



BRIEF REPORT

Greater Combined Reductions of HbA_{1c} \geq 1.0% and Body Weight Loss \geq 5.0% or \geq 10.0% with Orally Administered Semaglutide Versus Comparators

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ABSTRACT

Introduction: A post hoc analysis of the PIONEER 1–5 and 8 trials assessed the clinically relevant composite endpoints of HbA_{1c} (glycated haemoglobin) reduction \geq 1% and body weight loss of \geq 5% or \geq 10% with orally administered semaglutide versus comparators.

Methods: In the PIONEER trials, people with type 2 diabetes were randomised to orally administered semaglutide versus placebo (PIONEER 1, 4, 5 and 8), empagliflozin

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(PIONEER 2), sitagliptin (PIONEER 3) and liraglutide (PIONEER 4) for 26–78 weeks. This analysis assessed the proportion of people achieving an HbA_{1c} reduction of \geq 1% and body weight loss of \geq 5% at week 26 and at end of treatment, and the proportion of people achieving an HbA_{1c} reduction of \geq 1% and body weight loss of \geq 10% at end of treatment.

Results: Overall, 3506 people in PIONEER 1–5 and 8 were included. At week 26 and at end of treatment, odds of achieving the composite endpoint of an HbA_{1c} reduction of \geq 1% and body weight loss of \geq 5% were significantly greater with orally administered semaglutide 14 mg than with placebo (PIONEER 1, 4, 5 and 8; all $p < 0.0001$), empagliflozin 25 mg (PIONEER 2, $p < 0.0001$), sitagliptin 100 mg (PIONEER 3, $p < 0.0001$) and liraglutide 1.8 mg (PIONEER 4, $p < 0.0001$). Odds of achieving the composite endpoint of HbA_{1c} reduction of \geq 1% and body weight loss of \geq 10% at end of treatment were also significantly greater with orally administered semaglutide versus comparators.

Conclusion: In PIONEER 1–5 and 8, odds of achieving clinically relevant reductions in both HbA_{1c} and body weight were significantly greater with orally administered semaglutide versus comparators.

Graphical Abstract:

Greater combined reductions of HbA_{1c} ≥1.0% and body weight loss ≥5.0% or ≥10.0% with orally administered semaglutide versus comparators

Kathleen M. Dungan, Lars Bardtrum, Erik Christiansen, Johanna Eliasson, Linda Mellbin, Vincent C. Woo, Tina Vilsbøll

What is the background?

For patients with type 2 diabetes, two important goals of treatment are bringing blood sugar levels under control and body weight loss¹

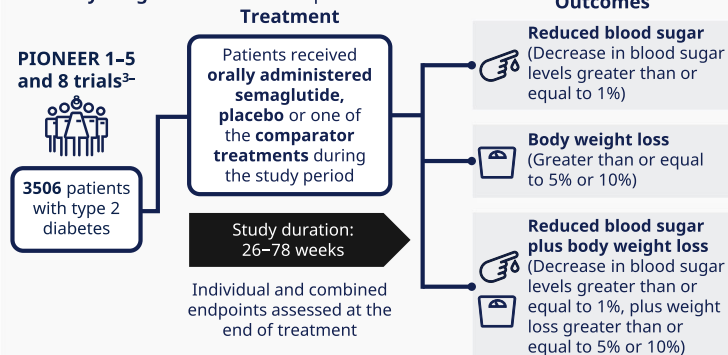


Why is this study needed?

Combined study outcomes provide a holistic view to help doctors decide what medicine to give to patients with type 2 diabetes²

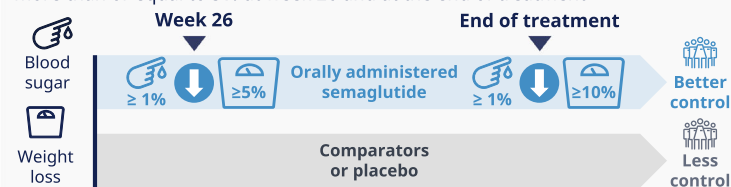
What was investigated?

This study looked at the extent at which patients with type 2 diabetes treated with orally administered semaglutide achieved both **lower blood sugar levels** and **body weight loss** versus comparators



What were the results?

Orally administered semaglutide was **better than** placebo and comparators in **reducing blood sugar levels** by more than or equal to 1% and **body weight loss** more than or equal to 5% at week 26 and at the end of treatment



Orally administered semaglutide was also **better than** placebo and comparators when the **larger body weight loss** target of more than or equal to 10% was used

What does this mean?

More patients who received treatment with orally administered semaglutide had improved blood sugar control and experienced greater body weight loss compared with patients who received placebo or comparators

Combined outcomes of reduced blood sugar levels and body weight loss may help doctors suggest suitable treatment options for patients with type 2 diabetes

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PEER-REVIEWED FEATURE

Keywords: Body weight loss; Composite endpoint; Glucagon-like peptide 1 analogue; Glycaemic control; Type 2 diabetes

Key Summary Points

Treatment guidelines for type 2 diabetes (T2D) recommend a comprehensive, individualised approach with multiple therapeutic goals (including HbA_{1c} reduction and body weight loss), as many people with T2D are associated with several comorbid conditions.

Composite endpoints provide physicians with a holistic view of the clinical benefit of treatments, and a foundation for clinical decision-making.

This post hoc analysis of the PIONEER 1–5 and 8 trials evaluated composite endpoints of $\geq 1\%$ reduction in HbA_{1c} and plus either a $\geq 5\%$ or $\geq 10\%$ reduction in body weight with orally administered semaglutide versus comparators in people with T2D.

The odds of achieving clinically relevant reductions in both HbA_{1c} and body weight were significantly greater with orally administered semaglutide versus comparators.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to <https://doi.org/10.6084/m9.figshare.22645201>.

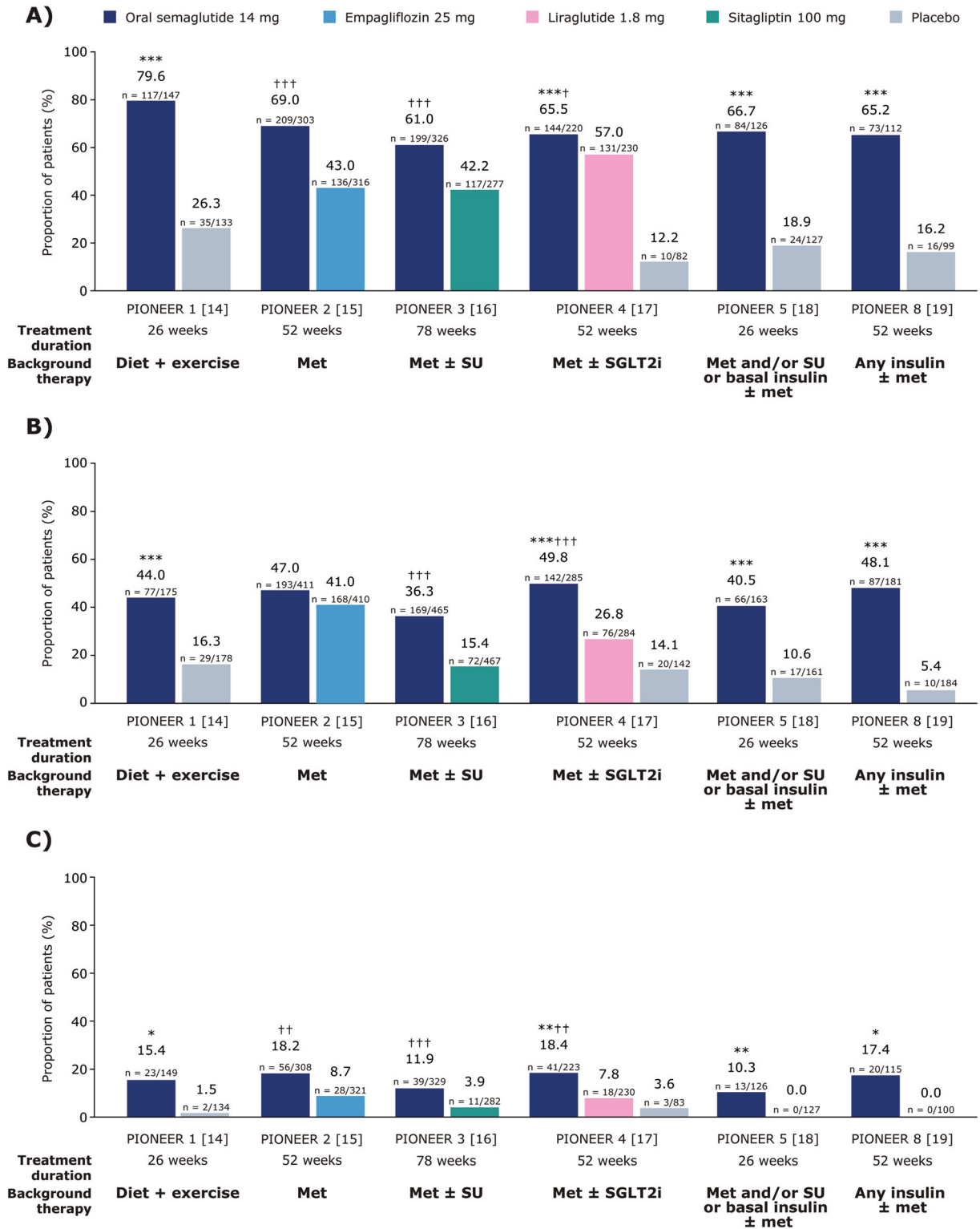
INTRODUCTION

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have been shown to reduce glycated haemoglobin (HbA_{1c}) and body weight in

people with type 2 diabetes (T2D), both of which are important therapeutic goals [1, 2]. The glucose and body weight lowering benefits and cardiovascular (CV) benefits of GLP-1RAs are becoming increasingly recognised, and GLP-1RAs are included in international T2D treatment recommendations and guidelines across the disease continuum [3]. Semaglutide is a long-acting GLP-1RA available as a once-weekly subcutaneous injection and a once-daily oral tablet for the treatment of people with inadequately controlled T2D [4]. The tablet formulation of semaglutide may remove the administrative burden on people and physicians (as compared to injectables) and facilitate initiation of GLP-1RAs earlier in the course of T2D [4, 5].

Treatment guidelines for T2D recommend a comprehensive, individualised approach with multiple therapeutic goals (including HbA_{1c} reduction and body weight loss), as many people with T2D also have overweight or obesity, which is associated with several comorbid conditions [1, 3]. Composite endpoints are useful to differentiate between treatment options in terms of overall efficacy and safety, thereby providing physicians with a holistic view of the clinical benefit of different treatments [6, 7]. Additionally, composite endpoints can provide a foundation for clinical decision-making, addressing the limitation of basing clinical decisions on a single outcome, such as change in HbA_{1c} [8].

HbA_{1c} reductions of $\geq 1\%$ and body weight loss of $\geq 5\%$ in people with T2D are considered important indicators of a clinically meaningful response to treatment, and have been shown to reduce the risk of diabetes-related complications [1, 9, 10]. Furthermore, the incidence rate of diabetes-related complications has been reported to decrease with every 1% reduction in HbA_{1c}, while a reduction in body weight of $\geq 5\%$ can confer metabolic improvement and reduce the risk of cardiometabolic disease [3, 9, 11]. In this post hoc analysis, data from several trials included in the PIONEER programme were evaluated to determine to what extent people with T2D treated with orally administered semaglutide versus comparators achieved composite endpoints of $\geq 1\%$



◀**Fig. 1** Proportion of people in PIONEER 1–5 and 8 trials achieving an HbA_{1c} reduction of $\geq 1\%$ (**A**), achieving a body weight loss of $\geq 5\%$ (**B**), or achieving a body weight loss of $\geq 10\%$ (**C**) at EOT. Data are observed proportions for the trial product estimand (on trial product without rescue medication). In panels **A** and **B** and for PIONEER 1–4 in panel **C**, *p* values are for the EORs for orally administered semaglutide 14 mg versus placebo or the active comparator. For PIONEER 5 and 8 in panel **C**, EORs could not be calculated as a result of 0 events in the comparator arms; *p* values for the risk difference were calculated instead. **p* < 0.01 versus placebo; ***p* < 0.001 versus placebo; ****p* < 0.0001 versus placebo; †*p* < 0.05 versus the active comparator; ††*p* < 0.001 versus the active comparator; †††*p* < 0.0001 versus the active comparator. *EOR* estimated odds ratio, *EOT* end of treatment, *HbA_{1c}* glycated haemoglobin, *met* metformin, *SGLT2i* sodium-glucose co-transporter 2 inhibitor, *SU* sulphonylurea

reduction in HbA_{1c} plus either a $\geq 5\%$ or $\geq 10\%$ reduction in body weight, as well as separate endpoints of $\geq 1\%$ decrease in HbA_{1c} and a $\geq 5\%$ or $\geq 10\%$ decrease in body weight.

METHODS

Trial Designs and Patient Populations

Data from the PIONEER 1–5 and 8 trials were assessed in this post hoc analysis. PIONEER 6 and 7 were excluded due to the use of different trial designs. PIONEER 6 was a CV outcomes trial in a population with established CV disease or at high risk of CV events, while PIONEER 7 included a flexible dose adjustment approach where not all people received orally administered semaglutide 14 mg [12, 13].

Designs and patient populations of the PIONEER 1–5 and 8 trials have been reported previously [14–19]. In brief, the PIONEER 1–5 and 8 trials were conducted across 26–78 weeks, and assessed the efficacy and safety of orally administered semaglutide (3 mg, 7 mg or 14 mg) versus placebo or active comparators (a sodium-glucose co-transporter 2 inhibitor [empagliflozin 25 mg], a dipeptidyl peptidase 4 inhibitor [sitagliptin 100 mg] or a GLP-1RA [subcutaneously administered liraglutide

1.8 mg]) in adults with T2D across a variety of background regimens (diet and exercise alone, metformin, 1–2 oral antidiabetic drugs, basal insulin \pm metformin or insulin \pm metformin) [14–19]. The protocols for the PIONEER 1–5 and 8 trials were approved by local independent ethics committees/institutional review boards at each trial site and conform to the provisions of the Declaration of Helsinki; all people provided written informed consent to participate in the trials.

Assessments

All people who received orally administered semaglutide 14 mg or comparators (active or placebo) during the PIONEER 1–5 and 8 trials were included in this analysis. The following individual and composite endpoints were assessed at the end of treatment (EOT; week 26, 52 or 78): achievement of (1) an HbA_{1c} reduction of $\geq 1\%$; (2) a body weight loss of $\geq 5\%$; (3) a body weight loss of $\geq 10\%$; (4) an HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 5\%$; and (5) an HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 10\%$. In addition, the proportion of people achieving an HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 5\%$ at week 26 in all trials was assessed to determine whether the results differed from the EOT.

Statistical Analysis

Data for the trial product estimand (on trial product without rescue medication) were analysed. Missing data were accounted for using an analysis of covariance-based sequential multiple imputation model. Separate logistic regression analyses were performed for complete data sets of each study. Endpoints were analysed with treatment, strata (background medication for PIONEER 3–5 and 8, renal function for PIONEER 5 and insulin regimen for PIONEER 8), region and interaction between strata (PIONEER 5 and 8) as categorical fixed effects, and continuous baseline value(s) as covariates. Results were combined by use of Rubin's rule to draw inference [20].

RESULTS

Baseline Characteristics

Overall, 3506 people with T2D in the PIONEER 1–5 and 8 trials were included. Baseline demographics and clinical characteristics grouped by trial and treatment arm are presented in Supplementary Table S1. Mean duration of diabetes was lowest in PIONEER 1 and highest in PIONEER 8. Likewise, the mean patient age was lowest in PIONEER 1 and highest in PIONEER 5 and 8. Baseline HbA_{1c} and body weight were similar across trials.

Changes from Baseline in HbA_{1c} and Body Weight

Individual Endpoints

In the PIONEER 1–5 and 8 trials, the odds of achieving the HbA_{1c} reduction of $\geq 1\%$ at EOT were significantly greater with orally administered semaglutide 14 mg compared with placebo (PIONEER 1, 4, 5 and 8, all $p < 0.0001$) and the active comparators empagliflozin 25 mg (PIONEER 2, $p < 0.0001$), sitagliptin 100 mg (PIONEER 3, $p < 0.0001$) and liraglutide 1.8 mg (PIONEER 4, $p < 0.05$) (Fig. 1A).

Similarly, the odds of achieving a body weight loss of $\geq 5\%$ at EOT were significantly greater with orally administered semaglutide 14 mg than with placebo (PIONEER 1, 4, 5 and 8, all $p < 0.0001$), sitagliptin 100 mg (PIONEER 3, $p < 0.0001$) and liraglutide 1.8 mg (PIONEER 4, $p < 0.0001$), while the odds were comparable for orally administered semaglutide 14 mg and empagliflozin 25 mg in PIONEER 2 (Fig. 1B).

The odds of achieving a body weight loss of $\geq 10\%$ at EOT were significantly greater with orally administered semaglutide 14 mg than with placebo (PIONEER 1, $p < 0.01$; PIONEER 4, $p < 0.001$; PIONEER 5, $p < 0.001$; PIONEER 8, $p < 0.01$), empagliflozin 25 mg (PIONEER 2, $p < 0.001$), sitagliptin 100 mg (PIONEER 3, $p < 0.0001$) and liraglutide 1.8 mg (PIONEER 4, $p < 0.001$) (Fig. 1C).

Composite Endpoints

The odds of achieving the composite endpoint of an HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 5\%$ were significantly greater with orally administered semaglutide 14 mg than with any of the comparators in PIONEER 1–5 and 8, including empagliflozin in PIONEER 2, at week 26 and at EOT (all $p < 0.0001$; Fig. 2A, B).

The odds of achieving both an HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 10\%$ at EOT were significantly greater with orally administered semaglutide 14 mg than with placebo (PIONEER 1, 4 and 5, all $p < 0.01$; PIONEER 8, $p < 0.05$), empagliflozin 25 mg (PIONEER 2, $p < 0.0001$), sitagliptin 100 mg (PIONEER 3, $p < 0.0001$) and liraglutide 1.8 mg (PIONEER 4, $p < 0.001$) (Fig. 3).

DISCUSSION

This post hoc analysis evaluated the composite endpoint of a body weight loss of $\geq 5\%$ or $\geq 10\%$ together with an HbA_{1c} reduction of $\geq 1\%$, arguably a more clinically relevant endpoint than that reported in the individual trials [14–19]. Indeed, current T2D treatment guidelines recommend multiple therapeutic goals, including HbA_{1c} $< 7\%$ with low or no incidence of hypoglycaemia and $\geq 5\%$ weight loss in people with T2D with overweight or obesity [3, 10, 21]. Composite endpoints are therefore preferred over individual endpoints for their ability to assess the net clinical benefit of an intervention by combining two or more events in one outcome. The extent of information achieved on the efficacy and safety of an intervention by analysing the composite endpoints may prove helpful to physicians and patients as a foundation for clinical decision-making [6].

Orally administered semaglutide 14 mg was better than placebo and active comparators in achieving a combined HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 5\%$ at week 26 and EOT. Orally administered semaglutide was also better than placebo and active comparators when a larger body weight loss target of $\geq 10\%$ was applied. The odds of achieving each target were also statistically significantly greater with

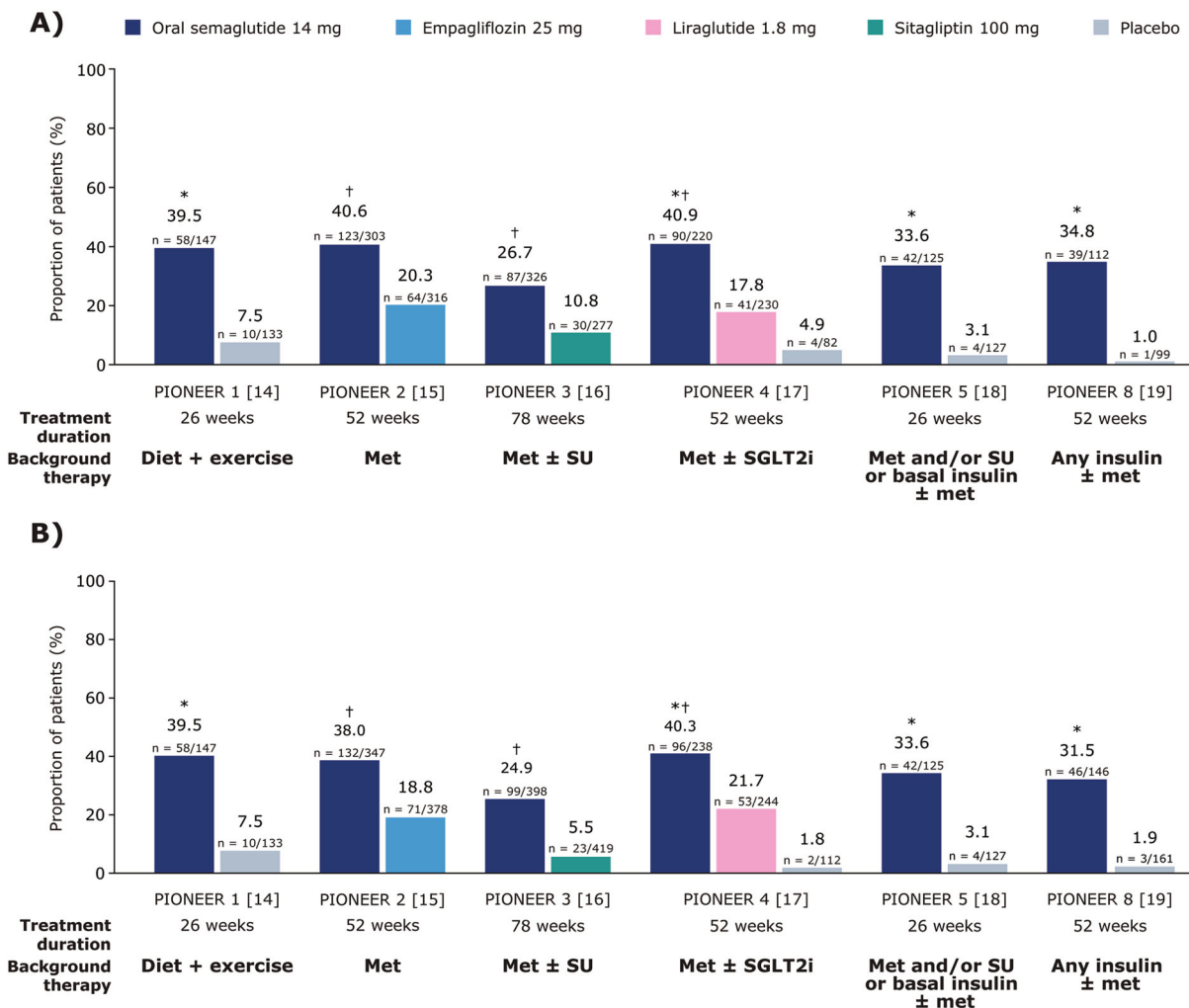


Fig. 2 Proportion of people achieving an HbA_{1c} reduction of ≥ 1% and body weight loss of ≥ 5% at EOT (A), or achieving an HbA_{1c} reduction of ≥ 1% and body weight loss of ≥ 5% at week 26 (B). Data are observed proportions for the trial product estimand (on trial product without rescue medication). *p < 0.0001 for the

EOR with orally administered semaglutide 14 mg versus placebo; †p < 0.0001 for the EOR with orally administered semaglutide 14 mg versus the active comparator. EOR estimated odds ratio, EOT end of treatment, HbA_{1c} glycated haemoglobin, met metformin, SGLT2i sodium-glucose co-transporter 2 inhibitor, SU sulphonylurea

orally administered semaglutide than with comparator.

Studies have previously shown that HbA_{1c} reductions of ≥ 1% and body weight loss of ≥ 5%, measured separately as individual endpoints, are associated with clinically meaningful health benefits [1, 2, 22]. Indeed, the UK Prospective Diabetes Study (UKPDS) of patients with T2D reported that each 1% reduction in HbA_{1c} has the potential to reduce the risk of microvascular complications by 37%,

myocardial infarction by 14% and diabetes-related deaths by 21% [9]. Reductions of body weight of ≥ 5% improve glycaemic control, lipid levels and blood pressure in people with overweight/obesity and T2D [1], and are recommended in the American Diabetes Association (ADA) guidelines. The guidelines also recommend considering the effect of medications on weight when selecting a glucose-lowering medication [3]. Furthermore, HbA_{1c} and body weight are considered surrogate endpoints

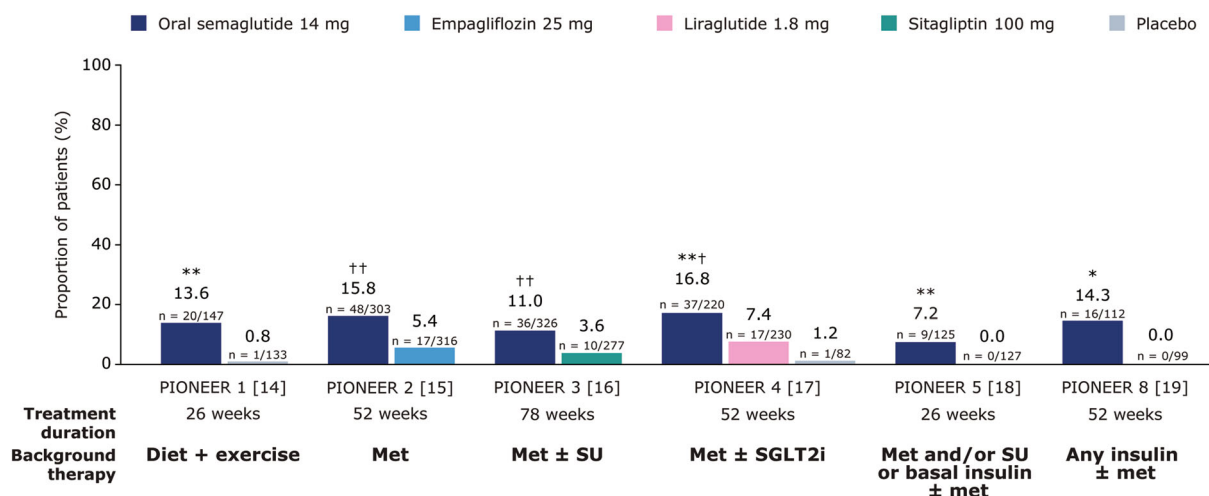


Fig. 3 Proportion of people achieving an HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 10\%$ at EOT. Data are observed proportions for the trial product estimand (on trial product without rescue medication). For PIONEER 1–4, *p* values are for the EORs for orally administered semaglutide 14 mg versus placebo or the active comparator. For PIONEER 5 and 8, EORs could not be calculated as a result of 0 events in the comparator

arms; *p* values for the risk difference were calculated instead. **p* < 0.05 versus placebo; ***p* < 0.01 versus placebo; ****p* < 0.001 versus placebo; †*p* < 0.001 versus the active comparator; ††*p* < 0.0001 versus the active comparator. *EOR* estimated odds ratio, *EOT* end of treatment, *HbA_{1c}* glycated haemoglobin, *met* metformin, *SGLT2i* sodium-glucose co-transporter 2 inhibitor, *SU* sulphonylurea

and powerful predictors of CV disease and chronic kidney disease in T2D management. A meta-analysis of five randomised controlled trials (ACCORD, ADVANCE, PROactive, UKPDS and VADT) showed that a reduction in HbA_{1c} of approximately 1% can lead to a 17% relative risk reduction in non-fatal myocardial infarction, while during the UKPDS study, a 33% risk reduction in incident microalbuminuria was reported for patients who achieved glycaemic control [23, 24]. Similarly, weight loss > 5% has been associated with improvements in lipid levels and blood pressure [3, 11, 25]. Evaluating these surrogate endpoints can help physicians draw clinically important conclusions about a therapeutic intervention because of their proven association with these outcomes. The composite endpoint of HbA_{1c} reduction of $\geq 1\%$ and body weight loss of $\geq 5\%$ could therefore be used in clinical practice to differentiate between T2D treatment options by comparing overall efficacy, as part of a holistic treatment approach. Furthermore, orally administered semaglutide provides an option

for people who prefer an oral medication over an injectable agent.

A key limitation of this study is that the individual PIONEER trials were not powered for this analysis; therefore, further investigation is warranted to determine whether this composite endpoint can be used as a basis for clinical decision-making in a real-world setting.

CONCLUSION

Significantly more people achieved clinically relevant reductions in both HbA_{1c} and body weight with orally administered semaglutide versus comparators in the PIONEER 1–5 and 8 trials.

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consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, MSD/Merck, Mundipharma, Novo Nordisk, Sanofi and Sun Pharmaceuticals.

Compliance with Ethics Guidelines. The protocols for the PIONEER 1–5 and 8 trials were approved by independent ethics committees/institutional review boards at each trial site, and the trials were conducted in accordance with International Council on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Data Availability. 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 (novonordisk-trials.com). Data will be made available after research completion and approval of the product and product use in the European Union 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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