Oral presentation 51

Efficacy of oral semaglutide according to baseline HbA_{1c}: an exploratory subgroup analysis of the PIONEER trial programme

JJ MEIER[1], R BAUER[2], TM BLICHER[2], I LINGVAY[3], MB TREPPENDAHL[2], B ZINMAN[4], J ROSENSTOCK[5]

[1]St Josef Hospital, Ruhr-University Bochum, Bochum, Germany; [2]Novo Nordisk A/S, Søborg, Denmark; [3]University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA; [4]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [5]Dallas Diabetes Research Center at Medical City, Dallas, TX, USA

Background and aims: The efficacy and safety of oral semaglutide, a glucagon-like peptide-1 receptor agonist, has been investigated in patients with type 2 diabetes in the global PIONEER Phase 3a trial programme. This exploratory subgroup analysis of the PIONEER programme evaluated the effect of baseline HbA_{1c} values on the overall HbA_{1c} and body weight reductions achieved during each trial.

Materials and methods: Data were included from all patients who participated in PIONEER 1–5, 7 and 8 (n=5657). Patients were grouped by trial and according to baseline HbA_{1c} (≤8.0%, >8.0–≤9.0% and >9.0%). In the PIONEER trials, patients were either randomised to once daily treatment with oral semaglutide (3, 7 or 14 mg, or flexibly dosed) or at least one comparator (placebo, empagliflozin 25 mg, sitagliptin 100 mg or liraglutide 1.8 mg). Endpoints were change from baseline in HbA_{1c} and body weight at week 26 (week 52 in PIONEER 7), and data were analysed for all randomised patients using the trial product estimand.

Results: Reductions from baseline in HbA_{1c} and body weight were greater with increasing oral semaglutide dose. HbA_{1c} reductions were also greater with higher baseline HbA_{1c}, but there was no consistent relationship between change in body weight and baseline HbA_{1c}. Reductions in HbA_{1c} were greater with oral semaglutide 7 mg and 14 mg versus placebo and versus active comparator in all subgroups (**Table**). Significant interactions by baseline HbA_{1c} were observed for oral semaglutide vs. the comparator in PIONEER 3 (14 mg), PIONEER 4 (14 mg vs. placebo), and PIONEER 8 (7 and 14 mg). The proportion of patients achieving an HbA_{1c} target of <7% was greater with oral semaglutide 7 mg and 14 mg versus comparators in all trials and all subgroups. Across the trials, an HbA_{1c} target of <7% was achieved with oral semaglutide 14 mg by 71–90% in the lowest HbA_{1c} subgroup (≤8%), by 49–71% in the middle HbA_{1c} subgroup (>8.0–≤9.0%) and by 29–62% in the highest HbA_{1c} subgroup (>9%).

Conclusion: Oral semaglutide consistently showed improved glycaemic control across baseline HbA_{1c} subgroups in the PIONEER trials with greater reductions in HbA_{1c} with oral semaglutide 7 and 14 mg versus all comparators in all subgroups. Reductions in HbA_{1c} were greater with higher oral semaglutide dose and higher baseline HbA_{1c}.

Table. Change from baseline in HbA_{1c} by baseline HbA_{1c} subgroup in 7 of the global Phase 3a PIONEER trials

Trial	HbA_{1c} (%) at baseline	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)	≤8 (n=409)	–0.5	–1.1	–1.2	-	0.0	-
	>8–≤9 (n=244)	–1.1	–1.6	–1.8	-	–0.1	-
	>9 (n=50)	–1.5	–1.8	–2.6	-	–0.6	-
PIONEER 2 (vs empagliflozin 25 mg)	≤8 (n=457)	-	-	–1.0	-	-	–0.5
	>8–≤9 (n=211)	-	-	–1.8	-	-	–1.1
	>9 (n=153)	-	-	–2.0	-	-	–1.7
PIONEER 3 (vs sitagliptin 100 mg)	≤8 (n=850)	–0.3	–0.6	–0.9	-	-	–0.5
	>8–≤9 (n=593)	–0.5	–1.1	–1.5	-	-	–0.8
	>9 (n=420)	–1.0	–1.9	–2.2	-	-	–1.4
PIONEER 4 (vs liraglutide 1.8 mg and pbo)	≤8 (n=403)	-	-	–1.0	-	–0.0	–0.8
	>8–≤9 (n=248)	-	-	–1.6	-	–0.1	–1.4
	>9 (n=60)	-	-	–2.2	-	–0.1	–2.0
PIONEER 5 (renal impairment)	≤8 (n=188)	-	-	–0.8	-	0.1	-
	>8–≤9 (n=108)	-	-	–1.5	-	–0.3	-
	>9 (n=28)	-	-	–2.1	-	–0.4	-
PIONEER 7 (flex vs sitagliptin 100 mg)	≤8 (n=201)	-	-	-	–1.0	-	–0.5
	>8–≤9 (n=246)	-	-	-	–1.5	-	–0.7
	>9 (n=57)	-	-	-	–2.0	-	–1.5
PIONEER 8 (added-on to insulin)	≤8 (n=329)	–0.3	–0.6	–1.0	-	0.2	-
	>8–≤9 (n=296)	–0.7	–1.2	–1.6	-	–0.2	-
	>9 (n=106)	–1.2	–1.8	–2.3	-	–0.1	-

Mixed model for repeated measures analysis with treatment, region, stratification factors and interaction between them, as well as baseline HbA_{1c} group and interaction between treatment and baseline HbA_{1c} groups as factors, and baseline value of dependent variable as covariate. -, not investigated in trial; flex, flexible dose adjustment; pbo, placebo

Clinical Trial Registration Numbers: NCT02906930; NCT02863328; NCT02607865; NCT02863419; NCT02827708; NCT02849080; NCT03021187