ORIGINAL ARTICLE

Efficacy and safety of oral semaglutide by subgroups of patient characteristics in the PIONEER phase 3 programme

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Abstract

Aims: To evaluate the efficacy and safety of oral semaglutide versus comparators by patient characteristic subgroups in patients with type 2 diabetes.

Materials and Methods: Change from baseline in glycated haemoglobin (HbA1c) and body weight, and achievement of HbA1c <7.0% with oral semaglutide 7 mg, oral semaglutide 14 mg, flexibly dosed oral semaglutide (flex) and comparators were assessed across baseline subgroups (age, race, ethnicity, diabetes duration, body mass index and HbA1c) from the PIONEER programme. Treatment differences were analysed using a mixed model for repeated measurements for continuous variables and a logistic regression model for the binary endpoint. Pooled safety data were analysed descriptively.

Results: Changes from baseline in HbA1c and body weight, and the odds of achieving HbA1c <7.0%, were greater with oral semaglutide 14 mg/flex (n = 1934) and higher or similar with oral semaglutide 7 mg (n = 823) versus comparators (n = 2077) across most subgroups. Changes in HbA1c with oral semaglutide 14 mg/flex were greater for patients with higher baseline HbA1c (HbA1c >9.0%: −1.7% to −2.6%; HbA1c <8.0%: −0.7% to −1.2%). In some trials, Asian patients experienced greater HbA1c reductions with oral semaglutide 14 mg/flex (−1.5% to −1.8%) than other racial groups (−0.6% to −1.6%). The overall incidence of adverse events (AEs) with oral semaglutide was similar to that with comparators and was consistent across subgroups. More gastrointestinal AEs were observed with oral semaglutide, versus comparators, across subgroups.

Conclusions: Oral semaglutide demonstrated consistently greater HbA1c and body weight reductions across a range of patient characteristics, with greater HbA1c reductions seen at higher baseline HbA1c levels.

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

1 | INTRODUCTION

Current guidelines emphasize the need for a patient-centric approach in type 2 diabetes (T2D), with treatment individualized to a patient's clinical characteristics.[1,2] The efficacy and safety response to a diabetes therapy may vary according to patient characteristics, such as age, body mass index (BMI) and race, as well as indicators of disease status, such as glycated haemoglobin (HbA1c) and duration of disease.[3-7] Clinical trials often enrol patient populations with a broad range of characteristics and provide mean data for the whole population studied. However, each patient a physician sees is an individual and is rarely, if ever, representative of the mean. It is, therefore, important to understand how different patients may respond to new therapies so that physicians can better understand what response to expect and thereby have better informed conversations with individual patients. Analyses of trials according to patient characteristic subgroups can help to inform physicians on how the efficacy and safety of therapies might vary in patients with different clinical characteristics.

Oral semaglutide is the first glucagon-like peptide-1 analogue available in a tablet that has been approved in Europe, Japan and the United States for the treatment of T2D.[8-10] The efficacy and safety of oral semaglutide have been established in patients with T2D in the global phase 3a PIONEER programme.[11-18] To provide physicians with data to support the decision-making process and to better understand what responses they might expect with oral semaglutide in different patient groups, a comprehensive exploratory analysis of the PIONEER programme detailing the glycaemic and weight loss efficacy, and safety of oral semaglutide versus comparators by patient subgroups was conducted.

2 | MATERIALS AND METHODS

2.1 | Trial designs

The design of trials within the global PIONEER phase 3a programme have been reported previously.[11-17] The PIONEER efficacy trials (PIONEER 1–5, 7 and 8) were used for the present analyses; PIONEER 6 was a cardiovascular (CV) outcomes trial[18] and was, therefore, not included in the subgroup analyses.

PIONEER 1, 4, 5 and 8 were placebo-controlled trials and PIONEER 2, 3, 4 and 7 were active-controlled trials (empagliflozin, sitagliptin or liraglutide; Table S1). PIONEER 1, 3 and 8 investigated three once-daily doses of oral semaglutide (3, 7 and 14 mg), PIONEER 2, 4 and 5 assessed oral semaglutide 14 mg, and PIONEER 7 employed a flexible dose adjustment approach (flex), where the dose could be increased or decreased according to predefined efficacy or tolerability criteria. Here, we report oral semaglutide 14 mg/flex data (with 7 mg data in Appendix S1). The 3 mg dose is for the purposes of dose escalation and is not a maintenance dose,[8,9] and was therefore not included in the analysis. Treatment durations were 26 weeks for PIONEER 1 and 5, 52 weeks for PIONEER 2, 4, 7 and 8 and 78 weeks for PIONEER 3.

The trials were performed according to relevant local regulatory guidance, and complied with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice.

For further details on the primary endpoint and patient populations in the PIONEER trials, please refer to Table S1.

2.2 | Subgroup analyses

All patients receiving oral semaglutide 7 or 14 mg (PIONEER 1–5 and 8), flex (PIONEER 7) or comparators were included in the subgroup analyses. Subgroup analyses were conducted for the following endpoints:

- Change from baseline in HbA1c to end of treatment
- Change from baseline in body weight to end of treatment
- Achievement of HbA1c <7.0% at end of treatment.

The PIONEER programme employed two estimands, which have been described in detail elsewhere.[11] Efficacy data for the trial product estimand (on trial product without rescue medication dataset) from the PIONEER 1–5, 7 and 8 trials were analysed for the following subgroups:

- Age: <45 years, ≥45 to <65 years, and ≥65 years
- Race: White, Black/African American, and Asian
- Ethnicity: Hispanic/Latino and non-Hispanic/Latino
- Diabetes duration: <5 years, ≥5 to <10 years, and ≥10 years
- BMI: <25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 to <35 kg/m^2, and ≥35 kg/m^2
- Baseline HbA1c: ≤8%, >8 to ≤9%, and >9%.

Due to the low numbers of some racial and ethnic subgroups in PIONEER 5, this trial was excluded from the racial and ethnic efficacy subgroup analyses.

2.3 | Statistical analyses

Data on the changes from baseline in HbA1c and body weight were analysed using a mixed model for repeated measurements, with treatment, region, strata (PIONEER 3–8), subgroup, interaction strata (PIONEER 5 and 8) and interaction between treatment and subgroup as categorical fixed effects and baseline value as covariate, all nested within visit and an unstructured residual covariance matrix.

The binary endpoint (achievement of HbA1c <7.0%) was analysed using a logistic regression model with treatment, region, strata (PIONEER 3–8), subgroup, interaction strata (PIONEER 5 and 8) and interaction between treatment and subgroup 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

TABLE 1 Baseline characteristics by study and subgroup

Trial	Subgroup	Patients, N	Mean age, y	Mean duration of diabetes, y	Mean HbA1c, %	Mean body weight, kg
Age						
PIONEER 1	<45 years	130	38	1.8	8.0	99.9
	≥45–<65 years	430	55	3.2	8.0	87.7
	≥65 years	143	69	6.2	7.8	78.7
PIONEER 2	<45 years	94	40	4.1	8.4	101.1
	≥45–<65 years	512	56	6.6	8.2	92.3
	≥65 years	215	69	10.8	7.9	85.9
PIONEER 3	<45 years	183	39	4.8	8.4	102.1
	≥45–<65 years	1179	56	8.2	8.4	91.7
	≥65 years	501	69	11.0	8.1	86.2
PIONEER 4	<45 years	86	40	5.3	8.1	100.5
	≥45–<65 years	475	55	7.0	8.0	94.9
	≥65 years	150	69	10.9	7.8	87.5
PIONEER 5	<45 years	–	–	–	–	–
	≥45–<65 years	65	59	11.1	8.0	102.7
	≥65 years	259	73	14.7	8.0	87.8
PIONEER 7	<45 years	46	39	4.9	8.3	90.7
	≥45–<65 years	321	55	8.0	8.3	90.6
	≥65 years	137	69	11.8	8.2	83.5
PIONEER 8	<45 years	43	40	9.5	8.3	88.5
	≥45–<65 years	410	57	13.2	8.2	88.9
	≥65 years	278	70	18.6	8.1	81.1
Race						
PIONEER 1	White	262	52	2.4	7.9	93.0
	Black/AA	20	59	3.6	7.6	92.2
	Asian	60	59	7.6	8.0	67.2
PIONEER 2	White	708	58	7.5	8.1	92.1
	Black/AA	59	55	6.9	8.4	97.0
	Asian	49	54	7.3	8.2	77.4
PIONEER 3	White	650	58	8.6	8.2	94.4
	Black/AA	84	56	7.6	8.3	94.9
	Asian	120	57	11.0	8.2	73.4
PIONEER 4	White	519	57	7.5	8.0	98.0
	Black/AA	29	54	8.7	8.1	96.8
	Asian	94	53	8.3	8.0	79.0
PIONEER 7	White	381	57	8.2	8.3	91.8
	Black/AA	47	60	9.9	8.4	91.5
	Asian	72	57	11.8	8.2	71.2
PIONEER 8	White	192	62	13.5	8.2	92.7
	Black/AA	24	59	14.1	8.3	98.6
	Asian	131	59	15.3	8.2	71.0
Ethnicity						
PIONEER 1	Hispanic/Latino	97	51	2.5	8.0	85.2
	Non-Hispanic/Latino	243	55	3.8	7.9	89.9
PIONEER 2	Hispanic/Latino	199	56	7.9	8.3	85.9
	Non-Hispanic/Latino	622	58	7.3	8.1	93.4

TABLE 1 (Continued)

Trial	Subgroup	Patients, N	Mean age, y	Mean duration of diabetes, y	Mean HbA1c, %	Mean body weight, kg
PIONEER 3	Hispanic/Latino	168	55	9.0	8.4	84.4
	Non-Hispanic/Latino	743	58	8.8	8.2	92.4
PIONEER 4	Hispanic/Latino	40	56	9.6	8.0	86.2
	Non-Hispanic/Latino	671	56	7.5	8.0	94.5
PIONEER 7	Hispanic/Latino	105	56	8.7	8.4	86.4
	Non-Hispanic/Latino	399	58	8.8	8.3	89.2
PIONEER 8	Hispanic/Latino	55	61	13.0	8.3	82.4
	Non-Hispanic/Latino	293	61	14.4	8.2	85.5
Duration of diabetes						
PIONEER 1	<5 years	529	53	1.3	7.9	90.9
	≥5–<10 years	108	58	7.1	7.9	82.2
	≥10 years	66	62	15.7	8.0	75.8
PIONEER 2	<5 years	347	54	2.6	8.1	96.3
	≥5–<10 years	274	58	7.4	8.1	90.3
	≥10 years	200	63	15.8	8.2	85.3
PIONEER 3	<5 years	577	54	2.8	8.2	96.5
	≥5–<10 years	687	58	7.5	8.3	91.1
	≥10 years	599	62	15.5	8.3	86.3
PIONEER 4	<5 years	278	54	2.6	7.9	96.5
	≥5–<10 years	238	55	7.5	8.1	95.1
	≥10 years	195	61	14.7	7.9	89.0
PIONEER 5	<5 years	30	69	3.6	7.9	95.4
	≥5–<10 years	82	69	7.5	7.9	92.9
	≥10 years	212	71	18.0	8.0	89.4
PIONEER 7	<5 years	168	53	2.9	8.3	94.6
	≥5–<10 years	153	57	7.4	8.3	88.6
	≥10 years	183	61	15.4	8.3	83.3
PIONEER 8	<5 years	69	55	3.3	8.2	92.1
	≥5–<10 years	145	57	7.8	8.2	87.1
	≥10 years	517	62	18.6	8.2	84.7
Baseline BMI						
PIONEER 1	<25 kg/m^2	95	61	7.5	8.0	60.6
	≥25–<30 kg/m^2	198	56	3.3	8.0	76.1
	≥30–<35 kg/m^2	223	54	2.6	8.0	90.3
	≥35 kg/m^2	187	50	2.9	7.9	112.3
PIONEER 2	<25 kg/m^2	52	58	9.6	8.2	68.0
	≥25–<30 kg/m^2	241	60	8.6	8.1	76.6
	≥30–<35 kg/m^2	265	58	7.2	8.2	90.6
	≥35 kg/m^2	262	56	6.2	8.2	111.0
PIONEER 3	<25 kg/m^2	185	61	11.2	8.2	62.8
	≥25–<30 kg/m^2	532	60	9.6	8.3	78.1
	≥30–<35 kg/m^2	557	58	8.2	8.4	90.7
	≥35 kg/m^2	589	55	7.3	8.3	112.6
PIONEER 4	<25 kg/m^2	50	58	8.8	7.9	66.0
	≥25–<30 kg/m^2	210	58	8.8	8.0	78.7
	≥30–<35 kg/m^2	217	56	7.4	7.9	93.5
	≥35 kg/m^2	234	55	6.5	8.0	114.2

(Continues)

TABLE 1 (Continued)

Trial	Subgroup	Patients, N	Mean age, y	Mean duration of diabetes, y	Mean HbA1c, %	Mean body weight, kg
PIONEER 5	<25 kg/m^2	20	74	17.4	7.8	67.6
	≥25–<30 kg/m^2	90	72	15.7	7.9	80.8
	≥30–<35 kg/m^2	129	71	13.7	8.0	89.2
	≥35 kg/m^2	84	67	12.0	8.0	109.7
PIONEER 7	<25 kg/m^2	61	62	11.9	8.3	66.3
	≥25–<30 kg/m^2	164	60	9.8	8.2	78.4
	≥30–<35 kg/m^2	162	56	8.6	8.3	92.0
	≥35 kg/m^2	117	54	6.1	8.4	110.0
PIONEER 8	<25 kg/m^2	139	62	17.1	8.0	60.8
	≥25–<30 kg/m^2	217	62	16.3	8.2	76.5
	≥30–<35 kg/m^2	199	60	14.0	8.2	91.2
	≥35 kg/m^2	176	59	13.1	8.3	111.3
Baseline HbA1c						
PIONEER 1	≤8%	409	55	3.5	7.5	89.0
	>8–≤9%	244	53	3.5	8.5	87.0
	>9%	50	54	3.7	9.3	86.8
PIONEER 2	≤8%	457	59	7.2	7.4	91.3
	>8–≤9%	211	57	7.9	8.5	92.9
	>9%	153	55	7.4	9.7	90.9
PIONEER 3	≤8%	850	59	8.4	7.5	90.6
	>8–≤9%	593	57	8.7	8.5	91.4
	>9%	420	56	8.8	9.7	92.4
PIONEER 4	≤8%	403	57	7.5	7.4	92.8
	>8–≤9%	248	56	7.8	8.5	94.1
	>9%	60	53	7.2	9.3	101.2
PIONEER 5	≤8%	188	71	13.1	7.5	91.5
	>8–≤9%	108	70	15.7	8.5	89.2
	>9%	28	69	13.4	9.3	92.6
PIONEER 7	≤8%	201	58	8.6	7.7	87.3
	>8–≤9%	246	57	8.9	8.5	88.2
	>9%	57	56	8.7	9.4	95.2
PIONEER 8	≤8%	329	62	15.6	7.5	83.6
	>8–≤9%	296	60	14.9	8.5	87.6
	>9%	106	58	13.5	9.3	88.1

Note: PIONEER 5 was not included in the race or ethnicity analyses due to small numbers of patients in some subgroups.
Abbreviations: AA, African American, BMI, body mass index; HbA1c, glycated haemoglobin; y, years.

using an analysis of covariance-based sequential multiple imputation model and the categorical endpoint derived from there. For the race (but not ethnicity) analyses, region was not included as a categorical fixed effect.

Subgroup interaction tests (5% significance level) were based on the estimated treatment differences for oral semaglutide versus comparator for the change from baseline endpoints and the estimated odds ratios (ORs) for the achievement of HbA1c <7.0%.

Because of the potential for type I errors due to multiple comparisons, findings should be interpreted as exploratory.

Safety data were pooled for all trials and analysed descriptively. For the age subgroup analyses, subgroups of <65 years and ≥65 years were used to assess for increased risk of adverse outcomes in patients aged ≥65 years with T2D.

3 | RESULTS

In the PIONEER 1–5, 7 and 8 trials, the numbers of patients randomized were: oral semaglutide 14 mg/flex, N = 1934;
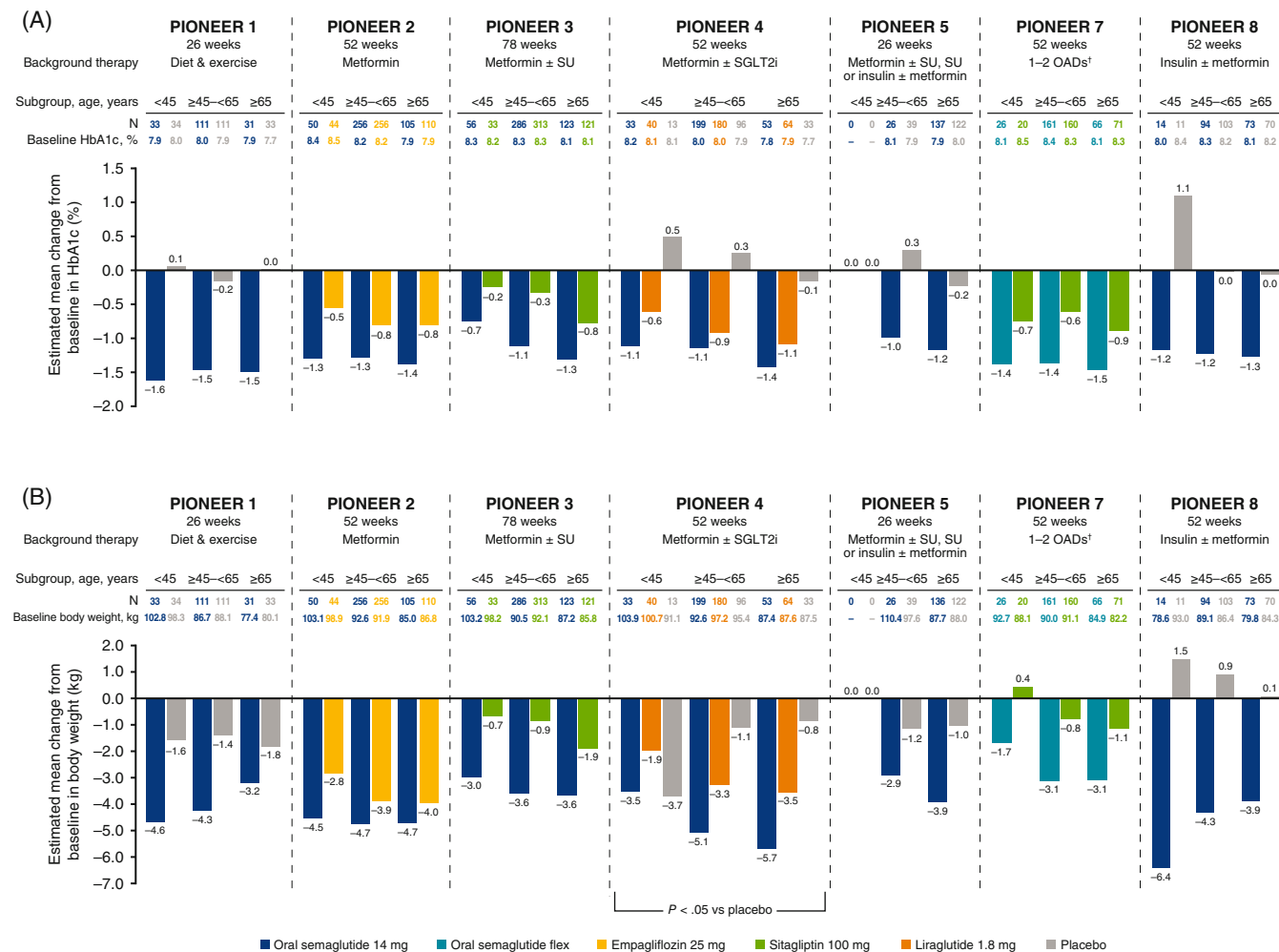
FIGURE 1 Change from baseline in A, glycated haemoglobin (HbA1c), and B, body weight, by baseline age. Abbreviations: flex, flexibly dosed; OAD, oral antidiabetes drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea. [†]Including metformin, an SU, an SGLT2i or a thiazolidinedione. Analyses were conducted at the end of treatment on data from the full analysis set using the trial product estimand. The *P* value indicates a significant treatment-by-subgroup interaction with regard to the estimated treatment differences for that trial (two-sided significance test)

oral semaglutide 7 mg, N = 823; and comparators, N = 2077 (placebo, n = 665[11,15-17]; empagliflozin, n = 410[12]; liraglutide, n = 284[15]; sitagliptin, n = 718[13,14]). Detailed baseline characteristics are described by study and patient subgroup in Table 1.

3.1 | Age subgroups

Baseline body weight tended to be higher in younger patients, while baseline HbA1c was similar across age groups (Table 1). HbA1c reductions with oral semaglutide 14 mg/flex were similar across age subgroups, and were larger with oral semaglutide 14 mg/flex than comparators, irrespective of age (Figure 1A). There were no significant subgroup interactions for treatment differences in HbA1c by age. Across age groups, the glycaemic efficacy of oral semaglutide 7 mg was greater than that of placebo (PIONEER 1 and 8), and similar to, or greater than, that of sitagliptin (PIONEER 3; Figure S1A). Across trials

and age subgroups, estimated ORs consistently favoured oral semaglutide 7 and 14 mg, and flex, over comparators for the achievement of the HbA1c <7.0% target at the end of treatment (Figure S2), and there was no interaction of subgroups on the estimated ORs.

Body weight reductions were generally greater with oral semaglutide 14 mg/flex than with comparators, largely without association between age subgroup and reduction in body weight, except for oral semaglutide 14 mg versus placebo in PIONEER 4 (Figure 1B). Oral semaglutide 7 mg was also associated with larger decreases in body weight than placebo and sitagliptin across age subgroups (Figure S1B).

3.2 | Racial and ethnic subgroups

Baseline characteristics were similar across race and ethnicity subgroups in each study except for body weight, which was generally
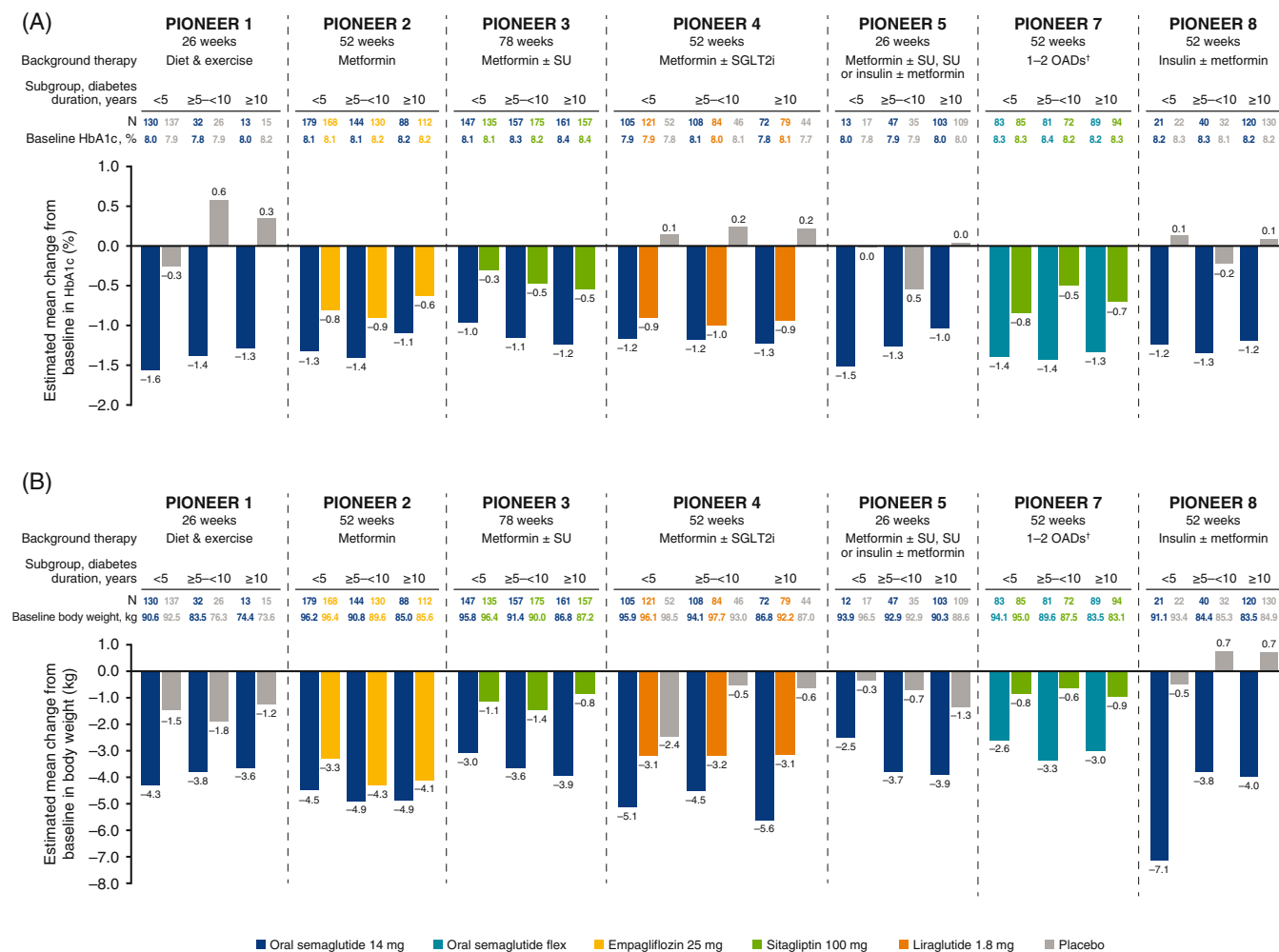
FIGURE 2 Change from baseline in A, glycated haemoglobin (HbA1c), and B, body weight, by duration of diabetes. Abbreviations: flex, flexibly dosed; OAD, oral antidiabetes drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea. †Including metformin, an SU, an SGLT2i or a thiazolidinedione. Analyses were conducted at the end of treatment on data from the full analysis set using the trial product estimand. No significant treatment-by-subgroup interactions were observed with regard to the estimated treatment differences for each trial (two-sided significance test)

lower in the Asian versus other racial subgroups (Table 1). HbA1c reductions were generally greater with oral semaglutide 14 mg/flex versus comparators across racial and ethnic subgroups (Figures S3A and S4A). In the placebo-controlled PIONEER 1, 4 and 8 trials, a significant interaction was seen between treatment and race, with the greatest HbA1c estimated treatment difference with oral semaglutide 14 mg in the Asian subgroup (Figure S3A). There were no significant subgroup interactions in the ethnicity analyses (Figure S4A). HbA1c reductions with oral semaglutide 7 mg were greater than with placebo and were similar to, or greater than, those observed with sitagliptin (Figures S5A and S6A). The odds of achieving HbA1c <7.0% by baseline race or ethnicity subgroup across the PIONEER trials generally favoured oral semaglutide over comparators, and there were no significant subgroup-by-treatment interactions (Figures S7 and S8).

Oral semaglutide 14 mg/flex generally reduced body weight to a greater extent than comparators, regardless of race or ethnicity, with no clear pattern in change across trials and racial subgroups

(Figures S3B and S4B); only one significant interaction was seen for ethnicity in PIONEER 7. Body weight reductions with oral semaglutide 7 mg were generally greater than with placebo and were similar to, or greater than, those observed with sitagliptin (Figures S5B and S6B).

3.3 | Diabetes duration subgroups

Mean age was lower and mean body weight was higher in the subgroup with the shortest diabetes duration (<5 years) at baseline. Mean HbA1c was similar at baseline across the diabetes duration subgroups within each trial (Table 1).

Across the PIONEER trials, the efficacy of oral semaglutide 14 mg/flex in reducing HbA1c was consistently greater than for comparators, irrespective of diabetes duration, with no treatment interactions across subgroups (Figure 2A). Oral semaglutide 7 mg was also associated with larger decreases in HbA1c than placebo, and larger or
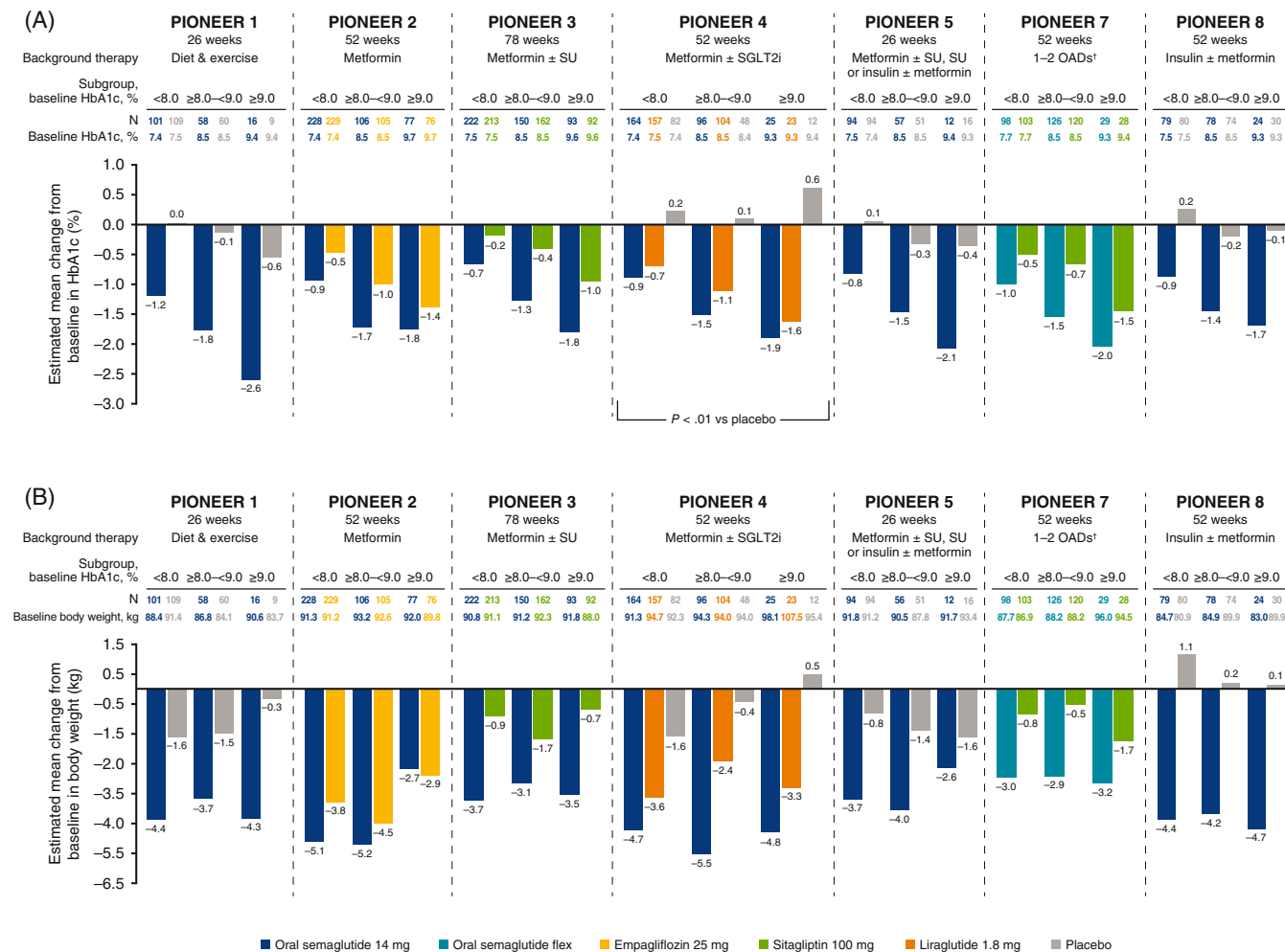
FIGURE 3 Change from baseline in A, glycated haemoglobin (HbA1c), and B, body weight, by baseline HbA1c. Abbreviations: flex, flexibly dosed; OAD, oral antidiabetes drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulphonylurea. †Including metformin, an SU, an SGLT2i or a thiazolidinedione. Analyses were conducted at the end of treatment on data from the full analysis set using the trial product estimand. The *P* value indicates a significant treatment-by-subgroup interaction with regard to the estimated treatment differences for that trial (two-sided significance test)

similar decreases compared with sitagliptin, across diabetes duration subgroups (Figure S9A). Across trials and diabetes duration subgroups, estimated ORs consistently favoured oral semaglutide 7 and 14 mg, and flex, over comparators for the achievement of HbA1c <7.0% (Figure S10), with no significant subgroup interaction observed.

Body weight reductions were generally greater with oral semaglutide 14 mg/flex than with comparators, without any significant association between treatment and diabetes duration subgroups (Figure 2B). Oral semaglutide 7 mg was also associated with larger decreases in body weight than placebo and sitagliptin across diabetes duration subgroups (Figure S9B).

3.4 | Baseline BMI subgroups

Across BMI subgroups, HbA1c levels were similar at baseline. In line with the observations from the age and diabetes duration subgroups

characteristics, patients with higher BMI tended to be younger and have a shorter diabetes duration (Table 1). Reductions in HbA1c with oral semaglutide 14 mg/flex were greater than with comparators across BMI subgroups and across trials (Figure S11A), and there was no significant interaction between subgroups and treatment differences. HbA1c reductions with oral semaglutide 7 mg were greater than placebo and similar to, or greater than, sitagliptin (Figure S12A). There were no significant subgroup interactions for the odds of achieving HbA1c <7.0% by baseline BMI subgroup across the PIONEER trials, and ORs generally favoured oral semaglutide over comparators (Figure S13).

Oral semaglutide 14 mg/flex also reduced body weight more than comparators across the PIONEER trials and across BMI subgroups. One significant subgroup-by-treatment interaction was observed for oral semaglutide 14 mg compared with liraglutide in PIONEER 4, but there was no clear pattern across the BMI subgroups: treatment differences in the <25 and ≥30 to <35 kg/m² subgroups were larger than

TABLE 2 Adverse events across subgroups in the PIONEER trials

Subgroup factor	Subgroup	Patients, N		Patients with ≥1 AE, %		Patients with an AE leading to trial product discontinuation, %		Patients with ≥1 GI AE, %	
		Oral semaglutide[a]	Comparator[b]	Oral semaglutide[a]	Comparator[b]	Oral semaglutide[a]	Comparator[b]	Oral semaglutide[a]	Comparator[b]
Age, y	<65	2519	1451	72.8	71.8	7.5	3.9	36.9	24.5
	≥65	1058	623	79.1	74.5	13.0	6.0	44.6	22.5
Race[c]	White	2579	1562	74.1	72.1	9.4	4.6	37.9	21.9
	Black/AA	248	146	70.3	72.1	7.3	7.2	37.9	24.9
	Asian	576	269	76.4	72.6	7.5	2.5	42.8	29.6
Ethnicity[d]	H/L	592	370	74.3	71.5	8.7	2.2	38.7	20.2
	Non-H/L	2903	1681	74.7	72.8	9.2	5.1	39.1	24.5
Duration of diabetes, y	<5	1259	736	70.9	70.3	7.0	4.5	34.5	23.3
	≥5–<10	1087	600	75.5	71.6	9.1	4.0	39.4	23.2
	≥10	1231	738	78.1	75.6	11.2	4.9	44.0	25.1
Baseline BMI, kg/m²	<25	413	187	75.2	73.1	13.5	5.6	44.6	28.2
	≥25–<30	1046	603	76.9	73.9	9.5	5.5	41.5	26.2
	≥30–<35	1086	665	73.6	69.0	8.6	2.8	37.0	20.1
	≥35	1030	619	73.2	75.3	7.6	5.1	36.9	24.5
Baseline HbA1c, %	≤8	1769	1066	75.1	71.6	10.5	4.4	39.8	23.8
	>8–≤9	1221	723	73.1	72.8	8.3	4.4	39.7	23.2
	>9	587	285	77.1	75.3	6.6	5.4	36.2	25.7

Note: Data are the on-treatment safety analysis set. Percentages are the Cochran–Mantel–Haenszel adjusted proportion of patients.

Abbreviations: AA, African American; AE, adverse event; BMI, body mass index; GI, gastrointestinal; H, Hispanic; HbA1c, glycated haemoglobin; L, Latino; y, years.

[a]Oral semaglutide included data from all three oral semaglutide doses (3, 7 and 14 mg).

[b]Comparators included placebo, empagliflozin 25 mg, sitagliptin 100 mg or liraglutide 1.8 mg, depending on the trial.

[c]Due to local regulations, collection of data on race was not permitted at French and Brazilian trial sites.

[d]Due to local regulations, collection of data on ethnicity was not permitted at French sites.

in the ≥25 to <30 and ≥35 kg/m^2 subgroups (Figure S11B). Body weight reductions with oral semaglutide 7 mg were generally greater than with placebo and sitagliptin (Figure S12B).

3.5 | Baseline HbA1c subgroups

At baseline, mean age, diabetes duration and body weight were generally similar across HbA1c subgroups (Table 1). Changes in HbA1c with oral semaglutide 14 mg/flex were greater for patients with higher baseline HbA1c (HbA1c >9%: −1.7% to −2.6%; HbA1c <8%: −0.7% to −1.2%; Figure 3A), and the HbA1c reductions were generally greater than with comparators across trials and subgroups of baseline HbA1c. When comparing subgroups, treatment differences with oral semaglutide 14 mg/flex were numerically greater in patients with higher baseline HbA1c, although only one significant treatment-by-subgroup interaction was observed for oral semaglutide 14 mg versus placebo in PIONEER 4 (Figure 3A). Because a consistent pattern of HbA1c responses with oral semaglutide 14 mg across subgroups was observed in all PIONEER trials, a pooled analysis of the placebo-controlled trials (only performed at Week 26 as this was the latest common timepoint) was performed to investigate further. This additional analysis confirmed the observed pattern with a significant treatment-by-subgroup interaction across the placebo-controlled trials (P < .0001), with the greatest HbA1c treatment differences in those with highest baseline HbA1c levels (Figure S14). Oral semaglutide 7 mg was also associated with larger decreases in HbA1c than placebo and larger, or similar, decreases compared with sitagliptin across HbA1c subgroups (Figure S15A).

Across trials and baseline HbA1c subgroups, estimated ORs consistently favoured oral semaglutide 7 and 14 mg, and flex, over comparators for the achievement of HbA1c <7.0% (Figure S16), with no significant interaction across HbA1c subgroups.

Reductions in body weight were generally greater with oral semaglutide 14 mg/flex versus comparators. However, there was no consistent relationship between change in body weight and baseline HbA1c (Figure 3B). Oral semaglutide 7 mg was also associated with larger decreases in body weight than placebo and sitagliptin across HbA1c subgroups (Figure S15B).

3.6 | Safety

The proportions of patients with adverse events (AEs) were generally similar across subgroups and between oral semaglutide and comparators (Table 2), and specific active comparators (Table S2).

Within individual subgroups, the proportion of patients with an AE leading to treatment discontinuation and the proportion of patients with ≥1 gastrointestinal (GI) AE were greater in the oral semaglutide treatment arm versus comparators, regardless of subgroup (Table 2). It should be noted that, in many of the PIONEER trials, at least one of the comparators was placebo, and the proportion of patients discontinuing trial product due to an AE or with ≥1 GI AE tended to be lowest in patients receiving placebo (Table S2).

The incidence of AEs leading to treatment discontinuation and the incidence of GI AEs was generally greater with oral semaglutide than with comparators. In patients taking oral semaglutide, there was a slight tendency for AEs leading to treatment discontinuation to occur more often in subgroups of patients who were older versus younger, in subgroups with a longer versus a shorter diabetes duration, in subgroups with a lower versus a higher baseline HbA1c and in subgroups with a lower versus a higher BMI (Table 2). This pattern of more discontinuations due to AEs in older versus younger patients was also seen for the active comparators (Table S2). In the oral semaglutide treatment group, the incidence of GI AEs was higher in the subgroups with older versus younger patients, and in subgroups with a longer versus a shorter diabetes duration, and was somewhat greater in subgroups of patients with a lower versus a higher BMI (Table 2).

4 | DISCUSSION

The PIONEER trials assessed the efficacy and safety of oral semaglutide across a wide range of patients reflective of those seen in clinical practice,[11-17] representing a large database for physicians to understand how responses might vary by patient characteristics (Tables 1 and 2, Figures 1–3). The efficacy of oral semaglutide was generally consistent across the age and diabetes duration subgroups studied. Notably, patients with higher baseline HbA1c experienced greater estimated treatment differences in HbA1c with oral semaglutide compared to placebo. A greater glycaemic response at higher baseline HbA1c levels is a known phenomenon as baseline HbA1c is often a predictor of glycaemic response for many glucose-lowering treatments,[19] including other glucagon-like peptide-1 receptor agonists (GLP-1RAs)[20-23] and once-weekly subcutaneous semaglutide.[24] Since this phenomenon also applies to other glucose-lowering treatments, it is not surprising that HbA1c level had less impact on the magnitude of estimated treatment differences in trials with an active comparator.

No significant subgroup interactions were seen for change in HbA1c by baseline BMI with oral semaglutide. This may be explained by the long half-life and adequate systemic exposure achieved with the 7 and 14 mg doses over a wide range of body weights (40–188 kg).[9] The lack of interaction for BMI subgroups on HbA1c treatment differences is consistent with a real-world study with liraglutide.[25] A meta-analysis of data with liraglutide suggested that a modest interaction between baseline BMI and change in HbA1c may be present for the 1.8 mg dose, but the authors suggested that reductions in HbA1c with liraglutide were largely independent of baseline BMI.[26]

Analyses of trials with once-weekly subcutaneous semaglutide have suggested a trend to greater absolute body weight loss in patients with a higher BMI. In addition, the observation of similar proportions of patients achieving body weight loss of ≥5% or ≥10% across BMI subgroups[27] would suggest that body weight loss may be relative to baseline. A real-world study has also reported a significant trend for greater weight reduction with liraglutide in patients with

higher baseline BMI.[25] In the present analyses with oral semaglutide, body weight reductions were seen across BMI subgroups, with a general pattern towards greater reductions in body weight in patients with higher baseline BMI within several of the PIONEER trials. However, when looking at treatment differences between oral semaglutide and comparators, a significant interaction between BMI subgroup and treatment differences in body weight was not shown in most PIONEER trials, indicating that BMI subgroup did not impact differences in body weight reductions versus comparators.

Evaluation by racial subgroups suggests potentially greater HbA1c reductions and greater treatment differences for semaglutide versus placebo and liraglutide in Asian subgroups compared to that seen in other populations. Asian patients with T2D are known to have greater β-cell dysfunction and to respond differently to treatment compared with European and US populations.[28] Indeed, the PIONEER 9 and 10 trials, conducted in Japanese patients, demonstrated reductions in HbA1c with oral semaglutide that were greater than those typically observed in the global PIONEER trials.[29,30] This could be attributable to the lower mean baseline body weight of patients in Japanese compared with global PIONEER trials,[29,30] which has been associated with higher exposure with semaglutide,[31,32] although other mechanisms cannot be excluded.

The safety and tolerability profile of oral semaglutide was generally consistent across the subgroups studied, and had a similar overall incidence of AEs versus comparators. Elderly patients may be more likely to have comorbidities and to be receiving multiple medications,[33] so the safety of diabetes treatment in these patients is of particular interest. Consistent with published subgroup analyses by age with once-weekly subcutaneous semaglutide[34] and dulaglutide,[35] the proportion of patients reporting AEs with oral semaglutide was generally similar across age subgroups. Treatment discontinuations due to an AE tended to be more common in older patients for both oral semaglutide and comparators, with the proportion discontinuing being greater for oral semaglutide than comparators. This is consistent with the observations from the subgroup analysis by age for once-weekly subcutaneous semaglutide.[34]

As expected for a GLP-1RA, GI AEs occurred more frequently with oral semaglutide than with comparators. This was consistent across the subgroups analysed and similar to subgroup analyses with once-weekly subcutaneous semaglutide.[24,34] Younger patients and those with a shorter duration of diabetes tended to experience fewer GI AEs than older patients and those with longer-standing disease. Clinical guidelines increasingly advocate the earlier consideration of GLP-1RAs for reasons of efficacy and CV protection in those at high CV risk,[1,36] and it could be argued that this approach is also sensible from a tolerability perspective, given that patients who are younger and whose T2D is relatively newly diagnosed may be expected to be more robust, and thus perhaps better equipped to deal with any side effects of medication. Nevertheless, in the PIONEER trials, GI AEs were usually mild or moderate in severity and subsided over time without the need to discontinue therapy.[11-18]

The main strength of the subgroup analyses in this paper is that the large and heterogeneous population included reflects a wide range of patients treated in everyday clinical practice. Treatment-by-subgroup interaction tests were based on the estimated treatment differences for oral semaglutide versus comparator, rather than the change from baseline, which is an additional strength of these analyses. Certain limitations should be taken into account when assessing our observations. Although subgroup analyses can provide useful information, they should be interpreted with caution because of the multiple comparisons being made, which can result in false-positive findings.[37] The subgroup analyses were exploratory and therefore may not have sufficient power to detect differences between individual subgroups. Patient numbers were low in some subgroups, which may have affected the variability and robustness of those observations, and prevented investigation of certain other subgroups of interest, such as in patients aged >75 years. Finally, although the PIONEER programme included a broad range of patients, some patient groups might be underrepresented.

Although Week 26 was the primary endpoint for most PIONEER trials, the present subgroup analyses focused on the end of treatment to capture the full effect on HbA1c and body weight during these trials. Importantly, the reductions in HbA1c observed at Week 26 following treatment with oral semaglutide in the PIONEER trials were generally sustained and similar to those at the end of treatment, with peak effect on body weight occurring after Week 26. Therefore, conclusions regarding the effects of patient subgroups on change in HbA1c in this analysis are generally consistent with the data previously reported for the PIONEER trials.

In conclusion, the PIONEER programme illustrates the heterogeneity of T2D, with differences in clinical characteristics most noticeable by age and by duration of diabetes: younger patients and those with shorter duration of diabetes were more obese, indicating distinct patient care goals and therapeutic needs for this population. The quantitative assessments of efficacy and tolerability by patient subgroups in the PIONEER programme suggest that oral semaglutide is efficacious at reducing HbA1c and body weight consistently more than most comparators, and is well tolerated across a diverse set of adults of different ages, who have had T2D for different lengths of time, with a range of baseline HbA1c levels, BMI values, races and ethnicities. Physicians may expect particularly greater glycaemic efficacy in patients with high HbA1c and in patients of Asian descent when receiving oral semaglutide. Moreover, better tolerability may be observed in patients with shorter diabetes duration, and in younger patients. Given the broad heterogeneity of T2D, understanding expected responses based on individual patient characteristics, as conducted in this study, may further support patient-centred dialogue and care.

AUTHOR CONTRIBUTIONS

CONFLICTS OF INTEREST

V.R.A. reports receiving consultancy fees from Applied Therapeutics, Fractyl, Novo Nordisk A/S, Pfizer and Sanofi, and research grant support (to institution) from Applied Therapeutics/Medpace; Eli Lilly; Premier/Fractyl, Novo Nordisk and Sanofi/Medpace. V.R.A.'s spouse is employed by Janssen. E.M. reports scientific advisory board, consulting, lecturing and/or research grants from AstraZeneca, Menarini, Merck Sharp & Dohme, Novo Nordisk and Sanofi. M.H. has served as an advisory board member for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Novo Nordisk and Sanofi; a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Sharp & Dohme, Mundipharma, Novartis, Novo Nordisk and Sanofi; and received research support from Eli Lilly and Sanofi. J.R. has served on advisory panels for Applied Therapeutics, Boehringer Ingelheim, Eli Lilly, Intarcia, Novo Nordisk, Oramed, Sanofi and Zealand, and has received research support from Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Genentech, GlaxoSmithKline, Intarcia, Janssen, Lexicon, Merck and company, Novo Nordisk, Oramed, Pfizer and Sanofi. J.J.M. has received grants from Merck and company, Novo Nordisk and Sanofi, and lecture/other fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck and company, Novo Nordisk, Sanofi and Servier. R.B., E.C. and K.K. are employees of Novo Nordisk. R.B. and E.C are shareholders in Novo Nordisk.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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 USA. Individual participant data will be shared in datasets in a de-identified/anonymized format.

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