



A Bioequivalence Study of Two Formulations of Oral Semaglutide in Healthy Participants

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ABSTRACT

Introduction: The glucagon-like peptide-1 (GLP-1) analogue semaglutide is approved as an oral formulation for the treatment of type 2 diabetes. This study aimed to confirm bioequivalence between a new, second-generation (2G) oral semaglutide formulation (1.5, 4 and 9 mg) and the initially approved first-generation (1G) formulation (3, 7 and 14 mg).

Methods: This was a randomised, multicentre, open-label, full replicate crossover study

to confirm bioequivalence between 2G and 1G oral semaglutide formulations at steady-state (SS) in healthy participants (NCT05227196). Participants were recruited to three groups. In each group, participants were randomised to one of two alternating sequences comparing once-daily oral semaglutide treatment of 9 and 14 mg (group 1), 4 and 7 mg (group 2) or 1.5 and 3 mg (group 3) at SS. Treatment duration was 20 weeks, comprising four 5-week steady-state periods on alternating formulations. Repeated 24-h blood sampling at the end of each steady-state period supported pharmacokinetic analysis. Co-primary endpoints were area under the semaglutide plasma concentration–time curve during a dosing interval at SS ($AUC_{0-24h,SS}$) and maximum semaglutide plasma concentration at SS ($C_{max, 0-24h,SS}$). Bioequivalence for co-primary endpoints was assessed using European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA) and Japan Pharmaceuticals and Medical Devices Agency (PMDA) criteria. Safety was monitored.

Results: A total of 222, 201 and 123 participants were recruited into groups 1, 2 and 3, respectively. The prespecified EMA, FDA and PMDA bioequivalence criteria were met for 2G versus 1G oral semaglutide for all three dose levels (1.5 vs 3 mg, 4 vs 7 mg and 9 vs 14 mg). The safety profile of 2G oral semaglutide was consistent with 1G oral semaglutide.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s13300-024-01674-8>.

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Conclusions: The 2G oral semaglutide formulation was confirmed as bioequivalent to 1G oral semaglutide, with no new safety concerns identified.

Trial registration: ClinicalTrials.gov identifier, NCT05227196.

Keywords: Antidiabetic drug; Bioavailability; Bioequivalence; GLP-1 analogue; Glycaemic control; Incretin therapy; Semaglutide; Type 2 diabetes

By demonstrating bioequivalence, the results of this study support that expected efficacy and safety outcomes will be comparable between each dose level of the initially approved 1G oral semaglutide formulation (3, 7 and 14 mg) and the corresponding dose level of the 2G oral semaglutide formulation (1.5, 4 and 9 mg), indicating patients can switch to the new, 2G formulation and obtain the same clinical benefits.

Key Summary Points

Why carry out this study?

The glucagon-like peptide-1 (GLP-1) analogue semaglutide is approved for oral administration as an adjunct to diet and exercise for treating adults with insufficiently controlled type 2 diabetes at once-daily doses of 3, 7 and 14 mg; a new, second-generation (2G) formulation of oral semaglutide has been developed to improve the oral bioavailability.

In this study, bioequivalence was evaluated by comparing semaglutide exposure at each dose level of the 2G oral semaglutide formulation (1.5, 4 and 9 mg) with the corresponding dose of the initially approved, first-generation (1G) oral formulation (3, 7 and 14 mg) in healthy participants.

What was learned from the study?

Bioequivalence between 2G oral semaglutide and 1G oral semaglutide formulations at each of the three investigated dose levels was confirmed in accordance with the criteria specified by the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA) and the Japan Pharmaceuticals and Medical Devices Agency (PMDA).

The overall safety profile of 2G oral semaglutide was consistent with the established safety profile of the 1G oral formulation, with no new safety concerns identified.

INTRODUCTION

Sustained glycaemic control and weight loss are key targets for people with type 2 diabetes (T2D) [1, 2], with current guidelines recommending a patient-centred approach for treatment selection [1]. Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) deliver effective glycaemic control with a low risk of hypoglycaemia, while increasing satiety, reducing body weight and blood pressure and improving cardiovascular disease (CVD) outcomes [3–5]. Semaglutide is a GLP-1 analogue that was initially approved as a once-weekly subcutaneous injection (Ozempic®, 0.5, 1.0 and 2.0 mg) for treating T2D [6, 7]. An initial oral formulation of semaglutide was subsequently developed as the first once-daily orally available GLP-1 analogue, using novel constituents to obtain oral bioavailability with the additional benefits of convenience and non-invasive administration [8, 9]. The Peptide InnOvation for Early diabetes treatment (PIONEER) phase 3 programme demonstrated the efficacy of oral semaglutide versus placebo and active comparators (including empagliflozin, sitagliptin and liraglutide) in achieving glycaemic control and weight loss, with a safety profile consistent with the GLP-1RA drug class [10–21]. Oral semaglutide (Rybelsus®) received U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval in 2019 and 2020, respectively, for the second-line treatment of adults with insufficiently controlled T2D to improve glycaemic control as an adjunct to diet and exercise at the once-daily oral doses of 3, 7 and 14 mg [22, 23]. In 2023, the FDA approved a label update for oral

semaglutide allowing use as a first-line treatment option for adults with T2D [24, 25].

Despite advances in oral delivery systems for peptides, improving the low oral bioavailability of peptide drugs remains a significant challenge due to their poor stability in the gastrointestinal tract and low epithelial permeability [26]. A second-generation (2G) oral semaglutide formulation has been developed with improved oral bioavailability and equivalent exposure at lower doses of the active pharmaceutical ingredient, semaglutide. This was evaluated against the initial, first-generation (1G) formulation in a previous comparative bioavailability study (NCT04097600) [27].

Bioequivalence between two pharmaceutical products means their efficacy and safety outcomes can be expected to be therapeutically equivalent. In bioequivalence studies, the plasma concentration–time curve is generally used to compare the rate and extent of absorption of the test and the reference drug [28]. EMA, FDA and Japan Pharmaceuticals and Medical Devices Agency (PMDA) guidance propose using both AUC (the area under the concentration–time curve) and $C_{\max}$ (the maximum plasma concentration or peak exposure); bioequivalence is concluded if certain criteria are met, including, but not limited to, the ratio of these pharmacokinetic (PK) parameters between the test and reference formulations falling between prespecified criteria with a certain assurance, which vary by each respective guideline [28–30].

We conducted a bioequivalence study to confirm if semaglutide exposure obtained with the 2G oral semaglutide formulation was equivalent to that of the 1G oral semaglutide formulation. The aim was to confirm bioequivalence of lower 1.5, 4 and 9 mg once-daily doses of 2G oral semaglutide with corresponding dose levels of 3, 7 and 14 mg once daily of 1G oral semaglutide, at steady-state (SS) in healthy participants.

METHODS

Study Design

This was an interventional, multicentre, randomised, open-label, three-group, full replicate

crossover study. Study participants were screened and assigned to one of three study intervention groups (groups 1–3) at three investigational sites in the United States ($n=2$; Kansas City and Los Angeles) and Canada ($n=1$; Montreal). Group 1 participants were recruited at the Kansas City site, group 2 participants were recruited at the Kansas City and Montreal sites and group 3 participants were recruited at the Los Angeles site. The study was designed to confirm bioequivalence between each of the three dose levels of 2G oral semaglutide (1.5, 4, 9 mg) and the three dose levels of 1G oral semaglutide (3, 7, 14 mg) at SS: 9 mg versus 14 mg (group 1), 4 mg versus 7 mg (group 2) and 1.5 mg versus 3 mg (group 3). Doses for the 2G formulation were selected based on a previous comparative bioavailability study (NCT04097600) [27]. The study protocol was approved by appropriate health authorities according to local guidelines and by the Institutional Review Board/Independent Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki [31] and International Council for Harmonization Good Clinical Practice guidelines [32]. Participants provided written informed consent prior to the commencement of any study-related activities. This study is registered with ClinicalTrials.gov (NCT05227196).

Participants

Key inclusion criteria included healthy male and female adults aged 18–64 years with a body mass index between 21.0 and 32.0 kg/m². Participants were required to be generally healthy as judged by the investigator. Full eligibility criteria are in Table S1 in the Supplementary Appendix. In accordance with regulatory guidelines, healthy participants were chosen and test conditions standardised to minimise variability in factors that may affect the assessment of PK parameters [28, 29].

Study Procedures

The study comprised a screening period of ≤ 28 days; a dose-escalation period for groups 1 and 2; and four steady-state periods, each of

5 weeks' duration (Fig. 1). Participants underwent a screening visit 1–28 days before recruitment to group 1, 2 or 3. Within each group, participants were randomised (1:1) to one of two treatment sequences of alternating oral formulations (1G and 2G) of semaglutide as detailed below (Fig. 1). An open-label approach was considered acceptable as the PK endpoints were not judged to be affected by knowledge of treatment allocation. It was not considered feasible to attain blinding by changing the formulation of the visually distinct tablets (e.g. by encapsulation) as this would affect absorption [29, 33]. However, the sponsor staff who were involved in the evaluation of PK data were blinded to treatment allocation until after database lock of the PK data. Randomisation was followed by 2 weeks of dose escalation for group 1 or 1 week of dose escalation for group 2 (Fig. 1). Each week of dose escalation was initiated with a single on-site dose on the first day, followed by self-administered once-daily home dosing for 6 days. Dose escalation ended with an on-site visit before initiation of the first 5-week steady-state period. Participants in group 3 did not undergo dose escalation and proceeded directly to the first steady-state period.

The four steady-state periods comprised a total duration of 20 weeks. For all groups, the 5-week steady-state periods started with a single on-site dose followed by self-administered once-daily home dosing. The half-life of semaglutide is approximately 1 week, therefore the participants were dosed daily for 5 weeks (corresponding to five half-lives) in each period to ensure evaluation of bioequivalence under SS conditions. A Test (T) and Reference (R) crossover design of TRTR/RTTR was used, whereby the two treatment arms within each group alternated between 2G oral semaglutide and 1G oral semaglutide (Fig. 1). Each steady-state period ended with a 24-h on-site PK sampling visit (visits 5, 7, 9 and 11) before proceeding to the next steady-state period (or follow-up). Participants arrived the day before the last dose in the 5-week period and stayed on-site overnight. The following morning, body weight was measured, and a pre-dose blood sample was taken before participants received the last dose of the 5-week period, and repeated blood sampling was subsequently performed over the next 24 h for the PK analyses supporting evaluation of the co-primary endpoints. Participants were instructed to fast overnight (≥ 6 h) prior to each dosing and before

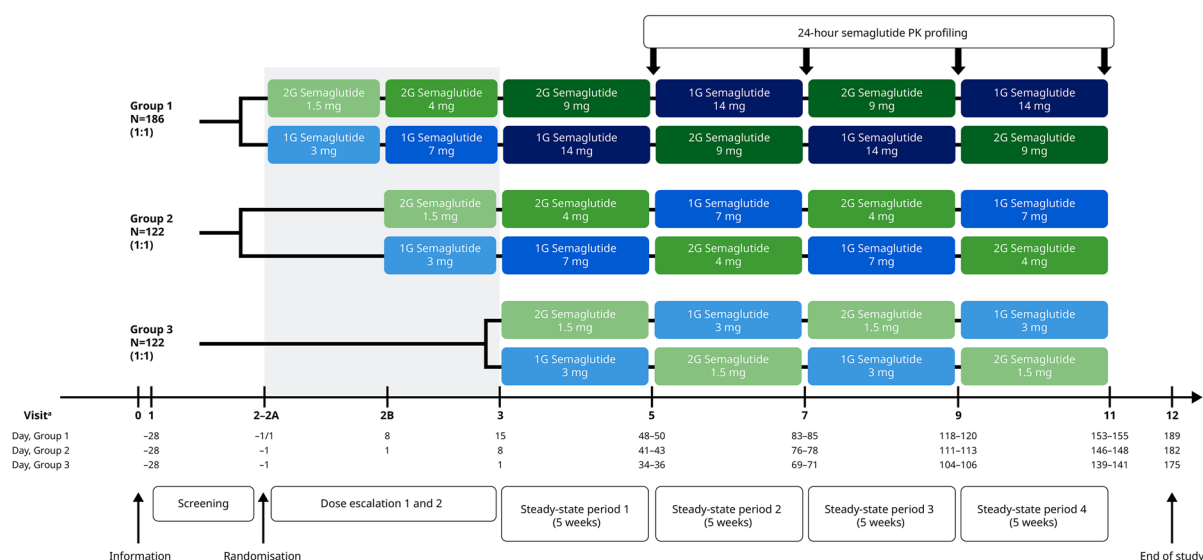


Fig. 1 Study design. ^aNot all visits are shown in the diagram. 1G first generation, 2A dose escalation visit (group 1: day 1), 2B dose escalation visit (group 1: day 8; group 2:

day 1), 2G second generation, *N* planned number of participants (please refer to Results and Fig. 2 for the actual number of participants enrolled); PK pharmacokinetic

on-site visits; water intake was not allowed ≤ 2 h before dosing. During the 30 min post-dose, no intake of food, liquid or other oral medication was allowed. Initiation of breakfast meal was carried out 30–35 min post-dosing for both on-site and home dosing.

A follow-up visit was scheduled ≥ 5 weeks after administration of the last dose for safety assessments. The planned total duration of study participation for each participant was 177–217 days (Fig. 1), depending on the group.

It was aimed to have an even distribution of male and female participants with $\geq 40\%$ of each sex recruited into each group.

Endpoints and Assessments

The primary study objective was to confirm bioequivalence of the two oral formulations of semaglutide (2G vs 1G) administered once daily at three dose levels at SS in healthy participants, namely 2G oral semaglutide 1.5 mg versus 1G oral semaglutide 3 mg, 2G oral semaglutide 4 mg versus 1G oral semaglutide 7 mg, and 2G oral semaglutide 9 mg versus 1G oral semaglutide 14 mg. The co-primary endpoints were area under the semaglutide plasma concentration–time curve during a dosing interval at SS ($AUC_{0-24h,SS}$) and maximum semaglutide plasma concentration at SS ($C_{max, 0-24h,SS}$). The co-primary endpoints were derived after the last dose administered at the end of each steady-state period, i.e. after dosing on days 49/42/35 (visit 5), 84/77/70 (visit 7), 119/112/105 (visit 9) and 154/147/140 (visit 11) for groups 1/2/3, respectively (Fig. 1). Supportive secondary endpoints were semaglutide plasma concentration 24 h after last dose at SS ($C_{tau, 24h,SS}$) and time to maximum semaglutide plasma concentration at SS ($t_{max, 0-24h,SS}$). The percentage swing was calculated post hoc as $((C_{max, 0-24h,SS} - C_{min, 0-24h,SS})/C_{min, 0-24h,SS}) \times 100$, where $C_{min, 0-24h,SS}$ is the minimum semaglutide plasma concentration at SS.

Statistical Analysis

In line with EMA, FDA and PMDA guidelines, a crossover design was chosen to leverage the

lower within-participant variability in PK measures and thereby limit the number of participants required for the study [28–30]. A replicate design was applied so that the within-participant variability for the reference product (1G oral semaglutide) could be determined, to enable the application of widened or reference-scaled bioequivalence acceptance criteria for highly variable drugs [28, 29].

The sample size was calculated to provide at least 90% power for showing bioequivalence between the 1G and 2G formulations for all three dose groups, based on the standard acceptance limits (0.8000–1.2500) to ensure sufficient power to confirm bioequivalence in accordance with the EMA, FDA and PMDA guidelines. Based on data from the previous bioavailability study [27], the expected $AUC_{0-24h,SS}$ treatment ratios (2G versus 1G) were 1.10 for group 1, and 1.08 for group 2 and group 3 and a coefficient of variation (CV) of 45% was considered reasonable. Due to the high correlation in treatment differences between $AUC_{0-24h,SS}$ and C_{max} , the sample size only needed to be calculated for one of the endpoints as the other was expected to be approximately similar. The sample size was determined to provide a marginal power of 96.6% for $AUC_{0-24h,SS}$ for each group, resulting in at least 90% combined power to confirm bioequivalence for all three groups. A total of 160 (group 1) and 122 (groups 2 and 3) participants would need to be randomised to confirm bioequivalence for all three groups for $AUC_{0-24h,SS}$, assuming that 85% of participants would complete the steady-state periods.

All dose comparisons of 2G oral semaglutide versus 1G oral semaglutide (1.5 mg vs 3 mg, 4 mg vs 7 mg and 9 mg vs 14 mg) were conducted separately. The primary endpoints were derived from the plasma concentration–time curve for 0–24 h following 5 weeks' administration of 2G oral semaglutide and 1G oral semaglutide; derivations were based on actual time since dosing. $AUC_{0-24h,SS}$ was approximated using the linear trapezoidal method. Missing AUC concentrations were handled by the linear trapezoidal method given that the AUC can be reliably calculated. Missing plasma semaglutide concentrations were ignored provided that C_{max} could be reliably determined. Missing endpoint

data for both AUC and $C_{\max}$ (e.g. due to missing concentrations that prevent AUC derivation) were assumed to be missing completely at random as they were not expected to be related to treatment. Primary endpoint analysis was performed on the full analysis set (FAS), comprising all randomised participants who were exposed to at least one dose of study product and completed at least one period on 2G oral semaglutide and at least one period on 1G oral semaglutide. All safety evaluations were made on the safety analysis set (SAS), which included all participants who were exposed to at least one dose of study product.

For each comparison of 2G oral semaglutide versus 1G oral semaglutide, two one-sided hypotheses were tested for $AUC_{0-24h,SS}$ and $C_{\max, 0-24h,SS}$ values at each dose level: 1: $H_0: \mu \geq 1.25$ against $H_a: \mu < 1.25$, and 2: $H_0: \mu \leq 0.80$ against $H_a: \mu > 0.80$ (where μ = the geometric mean under treatment with 2G oral semaglutide, divided by the geometric mean under treatment with 1G oral semaglutide); a (one-sided) alpha of 5% was used for each comparison for each one-sided test, controlling for type 1 error at 5%.

Bioequivalence Analysis

For EMA bioequivalence analysis, co-primary endpoints were log-transformed and analysed separately using an analysis of variance (ANOVA) model with treatment (2G oral semaglutide or 1G oral semaglutide), period (PK-sampling visits), sequence (starting with 2G oral semaglutide or 1G oral semaglutide) and participant nested within sequence as fixed effects. For group 2 (in which participants were recruited from different sites), site was added to the model, so the full model included site, treatment, period nested within site, sequence, sequence nested within site and participant nested within sequence and site. The estimated treatment difference and the corresponding two-sided 90% confidence interval (CI) were back-transformed to the original scale. The 90% CI was then used for testing bioequivalence. The within-participant CV of the reference product (1G oral semaglutide) was $>30\%$ for $C_{\max, 0-24h,SS}$, thus qualifying

as a highly variable drug, in line with recent reports [22, 28]. Therefore, the acceptance limits were extended for $C_{\max, 0-24h,SS}$ depending on the observed CV [28]. The standard limits of 0.8000–1.2500 were used for AUC. To establish bioequivalence, the $C_{\max, 0-24h,SS}$ estimated treatment ratio was required to be fully contained within 0.8000–1.2500 and the 90% CI of the $C_{\max, 0-24h,SS}$ estimated treatment ratio fully contained within 0.6984–1.4319 for group 1, 0.7273–1.3749 for group 2 and 0.7328–1.3646 for group 3, and the 90% CI of the $AUC_{0-24h,SS}$ treatment ratio was required to be fully contained within 0.8000–1.2500. Additional details are provided in Supplementary Table S2.

For FDA bioequivalence analysis, as the estimated within-participant standard deviation for oral semaglutide, $s(WR)$, was ≥ 0.294 for both co-primary endpoints, the reference-scaled average bioequivalence (RSABE) analysis was the primary analysis for $AUC_{0-24h,SS}$ and $C_{\max, 0-24h,SS}$ [34]. For the RSABE analysis, only participants with a value for an endpoint at all four steady-state periods contributed to the statistical analysis of the respective endpoint. To establish bioequivalence, the estimated treatment ratio should be fully contained within 0.8000–1.2500 and the 95% upper CI for $(\mu T - \mu R)^2 - \theta_s \sigma_{WR}^2$, based on Howe's approximation, should be ≤ 0 . Additional details are provided in Supplementary Table S2.

The PMDA guideline required that the 90% CI of the $AUC_{0-24h,SS}$ and $C_{\max, 0-24h,SS}$ treatment ratios were between 0.8000 and 1.2500 [30]. The analysis used the same ANOVA model as for the EMA guidelines above, except that the standard acceptance interval of 0.8000–1.2500 for both AUC and $C_{\max}$ was used.

Safety

A treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) that occurs or worsens after receiving a treatment or intervention. TEAEs were coded using the current Medical Dictionary for Regulatory Activities (MedDRA) version and were reported

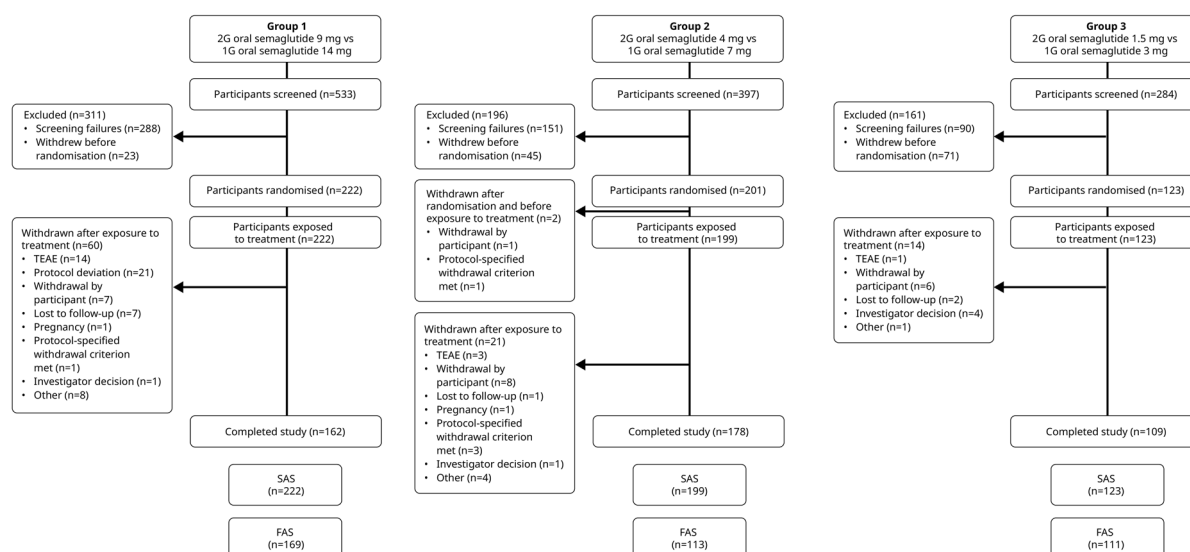


Fig. 2 Participant disposition. FAS: all randomised participants who were exposed to at least one dose of study product and completed at least one period on 2G oral semaglutide and one period on 1G oral semaglutide. SAS: all

randomised participants who were exposed to at least one dose of study product. 1G first generation, 2G second generation, FAS full analysis set, SAS safety analysis set, TEAE treatment-emergent adverse event

in MedDRA version 26.0 [35]. TEAEs were summarised using descriptive statistics.

RESULTS

Participants

Between February 4, 2022, and August 8, 2023, 1214 individuals signed informed consent, of whom 546 were randomised and 544 exposed to treatment. The study was completed by 449 (82.2%) participants. Participant disposition by group is shown in Fig. 2. For group 1, 222 participants were randomised, of whom all initiated treatment with oral semaglutide. Sixty participants in group 1 withdrew after being exposed to treatment, with 162 completing the study. In group 2, of the 201 participants randomised, 199 were exposed to the dosing regimen, with two participants excluded prior to treatment due to participant withdrawal, and protocol-specified withdrawal criterion being met. An additional 21 participants in group 2 withdrew from the study after treatment initiation, with 178 completing the study. For group 3, 123 participants

were randomised, all of whom initiated treatment with oral semaglutide. Fourteen participants withdrew from the study in group 3, with 109 completing the study. In group 1, an extra 26 participants were to be randomised to compensate for participants with partially non-evaluable PK data, to a total of 186 participants in group 1. The SAS comprised 222, 199 and 123 participants from groups 1, 2 and 3, respectively. The FAS comprised 169, 113 and 111 participants from groups 1, 2 and 3, respectively. The primary reason for the difference in the number of participants randomised compared with the planned sample sizes and between the FAS and SAS for groups 1 and 2 was a dosing deviation impacting the 24-h PK profile. The affected PK data were excluded from the primary analysis and relevant measures were implemented to safeguard trial integrity.

Demographics and Baseline Characteristics

Participant demographics and baseline characteristics for the FAS of each group are shown in Table 1. Over half of the participants were White (53.3%, 71.7% and 56.8% for groups 1,

2 and 3, respectively) and male (55.0%, 50.4% and 50.5% for groups 1, 2 and 3, respectively). Overall, demographics were balanced between groups. A lower proportion of Hispanic or Latino participants was observed in group 1 (11.8%) compared with group 2 (24.8%) and group 3 (29.7%).

Bioequivalence of Pharmacokinetic Endpoints

Semaglutide dosing interval profiles at SS for each dose comparison (9 vs 14 mg [group 1], 4 vs 7 mg [group 2] and 1.5 vs 3 mg [group 3]) are shown in Fig. 3a, b and c respectively. Overall, the shapes of the concentration–time curves for 2G

oral semaglutide and 1G oral semaglutide were similar in all three groups, with early absorption occurring within the first hour, and a gradual decline observed thereafter. The prespecified bioequivalence criteria according to EMA, FDA and PMDA guidelines were met across the three investigated dose levels of 2G versus 1G oral semaglutide (9 mg vs 14 mg, 4 mg vs 7 mg, 1.5 mg vs 3 mg) (Table 2). Prespecified bioequivalence criteria according to EMA guidelines were met as the 90% CIs for the estimated treatment ratio of AUC_{0–24h,SS} were within the standard acceptance limits (0.8000–1.2500). For $C_{\max, 0–24h,SS}$, the estimated treatment ratio was within the 0.8000–1.2500 limits, and the 90% CIs were within the scaled acceptance limits. Per the FDA guidelines, estimated treatment ratios for AUC_{0–24h,SS} and

Table 1 Participant characteristics and baseline demographics

	Group 1	Group 2	Group 3
<i>N</i>	169	113	111
Age (years), mean (SD) [range]	39.6 (11.9) [18.0–64.0]	42.4 (11.3) [19.0–63.0]	40.4 (11.8) [21.0–64.0]
Sex, <i>n</i> (%)			
Female	76 (45.0)	56 (49.6)	55 (49.5)
Male	93 (55.0)	57 (50.4)	56 (50.5)
Race, <i>n</i> (%)			
White	90 (53.3)	81 (71.7)	63 (56.8)
Black or African American	70 (41.4)	26 (23.0)	29 (26.1)
Asian	4 (2.4)	6 (5.3)	10 (9.0)
American Indian or Alaska Native	3 (1.8)	0	0
Native Hawaiian or Other Pacific Islander	0	0	1 (0.9)
Other	2 (1.2)	0	8 (7.2)
Ethnicity, <i>n</i> (%)			
Hispanic or Latino	20 (11.8)	28 (24.8)	33 (29.7)
Not Hispanic or Latino	149 (88.2)	85 (75.2)	78 (70.3)
Body weight (kg), mean (SD) [range]	79.1 (12.8) [49.7–115.5]	76.2 (11.3) [51.7–97.6]	76.9 (12.0) [46.3–101.2]
BMI (kg/m ²), mean (SD) [range]	27.1 (3.1) [20.6–33.0]	26.3 (2.6) [21.0–32.2]	26.7 (3.1) [20.0–32.3]

Full analysis set: all randomised participants who were exposed to at least one dose of study product and completed at least one period on 2G oral semaglutide and one period on 1G oral semaglutide

BMI body mass index, *N/n* number of participants, *SD* standard deviation

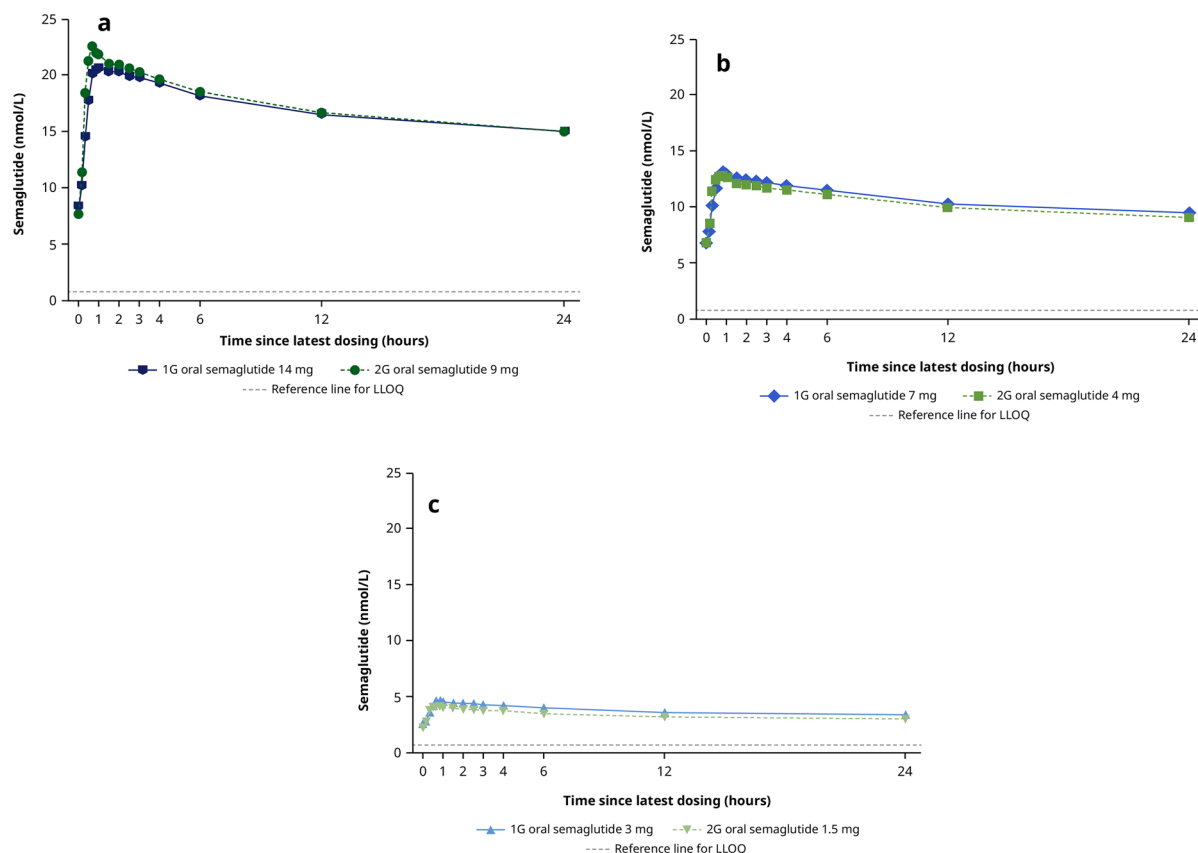


Fig. 3 Semaglutide dosing interval profiles at steady-state in group 1 (a), group 2 (b) and group 3 (c). Geometric mean semaglutide plasma concentrations after 5 weeks of once-daily dosing of oral semaglutide at doses of 9 and 14 mg (a), 4 and 7 mg (b) and 1.5 and 3 mg (c) in healthy

participants. $C_{\max, 0-24h, SS}$ were within the standard acceptance limits (0.8000–1.2500) and the critical bound upper 95% CI limits for both endpoints were ≤ 0 . Prespecified PMDA bioequivalence criteria were also met, with 90% CIs for the estimated treatment ratios of $AUC_{0-24h, SS}$ and $C_{\max, 0-24h, SS}$ within the standard acceptance limits (0.8000–1.2500). Median $t_{\max, 0-24h}$ was 0.8–1.0 h across all dose levels. $C_{\tau, 24h}$ values were similar between formulations and reduced with decreasing dose. Descriptive statistics for the PK endpoints are presented in Table 3.

participants. Full analysis set: all randomised participants who were exposed to at least one dose of study product and completed at least one period on 2G oral semaglutide and one period on 1G oral semaglutide. *1G* first generation, *2G* second generation, *LLOQ* lower limit of quantification

Safety

Adverse Events

The number of TEAEs and the proportion of participants reporting TEAEs were comparable between 2G oral semaglutide and 1G oral semaglutide in all three groups. The majority of the TEAEs were reported as mild, resolved by the end of the study and were assessed as probably or possibly related to study product

Table 2 Bioequivalence of 2G oral semaglutide and 1G oral semaglutide as per EMA, FDA and PMDA guidelines

Guideline	Endpoint	2G oral semaglutide to 1G oral semaglutide ETR (90% CI)	Scaled acceptance limits for bioequivalence for C_{max}	Critical bound upper 95% CI limit	Bioequivalence criteria met
Group 1: 2G oral semaglutide 9 mg versus 1G oral semaglutide 14 mg					
EMA ^a ($N = 169$)	$AUC_{0-24h,SS}$	1.0512 (0.9694; 1.1399)	NA ^e	NA ^f	YES
	$C_{max, 0-24h,SS}$ ^d	1.0870 (1.0010; 1.1805)	[0.6984; 1.4319]	NA ^f	YES
FDA ^b ($N = 111$)	$AUC_{0-24h,SS}$ ^d	1.0592 (0.9643; 1.1634)	NA ^e	− 0.2256	YES
	$C_{max, 0-24h,SS}$ ^d	1.1025 (1.0010; 1.2143)	NA ^e	− 0.2090	YES
PMDA ^c ($N = 169$)	$AUC_{0-24h,SS}$	1.0512 (0.9694; 1.1399)	NA ^e	NA ^f	YES
	$C_{max, 0-24h,SS}$	1.0870 (1.0010; 1.1805)	NA ^e	NA ^f	YES
Group 2: 2G oral semaglutide 4 mg versus 1G oral semaglutide 7 mg					
EMA ^a ($N = 113$)	$AUC_{0-24h,SS}$	0.9798 (0.9129; 1.0516)	NA ^e	NA ^f	YES
	$C_{max, 0-24h,SS}$ ^d	0.9952 (0.9263; 1.0692)	[0.7273; 1.3749]	NA ^f	YES
FDA ^b ($N = 109$)	$AUC_{0-24h,SS}$ ^d	0.9970 (0.9316; 1.0670)	NA ^e	− 0.1155	YES
	$C_{max, 0-24h,SS}$ ^d	1.0125 (0.9429; 1.0873)	NA ^e	− 0.1120	YES
PMDA ^c ($N = 113$)	$AUC_{0-24h,SS}$	0.9798 (0.9129; 1.0516)	NA ^e	NA ^f	YES
	$C_{max, 0-24h,SS}$	0.9952 (0.9263; 1.0692)	NA ^e	NA ^f	YES
Group 3: 2G oral semaglutide 1.5 mg versus 1G oral semaglutide 3 mg					
EMA ^a ($N = 111$)	$AUC_{0-24h,SS}$	0.8887 (0.8245; 0.9580)	NA ^e	NA ^f	YES
	$C_{max, 0-24h,SS}$ ^d	0.9005 (0.8395; 0.9660)	[0.7328; 1.3646]	NA ^f	YES
FDA ^b ($N = 102$)	$AUC_{0-24h,SS}$ ^d	0.8922 (0.8251; 0.9648)	NA ^e	− 0.0992	YES
	$C_{max, 0-24h,SS}$ ^d	0.9039 (0.8388; 0.9741)	NA ^e	− 0.0908	YES
PMDA ^c ($N = 111$)	$AUC_{0-24h,SS}$	0.8887 (0.8245; 0.9580)	NA ^e	NA ^f	YES
	$C_{max, 0-24h,SS}$	0.9005 (0.8395; 0.9660)	NA ^e	NA ^f	YES

Full analysis set: all randomised participants who were exposed to at least one dose of study product and completed at least one period on 2G oral semaglutide and one period on 1G oral semaglutide

1G first generation, 2G second generation, AUC area under the semaglutide plasma concentration–time curve, CI confidence interval, C_{max} maximum semaglutide plasma concentration, EMA European Medicines Agency, ETR estimated treatment ratio, FDA U.S. Food and Drug Administration, N number of participants contributing to the analysis, NA not applicable, $PMDA$ Pharmaceuticals and Medical Devices Agency, SS steady-state

^aBioequivalence criteria as per EMA guideline: 90% CI within 0.8000–1.2500 for AUC and ratio within 0.8000–1.2500 and 90% CI within scaled acceptance limits for C_{max}

^bBioequivalence criteria as per FDA guideline: Critical bound upper 95% CI limit ≤ 0 and ratio within 0.8000–1.2500. Only participants with a value for an endpoint at all four steady-state periods were included in the analyses using the FDA guideline

^cBioequivalence criteria as per PMDA guideline: 90% CI within 0.8000–1.2500

^dRecommended approach for highly variable drugs has been used; see Supplementary Table S2 for more details

^eScaled acceptance limits not relevant for $AUC_{0-24h,SS}$, or FDA and PMDA

^fCritical bound upper 95% CI limit is not relevant for EMA and PMDA

Table 3 Descriptive statistics of pharmacokinetic endpoints at steady-state

	1G oral semaglutide	2G oral semaglutide
Group 1 (<i>N</i> = 169)		
Number of PK profiles	298	296
AUC _{0–24 h} (nmol·h/l), geometric mean (CV ^a)	407 (142.8)	416 (128.0)
<i>C</i> _{max} (nmol/l), geometric mean (CV ^a)	22.8 (133.9)	24.0 (121.9)
<i>C</i> _{tau, 24 h} (nmol/l), geometric mean (CV ^a) ^b	15.0 (148.0)	15.0 (134.9)
<i>t</i> _{max, 0–24 h} (h), median (range)	1.0 (0.0–24.0)	0.8 (0.0–24.0)
Swing (%), geometric mean (CV ^a)	141.0 (258.9)	176.2 (256.9)
AUC _{0–24 h} (nmol·h/l), within-participant CV	64.9	58.1
<i>C</i> _{max} (nmol/l), within-participant CV	63.9	60.9
Group 2 (<i>N</i> = 113)		
Number of PK profiles	223	225
AUC _{0–24 h} (nmol·h/l), geometric mean (CV ^a)	258 (90.9)	250 (95.2)
<i>C</i> _{max} (nmol/l), geometric mean (CV ^a)	14.1 (84.9)	13.9 (91.1)
<i>C</i> _{tau, 24 h} (nmol/l), geometric mean (CV ^a)	9.5 (95.4)	9.1 (99.0)
<i>t</i> _{max, 0–24 h} (h), median (range)	0.8 (0.3–6.0)	0.8 (0.0–24.0)
Swing (%), geometric mean (CV ^a)	92.5 (135.1)	92.3 (126.4)
AUC _{0–24 h} (nmol·h/l), within-participant CV	44.4	52.9
<i>C</i> _{max} (nmol/l), within-participant CV	43.8	53.4
Group 3 (<i>N</i> = 111)		
Number of PK profiles	217	216
AUC _{0–24 h} (nmol·h/l), geometric mean (CV ^a)	91 (86.6)	81 (95.0)
<i>C</i> _{max} (nmol/l), geometric mean (CV ^a)	5.1 (76.8)	4.6 (83.2)
<i>C</i> _{tau, 24 h} (nmol/l), geometric mean (CV ^a)	3.4 (93.9)	3.0 (100.1)
<i>t</i> _{max, 0–24 h} (hours), median (range)	1.0 (0.0–12.1)	0.8 (0.0–24.1)
Swing (%), geometric mean (CV ^a)	94.9 (100.1)	96.6 (109.9)
AUC _{0–24 h} (nmol·h/l), within-participant CV	45.3	51.0
<i>C</i> _{max} (nmol/l), within-participant CV	42.7	47.0

Full analysis set: all randomised participants who were exposed to at least one dose of study product and completed at least one period on 2G oral semaglutide and one period on 1G oral semaglutide

1G first generation, 2G second generation, AUC_{0–24 h} area under the semaglutide plasma concentration–time curve, *C*_{max} maximum semaglutide plasma concentration, *C*_{tau, 24 h} semaglutide plasma concentration 24 h after last dose, CV coefficient of variation in %, *N* number of participants, PK pharmacokinetic, *t*_{max, 0–24 h} time to maximum semaglutide plasma concentration

^aData presented are the total CV

^b297 PK profiles for 1G group and 593 PK profiles in total for *C*_{tau} measurements in Group 1

by the investigator (Tables 4, 5, 6). The most frequently reported TEAEs in all three groups were gastrointestinal TEAEs, most of which were mild and similarly distributed between the two respective formulations in each group (Tables 4, 5, 6, respectively).

Group 1

Overall, 186 (83.8%) of 222 participants reported a total of 904 TEAEs (Table 4). Two deaths were reported; one participant died due to a TEAE of completed suicide and the other died due to two non-TEAEs of cervical carcinoma and

cardiac arrest. All three fatal AEs were considered unlikely to be related to study product by investigators and the participants were exposed to both 1G oral semaglutide and 2G oral semaglutide. A total of six treatment-emergent serious AEs (SAEs) were reported in three participants, of which five SAEs were with 2G oral semaglutide 9 mg in two participants (panic attack in one participant; concussion, clavicle fracture, rib fracture and retinal oedema in another participant due to an assault), and one was with 1G oral semaglutide 14 mg (completed suicide). Additional details on TEAEs for all groups are in Supplementary Table S3.

Table 4 Summary of treatment-emergent adverse events—Group 1

	1G oral semaglutide		2G oral semaglutide		Total	
	<i>n</i> (%)	<i>E</i>	<i>n</i> (%)	<i>E</i>	<i>n</i> (%)	<i>E</i>
Number of participants	213		210		222	
TEAEs	138 (64.8)	483	146 (69.5)	421	186 (83.8)	904
Treatment-emergent SAEs	1 (0.5)	1	2 (1.0)	5	3 (1.4)	6
Events leading to treatment discontinuation	11 (5.2)	24	4 (1.9)	7	14 (6.3)	31
Severity						
Severe	1 (0.5)	1	2 (1.0)	5	3 (1.4)	6
Moderate	17 (8.0)	24	23 (11.0)	30	37 (16.7)	54
Mild	137 (64.3)	458	142 (67.6)	386	185 (83.3)	844
Most common TEAEs by SOC and PT in ≥ 15% of participants in total						
Gastrointestinal AEs	107 (50.2)	261	98 (46.7)	206	155 (69.8)	467
Nausea	65 (30.5)	74	62 (29.5)	67	113 (50.9)	141
Vomiting	51 (23.9)	58	42 (20.0)	48	80 (36.0)	106
Diarrhoea	26 (12.2)	30	22 (10.5)	22	44 (19.8)	52
Dyspepsia	21 (9.9)	24	22 (10.5)	23	39 (17.6)	47
Nervous system AEs	57 (26.8)	70	56 (26.7)	69	95 (42.8)	139
Headache	47 (22.1)	52	42 (20.0)	49	75 (33.8)	101
Metabolism and nutrition AEs	46 (21.6)	48	40 (19.0)	41	84 (37.8)	89
Decreased appetite	44 (20.7)	46	37 (17.6)	37	81 (36.5)	83

Safety analysis set: all randomised participants who were exposed to at least one dose of study product

1G first generation, 2G second generation, AE adverse event, E number of events, n number of participants, PT preferred term, SAE serious adverse event, SOC system organ class, TEAE treatment-emergent adverse event

Table 5 Summary of treatment-emergent adverse events—Group 2

	1G oral semaglutide		2G oral semaglutide		Total	
	<i>n</i> (%)	<i>E</i>	<i>n</i> (%)	<i>E</i>	<i>n</i> (%)	<i>E</i>
Number of participants	193		195		199	
TEAEs	112 (58.0)	559	110 (56.4)	528	146 (73.4)	1087
Treatment-emergent SAEs	0		1 (0.5)	1	1 (0.5)	1
Events leading to treatment discontinuation	1 (0.5)	1	5 (2.6)	6	6 (3.0)	7
Severity						
Severe	2 (1.0)	2	5 (2.6)	11	7 (3.5)	13
Moderate	24 (12.4)	35	28 (14.4)	66	43 (21.6)	101
Mild	111 (57.5)	522	107 (54.9)	451	144 (72.4)	973
Most common TEAEs by SOC and PT in ≥ 15% of participants in total						
Gastrointestinal AEs	77 (39.9)	268	69 (35.4)	263	112 (56.3)	531
Nausea	53 (27.5)	101	46 (23.6)	117	88 (44.2)	218
Diarrhoea	22 (11.4)	37	19 (9.7)	33	34 (17.1)	70
Nervous system AEs	56 (29.0)	113	44 (22.6)	105	76 (38.2)	218
Headache	26 (23.8)	90	39 (20.0)	73	67 (33.7)	163
Metabolism and nutrition AEs	35 (18.1)	43	32 (16.4)	42	61 (30.7)	85
Decreased appetite	29 (15.0)	35	30 (15.4)	34	55 (27.6)	69
General AEs and administration site conditions	31 (16.1)	66	24 (12.3)	31	50 (25.1)	97
Fatigue	22 (11.4)	54	13 (6.7)	17	34 (17.1)	71

Safety analysis set: all randomised participants who were exposed to at least one dose of study product

1G first generation, 2G second generation, AE adverse event, E number of events, n number of participants, PT preferred term, SAE serious adverse event, SOC system organ class, TEAE treatment-emergent adverse event

Group 2

A total of 1087 TEAEs were reported in 146 (73.4%) of 199 participants (Table 5). One treatment-emergent SAE of dehydration was reported (2G oral semaglutide 4 mg, probably related to treatment). One non-treatment-emergent SAE of spontaneous abortion (2G oral semaglutide 4 mg) was reported in a participant who discontinued study treatment after 2 weeks comprising one week of dose escalation (1.5 mg) and one week of the

first steady-state period (4 mg). This SAE was reported 77 days after initial treatment began and was judged unrelated to treatment by the investigator.

Group 3

In group 3, 64 (52.0%) of 123 participants reported a total of 201 TEAEs (Table 6); no SAEs were reported.

Table 6 Summary of treatment-emergent adverse events—Group 3

	1G oral semaglutide		2G oral semaglutide		Total	
	<i>n</i> (%)	<i>E</i>	<i>n</i> (%)	<i>E</i>	<i>n</i> (%)	<i>E</i>
Number of participants	122		120		123	
TEAEs	47 (38.5)	110	39 (32.5)	91	64 (52.0)	201
Treatment-emergent SAEs	0		0		0	
Events leading to treatment discontinuation	0		1 (0.8)	1	1 (0.8)	1
Severity						
Severe	0	0	0	0	0	0
Moderate	4 (3.3)	4	1 (0.80)	1	5 (4.1)	5
Mild	45 (36.9)	106	38 (31.7)	90	62 (50.4)	196
Most common TEAEs by SOC and PT in ≥ 15% of participants in total						
Gastrointestinal AEs	26 (21.3)	51	24 (20.0)	41	41 (33.3)	92
Nausea	12 (9.8)	16	13 (10.8)	16	22 (17.9)	32
Nervous system AEs	14 (11.5)	16	15 (12.5)	21	23 (18.7)	37
Headache	12 (9.8)	14	13 (10.8)	16	19 (15.4)	30
Metabolism and nutrition AEs	14 (11.5)	18	12 (10.0)	14	23 (18.7)	32
Decreased appetite	13 (10.7)	14	12 (10.0)	14	22 (17.9)	28

Safety analysis set: all randomised participants who were exposed to at least one dose of study product

1G first generation, 2G second generation, AE adverse event, E number of events, *n* number of participants, PT preferred term, SAE serious adverse event, SOC system organ class, TEAE treatment-emergent adverse event

DISCUSSION

In this interventional, randomised, three-group, full replicate crossover study, bioequivalence was confirmed between 2G oral semaglutide and the initially approved formulation, 1G oral semaglutide, at SS in healthy participants across the three investigated dose levels of 1.5 versus 3 mg, 4 versus 7 mg and 9 versus 14 mg, all once daily. This was based on the comparison of $AUC_{0-24h,SS}$ and C_{max} values, which showed bioequivalence between formulations at all three dose levels in accordance with the prespecified criteria designated in EMA, FDA and PMDA guidelines. Furthermore, $C_{tau, 24h}$ and $t_{max, 0-24h}$ were comparable across formulations. Given the successful demonstration of bioequivalence across the two formulations,

these results demonstrate that the change in excipients in the 2G formulation of oral semaglutide improved the bioavailability of semaglutide.

The overall safety profile of 2G oral semaglutide was consistent with the established safety profile of 1G oral semaglutide [36] and with that of the GLP-1RA class [37]; no new safety concerns were identified. Comparison of PK parameters with those reported in other studies of oral semaglutide is challenging due to differences in doses and study designs. However, the reported geometric means for AUC_{0-24h} and C_{max} were within the expected range and median t_{max} values were comparable to previous reports [33, 38–41]. The shapes of the semaglutide dosing interval profiles were also similar to curves reported by van Hout et al. and Bækdal et al. [38–41].

Study limitations include that the full replicate crossover study design without wash-out periods utilised here is not optimised for a head-to-head safety comparison between the two formulations. TEAEs were allocated to the formulation the participant was taking at the time of TEAE onset, and therefore it is possible that a TEAE could have occurred due to the previously administered formulation.

The comprehensive PIONEER clinical programme, comprising 12 phase 3a studies including > 7000 participants with T2D treated with once-daily oral semaglutide, assessed the safety and efficacy of oral semaglutide (3, 7 and 14 mg) versus placebo, empagliflozin, sitagliptin, liraglutide and dulaglutide [10–21]. The programme demonstrated the superiority of oral semaglutide versus placebo and most active comparators for reductions in glycated haemoglobin (HbA_{1c}) levels and body weight, with a safety profile consistent with that observed in other GLP-1RA studies [10–21]. The effectiveness and safety of 1G oral semaglutide has been further demonstrated in a real-world setting in the PIONEER REAL studies [42–46]. The Semaglutide cardiOvascular oUtcomes trial (SOUL), which investigated the effects of oral semaglutide on cardiovascular outcomes in individuals with T2D and atherosclerotic CVD and/or chronic kidney disease, also recently completed with results expected to be published in 2025 [47, 48]. As this study showed comparable exposures between the 1G and 2G formulations of oral semaglutide that met stringent regulatory bioequivalence criteria, it is considered unlikely that there will be any clinically meaningful differences in efficacy or safety between these formulations.

The bioequivalence between the 1G formulation and the 2G formulation demonstrated in the present study allows switching from the 1G formulation to the 2G formulation [22, 24].

CONCLUSIONS

Confirmation of bioequivalence in the present study provides support that the safety profile and efficacy of each dose level of once-daily 2G oral semaglutide (1.5, 4 and 9 mg), in terms of

reductions in HbA_{1c} and body weight, will be equivalent to the corresponding dose level of once-daily 1G oral semaglutide (3, 7 and 14 mg), therefore allowing switching from the 1G to the 2G formulation.

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Data Availability. The datasets generated during and/or analysed during the current study are available from Novo Nordisk on reasonable request. Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at 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 United States. Individual participant data will be shared in data sets in a de-identified/anonymised format.

Declarations

Conflict of interest. Mette Søndergaard Nielsen—Employee and shareholder of Novo Nordisk A/S. Lise Brøndsted—Employee and shareholder of Novo Nordisk A/S. Martin Kankam—One of the clinical investigators who participated in the conduct of the study, which was sponsored by Novo Nordisk; employee at Altasciences and has received clinical trial funding from Amgen, Biogen, Biohaven, Camino, DynPort, Eli Lilly, EncuraGen, NIH/DMID, Staidson and Vertex. Gaetano Morelli—Employee at Altasciences. David Nguyen—Employee at Altasciences. Trine Vang Skjøth—Employee and shareholder of Novo Nordisk A/S. Usha Rani Patte—Employee of Novo Nordisk India Private Ltd. Marloes van Hout—Employee and shareholder of Novo Nordisk A/S.

Ethical approval. The study protocol was approved by appropriate health authorities according to local guidelines and by the Institutional Review Board/Independent Ethics Committee Institutional Review Board, listed in the Supplementary Appendix. The study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonization (ICH) Good Clinical Practice guidelines. Participants provided written informed consent prior to commencement of any study-related activities.

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REFERENCES

1. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2022;65(12):1925–66.
2. Blüher M, Ceriello A, Davies M, et al. Managing weight and glycaemic targets in people with type 2 diabetes—How far have we come? *Endocrinol Diabetes Metab*. 2022;5(3): e00330.
3. Tran S, Retnakaran R, Zinman B, Kramer CK. Efficacy of glucagon-like peptide-1 receptor agonists compared to dipeptidyl peptidase-4 inhibitors for the management of type 2 diabetes: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab*. 2018;20(Suppl 1):68–76.
4. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392(10157):1519–29.
5. Meier JJ. Efficacy of semaglutide in a subcutaneous and an oral formulation. *Front Endocrinol (Lausanne)*. 2021;12: 645617.
6. U.S. Food and Drug Administration. Ozempic® Prescribing Information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf. Accessed 20 June 2024.
7. European Medicines Agency. Ozempic® Summary of Product Characteristics. 2018. https://www.ema.europa.eu/en/documents/product-information/ozempic-epar-product-information_en.pdf. Accessed 20 June 2024.
8. Granhall C, Donsmark M, Blicher TM, et al. Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1

- analogue, oral semaglutide, in healthy subjects and subjects with type 2 diabetes. *Clin Pharmacokinet.* 2019;58(6):781–91.
9. Nauck MA, Meier JJ. Pioneering oral peptide therapy for patients with type 2 diabetes. *Lancet Diabetes Endocrinol.* 2019;7(7):500–2.
 10. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care.* 2019;42(9):1724–32.
 11. Rodbard HW, Rosenstock J, Canani LH, et al. Oral semaglutide versus empagliflozin in patients with type 2 diabetes uncontrolled on metformin: The PIONEER 2 trial. *Diabetes Care.* 2019;42(12):2272–81.
 12. Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of additional oral semaglutide vs sitagliptin on glycated hemoglobin in adults with type 2 diabetes uncontrolled with metformin alone or with sulfonylurea: The PIONEER 3 randomized clinical trial. *JAMA.* 2019;321(15):1466–80.
 13. Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet.* 2019;394(10192):39–50.
 14. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):515–27.
 15. Zinman B, Aroda VR, Buse JB, et al. Efficacy, safety, and tolerability of oral semaglutide versus placebo added to insulin with or without metformin in patients with type 2 diabetes: The PIONEER 8 trial. *Diabetes Care.* 2019;42(12):2262–71.
 16. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2019;381(9):841–51.
 17. 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(5):377–91.
 18. Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):528–39.
 19. 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(5):392–406.
 20. Wang W, Bain SC, Bian F, et al. Efficacy and safety of oral semaglutide monotherapy vs placebo in a predominantly Chinese population with type 2 diabetes (PIONEER 11): a double-blind, Phase IIIa, randomised trial. *Diabetologia.* 2024;67:1783–99.
 21. Ji L, Agesen RM, Bain SC, et al. Efficacy and safety of oral semaglutide vs sitagliptin in a predominantly Chinese population with type 2 diabetes uncontrolled with metformin: PIONEER 12, a double-blind, Phase IIIa, randomised trial. *Diabetologia.* 2024;67:1800–16.
 22. European Medicines Agency. Rybelsus® Summary of Product Characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf. Accessed 20 June 2024.
 23. U.S. Food and Drug Administration. Rybelsus® Prescribing Information. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. Accessed 20 June 2024.
 24. U.S. Food and Drug Administration. Rybelsus® Prescribing Information. 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/213051s018lbl.pdf. Accessed 20 June 2024.
 25. Novo Nordisk. Novo Nordisk announces FDA approval of label update for Rybelsus® (semaglutide) allowing use as a first-line option for adults with type 2 diabetes [press release]. 2023. <https://www.novonordisk-us.com/media/news-archive/news-details.html?id=154651>. Accessed 20 June 2024.
 26. Tran H, ElSayed MEH. Progress and limitations of oral peptide delivery as a potentially transformative therapy. *Expert Opin Drug Deliv.* 2022;19(2):163–78.
 27. ClinicalTrials.gov. A Research Study Comparing Active Drug in the Blood in Healthy Participants Following Dosing of the Current and a New Formulation (D) Semaglutide Tablets (NCT04097600). 2022. <https://clinicaltrials.gov/study/NCT04097600>. Accessed 20 June 2024.

28. European Medicines Agency. Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). 2010. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed 20 June 2024.
29. U.S. Food and Drug Administration. Bioavailability Studies Submitted in NDAs or INDs—General Considerations Guidance for Industry. 2022. <https://www.fda.gov/media/121311/download>. Accessed 20 June 2024.
30. Pharmaceuticals and Medical Devices Agency and Ministry of Health Labour and Welfare. Guideline for Bioequivalence Studies of Generic Products, PSEHB/PED Notification No. 0319-1. 2020. [https://www.nih.go.jp/drug/be-guide\(e\)/2020/GL1_BE_2020.pdf](https://www.nih.go.jp/drug/be-guide(e)/2020/GL1_BE_2020.pdf). Accessed 20 June 2024.
31. World Medical Association. WMA declaration of Helsinki—ethical principles for medical research involving human subjects. 2013. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>. Accessed 20 June 2024.
32. International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH). ICH Harmonised Guideline. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice, E6(R2). 2016. https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf. Accessed 20 June 2024.
33. Overgaard RV, Navarria A, Ingwersen SH, Bækdal TA, Kildemoes RJ. Clinical pharmacokinetics of oral semaglutide: analyses of data from clinical pharmacology trials. *Clin Pharmacokinet*. 2021;60(10):1335–48.
34. U.S. Food and Drug Administration. Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA guidance for industry. 2021. <https://www.fda.gov/media/87219/download>. Accessed 20 June 2024.
35. MedDRA. Introductory Guide for Standardised MedDRA Queries (SMQs) Version 26.0. 2023. https://admin.meddra.org/sites/default/files/guidance/file/SMQ_intguide_26_0_English.pdf. Accessed 20 June 2024.
36. 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(8):1263–77.
37. 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(4):524–36.
38. Bækdal TA, Breitschaft A, Donsmark M, Maarbjerg SJ, Sondergaard FL, Borregaard J. Effect of various dosing conditions on the pharmacokinetics of oral semaglutide, a human glucagon-like peptide-1 analogue in a tablet formulation. *Diabetes Ther*. 2021;12(7):1915–27.
39. Bækdal TA, Breitschaft A, Navarria A, Hansen CW. A randomized study investigating the effect of omeprazole on the pharmacokinetics of oral semaglutide. *Expert Opin Drug Metab Toxicol*. 2018;14(8):869–77.
40. Bækdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, safety, and tolerability of oral semaglutide in subjects with hepatic impairment. *J Clin Pharmacol*. 2018;58(10):1314–23.
41. van Hout M, Forte P, Jensen TB, Boschini C, Bækdal TA. Effect of various dosing schedules on the pharmacokinetics of oral semaglutide: a randomised trial in healthy subjects. *Clin Pharmacokinet*. 2023;62(4):635–44.
42. Jain AB, Reichert SM, Amadid H, et al. Use of once-daily oral semaglutide and associated clinical outcomes among adults with type 2 diabetes in routine clinical practice in Canada: a multicentre, prospective real-world study (PIONEER REAL Canada). *Diabetes Obes Metab*. 2024;26(5):1799–807.
43. Kick A, M'Rabet-Bensalah K, Acquistapace F, et al. Real-world use of oral semaglutide in adults with type 2 diabetes: The PIONEER REAL Switzerland multicentre, prospective, observational study. *Diabetes Ther*. 2024;15(3):623–37.
44. van Houtum W, Schrömbges P, Amadid H, et al. Real-world use of oral semaglutide in adults with type 2 diabetes in the PIONEER REAL Netherlands multicentre, prospective, observational study. *Diabetes Ther*. 2024;15(8):1749–68.
45. Catrina SB, Amadid H, Braae UC, et al. PIONEER REAL Sweden: a multicentre, prospective, real-world observational study of oral semaglutide use in adults with type 2 diabetes in Swedish clinical practice. *Diabetes Ther*. 2024;15:2079–95.
46. Yabe D, Hamamoto Y, Kawanami D, et al. PIONEER REAL Japan: primary results from a multicenter, prospective, real-world study of oral semaglutide in adults with type 2 diabetes in Japanese clinical practice. *J Diabetes Investig*. 2024;15:1566–77.

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47. McGuire DK, Busui RP, Deanfield J, et al. Effects of oral semaglutide on cardiovascular outcomes in individuals with type 2 diabetes and established atherosclerotic cardiovascular disease and/or chronic kidney disease: design and baseline characteristics of SOUL, a randomized trial. *Diabetes Obes Metab*. 2023;25(7):1932–41.
 48. Novo Nordisk. Novo Nordisk A/S: Oral semaglutide demonstrates a 14% reduction in risk of major adverse cardiovascular events in adults with type 2 diabetes in the SOUL trial. 2024. <https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=171480>. Accessed 01 Nov 2024.