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ORIGINAL RESEARCH

Patient-Reported Outcomes in People with Type 2 Diabetes Receiving Tirzepatide in the SURPASS Clinical Trial Programme

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ABSTRACT

Introduction: Tirzepatide, a novel glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist, is approved for glycaemic control for people with type 2 diabetes (T2D). The SURPASS-1 to -5 clinical trials assessed the efficacy of once weekly tirzepatide (5, 10 and 15 mg) versus placebo or active comparators (semaglutide 1 mg, insulin degludec and insulin glargine) in T2D. We evaluated patient-reported outcomes (PROs) that measured overall quality of life (QoL), treatment satisfaction and weight-related attributes across the five SURPASS studies.

Methods: PRO instruments utilised at baseline and primary timepoint (40 weeks for SURPASS-1, -2 and -5; 52 weeks for SURPASS-3 and -4) or early termination visit were EQ-5D-5L (SURPASS-1 to -5); Impact of Weight on Self-Perceptions (SURPASS-1 to -5); Ability to Perform Physical Activities of Daily Living (SURPASS-1 to -5); Diabetes Treatment Satisfaction Questionnaire (SURPASS-2 to -5); and Impact of Weight on Quality of Life-Lite Clinical Trials Version (SURPASS-2 only).

Results: Across all five studies at week 40/52, tirzepatide improved patients' QoL measured by general health and weight-related PROs over the comparator. Generally, higher doses of tirzepatide resulted in greater increases in PRO scores.

Conclusion: Overall, tirzepatide produced significant health and weight-related QoL improvements versus comparators in the five SURPASS studies.

Clinical Trial Registration: SURPASS-1: NCT03954834; SURPASS-2: NCT03987919; SURPASS-3: NCT03882970; SURPASS-4: NCT03730662; SURPASS-5: NCT04039503.

PLAIN LANGUAGE SUMMARY

Tirzepatide is the first glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist approved for the treatment of people with type 2 diabetes. The SURPASS-1 to -5 clinical trials evaluated the efficacy and safety of tirzepatide (5, 10 and 15 mg) compared with placebo or active comparators (including semaglutide 1 mg and basal insulins) in people with type 2 diabetes. We evaluated other outcomes reported by patients that measured overall quality of life, treatment

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satisfaction and weight-related attributes across the five SURPASS studies.

Five validated questionnaires were completed by patients at the beginning and end of the clinical trials, which was after 40 weeks for SURPASS-1, -2 and -5 and after 52 weeks for SURPASS-3 and -4, or when the person left the trial if this was before the official end. These questionnaires were EQ-5D-5L (SURPASS-1 to -5); Impact of Weight on Self-Perceptions (SURPASS-1 to -5); Ability to Perform Physical Activities of Daily Living (SURPASS-1 to -5); Diabetes Treatment Satisfaction Questionnaire (SURPASS-2 to -5); and Impact of Weight on Quality of Life-Lite Clinical Trials Version (SURPASS-2 only).

Across all five studies, treatment with tirzepatide resulted in greater improvements in people's quality of life at the end of the study compared with placebo or treatment with the comparators. Generally, higher doses of tirzepatide resulted in greater increases in questionnaire scores than lower doses of tirzepatide.

Overall, tirzepatide 5, 10 or 15 mg treatment resulted in significant health- and weight-related quality of life improvements versus comparators in the five SURPASS studies.

Keywords: Health-related quality of life patient-reported outcomes; Quality of life; SURPASS; Tirzepatide; Type 2 diabetes; Weight-related quality of life

Key Summary Points

Why carry out the study?

Type 2 diabetes is a chronic disease that can have a huge impact on people's quality of life, and patient-reported outcomes collected during clinical trials can be helpful in understanding patients' perceptions of their treatment and their quality of life while receiving new medications.

We present patient-reported outcome data from the SURPASS-1 to -5 clinical trials of tirzepatide, a novel once weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 receptor agonist approved for the treatment of people with type 2 diabetes.

What was learned from the study?

Tirzepatide produced significant health- and weight-related quality of life improvements versus comparators in the SURPASS-1 to -5 studies.

These patient-reported outcome results further add to the previously reported benefits of tirzepatide treatment for people with type 2 diabetes, namely substantial improvements in glycaemic control and body weight.

INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease that can have a huge impact on people's quality of life (QoL). Tirzepatide, a once weekly glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist that combines both GIP receptor agonism and GLP-1 receptor agonism in a single molecule, is approved for the treatment of people with T2D [1–3] and is in development for chronic weight management. The SURPASS-1 to -5 clinical trials assessed the efficacy of once weekly tirzepatide (5, 10 or 15 mg) versus placebo and active comparators. In these studies, tirzepatide demonstrated statistically significant and clinically meaningful reductions in glycated haemoglobin (HbA1c) and body weight, which were greater than those with placebo, semaglutide 1 mg, titrated insulin degludec and titrated insulin glargine [4–8]. These treatment effects were sustained up to 104 weeks [7]. Tirzepatide has been shown to normalise blood glucose levels, defined as HbA1c < 5.7%, as these levels were achieved by up to 62% of

participants treated with tirzepatide 15 mg [4–9].

Patient-reported outcomes (PROs) are standardised questionnaires used to assess outcomes from the patients' perspective, including perceptions, symptoms, satisfaction with treatment and adherence to prescribed regimens. PROs provide information of value when deciding which treatment will suit which patient that is additional to clinical endpoints such as HbA1c and body weight. The collection of PROs during clinical trials can be useful in understanding patients' perceptions of their treatment and their QoL while receiving new medications. Indeed, there continues to be a growing emphasis on the importance of collecting and publishing patient-reported information directly from clinical trials, so that the patient voice can be considered in drug development and the regulatory/licensing process [10, 11].

A range of PROs are available for use in T2D clinical trials [12], and these can be tailored to each trial depending on the medication studied. Irrespective of class of glucose-lowering therapy, the selection of appropriate PROs should be both relevant to the patients being treated and reflect their assessment of the treatment, disease state and burden. There is substantial value in collecting PRO data from patients receiving treatment for T2D, as it is a chronic disease with a significant impact on QoL, which can also be affected by adverse events (AEs) experienced during treatment.

It was particularly important to collect PRO data from the SURPASS clinical development programme, as tirzepatide is a novel GIP and GLP-1 receptor agonist. Collecting and reporting PROs from clinical trials associated with a new class of medication can be particularly insightful for clinicians, helping them to fully understand the patients' experience while establishing their own prescribing experience. In the SURPASS-1 to -5 clinical trials, the focus was on consistent use of PROs, collecting outcomes relevant across the continuum of T2D treatment, from early stages treated with oral medications to later stages requiring injectable therapy. The collected PROs had a particular focus on health-related QoL (HRQoL) and weight loss measures, given the clinically meaningful HbA1c- and weight-reducing attributes of tirzepatide demonstrated in clinical trials [4–9].

American Diabetes Association guidance recommends that patient preference and experience play a major role in decisions made by healthcare providers, forming part of the discussion when choosing treatment for individual patients [13]. Furthermore, patient perspective is now an important consideration for regulatory boards, such as the US Food and Drug Administration and the European Medicine Agency, when assessing new drug candidates [14, 15]. This paper presents PRO data from the SURPASS-1 to -5 clinical trials.

METHODS

Study Design

SURPASS-1 to -5 Studies

Figure S1 (in the supplementary material) provides a summary of the study design of the five phase 3 SURPASS studies included in these analyses. All were randomised, parallel group, multinational trials of 40 or 52 weeks treatment duration at the primary timepoint that compared the efficacy and safety of once weekly tirzepatide 5, 10 or 15 mg versus placebo or active comparator in adults with T2D. Additional study design details and inclusion/exclusion criteria have been previously reported [4–8].

Tirzepatide Versus Placebo In the double-blind SURPASS-1 and -5 studies, patients were randomised to once weekly tirzepatide 5, 10 or 15 mg or placebo as monotherapy or all with background insulin glargine (titrated following a treat-to-target algorithm) ± metformin, respectively, for 40 weeks.

Tirzepatide Versus Semaglutide In the open-label SURPASS-2 study, patients were randomised to once weekly tirzepatide 5, 10 or 15 mg (blinded) versus semaglutide 1 mg, all with background metformin (minimum 1500 mg/day) for 40 weeks.

Table 1 Summary of PRO instruments included in the SURPASS-1 to -5 clinical trials

PRO instruments	Description
EQ-5D-5L [33]	Consists of two parts: descriptive system and EQ VAS
	Descriptive system
	Measures health status
	Used for clinical and economic appraisal
	Five dimensions measured
	Mobility
	Self-care
	Usual activities
	Pain/discomfort
	Anxiety/depression
	Scale − 0.59 to 1
	EQ VAS
	Records the patient's self-rated HRQoL on a vertical VAS
	Scale 0–100
	Higher scores indicate better outcomes
	EQ-ED-5L index score MID = 0.03–0.0549 [34]
IW-SP [22]	Measures patients' self-perceptions related to their body weight
	Three items measured
	Feel unhappy with appearance due to weight
	Feel self-conscious in public due to weight
	Feel unhappy due to comparing weight with others
	Transformed score 0–100
	A higher score indicates better outcomes
	MID = 25 points (transformed score) [35]

Table 1 continued

PRO instruments	Description
APPADL [23]	Contains seven items that assess how difficult it is for participants to engage in certain activities considered to be integral to normal daily life, such as walking, standing and climbing stairs
	Seven items measured
	How difficult getting up from the floor
	How difficult to get down
	How difficult to stand for 2 h
	How difficult to walk up two flights of stairs
	How difficult to do household chores
	How difficult to engage in moderate physical activity
	How difficult to engage in strenuous physical activity
	Items are scored on a 5-point numeric rating scale where 5 = 'not at all difficult' and 1 = 'unable to do'
	Transformed score 0–100
	A higher score indicates better outcomes
	MID = 6–14 points (transformed score)
DTSQs [21, 36]	Satisfaction with treatment, as well as concerns about hyperglycaemia and hypoglycaemia
	Eight items measured
	Satisfied with current treatment
	Feel convenient about recent treatment
	Feel flexible about recent treatment
	Satisfied with diabetes understanding
	Recommend present treatment to others
	Continue with present treatment
	Times of unacceptably high blood glucose
	Times of unacceptably low blood glucose
	Items concerning times of unacceptably high and low blood glucose are scored separately from the satisfaction items and from each other
	Score 0–36
	Score 0–36 should be as follows
	Treatment satisfaction score: 0–36 where a higher score indicates greater treatment satisfaction
	Hyperglycaemia score: 0–6 where a lower score indicates lower perceived hyperglycaemia frequency
	Hypoglycaemia score: 0–6 where a lower score indicates lower perceived hypoglycaemia frequency
	No MID published for DTSQs

Table 1 continued

PRO instruments	Description
DTSQc [21, 36]	Change in satisfaction with current treatment compared to before the study began, as well as concerns about hyperglycaemia and hypoglycaemia
	Eight items measured (change)
	Satisfied with current treatment
	Feel convenient about recent treatment
	Feel flexible about recent treatment
	Satisfied with diabetes understanding
	Recommend present treatment to others
	Continue with present treatment
	Times of unacceptably high blood glucose
	Times of unacceptably low blood glucose
	Items concerning times of unacceptably high and low blood glucose are scored separately from the satisfaction items and from each other
	Score − 18 to 18
	Score – 18 to 18 should be as follows
	Treatment satisfaction score: − 18 to 18 where a higher score indicates greater treatment satisfaction
	Hyperglycaemia score: − 3 to 3 where a lower score indicates lower perceived hyperglycaemia frequency
	Hypoglycaemia score: − 3 to 3 where a lower score indicates lower perceived hypoglycaemia frequency
	No MID published for DTSQc

Table 1 continued

PRO instruments	Description
IWQOL-Lite-CT [24, 37]	Measure of weight-related functioning in the populations commonly targeted for clinical trials
	The IWQOL-Lite-CT is a 20-item measure with two primary domains (physical [seven items with physical function comprising five of seven items*] and psychosocial [13 items])
	Physical items
	Trouble bending over*
	Tired or winded*
	Unable to stand comfortably*
	Not physically active*
	Unable to walk far/quickly*
	Uncomfortable in small seats
	Bodily pain
	Psychosocial items
	Self-conscious eating in social settings
	Less confident
	Feel judged by others
	Frustrated shopping for clothes
	Feel bad or upset about pictures of self
	Down or depressed about weight
	Less interested in sexual activity
	Avoid social gatherings
	Less productive
	Lack of energy
	Worried about health
	Self-conscious about weight
	Frustrated or upset about weight
	The IWQOL-Lite-CT has also a total score, which includes all 20 items
	Score 0–100
	Higher composite scores indicate higher levels of functioning
	No MID published for IWQOL-Lite-CT

APPADL Ability to Perform Physical Activities of Daily Living, *DTSQc* Diabetes Treatment Satisfaction Questionnaire change, *DTSQs* Diabetes Treatment Satisfaction Questionnaire status, *HRQoL* health-related quality of life, *IWQOL-Lite-CT* Impact of Weight on Quality of Life-Lite Clinical Trials Version, *IW-SP* Impact of Weight on Self-Perceptions, *MID* minimally important difference, *PRO* patient-reported outcome, *VAS* visual analogue scale

Tirzepatide Versus Insulin Degludec In the open-label SURPASS-3 study, patients were randomised to once weekly tirzepatide 5, 10 or 15 mg or once daily insulin degludec (titrated following a treat-to-target algorithm), all with metformin ± sodium-glucose cotransporter 2 (SGLT2) inhibitor for 52 weeks.

Tirzepatide Versus Insulin Glargine In the open-label SURPASS-4 study, patients at increased cardiovascular risk on one to three oral glucose-lowering medications (± metformin ± sulfonylurea ± SGLT2 inhibitor) were randomised to once weekly tirzepatide 5, 10 or 15 mg or once daily insulin glargine (titrated following a treat-to-target algorithm) for up to 104 weeks with the primary timepoint at 52 weeks.

Ethical Considerations

The SURPASS-1 to -5 studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocols were approved by ethical review boards and all patients provided written informed consent. This particular 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.

PRO Instruments

Five different PRO instruments were completed at baseline and primary timepoint (week 40/52) by participants enrolled in the five phase 3 SURPASS clinical trials (Table 1). Overall HRQoL was measured using the EQ-5D-5L instrument, while treatment satisfaction was evaluated using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Different concepts associated with weight-related QoL were measured using the Impact of Weight on Self-Perceptions (IW-SP) questionnaire, the Ability to Perform Physical Activities of Daily Living (APPADL) questionnaire and the Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT). The PRO instruments selected for inclusion in each SURPASS-1 to -5 trial were determined by the availability of the measures at the time of protocol approval and the individual study characteristics.

EQ-5D-5L

The EQ-5D-5L is a generic health status measure used for clinical and economic appraisal that assesses five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five levels of response (no problems, slight problems, moderate problems, severe problems and unable to/extreme problems) [16]. EQ-5D-5L index scores were based on the UK value set [17]. Index scores range in value from − 0.59 to 1.00 and are anchored at 0 (death), with higher scores indicating better health utility and negative scores representing health states considered worse than death. The EQ visual analogue scale (VAS), which provides a quantitative measure of the patient's perception of their overall health, allows a patient to rate their perceived health state from 0 (worst imaginable health state) to 100 (best imaginable health state) [18].

DTSQ

DTSQ Status (DTSQs) The DTSQs measures satisfaction with treatment, as well as concerns about hyperglycaemia and hypoglycaemia, at baseline [19, 20]. Eight items are measured: satisfied with current treatment; feel convenient about recent treatment; feel flexible about recent treatment; satisfied with diabetes understanding; recommend present treatment to others; continue with present treatment; times of unacceptably high; and unacceptably low blood glucose. Items concerning times of unacceptably high and low blood glucose are scored separately from the satisfaction items and from each other. The treatment satisfaction scores are measured from 0 to 36 where a higher score indicates greater treatment satisfaction. The hyperglycaemia and hypoglycaemia scores are measured from 0 to 6 where a lower score indicates lower perceived hyper- or hypoglycaemia frequency.

DTSQ Change (DTSQc) The DTSQc measures the change in satisfaction with current

treatment compared to before the study began (i.e. baseline), as well as changes in concerns about hyperglycaemia and hypoglycaemia [21].

IW-SP

The IW-SP questionnaire assesses the self-perceptions of an individual related to his/her weight [22]. The IW-SP contains three items, each rated on a 5-point scale, averaged and linearly transformed to produce a measure from 0 to 100. Higher raw and transformed scores are indicative of better self-perceptions in relation to one's weight.

APPADL

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 [23]. Items are scored on a 5-point numeric rating scale ranging from 1 'unable to do' to 5 'not at all difficult'. Raw scores, derived by summing the item scores and dividing by the number of items, are linearly transformed to a range from 0 to 100. Higher raw and transformed scores correspond to better self-reported APPADL.

IWQOL-Lite-CT

The IWQOL-Lite-CT is a measure of weight-related functioning in populations commonly targeted for clinical trials [24]. The IWQOL-Lite-CT is a 20-item measure with two primary domains (physical [7 items, with physical function comprising 5 of the 7 items] and psychosocial [13 items]). The IWQOL-Lite-CT also has a total score, which includes all 20 items. It is scored from 0 to 100 where higher composite scores indicate higher levels of functioning.

Statistical Methods

Statistical analyses were performed on the modified intent-to-treat population composed of all randomly assigned patients exposed to at least one dose of the study drug and assigned to the treatment the patient was randomised to regardless of the treatment received. In addition, patients who discontinued the study drug after randomisation for not fulfilling any of the eligibility criteria were excluded. Observations occurring after rescue therapy with other anti-hyperglycaemic treatment or prematurely stopping study drug were also excluded. PRO at early termination visit was used in lieu of primary timepoint PRO assessment, where missing. The last post-baseline observation was carried forward to impute missing post-baseline values. Overall scoring and calculation of scores in the presence of missing items was handled according to the developer's instruction. Changes from baseline in PRO measures at specified timepoints were analysed using analysis of covariance with the baseline value of the PRO measure, treatment and study-specific stratification variables included in the model. In order to understand the impact that the most common AEs had on PRO outcomes, exploratory analyses evaluated changes from baseline to week 40 in PRO measures for patients receiving tirzepatide pooled doses (5, 10 or 15 mg) or semaglutide 1 mg in SURPASS-2 by gastrointestinal AE category (i.e. with or without nausea, vomiting or diarrhoea) at week 40. A two-sided alpha-level of 0.05 was used for all statistical comparisons. All statistical analyses were performed using SAS, Version 9.4 (The SAS Institute, Cary, NC).

RESULTS

Patient Demographics

The baseline characteristics and demographics of patients in the SURPASS-1 to -5 clinical trials were described in detail in the respective study publications [4–8] and, within each study, baseline characteristics were similar across treatment arms. The baseline characteristics and demographics of patients pooled by study are summarised in Table S1 (in the supplementary material).

AEs

Summary data on any AEs leading to study treatment discontinuation and specific gastrointestinal

Table 2 Changes from baseline to endpoint (week 40/52) in HbA1c and body weight in the SURPASS-1 to -5 clinical trials

Outcome	SURPASS-1[a] (*N* = 478) Monotherapy vs placebo	SURPASS-2[a] (*N* = 1878) + MET vs semaglutide 1 mg	SURPASS-3[b] (*N* = 1437) + MET ± SGLT2i vs insulin degludec	SURPASS-4[b] (*N* = 1995) ± MET ± SGLT2i ± SU vs insulin glargine	SURPASS-5[a] (*N* = 475) + Insulin glargine ± MET vs placebo
Mean (SD) baseline HbA1c (%)	7.95 (0.87)	8.28 (1.03)	8.18 (0.91)	8.53 (0.88)	8.31 (0.84)
LSM change (SE) in HbA1c from baseline (%)[c]					
Tirzepatide 5 mg	− 1.87 (0.09)*	− 2.09 (0.05)*	− 1.93 (0.05)*	− 2.24 (0.05)*	− 2.23 (0.08)*
Tirzepatide 10 mg	− 1.89 (0.10)*	− 2.37 (0.05)*	− 2.20 (0.05)*	− 2.43 (0.05)*	− 2.59 (0.08)*
Tirzepatide 15 mg	− 2.07 (0.10)*	− 2.46 (0.05)*	− 2.37 (0.05)*	− 2.58 (0.05)*	− 2.59 (0.08)*
Comparator	0.04 (0.11)	− 1.86 (0.05)	− 1.34 (0.05)	− 1.44 (0.03)	− 0.93 (0.08)
Mean (SD) baseline body weight (kg)	85.8 (19.8)	93.8 (21.9)	94.5 (20.2)	90.3 (18.6)	95.3 (21.6)
LSM change (SE) in body weight from baseline (kg)[c]					
Tirzepatide 5 mg	− 7.0 (0.5)*	− 7.8 (0.3)*	− 7.5 (0.4)*	− 7.1 (0.3)*	− 6.2 (0.6)*
Tirzepatide 10 mg	− 7.8 (0.5)*	− 10.3 (0.3)*	− 10.7 (0.4)*	− 9.5 (0.3)*	− 8.2 (0.6)*
Tirzepatide 15 mg	− 9.5 (0.5)*	− 12.4 (0.3)*	− 12.9 (0.4)*	− 11.7 (0.3)*	− 10.9 (0.6)*
Comparator	− 0.7 (0.6)	− 6.2 (0.3)	2.3 (0.4)	1.9 (0.2)	1.7 (0.6)
Weight loss ≥ 5% (% of patients)[d]					
Tirzepatide 5 mg	66.9*	68.6*	66.0*	62.9*	53.9*
Tirzepatide 10 mg	78.0*	82.4*	83.7*	77.6*	64.6*

Table 2 continued

Outcome	SURPASS-1[a] (*N* = 478) Monotherapy vs placebo	SURPASS-2[a] (*N* = 1878) + MET vs semaglutide 1 mg	SURPASS-3[b] (*N* = 1437) + MET ± SGLT2i vs insulin degludec	SURPASS-4[b] (*N* = 1995) ± MET ± SGLT2i ± SU vs insulin glargine	SURPASS-5[a] (*N* = 475) + Insulin glargine ± MET vs placebo
Tirzepatide 15 mg	76.7*	86.2*	87.8*	85.3*	84.6*
Comparator	14.3	58.4	6.3	8.0	5.9
Weight loss ≥ 10% (% of patients)[d]					
Tirzepatide 5 mg	30.6*	35.8*	37.4*	35.9*	22.6*
Tirzepatide 10 mg	39.8*	52.9*	55.7*	53.0*	46.9*
Tirzepatide 15 mg	47.4*	64.9*	69.4*	65.6*	51.3*
Comparator	0.9	25.3	2.9	1.5	0.9
Weight loss ≥ 15% (% of patients)[d]					
Tirzepatide 5 mg	13.2*	15.2*	12.5*	13.8*	7.0*
Tirzepatide 10 mg	17.0*	27.7*	28.3*	24.0*	26.6*
Tirzepatide 15 mg	26.7*	39.9*	42.5*	36.5*	31.6*
Comparator	0	8.7	0	0.5	0

HbA1c glycated haemoglobin, *LSM* least squares mean, *MET* metformin, *SD* standard deviation, *SE* standard error, *SGLT2i* sodium-glucose cotransporter 2 inhibitor, *SU* sulfonylurea

[a]Primary timepoint week 40

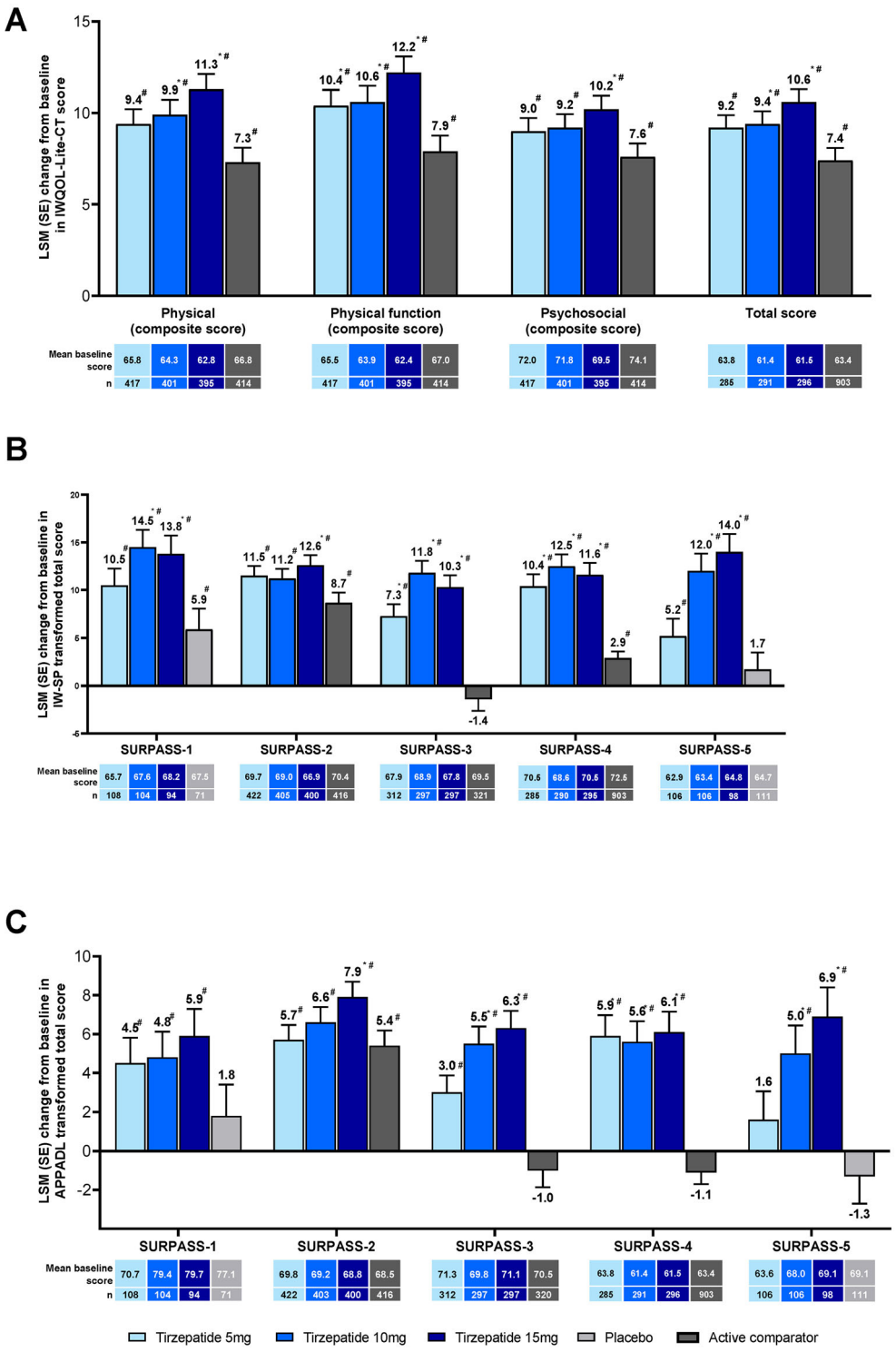
[b]Primary timepoint week 52

[c]Data are presented as LSM (SE) from the efficacy analysis set for SURPASS-1 to -5. Modified intent-to-treat population from mixed model repeated measures analysis

[d]Body weight change from baseline to primary timepoint. Logistic regression with imputation of missing data at the primary timepoint using mixed model for repeated measures analysis

*$p < 0.05$, vs placebo or active comparator

AEs of interest (nausea, vomiting and diarrhoea) of any severity in SURPASS-1 to -5 are included in Table S2. Any AEs leading to study treatment discontinuation were reported by 3–11% of patients who received tirzepatide across these studies, compared with placebo (3%), semaglutide 1 mg (4%), basal insulins (1–5%) and placebo with background insulin (3%). Nausea, vomiting or diarrhoea of any severity occurred in 2–24%, 1–13% and 4–22% of patients, respectively, across all treatment groups in all SURPASS-1 to -5 studies (Table S2).


A
LSM (SE) change from baseline in IWQOL-Lite-CT score
Physical (composite score)
Physical function (composite score)
Psychosocial (composite score)
Total score
Mean baseline score
n
B
LSM (SE) change from baseline in IW-SP transformed total score
SURPASS-1
SURPASS-2
SURPASS-3
SURPASS-4
SURPASS-5
C
LSM (SE) change from baseline in APPADL transformed total score
Tirzepatide 5mg
Tirzepatide 10mg
Tirzepatide 15mg
Placebo
Active comparator

◀ **Fig. 1** Changes from baseline to primary timepoint (week 40/52) in **A** IWQOL-Lite-CT scores from SURPASS-2, **B** IW-SP transformed total scores from SURPASS-1 to -5), and **C** APPADL transformed total scores from SURPASS-1 to -5, for patients receiving tirzepatide (5, 10 or 15 mg), placebo or active comparator. Data are presented as LSM (SE) from the efficacy analysis set. Primary timepoint is 40 weeks for studies SURPASS-1, SURPASS-2 and SURPASS-5, and 52 weeks for studies SURPASS-3 and SURPASS-4. $^{*}p < 0.05$ versus placebo or active comparator; $^{\#}p < 0.05$ versus baseline. *APPADL* Ability to Perform Physical Activities of Daily Living, *IWQOL-Lite-CT* Impact of Weight on Quality of Life-Lite Clinical Trials Version, *IW-SP* Impact of Weight on Self-Perceptions, *LSM*, least squares mean, *SE* standard error

Consistent with the low rate of study treatment discontinuation, at most 3% of patients who received at least one dose of tirzepatide in SURPASS-1 to -5 discontinued treatment because of nausea, vomiting or diarrhoea [9].

HbA1c and Body Weight

Across the five global phase 3 SURPASS studies, which spanned the T2D disease continuum from no background therapy to multiple background treatment combinations, and included several comparators representative of clinical practice, administration of all tirzepatide doses (5, 10 and 15 mg) led to consistent improvements in glycaemic control, as shown by reductions in HbA1c from baseline to 40 or 52 weeks (Table 2) [4–8].

Similarly, across the five phase 3 studies, participants receiving tirzepatide showed consistent reductions in body weight at all doses at the primary timepoint (40 or 52 weeks). Weight loss with tirzepatide was observed irrespective of background therapy, even medications associated with increased weight such as insulin (SURPASS-5) or sulfonylureas (SURPASS-4) (Table 2). Across the trials, 53.9–87.8% of patients receiving tirzepatide (5, 10 and 15 mg) achieved a weight loss of at least 5%, 22.6–69.4% achieved a weight loss of at least 10% and 7.0–42.5% achieved a weight loss of at least 15% (Table 2) [4–8].

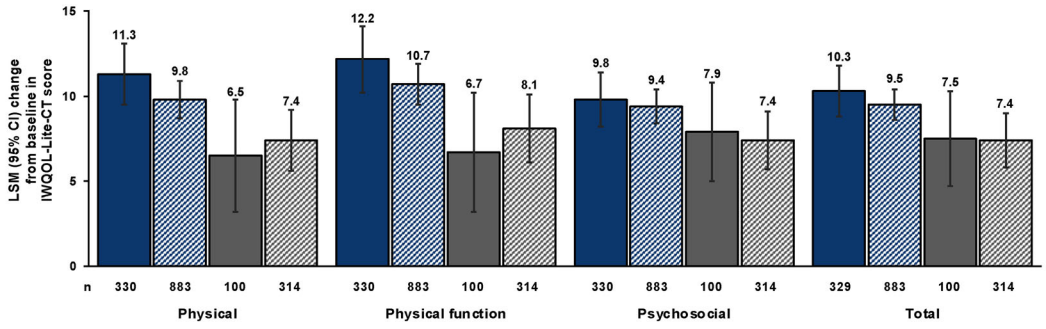
PROs

Tirzepatide Versus Placebo (SURPASS-1 and -5)

In SURPASS-1, participants receiving all doses of tirzepatide had significantly improved scores from baseline to week 40 across all PRO measures ($p < 0.05$) while significant improvements from baseline only in IW-SP score were observed in the placebo group (Fig. 1, Table S3). Higher doses of tirzepatide (10 and 15 mg) were associated with significantly improved IW-SP (Fig. 1) scores and all tirzepatide doses (5, 10 and 15 mg) were associated with significantly improved EQ VAS (Table S3) scores at week 40 versus placebo ($p < 0.05$), suggesting improvements in patients' overall health and body weight-related self-perception. There were no statistically significant differences in APPADL and EQ-5D-5L index scores between participants receiving any dose of tirzepatide and placebo (Fig. 1, Table S3).

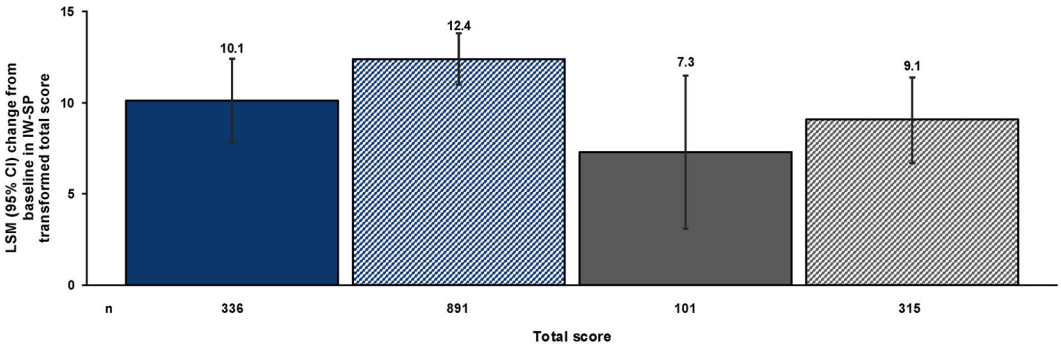
In SURPASS-5, all participants received background treatment with insulin glargine (titrated following a treat-to-target algorithm) ± metformin. Patients' overall assessments of their health, body weight-related self-perceptions and physical well-being improved with higher doses of tirzepatide compared with placebo; participants receiving tirzepatide 10 or 15 mg had significantly improved EQ-5D-5L index, IW-SP and APPADL scores at week 40 compared with placebo ($p < 0.05$) (Fig. 1, Table S3). However, there were no significant differences in these three PRO scores between participants receiving 5 mg tirzepatide and those receiving placebo. There were no significant differences in EQ VAS between participants receiving tirzepatide 5 or 15 mg and the placebo group (Table S3). Participants taking any dose of tirzepatide showed significantly greater total DTSQc scores versus placebo ($p < 0.05$), indicating greater improvement in treatment satisfaction (Table S3). There was a significant difference in the self-reported DTSQc score for perceived hyperglycaemia for each of the three tirzepatide dose groups versus the placebo group ($p < 0.05$), indicating a lowered perceived frequency of hyperglycaemia versus placebo, while the self-reported DTSQc score for

A



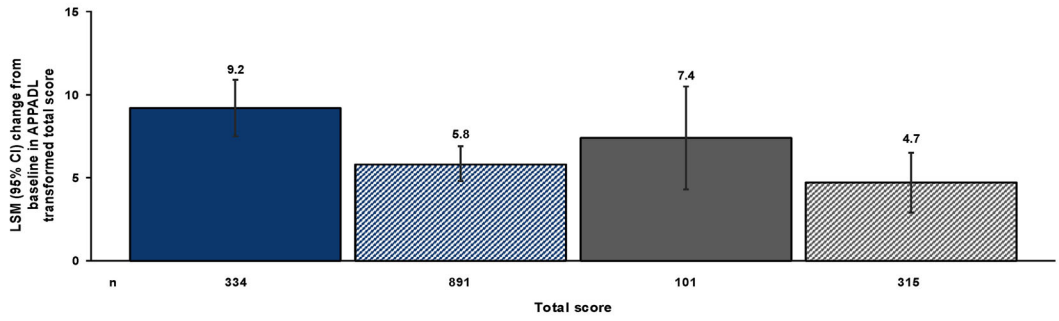
Mean baseline score	58.5	66.6	60.5	68.2	58.4	66.2	61.1	68.3	64.7	74.1	65.4	76.9	62.5	71.5	63.7	73.8
n	411	997	123	345	411	997	123	345	411	997	123	345	411	997	123	345

B



Mean baseline score	60.5	71.9	59.0	74.7
n	411	997	123	345

C



Mean baseline score	65.3	70.5	62.8	70.5
n	409	997	123	345

◀ **Fig. 2** Changes from baseline to primary timepoint (week 40) in **A** IWQOL-Lite-CT scores, **B** IW-SP transformed total scores, and **C** APPADL transformed total scores from SURPASS-2, by gastrointestinal adverse event category (with or without nausea, vomiting or diarrhoea) at primary timepoint for patients receiving tirzepatide-pooled (5, 10 or 15 mg) or semaglutide (1 mg). Nausea, vomiting or diarrhoea (NVD) is an NVD adverse event of any severity. Data are presented as LSM (95% CI) from the efficacy analysis set. *APPADL* Ability to Perform Physical Activities of Daily Living, *CI* confidence interval, IWQOL-Lite-*CT* Impact of Weight on Quality of Life-Lite Clinical Trials Version, *IW-SP* Impact of Weight on Self-Perceptions, *LSM* least squares mean

perceived hypoglycaemia in the three tirzepatide groups showed no significant difference compared with the placebo group.

Tirzepatide Versus Semaglutide (on Background Metformin) (SURPASS-2)

In SURPASS-2, at the 40-week primary timepoint, total APPADL and IW-SP scores increased in all groups from baseline, indicating better self-reported ability to perform physical activities of daily living and better self-perceptions related to weight (Fig. 1, Table S3). There was a significantly greater improvement in these scores with tirzepatide 15 mg versus semaglutide ($p < 0.05$). IWQOL-Lite-CT scores increased from baseline to week 40 with all doses of tirzepatide (5, 10 and 15 mg) and semaglutide (1 mg), indicating better overall HRQoL and functioning associated with weight (Fig. 1, Table S3). Treatment with tirzepatide significantly improved IWQOL-Lite-CT physical scores (10 and 15 mg), physical function scores (all doses), psychosocial scores (15 mg) and total scores (10 and 15 mg) compared with semaglutide (all $p < 0.05$) (Table S3). DTSQ and EQ-5D-5L score improvements with tirzepatide were not significantly different to those with semaglutide, apart from in the 15 mg group, which had a lower perceived frequency of hyperglycaemia versus semaglutide (Table S3).

Tirzepatide Versus Insulin Degludec (SURPASS-3)

In SURPASS-3, all tirzepatide doses significantly improved EQ-5D-5L index, EQ VAS, IW-SP and APPADL scores from baseline to week 52 ($p < 0.05$), indicating better outcomes (Fig. 1, Table S3). The EQ VAS was the only significantly improved PRO measure at week 52 in the insulin degludec group ($p < 0.05$) (Table S3). Increases in EQ VAS, IW-SP and APPADL scores were significantly greater at week 52 for all tirzepatide dose groups compared with the insulin degludec group, indicating better patient-reported HRQoL, weight-related self-perceptions and self-reported APPADL (Fig. 1, Table S3). There was no significant difference in change from baseline to week 52 for EQ-5D-5L index score between tirzepatide (any dose) and insulin degludec (Table S3). The DTSQc total score was significantly higher for all tirzepatide dose groups compared with the insulin degludec group ($p < 0.05$), indicating that patients receiving tirzepatide experienced greater improvement in overall treatment satisfaction. The DTSQc score for perceived hyperglycaemia was significantly lower with tirzepatide 15 mg compared with insulin degludec; whereas the DTSQc score for perceived hypoglycaemia was significantly lower with tirzepatide 5 mg versus insulin degludec (both $p < 0.05$) (Table S3).

Tirzepatide Versus Insulin Glargine (SURPASS-4)

In the SURPASS-4 study, participants in all tirzepatide dose groups showed significant improvements from baseline to week 52 in EQ-5D-5L, EQ VAS, IW-SP and APPADL scores ($p < 0.05$) (Fig. 1, Table S3). Of these PRO measures, only the IW-SP and the EQ VAS showed significant increases at the week 52 primary timepoint with insulin glargine (titrated following a treat-to-target algorithm) (both $p < 0.05$). Changes from baseline to primary timepoint in IW-SP, APPADL, EQ-5D-5L and EQ VAS were significantly higher for all tirzepatide dose groups compared with the insulin glargine group ($p < 0.05$), indicating better HRQoL, weight-related self-perceptions and self-reported APPADL. Overall treatment satisfaction at week 52 was significantly higher for

participants receiving all doses of tirzepatide versus insulin glargine ($p < 0.05$), as demonstrated by the DTSQc score (Table S3). The DTSQc perceived frequency of hypoglycaemia score at week 52 was significantly lower with all doses of tirzepatide compared with insulin glargine, whereas the DTSQc perceived frequency of hyperglycaemia score was significantly lower for tirzepatide 10 and 15 mg versus insulin glargine.

Association Between Gastrointestinal AEs of Interest and PROs (SURPASS-2)

Across all PRO measures in the SURPASS-2 study, changes from baseline to week 40 were in the direction of better outcomes in both subgroups of patients who did and did not report gastrointestinal AEs (nausea, vomiting or diarrhoea) and all treatment groups (tirzepatide 5, 10 or 15 mg or semaglutide 1 mg) (Fig. 2, Table S4).

DISCUSSION

The SURPASS-1 to -5 clinical trials assessed the efficacy and safety of once weekly tirzepatide (5, 10 or 15 mg) versus placebo or active comparators (semaglutide 1 mg, insulin degludec and insulin glargine) in patients with T2D. All three tirzepatide doses provided superior HbA1c and weight reductions compared to placebo or active comparators in all five SURPASS trials. Here we describe the PROs measured across the five SURPASS studies from baseline to primary timepoint that evaluated overall QoL, treatment satisfaction and patient perspectives regarding weight-related attributes.

Overall, tirzepatide improved patients' QoL as measured by general health- and weight-related PRO instruments from baseline to primary timepoint. Tirzepatide-treated patients demonstrated significantly greater improvements than comparators for most of the measured PROs at primary timepoint in all five studies. Notably, tirzepatide 15 mg was associated with significantly larger improvements than comparators in physical functioning, as measured using the APPADL and IWQOL-Lite-CT (physical and physical function) in most studies. Moreover, higher tirzepatide doses, in general, resulted in greater improvements in QoL.

The patient perspective is key; patients are more likely to adhere to treatments that they value, thereby resulting in better clinical outcomes [12]. If patients are to effectively engage in their disease management, it is crucial that they are involved in the decision-making process and that their needs and wishes are accounted for when choosing treatment options. This patient-centred approach to T2D management is becoming increasingly recognised in treatment guidelines [25]. Furthermore, other bodies are recognising the value of capturing QoL data. For example, the Institute for Clinical and Economic Review 'Tirzepatide for Type 2 Diabetes: Final Policy Recommendations' published in 2022 stated that the 'inclusion of several validated QoL measures [in trials of treatments for T2D], including versions of the DTSQ and EQ-5D are to be commended and should be replicated by all manufacturers when designing trials testing new therapies to treat T2D' [26]. Evidence is growing to suggest that patients place value on a variety of different treatment attributes that are related to efficacy, safety and ease of use [27–29]. It is becoming apparent, for example, that oral therapy is not the default preference over injectable medications [30]. If medication adherence and ultimately clinical outcomes are to be improved, it is fundamental that these patient perspectives and preferences are fully understood. The findings reported here may assist clinicians and patients in their decision-making and help patients' persistence with therapy.

In addition to the PRO measures reported here, qualitative exit interviews were conducted in a subset of patients from two open-label SURPASS trials (SURPASS-2 and -3) to provide additional details of the patients' experience while receiving tirzepatide [31]. All patients interviewed reported at least one treatment benefit with 96% of patients reporting improved glycaemic control and 93% reporting weight loss. All 28 patients enrolled in exit interviews said they would recommend tirzepatide to others and 27 patients said they would be willing to continue treatment. While the

published clinical trial outcomes demonstrate the efficacy of tirzepatide, these exit interviews indicate that the benefits obtained are important to patients and likely have an impact on their overall QoL.

Limitations of this analysis include the administration of the PRO questionnaires in a clinical trial setting. Thus, PRO results obtained in a real-world setting, where patients might have less contact with healthcare professionals, may differ. Furthermore, the data from these studies on specific aspects of QoL of interest are limited by the extent to which the available PRO questionnaires examine those particular aspects of QoL. In addition, the PRO results reported at study endpoint likely do not capture the overall impact of AEs, such as nausea, vomiting and diarrhoea, at the time of the event. Another potential limitation is the open-label clinical trial study design of SURPASS-2, -3 and -4, which may influence patients to over- or underestimate their treatment assessments on the basis of beliefs they have regarding their assigned treatment arm. Furthermore, weight loss had not plateaued in the SURPASS-1 to -5 clinical trials; therefore, it is possible that PROs could have improved further with a longer follow-up period. Finally, at the time that SURPASS-2 was designed and implemented, semaglutide was approved for the treatment of T2D up to a dosage of 1 mg once weekly; semaglutide 2 mg is now available for patients with T2D who require additional glycaemic control after at least 4 weeks on the 1 mg dosage [32].

CONCLUSION

Tirzepatide produced significant health- and weight-related QoL improvements versus comparators in the SURPASS-1 to -5 studies along with substantial improvements in glycaemic control and body weight. These PRO results further confirm the benefits of tirzepatide for the treatment of T2D. Further real-world PRO research in T2D is needed, as well as new or modified PRO measures, given that advancements in T2D treatment regimens are affecting patients in ways that were previously unachievable with older medications.

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Compliance with Ethics Guidelines. The SURPASS-1 to -5 studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocols were approved by ethical review boards and all patients provided written informed consent. This particular 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.

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 United States and 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.

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