Effect of Oral Semaglutide Versus Comparators on Multiple Cardiometabolic Risk Factor Control in Adults With Type 2 Diabetes

Short running title (47/47 characters including spaces): Cardiometabolic risk factors & oral semaglutide

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## Twitter summary (199 characters including spaces):

Individuals with type 2 diabetes from the PIONEER 1–5, 7, and 8 trials were more likely to achieve reductions in cardiometabolic risk factors with oral semaglutide than placebo or active comparators.

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Type 2 diabetes is associated with multimorbidity, microvascular and macrovascular complications, and increased mortality (1). A holistic approach to treatment with multifactorial risk-reduction strategies is recommended to improve long-term diabetes outcomes (2). This *post hoc* analysis of the PIONEER 1–8 (excluding PIONEER 6) trials evaluated the efficacy of oral semaglutide versus placebo or active comparators in reducing four cardiometabolic risk factors.

The PIONEER trials compared once-daily oral semaglutide 3, 7, or 14 mg with (one or more of) placebo (PIONEER 1, 4, 5, and 8); empagliflozin 25 mg (PIONEER 2); sitagliptin 100 mg (PIONEER 3 and 7); or liraglutide 1.8 mg (PIONEER 4) in adults aged ≥18 years with type 2 diabetes. We assessed the proportion of participants with reductions of ≥1%-point glycated hemoglobin (HbA1c); ≥5% body weight (BW); ≥5 mmHg systolic blood pressure (SBP); and ≥0.5 mmol/L low-density lipoprotein (LDL) cholesterol. For each endpoint, an odds ratio was estimated for oral semaglutide 14 mg (or flexible dose adjustment for PIONEER 7) versus placebo or active comparator using the trial product estimand. We also assessed the proportion of participants and corresponding estimated odds ratios for achieving any two or three of the endpoints during the respective trials. Data were from the on-treatment without rescue medication period for all randomized participants. Binary endpoint was analyzed using a logistic regression model, and missing values for continuous endpoints that contribute to the binary endpoint were imputed using an ANCOVA model.

The proportion of participants reaching a defined reduction in each individual risk factor at the end of treatment were greater with oral semaglutide versus placebo or active comparators in all trials, except for comparable proportions for SBP ≥5 mmHg in the PIONEER 2 and 7 trials (Fig. 1A). The odds of reaching a HbA1c reduction of ≥1%-point were significantly greater with oral semaglutide versus placebo or active comparator in all trials (*P* < 0.001 for all comparisons, apart from liraglutide 1.8 mg in PIONEER 4; *P* = 0.048) (Fig. 1A). The odds of reaching a BW reduction of ≥5% were significantly greater with oral semaglutide versus placebo or all active comparators (all *P* < 0.001), except for the comparison with empagliflozin 25 mg in PIONEER 2 (*P* = 0.116) (Fig. 1A). The odds of reaching a SBP reduction of ≥5 mmHg were significantly greater with oral semaglutide versus placebo in PIONEER 1, 4, and 5, and versus sitagliptin 100 mg in PIONEER 3 (all *P* < 0.05); the odds were not significantly greater in PIONEER 2, 4 (versus liraglutide 1.8 mg), 7 and 8 (Fig. 1A). Additionally, the odds of reaching a reduction in LDL cholesterol of ≥0.5 mmol/L were significantly greater with oral semaglutide versus placebo in PIONEER 1 and 4, and with oral semaglutide versus empagliflozin 25 mg in PIONEER 2 (all *P* < 0.05) (Fig. 1A).

A greater proportion of participants across all the analyzed PIONEER trials also met the composite outcomes of reductions in any two or three endpoints with oral semaglutide versus placebo and all active comparators (Fig. 1B). The odds of meeting two- and three-endpoints were significantly greater with oral semaglutide versus any comparator across all trials (all *P* < 0.05) (Fig. 1B).

Cardiovascular (CV) diseases are the leading cause of mortality in individuals with type 2 diabetes; therefore, controlling cardiometabolic risk factors is vital, given their strong association with CV disease (2). Our analysis showed that the odds of reaching reductions in four cardiometabolic risk factors were greater with oral semaglutide versus comparators in most of the trials analyzed. Although our analysis did not investigate the effect of multifactor risk reduction on CV outcomes due to the relatively short trial lengths and, therefore, minimal number of events to analyze, glucagon-like peptide-1 receptor agonists have previously demonstrated CV safety or benefit (3–5).

Our analysis uses robust individual participant data from multiple phase 3 trials covering a wide variety of populations, comparators, and background medications, with minimal missing values. Limitations of our analysis included variations in trial length, with some trials being short (only PIONEER 3 extended beyond 52 weeks), leading to a lack of recorded CV events available to assess CV benefit or safety.

In summary, this analysis of seven PIONEER trials indicates that oral semaglutide 14 mg (or flexible dosing in PIONEER 7) was generally more effective at improving multiple cardiometabolic risk factors – including HbA1c, BW, SBP, and LDL cholesterol – versus placebo and active comparators. Therefore, oral semaglutide has the potential to improve the multimorbidity and adverse cardiometabolic profile associated with type 2 diabetes.

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CONFLICT OF INTEREST

B.M. and M.T.A. are employees and shareholders of Novo Nordisk A/S. P.K. is an employee of Novo Nordisk India Pvt. Ltd. V.R.A. reports receiving consultancy fees from Applied Therapeutics, Fractyl Health, Inc., Mediflix, Novo Nordisk A/S, Pfizer, and Sanofi; and research grant support (to institution) from Amgen, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Corcept, Eli Lilly, Fractyl Health, Inc., Novo Nordisk A/S, Pfizer, Rhythm, and Servier. J.J.M. has received grants from Merck Sharp & Dohme (MSD), Novo Nordisk, and Sanofi; and lecture/other fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, MSD, Novo Nordisk, Sanofi, and Servier. T.V. has served on scientific advisory panels, been part of speakers’ bureaus for, served as a consultant to, and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, MSD/Merck, Novo Nordisk, Sanofi, and Sun Pharmaceuticals. K.K. has served as a consultant to, and received speaker fees from, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Roche, Sanofi-Aventis, and Servier; has served on advisory boards for AstraZeneca, Eli Lilly, MSD, Novo Nordisk, and Sanofi-Aventis; and has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, and Servier. K.K. is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM), NIHR Global Research Centre for Multiple Long Term Conditions, NIHR Cross NIHR Collaboration for Multiple Long Term Conditions, NIHR Leicester Biomedical Research Centre (BRC) and the British Heart Foundation (BHF) Centre of Excellence. AUTHOR CONTRIBUTIONS

All authors were involved in the study design, in conducting the study and data collection, and/or involved in analyzing the data. All authors were involved in the interpretation of the data and critically reviewing, editing, and approving the letter.

M.T.A. and V.R.A. are the guarantors of this work and, as such, had full access to all the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure 1. Once-weekly oral semaglutide versus comparator for achieving either A) an individual endpoint, or B) multiple endpoints per trial.

Data show the proportion of participants and EOR per trial of achieving A) an individual endpoint of HbA1c reduction of ≥1%-point, body weight reduction of ≥5%, SBP reduction of ≥5 mmHg, or LDL cholesterol reduction of ≥0.5 mmol/L, or B) any two or three endpoints.

Observed data are from the on-treatment without rescue medication period. The odds ratios were estimated using the trial product estimand. Binary endpoint were analyzed using a logistic regression model for each of the 1000 imputed complete datasets and pooled by Rubin’s rule to draw inference. Missing values for continuous endpoints that enter the binary endpoint were imputed using an ANCOVA-based sequential multiple imputation model. Endpoints were analyzed at end of trial (week 26 for PIONEER 1 and 5, week 52 for PIONEER 2, 4, 7, and 8, and week 78 for PIONEER 3).

ANCOVA, analysis of covariance; BW, body weight; EOR, estimated odds ratio; empa, empagliflozin; flex, flexible dose adjustment; LDL, low-density lipoprotein; lira, liraglutide; SBP, systolic blood pressure; sema, semaglutide; sita, sitagliptin.