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Greater time spent in glycaemic control with oral semaglutide vs oral comparators

F.K. Knop[1,2], B. Cariou[3], J. Eliasson[4], G. Frappin[4], M.S. Kaltoft[4], E. Montanya[5], J. Rosenstock[6]; [1]Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark, [2]Steno Diabetes Center Copenhagen, Gentofte, Denmark, [3]Nantes Université, CHU Nantes, CNRS, Inserm, l'institut du thorax, Nantes, France, [4]Novo Nordisk A/S, Søborg, Denmark, [5]Hospital Universitari Bellvitge-IDIBELL, CIBERDEM, and University of Barcelona, Barcelona, Spain, [6]Dallas Diabetes Research Center at Medical City, Dallas, USA.

Background and aims: This exploratory analysis aimed to determine how long patients spent with HbA_{1c} <7.0% (53 mmol/mol), and how likely patients were to maintain this glycaemic target in PIONEER efficacy trials of ≥52 weeks' duration.

Materials and methods: Patients with uncontrolled type 2 diabetes in the PIONEER 2, 3, 4 and 7 trials were randomised to oral semaglutide vs active comparators (empagliflozin 25 mg, sitagliptin 100 mg, liraglutide 1.8 mg once daily). Oral semaglutide dose was escalated, starting at 3 mg once daily and increasing to 7 mg after 4 weeks and then to 14 mg after 8 weeks in all trials except PIONEER 7, which used a flexible dose adjustment approach based on HbA_{1c} and gastrointestinal tolerability. Empagliflozin was initiated at 10 mg and escalated to 25 mg after 8 weeks. Sitagliptin was initiated at 100 mg and not escalated. Liraglutide was initiated at 0.6 mg and escalated to 1.2 mg and then 1.8 mg after 1 and 2 weeks, respectively. Outcomes were evaluated for oral semaglutide vs active comparators using on-treatment without rescue medication data for all randomised patients. A binary endpoint of achieving HbA_{1c} <7.0% (53 mmol/mol) at both week 26 and 52 of each trial (and at week 78 for PIONEER 3) was analysed using a logistic regression model, with treatment, region and strata as categorical fixed effects and baseline value as a covariate.

Results: Mean baseline HbA_{1c} ranged from 8.0 to 8.3% (64-67 mmol/mol). The median duration of time spent with HbA_{1c} <7.0% (53 mmol/mol) was greater with oral semaglutide (26.3-33.7 weeks) vs oral comparators (0-10.9 weeks) (Table). The mean duration of time spent with HbA_{1c} <7.0% (53 mmol/mol) was also greater for oral semaglutide vs oral comparators (Table). The mean and median duration of time spent in glycaemic control with oral semaglutide was similar to that seen with liraglutide. Greater proportions of patients had HbA_{1c} <7.0% (53 mmol/mol) for ≥38 weeks with oral semaglutide than with empagliflozin (46% vs 28%, respectively) and sitagliptin (PIONEER 3: 45% vs 28%, respectively; PIONEER 7: 27% vs 14%, respectively) but not liraglutide (46% vs 48%, respectively). The odds of patients achieving HbA_{1c} <7.0% (53 mmol/mol) at both week 26 and 52 were significantly greater with oral semaglutide vs comparators (Table).

Conclusion: In PIONEER trials of ≥52 weeks, oral semaglutide resulted in greater time spent at glycaemic target and a greater likelihood of maintaining glycaemic control vs oral comparators. Patients receiving oral semaglutide spent a similar time in glycaemic control vs liraglutide, despite a longer dose-escalation with oral semaglutide.

Table: Time spent in glycaemic control (HbA_{1c} <7.0% [53 mmol/mol]) with oral semaglutide vs active comparators in PIONEER trials of ≥52 weeks' duration

Trial (duration)	Treatment	FAS, N	Mean ± SD time in control, weeks	Median time in control, weeks	EOR [95% CI] of HbA_{1c} <7.0% (53 mmol/mol) at week 26[†] and 52[‡]
PIONEER 2 (52 weeks)	Oral semaglutide 14 mg	411	26.6 ± 19.7	33.7	
	Empagliflozin 25 mg	410	19.0 ± 19.9	10.9	4.1 [2.9; 5.8]***
PIONEER 3 (78 weeks)	Oral semaglutide 14 mg	465	34.3 ± 28.9	32.8	
	Sitagliptin 100 mg	467	21.9 ± 27.8	3.0	3.8 [2.7; 5.4]***
PIONEER 4 (52 weeks)	Oral semaglutide 14 mg	285	27.0 ± 19.6	33.5	
	Liraglutide 1.8 mg	284	27.9 ± 20.6	36.5	1.6 [1.1; 2.3]*
PIONEER 7 (52 weeks)	Oral semaglutide flex	253	22.2 ± 17.4	26.3	
	Sitagliptin 100 mg	251	12.8 ± 16.7	0.0	6.4 [3.9; 10.5]***

*p<0.05, ***p<0.0001 vs comparator; [†]Week 26 data were unavailable for PIONEER 7 and so week 24 data were used instead; [‡]and week 78 for PIONEER 3 only.
EOR, estimated odds ratio; FAS, full analysis set; flex, flexible dose adjustment.

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