

BRIEF REPORT

Effect of Oral Semaglutide Versus Dulaglutide on Diabetes-Related Quality of Life in Japanese Patients With Type 2 Diabetes: The PIONEER 10 Randomized, Active-Controlled Trial

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ABSTRACT

Introduction: In the randomized PIONEER 10 trial, once-daily oral semaglutide – the first oral glucagon-like peptide-1 receptor agonist (GLP-1RA) – was similarly tolerated with comparable (at 7 mg) or better (at 14 mg) efficacy versus the injectable GLP-1RA dulaglutide 0.75 mg. Health-related quality of life (HRQoL) in PIONEER 10 was assessed using the Japanese-specific Diabetes Therapy-Related Quality of Life (DTR-QoL) questionnaire.

Methods: The DTR-QoL comprises 29 questions, providing four domain and total scores. Answers were converted to a score between 0 and 100, with higher scores indicating greater HRQoL. Two estimands were prespecified: treatment policy (regardless of treatment discontinuation or rescue medication use) and trial product (assuming on treatment without rescue medication) in all randomized patients. Outcomes were assessed at weeks 26 and 52.

Results: Mean baseline DTR-QoL domain scores were similar between treatment arms and were generally lower (giving more scope for improvement) for ‘anxiety and dissatisfaction with treatment’ (62.1–65.3) and ‘satisfaction with treatment’ (53.9–57.9) than ‘burden on social activities and daily activities’ (76.5–77.7) and ‘hypoglycemia’ (83.5–88.2). Using the treatment policy estimand, oral semaglutide 7 and 14 mg improved HRQoL versus dulaglutide 0.75 mg for the total score (estimated mean change from baseline [CfB]: 7.3 and 8.1 vs 3.3; estimated treatment difference [ETD]: 3.9 and 4.8) and the ‘anxiety and dissatisfaction with treatment’ domain (CfB: 9.7 and 10.9 vs 3.7; ETD: 6.0 and 7.2) at week 52. Oral semaglutide 14 mg improved the ‘satisfaction with treatment’ domain versus dulaglutide 0.75 mg (CFB: 13.8 vs 5.7; ETD: 8.1). DTR-QoL scores for oral semaglutide tended to be more durable (sustained over time) than for dulaglutide. Outcomes for the trial product estimand were similar.

Conclusion: Oral semaglutide 7 and 14 mg improved the patients’ HRQoL measured by the Japanese-specific DTR-QoL instrument versus dulaglutide 0.75 mg at week 52.

Trial Registration: ClinicalTrials.gov: NCT03015220.

Keywords: Clinical trial; Diabetes treatment-related quality of life; Dulaglutide; GLP-1 receptor agonist; Health-related quality of life; Japan; Oral semaglutide; Phase 3; Type 2 diabetes

KEY SUMMARY POINTS

Why carry out this study?

- Oral semaglutide is the first oral glucagon-like peptide-1 receptor agonist (GLP-1RA) and has been developed to provide an option for people with type 2 diabetes (T2D) who could benefit from this class of treatment but who may not wish to initiate injection therapy.
- Oral semaglutide has been shown to be effective and well tolerated compared with other oral and injectable glucose-lowering medications in phase 3 trials; the comparative effect on health-related quality of life is also important.

What did the study ask?

- The randomized PIONEER 10 trial assessed the efficacy and safety of once-daily oral semaglutide compared with the once-weekly GLP-1RA dulaglutide in Japanese patients with T2D; here, we report health-related quality of life outcomes from this trial assessed using the Japanese-specific Diabetes Therapy-Related Quality of Life (DTR-QoL) questionnaire.

What was learned from the study?

- Oral semaglutide 7 and 14 mg improved the total DTR-QoL score to a greater extent than dulaglutide 0.75 mg after 52 weeks' treatment, as well as the individual domain of 'anxiety and dissatisfaction with treatment'; furthermore, oral semaglutide 14 mg improved the 'satisfaction with treatment' domain versus dulaglutide 0.75 mg.
- DTR-QoL scores for oral semaglutide tended to be more durable (sustained over time), with similar scores at weeks 26 and 52, whereas scores declined for dulaglutide between weeks 26 and 52.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13360163>.

INTRODUCTION

Semaglutide is one of a number of glucagon-like peptide-1 receptor agonists (GLP-1RAs) recommended for the control of hyperglycemia in patients with type 2 diabetes (T2D) [1, 2]. Of these agents, subcutaneous once-weekly semaglutide, once-weekly dulaglutide, and once-daily liraglutide are also indicated for patients with T2D and established cardiovascular disease [3–5], as they have been shown to reduce the risk of major adverse cardiovascular events in this population [6–8].

Semaglutide is the first and, so far, only GLP-1RA to be formulated in a tablet, and uses the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) to protect semaglutide from enzymatic degradation and facilitate its gastric absorption after oral administration [9]. Prior to the development of oral semaglutide, all GLP-1RAs were administered by injection. Based on experiences with insulin, the injectable route of administration may discourage some patients and healthcare providers from using these agents when oral glucose-lowering therapies are available [10, 11]. Among the injectable GLP-1RAs, those that are administered once weekly were associated with improved health-related quality of life (HRQoL) than those given more frequently [12]. Oral semaglutide may help more patients with uncontrolled T2D to access GLP-1RA therapy [13] by overcoming some of the barriers associated with injectable therapies, and has now been approved for once-daily dosing in Japan [14] and elsewhere [15, 16].

Oral semaglutide was effective and well tolerated in the phase 3a PIONEER clinical trial program, which comprised 10 studies [17–26], including two dedicated trials in Japanese patients [25, 26]. One of the two Japanese trials, PIONEER 10, compared once-daily oral semaglutide with once-weekly dulaglutide 0.75 mg in patients whose T2D was inadequately controlled on one or more existing oral glucose-lowering drugs [26]. In this trial, oral semaglutide 7 mg had similar glycemic efficacy, but greater body weight reductions, and oral semaglutide 14 mg had significantly greater reductions in glycated hemoglobin (HbA_{1c}) and body weight, than dulaglutide 0.75 mg after 26 and 52 weeks' treatment [26].

Several globally used measures of HRQoL were employed in the PIONEER program. These scales are potentially useful but do not take account of potential differences between Japanese and global patients with T2D [27]. In PIONEER 10, the effect of treatment on patients' HRQoL was assessed using the validated and widely used Japan-specific Diabetes

Therapy-Related Quality of Life (DTR-QoL) questionnaire [28]. Here, we present the full results of these Japanese disease-specific patient-reported outcomes.

METHODS

PIONEER 10 Study Design

The full methods and primary results of the PIONEER 10 trial are reported in the primary manuscript [26]. In brief, this was a 52-week randomized, open-label, active-controlled, parallel-group, multicenter, phase 3a trial carried out in Japan. Japanese adults aged ≥ 20 years with T2D, and with HbA_{1c} 7.0–10.5% (53–91 mmol/mol) despite receiving stable oral glucose-lowering monotherapy (sulfonylurea, glinide, thiazolidinedione, α -glucosidase inhibitor, or sodium-glucose co-transporter-2 inhibitor [SGLT2i]) were eligible to participate. Patients were randomized 2:2:2:1 to receive either once-daily oral semaglutide 3, 7, or 14 mg, or once-weekly subcutaneous dulaglutide 0.75 mg, as add-on to their background medication; efficacy was assessed at 26 weeks and at the end of treatment at 52 weeks.

Institutional review boards/independent ethics committees at each site provided approval before the start of the trial and all patients provided informed consent. The trial was conducted according to relevant national requirements, and complied with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. Full information on study ethics is reported in the primary manuscript [26].

Assessment of the Diabetes Therapy-Related Quality of Life Scale

The DTR-QoL questionnaire is a Japanese diabetes-specific HRQoL measure that contains 29 items (**Table S1**) to assess the influence of diabetes treatment on HRQoL across four domains [28]: burden on social activities and daily activities; anxiety and dissatisfaction with treatment; hypoglycemia; and satisfaction with treatment.

The questionnaire was delivered in Japanese and was ideally answered before any other trial-related activities. Patients were able to complete the questionnaire by themselves without interruption.

The questionnaire was completed at baseline, and after 26 and 52 weeks. Scores were converted to a 1–100 scale, with higher numbers indicating greater diabetes-related quality of life. A total score was derived based on the responses to all questions. This manuscript will focus on the results after 52 weeks of treatment to align with the reported clinical outcomes, but data after 26 weeks are also presented.

The approved maintenance dose for oral semaglutide in Japan is 7 mg once daily, with the option of increasing this to 14 mg if glycemic control remains insufficient [14]; in Europe and the USA, either 7 or 14 mg may be used depending on glycemic efficacy [15, 16]. Therefore, we focus on the DTR-QoL outcomes for the 7 and 14 mg doses below, but results for the 3 mg dose are also presented.

In the PIONEER trials, two scientific questions related to the efficacy objectives (including patient-reported outcomes) were addressed through the definition of two estimands ('treatment policy' and 'trial product') [29]. The treatment policy estimand evaluated the treatment effect for all randomized patients, regardless of trial product discontinuation or use of rescue medication and was the primary estimand in PIONEER 10. The trial product estimand evaluated the treatment effect for all randomized patients, under the assumption that all patients remained on trial product for the entire planned duration of the trial and did not use rescue medication. Here, DTR-QoL results for the treatment policy estimand are the focus.

Statistical Analysis

As previously explained [26], patient-reported outcomes were analyzed as follows, with stratification factor (background oral glucose-lowering medication at screening) as a categorical fixed effect and baseline value as a covariate. The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing data at weeks 26 and 52. Data were collected from all randomized patients, irrespective of premature discontinuation of trial product or initiation of rescue medication. Imputation was done within five groups: one group of patients who had discontinued treatment or initiated rescue medication at the analysis timepoint (either week 26 or 52), regardless of randomized treatment arm; and four groups of patients who were still taking trial product without rescue medication, defined by randomized treatment arm. Both the imputation and the analysis were based on analysis of covariance models. The results were combined by use of Rubin's

rule [30]. The trial product estimand was estimated by a mixed model for repeated measurements that used data collected prior to premature trial product discontinuation or initiation of rescue medication from all randomized patients.

Results are presented as estimated change from baseline in DTR-QoL scores and estimated treatment differences (ETDs) with 95% confidence intervals (CIs). Statistical analyses were not controlled for multiplicity. All analyses were performed using SAS Version 9.4M2.

RESULTS

Participants

As previously reported, 458 patients were randomized to oral semaglutide 3 mg ($n = 131$), 7 mg ($n = 132$), or 14 mg ($n = 130$), or dulaglutide 0.75 mg ($n = 65$) [26]. Baseline clinical characteristics are summarized in **Table S2** in the supplementary appendix. Baseline mean DTR-QoL domain scores were similar between the treatment arms (**Table 1**), but were generally lower for 'anxiety and dissatisfaction from treatment' (62.1–65.3) and 'satisfaction with treatment' (53.9–57.9), compared with 'burden on social activities and daily activities' (76.5–77.7), and 'hypoglycemia' (83.5–88.2).

DTR-QoL Outcomes

Outcomes for the four domains and total score are shown in **Figure 1** for the treatment policy (primary) estimand. Data were imputed for <5% of patients. Observed changes from baseline in the scores for each question are shown in **Table S1**, and ETDs in the changes from baseline in the four domains and total score are shown in **Table S3**.

Burden on Social Activities and Daily Activities

Improvements in burden on social activities and daily activities were not significantly different (lower bound of 95% CI for the ETD crossed zero) with oral semaglutide 7 and 14 mg compared with dulaglutide 0.75 mg at week 26 (change from baseline: 6.5 and 5.1 points, respectively, vs 4.6 points) and week 52 (6.6 and 6.1 vs 3.6) for the treatment policy estimand (**Fig. 1(i)**). The higher numerical values for oral semaglutide appear to have been

influenced by the scoring of questions concerning managing treatment and associated pain/discomfort of injections, such as 'my current diabetes treatment interferes with my work and activities' and 'pain due to my current diabetes treatment is uncomfortable' (**Table S1**). There seemed to be no negative impact of the dosing and administration regimen of once-daily oral semaglutide on the perception of burden compared with once-weekly subcutaneous dulaglutide 0.75 mg.

Anxiety and Dissatisfaction with Treatment

The changes from baseline in scores for anxiety and dissatisfaction with treatment for oral semaglutide 7 and 14 mg compared with dulaglutide 0.75 mg (10.5 and 11.6, respectively, vs 9.2) were not significantly different at week 26 (**Fig. 1(ii)**). At week 52, the scores (9.7 and 10.9 vs 3.7) indicated that oral semaglutide 7 and 14 mg were associated with significantly reduced anxiety and dissatisfaction with treatment versus dulaglutide 0.75 mg (ETD: 6.0; 95% CI: 0.8, 11.3; and ETD: 7.2; 95% CI: 1.9, 12.5; respectively) (**Table S3**). In particular, concerns about weight gain and control of blood glucose appear to have driven the difference between outcomes for oral semaglutide 7 and 14 mg compared with dulaglutide 0.75 mg (**Table S1**).

Hypoglycemia

Scores for patient perceptions of hypoglycemia were similar between oral semaglutide 7 and 14 mg compared with dulaglutide 0.75 mg at week 26 (change in scores from baseline 3.4 and 2.5, respectively, vs 3.1) and were not statistically different at week 52 (3.5 and 3.6 vs – 0.5) (**Fig. 1(iii)** and **Table S1**). However, whereas the improvement in hypoglycemia score from baseline with all oral semaglutide doses remained similar between week 26 and week 52, the score for dulaglutide 0.75 mg decreased (worsened).

Satisfaction with Treatment

At week 26, the change from baseline in score for satisfaction with treatment was similar between oral semaglutide 7 and 14 mg (11.3 and 13.3) and dulaglutide 0.75 mg (11.6) (**Fig. 1(iv)**). At week 52, oral semaglutide 14 mg (change from baseline in score 13.8) was associated with significantly greater satisfaction with treatment compared with dulaglutide 0.75 mg (5.7) at week 52 (ETD: 8.1; 95% CI: 1.9, 14.3) (**Table S3**). Patients receiving oral semaglutide 14 mg recorded higher improvements in questions regarding blood glucose control, satisfaction, and hope for the future compared with dulaglutide 0.75 mg (**Table S1**).

Total Score

At week 26, the overall change from baseline in DTR-QoL score was similar between oral semaglutide 7 and 14 mg compared with dulaglutide 0.75 mg (estimated change from baseline 7.8 and 7.7, respectively, vs 6.7) (**Fig. 1(v)**). At week 52, the score for dulaglutide 0.75 mg (3.3) was decreased versus week 26, whereas scores for oral semaglutide 7 mg (7.3) and 14 mg (8.1) remained durable between week 26 and 52. Oral semaglutide 7 mg and 14 mg were associated with significantly increased total DTR-QoL scores at week 52 from baseline compared with dulaglutide 0.75 mg (ETD: 3.9; 95% CI: 0.2, 7.7; and ETD: 4.8; 95% CI: 1.0, 8.6; respectively) (**Table S3**).

DTR-QoL scores and estimated treatment differences between oral semaglutide and dulaglutide for the individual domains and the overall score were generally similar to those reported above for the treatment policy estimand when assessed using the trial product estimand (**Fig. S1**). For the trial product estimand, only oral semaglutide 14 mg significantly increased total score versus dulaglutide 0.75 mg at week 52.

DISCUSSION

Oral semaglutide 7 and 14 mg showed greater improvements in Japanese patients' DTR-QoL scores at week 52 compared with dulaglutide 0.75 mg. DTR-QoL scores for oral semaglutide tended to be more durable (sustained over time), with similar scores at weeks 26 and 52, whereas scores declined for dulaglutide 0.75 mg between weeks 26 and 52 across the four domains and for the total score. It should be noted that the greatest room for improvement was in the domains of 'satisfaction with treatment' and 'anxiety and dissatisfaction with treatment', whereas the high baseline scores in the other domains may have contributed to a limited scope for improvement with treatment.

Both western and Japanese patients are known to have concerns about injectable therapy with insulin [10, 11], and Japanese patients have been shown to have a higher preference for an oral, rather than injectable, GLP-1RA drug profile [31]. Oral semaglutide has been formulated to address this barrier, but has specific dosing requirements because of the effect of food, liquid, and concomitant medication on its absorption [9]. In PIONEER 10, patients were instructed to take their tablet in the morning, fasted, with no more than approximately 120 mL of water, and then to wait at least 30 minutes before consuming any food, other beverage, or other oral medication [26]. The change from baseline scores for the domain 'burden on social activities and daily activities' were numerically (but not statistically) higher (better) with oral semaglutide 7 and 14 mg compared with dulaglutide 0.75 mg, indicating

that patients considered the once-daily oral semaglutide schedule to be, at least, no more burdensome than a once-weekly injection of dulaglutide. This clinically important observation is supported by previous work suggesting that the treatment burden associated with once-daily oral therapy may be similar to that for once-weekly injections [32]. Individual question scores for this domain indicated concerns around managing injectable treatment and any associated pain or discomfort. The preference for oral therapy among Japanese patients [31] could also have contributed to the durable effect of oral semaglutide on HRQoL over 52 weeks, compared with the decline in score observed with dulaglutide. Of note, in the global PIONEER 7 trial, patients answering the Diabetes Treatment Satisfaction Questionnaire reported similar treatment satisfaction with oral semaglutide and oral sitagliptin after 52 weeks, regardless of the dosing conditions for oral semaglutide [23].

Domain scores closely reflected the objective primary clinical outcomes (HbA_{1c} and body weight reduction) in the PIONEER 10 trial [26], suggesting a high sensitivity for the DTR-QoL questionnaire in measuring diabetes-related HRQoL. The domain 'anxiety and dissatisfaction with treatment' included the statements "I am bothered by weight gain with my current diabetes treatment", "I am worried about high blood sugar", and "I am dissatisfied that my blood sugar is unstable (high and low)"; higher scores for oral semaglutide 7 and 14 mg versus dulaglutide 0.75 mg in scores for this domain (reaching statistical significance at week 52) appeared to align with the significantly greater reductions in HbA_{1c} seen with oral semaglutide 14 mg, and body weight with both the 7 and 14 mg doses, versus dulaglutide 0.75 mg at weeks 26 and 52. Patients gained, on average, 1 kg of body weight with dulaglutide 0.75 mg at week 52 compared with baseline, whereas they lost weight with oral semaglutide 7 mg (−0.9 kg) and 14 mg (−1.6 kg), assessed using the treatment policy estimand [26]. These effects on the clinical outcomes could have contributed to the decline in HRQoL between weeks 26 and 52 with dulaglutide, measured by the DTR-QoL.

The low and similar changes from baseline across treatments for the domain 'hypoglycemia' correlated with the fact that there were few severe or blood-glucose confirmed hypoglycemic events during oral semaglutide or dulaglutide treatment [26]; in addition, baseline scores were high, indicating a higher quality of life for this domain at the start of the trial.

Change from baseline scores for the 'satisfaction with treatment' domain remained largely stable for oral semaglutide 7 and 14 mg, but worsened with dulaglutide 0.75 mg between weeks 26 and 52. This domain included the statements "Overall, I am satisfied with my current blood sugar control" and "I am confident that I can maintain good blood sugar control with my current diabetes treatment". The difference between oral semaglutide 14 mg and

dulaglutide 0.75 mg at week 52 for this domain reflected a statistically significantly greater reduction in HbA_{1c} between treatments [26]. Patients' scores for the statements "I am hopeful about the future with my current diabetes treatment" and "I am satisfied with my current treatment methods as diabetes treatment" also contributed to overall treatment satisfaction with oral semaglutide.

The DTR-QoL is a Japanese-specific measure of HRQoL that has been extensively employed in studies of glucose-lowering medication, including several involving GLP-1RAs [33–35], dipeptidyl peptidase-4 inhibitors [36–38], and the SGLT2i ipragliflozin [39]. As in the current trial, the questionnaire has shown a high sensitivity for detecting and measuring diabetes-related HRQoL compared with, for example, the EQ-5D questionnaire [40]. In PIONEER 9, similar DTR-QoL domain and total scores were recorded for oral semaglutide 3, 7, and 14 mg compared with subcutaneous liraglutide at the Japanese-approved dose of 0.9 mg once daily, when both were given as monotherapy [25].

The background medications allowed in this trial were reflective of a typical first-line pharmacotherapeutic approach to glucose-lowering treatment in Japanese patients with type 2 diabetes. Data were imputed for <5% of patients, which was unlikely to substantially affect the results. Nevertheless, a limitation of the current study is that the potential difference in adherence between a clinical trial and the real-world setting may lead to differences in HRQoL and treatment satisfaction for oral semaglutide, liraglutide, and dulaglutide. A further limitation is that the statistical analyses were not controlled for multiplicity.

CONCLUSION

Among Japanese patients with T2D receiving one background oral antidiabetic drug, treatment with once-daily oral semaglutide 7 and 14 mg was associated with improved HRQoL compared with once-weekly subcutaneous dulaglutide 0.75 mg. The DTR-QoL has a high degree of sensitivity for measuring diabetes-related HRQoL, as demonstrated by the close alignment between the domain scores and the objective clinical outcomes. Oral semaglutide may help more patients with T2D to benefit from GLP-1RA therapy.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Prior Presentation

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Compliance with Ethics Guidelines

Institutional review boards/independent ethics committees at each site provided approval before the start of the trial and all patients provided informed consent. The trial was conducted according to relevant national requirements, and complied with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice.

Data Availability

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

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Pre-typeset version

FIGURE LEGEND

Figure 1. Estimated changes from baseline in DTR-QoL domain scores at weeks 26 and 52 for the treatment policy estimand. (i) Burden on social activities and daily activities; (ii) Anxiety and dissatisfaction with treatment; (iii) Hypoglycemia; (iv) Satisfaction with treatment; and (v) Total score.

Data are for the treatment policy estimand. Missing post-baseline values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by treatment arm and treatment status (premature trial product discontinuation and/or initiation of rescue medication), and imputations were based on an ANCOVA model. Imputation was from own treatment arm and same treatment status. Change from baseline was analyzed using an ANCOVA model with treatment and strata as categorical fixed effects and baseline value as the covariate for each of the 1,000 imputed complete datasets, and pooled by Rubin's rule to draw inference [30]. No statistical analyses were controlled for multiplicity as there are no confirmatory endpoints.

^aLower bound of 95% confidence interval > 0 for the estimated treatment difference vs dulaglutide 0.75 mg, favoring oral semaglutide.

ANCOVA analysis of covariance, *DTR-QoL* Diabetes Therapy-Related Quality of Life

Table 1. Baseline DTR-QoL domain scores.

	Oral semaglutide 3 mg	Oral semaglutide 7 mg	Oral semaglutide 14 mg	Dulaglutide 0.75 mg
Number of patients	131	132	130	65
Burden on social activities and daily activities	76.9 ± 19.0	76.5 ± 18.4	77.7 ± 16.2	77.1 ± 19.1
Anxiety and dissatisfaction with treatment	64.6 ± 21.5	62.7 ± 20.9	62.1 ± 20.0	65.3 ± 23.6
Hypoglycemia	83.5 ± 20.0	88.2 ± 16.6	85.3 ± 20.6	86.3 ± 18.2
Satisfaction with treatment	55.6 ± 18.3	57.9 ± 17.2	53.9 ± 20.7	54.2 ± 20.9
Total score	71.5 ± 15.7	71.7 ± 14.8	71.2 ± 14.1	71.9 ± 16.2

Values are mean ± standard deviation unless otherwise stated.

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