Adv Ther (2024) 41:4266–4281
https://doi.org/10.1007/s12325-024-02973-z

ORIGINAL RESEARCH

PIONEER REAL UK: A Multi-Centre, Prospective, Real-World Study of Once-Daily Oral Semaglutide Use in Adults with Type 2 Diabetes

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Received: July 17, 2024 / Accepted: August 14, 2024 / Published online: September 24, 2024

ABSTRACT

***Introduction*:** Oral semaglutide provides an alternative to injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) for treatment of type 2 diabetes (T2D). The PIONEER REAL studies evaluate clinical outcomes of oral semaglutide treatment of T2D in a real-world setting. PIONEER REAL UK focused on adults living with T2D in the UK.

***Methods*:** The multi-centre, prospective and non-interventional single-arm study enrolled 333 participants and followed them for 34–44 weeks. Participants were treated as part of routine clinical practice and had not been previously treated with injectable glucose-lowering medication. The primary endpoint was change in glycated haemoglobin (HbA_{1C}) from baseline to end of study (EOS). Secondary endpoints included change in body weight, proportion of participants with HbA_{1C} < 7% (53 mmol/mol) at EOS and proportion of participants with ≥ 1%-point HbA_{1C} reduction and body weight reduction of ≥ 3% or ≥ 5% at EOS. Treatment satisfaction was assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ) status and change.

***Results*:** Of 333 participants, 299 completed the study and 227 were on treatment at EOS. People treated with oral semaglutide experienced significantly reduced HbA_{1C} by an estimated

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-02973-z.

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change of – 1.1%-points (95% CI – 1.27 to – 0.96; $P<0.0001$) or – 12.2 mmol/mol (CI – 13.87 to – 10.47; $P<0.0001$). Estimated change in body weight was – 4.8 kg (CI – 5.47 to – 4.12; $P<0.0001$). At EOS, an HbA_{1C} level < 7% (53 mmol/mol) was recorded in 46.3% of participants. A ≥ 1%-point reduction in HbA_{1C} combined with a ≥ 3% reduction in body weight was observed in 36.4% of participants, and 27.1% had a ≥ 1%-point reduction in HbA_{1C} and a ≥ 5% body weight reduction. Treatment satisfaction improved significantly during the study. No new safety concerns or cases of severe hypoglycaemia were reported.

Conclusion: People living with T2D in the UK experienced a meaningful decrease in HbA_{1C} and body weight after initiation of oral semaglutide treatment. No new safety issues were observed.

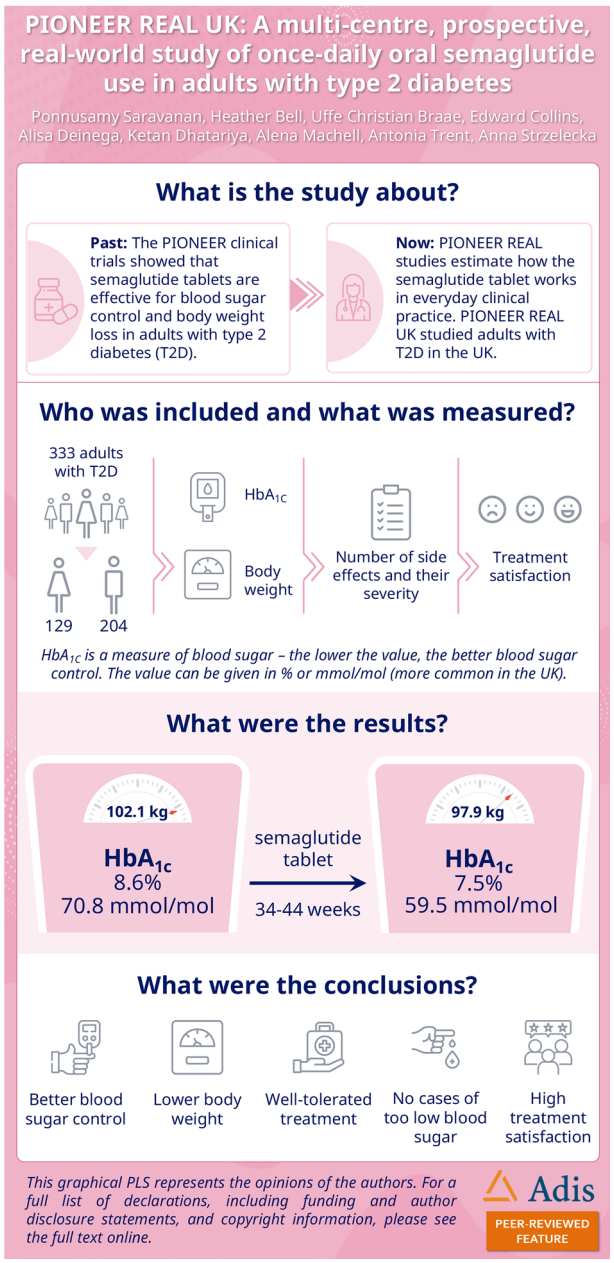
Trial Registration: ClinicalTrials.gov: NCT04862923.

Graphical plain language summary available for this article.

PLAIN LANGUAGE SUMMARY

PIONEER REAL UK investigated the use of a tablet form of the medicine semaglutide in people living with type 2 diabetes in the UK. The purpose was to determine how well the tablet works for blood sugar control and weight loss in everyday clinical practice. The study followed 333 participants whose doctors had given them semaglutide tablets. Their blood sugar levels and body weight were measured before and after taking the semaglutide tablet for 34–44 weeks. The participants were also asked to fill out questionnaires about their treatment satisfaction and how it changed when taking the semaglutide tablet. The participants' blood sugar levels dropped a lot, and body weight was lowered by an average of 4.8 kg during the 34–44 weeks of the study. The participants were also more satisfied with their treatment at the end of the study than before taking the semaglutide tablet. Doctors treating the participants found the treatment to be a success in more than two-thirds of participants. The study also found that the semaglutide tablet was not associated with cases of too low blood sugar and was generally well tolerated. In summary, the semaglutide tablet is a good option for people living with type 2 diabetes who need better blood sugar control and would benefit from weight loss. The treatment is generally well tolerated, and people are very satisfied with it.

GRAPHICAL PLAIN LANGUAGE SUMMARY



Keywords: Body weight; GLP-1 receptor agonist; Glucose-lowering medication; Glycaemic control; HbA_{1C}; Incretin therapy; Real-world evidence; Semaglutide; Type 2 diabetes

Key Summary Points

Why carry out this study?

During the PIONEER phase 3 clinical programme, oral semaglutide showed efficacy in achieving glycaemic control and body weight loss in people living with type 2 diabetes (T2D)

The PIONEER REAL programme was initiated as a follow-up to investigate clinical outcomes of oral semaglutide treatment in a real-world setting

PIONEER REAL UK, one of the 13 PIONEER REAL studies worldwide, enrolled 333 participants with T2D who had not previously been treated with injectable glucose-lowering medication and who were prescribed oral semaglutide as part of routine clinical practice

What was learned from the study?

After 34–44 weeks of oral semaglutide treatment, clinically significant improvements in glycaemic control and reductions in body weight were observed, treatment satisfaction improved, and no new safety concerns or cases of severe hypoglycaemia were reported

Data from PIONEER REAL UK complement the findings of the PIONEER clinical programme and support oral semaglutide as a generally well tolerated and effective option in primary care for T2D management

DIGITAL FEATURES

This article is published with digital features, including graphical plain language summary, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.26583082.

INTRODUCTION

Approximately 3.9 million people are living with type 2 diabetes (T2D) in the UK, and it is estimated that approximately 1 million people are living with undiagnosed T2D [1]. Furthermore, more than 2.4 million people are at increased risk of developing T2D. National [2] as well as international [3] guidelines recommend early treatment of T2D for reducing the risk of both microvascular and macrovascular complications. Treatment options include lifestyle changes, such as healthy diet and regular physical activity, in combination with pharmacological interventions [3]. Weight loss has been shown to lead to better outcomes [4] and is recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus as part of T2D management [3]. The ADA/EASD guideline also recommends early use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) because of their cardiovascular, glycaemic and weight benefits [3].

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines for T2D management in adults [2] recommend metformin as the first-line pharmacological treatment alongside lifestyle changes for those at low cardiovascular disease risk. If further glycaemic control is required, this is followed by another oral anti-diabetic agent (OAD), such as a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, sulphonylurea or a dipeptidyl peptidase-4 (DPP-4) inhibitor. GLP-1RAs are considered part of the treatment regimen when the combination of metformin and two other OADs is insufficient. The need for injections is often seen as a barrier to use of GLP-1RAs [5], but an oral alternative, a once-daily semaglutide tablet, has been available in the UK since 2020 [6].

The safety and efficacy of oral semaglutide have been demonstrated across adult T2D populations with different ages, duration of diabetes,

body mass index (BMI), baseline glycated haemoglobin (HbA_{1C}) levels and races during the PIONEER clinical development programme [7–13]. PIONEER REAL is a collection of 13 non-interventional studies across Europe, North America, the Middle East and Asia that aims to complement the findings from the PIONEER clinical development programme in real-world settings. Such real-world evidence (RWE) studies can be valuable for guiding clinical decision making. In the UK, NICE has established a real-world evidence framework and uses real-world data in decision making, for example when formulating guidelines for health care professionals and evaluating new medicines [14]. In the PIONEER REAL studies, clinical outcomes of oral semaglutide treatment are investigated as part of routine clinical practice in adults with T2D who have not previously been treated with injectable glucose-lowering medication. Results from PIONEER REAL Switzerland [15], Canada [16], The Netherlands [17] and Sweden [18] are already available, as well as baseline data from Japan [19]. Here, we report results from PIONEER REAL UK (NCT04862923) with data collected across 32 centres in the UK.

METHODS

Study Design

PIONEER REAL UK was a 34–44-week, non-interventional, multi-centre, phase 4, prospective, single-arm clinical study assessing use of oral semaglutide in adults with T2D in clinical routine practice. List of centres and physicians can be found in Supplemental Table S1. Participants received oral semaglutide based on the treating physician's and participant's decision; the decision to prescribe oral semaglutide preceded recruitment to participate in the study. Data were collected in accordance with local clinical practice without any additional diagnostic or monitoring procedures. The study protocol was approved by the UK National Health Services Health Research Authority (NHS HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA) after review by the London-Chelsea Research Ethics Committee (for all sites). The study was conducted following good pharmacoepidemiology practices (GPP) [20] and good pharmacovigilance practices (GVP) [21] in accordance with the Declaration of Helsinki [22]. All participants signed an informed consent. Similar methodologies have been presented elsewhere in the other PIONEER REAL studies in different countries [15–19].

Participants

Adults with T2D were eligible for inclusion if a decision to initiate oral semaglutide treatment had been made, they were treatment naïve to injectable glucose-lowering drugs and had an available HbA_{1c} value ≤ 90 days prior to visit 1 or taken at visit 1 in line with local clinical practice. All participants were ≥ 18 years old and could be male or female.

Study Procedures

Baseline data were collected either at the time of oral semaglutide prescription at visit 1 or from existing records collected prior to visit 1. Oral semaglutide dose titration and other treatment decisions were at the treating physician's discretion. All data were collected in an electronic case report form (eCRF). The first visit occurring between weeks 34 and 44 was recorded as the end of study (EOS) visit. If an HbA_{1C} value was not recorded during the 34–44-week window, the first available result thereafter was recorded. Any visits between visit 1 and the EOS visit were categorised as intermediate visits. If a participant discontinued oral semaglutide treatment, information on circumstances was recorded as close to the stopping date as possible. Unless consent was withdrawn, data collection continued until EOS regardless of treatment status.

Endpoints and Assessments

The primary endpoint was %-point change in HbA_{1C} from baseline to EOS. Secondary endpoints were relative (%) and absolute (kg) change in body weight from baseline to EOS, proportion

of participants with an HbA_{1C} level < 7% (53 mmol/mol) at EOS, composite endpoints of HbA_{1C} reduction ≥ 1%-points (approximately 11 mmol/mol) combined with body weight reduction of ≥ 3% or ≥ 5% from baseline to EOS and participant reported outcomes of change in relative (Diabetes Treatment Satisfaction Questionnaire change, DTSQc) and absolute (Diabetes Treatment Satisfaction Questionnaire status, DTSQs) treatment satisfaction at EOS. Exploratory endpoints included oral semaglutide dose (mg/day) at EOS, proportion of participants treated with oral semaglutide at EOS, addition of new glucose-lowering medication or increased dose of baseline glucose-lowering medication (other than oral semaglutide) during the study period, removal of glucose-lowering medication or reduced dose of baseline glucose-lowering medication during the study period, clinical success as assessed by physician at EOS, change in waist circumference (cm) from baseline to EOS and self-reported severe hypoglycaemia during the study period. Additionally, the change in HbA_{1C} was analysed stratified by baseline HbA_{1C} (< 7.0, ≥ 7 to < 8.0, ≥ 8.0 to < 9.0 and ≥ 9.0% or < 53, ≥ 53 to < 64, ≥ 64 to < 75 and ≥ 75 mmol/mol) and diabetes duration (≤ 1, > 1 to ≤ 5, > 5 to ≤ 10 and > 10 years) while the change in body weight was analysed stratified by baseline HbA_{1C}, BMI (≥ 25 to < 30 and ≥ 30 kg/m^2) and diabetes duration.

Subgroup Analysis

The study included a subgroup analysis on participants with a glucose-lowering treatment regimen of metformin and one OAD immediately prior to initiating oral semaglutide. Full definition of the subgroup is included in Supplementary Material and Methods. All endpoints mentioned in the above section except for HbA_{1C} and body weight stratified by baseline data were analysed for the subgroup as well as the full analysis set (FAS).

Statistical Analysis

The sample size was determined based on a 90% probability of obtaining a 95% confidence interval for the primary endpoint of mean change in HbA_{1C} from baseline with a half-width of maximum 0.30, assuming a SD of 1.7%. Based on these assumptions, 145 participants were needed for analysis. However, since data were collected as part of routine clinical practice, it was expected that only 75% of participants would have an EOS HbA_{1C} measurement. Therefore, the sample size was increased to 194. Furthermore, the inclusion of a subgroup analysis of participants with baseline metformin and one OAD immediately prior to initiation of oral semaglutide had to be accounted for, and these participants were assumed to constitute 51% of participants (based on market research findings). To ensure sufficient power for the primary endpoint analysis in the subgroup, the plan was to enrol a total of 381 participants.

FAS included all eligible participants who signed the informed consent and initiated oral semaglutide treatment. During the 'in-study' observation period, participants were considered in the study regardless of potential discontinuation of oral semaglutide treatment, while participants were considered treated with oral semaglutide during the 'on-treatment' observation period. Primary analysis of the primary, secondary and exploratory endpoints was based on the FAS and in-study observation period while the secondary analysis of the primary, secondary and exploratory endpoints was based on the FAS and on-treatment observation period. For the stratified HbA_{1C} analyses, all participants in the FAS with at least one post-baseline HbA_{1C} in the in-study observation period were included while all participants in the FAS with at least one body weight measurement in the in-study observation period were included in the stratified body weight analyses. If number of subjects in a category was < 30, the category was combined with the corresponding next or preceding level.

While the EOS visit could take place anywhere between weeks 34 and 44, the analyses of HbA_{1C} and body weight change from baseline to EOS were estimated from baseline to week 38. For other endpoints, data from EOS visit were used. It should also be noted that not all participants had data available for all analyses; therefore, the *n* varies between endpoints and is reported with the results.

Random coefficient mixed model for repeated measurements (MMRM) with random intercept and time (slope) based on the in-study observation period was used for primary analysis of the primary endpoint. Secondary analysis of the primary endpoint was otherwise similar but based on the on-treatment observation period. All MMRM models were performed both as crude and adjusted models. Crude models were adjusted for baseline values of the dependent variable, i.e. baseline HbA_{1C} or body weight, respectively. Covariates included in the adjusted analysis of the primary endpoint were baseline HbA_{1C}, age and BMI as well as time and time square. A sensitivity analysis of the primary endpoint was completed using a pattern-mixture model (PMM) fitted to all participants in FAS and in-study observation period. Additional post hoc sensitivity analyses, similar to the primary analyses, were performed where participants with an EOS visit outside of weeks 34–44 were excluded because their EOS visit was affected by the COVID-19 pandemic.

MMRM or analysis of covariance (ANCOVA) was used for primary and secondary analyses of secondary and exploratory continuous endpoints. Primary analyses were based on the in-study observation period while secondary analyses were based on the on-treatment observation period. Continuous secondary endpoints relative and absolute change in body weight as well as the exploratory endpoint waist circumference were analysed in the same manner as the primary endpoint. Change from baseline to EOS in DTSQs and EOS score for DTSQc were analysed using an ANCOVA model. For secondary and exploratory categorical endpoints, proportions at EOS are displayed. HbA_{1C} stratified by baseline HbA_{1C} and diabetes duration as well as body weight stratified by baseline HbA_{1C}, BMI and diabetes duration are presented as the adjusted mean estimated change from baseline to week 38 with 95% CI based on MMRM and a *p*-value testing the null-hypothesis of no change in HbA_{1C} and body weight, respectively. All statistical analyses were also performed separately for the subgroup. All statistical analyses were performed using SAS, Version 9.3 (SAS Institute, Cary, NC). All statistical testing was two-sided with a significance level of 0.05.

RESULTS

Participants and Baseline Characteristics

PIONEER REAL UK study took place between 12 May 2021 (first participant first visit) and 31 August 2023 (last participant last visit). The participant disposition is summarized in Fig. 1. Informed consent was signed by 356 participants, of which 333 met the eligibility criteria and initiated oral semaglutide treatment. At EOS, 227 participants of the 299 who completed the study were on treatment. Reasons to discontinue oral semaglutide treatment included, as evaluated by the physician, safety concern related to gastrointestinal intolerability (51 participants), supply issues (11), change in treatment strategy (4), insufficient effect on glycaemic control (2), epi-/pandemic (2), intentions to become pregnant (1) and other reasons, most of which were related to side effects (13). Treatment status at EOS could not be determined for 22 participants.

Participant demographics and baseline characteristics are summarized in Table 1 for the FAS and in Supplemental Table S2 for the subgroup of participants with baseline metformin and one other OAD. The majority of participants were male (61.3%). At baseline, the mean (SD) age of participants was 58.5 (11.94) years and 75.5% of the participants were living with obesity (BMI ≥ 30) with a mean (SD) BMI of 35.5 (7.96) kg/m^2 and body weight of 102.8 (24.13) kg. Notably, there was a wide range of baseline HbA_{1C} levels from < 7% (53 mmol/mol) to > 12% (108 mmol/mol) with mean (SD) baseline HbA_{1C} at 8.6% (1.44) or 70.8 (15.75) mmol/mol. Diabetes duration varied from < 1 year to > 10 years. Mean number of anti-diabetic medications was 1.6 at baseline and 2.5 at EOS, with oral semaglutide included only at EOS. Cardiovascular (CV)-related medical history was recorded in 65.8% of participants at baseline.

Most participants were seen in primary care (70.6%) by non-diabetes specialists (primary

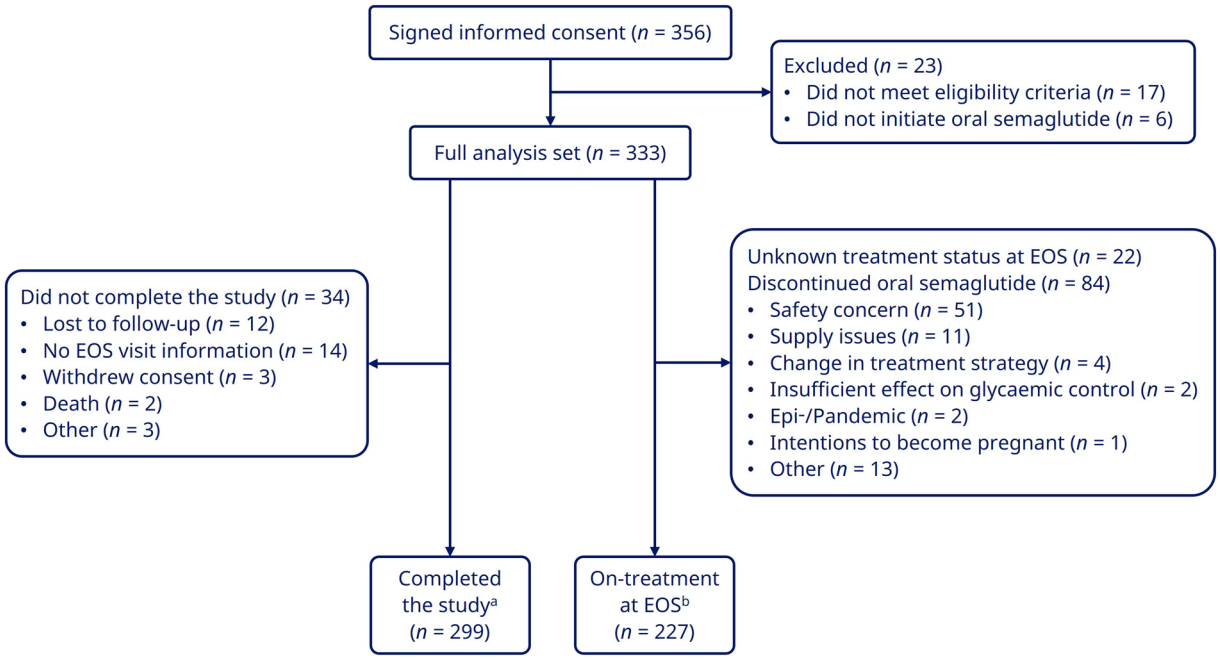


Fig. 1 Participant disposition. [a]Participants who initiated the oral semaglutide treatment and attended the EOS visit. [b]Participants who were on oral semaglutide treatment and attended the EOS visit. *EOS* end of study; *Epi-/Pandemic* COVID-19-related issue or similar

care physicians; also 70.6%). Reasons to initiate oral semaglutide treatment included (more than one option could be chosen) improving glycaemic control (94%), weight reduction (73.6%), addressing cardiovascular risk factors (15.6%), convenience (9.3%), simplifying treatment regimen (3.9%) and issues with hypoglycaemia (1.2%). All but one participant (99.7%) started on the 3 mg oral semaglutide dose; the one remaining participant (0.3%) started on the 7 mg dose.

Changes in HbA_{1C} and Body Weight

The estimated change in HbA_{1C} from baseline to 38 weeks (Fig. 2A) was −1.1%-points (95% CI −1.27 to −0.96; $P<0.0001$) or −12.2 mmol/mol (CI −13.87 to −10.47; $P<0.0001$), based on assessment in 286 participants who had required data for analysis (i.e. $n=286$). Secondary and sensitivity analysis showed comparable results to the primary analysis (Supplemental Figure S1). At EOS, 46.3% of the participants ($n=255$) had an HbA_{1C} level < 7% (53 mmol/mol). Analysing change in HbA_{1C} stratified by baseline HbA_{1C} showed that higher baseline HbA_{1C} level resulted in numerically greater HbA_{1C} change during the study (Fig. 2B). Notable decreases in HbA_{1C} levels were observed at all durations of diabetes, although reductions were greater in those within the first 5 years of their disease course (Supplemental Table S3).

Change in body weight was assessed in 276 participants. A significant reduction from baseline to 38 weeks was observed in the primary statistical analysis in both absolute and relative body weight, −4.8 kg (CI −5.47 to −4.12; $P<0.0001$) and −4.6% (CI −5.24 to −3.99; $P<0.0001$), respectively (Fig. 2C). Estimates were similar in the secondary and sensitivity analyses. Body weight reductions were seen regardless of baseline HbA_{1C}, BMI and diabetes duration (Supplemental Table S3). Composite analysis of changes in HbA_{1C} and body weight from baseline to EOS showed that 36.4% ($n=225$) had at least 1%-point reduction in HbA_{1C} as well as at

Table 1 Participant demographics and baseline characteristics

Characteristic	Values, *N* (%)
Sex (*N* = 333)	
Female	129 (38.7)
Male	204 (61.3)
Age groups (*N* = 333)	
< 45 years	41 (12.3)
45–65 years	188 (56.5)
65–75 years	74 (22.2)
75 + years	30 (9.0)
Race (*N* = 332)	
Asian	23 (6.9)
Black	5 (1.5)
White	297 (89.5)
Other	7 (2.1)
Duration of T2D (*N* = 332)	
≤ 1 year	33 (9.9)
> 1 to ≤ 5 years	82 (24.7)
> 5 to ≤ 10 years	103 (31.0)
> 10 years	114 (34.3)
HbA_{1C} level (*N* = 333)	
< 14% (130 mmol/mol)	333 (100.0)
< 12% (108 mmol/mol)	323 (97.0)
< 10% (86 mmol/mol)	278 (83.5)
< 8% (64 mmol/mol)	124 (37.2)
< 7.5% (58 mmol/mol)	74 (22.2)
< 7% (53 mmol/mol)	37 (11.1)
BMI categories (*N* = 322)	
Normal (18.5 to < 25 kg/m^2)	8 (2.5)
Overweight (25 to < 30 kg/m^2)	71 (22.0)
Obese (≥ 30 kg/m^2)	243 (75.5)
CV-related[a] medical history[b] (*N* = 333)	
Yes	219 (65.8)
CV-related[a] medical history including CKD, microalbuminuria, haemoglobinopathy, dyslipidaemia (*N* = 333)	
Yes	249 (74.8)
Tobacco use (*N* = 327)	
Never smoked	173 (52.9)
Previous smoker	117 (35.8)
Current smoker	37 (11.3)
At least 150 min/week of moderate physical activity (*N* = 308)	
Yes	89 (28.9)
No	219 (71.1)
Concomitant anti-diabetic medications (*N* = 333)	
Metformin	266 (79.9)
SGLT2 inhibitors	147 (44.1)
Sulphonylureas	73 (21.9)
DPP-4 inhibitors	12 (3.6)
Thiazolidinediones	11 (3.3)
Other	11 (3.3)
Fixed dose combinations	9 (2.7)
No medication	27 (8.1)

% percentages based on participants with responses; *BMI* body mass index; *CKD* chronic kidney disease; *CV* cardiovascular; *DPP-4* dipeptidyl peptidase 4; *FAS* full analysis set; *HbA_{1C}* glycated haemoglobin; *N* number of participants with response; *SGLT2* sodium-glucose co-transporter 2; *T2D* type 2 diabetes

[a]Cardiovascular-related medical history includes atrial fibrillation, chronic heart failure, coronary heart disease, hypertension, peripheral artery disease, revascularization, stroke or transient ischaemic attack

[b]*N* is number of participants in FAS

least 3% reduction in body weight, and 27.1% (*n* = 225) had at least 1%-point reduction in HbA_{1C} as well as at least 5% reduction in body weight (Fig. 2D).

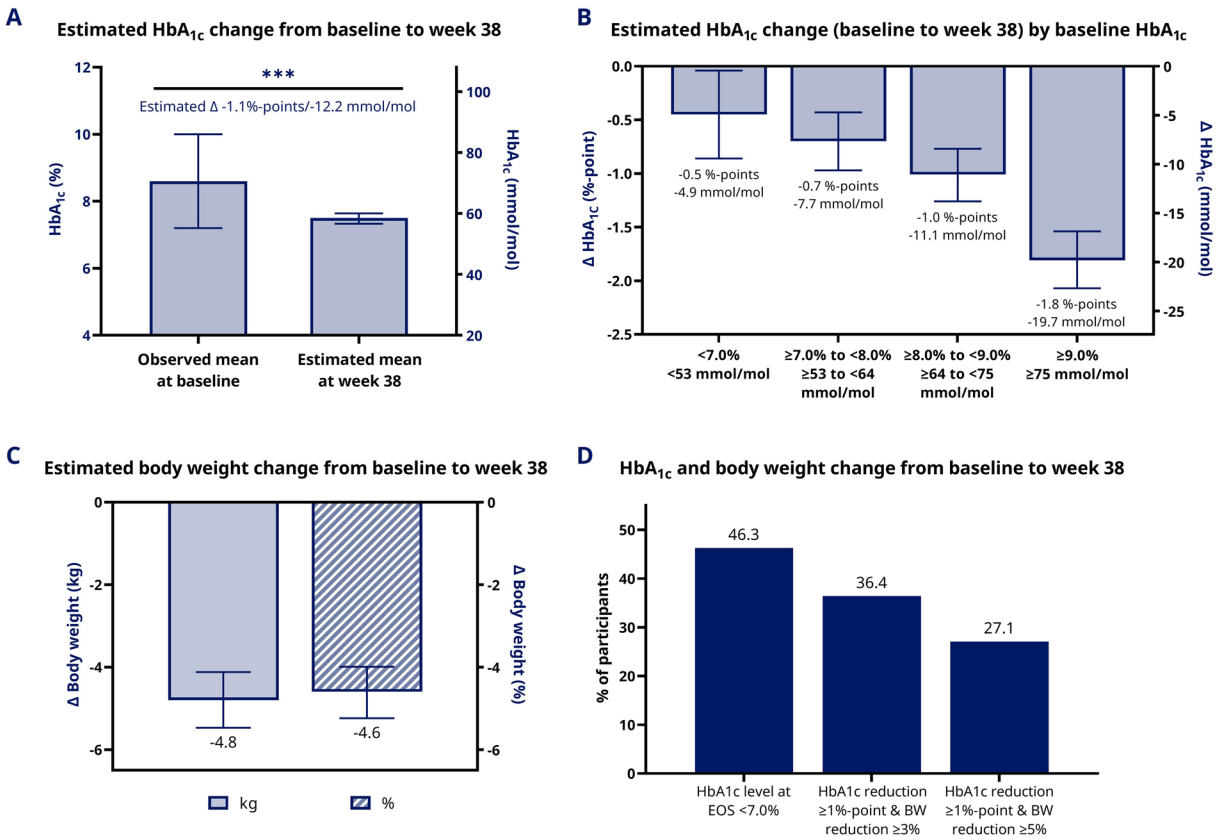


Fig. 2 Changes in HbA_{1c} and body weight. **A** Observed HbA_{1C} at baseline (mean with SD is plotted) and estimated mean HbA_{1C} at week 38 (plotted with 95% CI) in % and mmol/mol as well as estimated change from baseline to week 38 in %-points and in mmol/mol. **B** Estimated HbA_{1C} change from baseline to week 38 stratified by baseline HbA_{1C} in %-points and mmol/mol (mean with 95% CI is plotted). **C** Absolute and relative estimated body weight change from baseline to week 38 in kg and in % (mean with 95% CI is plotted). **D** Proportion of participants at HbA_{1C} target at EOS and composite endpoints of HbA_{1C} and body weight reduction at EOS. *BW* body weight; *CI* confidence interval; *EOS* end of study; *HbA_{1C}* glycated haemoglobin; *SD* standard deviation

Similar changes in HbA_{1C} and body weight were observed in the subgroup (Supplemental Figure S2).

Treatment Satisfaction

Absolute DTSQ (DTSQs) is measured on a scale from 0 to 36, and answers that indicate being very satisfied with the treatment and finding it convenient score the highest. Relative DTSQ (DTSQc) corrects for the so-called ceiling effect when baseline treatment satisfaction is high and is measured on a scale from −18 to 18 [23]. An improvement in both DTSQ scores was observed at EOS (Fig. 3; Supplemental Figure S3 for the subgroup): estimated mean DTSQs increased by 2.0 points (CI 1.29–2.78; $P<0.0001$) from baseline ($n=219$) and the estimated mean DTSQc score was 13.6 (CI 12.91–14.29; $P<0.0001$) at EOS ($n=218$).

Exploratory Endpoints

Results for exploratory endpoints are summarized in Supplemental Table S4. At EOS, 227 participants of 333 (68.2%) were treated with oral semaglutide. Of those, 73.1% were at the 14 mg oral semaglutide dose while 21.6% were at the

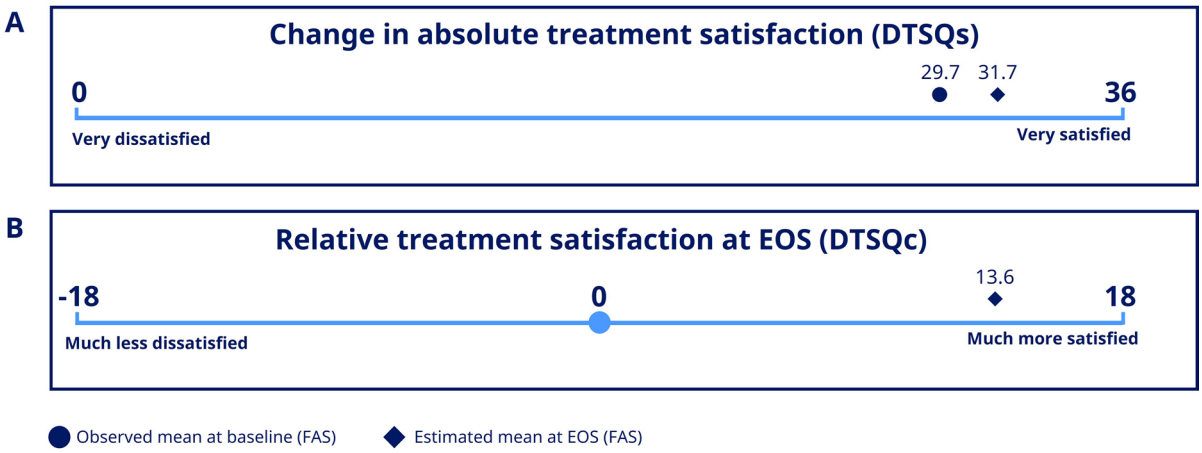


Fig. 3 Change in treatment satisfaction. **A** Change in absolute treatment satisfaction. **B** Relative treatment satisfaction at EOS. *DTSQc* diabetes treatment satisfaction questionnaire-change; *DTSQs* diabetes treatment satisfaction questionnaire-status; *EOS* end of study; *FAS* full analysis set

7 mg and 5.3% at the 3 mg dose. New glucose-lowering medication or increased dose of baseline glucose-lowering medication was recorded in 25.2% of all participants ($n=333$) and in 15% of participants who were taking semaglutide at EOS. Removal of glucose-lowering medication or decreased dose of baseline glucose-lowering medication was observed in 17.4% of all participants ($n=333$) and in 16.3% of participants who were taking semaglutide at EOS ($n=227$). For 72.6% of participants ($n=296$), the treating physician assessed their treatment to be a clinical success. Waist circumference was assessed in 162 participants and was significantly reduced by 5.0 cm from baseline to EOS (CI −5.99 to −4.05; $P<0.0001$).

Safety

Altogether, 487 adverse events (AEs) were reported in 191 participants (57.4%) during the in-study observation period, and most of the AEs were mild or moderate in severity (Table 2). A total of 32 serious AEs were reported in 18 participants (5.4%). Gastrointestinal disorders, reported in 137 participants (41.1%), were the most common AEs. As an outcome of AEs, oral semaglutide was withdrawn in 60 participants (18%) and interrupted in 16 participants (4.8%), and the dose was reduced in 19 participants (5.7%). Three AEs had a fatal outcome (asthenia, endometrial cancer and cardiac arrest by preferred term), and all three fatal events were assessed to be unlikely related to oral semaglutide treatment. No pregnancies were observed during the study. Participants ($N=314$) reported 0 cases of severe hypoglycaemia.

DISCUSSION

The PIONEER REAL programme provides insights into how oral semaglutide performs and is utilised in routine clinical practice in a real-world population of adults with T2D who have not previously been treated with injectable glucose-lowering drugs. In PIONEER REAL UK, clinically significant improvements in glycaemic control and reductions in body weight were observed in a population with a large range of T2D duration and HbA_{1C} levels as well as a high prevalence of cardiovascular diseases. Improvements in treatment satisfaction were also observed. Observations were similar in the FAS and in subgroup analysis of participants who were taking metformin and one other OAD

Table 2 Adverse events

	Total		
	N (%)	*E*	*R*
Adverse events	191 (57.4)	487	185.8
Mild	155 (46.5)	332	126.7
Moderate	75 (22.5)	138	52.7
Severe	10 (3.0)	16	6.1
Serious adverse events	18 (5.4)	32	12.2
Deaths	3 (0.9)	3	1.1
Severe hypoglycaemic episodes[a]	0 (0)	0	0
Action taken			
Drug interrupted	16 (4.8)	25	9.5
Drug withdrawn	60 (18.0)	116	44.3
Dose reduced	19 (5.7)	26	9.9
Dose increased	7 (2.1)	8	3.1
Dose not changed	120 (36.0)	284	108.4
N/A	16 (4.8)	28	10.7
Most common AEs by SOC (≥ 3% of participants)			
Gastrointestinal disorders	137 (41.1)	238	90.8
Infections and infestations	37 (11.1)	47	17.9
Nervous system disorders	29 (8.7)	35	13.4
Musculoskeletal and connective tissue disorders	26 (7.8)	31	11.8
General disorders and administration site conditions	23 (6.9)	24	9.2
Respiratory, thoracic and mediastinal disorders	17 (5.1)	19	7.3
Skin and subcutaneous tissue disorders	15 (4.5)	18	6.9
Investigations	10 (3.0)	12	4.6
Metabolism and nutrition disorders	10 (3.0)	11	4.2

Data are for the in-study observation period, which represents the time period during which participants were in the study, regardless of oral semaglutide treatment status

% percentage of participants; *AE* adverse event; *E* number of events; *N* number of participants; *N/A* not applicable; *R* event rate per 100 years of observation time; *SOC* system organ class

[a]Severe hypoglycaemia can be defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery

at baseline or no longer than 90 days prior to the first study visit.

In PIONEER REAL UK, a −1.1%-point (−12.2 mmol/mol) reduction in HbA_{1C} was estimated at week 38 after initiation of oral semaglutide treatment. Notably, 27% of participants were not at the highest oral semaglutide dose at EOS. The HbA_{1C} reduction in PIONEER REAL UK is in line with the −1.09%-point (−11.94 mmol/mol) reduction estimated in PIONEER REAL Canada [16], −0.91%-point (−9.89 mmol/mol) reduction estimated in PIONEER REAL Switzerland [15], −1.16%-point (−12.72 mmol/mol) reduction estimated in PIONEER REAL Netherlands [17] and −0.88%-point (−9.64 mmol/mol) reduction estimated in PIONEER REAL Sweden [18]. The PIONEER REAL UK results are also in line with observations in the PIONEER clinical development programme, where HbA_{1C} reductions from −1.2 to −1.3%-point (approximately 12–14 mmol/mol) were found [10–13, 24]. Besides the PIONEER REAL programme, a US-based retrospective observational cohort study called IGNITE has investigated oral semaglutide use in adults with T2D in clinical practice [25]. After approximately 6 months of treatment, a −0.9%-point (approximately −10 mmol/mol) reduction in HbA_{1C} was observed for the full study cohort and a −1.0%-point (approximately −11 mmol/mol) reduction in GLP-1RA-naïve individuals. It should be noted that 37% of the full IGNITE cohort received only the 3 mg starting dose of oral semaglutide. Real-world studies have also been conducted on clinical outcomes of once-weekly subcutaneous semaglutide use. These studies have reported slightly higher reductions in HbA_{1C} than what has been seen in the PIONEER REAL studies. An estimated −1.5%-point (−16.3 mmol/mol) reduction from baseline to week 30 was observed in SURE UK [26], while a −1.4%-point (−14.9 mmol/mol) reduction was reported at 180 days in GLP-1RA-naïve people in a Danish observational study [27].

The primary reason to initiate oral semaglutide treatment in PIONEER REAL UK was to improve glycaemic control (94%) but weight reduction was also an important reason (73.6%). This is in line with evidence that supports targeting body weight as an essential part of T2D management [4]. The estimated −4.6% (−4.8 kg) body weight loss in PIONEER REAL UK is very similar to the estimated −4.85% (−4.72 kg) change in PIONEER REAL Switzerland [15] and −4.72% (−4.62 kg) change in PIONEER REAL Sweden [18] and also similar to the estimated −5.65% (−5.84 kg) change in PIONEER REAL Netherlands [17]. In PIONEER REAL Canada, the estimated change in body weight was higher at −7.17% (−7.19 kg) [16], which was also higher than observed in the PIONEER clinical development programme, where weight loss varied between −2.6 and −4.4 kg [10–13, 24]. In the real-world study SURE UK investigating once-weekly subcutaneous semaglutide, mean body weight change was −5.8 kg after 30 weeks of treatment [26].

While 11% of the PIONEER REAL UK participants had a baseline HbA_{1C} value < 7% (53 mmol/mol), i.e. the recommended glycaemic target for nonpregnant adults with T2D [28], a total of 46.3% were below the target value at EOS. The treating physicians evaluated 72.6% of participants to reach clinical success. Even though treatment satisfaction among participants was high at baseline, the scores measured by DTSQs as well as DTSQc were significantly increased at EOS. No new safety concerns were observed and, notably, no cases of severe hypoglycaemia were reported during the study.

The PIONEER REAL UK study was observational and designed without a comparator arm, thus alternative explanations for changes from baseline in HbA_{1C} and other evaluated endpoints cannot be ruled out. Data were collected as part of the routine clinical practice and not through mandatory assessments at prespecified time points, which may impact the robustness and completeness of the data and the conclusions. Moreover, the study was conducted during the COVID-19 pandemic; consequently, several participants could not complete the EOS assessment in the predefined timeframe. Also, due to inconsistencies in data collection, data on microvascular complications at baseline were incomplete and were omitted from the manuscript. Supply constraints led to a small number of participants discontinuing treatment.

CONCLUSION

PIONEER REAL UK gives valuable insight into efficacy and safety of oral semaglutide in routine clinical practice. After 34–44 weeks of treatment, significant improvement in glycaemic control and reduction in body weight were observed. High treatment satisfaction and a strong safety profile further support oral semaglutide as a generally well tolerated and effective option in primary care for T2D management.

ACKNOWLEDGEMENTS

The authors thank all participants, investigators and site staff who were involved in the conduct of the PIONEER REAL UK study. The authors would also like to thank Dr. Kabirdev Mandavya of Novo Nordisk A/S for his review and valuable comments on the manuscript. Medical writing support was provided by Riia K. Sustarsic (PhD) of Novo Nordisk A/S.

Author Contributions. Data were analysed by the sponsor. Ponnusamy Saravanan, Heather Bell, Uffe Christian Braae, Edward Collins, Alisa Deinega, Ketan Dhatariya, Alena Machell, Antonia Trent and Anna Strzelecka contributed to interpretation of data as well as writing, reviewing and editing the manuscript. Ponnusamy Saravanan was the Chief Investigator for the study. All authors approved the final version of the manuscript.

Funding. This study was sponsored by Novo Nordisk A/S. The journal's Rapid Service Fee was funded by Novo Nordisk A/S.

Data Availability. Data are available upon reasonable request. Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com. Data will be made available after research completion and approval of the product and product use in the European Union and the United States. Individual participant data will be shared in datasets in a de-identified/anonymised format.

Declarations

Conflict of Interest. The authors disclose the following competing interests: Ponnusamy Saravanan: honoraria or travel support from Novo Nordisk and Abbott, UK; an unrestricted educational grant from Novo Nordisk A/S to set up an international Doctoral Training Partnership. Heather Bell: honoraria, travel support or fees for advisory boards from Abbott, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Menarini, Novo Nordisk, PCDS, Roche. Uffe Christian Braae: employee and shareholder of Novo Nordisk A/S. Edward Collins: employee and shareholder of Novo Nordisk A/S. Alisa Deinega: employee of Novo Nordisk A/S. Ketan Dhatariya: honoraria, travel support or fees for advisory boards from AstraZeneca, Novo Nordisk, Boehringer-Ingelheim, Eli Lilly, Abbott Diabetes, Menarini, Sanofi. Alena Machell: honoraria, travel support or fees for advisory boards from Novo Nordisk, Abbott. Antonia Trent: employee of Novo Nordisk A/S. Anna Strzelecka: honoraria from Astra Zeneca, Boehringer Ingelheim, Janssen, Lilly, MSD, Novo Nordisk, NAPP.

Ethical Approval. The study protocol was approved centrally by the UK National Health Services Health Research Authority (NHS HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA) after review by the London-Chelsea Research Ethics Committee (for all sites). The study was conducted following good pharmacoepidemiology practices (GPP) [20]) and good pharmacovigilance practices (GVP) [21] in accordance with the Declaration of Helsinki [22]. All participants signed an informed consent.

REFERENCES

1. National Institute for Health and Care Excellence (NICE). NICE clinical knowledge summaries type 2 Diabetes. https://cks.nice.org.uk/topics/diabetes-type-2/background-information/prevalence/. Accessed 10 April 2024.

2. National Institute for Health and Care Excellence (NICE). Type 2 diabetes in adults: management NICE guideline [NG28]. 2022:1–55. https://www.nice.org.uk/guidance/ng28. Accessed 19 March 2024.

3. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes 2022. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetes Care. 2022;45(11):2753–86. https://doi.org/10.2337/dci22-0034.

4. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet. 2022;399(10322):394–405. https://doi.org/10.1016/S0140-6736(21)01919-X.

5. Rasalam R, Abdo S, Deed G, O'Brien R, Overland J. Early type 2 diabetes treatment intensification with glucagon-like peptide-1 receptor agonists in primary care: an Australian perspective on guidelines and the global evidence. Diabetes Obes Metab. 2023;25(4):901–15. https://doi.org/10.1111/dom.14953.

6. Novo Nordisk A/S. Rybelsus® (semaglutide tablets), the world's first and only oral GLP-1 RA, now available in the UK to treat type 2 diabetes. 2020. https://www.novonordisk.co.uk/content/dam/nncorp/gb/en/pdfs/media-and-news/Medical_trade_media_press_release_Rybelsus_now_available_in_the_UK_for_T2D.pdf. Accessed 21 March 2024.

7. Aroda VR, Bauer R, Christiansen E, et al. Efficacy and safety of oral semaglutide by subgroups of patient characteristics in the PIONEER phase 3 programme. Diabetes Obes Metab. 2022;24(7):1338–50. https://doi.org/10.1111/dom.14710.

8. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. Diabetes Care. 2019;42(9):1724–32. https://doi.org/10.2337/dc19-0749.

9. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):515–27. https://doi.org/10.1016/S2213-8587(19)30192-5.

10. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. Lancet Diabetes Endocrinol. 2019;7(7):528–39. https://doi.org/10.1016/S2213-8587(19)30194-9.

11. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. Lancet. 2019;394(10192):39–50. https://doi.org/10.1016/S0140-6736(19)31271-1.

12. Rodbard HW, Rosenstock J, Canani LH, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: the PIONEER 2 trial. Diabetes Care. 2019;42(12):2272–81. https://doi.org/10.2337/dc19-0883.

13. Zinman B, Aroda VR, Buse JB, et al. Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: the PIONEER 8 trial. Diabetes Care. 2019;42(12):2262–71. https://doi.org/10.2337/dc19-0898.

14. National Institute for Health and Care Excellence (NICE). NICE real-world evidence framework: Corporate document [ECD9]. https://www.nice.org.uk/corporate/ecd9/chapter/overview. Accessed 08 May 2024.

15. Kick A, M'Rabet-Bensalah K, Acquistapace F, et al. Real-world use of oral semaglutide in adults with type 2 diabetes: the PIONEER REAL Switzerland multicentre, prospective, observational study.

Diabetes Ther. 2024;15(3):623–37. https://doi.org/10.1007/s13300-023-01525-y.

16. Jain AB, Reichert SM, Amadid H, et al. Use of once-daily oral semaglutide and associated clinical outcomes among adults with type 2 diabetes in routine clinical practice in Canada: a multicentre, prospective real-world study (PIONEER REAL Canada). Diabetes Obes Metab. 2024. https://doi.org/10.1111/dom.15493.

17. van Houtum W, Schrömbges P, Amadid H, et al. Real-world use of oral semaglutide in adults with type 2 diabetes in the PIONEER REAL Netherlands multicentre, prospective, observational study. Diabetes Ther. 2024. https://doi.org/10.1007/s13300-024-01588-5.

18. Catrina SB, Amadid H, Braae UC, Dereke J, Ekberg NR, Klanger B, Jansson S. PIONEER REAL Sweden: a multicentre, prospective, real-world observational study of oral semaglutide use in adults with type 2 diabetes in swedish clinical practice. Diabetes Ther. 2024. https://doi.org/10.1007/s13300-024-01614-6.

19. Suzuki R, Amadid H, Major-Pedersen A, Yabe D. PIONEER REAL Japan: baseline characteristics of a multicenter, prospective, real-world study of oral semaglutide in adults with type 2 diabetes in clinical practice in Japan. J Diabetes Investig. 2024. https://doi.org/10.1111/jdi.14219.

20. International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). 2015.

21. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – management and reporting of adverse reactions to medicinal products (Rev 1) (EMA/873138/2011 Rev 1). 2014.

22. World medical association. WMA declaration of Helsinki - ethical principles for medical research involving human subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil.; 2013.

23. Bradley C, Plowright R, Stewart J, Valentine J, Witthaus E. The diabetes treatment satisfaction questionnaire change version (DTSQc) evaluated in insulin glargine trials shows greater responsiveness to improvements than the original DTSQ. Health Qual Life Outcomes. 2007;5:57. https://doi.org/10.1186/1477-7525-5-57.

24. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: the PIONEER 3 randomized clinical trial. JAMA. 2019;321(15):1466–80. https://doi.org/10.1001/jama.2019.2942.

25. Aroda VR, Faurby M, Lophaven S, Noone J, Wolden ML, Lingvay I. Insights into the early use of oral semaglutide in routine clinical practice: the IGNITE study. Diabetes Obes Metab. 2021;23(9):2177–82. https://doi.org/10.1111/dom.14453.

26. Holmes P, Bell HE, Bozkurt K, et al. Real-world use of once-weekly semaglutide in type 2 diabetes: results from the sure UK multicentre, prospective, observational study. Diabetes Ther. 2021;12(11):2891–905. https://doi.org/10.1007/s13300-021-01141-8.

27. Vilsbøll T, Lindahl C, Nielsen NF, Tikkanen CK. Real-world impact of once-weekly subcutaneous semaglutide after 2 years of follow-up: results from a nationwide observational study in people with type 2 diabetes. Diabetes Obes Metab. 2023;25(6):1740–9. https://doi.org/10.1111/dom.15031.

28. American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: standards of care in diabetes-2024. Diabetes Care. 2024;47(Suppl 1):S111–25. https://doi.org/10.2337/dc24-S006.