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BRIEF REPORT

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Efficacy and safety of oral semaglutide by baseline age in Japanese patients with type 2 diabetes: A subgroup analysis of the PIONEER 9 and 10 Japan trials

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Abstract

A post-hoc exploratory analysis of the PIONEER 9 and 10 trials evaluated the effect of baseline age (<65 and ≥65 years) on the efficacy and safety of oral semaglutide in Japanese patients with type 2 diabetes. In PIONEER 9 and 10, patients were randomized to once-daily oral semaglutide (3, 7 or 14 mg) or a comparator (placebo or once-daily subcutaneous liraglutide 0.9 mg [PIONEER 9]; once-weekly subcutaneous dulaglutide 0.75 mg [PIONEER 10]) for 52 weeks, with 5 weeks' follow-up. In total, 701 patients were included (PIONEER 9: N = 243; PIONEER 10: N = 458). Glycaemic efficacy of oral semaglutide was similar in Japanese patients aged <65 years compared with those ≥65 years, and there did not appear to be a clear pattern between age subgroup and body weight changes. Across treatment arms, adverse events generally occurred in greater proportions of patients aged ≥65 versus <65 years. There was generally a higher rate of premature trial product discontinuation because of adverse events in the older age group. These results indicate that oral semaglutide is efficacious in Japanese patients irrespective of age.

KEYWORDS
antidiabetic drug, glucagon-like peptide-1 analogue, glycaemic control, incretin therapy, randomized trial, type 2 diabetes

1 | INTRODUCTION

The efficacy and safety of oral semaglutide in patients with type 2 diabetes (T2D) was investigated in the global PIONEER programme.[1] As there are established phenotypic differences between T2D in Japanese and Western populations,[2,3] two trials were conducted exclusively in Japanese patients. The PIONEER 9 trial assessed the dose–response of oral semaglutide and compared the efficacy and safety of oral semaglutide with placebo and liraglutide 0.9 mg.[4] The PIONEER 10 trial evaluated the safety and efficacy of oral semaglutide versus dulaglutide 0.75 mg added on to existing background medication.[5] The results of these trials supported the efficacy and tolerability of oral semaglutide in Japanese patients.[4,5]

Japan has an increasingly ageing population and the incidence of T2D is also rising, leading to an increase in elderly patients with the disease.[6] There may be differences between elderly and younger patients

Trial registration numbers: NCT03018028 and NCT03015220.

with T2D in terms of their clinical presentation, prevalence of comorbidities and polypharmacy, and risk of adverse events (AEs) such as hypoglycaemia.[7-9] It is therefore important to understand if the efficacy and safety of therapies differ between younger and older patients.

A post-hoc exploratory analysis of the PIONEER 9 and 10 trials was performed to investigate the effects of oral semaglutide in subgroups of Japanese patients aged <65 years and ≥65 years.

2 | MATERIALS AND METHODS

2.1 | Individual trial designs

PIONEER 9 was a randomized, double-blind, placebo-controlled and open-label, active-controlled, phase 2/3a trial (NCT03018028). The primary endpoint was change in glycated haemoglobin (HbA1c) from baseline to week 26.[4] PIONEER 10 was a randomized, open-label, active-controlled, multicentre, phase 3a trial (NCT03015220). The primary endpoint was the number of treatment-emergent AEs over 57 weeks.[5]

Efficacy data in PIONEER 9 and 10 were assessed according to two estimands: the treatment policy estimand (treatment effect regardless of rescue medication use or treatment discontinuation), and the trial product estimand (treatment effect assuming patients remained on trial product without the use of rescue medication).[10] The primary estimand in PIONEER 9 was the trial product estimand, whereas the primary estimand in PIONEER 10 was the treatment policy estimand.[4,5]

Further information on the trial designs is provided in the Supporting Information.

2.2 | Patient populations

In PIONEER 9, Japanese patients aged ≥20 years and diagnosed with T2D (HbA1c 6.5%-9.5% [48-80 mmol/mol] if managed with oral agents, or HbA1c 7.0%-10.0% [53-86 mmol/mol] if managed by diet/exercise) for ≥30 days before screening were included. In PIONEER 10, Japanese patients were included if they were ≥20 years of age and diagnosed with T2D (HbA1c 7.0%-10.5% [53-91 mmol/mol]) for ≥60 days before screening. Full inclusion and exclusion criteria have been previously described.[4,5]

2.3 | Subgroup analyses

All patients from PIONEER 9 (N = 243) and PIONEER 10 (N = 458) were included in this post-hoc exploratory analysis and grouped by baseline age <65 and ≥65 years.

2.4 | Endpoints and assessments

In this post-hoc exploratory analysis of PIONEER 9 and 10, the changes from baseline in HbA1c and body weight at week 26 were assessed using the treatment policy estimand. AEs up to the end of follow-up (week 57) were assessed during the on-treatment observation period (the period in which the patient was considered treated with trial product).

Other endpoints included the change from baseline in estimated glomerular filtration rate (eGFR) at week 26.

2.5 | Statistical analyses

The changes from baseline in HbA1c and body weight were analysed using a pattern mixture model with an analysis of covariance (ANCOVA)-based multiple imputation to impute missing data. After imputation, the complete data sets were analysed using an ANCOVA model with treatment, stratification, subgroup, and interaction between treatment and subgroup as categorical fixed effects and the baseline value as a covariate, and results were combined using Rubin's rule.

Baseline demographic information of participants and safety data were reported using descriptive statistics.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

In both studies, there were more patients aged <65 years (PIONEER 9, n = 160; PIONEER 10, n = 321) than ≥65 years (PIONEER 9, n = 83; PIONEER 10, n = 137). Patients in the <65 years subgroup had, on average, a shorter duration of T2D, higher body weight and better renal function than those in the ≥65 years subgroup (Table S1). The proportions of patients on background glucose-lowering medication in PIONEER 10 are shown in Table S1.

3.2 | Efficacy by subgroup

3.2.1 | Effect of baseline age on change in glycated haemoglobin (PIONEER 9 and 10)

Oral semaglutide reduced HbA1c from baseline in a dose-dependent manner in patients aged <65 years and ≥65 years in both trials after 26 weeks of treatment, and these reductions were broadly similar between the two age subgroups (Figure 1A).

One statistically significant treatment-by-subgroup interaction was observed for oral semaglutide 3 mg versus placebo in PIONEER 9 ($P = .0210$) and none were observed in PIONEER 10 (Figure S1).

3.2.2 | Effect of baseline age on change in body weight (PIONEER 9 and 10)

Reductions in body weight with oral semaglutide were dose dependent across both trials but with no consistent pattern between patients aged <65 years and ≥65 years (Figure 1B).

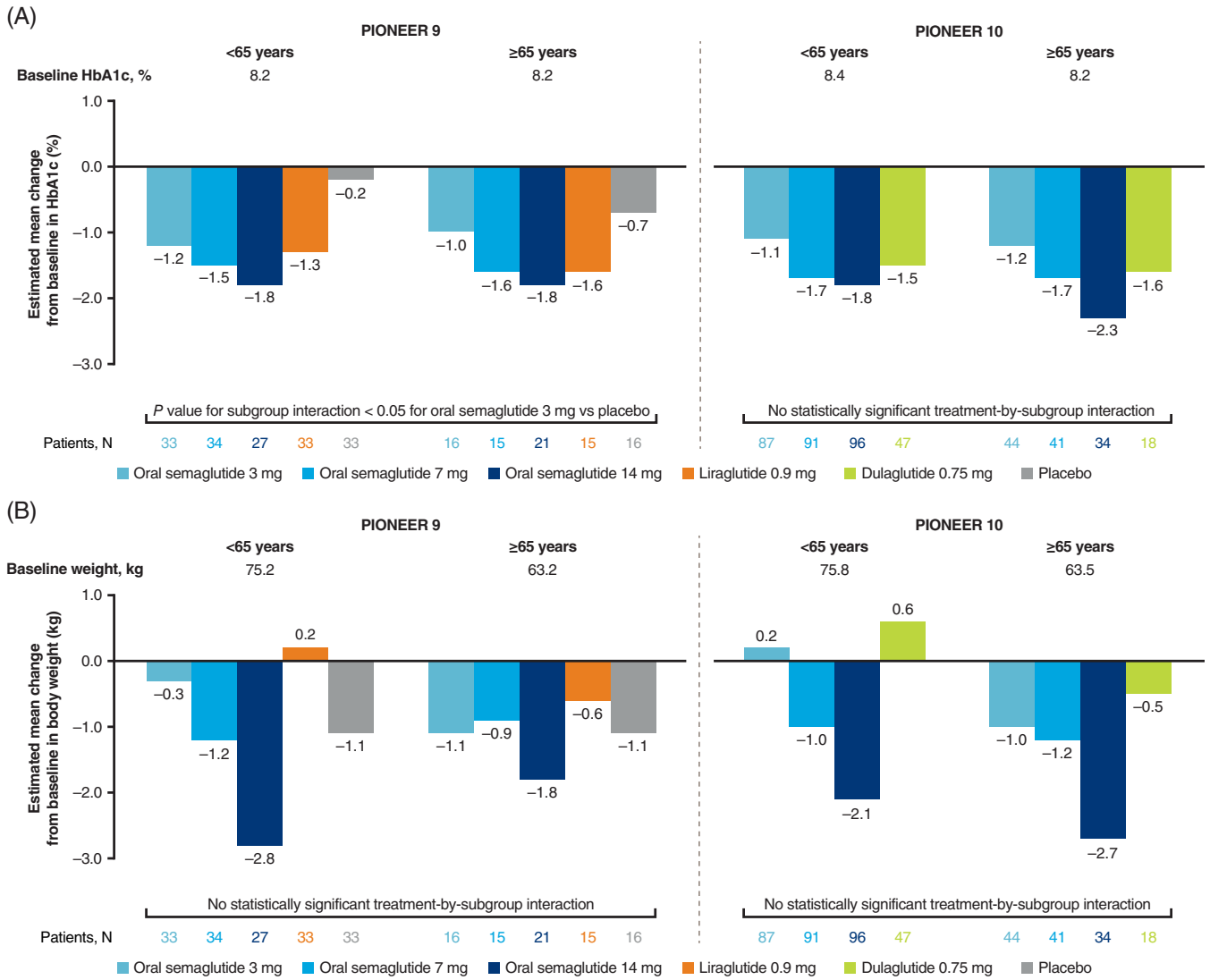

FIGURE 1 A, Change from baseline in HbA1c by age subgroup at week 26. B, Change from baseline in body weight by age subgroup at week 26. Data are for the treatment policy estimand (treatment effect regardless of trial product discontinuation and/or rescue medication use). HbA1c, glycated haemoglobin

There were no statistically significant treatment-by-subgroup interactions for change from baseline in body weight in neither PIONEER 9 nor in PIONEER 10 (Figure S2).

3.3 | Safety outcomes

In PIONEER 9, the occurrence of AEs did not appear to be dose dependent. In both trials, AEs generally occurred in larger proportions of patients aged ≥65 years than those aged <65 years (Table 1). The frequency of serious AEs was low in patients receiving oral semaglutide in PIONEER 9 and 10, and generally occurred in similar numbers of patients aged ≥65 years than <65 years. Most AEs in PIONEER 9 and in PIONEER 10 were mild to moderate in severity for both age subgroups (Table 1). The frequency of premature trial product discontinuation was low across treatment arms and in both age subgroups in PIONEER 9. In PIONEER 10, a higher proportion of patients discontinued trial product prematurely in the ≥65 years subgroup (Table 1).

Gastrointestinal events were the most frequently observed class of AEs in PIONEER 9 and 10 (Table 1). The proportions of patients with gastrointestinal AEs in both trials tended to be higher in the ≥65 years subgroup compared with the <65 years subgroup (Table 1).

There were very few severe or blood glucose-confirmed symptomatic hypoglycaemic events in any treatment group in either trial, with a similar occurrence between age subgroups (Table S2).

In PIONEER 9, in-trial diabetic retinopathy and related complications (defined using the Medical Dictionary for Regulatory Activities version 20.1) appeared to occur more frequently in patients aged ≥65 years whereas in PIONEER 10, the opposite was observed (Table S3).

TABLE 1 Summary of adverse events in PIONEER 9 and 10 by age subgroup

	Age subgroup (years)	PIONEER 9					PIONEER 10			
		Oral semaglutide			Lira		Oral semaglutide			Dula
		3 mg	7 mg	14 mg	0.9 mg	Placebo	3 mg	7 mg	14 mg	0.75 mg
Number of patients	<65	33	34	27	33	33	87	91	96	47
	≥65	16	15	21	15	16	44	41	34	18
All AEs, n (%)	<65	23 (69.7)	24 (70.6)	17 (63.0)	25 (75.8)	25 (75.8)	68 (78.2)	74 (81.3)	79 (82.3)	38 (80.9)
	≥65	14 (87.5)	13 (86.7)	17 (81.0)	7 (46.7)	14 (87.5)	33 (75.0)	32 (78.0)	32 (94.1)	15 (83.3)
Severe, n (%)	<65	1 (3.0)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.0)	0 (0.0)
	≥65	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	1 (2.4)	0 (0.0)	0 (0.0)
Moderate, n (%)	<65	3 (9.1)	3 (8.8)	1 (3.7)	2 (6.1)	4 (12.1)	9 (10.3)	4 (4.4)	6 (6.3)	1 (2.1)
	≥65	0 (0.0)	2 (13.3)	3 (14.3)	0 (0.0)	4 (25.0)	6 (13.6)	5 (12.2)	6 (17.6)	0 (0.0)
Mild, n (%)	<65	21 (63.6)	24 (70.6)	16 (59.3)	24 (72.7)	24 (72.7)	66 (75.9)	73 (80.2)	78 (81.3)	38 (80.9)
	≥65	14 (87.5)	11 (73.3)	17 (81.0)	7 (46.7)	13 (81.3)	32 (72.7)	32 (78.0)	31 (91.2)	15 (83.3)
Serious AEs, n (%)	<65	1 (3.0)	2 (5.9)	0 (0.0)	0 (0.0)	1 (3.0)	4 (4.6)	2 (2.2)	5 (5.2)	1 (2.1)
	≥65	1 (6.3)	1 (6.7)	0 (0.0)	0 (0.0)	2 (12.5)	5 (11.4)	2 (4.9)	2 (5.9)	0 (0.0)
AEs leading to premature trial product discontinuation, n (%)	<65	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	2 (2.2)	3 (3.1)	1 (2.1)
	≥65	0 (0.0)	1 (6.7)	2 (9.5)	0 (0.0)	0 (0.0)	3 (6.8)	6 (14.6)	5 (14.7)	1 (5.6)
All GI AEs, n (%)	<65	12 (36.4)	11 (32.4)	7 (25.9)	12 (36.4)	6 (18.2)	23 (26.4)	32 (35.2)	44 (45.8)	19 (40.4)
	≥65	5 (31.3)	7 (46.7)	9 (42.9)	6 (40.0)	4 (25.0)	17 (38.6)	19 (46.3)	26 (76.5)	7 (38.9)
Constipation	<65	3 (9.1)	5 (14.7)	2 (7.4)	5 (15.2)	3 (9.1)	5 (5.7)	9 (9.9)	15 (15.6)	3 (6.4)
	≥65	2 (12.5)	1 (6.7)	4 (19.0)	4 (26.7)	0 (0.0)	7 (15.9)	7 (17.1)	5 (14.7)	3 (16.7)
Nausea	<65	2 (6.1)	3 (8.8)	3 (11.1)	0 (0.0)	1 (3.0)	4 (4.6)	7 (7.7)	10 (10.4)	4 (8.5)
	≥65	0 (0.0)	2 (13.3)	1 (4.8)	0 (0.0)	0 (0.0)	3 (6.8)	4 (9.8)	2 (5.9)	2 (11.1)
Diarrhoea	<65	1 (3.0)	1 (2.9)	2 (7.4)	2 (6.1)	0 (0.0)	2 (2.3)	2 (2.2)	7 (7.3)	3 (6.4)
	≥65	3 (18.8)	0 (0.0)	1 (4.8)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	3 (8.8)	1 (5.6)
Abdominal discomfort	<65	1 (3.0)	1 (2.9)	0 (0.0)	2 (6.1)	0 (0.0)	2 (2.3)	5 (5.5)	5 (5.2)	1 (2.1)
	≥65	0 (0.0)	2 (13.3)	1 (4.8)	0 (0.0)	1 (6.3)	1 (2.3)	1 (2.4)	4 (11.8)	0 (0.0)

Abbreviations: AE, adverse event; Dula, dulaglutide; GI, gastrointestinal; Lira, liraglutide.

3.4 | Other outcomes

Overall, in PIONEER 9 and 10, eGFR remained unchanged at week 26 for patients aged <65 and ≥65 years across all treatment groups (Table S4).

4 | DISCUSSION

In the overall study populations in PIONEER 9 and 10, reductions in HbA1c were similar with oral semaglutide 7 mg, liraglutide 0.9 mg and dulaglutide 0.75 mg, while oral semaglutide 14 mg provided greater reductions in HbA1c than comparators.[4,5] In this subgroup analysis, reductions in HbA1c were similar in both trials regardless of age subgroup, which is consistent with findings in patients aged <65 and ≥65 years from the overall PIONEER trial programme[11] and post-hoc analyses of once-weekly subcutaneous semaglutide in the global SUSTAIN trial programme.[12]

In the subgroup analysis, reductions in body weight were consistent with the overall population in PIONEER 9 and 10[4,5] and there did not appear to be a clear relationship between age subgroup and body weight reductions in either trial. Similarly, in the exploratory analysis of the global PIONEER trial population, there did not appear to be a relationship between body weight reductions with oral semaglutide and age subgroup, and baseline body weight also tended to be higher in the younger subgroup.[11] Furthermore, age did not affect body weight reductions achieved with once-weekly subcutaneous semaglutide in a post-hoc analysis of the global SUSTAIN trial programme.[12] In the current analysis, baseline body mass index (BMI) was greater in the younger subgroup in both PIONEER 9 and 10. Given that BMI is known to influence beta-cell function in Japanese patients with T2D,[13] further investigation would be required to assess whether

age affects endogenous insulin secretory ability and efficacy of oral semaglutide.

Given that older patients are likely to have an increased risk of experiencing treatment-related AEs, it was not unexpected that the proportions of patients reporting any AEs with oral semaglutide were greater in the ≥65 years subgroup compared with the <65 years subgroup in PIONEER 9. The picture was less clear in PIONEER 10 but for oral semaglutide 14 mg, a higher proportion of patients experienced AEs in the older age group than the younger age group. These results are consistent with the global population of the PIONEER trial programme.[11] In the present analysis, baseline mean eGFR was slightly lower for patients aged ≥65 than those <65 years, which could have contributed to the increased incidence of AEs in the ≥65 years subgroup for some treatment groups. Serious AEs generally occurred in similar numbers of patients aged <65 and ≥65 years in PIONEER 9 and 10, and there were few severe or blood-glucose confirmed hypoglycaemic events in any treatment group or age group in PIONEER 9 and 10.

In both PIONEER 9 and PIONEER 10, gastrointestinal AEs were the most frequent AEs with oral semaglutide, which is expected for the glucagon-like peptide-1 receptor agonist class.[14] Overall, gastrointestinal AEs and events leading to a premature trial product discontinuation tended to increase with age in both trials, potentially due to an increased risk of AEs in older patients.[7]

The main limitation to this post-hoc analysis was low numbers of patients in some subgroups, particularly those ≥65 years in PIONEER 9, so data must be interpreted with caution. In addition, the numbers of patients >75 years of age were too low to be included as a subgroup, and therefore, insights into the efficacy and safety of oral semaglutide in Japanese patients aged >75 years could not be provided.

This post-hoc analysis of PIONEER 9 and 10 shows that the glycaemic efficacy of oral semaglutide appeared to be similar between Japanese patients aged <65 years and ≥65 years, with no clear pattern between age subgroups for body weight changes. Premature trial product discontinuation due to AEs was slightly increased in Japanese patients ≥65 years of age across oral semaglutide and dulaglutide treatment groups in PIONEER 10.

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CONFLICT OF INTEREST

K.F. is an employee of Novo Nordisk Pharma Limited. C.L.H. and A.M.N. are employees and shareholders of Novo Nordisk A/S, the sponsor of this trial. H.H. is an employee and shareholder of Novo Nordisk Pharma Limited. Y.Y. has received consulting or speaker fees from Daiichi Sankyo, Mitsubishi Tanabe Pharma, MSD, Novo Nordisk Pharma Limited, Ono Pharmaceutical, Sanofi, Sumitomo Dainippon and Takeda Pharmaceutical Company; and research grants from Daiichi Sankyo, Mitsubishi Tanabe Pharma, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho and Takeda Pharmaceutical Company. D.Y. has received consulting or speaker fees from Astellas, Eli Lilly Japan, MSD, Nippon Boehringer Ingelheim, Novo Nordisk Pharma Limited, Ono Pharmaceutical, Sumitomo Dainippon and Takeda Pharmaceutical Company; and clinically commissioned and joint research grants from Arklay, Novo Nordisk Pharma Limited, Ono Pharmaceutical, Taisho Pharmaceutical, Takeda Pharmaceutical Company and Terumo. J.N. has received lecture fees from Astellas Pharma, AstraZeneca, Boehringer Ingelheim Japan, Daiichi Sankyo, Eli Lilly Japan, Kowa Pharmaceutical, Mitsubishi Tanabe Pharma, MSD, Novartis Pharma, Novo Nordisk, Ono Pharmaceutical, Sanofi, Takeda Pharmaceutical Company and Terumo; research funding from Boehringer Ingelheim Japan, EPS Corporation and Kissei Pharmaceuticals; and donations from Astellas Pharma, Daiichi Sankyo, Eli Lilly Japan, Japan Tobacco, MSD, Novartis Pharma, Novo Nordisk Pharma Limited, Ono Pharmaceuticals, Sanofi, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceuticals and Takeda Pharmaceuticals. Y.S. has received consulting or speaker fees from Eli Lilly and Company, MSD, Nippon Boehringer Ingelheim, Novo Nordisk Pharma Limited, Taisho Pharmaceutical and Takeda Pharmaceutical Company; and clinically commissioned and joint research grants from Arklay, Eli Lilly and Company, MSD, Nippon Boehringer Ingelheim, Novo Nordisk, Ono Pharmaceutical, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical Company and Terumo Corporation.

AUTHOR CONTRIBUTIONS

Design of the subgroup analyses was performed by H.H. Trial conduct and data collection: D.Y., J.N., Y.Y., Y.S. Analysis of data: A.M.N., C.L.H., H.H. Interpretation of data: all. Writing, revision, and final approval of manuscript: all.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data will be shared with researchers submitting a research proposal approved by the independent review board. Access request proposals can be found on the Novo Nordisk Trials website. Data will be made available after research completion, and approval of the product and product use in the EU and the USA. Individual participant data will be shared in data sets in a de-identified and anonymised format, with no limitations on how the data can be used.

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REFERENCES

1. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: the PIONEER programme. *Diabetes Obes Metab*. 2020;22:1263-1277.
2. Yabe D, Seino Y, Fukushima M, Seino S. β cell dysfunction versus insulin resistance in the pathogenesis of type 2 diabetes in East Asians. *Curr Diab Rep*. 2015;15:602.
3. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: focus on East Asian perspectives. *J Diabetes Investig*. 2016;7:102-109.
4. Yamada Y, Katagiri H, Hamamoto Y, et al. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. *Lancet Diabetes Endocrinol*. 2020;8:377-391.
5. Yabe D, Nakamura J, Kaneto H, et al. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. *Lancet Diabetes Endocrinol*. 2020;8:392-406.
6. Yuan H, Li X, Wan G, et al. Type 2 diabetes epidemic in East Asia: a 35-year systematic trend analysis. *Oncotarget*. 2017;9:6718-6727.
7. Abbatecola AM, Maggi S, Paolisso G. New approaches to treating type 2 diabetes mellitus in the elderly: role of incretin therapies. *Drugs Aging*. 2008;25:913-925.
8. Kim KS, Kim SK, Sung KM, Cho YW, Park SW. Management of type 2 diabetes mellitus in older adults. *Diabetes Metab J*. 2012;36:336-344.
9. Pratley RE, Heller SR, Miller MA. Treatment of type 2 diabetes mellitus in the older adult: a review. *Endocr Pract*. 2014;20:722-736.
10. Aroda VR, Saugstrup T, Buse JB, Donsmark M, Zacho J, Davies MJ. Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: the PIONEER 1 randomized clinical trial as an example. *Diabetes Obes Metab*. 2019;21:2203-2210.
11. Aroda VR, Bauer R, Hertz CL, et al. Efficacy and safety of oral semaglutide by baseline age in the PIONEER clinical trial program. *Diabetes*. 2020;69:932-93P. https://doi.org/10.2337/db20-932-P
12. Warren M, Chaykin L, Trachtenbarg D, Nayak G, Wijayasinghe N, Cariou B. Semaglutide as a therapeutic option for elderly patients with type 2 diabetes: pooled analysis of the SUSTAIN 1-5 trials. *Diabetes Obes Metab*. 2018;20:2291-2297.
13. Funakoshi S, Fujimoto S, Hamasaki A, et al. Analysis of factors influencing pancreatic beta-cell function in Japanese patients with type 2 diabetes: association with body mass index and duration of diabetic exposure. *Diabetes Res Clin Pract*. 2008;82:353-358.
14. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19:524-536.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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