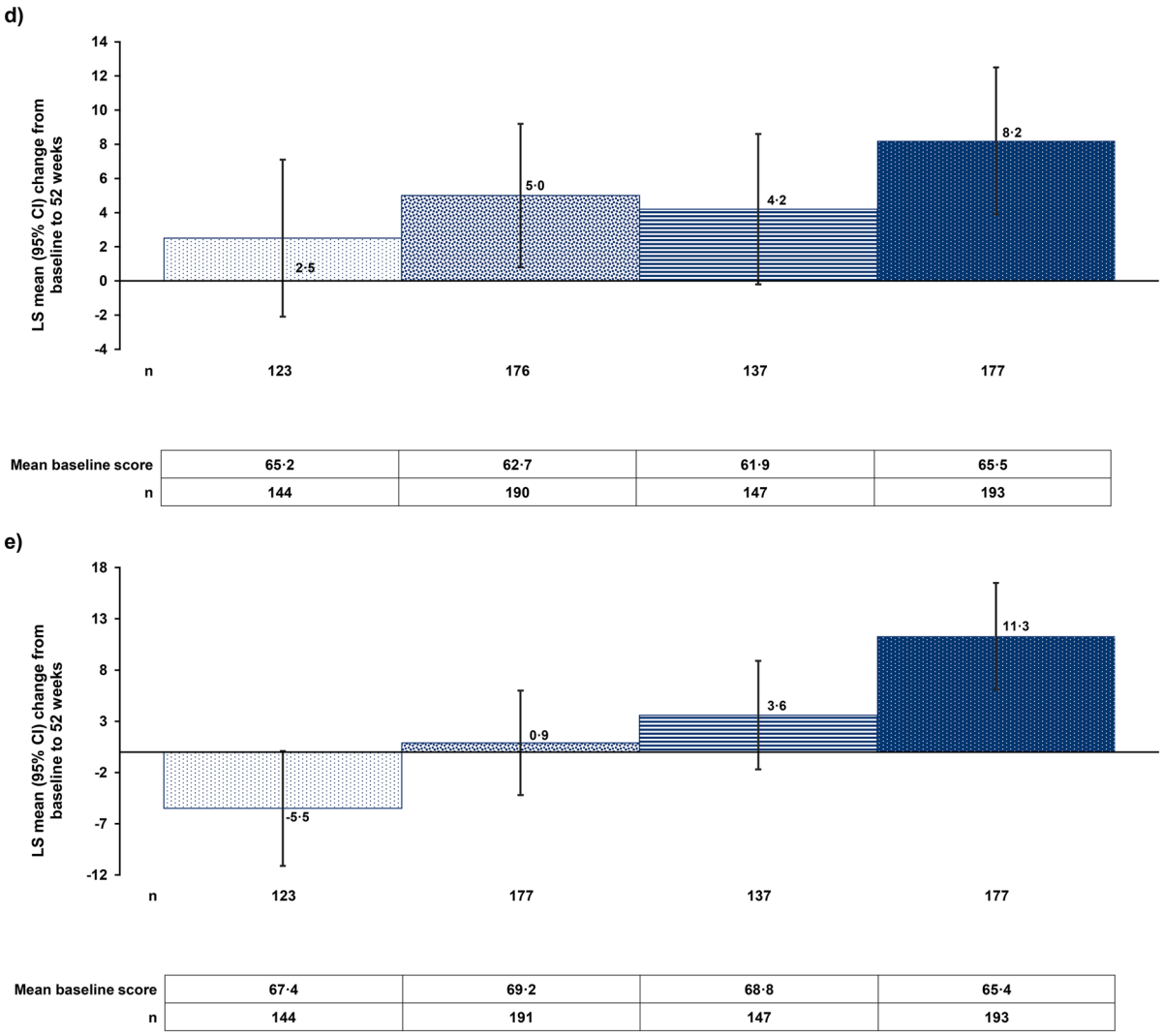


Fig. 5 continued

CONCLUSIONS

Tirzepatide treatment was associated with greater improvements in HRQoL than prandial insulin, in addition to clinically significant improvements in glycaemic and body weight-related parameters, in adult patients with T2D and inadequate glycaemic control with basal insulin.

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substantial contributions to the interpretation of the data for the work and critical revision of the manuscript for important intellectual content. H.S. directly accessed and verified the underlying data reported in the manuscript, has made substantial contributions to the analysis and interpretation of the data for the work and critical revision of the manuscript for important intellectual content. R.H. directly accessed and verified the underlying data reported in the manuscript, has made substantial contributions to the analysis and interpretation of the data for the work and critical revision of the manuscript for important intellectual content. M.W. has made substantial contributions to the analysis and interpretation of the data for the work and critical revision of the manuscript for important intellectual content. S.W. has made substantial contributions to the interpretation of the data for the work, the drafting and critical revision of the manuscript for important intellectual content. H.P. has made substantial contributions to the conception and design of the work, the interpretation of the data for the work and critical revision of the manuscript. All authors had full access to all the data in the study and accept responsibility for submission of the manuscript for publication.

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Data Availability. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymisation, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at: www.vivli.org.

Declarations

Conflict of Interest. Kristina Secnik Boye, Jiat Ling Poon, Laura Fernandez Lando, Helene Sapin, Ruth Huh, and Hiren Patel are minor stockholders of Eli Lilly and Company. Mianbo Wang and Suzanne Williamson work as consultants for Eli Lilly and Company.

Ethical Approval. The study protocol was approved by the Ethical Review Board at each site (Supplementary Material Table 1), including the Ethical Review Board at the Principal Investigator site (Advarra Inc., Columbia, Maryland, US). This study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki of 1964 and its later amendments, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice guidelines and applicable local laws and regulations. All participants provided written informed consent. This article is based on a previously conducted study and does not contain any new studies with human participants or animals performed by any of the authors.

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