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Original Article

Real-world use of oral semaglutide in adults with type 2 diabetes

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ABSTRACT

INTRODUCTION. PIONEER REAL Denmark assessed changes in HbA_{1c}, body weight and treatment satisfaction with once-daily oral semaglutide in adults with type 2 diabetes.

METHODS. In this multicentre, prospective, open-label, non-interventional study, participants initiated oral semaglutide in routine clinical practice and were followed up for 34-44 weeks. The primary endpoint was change in HbA_{1c} from baseline to the end of study (EOS). Secondary endpoints assessed at EOS included change in body weight (BW), proportion of participants reaching HbA_{1c} < 7% and treatment satisfaction using Diabetes Treatment Satisfaction Questionnaire status/change (DTSQs/DTSQc).

RESULTS. In total, 96 participants from a primary care setting were included (median age: 63.5 years, HbA_{1c}: 7.6% (60.0 mmol/mol), BW: 97.4 kg). Estimated changes from baseline to EOS in HbA_{1c} (n = 96) and BW (n = 86) were −0.9 percentage points (9.9 mmol/mol) (95% CI: −1.20; −0.61 percentage points) and −4.4 (95% CI: −5.44; −3.41) kg, respectively. At baseline, 28.1% of participants had HbA_{1c} < 7.0% (< 53 mmol/mol); at EOS, 66.7% of participants had HbA_{1c} < 7.0% (53 mmol/mol). Improvements in treatment satisfaction were observed in DTSQs (1.9 points) and DTSQc (10.5 points) scores. No new safety signals were identified for oral semaglutide.

CONCLUSIONS. In PIONEER REAL Denmark, participants treated with oral semaglutide in a primary care setting experienced reductions in HbA_{1c} and BW.

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TRIAL REGISTRATION. ClinicalTrials.gov (NCT04537637).

In 2024, an estimated 330,000 individuals in Denmark were living with type 2 diabetes (T2D) [1]. More than 80% of individuals with T2D in Denmark are managed in primary care, whereas specialist care is restricted to those who experience complications or do not reach treatment targets [2]. Semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is available as a once-weekly subcutaneous injection (0.5, 1.0 and 2.0 mg) [3, 4] and a once-daily oral formulation (3, 7 and 14 mg), which serve as an adjunct to diet and exercise in adults with insufficiently controlled T2D [5]. Changes to the oral formulation to improve bioavailability have introduced new doses (1.5, 4 and 9 mg) [5, 6]. The phase 3 PIONEER programme demonstrated the superiority of oral semaglutide over placebo and most active comparators for glycaemic control and weight loss, with a safety profile consistent with the GLP-1RA class. PIONEER REAL comprises 13 non-interventional studies, supporting the PIONEER clinical trial programme by investigating oral semaglutide in a real-world setting in adults with T2D. Here, we assessed changes in HbA_{1c}, body weight and treatment satisfaction associated with the use of

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once-daily oral semaglutide within routine clinical practice in Denmark.

Methods

Study design

PIONEER REAL Denmark (ClinicalTrials.gov NCT04537637) was a 34-44-week, prospective, open-label, non-interventional, single-arm study across 21 sites in Denmark. Clinical data and patient-reported outcomes (PROs) were collected in accordance with local clinical practice. The study design, procedure and endpoints are similar across the PIONEER REAL studies [7], cited therein.

Participants

The study included adults aged ≥ 18 years with T2D, treatment-naïve to injectable glucose-lowering medication (except for insulin use ≤ 14 days for acute illness) and with an HbA_{1c} value within 90 days prior to visit (V) 1 or at V1 in accordance with local clinical practice. See Supplementary table S1 for full eligibility criteria. According to local regulations, institutional review board/ethics committee approval for this non-interventional study was not required. This study was conducted in accordance with the Declaration of Helsinki (2013) and the Guidelines for Good Pharmacoepidemiology Practices (2015). Participants provided written informed consent.

Study procedures and visits

Participants received once-daily oral semaglutide (3, 7 and 14 mg) per local label and local clinical practice, which recommended GLP-1RAs as the first choice for those with known cardiovascular (CV) or kidney disease, and as the second choice for those without known CV or kidney disease after treatment with metformin [8, 9]. Participants attended an initiation visit (V1, week 0), several intermediate visits depending on the local clinical practice (V2.X, week 1-33) and an end-of-study (EOS) visit (V3, week 34-44) (Supplementary figure S1). Baseline (BL) (week 0) assessments were recorded < 90 days prior to the informed consent and treatment initiation visit (V1). The first visit between week 34 and 44 was considered the EOS visit.

Endpoints and assessments

The primary endpoint was change in HbA_{1c} (percentage points or mmol/mol) from BL to EOS. Key secondary endpoints included relative (%) and absolute (kg) change in body weight from BL to EOS, percentage of participants achieving HbA_{1c} < 7% (< 53 mmol/mol) at EOS, and composite endpoints of achieving an HbA_{1c} reduction ≥ 1 percentage points (≥ 11 mmol/mol) and body weight reduction of ≥ 3% or ≥ 5% from BL to EOS. PROs were measured using the Diabetes Treatment Satisfaction Questionnaire status/change (DTSQs/DTSQc). DTSQs and DTSQc scores correspond to changes in absolute treatment satisfaction from BL to EOS and relative treatment satisfaction at EOS, respectively [10, 11] (Supplementary table S2). DTSQs was completed at V1 and V3, and DTSQc at V3 only. Exploratory endpoints at EOS included oral semaglutide dose, treatment with oral semaglutide, addition of a new/removal or a dose increase/reduction of a glucose-lowering medication from BL (other than oral semaglutide), and physician-reported clinical success. Change in waist circumference and self-reported severe hypoglycaemia were assessed (BL to EOS). All adverse events (AEs) that occurred from informed consent until the EOS visit were monitored and recorded by the treating physician, who asked participants whether they experienced AEs at the treatment initiation visit, the EOS visit and all intermediate clinic visits, which were scheduled per local clinical practice.

Statistical analysis

This was described previously [7]. Clinical endpoints and safety evaluations were based on the full analysis set (FAS). Primary analyses of primary and secondary endpoints were based on the FAS during the in-study

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observation period, regardless of discontinuation of oral semaglutide. Secondary analyses of the primary and secondary endpoints were based on the FAS in the on-treatment observation period (i.e. during treatment with oral semaglutide). Additional sensitivity analyses were performed, excluding participants with an EOS visit outside of week 34-44 due to COVID-19. See the Supplement for details.

Data availability

The datasets generated and/or analysed during the present study are available from Novo Nordisk 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 completion of the research and approval of the product and its use in the European Union and the United States. Individual participant data will be shared as datasets in a de-identified/ anonymised format.

Trial registration: ClinicalTrials.gov (NCT04537637).

Results

Participant disposition and characteristics

Between 28 August 2020 and 8 May 2023, 99 participants provided informed consent; 97 enrolled and 96 initiated oral semaglutide. A total of 93 participants (96.9%) completed the study, with 76 (79.2%) remaining on semaglutide treatment at EOS (Supplementary figure S2).

Most participants were male (65.6%), with a median BMI of 31.8 kg/m^2, an HbA_{1c} of 7.6% (60.0 mmol/mol) and a diabetes duration of 3.5 years. At BL, 28.1% of participants had HbA_{1c} < 7.0% (53 mmol/mol) (**Table 1**). Among the 96 participants, 39 (40.6%) had a CV-related medical history; 33 (34.4%) had hypertension and 16 (16.7%) had dyslipidaemia (Supplementary table S3). Metformin and sodium-glucose co-transporter-2 inhibitors (SGLT2is) were the most frequent concomitant medications at BL (61.5% and 13.5%, respectively) and EOS (65.6% and 13.5%, respectively). At BL, 35.4% of participants were not receiving any concomitant glucose-lowering medications (Supplementary table S4).

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TABLE 1 Baseline characteristics of the full analysis set, i.e. all eligible patients who provided informed consent and initiated treatment with oral semaglutide (N_{tot} = 96)[a].

Sex, n (%)	
Female	33 (34.4)
Male	63 (65.6)
Age	
Median (IQR), yrs	63.5 (56.0; 69.0)
Age groups, n (%):	
< 45 yrs	7 (7.3)
45-64 yrs	44 (45.8)
65-74 yrs	36 (37.5)
≥ 75 yrs	9 (9.4)
Race, n (%)	
Asian	2 (2.1)
Black or African American	0
White	93 (96.9)
Other	1 (1.0)
Duration of T2D[b]	
Median (IQR), yrs (N = 72)	3.5 (0.8; 6.8)
Duration groups, n (%) (N = 96):	
< 1 yr	21 (21.9)
1-5 yrs	29 (30.2)
5-10 yrs	30 (31.3)
> 10 yrs	16 (16.7)
HbA_{1c}	
Median (IQR), %	7.6 (6.9; 8.4)
HbA_{1c} levels, n (%):	
< 10.0%	89 (92.7)
< 8.0%	61 (63.5)
< 7.5%	47 (49.0)
< 7.0%	27 (28.1)
Body weight, median (IQR), kg	97.4 (85.1; 110.2)
BMI, median (IQR), kg/m² (N = 95)	31.8 (29.1; 36.6)
Waist circumference, median (IQR), cm (N = 62)	112.5 (104.0; 124.0)
Calculated eGFR: CKD-EPI, median (IQR), ml/min./1.73 m² (N = 78)	91 (80.2; 100.4)
LDL cholesterol, median (IQR), mmol/l (N = 66)	2.1 (1.5; 2.8)
Blood pressure, median (IQR), mmHg (N = 94)	
Systolic	139.5 (130.0; 147.0)
Diastolic	85.5 (78.0; 90.0)
CV-related medical history[c], n (%)	39 (40.6)
History of microvascular complications, n	0
Diabetes medications, mean, n	
BL	0.8
EOS[d]	1.6
Prescribed starting dose of oral semaglutide, n (%)	
3.0 mg	96 (100)
7.0 mg	0
14.0 mg	0
Reasons to initiate oral semaglutide, n (%)	
Improve glycaemic control	93 (96.9)
Weight reduction	74 (77.1)
Hypoglycaemia on current treatment	0
Address CV risk factors	13 (13.5)
Simplify current treatment regimen	0
Convenience	0
Other	2 (2.1)

BL = baseline; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EOS = end of study; LDL = low-density lipoprotein; T2D = type 2 diabetes.
a) Characteristics with a total number of participants < 96 are marked.
b) For individuals who provided a date of T2D diagnosis.
c) CV-related medical history includes atrial fibrillation, chronic heart failure, coronary heart disease, hypertension, peripheral artery disease, revascularisation and stroke or transient ischaemic attack; see Supplementary table S3 for a summary of the proportion of participants with these conditions.
d) Oral semaglutide incl. at EOS only.

All participants were treated in a primary care setting, with one participant (1.0%) treated by an independent diabetes specialist (endocrinologist) and the remaining 95 (99.0%) by primary care physicians. All participants were initiated on 3 mg oral semaglutide. Median oral semaglutide exposure was 38.7 (IQR: 33.1; 42.1) weeks.

Glycaemic parameters and body weight

For the primary endpoint, a reduction in HbA_{1c} from 7.9% (63 mmol/mol) to 6.9% (52 mmol/mol) was observed from BL to EOS, with an estimated mean change of −0.9 (95% CI: −1.2; −0.6) percentage points ($p < 0.0001$) or −9.9 (95% CI: −13.1; −6.6) mmol/mol (**Figure 1**, Supplementary table S5). Secondary and sensitivity analyses were consistent with the primary analysis (Figure 1). A total of 86 participants had complete covariates and dependent variable information and were included in the primary analysis of mean change in body weight. Mean body weight decreased from BL to EOS (estimated mean change: −4.4 (95% CI: −5.4; −3.4) kg, −4.5 (95% CI: −5.5; −3.5)%; Supplementary table S5). At EOS, 66.7% and 50.7% of participants had HbA_{1c} < 7.0% (53 mmol/mol) or < 6.5% (48 mmol/mol), respectively, with 32.4% and 20.6% of participants achieving HbA_{1c} reduction ≥ 1.0 percentage points plus a body weight reduction of ≥ 3% or ≥ 5%, respectively (**Figure 2**).

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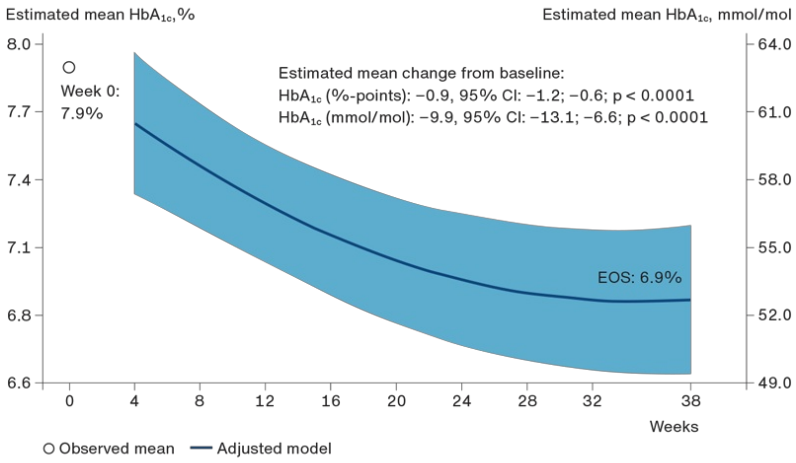
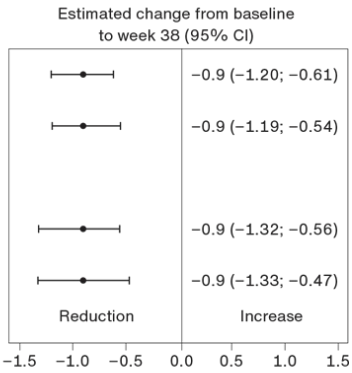
FIGURE 1 Primary endpoint: change in HbA_{1c} (%) from baseline to week 38 – secondary and sensitivity analyses. Full analysis set: all eligible patients who provided informed consent and initiated treatment with oral semaglutide. **A**. Estimated mean over time. **B**. Forest plot of estimated change. Data are from the in-study observation period, when participants were considered in the study regardless of potential discontinuation of oral semaglutide, and the on-treatment observation period, referring to the time period when participants were considered treated with oral semaglutide. At week 0, the observed mean HbA_{1c} at baseline for participants having at least one post-baseline assessment is plotted. Estimated HbA_{1c} change was analysed using an adjusted model, with baseline HbA_{1c}, age, baseline BMI, time and time-squared as covariates, and sex, oral antidiabetics at baseline, diabetes duration and site as fixed factors with random intercept and time (slope). The outer lines of the band represent 95% CI in A; estimates from the adjusted model along with 95% CI are plotted in B.

A



B

Group	n	Observed mean at baseline, %	Estimated mean at week 38, %
Primary (MMRM-In-study)	93	7.9	6.9
Secondary (MMRM-On-treatment)	89	7.9	6.9
Sensitivity (PMM-In-study)[a]	93	7.9	
Additional sensitivity (MMRM-In-study)[b]	63	7.9	6.9
Additional sensitivity (MMRM-On-treatment)[b]	59	7.9	6.9



EOS = end of study; MMRM = mixed model for repeated measures; PMM = pattern mixture model.
a) The PMM in-study sensitivity analysis was not carried out due to insufficient numbers of participants discontinuing treatment.
b) Participants with an EOS visit outside the EOS window were excluded from the analyses.

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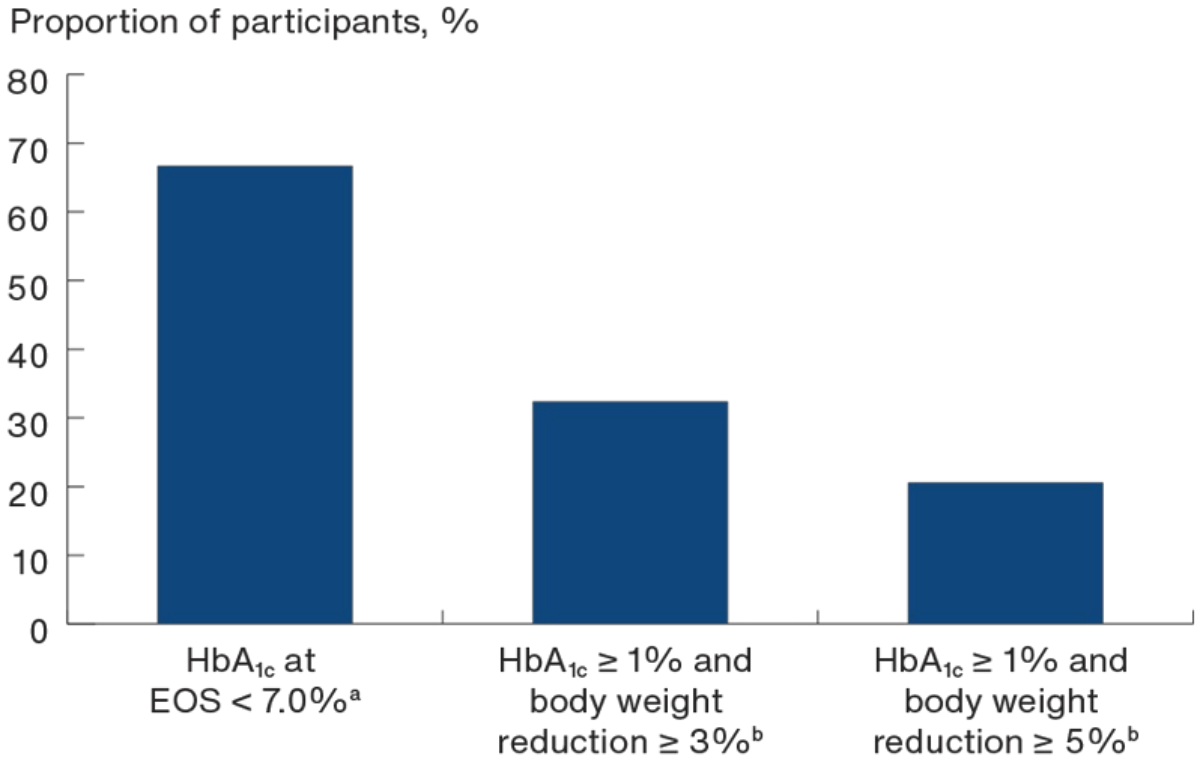
FIGURE 2 Secondary endpoint: proportion of participants reaching HbA_{1c} and body weight loss targets at EOS (in-study population). Data are from the in-study observation period, when participants were considered in the study regardless of potential discontinuation of oral semaglutide.



EOS = end of study.
a) n = 75.
b) n = 68.

Treatment satisfaction

Treatment satisfaction improved with oral semaglutide by EOS in DTSQs (absolute treatment satisfaction; estimated mean change from BL: 1.9 (95% CI: 0.22; 3.52) points) and DTSQc (relative treatment satisfaction; estimated mean change from BL: 10.5 (95% CI: 8.86; 12.23) points) scores (Supplementary table S5).

Exploratory endpoints

At EOS, 76 participants (79.2%) were treated with oral semaglutide: 13 (17.1%), 23 (30.3%) and 40 (52.6%) received 3, 7 and 14 mg, respectively. The mean dose was 10.0 (SD = 4.5) mg. A total of 12 (12.5%) participants had an additional/increased dose of glucose-lowering medications, and six (6.3%) ceased medication/decreased dose. The mean change in waist circumference from BL to EOS was −3.4 (SEM = 0.96; 95% CI: −5.33; −1.43) cm. Among treating physicians, oral semaglutide was considered a clinical success for 69 (73.4%) participants. There were

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no issues with self-reported severe hypoglycaemia.

Safety

Overall, 20 AEs were reported in 13 participants (13.5%); all except one AE were reported as mild or moderate in severity (**Table 2**). One serious AE, reported in a single participant (benign, malignant or unspecified neoplasm), resolved by EOS and was considered unrelated to oral semaglutide. Consistent with the GLP-1RA class safety profile, gastrointestinal disorders were most frequently reported, observed in 12 participants (12.5%). AEs led to oral semaglutide withdrawal in ten (10.4%) participants and a dose reduction in one participant (1.0%). No deaths were reported.

TABLE 2 Summary of adverse events of the full analysis set, i.e. all eligible patients who provided informed consent and initiated treatment with oral semaglutide.

	Adverse events								
	serious			non-serious			total		
	n (%)	E	R	n (%)	E	R	N (%)	E	R
Participants, n	96								
Adverse event									
Mild	0	-	-	6 (6.3)	8	10.9	6 (6.3)	8	10.9
Moderate	0	-	-	7 (7.3)	11	15.0	7 (7.3)	11	15.0
Severe	1 (1.0)	1	1.4	0	-	-	1 (1.0)	1	1.4
Subtotal[a]	1 (1.0)	1	1.4	13 (13.5)	19	25.9	13 (13.5)	20	27.3
Causality:									
Probable	0	-	-	11 (11.5)	14	19.1	11 (11.5)	14	19.1
Possible	0	-	-	2 (2.1)	3	4.1	2 (2.1)	3	4.1
Unlikely	1 (1.0)	1	1.4	2 (2.1)	2	2.7	3 (3.1)	3	4.1
Outcome:									
Recovered/resolved	1 (1.0)	1	1.4	10 (10.4)	13	17.7	11 (11.5)	14	19.1
Recovering/resolving	0	-	-	3 (3.1)	5	6.8	3 (3.1)	5	6.8
Not recovered/not resolved	0	-	-	1 (1.0)	1	1.4	1 (1.0)	1	1.4
Fatal	0	-	-	0	-	-	0	-	-
Unknown	0	-	-	0	-	-	0	-	-
Action taken:									
Drug interrupted	0	-	-	2 (2.1)	2	2.7	2 (2.1)	2	2.7
Drug withdrawn	0	-	-	10 (10.4)	12	16.4	10 (10.4)	12	16.4
Dose reduced	0	-	-	1 (1.0)	1	1.4	1 (1.0)	1	1.4
Dose increased	0	-	-	0	-	-	0	-	-
Dose not changed	1 (1.0)	1	1.4	3 (3.1)	4	5.5	3 (3.1)	5	6.8
Unknown	0	-	-	0	-	-	0	-	-
Adverse event by SOC and PT									
Gastrointestinal adverse event:									
Nausea	0	-	-	5 (5.2)	5	6.8	5 (5.2)	5	6.8
Diarrhoea	0	-	-	3 (3.1)	3	4.1	3 (3.1)	3	4.1
Constipation	0	-	-	2 (2.1)	3	4.1	2 (2.1)	3	4.1
Abdominal pain upper	0	-	-	2 (2.1)	2	2.7	2 (2.1)	2	2.7
Vomiting	0	-	-	2 (2.1)	2	2.7	2 (2.1)	2	2.7
Abdominal pain	0	-	-	1 (1.0)	1	1.4	1 (1.0)	1	1.4
Haematochezia	0	-	-	1 (1.0)	1	1.4	1 (1.0)	1	1.4
Subtotal[a]	0	-	-	12 (12.5)	17	23.2	12 (12.5)	17	23.2
Investigations	0	-	-	1 (1.0)	1	1.4	1 (1.0)	1	1.4
Neoplasms benign, malignant and unspecified, incl. cysts and polyps	1 (1.0)	1	1.4	0	-	-	1 (1.0)	1	1.4
Nervous system disorders	0	-	-	1 (1.0)	1	1.4	1 (1.0)	1	1.4

E = number of events; n/N = number of participants; PT = preferred term; R = event rate per 100 person-years; SOC = standard of care.
a) Some participants experienced > 1 adverse event.

Discussion

Use of oral semaglutide in Denmark was associated with clinically significant improvements in glycaemic control and body weight reduction in adults with T2D, the majority of whom were treated in primary care.

A reduction in HbA_{1c} of 0.9 percentage points was observed from BL to EOS. HbA_{1c} reductions for oral semaglutide 14 mg from the PIONEER programme ranged from 1.0 to 2.0 percentage points (treatment policy estimand) [12], and −1.0 (95% CI: −1.08; −0.97) percentage point from the PIONEER REAL pooled analysis [7]. The

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0.9 percentage point HbA_{1c} reduction reported here (BL: 7.9%) was greater than the 0.7 percentage point reduction (BL: ≥ 7% to < 8.0%) from the pooled analysis [7]. A similar 0.9 percentage point HbA_{1c} reduction was reported in the IGNITE study [13]. Similarly, the 4.4 kg weight loss observed here was in line with the PIONEER programme (~ 1.6-4.4 kg; treatment policy estimand) [12]. The −4.5% body weight reduction lies within the range in the PIONEER REAL studies (−4.2% to −7.2%) and is consistent with the pooled analysis [7]. The weight loss noted here may be partly due to lifestyle changes (diet optimisation and increased exercise) [14-16]. Weight loss related to uncontrolled T2D may have contributed. However, the degree of weight loss observed here exceeds that reported in lifestyle intervention studies in T2D (ranging from a weight reduction of 1.7 kg to 3.2 kg) [14, 16]. Additionally, age may impact weight loss, with higher age associated with greater and sustained weight loss following diabetes diagnosis [17]. As such, the weight loss seen here may result from a combination of factors, but it was most likely driven by the initiation of semaglutide. Treatment was considered a clinical success by the treating physician in almost three-quarters of participants; however, this is a subjective assessment that depends on individual glycaemic targets. The DTSQs and DTSQc supported physician evaluation, with treatment satisfaction improved at EOS.

Danish participants were almost exclusively from primary care, in contrast to previous PIONEER REAL studies that included individuals from secondary/specialist care. Approximately 35% were not receiving concomitant medication at BL. This does not reflect local labelling or local clinical practice at the time of the study. The reasons for this remain unknown. The relatively low proportion of participants not receiving concomitant medication at BL and the high proportion (67%) of individuals who reached HbA_{1c} < 7.0% by EOS indicate that the population was not highly dysregulated regarding T2D. Although 41% of participants had a medical history of CV-related conditions, hypertension (34%) and dyslipidaemia (17%) were most common. Therefore, this population presents limited CV disease risk factors as opposed to markers of established disease (e.g. heart failure, stroke or chronic kidney disease).

At EOS, 53% of participants were receiving the maximum approved oral semaglutide dose (14 mg). This proportion was similar to the PIONEER 7 trial (59%) at week 52, which, as a treat-to-target study, reflects clinical practice [18]. Here, the duration of diabetes was reported as ≥ 1 year in 78% of participants; however, 35% were not taking any glucose-lowering agents at BL. Metformin (62%) and SGLT2is (14%) were most commonly prescribed.

The tolerability profile of oral semaglutide was consistent with the phase 3 PIONEER trials, with no new safety concerns. Consistent with the GLP-1RA class, gastrointestinal AEs were most commonly reported (13% of participants), with the majority being mild to moderate. Treatment-emergent AEs led to oral semaglutide withdrawal in 10% of participants; within the range of 2-15% for the maintenance doses of 7 mg and 14 mg in phase 3 PIONEER trials [12]. A dose reduction occurred in one participant, indicating that oral semaglutide efficacy was high.

Study limitations include the observational, single-arm design, which cannot exclude alternative explanations for changes from BL in HbA_{1c} and other evaluated endpoints. The observed changes in HbA_{1c} may have been influenced by the clinical reason for initiating semaglutide (confounding by indication). Data collected through routine clinical practice versus compulsory prespecified assessments may impact the study's robustness and completeness. Challenges in enrolment at secondary sites and in secondary care settings resulted in fewer participants than planned, despite extending the enrolment period. Consequently, the study was not sufficiently powered to allow meaningful statistical significance analysis. However, assessment of the impact of a reduced participant number indicated that the data remain robust and acceptable for further interpretation.

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Conclusions

The PIONEER REAL programme provides insights into the efficacy of oral semaglutide and its use in clinical practice in adults with T2D. Despite low participant numbers, PIONEER REAL Denmark demonstrated improved glycaemic control and body weight loss in participants treated with oral semaglutide in primary care, reflecting real-world practice.

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Supplementary material https://content.ugeskriftet.dk/sites/default/files/2026-06/a06250520_supplementary.pdf

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