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Efficacy of oral semaglutide according to diabetes duration: an exploratory subgroup analysis of the PIONEER trial programme

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Background and aims: Oral semaglutide is the first oral glucagon-like peptide-1 receptor agonist for the treatment of type 2 diabetes. An exploratory analysis of data from the global Phase 3a PIONEER clinical development programme (PIONEER 1–5 and 7–8 trials) was conducted to assess the efficacy of once daily oral semaglutide 3, 7, 14 mg versus comparators by duration of diabetes at baseline.

Materials and methods: Data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5657). Patients were grouped according to diabetes duration (<5, 5–<10 and ≥10 years) and by trial. In the PIONEER trials, patients were randomised to treatment with oral semaglutide (3, 7 or 14 mg) or comparator (placebo, empagliflozin, sitagliptin or liraglutide). Endpoints were change from baseline in HbA_{1c} (%) and body weight (kg) at Week 26 (Week 52 in PIONEER 7) and data were analysed for all randomised patients using the trial product estimand.

Results: Mean duration of diabetes at baseline ranged from 3.5 (PIONEER 1) to 15.0 years (PIONEER 8) across the trials. At baseline the mean HbA_{1c} (%) was similar across the diabetes duration subgroups within each trial, whereas the mean body weight was higher and age was lower in the subgroup with diabetes duration <5 years. Reductions in HbA_{1c} were generally greater with increasing oral semaglutide dose but were not affected by diabetes duration (**Table**). Estimated treatment differences in HbA_{1c} (%) at Week 26 (Week 52 in PIONEER 7) were consistent across the range of diabetes durations. In general, there were no statistically significant interactions between treatment and diabetes duration (**Table**). The estimated odds of achieving HbA_{1c} target <7.0% were greater with oral semaglutide 7 mg and 14 mg versus comparators in all groups, irrespective of diabetes duration subgroup.

Conclusion: Across the PIONEER trials, oral semaglutide improved glycaemic control versus comparators, with an effect that was consistent across subgroups of diabetes duration. These findings support the use of oral semaglutide across a broad population of patients with type 2 diabetes.

Table. Change from baseline in HbA_{1c} by diabetes duration in 7 global Phase 3a PIONEER trials

Trial	Diabetes duration (years)	Number of patients	Baseline HbA_{1c} (%)	Estimated mean change from baseline in HbA_{1c} (%-points)					
				Oral semaglutide				Comparator(s)	
				3 mg	7 mg	14 mg	Flex	Pbo	Active
PIONEER 1 (diet and exercise)	<5	529	7.9	–0.9	–1.4	–1.6	-	–0.3	-
	5–<10	108	7.9	–0.6	–1.1	–1.4	-	0.6	-
	≥10	66	8.0	–0.3	–1.0	–1.3	-	0.3	-
PIONEER 2 (vs empagliflozin 25 mg)	<5	347	8.1	-	-	–1.5	-	-	–0.9
	5–<10	274	8.1	-	-	–1.5	-	-	–0.9
	≥10	200	8.2	-	-	–1.1	-	-	–0.7
PIONEER 3 (vs sitagliptin 100 mg)	<5	577	8.2	–0.5	–1.3*	–1.4	-	-	–0.8
	5–<10	687	8.3	–0.5	–1.0	–1.4	-	-	–0.7
	≥10	599	8.3	–0.6	–0.9	–1.4	-	-	–0.9
PIONEER 4 (vs liraglutide 1.8 mg and pbo)	<5	278	7.9	-	-	–1.3	-	–0.1	–1.2
	5–<10	238	8.1	-	-	–1.3	-	–0.1	–1.2
	≥10	195	7.9	-	-	–1.3	-	–0.1	–1.0
PIONEER 5 (renal impairment)	<5	30	7.9	-	-	–1.5	-	0.0	-
	5–<10	82	7.9	-	-	–1.3	-	–0.5	-
	≥10	212	8.0	-	-	–1.0	-	0.0	-
PIONEER 7 (flex vs sitagliptin 100 mg)	<5	168	8.3	-	-	-	–1.4	-	–0.8
	5–<10	153	8.3	-	-	-	–1.4	-	–0.5
	≥10	183	8.3	-	-	-	–1.3	-	–0.7
PIONEER 8 (added-on to insulin)	<5	69	8.2	–0.5*	–0.7	–1.3	-	–0.1	-
	5–<10	145	8.2	–0.2	–0.9	–1.6	-	–0.3	-
	≥10	517	8.2	–0.7	–1.1	–1.4	-	0.0	-

Mixed model for repeated measures analysis with treatment, region, stratification factors and interaction between them, as well as diabetes duration group and interaction between treatment and diabetes duration groups as factors, and baseline value of dependent variable as covariate. *p<0.05 unadjusted two-sided test of no treatment by subgroup interaction (no * indicates that the p-value did not reach statistical significance). -, dose/treatment was not investigated in trial; BL, baseline; flex, flexible dose adjustment; pbo, placebo.

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