Effect and safety of oral semaglutide monotherapy in type 2 diabetes: PIONEER 1 trial

M. HALUZIK[1], J. ROSENSTOCK[2], Y. TERAUCHI[3], O. JEPPESEN[4], E. CHRISTIANSEN[4], C.L. HERTZ[4], V.R. ARODA[5,6]

[1]Institute for Clinical and Experimental Medicine, Prague, Czech Republic, [2]Dallas Diabetes Research Center at Medical City, Dallas, USA, [3]Yokohama City University, Yokohama, Japan, [4]Novo Nordisk A/S, Søborg, Denmark, [5]Brigham and Women's Hospital, Boston, USA, [6]MedStar Health Research Institute Hyattsville, Hyattsville, USA

Background and aims: Oral semaglutide, the first glucagon-like peptide-1 (GLP-1) receptor agonist in a tablet formulation, is in late-stage development for the treatment of type 2 diabetes (T2D).

Materials and methods: The effect and safety of oral semaglutide (3, 7, or 14 mg once daily) was assessed in this randomised, double-blind, placebo-controlled phase 3a trial in drug-naïve patients with T2D uncontrolled on diet and exercise (n=703). The primary endpoint was change from baseline in HbA_{1c} at week 26. The primary estimand (treatment policy) evaluated the effectiveness regardless of trial product discontinuation or rescue medication use. A secondary estimand (hypothetical) evaluated the efficacy of trial product while on treatment without rescue medication using a mixed model for repeated measures (MMRM), and is the conventional statistical method used in many previous T2D studies.

Results: Baseline characteristics were balanced between treatment groups: approximately 49% of patients were female, mean age was 55 years and mean duration of diabetes was 3.5 years. Oral semaglutide resulted in clinically meaningful reductions in both HbA_{1c} (all doses) and body weight (higher doses) at week 26 (Table). Adverse events (AEs) occurred in 58%, 53% and 57% for 3, 7, and 14 mg oral semaglutide, respectively, and 56% with placebo. The most common AE with oral semaglutide was transient mild or moderate nausea. Nausea occurred in 5–16% of patients with oral semaglutide vs. 6% with placebo.

Conclusion: This trial represents the first phase 3 demonstration of the effect and safety of an orally administered GLP-1 receptor agonist. In conclusion, oral semaglutide demonstrated superiority vs. placebo in reducing HbA_{1c} (all dose levels) and body weight (14 mg) and, consistent with the GLP-1 receptor agonist class, it was well tolerated in T2D uncontrolled on diet and exercise.

	Oral semaglutide 3 mg (n=175)		Oral semaglutide 7 mg (n=175)		Oral semaglutide 14 mg (n=175)		Placebo (n=178)	
Baseline HbA_{1c}, %-points	7.9		8.0		8.0		7.9	
Baseline body weight, kg	86.9		89.0		88.1		88.6	
ENDPOINTS AT WEEK 26 BY PRIMARY AND SECONDARY ESTIMANDS								
	PRIMARY	**SECONDARY**	**PRIMARY**	**SECONDARY**	**PRIMARY**	**SECONDARY**	**PRIMARY**	**SECONDARY**
Change from baseline in HbA_{1c}, %-points ± SE (primary endpoint)	-0.9 ± 0.1	-0.8 ± 0.1	-1.2 ± 0.1	-1.3 ± 0.1	-1.4 ± 0.1	-1.5 ± 0.1	-0.3 ± 0.1	-0.1 ± 0.1
HbA_{1c} (%-points) treatment difference vs placebo [95%CI]	-0.6‡ [-0.8; -0.4]	-0.7‡ [-0.9; -0.5]	-0.9‡ [-1.1; -0.6]	-1.2‡ [-1.5; -1.0]	-1.1‡ [-1.3; -0.9]	-1.4‡ [-1.7; -1.2]	–	–
Change from baseline in body weight, kg ± SE (secondary confirmatory endpoint)	-1.5 ± 0.3	-1.7 ± 0.3	-2.3 ± 0.4	-2.5 ± 0.3	-3.7 ± 0.3	-4.1 ± 0.3	-1.4 ± 0.3	-1.5 ± 0.3
Weight (kg) treatment difference vs placebo [95%CI]	-0.1 [-0.9; 0.8]	-0.2 [-1.0; 0.6]	-0.9 [-1.9; 0.1]	-1.0* [-1.8; -0.2]	-2.3‡ [-3.1; -1.5]	-2.6‡ [-3.4; -1.8]	–	–
Proportion of subjects with HbA_{1c} <7%, %	55.1‡	59.1‡	68.8‡	71.9‡	76.9‡	80.3‡	31.0	33.8
Proportion of subjects with weight loss ≥5%, %	19.6	21.3	26.9*	28.7*	41.3‡	44.3‡	14.9	15.7

n, number of randomised subjects in the full analysis set; SE, standard error; *p<0.05; ‡p<0.001 vs placebo. Baseline data are means. Changes and treatment differences are LSmeans; proportions are observed. The primary and confirmatory secondary endpoints were controlled for multiplicity for the primary estimand. The primary estimand (treatment policy) was evaluated by a pattern-mixture model using multiple imputation to handle missing data. The secondary estimand (hypothetical) was evaluated by a MMRM.