

A multicenter, prospective, real-world study of oral semaglutide in adults with type 2 diabetes in Japanese clinical practice (PIONEER REAL Japan): Subgroup analyses

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Keywords

Oral semaglutide, Real-world study, Type 2 diabetes

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ABSTRACT

Aims: HbA_{1c} and body weight were assessed across selected subgroups of adults with type 2 diabetes receiving oral semaglutide in clinical practice.

Methods: In this non-interventional study, changes in HbA_{1c} and body weight to end of study (EoS) and safety were assessed by subgroup: baseline age, body mass index (BMI), type 2 diabetes duration, participants switching from dipeptidyl peptidase-4 inhibitors, and semaglutide dose at EoS.

Results: All subgroups experienced reductions in HbA_{1c} and body weight. Younger participants had greater reductions in HbA_{1c} than older participants (−0.9, −0.7, −0.7, and −0.5 percentage points for participants aged <55, ≥55–<65, ≥65–<75, and ≥75 years, respectively [*P* = 0.0467]). Shorter type 2 diabetes duration and lower EoS semaglutide dose were associated with greater HbA_{1c} reductions (−0.8, −0.7, and −0.6 percentage points with ≤5, >5–≤10, and >10 years' duration, respectively [*P* < 0.0001]; −1.2, −0.7, and −0.4 percentage points with 3, 7, and 14 mg, respectively [*P* < 0.0001]). Changes in HbA_{1c} were not significantly different across other subgroups. Lower EoS semaglutide dose was associated with greater body weight reductions (−3.8, −2.9, and −2.8 kg with 3, 7, and 14 mg, respectively [*P* < 0.0001]); body weight reductions were not significantly different across other subgroups. Adverse events were similar between subgroups, except that older subgroups experienced more events.

Conclusions: HbA_{1c} and body weight decreased across all subgroups, providing insights into oral semaglutide use in clinical practice for individuals with different characteristics in the real-world setting.

INTRODUCTION

Multiple treatment options are available for individuals with type 2 diabetes in Japan^{1,2}, of which dipeptidyl peptidase-4

inhibitors (DPP-4is) are the most frequently prescribed^{3,4}. However, DPP-4i use has plateaued or even decreased in recent years as sodium–glucose cotransporter 2 inhibitors, metformin, and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have become more frequently used^{4–6}.

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Guidelines recommend a personalized approach to diabetes management that takes into account an individual's clinical characteristics, such as age, HbA_{1c} levels, and body weight, among other factors^{1,2,7-9}. Therefore, it is important to understand any potential effects of these characteristics on an individual's response to treatment¹⁰. Individuals also may need to switch treatments if glycemic targets are not reached with current treatments^{8,9}. Subgroup analyses can help inform personalized management strategies¹¹ and could provide information on outcomes when switching from other treatments.

The PIONEER REAL program is studying the oral formulation of semaglutide, a GLP-1 analog, in individuals with type 2 diabetes in routine clinical practice and comprises 13 real-world studies conducted in separate countries. The PIONEER REAL study in Japan (PIONEER REAL Japan; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04878393) NCT04878393) investigated glycemic control, body weight changes, and safety in adults with type 2 diabetes who had not previously received injectable glucose-lowering medications and were initiating oral semaglutide treatment. Baseline characteristics, primary clinical outcome, patient-reported outcomes, and safety data from PIONEER REAL Japan have been published^{12,13}. Here, we present findings from subgroup analyses of PIONEER REAL Japan that investigated clinical outcomes and safety across baseline HbA_{1c} levels, age, body mass index (BMI), type 2 diabetes duration, oral semaglutide dose at end of study, and prior DPP-4i use in people initiating oral semaglutide. These analyses address specific interest from regulatory authorities in investigating oral semaglutide in individuals who switched from DPP-4i to oral semaglutide, as well as in individuals aged ≥ 75 years.

MATERIALS AND METHODS

Study design and participants

The design of this prospective, non-interventional, single-arm, real-world study has been previously described¹². In summary, participants initiated oral semaglutide as per routine clinical practice and were followed for 34–44 weeks (end of study [EoS]). The treating physician's decision to enroll participants was independent of their decision to initiate oral semaglutide. Baseline measurements were taken at the first visit, when participants provided informed consent and initiated oral semaglutide treatment, or ≤ 90 days before this visit.

Eligible participants were adults aged ≥ 20 years with a type 2 diabetes diagnosis who had not previously received injectable glucose-lowering medication (except for ≤ 14 days of insulin for acute illness). Regulatory compliance, including Good Post-Marketing Study Practice and Good Pharmacovigilance Practice, informed consent, and study approvals have been previously described^{12,13}.

Subgroups

Participants were split into subgroups according to baseline HbA_{1c} (< 7 , ≥ 7 – < 8 , ≥ 8 – < 9 , and $\geq 9\%$), age (< 55 , ≥ 55 – < 65 ,

≥ 65 – < 75 , and ≥ 75 years), BMI (< 20 , < 22 , ≥ 22 – < 25 , ≥ 25 – < 30 , and ≥ 30 kg/m²), and duration of type 2 diabetes (≤ 5 , > 5 – ≤ 10 , and > 10 years). Participants were also split into subgroups based on their oral semaglutide dose at EoS (3, 7, and 14 mg and other). In addition, participants were split into two subgroups based on prior DPP-4i use. "DPP-4i switchers" were participants who had used DPP-4i treatment ≤ 180 days before initiating treatment with oral semaglutide. "DPP-4i non-users" were those who had not taken DPP-4i previously or had discontinued DPP-4i use ≥ 180 days before initiating oral semaglutide.

Endpoints

The primary endpoint was the change in HbA_{1c} from baseline to EoS, measured in percentage points. The co-primary safety endpoint was the number of adverse events (AEs) from baseline to EoS.

Secondary endpoints included the relative (percentage points) and absolute (kg) change in body weight from baseline to EoS, and the proportion of participants reaching HbA_{1c} $< 7\%$ at EoS.

Secondary safety endpoints assessed between baseline and EoS included the numbers of adverse drug reactions (ADRs), serious AEs, and serious ADRs. ADRs were defined as AEs for which a causal relationship between oral semaglutide and the AE was suspected and judged as possible or probable by the study sponsor or investigator.

The exploratory endpoint of oral semaglutide dose at EoS was also assessed.

Statistical analyses

Eligible participants who provided informed consent and initiated oral semaglutide comprised the full analysis set^{12,13}. Analyses were performed on the in-study observation period, which represented the time participants were in the study regardless of whether they discontinued oral semaglutide. Statistical tests were performed as two-sided tests with a significance level of 0.05; no adjustments were made for multiple comparisons.

Participants with ≥ 1 post-baseline HbA_{1c} measurement were included in the primary endpoint analysis for each subgroup. Estimated change in HbA_{1c} was analyzed from baseline to the EoS visit using baseline HbA_{1c}, age, baseline BMI, time, and time-squared as covariates, and sex, oral glucose-lowering medication at baseline, type 2 diabetes duration, and site as fixed factors with a random intercept and time. Tests for interaction were performed using a mixed model for repeated measurements (MMRM) to investigate whether the primary endpoint changed differently over time between subgroups; no test for interaction was performed for the DPP-4i switchers/non-users subgroup.

For secondary endpoints, change in body weight from baseline to EoS was analyzed as per the primary endpoint. Categorical endpoints were summarized as percentages and oral semaglutide doses at EoS are presented as means with standard deviation.

RESULTS

Participants

In total, 624 participants initiated oral semaglutide treatment, 578 of whom completed the study. All participants initiated oral semaglutide at the 3 mg dose¹². Reasons for treatment discontinuation as well as semaglutide dose at the time of discontinuation are provided in Table S1. The time points of discontinuation and doses of semaglutide at the time of discontinuation are shown in Figure S1.

Overall participant demographics, baseline characteristics, and study drug exposures have been reported previously^{12,13}; participant characteristics for each subgroup are presented in Tables 1 and baseline comorbidities are presented in Tables S2 and S3. Only 21 participants were in the BMI <20 kg/m² subgroup, precluding MMRM analysis because of the low participant numbers. Therefore, data are not presented for this subgroup.

Baseline demographics and characteristics showed some differences between subgroups (Table 1). Participants in the higher baseline HbA_{1c} subgroups tended to have a longer type 2 diabetes duration than those in the lower baseline HbA_{1c} subgroups, with a corresponding trend toward higher baseline HbA_{1c} in the longer type 2 diabetes duration subgroups. A greater proportion of participants in the highest baseline HbA_{1c} subgroup had normal kidney function than those with lower baseline HbA_{1c}. Participants in the older subgroups tended to have lower baseline BMI, more kidney impairment, and longer type 2 diabetes duration vs those in the younger subgroups. A greater proportion of participants in the lower age subgroup had a baseline HbA_{1c} <7% vs higher age subgroups; this was also the case for shorter vs longer type 2 diabetes duration subgroups. The proportion of participants with a baseline HbA_{1c} <7% was similar across the BMI subgroups, except for the ≥30 kg/m² group, which had a greater proportion than the other groups.

Overall, 364 participants had switched from a DPP-4i ≤180 days before initiating oral semaglutide (DPP-4i switchers), and 260 participants had not switched (DPP-4i non-users). Baseline age, type 2 diabetes duration, and the proportion of participants with renal impairment were higher, and baseline BMI and the proportion of participants with baseline HbA_{1c} <7% were lower, in DPP-4i switchers than in DPP-4i non-users (Table S2).

Clinical outcomes

Overall, HbA_{1c} and body weight were reduced following oral semaglutide initiation across all subgroups (Figures 1 and 2, Figure S2)¹³.

Greater reductions in HbA_{1c} were observed in participants in younger subgroups, those with shorter type 2 diabetes duration, and participants receiving lower oral semaglutide doses at EoS, compared with their counterparts (Figure 1b,d,e). Trends were observed toward greater reductions in HbA_{1c} in participants with higher baseline HbA_{1c} or higher baseline BMI vs those with lower baseline HbA_{1c} or lower baseline BMI, but these did

Table 1 | Participant demographics and baseline characteristics in subgroups of interest (FAS)

Subgroup	Baseline HbA _{1c} (%)				Baseline age (years)				BMI (kg/m ²)				Type 2 diabetes duration (years)				Dose at EoS (mg)			
	<7%	≥7–8	≥8–9	≥9	<55	≥55–65	≥65–75	≥75	<22	≥22–<25	≥25–<30	≥30	≤5	>5–≤10	>10	3	7	14	Other	
N	136	265	153	70	168	123	132	201	59	128	237	142	142	149	333	124	288	52	2	
Male	75 (55.1)	151 (57.0)	90 (58.8)	39 (55.7)	105 (62.5)	71 (57.7)	66 (50.0)	113 (56.2)	34 (57.6)	81 (63.3)	141 (59.5)	65 (45.8)	75 (52.8)	85 (57.0)	195 (58.6)	52 (41.9)	174 (60.4)	34 (65.4)	0	
Age (years)	61.3 ± 14.6	64.1 ± 13.8	67.8 ± 12.9	61.7 ± 15.5	45.3 ± 7.7	59.5 ± 2.8	70.0 ± 2.9	78.9 ± 3.3	72.9 ± 9.1	70.5 ± 11.1	64.7 ± 13.0	53.2 ± 14.1	55.9 ± 14.5	62.0 ± 14.0	68.6 ± 12.1	67.5 ± 13.3	61.3 ± 14.0	59.5 ± 13.2	75.5 ± 20.5	
Type 2 diabetes duration (years) [†]	8.2 ± 8.5	10.9 ± 8.0	13.7 ± 8.3	11.3 ± 9.2	6.4 ± 5.5	10.1 ± 8.1	12.5 ± 7.5	14.6 ± 9.8	14.1 ± 10.1	14.8 ± 9.2	9.8 ± 7.2	6.3 ± 5.8	2.0 ± 1.6	7.7 ± 1.5	17.8 ± 7.2	11.3 ± 8.3	10.2 ± 8.4	10.3 ± 7.6	9.2 ± NA	
BMI (kg/m ²)	28.5 ± 5.6	27.3 ± 4.5	26.9 ± 4.8	27.4 ± 5.5	31.0 ± 5.6	28.3 ± 4.5	26.0 ± 3.8	25.1 ± 3.4	20.4 ± 1.2	23.7 ± 0.9	27.2 ± 1.4	34.3 ± 3.7	29.8 ± 5.6	27.6 ± 4.3	26.4 ± 4.6	26.5 ± 4.0	27.9 ± 5.0	29.4 ± 5.8	29.4 ± 6.3	
Body weight (kg)	76.2 ± 17.9	71.8 ± 15.2	69.8 ± 14.5	72.9 ± 17.5	85.9 ± 17.8	74.8 ± 12.6	66.8 ± 11.2	63.3 ± 9.9	53.1 ± 5.6	62.7 ± 7.7	72.1 ± 9.0	90.4 ± 15.9	79.7 ± 19.4	74.1 ± 14.9	68.4 ± 13.6	67.0 ± 12.7	75.1 ± 16.8	78.2 ± 18.2	71.3 ± 21.6	
HbA _{1c} (%)	6.4 ± 0.4	7.5 ± 0.3	8.4 ± 0.3	9.9 ± 1.1	7.7 ± 1.3	7.6 ± 1.1	7.9 ± 1.0	7.8 ± 1.0	8.1 ± 1.6	7.8 ± 0.9	7.6 ± 1.0	7.7 ± 1.3	7.4 ± 1.5	7.8 ± 1.0	7.9 ± 1.0	7.7 ± 1.0	7.7 ± 1.1	7.9 ± 1.4	7.9 ± 1.3	
Participants with HbA _{1c} <7%	136 (100.0)	0	0	0	47 (28.0)	31 (25.2)	20 (15.2)	38 (18.9)	12 (20.3)	24 (18.8)	52 (21.9)	43 (30.3)	64 (45.1)	21 (14.1)	51 (15.3)	23 (18.5)	63 (21.9)	13 (25.0)	0	
Kidney function, M [‡]	124	237	135	61	150	108	121	178	55	112	218	125	127	129	301	112	254	48	2	
Normal	68 (54.8)	118 (49.8)	63 (46.7)	43 (70.5)	131 (87.3)	84 (77.8)	54 (44.6)	23 (12.9)	22 (40.0)	47 (42.0)	101 (46.3)	95 (76.0)	91 (71.7)	78 (60.5)	123 (40.9)	48 (42.9)	155 (61.0)	32 (66.7)	1 (50.0)	
Mild impairment	48 (38.7)	97 (40.9)	52 (38.5)	11 (18.0)	16 (10.7)	19 (17.6)	15 (12.1)	122 (68.5)	26 (47.3)	53 (47.3)	91 (41.7)	23 (18.4)	28 (22.0)	44 (34.1)	136 (45.2)	51 (45.5)	76 (29.9)	11 (22.9)	1 (50.0)	
Moderate impairment	8 (6.5)	21 (8.9)	19 (14.1)	7 (11.5)	3 (2.0)	5 (4.6)	15 (12.4)	32 (18.0)	7 (12.7)	12 (10.7)	24 (11.0)	7 (5.6)	8 (6.3)	7 (5.4)	40 (13.3)	13 (11.6)	22 (8.7)	5 (10.4)	0	
Severe impairment	0	1 (0.4)	1 (0.7)	0	0	0	1 (0.8)	1 (0.6)	0	0	2 (0.9)	0	0	0	2 (0.7)	0	1 (0.4)	0	0	
eGFR	91.2 ± 18.2	89.0 ± 20.1	85.3 ± 20.5	95.3 ± 22.6	107.8 ± 15.9	94.1 ± 14.1	82.9 ± 16.0	75.0 ± 15.6	84.4 ± 16.7	84.6 ± 19.0	87.1 ± 20.4	99.7 ± 19.2	97.7 ± 19.7	93.4 ± 18.7	83.9 ± 19.5	86.8 ± 20.0	91.7 ± 20.2	93.0 ± 21.8	77.4 ± 24.1	

Data are presented as n (%) or mean ± SD. [†]Presented for those participants who provided date of type 2 diabetes diagnosis. [‡]Based on calculated eGFR of ≥90 mL/min/1.73 m² (normal function), 60–<90 mL/min/1.73 m² (mild impairment), 30–<60 mL/min/1.73 m² (moderate impairment), and <30 mL/min/1.73 m² (severe impairment). eGFR calculated based on the creatinine value using the Chronic Kidney Disease Epidemiology Collaboration equation²⁹. BMI, body mass index; eGFR, estimated glomerular filtration rate; EoS, end of study; FAS, full analysis set; N, number of participants evaluated; n, number of participants with a given characteristic; M1, number of participants evaluated if different from N; NA, not applicable; SD, standard deviation.

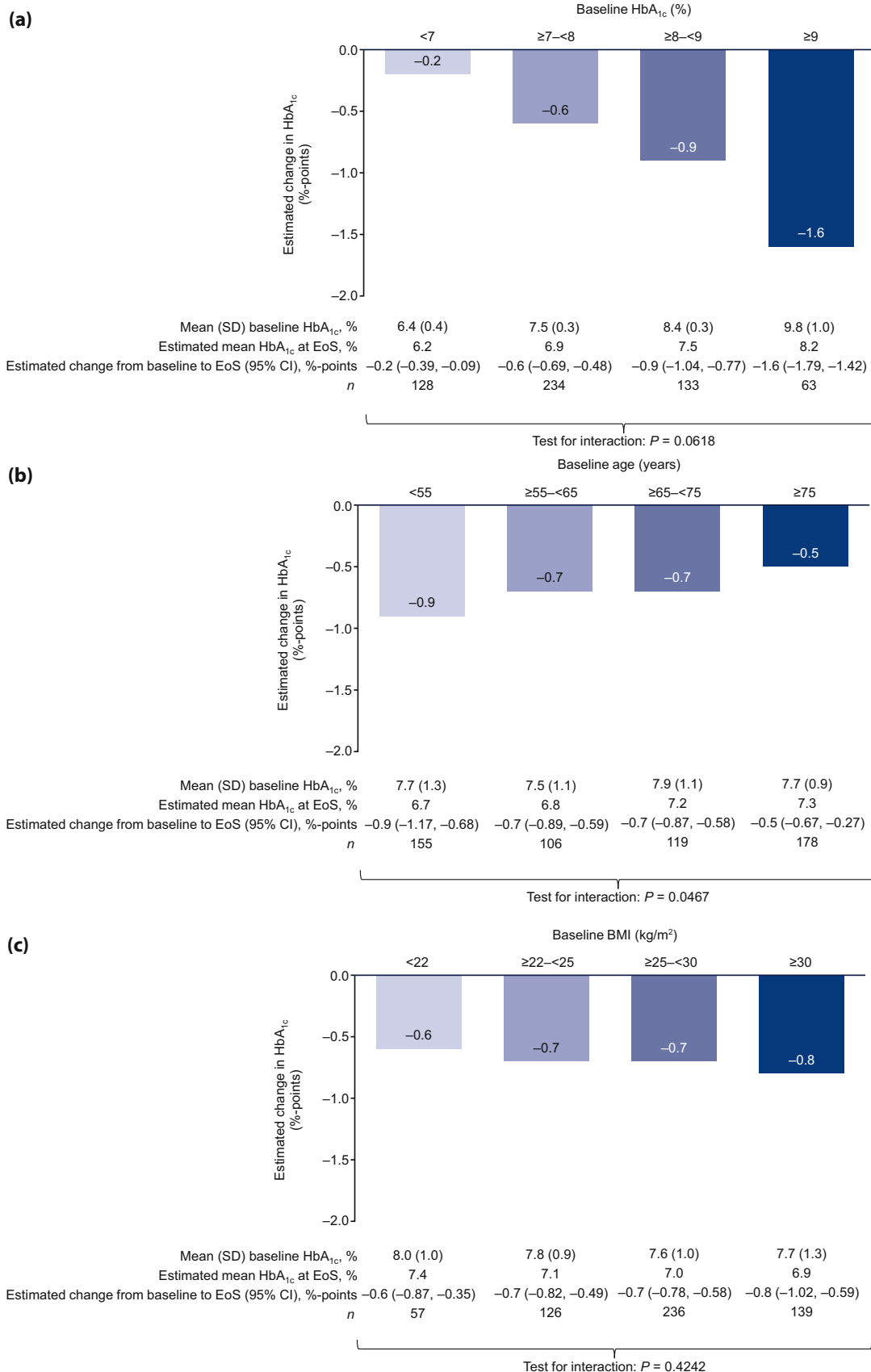


Figure 1 | Estimated change from baseline to week 38 in HbA_{1c} by (a) baseline HbA_{1c}; (b) baseline age; (c) baseline BMI; (d) type 2 diabetes duration; (e) semaglutide dose at EoS (MMRM adjusted, in-study observation period, FAS). BMI, body mass index; CI, confidence interval; EoS, end of study; FAS, full analysis set; MMRM, mixed model for repeated measurements; *n*, number of participants evaluated for endpoint; SD, standard deviation.

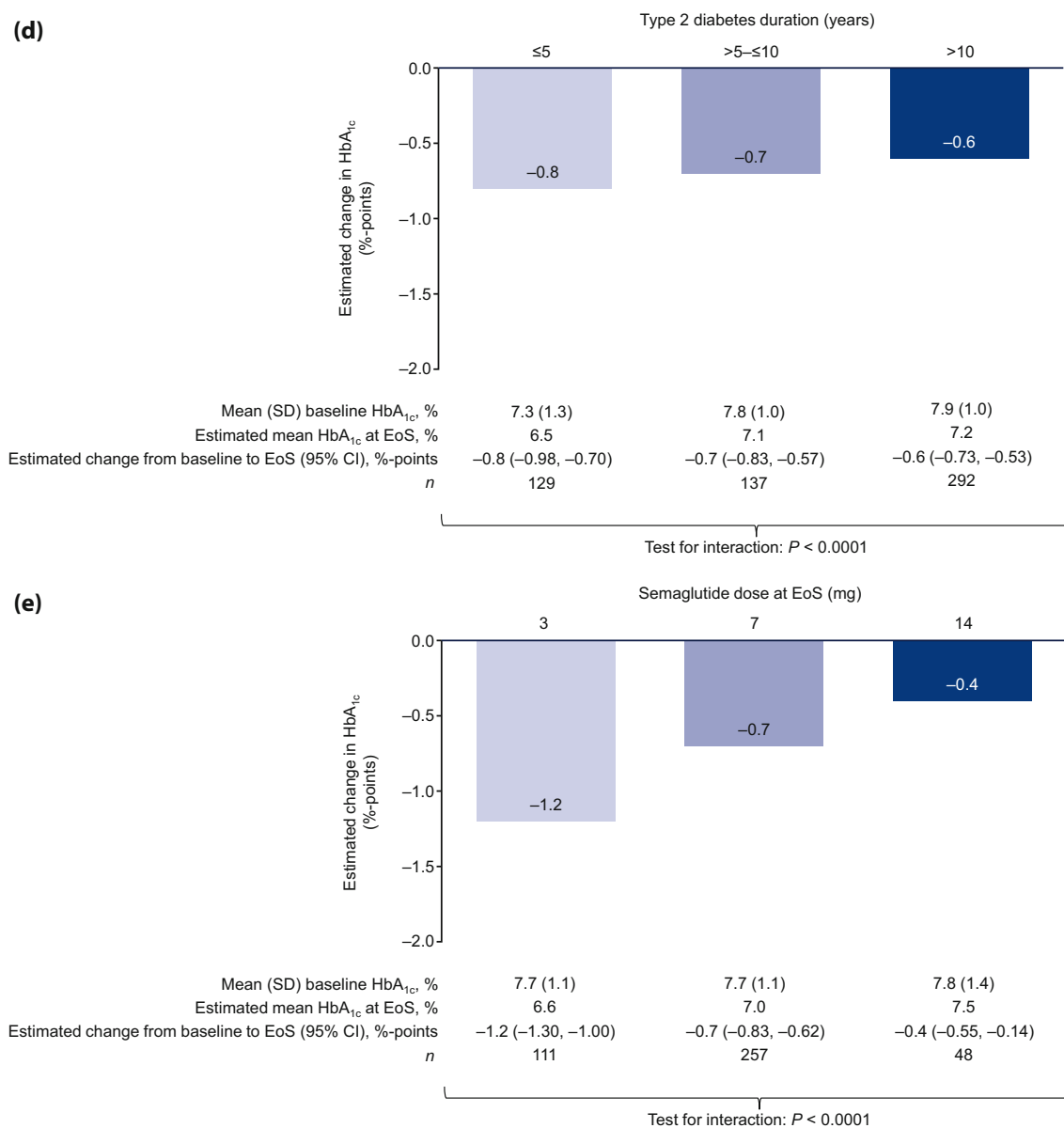


Figure 1 | Continued

not reach statistical significance for either characteristic (Figure 1a,c). DPP-4i non-users had greater reductions in HbA_{1c} than DPP-4i switchers (Figure S2a).

Participants receiving lower oral semaglutide doses at EoS had greater reductions in body weight compared with those

receiving higher doses (Figure 2e). Trends toward greater body weight loss were observed in participants with baseline HbA_{1c} $\geq 7\%$ or lower age, compared with their counterparts with lower baseline HbA_{1c} or higher age, respectively; however, none reached statistical significance (Figure 2a,b). No consistent

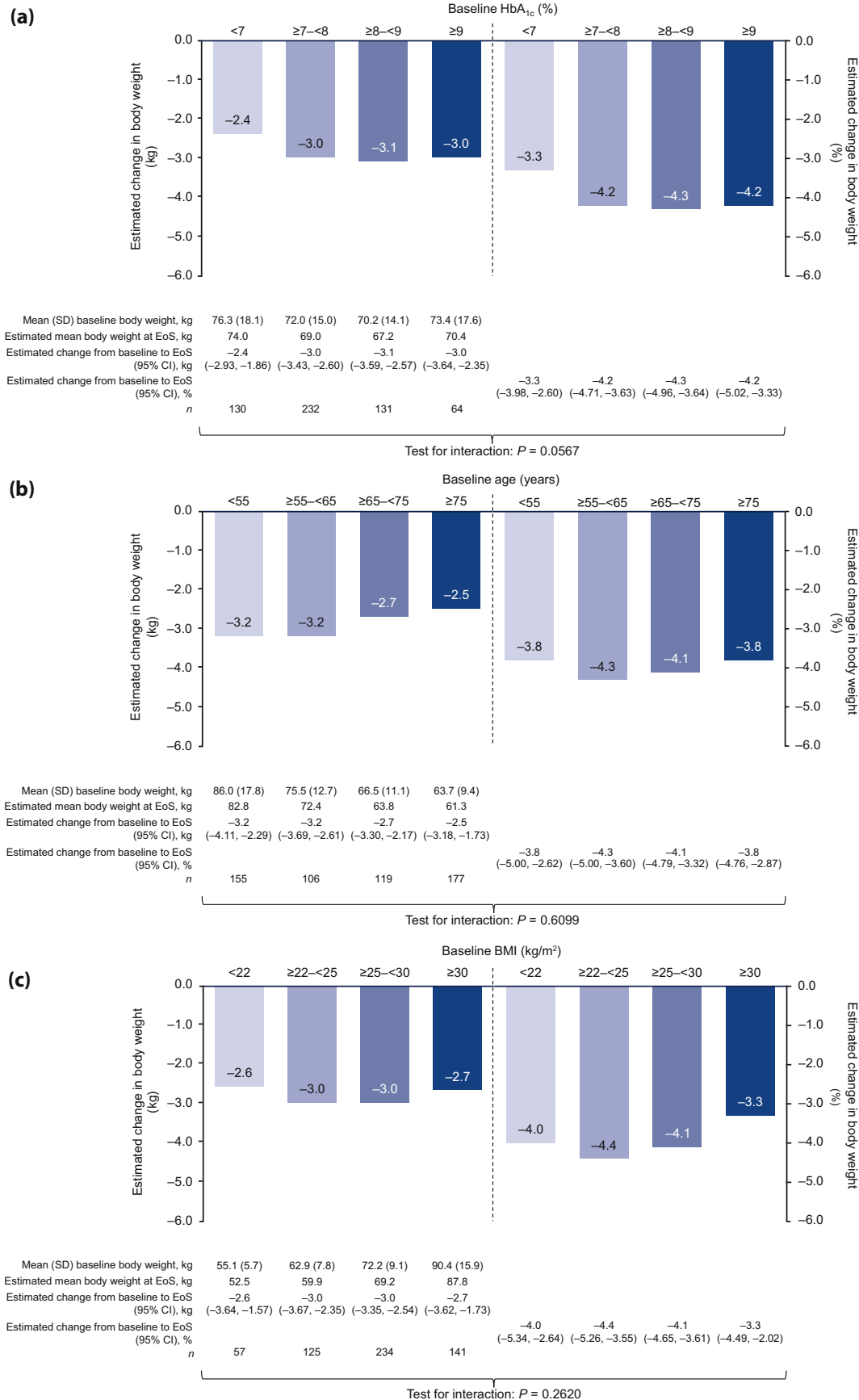


Figure 2 | Estimated change from baseline to week 38 in body weight by (a) baseline HbA_{1c}; (b) baseline age; (c) baseline BMI; (d) type 2 diabetes duration; (e) semaglutide dose at EoS (MMRM adjusted, in-study observation period, FAS). BMI, body mass index; CI, confidence interval; EoS, end of study; FAS, full analysis set; MMRM, mixed model for repeated measurements; *n*, number of participants evaluated for endpoint; SD, standard deviation.

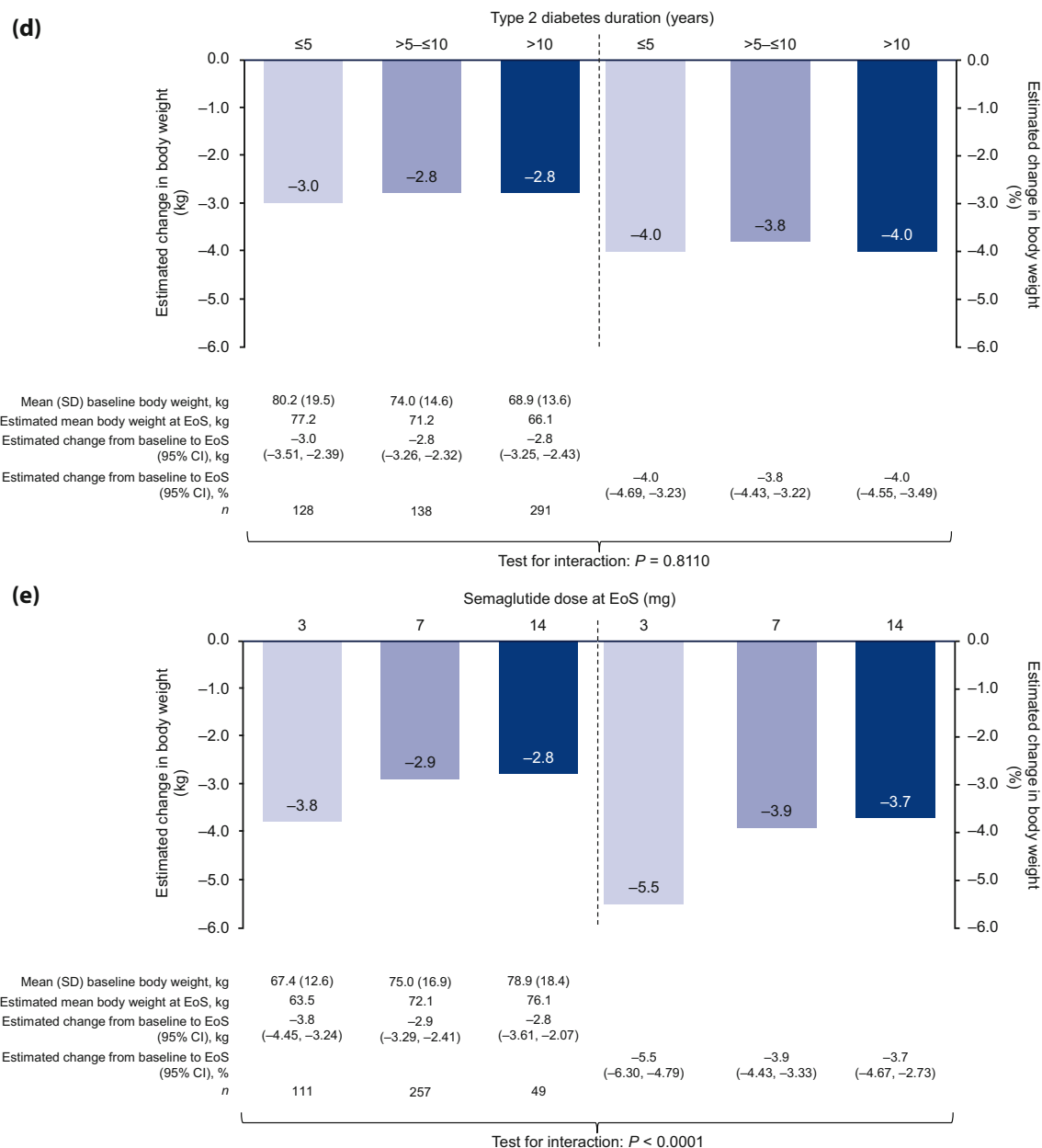


Figure 2 | Continued

effects of baseline BMI or type 2 diabetes duration on body weight reductions were observed (Figure 2c,d). Body weight reductions were similar for the DPP-4i switchers and DPP-4i non-users subgroups (Figure S2b).

The proportion of participants reaching HbA_{1c} <7% at EoS was greater among those with lower baseline HbA_{1c}, higher baseline BMI, shorter type 2 diabetes duration, and in younger participants, compared with their counterparts (Table 2). Most

Table 2 | Participants reaching HbA_{1c} <7% at EoS, by subgroups of interest (FAS)

Subgroup	N	Participants, n (%)
Baseline HbA _{1c} (%)		
<7	119	107 (89.9)
≥7–<8	250	139 (55.6)
≥8–<9	132	46 (34.8)
≥9	63	20 (31.7)
Baseline age (years)		
<55	154	102 (66.2)
≥55–<65	103	63 (61.2)
≥65–<75	127	67 (52.8)
≥75	180	80 (44.4)
Baseline BMI (kg/m ²)		
<22	49	20 (40.8)
≥ 22–<25	121	55 (45.5)
≥25–<30	216	129 (59.7)
≥ 30	126	82 (65.1)
Type 2 diabetes duration (years)		
≤5	126	100 (79.4)
>5–≤10	135	74 (54.8)
>10	303	138 (45.5)
Semaglutide dose at end of study (mg)		
3	123	73 (59.3)
7	281	174 (61.9)
14	50	22 (44.0)
Other	2	0

BMI, body mass index; EoS, end of study; FAS, full analysis set; N, number of participants assessed in subgroup; n, number of participants achieving HbA_{1c} <7%.

Table 3 | Participants reaching HbA_{1c} <7% at EoS, by DPP-4i switching status (FAS)

Subgroup	N	Participants, n (%)
DPP-4i switchers	262	125 (47.7)
Switchers on 3 mg semaglutide dose at end of study	70	35 (50.0)
Switchers on 7 mg semaglutide dose at end of study	167	87 (52.1)
Switchers on 14 mg semaglutide dose at end of study	23	3 (13.0)
DPP-4i non-users	194	144 (74.2)
Non-users on 3 mg semaglutide dose at end of study	53	38 (71.7)
Non-users on 7 mg semaglutide dose at end of study	114	87 (76.3)
Non-users on 14 mg semaglutide dose at end of study	27	19 (70.4)

DPP-4i, dipeptidyl peptidase-4 inhibitor; EoS, end of study; FAS, full analysis set; N, number of participants assessed in subgroup; n, number of participants achieving HbA_{1c} <7%.

DPP-4i non-users (70.5%) reached HbA_{1c} <7% at EoS (Table 3); 31.2% of DPP-4i non-users had HbA_{1c} <7% at baseline (Table S2). At baseline, only 15.1% of DPP-4i switchers had HbA_{1c} <7% (Table S2), which increased to 47.7% at EoS (Table 3).

Oral semaglutide dose at EoS

Across all subgroups, at least half of participants were receiving oral semaglutide 7 mg at EoS (Table S5). Proportionally more men than women received higher doses of oral semaglutide at EoS (Table 1). In addition, a larger proportion of participants with baseline HbA_{1c} ≥9% received oral semaglutide 14 mg at EoS, compared with those with lower baseline HbA_{1c} (Table S5). Similarly, participants with higher baseline BMI and body weight were more likely to receive higher doses of oral semaglutide at EoS than those with lower BMI and body weight (Table 1 and Table S5).

Although participants in the younger subgroups received higher oral semaglutide doses at EoS than their older counterparts, type 2 diabetes duration did not appear to affect mean dose nor the proportions of participants receiving each dose (Table S5). Similar proportions of DPP-4i switchers and DPP-4i non-users received oral semaglutide 3 mg at EoS; however, proportionally more DPP-4i non-users received 14 mg than DPP-4i switchers (Table S5).

Safety

No new safety concerns were identified in these analyses¹³. The most frequent AEs across all subgroups were gastrointestinal in nature (Table 4).

In general, the frequency of AEs was similar across subgroups with a few exceptions (Table 4): The ≥75-year subgroup had a higher frequency of AEs than the younger subgroups; also, AE frequency was higher in participants receiving lower oral semaglutide doses at EoS compared with those receiving higher doses.

The number of serious AEs was very low overall, with the highest frequency observed in the ≥75-year subgroup (Table 4). Similarly, AEs leading to semaglutide discontinuation were more frequent in participants in the lower BMI and higher age subgroups and in those with longer type 2 diabetes duration (Table 4).

The frequency of AEs and AEs leading to discontinuation were both higher among DPP-4i switchers than DPP-4i non-users, although the rates of serious AEs were similar between the subgroups (Table S6).

Across all subgroups, ADRs followed a similar pattern to AEs (Table 4 and Table S7). The most frequent ADRs were gastrointestinal in nature, in particular nausea, vomiting, and diarrhea; gastrointestinal ADRs increased in frequency in the older subgroups, from 21 of 168 individuals (12.5%) in the < 55-year subgroup to 40 of 201 individuals (19.9%) in the ≥75-year subgroup (Table S7). Serious ADRs occurred in two participants. One case was a report of “intestinal obstruction”

Table 4 | Summary of safety for subgroups of interest—in-study observation period (FAS)

Subgroup	Baseline HbA _{1c} (%)				Baseline age (years)				BMI (kg/m ²)				Type 2 diabetes duration (years)				Semaglutide dose at EoS (mg)																					
	<7%	≥7–<8	≥8–<9	≥9	<55	≥55–<65	≥65–<75	≥75	<22	≥22–<25	≥25–<30	≥30	≤5	>5	>10	3	7	14	Other																			
N	136	265	153	70	168	123	132	201	59	128	237	142	142	149	333	124	288	52	2																			
Observation time (years)	91.7	187.8	107.1	48.7	119.1	84.5	93.6	138.3	40.0	89.3	165.4	98.8	100.0	103.7	231.7	89.1	204.7	36.7	1.5																			
AEs	36	61	44	20	36	28	35	62	17	33	54	39	32	40	89	27	43	6	2																			
	(26.5)	(23.0)	(28.8)	(28.6)	(21.4)	(22.8)	(26.5)	(30.8)	(28.8)	(25.8)	(22.8)	(27.5)	(22.5)	(26.8)	(26.7)	(21.8)	(14.9)	(11.5)	(100.0)																			
AE severity																																						
Mild	30	52	37	17	32	26	27	51	14	26	46	35	27	33	76	25	40	5	2																			
	(22.1)	(19.6)	(24.2)	(24.3)	(19.0)	(21.1)	(20.5)	(25.4)	(23.7)	(20.3)	(19.4)	(24.6)	(19.0)	(22.1)	(22.8)	(20.2)	(13.9)	(9.6)	(100.0)																			
Moderate	8	(5.9)	13	4	(5.7)	7	(4.2)	8	(6.1)	18	5	(8.5)	10	11	6	(4.2)	7	(4.7)	1	0																		
	(4.9)	(6.5)						(9.0)		(7.8)	(4.6)				(6.3)			(1.9)																				
Severe	2	(1.5)	2	(0.8)	0	0	1	(0.8)	3	(1.5)	1	(0.4)	0	0	4	(1.2)	0	0	0	0																		
Serious AEs	7	(5.1)	9	(3.4)	5	(3.3)	0	6	(3.6)	2	(1.5)	11	1	(1.7)	4	(3.1)	3	(2.4)	6	(2.1)	1	0																
								(5.5)			(4.2)				(3.3)			(1.9)																				
AEs with fatal outcome	2	(1.5)	0	0	0	0	0	2	(1.0)	1	(0.8)	0	0	0	2	(0.6)	0	0	0	0	0	0																
Causality to study drug																																						
Probable	22	39	23	11	17	20	22	36	12	22	26	26	15	27	53	19	14	1	2																			
	(16.2)	(14.7)	(15.0)	(15.7)	(10.1)	(16.3)	(16.7)	(17.9)	(20.3)	(17.2)	(11.0)	(18.3)	(10.6)	(18.1)	(15.9)	(15.3)	(4.9)	(1.9)	(100.0)																			
Possible	11	11	12	3	(4.3)	9	(5.4)	3	(2.4)	5	(3.8)	20	4	(6.8)	11	12	6	(4.2)	8	(5.6)	7	(4.7)	22	4	(3.2)	12	3	0										
	(8.1)	(4.2)	(7.8)					(10.0)		(8.6)	(5.1)				(6.6)		(4.2)	(5.8)																				
Unlikely	11	21	19	11	16	11	14	21	6	11	25	13	17	12	33	10	27	4	0																			
	(8.1)	(7.9)	(12.4)	(15.7)	(9.5)	(8.9)	(10.6)	(10.4)	(10.2)	(8.6)	(10.5)	(9.2)	(12.0)	(8.1)	(9.9)	(8.1)	(9.4)	(7.7)																				
ADRs [†]	30	49	35	14	26	23	26	53	15	31	37	32	22	34	72	23	25	4	2																			
	(22.1)	(18.5)	(22.9)	(20.0)	(15.5)	(18.7)	(19.7)	(26.4)	(25.4)	(24.2)	(15.6)	(22.5)	(15.5)	(22.8)	(21.6)	(18.5)	(8.7)	(7.7)	(100.0)																			
AEs leading to study drug discontinuation	18	23	18	9	9	(5.4)	9	(7.3)	15	35	11	15	23	10	15	43	0	0	0	0																		
	(13.2)	(8.7)	(11.8)	(12.9)			(11.4)	(17.4)	(18.6)	(11.7)	(9.7)	(9.2)	(7.0)	(10.1)	(12.9)																							
Most frequent AEs in ≥2% of participants in any group by preferred term																																						
Gastrointestinal AEs	26	45	30	13	21	23	27	43	13	23	41	27	17	34	63	21	24	3	2																			
	(19.1)	(17.0)	(19.6)	(18.6)	(12.5)	(18.7)	(20.5)	(21.4)	(22.0)	(18.0)	(17.3)	(19.0)	(12.0)	(22.8)	(18.9)	(16.9)	(8.3)	(5.8)	(100.0)																			
Nausea	10	10	15	5	(7.1)	7	(4.2)	8	(6.5)	10	15	4	(6.8)	12	11	9	(6.3)	4	(2.8)	9	(6.0)	27	9	(7.3)	6	(2.1)	1	1										
	(7.4)	(3.8)	(9.8)				(7.6)	(7.5)		(9.4)	(4.6)				(8.1)			(1.9)	(50.0)																			
Vomiting	3	(2.2)	3	(1.1)	2	(1.3)	6	(8.6)	2	(1.2)	3	(2.4)	2	(1.5)	7	(3.5)	3	(5.1)	3	(2.3)	6	(2.5)	2	(1.4)	5	(3.5)	5	(3.4)	4	(1.2)	3	(2.4)	1	(0.3)	0	1		
Diarrhea	6	(4.4)	12	5	(3.3)	1	(1.4)	5	(3.0)	5	(4.1)	5	(3.8)	9	(4.5)	4	(6.8)	3	(2.3)	5	(2.1)	7	(4.9)	4	(2.8)	7	(4.7)	13	4	(3.2)	6	(2.1)	1	1				
	(4.5)																																					
Constipation	4	(2.9)	8	(3.0)	3	(2.0)	2	(2.9)	4	(2.4)	2	(1.6)	7	(5.3)	4	(2.0)	1	(1.7)	8	(6.3)	4	(1.7)	4	(2.8)	2	(1.4)	5	(3.4)	10	1	(0.8)	5	(1.7)	1	0			
Abdominal discomfort	1	(0.7)	7	(2.6)	2	(1.3)	0	1	(0.6)	3	(2.4)	0	6	(3.0)	2	(3.4)	0	5	(2.1)	2	(1.4)	1	(0.7)	5	(3.4)	4	(1.2)	4	(3.2)	1	(0.3)	1	0	0	0			
Metabolism and nutrition AEs	5	(3.7)	9	(3.4)	6	(3.9)	2	(2.9)	3	(1.8)	1	(0.8)	5	(3.8)	13	5	(8.5)	7	(5.5)	7	(3.0)	3	(2.1)	4	(2.8)	2	(1.3)	16	3	(2.4)	6	(2.1)	0	0	0			

Table 4. (Continued)

Subgroup	Baseline HbA _{1c} (%)				Baseline age (years)				BMI (kg/m ²)				Type 2 diabetes duration (years)				Semaglutide dose at EoS (mg)			
	<7%	≥7–<8	≥8–<9	≥9	<55	≥55–<65	≥65–<75	≥75	<22	≥22–<25	≥25–<30	≥30	≤5	>5–≤10	>10		3	7	14	Other
Decreased appetite	3 (2.2)	7 (2.6)	3 (2.0)	2 (2.9)	2 (1.2)	1 (0.8)	3 (2.3)	9 (4.5)	4 (6.8)	3 (2.3)	6 (2.5)	2 (1.4)	3 (2.1)	1 (0.7)	11 (3.3)		3 (2.4)	2 (0.7)	0	0
Infections and infestations	6 (4.4)	6 (2.3)	1 (0.7)	3 (4.3)	8 (4.8)	2 (1.6)	4 (3.0)	2 (1.0)	2 (3.4)	1 (0.8)	5 (2.1)	6 (4.2)	6 (4.2)	2 (1.3)	8 (2.4)		1 (0.8)	11 (3.8)	0	0
COVID-19	3 (2.2)	3 (1.1)	0	2 (2.9)	5 (3.0)	1 (0.8)	2 (1.5)	0	1 (1.7)	0	2 (0.8)	4 (2.8)	4 (2.8)	0	4 (1.2)		1 (0.8)	6 (2.1)	0	0
General disorders and administration site conditions	0	4 (1.5)	5 (3.3)	2 (2.9)	4 (2.4)	1 (0.8)	1 (0.8)	5 (2.5)	3 (5.1)	0	3 (1.3)	2 (1.4)	2 (1.4)	3 (2.0)	6 (1.8)		1 (0.8)	4 (1.4)	0	0
Malaise	0	1 (0.4)	3 (2.0)	1 (1.4)	1 (0.6)	0	0	4 (2.0)	2 (3.4)	0	1 (0.4)	1 (0.7)	1 (0.7)	0	4 (1.2)		1 (0.8)	0	0	0

Data are presented as *n* (%), except where indicated. †ADRs are defined as AEs for which a causal relationship between oral semaglutide and the AE was suspected and judged as possible or probable by the study sponsor or investigator. ADR, adverse drug reaction; AE, adverse event; BMI, body mass index; EoS, end of study; FAS, full analysis set; *N*, number of participants assessed; *n*, number of participants with AE.

in a participant receiving oral semaglutide 3 mg and in the baseline HbA_{1c} <7%, ≥75 years, BMI ≥22–<25 kg/m², and type 2 diabetes duration of >10-years subgroups. The second case was a report of “drug eruption” in a participant receiving oral semaglutide 3 mg and in the baseline HbA_{1c} <7%, age ≥75 years, BMI ≥22–<25 kg/m², and type 2 diabetes duration ≤5-years subgroups. In both cases, oral semaglutide was discontinued and the participant recovered.

DISCUSSION

In this subgroup analysis of PIONEER REAL Japan, participants with type 2 diabetes experienced improvements in HbA_{1c} and body weight following oral semaglutide initiation across all baseline age, HbA_{1c}, BMI, type 2 diabetes duration, and prior DPP-4i use subgroups.

Greater reductions in HbA_{1c} were observed in younger participants compared with their older counterparts, as previously reported in participants aged <75 years vs ≥75 years in the primary PIONEER REAL Japan study results¹³. Younger participants also had higher baseline BMI and shorter type 2 diabetes duration and were more likely to be DPP-4i non-users. This may explain why: (1) participants with shorter type 2 diabetes duration had significantly greater HbA_{1c} reductions than those with longer type 2 diabetes duration; and (2) participants with higher baseline BMI or shorter disease duration and DPP-4i non-users were more likely to reach HbA_{1c} <7% at EoS. The observations may reflect management guidelines, which recommend determining an individual’s HbA_{1c} target based on age and diabetes duration, among other factors^{7–9}. Our findings are also consistent with a retrospective study of oral semaglutide in 88 participants with type 2 diabetes in Japanese clinical practice, which reported greater reductions in HbA_{1c} among younger vs older individuals¹⁴. Although that study reported a slightly greater reduction in HbA_{1c} among individuals with >10 years’ diabetes duration, HbA_{1c} reductions were smaller for those with ≥20 years’ disease duration, which is in line with our observations here in participants with >10 years’ type 2 diabetes duration¹⁴.

A subanalysis of the pivotal PIONEER 9 and 10 trials of oral semaglutide in Japanese individuals with type 2 diabetes reported comparable HbA_{1c} reductions across BMI subgroups¹⁰. Our observations found a non-significant trend toward greater reductions in HbA_{1c} in participants in the higher BMI subgroups. These results align with a Japanese retrospective study of oral semaglutide in people with type 2 diabetes, which also found that people with baseline BMI ≥30.3 kg/m² were more likely to have a greater HbA_{1c} reduction than those with BMI <30.3 kg/m², but the difference was not statistically significant¹⁵. Furthermore, another Japanese retrospective study reported similar HbA_{1c} reductions with oral semaglutide across BMI subgroups of <25, ≥25–<30, and ≥30 kg/m²²¹⁴.

We observed a non-significant trend toward participants with higher baseline HbA_{1c} having greater reductions in HbA_{1c} than those with lower baseline HbA_{1c}. Conversely, proportionally

more participants in the lower baseline HbA_{1c} subgroups reached HbA_{1c} <7% at EoS vs those in higher baseline HbA_{1c} subgroups, likely due to many in the lower baseline HbA_{1c} subgroups already having HbA_{1c} close to or below 7% at baseline. Nevertheless, it is noteworthy that nearly one-third of participants with baseline HbA_{1c} ≥9% reached HbA_{1c} <7% at EoS, which is in line with the large reductions in HbA_{1c} observed in the higher baseline HbA_{1c} subgroups. These observations correspond with findings from the subanalysis from the PIONEER 9 and 10 trials, in which higher HbA_{1c} levels were associated with greater reductions in HbA_{1c}¹⁰.

Notable reductions in HbA_{1c} were observed in both the DPP-4i switchers and non-users subgroups, albeit smaller for DPP-4i switchers. Nonetheless, this indicates that switching from DPP-4i to oral semaglutide can provide additional glucose-lowering benefits. In our study, all participants initiated with oral semaglutide 3 mg, and 90% of DPP-4i switchers were receiving 3 mg or 7 mg at EoS. Furthermore, the proportion of DPP-4i switchers with HbA_{1c} <7% increased from 15% at baseline to 48% at EoS (50% and 52% of those receiving oral semaglutide 3 and 7 mg, respectively, vs 13% of the 14 mg group). This agrees with a recent randomized study in Japanese participants, in which participants switching from DPP-4i to oral semaglutide had significant reductions in their HbA_{1c} at 24 weeks vs those remaining on DPP-4i, at which point 80% of the oral semaglutide recipients were on doses of 3 or 7 mg¹⁶. Furthermore, a retrospective observational study undertaken in people with type 2 diabetes in Japan found significant reductions in HbA_{1c} switching from DPP-4is to oral semaglutide, with the reductions being similar across oral semaglutide doses (3, 7, and 14 mg)¹⁷. Similarly, a Japanese retrospective study revealed significant reductions in HbA_{1c} among DPP-4i switchers receiving oral semaglutide doses of 7 or 14 mg¹⁴. In contrast, another study found that HbA_{1c} reductions were more pronounced with higher oral semaglutide doses in people switching from DPP-4is¹⁸. Both the DPP-4i switchers and non-users groups experienced substantial weight loss, but with no notable difference between the groups. This may be because DPP-4is are not associated with reductions in body weight^{19–21}, whereas GLP-1RAs have been associated with significant weight loss^{13,22–25}, meaning that both DPP-4i groups were likely to be affected by the weight loss effects of GLP-1RAs to the same degree.

Differences in the end-of-study oral semaglutide dose were observed between subgroups. Participants in the younger subgroups had higher end-of-study oral semaglutide doses. This could have been due to differences in participant characteristics, where lower semaglutide doses were prescribed to older participants with lower body weight and higher doses prescribed to younger participants who were potentially more prone to obesity. This observation could also reflect prescribing decisions in routine clinical practice; lower doses prescribed to older individuals would be in line with Japanese guidelines advising caution relating to gastrointestinal symptoms and weight loss when prescribing GLP-1RAs to older individuals with type 2 diabetes^{1,8,9}.

The higher end-of-study oral semaglutide dose in men vs women may also relate to differences in body size between the sexes, such that women did not receive higher semaglutide doses per body weight. The higher end-of-study oral semaglutide dose in the higher baseline HbA_{1c} subgroups could be due to those participants being prescribed higher doses to achieve glycemic control.

Reductions in both HbA_{1c} and body weight were greater in participants receiving oral semaglutide 3 mg at EoS compared with those receiving higher doses. Also, a greater proportion of participants achieved HbA_{1c} <7% with oral semaglutide 3 mg or 7 mg vs 14 mg. This observation is contrary to a retrospective study in Japanese individuals with type 2 diabetes that reported that higher oral semaglutide doses led to greater reductions in HbA_{1c}¹⁴. Reasons for our findings are not clear. In European and Canadian studies from the PIONEER REAL program, most participants received oral semaglutide 14 mg at EoS, unlike PIONEER REAL Japan where most participants received the 7 mg dose at EoS; nevertheless, reductions in HbA_{1c} were comparable for these studies^{22–25}. This supports other research that suggests incretin-related drugs such as DPP-4is and GLP-1RAs might be more effective at reducing HbA_{1c} in Japanese individuals with type 2 diabetes than in their Western counterparts^{26–28}. This likely reflects underlying differences in type 2 diabetes pathology between these geographical populations¹. This also explains why participants in PIONEER REAL Japan could achieve comparable glycemic control at lower oral semaglutide doses compared with the other PIONEER REAL studies; it also suggests that participants with more treatment-resistant disease may have had their dose increased, leading to our observation. However, the reasons why oral semaglutide doses were increased during this study are unknown.

Overall, the frequency of AEs was similar between subgroups. However, participants in the older subgroups experienced more AEs and were more likely to discontinue treatment vs younger subgroups. The older subgroups also had lower body weight and therefore would have received higher semaglutide doses per body weight, as previously discussed¹³. This may also explain why discontinuations because of AEs were higher in the lower BMI subgroup. However, a higher frequency of AEs was seen in participants receiving lower oral semaglutide doses at EoS. This may be due to participants who showed good tolerability to lower oral semaglutide doses having their dose increased, as well as dose reductions during the study to manage any treatment-emergent AEs.

A particular strength of the study was its real-world setting, which allowed for the investigation of routine clinical treatment with oral semaglutide. However, the observational, single-arm study design also had limitations in that results may be less robust than those from randomized controlled trials, and the study is not designed to test causal relationships. Alternative explanations for the observed changes in HbA_{1c} and body weight cannot be ruled out. Some subgroups contained

relatively few participants, which may have impacted the statistical testing. Semaglutide dosage was determined at the discretion of the physician, limiting comparisons between end-of-study dose groups.

In conclusion, this study showed that HbA_{1c} and body weight were both reduced following oral semaglutide initiation for all subgroups investigated. Our findings indicate that, in its approved dose range, oral semaglutide is effective, with an unaltered favorable benefit–risk balance and no new safety concerns, in a diverse range of individuals with type 2 diabetes in routine clinical practice in Japan. The analysis provides insights into oral semaglutide prescribing practices for participants with different characteristics in the real-world setting.

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Approval of the research protocol: The protocol for this research project was approved by suitably constituted ethics committees or institutional review boards of the institutions, and it conforms to the provisions of the Declaration of Helsinki. Ethics committees, institutional review boards, and approval numbers have been previously described¹².

Informed consent: All informed consent was obtained from the participants and/or their guardians.

Registry and the registration no. of the study/trial: This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04878393; first submitted May 5, 2021).

Animal studies: N/A.

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

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SUPPORTING INFORMATION

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

Table S1 | Reasons for treatment discontinuation and semaglutide dose at time of discontinuation.

Table S2 | Participant demographics and baseline characteristics in DPP-4i switchers and DPP-4i non-user subgroups (FAS).

Table S3 | Baseline comorbidities affecting $\geq 5\%$ of participants in any subgroup, by subgroups of interest (FAS).

Table S4 | Baseline comorbidities affecting $\geq 5\%$ of participants in DPP-4i switchers and DPP-4i non-user subgroups (FAS).

Table S5 | Oral semaglutide dose at EoS, by subgroups of interest (FAS).

Table S6 | Summary of safety for DPP-4i switchers and DPP-4i non-users—in-study observation period (FAS).

Table S7 | Most frequent ADRs[†] in $\geq 2\%$ of participants in any subgroup—in-study observation period (FAS).

Figure S1 | Time point of study discontinuation and semaglutide dose at time of discontinuation.

Figure S2 | Change from baseline in (a) HbA_{1c} and (b) body weight in DPP-4i switchers and DPP-4i non-users (MMRM adjusted, in-study observation period, FAS).