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Greater time spent with HbA1c less than 7.0% with oral semaglutide versus oral comparators: An exploratory analysis of the PIONEER studies

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Abstract

Aim: To assess how long participants with type 2 diabetes spent with HbA1c less than 7.0% and how likely they were to maintain this target with oral semaglutide 7 mg versus sitagliptin 100 mg or oral semaglutide 14 mg versus empagliflozin 25 mg, sitagliptin 100 mg or subcutaneous liraglutide 1.8 mg.

Materials and Methods: Analyses used on-treatment data without rescue medication for all randomized participants (semaglutide [approved maintenance doses], $n = 1880$; comparators [not including placebo], $n = 1412$). Duration of time with HbA1c less than 7.0% was calculated using an HbA1c time curve. A binary endpoint of achieving HbA1c less than 7.0% at weeks 26 (week 24 for PIONEER 7) and 52 of each trial (and week 78 for PIONEER 3) was analysed.

Results: Mean duration of time with HbA1c less than 7.0% was greater with oral semaglutide 7 mg versus sitagliptin in PIONEER 3 (27 vs. 22 weeks) and with oral semaglutide 14 mg versus empagliflozin and sitagliptin (27-34 vs. 19 vs. 22 weeks, respectively), and similar versus subcutaneous liraglutide. A greater proportion of participants achieved and maintained HbA1c less than 7.0% for more than 75% of the trial with oral semaglutide 14 mg versus oral comparators. The odds of achieving HbA1c less than 7.0% at weeks 24/26 and 52/78 were significantly greater with oral

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semaglutide 14 mg versus oral comparators or subcutaneous liraglutide, and with oral semaglutide 7 mg versus sitagliptin.

Conclusions: Oral semaglutide 7 and 14 mg resulted in greater time spent with HbA1c less than 7.0%, and a greater likelihood of achieving and maintaining HbA1c less than 7.0% versus oral comparators.

KEYWORDS

antidiabetic drug, GLP-1 analogue, glycaemic control, incretin therapy, semaglutide, type 2 diabetes

1 | INTRODUCTION

One of the main objectives for the management of type 2 diabetes is the achievement and maintenance of personalized HbA1c targets, applying a patient-centred approach that takes into consideration factors including the individual's lifestyle, key clinical characteristics and comorbidities.[1–3] A target HbA1c of less than 7.0% (< 53 mmol/mol) without significant hypoglycaemia is recommended for the majority of individuals with type 2 diabetes[2,4] and is important to reduce the risk of long-term microvascular complications such as nephropathy and retinopathy, and major cardiovascular disease.[5–8] Recent guidelines recommend choosing antihyperglycaemic medications, ideally with dual glucose-lowering and weight-loss efficacy and a low risk of hypoglycaemia.[1,2]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a key component of type 2 diabetes management, based on their potent glucose-lowering and body weight-loss effects.[1] The American Diabetes Association (ADA) and European Association for the Study of Diabetes recommend GLP-1RAs if HbA1c levels remain above the target of less than 7.0% (< 53 mmol/mol) and independent of HbA1c in people with established, or at high risk of, atherosclerotic cardiovascular disease.[1,2] Semaglutide is a GLP-1RA recognized for substantially improving HbA1c levels and reducing body weight, alongside proven cardiovascular benefits in individuals with atherosclerotic cardiovascular disease when administered subcutaneously.[1,2] Once-weekly subcutaneous semaglutide was approved in 2017 by the U.S. Food and Drug Administration (FDA) and in 2018 by the European Medicines Agency (EMA) for the treatment of adults with insufficiently controlled type 2 diabetes, to improve glycaemic control as an adjunct to diet and exercise.[9,10] Oral semaglutide was additionally approved as a once-daily oral formulation in 2019 by the FDA and in 2020 by the EMA.[11,12] Semaglutide is the first and only GLP-1RA available as an oral formulation, and offers an alternative for individuals who would prefer an oral route of semaglutide, instead of a once-weekly administration of subcutaneous semaglutide.[13,14] The global phase 3a PIONEER trials investigated the effect of oral semaglutide on glycaemic control in individuals with type 2 diabetes on a variety of different background regimens, versus active comparators and placebo.[15–21] In the PIONEER trials, consistently greater proportions of individuals were able to achieve the target HbA1c of less than 7.0% (< 53 mmol/mol) with oral semaglutide 14 mg or flexibly dosed (HbA1c < 7.0% achieved by 55%-77% of participants) versus placebo (7%-31% of participants) or oral comparators (sitagliptin [PIONEER 3 and 7] or empagliflozin [PIONEER 2]; 25%-40%) at week 26 (or week 52 for PIONEER 7).[15–22]

Conventional binary assessments of glycaemic control have historically been used in clinical trials, including in the PIONEER studies.[15–22] However, the amount of time participants spent with HbA1c less than 7.0% (< 53 mmol/mol), and how likely participants were to maintain this glycaemic target in efficacy trials of 52 weeks' duration or longer, have not previously been reported across the PIONEER clinical trial programme, or in fact across most randomized clinical trials assessing glucose-lowering treatments.

The present exploratory analysis using individual patient-level data was designed to assess whether individuals in the PIONEER 2-4 and 7 trials spent more time with HbA1c less than 7.0% (< 53 mmol/mol) and were more likely to maintain HbA1c less than 7.0% (< 53 mmol/mol) over time with oral semaglutide versus oral comparators empagliflozin (a sodium-glucose co-transporter-2 [SGLT2] inhibitor), sitagliptin (a dipeptidyl peptidase-4 inhibitor) or subcutaneous liraglutide (a once-daily GLP-1 analogue).

2 | MATERIALS AND METHODS

2.1 | Trial designs

The trial designs for PIONEER 2-4 and 7 have been reported previously.[17–20] In PIONEER 2 and 4, participants with uncontrolled type 2 diabetes were randomized to either oral semaglutide 14 mg ($n = 412$) or empagliflozin 25 mg ($n = 410$), and oral semaglutide 14 mg ($n = 285$), subcutaneous liraglutide 1.8 mg ($n = 284$) or placebo ($n = 142$, not included in this analysis), respectively. In PIONEER 3, such individuals were randomized to either oral semaglutide 3 mg ($n = 466$, not included in this analysis), 7 mg ($n = 465$) or 14 mg ($n = 465$), or sitagliptin 100 mg ($n = 467$). In PIONEER 7, they were randomized to either sitagliptin 100 mg ($n = 251$) or oral semaglutide (flexibly dosed; $n = 253$); the latter group was initiated at semaglutide 3 mg until week 8 and thereafter the dose could be adjusted up or down every 8 weeks depending on their HbA1c level (< 7.0% or ≥ 7.0%) and experience of gastrointestinal adverse events. Trial durations were 52 weeks for PIONEER 2, 4 and 7, and 78 weeks for PIONEER 3.

Background medication included metformin alone for PIONEER 2, metformin with or without a sulphonylurea for PIONEER 3, metformin with or without an SGLT2 inhibitor for PIONEER 4, and one or two oral glucose-lowering drugs (metformin, a sulphonylurea, an SGLT2 inhibitor or a thiazolidinedione) for PIONEER 7.

2.2 | Endpoints and assessments

2.2.1 | Efficacy

The mean and median durations (weeks) of time spent with HbA1c less than 7.0% (< 53 mmol/mol) were assessed for PIONEER 2-4 and 7. Weeks spent with HbA1c less than 7.0% (< 53 mmol/mol) were not necessarily consecutive for each individual. Estimated odds ratios were calculated for achieving HbA1c less than 7.0% (< 53 mmol/mol) at both week 26 and week 52 for PIONEER 2 and 4; week 24 and week 52 for PIONEER 7 (week 26 data for PIONEER 7 were unavailable so week 24 data were used instead); and week 26, week 52 and week 78 for PIONEER 3.

For each trial, the proportion of individuals achieving HbA1c less than 7.0% (< 53 mmol/mol) was assessed for the following duration categories: no achievement of HbA1c less than 7.0% (< 53 mmol/mol), and > 0%-≤ 25%, > 25%-≤ 50%, > 50%-≤ 75% and > 75%-≤ 100% of the trial duration with HbA1c less than 7.0% (< 53 mmol/mol).

Mean change (kg) in body weight from baseline to end of treatment (week 52 for PIONEER 2-4 and week 78 for PIONEER 7) by HbA1c less than 7.0% (< 53 mmol/mol) duration category was assessed for each trial.

Study visits were scheduled at weeks 0, 4, 8 and then for every 6 weeks up to week 52 for PIONEER 2 and 4, or up to week 78 for PIONEER 3, and approximately every 8 weeks up to week 52 for PIONEER 7. HbA1c and body weight were measured at each study visit.

2.2.2 | Safety

For PIONEER 2-4 and 7, the number and proportion of participants with on-treatment severe or blood glucose-confirmed symptomatic hypoglycaemic episodes, or ADA 2013-classified hypoglycaemic and severe hypoglycaemic episodes, were assessed by HbA1c less than 7.0% (< 53 mmol/mol) duration category. A glucose value was to be self-measured and recorded using a blood glucose monitor if a hypoglycaemic episode was suspected.

2.3 | Statistical analysis

Outcomes were evaluated using the on-treatment without rescue medication observation period, in all randomized participants. For each participant, time in control (HbA1c < 7.0% [< 53 mmol/mol]) was calculated in two steps. First, the HbA1c measurements taken at the regular study visits were used to derive a continuous HbA1c time curve, using linear interpolation between two consecutive visits. Second, time in control was calculated as the sum of all the time intervals when the HbA1c time curve was less than the 7.0% (< 53 mmol/mol) limit. Participants who discontinued treatment early, or who used rescue medication, were considered not in control after discontinuation or initiation of rescue medication.

The binary endpoint achievement of HbA1c less than 7.0% (< 53 mmol/mol) at week 26 (week 24 for PIONEER 7) and week 52 (and week 78 for PIONEER 3) was analysed using a logistic regression model, with treatment, strata (except for PIONEER 2) and region as categorical fixed effects and baseline value as covariate for each of the 1000 imputed complete datasets, and pooled by Rubin's rule to draw inference. Missing values for continuous endpoints that enter the binary endpoint were imputed using an analysis of covariance-based sequential multiple imputation model and the categorical endpoint derived from there.

Body weight data were summarized using descriptive statistics only.

3 | RESULTS

3.1 | Demographics and baseline characteristics

Baseline characteristics were comparable between the PIONEER 2-4 and 7 trials, with similar mean age, HbA1c, body weight and duration of diabetes at baseline between all treatment arms (Table 1). Mean baseline HbA1c ranged from 8.0% to 8.4% (64-68 mmol/mol). Mean duration of diabetes at baseline ranged from 7.2 to 9.0 years.

3.2 | Duration of time spent with HbA1c less than 7.0% (< 53 mmol/mol)

In PIONEER 2 and 3, the mean duration of time spent with HbA1c less than 7.0% (< 53 mmol/mol) was greater for oral semaglutide 14 mg versus empagliflozin 25 mg (27 vs. 19 weeks) and sitagliptin 100 mg (34 vs. 22 weeks; Table 2). The median duration of time spent with HbA1c less than 7.0% (< 53 mmol/mol) was also greater with oral semaglutide 14 mg (33-34 weeks) than with oral comparators empagliflozin 25 mg (11 weeks) and sitagliptin 100 mg (3 weeks; Table 2). In PIONEER 3, the mean and median durations of time spent with HbA1c less than 7.0% (< 53 mmol/mol) were also longer with oral semaglutide 7 mg compared with sitagliptin 100 mg (27 vs. 22 weeks, and 15 vs. 3 weeks, respectively; Table 2). Similarly, in PIONEER 7, patients treated with oral semaglutide flexibly dosed (of whom 59% were on 14 mg, 30% on 7 mg and 9% on 3 mg at 52 weeks)[17] had greater mean and median durations of time spent with HbA1c less than 7.0% (< 53 mmol/mol) compared with sitagliptin 100 mg (22 vs. 13 weeks, and 26 vs. 0 weeks, respectively). In PIONEER 4, the mean and median durations of time spent with HbA1c less than 7.0% (< 53 mmol/mol) were similar between oral semaglutide 14 mg and subcutaneous liraglutide 1.8 mg (27 vs. 28 weeks, and 34 vs. 37 weeks, respectively; Table 2).

TABLE 1 Demographics and baseline characteristics.

Trial	Treatment arm	Randomized participants, *N*	Age, years	Female, *n* (%)	HbA1c, %|mmol/mol	Body weight, kg	Duration of diabetes, years
PIONEER 2[19]	Oral semaglutide 14 mg	412	57 ± 10	205 (50)	8.1 ± 0.9|65 ± 10	91.9 ± 20.5	7.2 ± 5.8
	Empagliflozin 25 mg	410	58 ± 10	201 (49)	8.1 ± 0.9|65 ± 10	91.3 ± 20.1	7.7 ± 6.3
PIONEER 3[20]	Oral semaglutide 14 mg	465	57 ± 10	218 (47)	8.3 ± 0.9|67 ± 10	91.2 ± 21.7	8.7 ± 6.1
	Oral semaglutide 7 mg	465	58 ± 10	220 (47)	8.4 ± 1.0|68 ± 10	91.3 ± 20.8	8.3 ± 5.8
	Sitagliptin 100 mg	467	58 ± 10	229 (49)	8.3 ± 0.9|67 ± 10	90.9 ± 21.0	8.8 ± 6.0
PIONEER 4[18]	Oral semaglutide 14 mg	285	56 ± 10	138 (48)	8.0 ± 0.7|64 ± 8	92.9 ± 20.6	7.8 ± 5.7
	Liraglutide 1.8 mg	284	56 ± 10	135 (48)	8.0 ± 0.7|64 ± 7	95.5 ± 21.9	7.3 ± 5.3
PIONEER 7[17]	Oral semaglutide flexibly dosed	253	57 ± 10	108 (43)	8.3 ± 0.6|67 ± 6	88.9 ± 19.6	8.6 ± 6.3
	Sitagliptin 100 mg	251	58 ± 10	111 (44)	8.3 ± 0.6|67 ± 7	88.4 ± 20.1	9.0 ± 6.2

Note: Data are mean ± standard deviation unless otherwise indicated.

TABLE 2 Mean and median durations of time spent with HbA1c less than 7.0% (< 53 mmol/mol).

Trial	Treatment arm	*N*	Mean (± SD) duration of time spent with HbA1c < 7.0% (< 53 mmol/mol), weeks	Median duration of time spent with HbA1c < 7.0% (< 53 mmol/mol), weeks	EOR of achieving HbA1c < 7.0% (< 53 mmol/mol) at weeks 26[a] and 52[b] versus comparator, EOR (95% CI); *P* value
PIONEER 2	Oral semaglutide 14 mg	411	26.6 ± 19.7	33.7	4.12 (2.94-5.76); *P* < .0001
	Empagliflozin 25 mg	410	19.0 ± 19.9	10.9	
PIONEER 3	Oral semaglutide 14 mg	465	34.3 ± 28.9	32.8	3.83 (2.70-5.43); *P* < .0001
	Oral semaglutide 7 mg	465	27.2 ± 29.6	15.1	2.15 (1.50-3.08); *P* < .0001
	Sitagliptin 100 mg	467	21.9 ± 27.8	3.0	
PIONEER 4	Oral semaglutide 14 mg	285	27.0 ± 19.6	33.5	1.58 (1.08-2.29); *P* = .0172
	Liraglutide 1.8 mg	284	27.9 ± 20.6	36.5	
PIONEER 7	Oral semaglutide flexibly dosed	253	22.2 ± 17.4	26.3	6.41 (3.93-10.46); *P* < .0001
	Sitagliptin 100 mg	251	12.8 ± 16.7	0.0	

Note: Data are for the on-treatment without rescue medication period.
Abbreviations: CI, confidence interval; EOR, estimated odds ratio; SD, standard deviation.
[a]Week 24 for PIONEER 7.
[b]And week 78 for PIONEER 3.

Participants treated with oral semaglutide 14 mg in PIONEER 2-4, or flexibly dosed in PIONEER 7, were significantly more likely to achieve HbA1c less than 7.0% (< 53 mmol/mol) at weeks 24/26 and week 52 (and week 78 for PIONEER 3), respectively, than those treated with empagliflozin 25 mg, sitagliptin 100 mg or subcutaneous liraglutide 1.8 mg (Table 2).

In PIONEER 3, participants treated with oral semaglutide 7 mg were also more likely to achieve HbA1c less than 7.0% (< 53 mmol/mol) at weeks 26, 52 and 78 than those treated with sitagliptin 100 mg (Table 2).

In PIONEER 2, greater proportions of participants receiving oral semaglutide 14 mg were able to achieve and maintain HbA1c less than 7.0% (< 53 mmol/mol) for more than 75% of the trial duration versus empagliflozin 25 mg (42% vs. 26%, respectively; Figure 1A). Across PIONEER 3 and 7, greater proportions of participants receiving oral semaglutide 7 mg, 14 mg or flexibly dosed also achieved and maintained HbA1c less than 7.0% (< 53 mmol/mol) for more than 75% of the trial duration versus sitagliptin 100 mg (PIONEER 3: 25% [7 mg] and 34% [14 mg] vs. 18%, respectively; Figure 1B; PIONEER 7: 22% vs. 13%, respectively; Figure 1D). In PIONEER 4, similar proportions of participants were able to achieve and maintain HbA1c less than 7.0% (< 53 mmol/mol) for more than 75% of the trial duration on oral semaglutide 14 mg versus subcutaneous liraglutide 1.8 mg (43% vs. 47%, respectively; Figure 1C).

3.3 | Body weight change by duration of time spent with HbA1c less than 7.0% (< 53 mmol/mol)

Mean change from baseline in body weight at end of treatment, by time spent (% of trial duration) with HbA1c less than 7.0% (< 53 mmol/mol), is shown for PIONEER 2-4 and 7 in Figure 2.

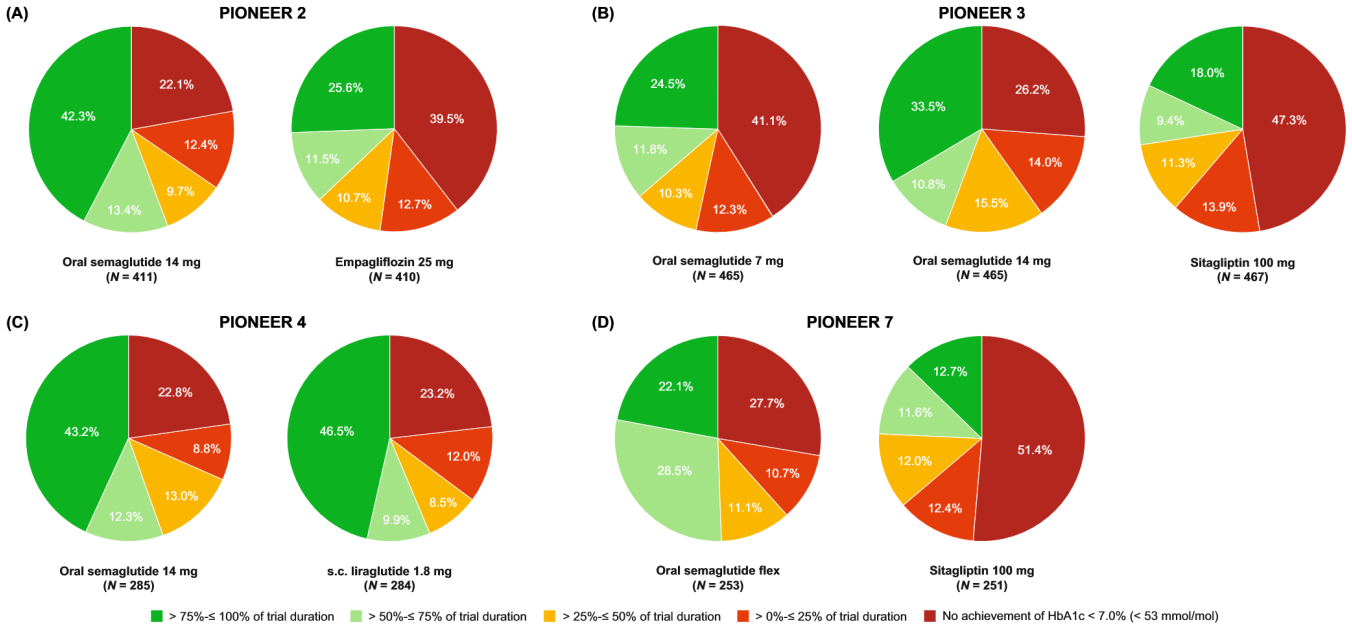

FIGURE 1 Proportion of participants by time spent (% of trial duration) with HbA1c less than 7.0% (< 53 mmol/mol) in A, PIONEER 2; B, PIONEER 3; C, PIONEER 4; and D, PIONEER 7. The trial duration was 52 weeks for PIONEER 2, 4 and 7, and 78 weeks for PIONEER 3. Data are for the on-treatment without rescue medication period. flex, flexibly dosed; s.c., subcutaneous.

For oral semaglutide, participants who spent most time (> 50-≤ 75% or > 75% of trial duration) with HbA1c less than 7.0% (< 53 mmol/mol) had greater body weight loss from baseline to the end of treatment than participants who spent less time with HbA1c less than 7.0% (< 53 mmol/mol; 0%, > 0%-≤ 25% or > 25%-≤ 50%) (Figure 2).

3.4 | Safety

Across all trials, the proportion of participants who reported at least one severe or blood glucose-confirmed symptomatic hypoglycaemic episode was 5% for oral semaglutide 7 mg, 1%-8% for oral semaglutide 14 mg, 6% for oral semaglutide flexibly dosed, 2% for empagliflozin 25 mg, 6%-8% for sitagliptin 100 mg and 2% for subcutaneous liraglutide 1.8 mg (Table S1). The proportion of participants with severe or blood glucose-confirmed symptomatic hypoglycaemic episodes was very low across all duration categories of time with HbA1c less than 7.0% (< 53 mmol/mol) (Table S1).

ADA-classified severe (level 3) hypoglycaemic episodes occurred in less than 1% of participants treated with oral semaglutide (3, 7, 14 mg or flexibly dosed), empagliflozin 25 mg, sitagliptin 100 mg or subcutaneous liraglutide 1.8 mg across PIONEER 2-4 and 7 (Table S1).

4 | DISCUSSION

These exploratory analyses show that, in PIONEER 2, 3 and 7, treatment with oral semaglutide 7 mg, 14 mg or flexibly dosed resulted in greater time spent with HbA1c less than 7.0% (< 53 mmol/mol) over 52 weeks (78 weeks for PIONEER 3) and a greater likelihood of maintaining HbA1c less than 7.0% (< 53 mmol/mol) over time versus oral comparators. To the best of our knowledge, the current analysis is the first of its kind to investigate the achievement and maintenance of HbA1c less than 7.0% (< 53 mmol/mol) over the whole trial period, and is a useful approach for assessing glucose control that can be utilized across other clinical trials.

The PIONEER phase 3a trials showed that significantly greater proportions of individuals treated with oral semaglutide achieved conventional binary assessments (such as HbA1c < 7.0% [< 53 mmol/mol] and body weight loss ≥ 5% or ≥ 10% at week 26 or week 52) versus comparators.[15–17,19–22]

Maintaining intensive glycaemic control is important to prevent long-term type 2 diabetes-related complications.[5–8] Despite guideline recommendations to maintain HbA1c less than 7.0% (< 53 mmol/mol), treatment inertia means that many individuals with type 2 diabetes do not have their treatment intensified and remain on suboptimal HbA1c levels.[23] An oral GLP-1RA, such as semaglutide, may facilitate acceptance for the earlier use of this class of agents. By allowing HbA1c to be maintained at lower levels over longer periods, oral semaglutide may lead to better long-term outcomes for individuals with type 2 diabetes. However, this requires investigation in further studies.

Although subcutaneously administered glucose-lowering treatments typically show greater efficacy than orally administered alternatives,[15,19,20,24–26] in PIONEER 4, individuals on oral semaglutide 14 mg spent a similar amount of time with HbA1c less than 7.0% (< 53 mmol/mol) versus those on subcutaneous liraglutide 1.8 mg, despite a longer dose-escalation period for oral semaglutide.[18] Liraglutide has previously been shown to maintain adequate glycaemic

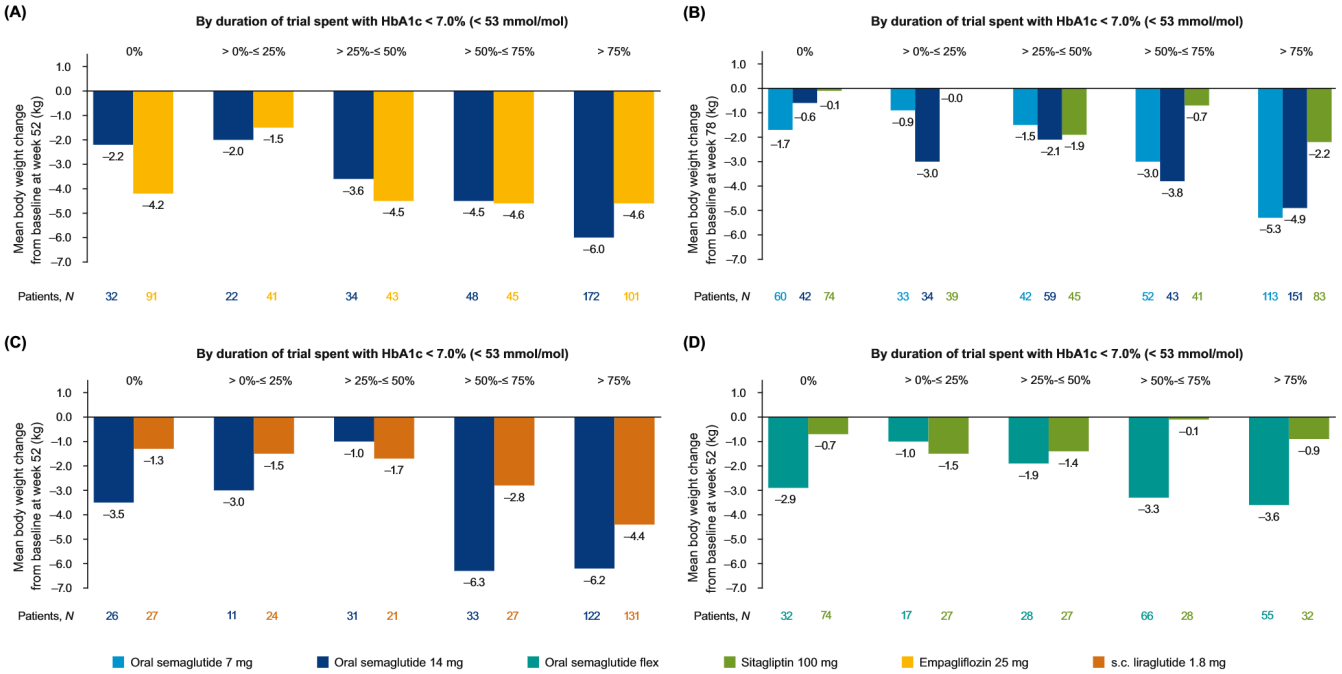

FIGURE 2 Change from baseline in body weight at end of trial by time spent (% of trial duration) with HbA1c less than 7.0% (< 53 mmol/mol) in A, PIONEER 2; B, PIONEER 3; C, PIONEER 4; and D, PIONEER 7. The trial duration was 52 weeks for PIONEER 2, 4 and 7, and 78 weeks for PIONEER 3. Data are for the on-treatment without rescue medication period. flex, flexibly dosed; s.c., subcutaneous.

control (HbA1c < 7.0% [< 53 mmol/mol]) for longer periods than oral antihyperglycaemic drugs, all added on to metformin.[27] The GRADE study, which compared four antihyperglycaemic medications in more than 5000 individuals with type 2 diabetes, found that liraglutide and basal insulin—prescribed and adjusted according to their labelling—were more effective at maintaining glycaemic control than sitagliptin and glimepiride, a sulphonylurea.[28]

In our analysis, individuals on oral semaglutide (7 mg, 14 mg or flexibly dosed) who spent a greater proportion of the trial with HbA1c less than 7.0% (< 53 mmol/mol) tended to have greater body weight loss than those who spent less time with HbA1c less than 7.0% (< 53 mmol/mol). Given that weight loss can lead to a reduction in insulin resistance and a subsequent improvement in glycaemic control,[29,30] the fact that participants who maintained glycaemic control were likely to have a greater body weight loss was an anticipated effect.

The incidence of severe or blood glucose-confirmed symptomatic hypoglycaemic episodes was similarly low across all four PIONEER trials in this analysis. Indeed, the rate of hypoglycaemic episodes in individuals treated with oral semaglutide 14 mg is considered low throughout the PIONEER phase 3a trials and across all categories of time in glycaemic control.

The use of patient-level data, with HbA1c assessed on an individual basis at each time point, is a key strength of this study. However, the limitations of the study include that the number of weeks spent with HbA1c less than 7.0% (< 53 mmol/mol) was not necessarily consecutive for each individual, and this approach does not allow us to investigate all time points continuously during the trial at which HbA1c less than 7.0% (< 53 mmol/mol) was achieved. Furthermore, the individual HbA1c time curves were approximated, as HbA1c was measured every 6 or 8 weeks. In addition, analysis of oral semaglutide 7 mg was based on one study only (PIONEER 3), and did not include the 30% of patients within the oral semaglutide flexibly dosed arm of PIONEER 7 who were on the 7 mg dose at the end of the study. It should also be noted that the number of individuals was low in some subgroups and so the data should be interpreted with caution.

In conclusion, treatment with oral semaglutide 7 mg, 14 mg or flexibly dosed resulted in greater time spent with HbA1c less than 7.0% (< 53 mmol/mol) and a greater likelihood of maintaining HbA1c less than 7.0% (< 53 mmol/mol) versus oral comparators (empagliflozin and sitagliptin). Time spent with HbA1c less than 7.0% (< 53 mmol/mol) was also similar between oral semaglutide 14 mg and the subcutaneous comparator, liraglutide. These outcomes were achieved alongside the additional benefit of weight loss, without an increase in hypoglycaemic episodes. This analysis provides evidence that progressive loss of glycaemic control can be delayed, and a mean level of HbA1c can be maintained at less than 7.0% (< 53 mmol/mol) for a longer period of time with oral semaglutide, compared with empagliflozin 25 mg and sitagliptin 100 mg.

AUTHOR CONTRIBUTIONS

JR, BC, JE, GF, MSK, EM and FKK analysed the data, contributed to the discussion, and wrote, reviewed and edited the manuscript. All the authors approved the manuscript for submission. JE is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

Julio Rosenstock: Has served on advisory panels for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Hanmi, Intarcia, Novo Nordisk, Oramed, Sanofi, Structure Therapeutics, Terns Pharmaceuticals and Zealand Pharma; and has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, Hanmi, Intarcia, Merck, Novartis, Novo Nordisk, Oramed, Pfizer and Sanofi. Bertrand Cariou: Reports grants and lecturing/consulting fees from Amgen and Sanofi; and lecturing/consulting fees from Akcea, AstraZeneca, Eli Lilly, Gilead, LVL, Novartis, Novo Nordisk and Pfizer. Johanna Eliasson: Employee of Novo Nordisk A/S. Guillaume Frappin: Employee of Novo Nordisk A/S. Margit S. Kaltoft: Employee of Novo Nordisk A/S and shareholder in Novo Nordisk A/S. Eduard Montanya: Reports serving on scientific advisory boards for, consulting for, lecturing for and/or receiving research grants from Menarini, MSD, Novo Nordisk, Roche and Sanofi. Filip K. Knop: Reports consulting for Carmot Therapeutics, Eli Lilly, Novo Nordisk, Structure Therapeutics and Zucara; receiving grants from AstraZeneca, Boehringer Ingelheim, Gubra, Novo Nordisk, Sanofi and Zealand Pharma; receiving honoraria from AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, MSD/Merck, Mundipharma, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma and Zucara; receiving lecturing/other fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD/Merck, Mundipharma, Novo Nordisk and Sanofi; and receiving non-financial support from AstraZeneca, Mundipharma, Novo Nordisk and Sanofi. Also a stock/shareholder in Antag Therapeutics.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15339.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed in the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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