

ORIGINAL RESEARCH ARTICLE

Pharmacokinetic bioequivalence of semaglutide injection in healthy adults under fasting conditions: A randomized study

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Abstract

Background: Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist used in the management of type 2 diabetes mellitus. Broader access to semaglutide therapy may be supported by clinically suitable alternative formulations if pharmacokinetic comparability with the reference product is established. **Aim:** To evaluate the pharmacokinetic bioequivalence of semaglutide 0.5 mg solution for injection developed by Dr. Reddy's Laboratories Limited, India, compared with Ozempic® (semaglutide) 0.5 mg solution for injection in a pre-filled pen under fasting conditions in healthy adult subjects. **Methods:** This was an open-label, balanced, randomized, two-treatment, single-dose, parallel-group bioequivalence study. Eighty healthy volunteers were enrolled, 78 were dosed, and 74 were included in the pharmacokinetic and statistical analyses. Plasma semaglutide concentrations were measured using a validated liquid chromatography–tandem mass spectrometry method across 31 sampling time points up to 816 hours after dosing. Primary pharmacokinetic endpoints were C_{max} , area under the curve (AUC_{0-t}) and $AUC_{0-\infty}$. Bioequivalence was concluded if the 90% confidence intervals for the test/reference ratio were within 80% to 125%. **Results:** The 90% confidence intervals were 93.11%–107.22% for C_{max} , 93.76%–112.65% for AUC_{0-t} , and 91.48%–104.47% for $AUC_{0-\infty}$, meeting bioequivalence criteria for all primary parameters. Forty-six non-serious adverse events were reported in 28 subjects. No serious adverse events or deaths occurred. **Conclusion:** The test semaglutide formulation was bioequivalent to the reference product and was generally well tolerated in healthy adult subjects under fasting conditions. **Relevance for patients:** A pharmacokinetically comparable semaglutide injection may help expand access to long-term semaglutide treatment where innovator product cost or availability may limit patient use.

Keywords: Semaglutide; Bioequivalence; Pharmacokinetics; Healthy adults; Injectable peptide; Access to therapy

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1. Introduction

Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that has become an important therapeutic option in the management of type 2 diabetes mellitus due to its integrated effects on glycemic control, glucagon suppression, and delayed gastric emptying.¹⁻⁵ Its clinical value lies not only in glucose lowering, but also in its ability to address several interconnected metabolic outcomes that matter in real-world diabetes care. The once-weekly dosing schedule further strengthens its therapeutic appeal by supporting convenience and treatment continuity.⁶⁻¹³

The therapeutic relevance of semaglutide is supported by its prolonged pharmacokinetic profile, exposure-response relationship, and clinical efficacy across the SUSTAIN clinical development program.^{2,12,14-21} Semaglutide has also demonstrated clinically relevant effects on broader cardiometabolic outcomes, including cardiovascular and renal-related outcomes in high-risk populations, supporting its increasing therapeutic importance beyond glycemic control alone.²²⁻²⁵ These clinical and pharmacological attributes make semaglutide an important molecule for comparative pharmacokinetic evaluation, particularly when alternative formulations are developed to support broader therapeutic availability.

Another important consideration is the evolving scientific interest in semaglutide pharmacokinetics and comparative formulation assessment. While semaglutide has been studied extensively in the context of clinical development and pharmacokinetics, published bioequivalence literature has largely focused on oral formulations or broader semaglutide pharmacokinetic evaluations, with relatively limited published data on generic injectable semaglutide products.²⁶⁻³⁰ This gap is relevant because injectable peptide products may require careful clinical pharmacokinetic assessment, supported by sensitive bioanalytical methods, adequate sampling duration, and appropriate statistical evaluation. For long-acting agents such as semaglutide, the study design must capture both peak exposure and total systemic exposure to enable formulation-related differences, if present, to be detected reliably.

The growing clinical use of semaglutide reflects a broader shift in diabetes treatment toward agents that can deliver meaningful metabolic benefit beyond glycemic correction alone. As treatment paradigms evolve, access to such therapies becomes increasingly important, particularly in healthcare settings where long-term affordability and sustainable supply may influence treatment uptake and persistence.^{31,32} This makes the generic development

pathway especially relevant for semaglutide, provided that equivalent systemic exposure to the reference product can be established using appropriate scientific and regulatory methods.³³⁻³⁷

For semaglutide, comparative systemic exposure can be evaluated using C_{max} , area under the curve (AUC)_{0-t}, and $AUC_{0-\infty}$.³³⁻³⁷ Because semaglutide has a prolonged elimination profile, a parallel-group design was selected to avoid the extended washout required for a crossover study while maintaining a robust pharmacokinetic comparison.^{6-13,33-37} In this context, extended pharmacokinetic sampling is important to adequately characterize the terminal phase and to minimize uncertainty in the estimation of $AUC_{0-\infty}$. Similarly, prespecified statistical analysis of log-transformed pharmacokinetic parameters and evaluation of 90% confidence intervals provide a structured basis for concluding bioequivalence when the test/reference ratios fall within the accepted equivalence range.³³⁻³⁷

The present study was conceived within that broader context. It evaluated semaglutide 0.5 mg solution for injection developed by Dr. Reddy's Laboratories Limited, India, against Ozempic® (semaglutide) 0.5 mg solution for injection in a pre-filled pen under fasting conditions in healthy adult subjects. The scientific objective was straightforward: to determine whether the test and reference products were bioequivalent on the basis of predefined pharmacokinetic criteria. At the same time, the study addresses a broader question in generic development: whether robust pharmacokinetic evidence can support access to therapies that are otherwise limited by cost or availability.

More broadly, the study is relevant in three ways: it addresses the clinical importance of semaglutide, supports the suitability of the selected study design, and highlights the potential access value of a pharmacokinetically equivalent generic formulation.

2. Materials and methods

2.1. Study design

The study was conducted as an open-label study because the primary endpoints were objective plasma concentration-derived pharmacokinetic parameters rather than subjective clinical outcomes.³³⁻³⁷ Therefore, treatment awareness was not expected to influence C_{max} , AUC_{0-t} , or $AUC_{0-\infty}$. Blinding was not considered necessary for the clinical phase; however, laboratory personnel involved in the bioanalysis were blinded to the randomization schedule. The parallel design was selected because semaglutide has a prolonged elimination profile, which would have required an extended washout period in a crossover design.^{6-13,33-37}

A separate formal simulation was not performed; however, the sample size was quantitatively justified using an expected mean difference of 5%, inter-subject coefficient of variation of 28%, expected test/comparator ratio of 95%–105%, and 80% power.^{33–37}

This investigation was conducted as an open-label, balanced, randomized, two-treatment, single-dose, parallel-group bioequivalence study under fasting conditions in healthy adult subjects. The study compared a test formulation, semaglutide 0.5 mg solution for injection developed by Dr. Reddy's Laboratories Limited, India, with the reference product, Ozempic® (semaglutide) 0.5 mg solution for injection in a pre-filled pen of Novo Nordisk Farmacêutica do Brasil Ltda. The study objective was to assess whether the test formulation was bioequivalent to the reference formulation with respect to the predefined primary pharmacokinetic parameters.

Eligible subjects were randomly assigned to receive either the test product or comparator product according to a randomization schedule generated using PROC PLAN in SAS® version 9.4. The randomization schedule was generated according to the study site standard operating procedure. Treatment assignment was implemented according to the approved randomization schedule.

The choice of a parallel-group design was driven by the pharmacokinetic behavior of semaglutide. Because semaglutide exhibits a prolonged elimination phase, a crossover design would have required an extended washout period and would have imposed a substantially greater operational burden. A parallel design was therefore the most appropriate approach, balancing scientific validity with participant feasibility and operational practicality.

Although the study was open-label, the bioanalytical evaluation was conducted using validated analytical procedures, and the pharmacokinetic endpoints were objective plasma concentration-derived measurements rather than subjective outcomes. This is important because the open-label design was unlikely to affect the main result.

2.2. Ethics and regulatory conduct

The study was conducted in accordance with Good Clinical Practice and relevant ethical and regulatory requirements. Independent Ethics Committee approval was obtained prior to study initiation, and the study conduct also included subsequently approved protocol errata. Written informed consent was obtained from all participants before the initiation of study procedures. The study was conducted in accordance with ANVISA RDC 742, Central Drugs Standard Control Organization requirements, Indian Council of Medical Research ethical guidance, International Council for Harmonisation–Good Clinical

Practice, and the Declaration of Helsinki.^{37–40}

The study protocol AZBE052311, version 1.0 dated June 2, 2023, together with the informed consent documents, was reviewed and approved on June 24, 2023, by the Independent Ethics Committee (IEC), #132/1, Bharathi Colony, Anna Nagar West, Chennai, Tamil Nadu, India. The approving IEC was registered with the Central Drugs Standard Control Organization under Registration No. ECR/111/Indt/TN/2013/RR-19. Erratum 1.0 to the approved protocol was approved on March 21, 2024, and Erratum 2.0 was approved on June 24, 2024.

Written informed consent was obtained from each volunteer before screening and again before enrollment into the study. The informed consent documents were provided to potential volunteers, read and explained by study staff, and volunteers were given adequate time to review and understand the study requirements.^{38–40} Individual counseling was provided by the investigator in private, and questions were addressed before consent was obtained.

These ethical and procedural safeguards are especially important in a bioequivalence study involving a long-acting injectable peptide administered to healthy volunteers. The extended duration of post-dose monitoring, the need for ambulatory sampling over several weeks, and the requirement for consistent safety follow-up all demand a study environment with strong procedural oversight and carefully documented quality control. Quality assurance procedures confirmed that protocol deviations were documented and evaluated and did not affect the overall study conclusion.

2.3. Study population

Healthy male and non-pregnant, non-breastfeeding female volunteers aged 18 to 45 years were eligible for enrollment if they met the protocol-defined health criteria and had a body mass index between 18.50 and 29.99 kg/m² with body weight greater than 50 kg. Subjects were evaluated through standard screening procedures that included medical history, clinical examination, vital signs, electrocardiography, and clinical laboratory testing. Subjects were excluded if they had clinically significant systemic disease, hypersensitivity to semaglutide or related agents, substance abuse, a history of pancreatitis, or recent exposure to medications or interventions that could influence semaglutide pharmacokinetics. Both male and female subjects were enrolled, and all participants were of Asian ethnicity.

From a design perspective, the selection of healthy adult volunteers is standard and appropriate for a pharmacokinetic bioequivalence trial.^{33–37} This allows

a clearer comparison of formulation-related exposure characteristics by minimizing confounding factors associated with disease pathology, concomitant medication, and variable clinical status.³³⁻³⁷ The inclusion of both sexes and a clinically reasonable body mass index range also supports the general robustness of the exposure comparison within the intended study framework.

2.4. Investigational products and dosing

The test product was semaglutide 0.5 mg solution for injection developed by Dr. Reddy's Laboratories Limited, India, and the comparator product was Ozempic® (semaglutide) 0.5 mg solution for injection in a pre-filled pen. Both products were 1.34 mg/mL formulations and were administered as a single subcutaneous dose under fasting conditions. Subjects were dosed in four groups on March 22, 24, 26, and 29, 2024.

Dosing was performed in four groups. Group 1 included 18 subjects (S01–S18) and was dosed on March 22, 2024; Group 2 included 15 subjects (S19–S33) and was dosed on March 24, 2024; Group 3 included 25 dosed subjects (S34–S59) and was dosed on March 26, 2024; and Group 4 included 20 dosed subjects (S60–S80) and was dosed on March 29, 2024. Although 80 subjects were enrolled, only 78 subjects were dosed because S37 and S71 withdrew consent before study drug administration. Overall, 39 subjects received the test product and 39 subjects received the comparator product. The distribution of enrolled and dosed subjects across the four dosing groups is summarized in Table 1.

The abdominal region was used as the injection site, and compliance with administration was monitored. A standardized dosing procedure was used, which is particularly important in injectable bioequivalence studies because administration technique may affect local delivery consistency. Even when minor procedural differences are unlikely to materially alter systemic exposure, a consistent administration process strengthens internal validity and reduces avoidable variability between treatment arms.

The identity and handling of investigational products were controlled under protocol-defined storage conditions. The investigational products were stored under refrigerated conditions, and product handling, inventory, and administration were managed in accordance with study procedures and standard operating requirements. This is important because peptide-based products require careful storage to maintain product integrity during comparative evaluation.

After an overnight fast of at least eight h, subjects received a single subcutaneous dose of either the test or

comparator product according to the randomization schedule. Dosing was performed in sitting posture at ambient temperature. The abdominal injection site was identified and marked before dosing, cleaned with an alcohol swab, and allowed to dry. The dose selector was set to deliver 0.5 mg, corresponding to 0.37 mL, and the dose was administered subcutaneously at a 90° angle into pinched abdominal skin. Compliance with drug administration was assessed by monitoring the injection site immediately after dosing.

2.5. Blood sampling and bioanalytical method

Pharmacokinetic blood sampling was designed to characterize semaglutide exposure comprehensively across both absorption and terminal elimination phases. A total of 31 blood samples of 4 mL each were scheduled at pre-dose and at 1, 2, 4, 8, 12, 16, 24, 26, 28, 30, 32, 34, 36, 40, 44, 48, 52, 56, 60, 64, 72, 84, 96, 120, 168, 240, 312, 480, 648, and 816 h after dosing. Samples up to 72 h were collected during in-house confinement, while samples from 84 to 816 h were collected during ambulatory visits. In-house post-dose samples up to 72 h were collected within two min of the scheduled time, and ambulatory samples were collected within ±2 h of the scheduled time. This extended sampling strategy is particularly appropriate for semaglutide because it supports a reliable estimate of total exposure and terminal disposition.^{2,6-13,33-37}

Blood samples were collected into pre-labeled tripotassium ethylenediaminetetraacetic acid vacutainers. Samples were centrifuged at 3,500 rpm at 4 °C for approximately 10 min. Plasma was separated into two aliquots in pre-labeled polypropylene tubes and stored at –70 °C ± 15 °C in an ultra-low-temperature freezer until shipment and bioanalytical analysis.

Plasma semaglutide concentrations were determined using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method with Nexera LC-40D/Nexera LC-40DXS HPLC pumps, Nexera SIL-40C/SIL-40CXS autosamplers, and CTO-40C/CTO-40S column ovens (Shimadzu, Japan), coupled with SCIEX Triple Quad 6500+ LC–MS/MS detectors and operated using Analyst software versions 1.7.3 and 1.7.2.⁴¹⁻⁴⁵ Semaglutide-D5 was used as the internal standard, and the bioanalytical process was performed using validated methods suitable for the plasma concentration range encountered in the study. The availability of a validated LC–MS/MS method is central to the integrity of any peptide bioequivalence evaluation, as reliable quantification across the terminal phase is essential for meaningful AUC_{0-∞} estimation.

Semaglutide concentrations in human tripotassium ethylenediaminetetraacetic acid plasma were quantified

Table 1. Treatment distribution by dosing group

Dosing group	Subject numbers assigned/enrolled	Dosing date	Number assigned/enrolled	Number dosed	Sex composition assigned/enrolled	Subjects not dosed/withdrawn before dosing	Treatment exposure
Group 1	S01–S18	March 22, 2024	18	18	18 males	None	Test: 9; Comparator: 9
Group 2	S19–S33	March 24, 2024	15	15	15 males	None	Test: 8; Comparator: 7
Group 3	S34–S59	March 26, 2024	26	25	12 females and 14 males	S37 withdrew consent before dosing	Test: 12; Comparator: 13
Group 4	S60–S80	March 29, 2024	21	20	14 males and 7 females	S71 withdrew consent before dosing	Test: 10; Comparator: 10
Total	—	—	80	78	47 males and 33 females assigned/enrolled	Two subjects withdrew before dosing	Overall: Test = 39; Comparator = 39

Notes Dosing was conducted in four groups on separate dates. Two subjects, S37 and S71, withdrew consent before study drug administration; therefore, 78 of 80 enrolled subjects were dosed. Overall treatment exposure was balanced, with 39 subjects receiving the test product and 39 subjects receiving the comparator product. Treatment/formulation $\times$ group effects were statistically non-significant for $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$, indicating that the bioequivalence conclusion was not driven by dosing date or group-related imbalance.

using validated LC–MS/MS methods (method protocol numbers AZ-BA-MP-023/2023, version 1.0, and AZ-BA-MP-015/2024, version 1.0). Semaglutide-D5 was used as the internal standard. Sample preparation involved protein precipitation followed by solid-phase extraction. The validated assay ranges were 4.885–199.435 ng/mL for the initial analytical set and 2.002–119.288 ng/mL for subsequent study sample analysis and incurred sample reanalysis. The lower limits of quantification were therefore 4.885 ng/mL and 2.002 ng/mL for the respective validated ranges. The method validation and study sample analysis were conducted using validated procedures suitable for clinical pharmacokinetic assessment.^{41–45}

Pharmacokinetic samples were collected from 78 dosed subjects, whereas the pharmacokinetic and statistical analyses were based on the 74 subjects who completed the study. This distinction is important because it clarifies the difference between the full set of analyzed samples and the evaluable dataset used for the bioequivalence assessment.

2.6. Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were calculated using non-compartmental analysis in Phoenix® WinNonlin® version 8.4.^{33–37} The predefined primary pharmacokinetic parameters were $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$. Secondary pharmacokinetic parameters included $T_{\max}$, terminal half-life, elimination rate constant, and percentage extrapolated AUC. Missing concentration data were recorded as missing and were not imputed. Concentrations below the

limit of quantification were set to zero for pharmacokinetic and statistical calculations.^{33–37,41–45} Pharmacokinetic and statistical analyses were performed on the 74 subjects who completed the study and had evaluable concentration–time data. Subjects who discontinued the study or withdrew consent were excluded from the pharmacokinetic and statistical analysis set.

Statistical analysis was performed using PROC GLM in SAS® version 9.4. Natural log-transformed $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$ values were analyzed using an analysis of variance model with treatment/formulation as the primary fixed effect.^{33–37} As dosing was conducted in four groups, an additional group-effect assessment was performed using a model including treatment/formulation $\times$ group. Least-squares means were estimated on the log scale, and the test/comparator geometric mean ratios and corresponding 90% confidence intervals were obtained by back-transformation. Bioequivalence was concluded if the 90% confidence intervals for $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$ were within 80% to 125%.^{33–37} Treatment-by-group effects were statistically non-significant, supporting the stability of the parallel-group comparison across dosing groups. Statistical significance was assessed using a two-one-sided *t*-test at an alpha level of 0.05.

The sample size calculation assumed an expected mean difference of 5% between formulations, an expected inter-subject coefficient of variation of 28%, and an expected test/comparator ratio within 95%–105%. Based on these assumptions, 68 subjects were required to establish

bioequivalence with 80% power in a parallel design. To account for potential dropouts, including discontinuations due to expected adverse drug reactions, 80 subjects were enrolled. The assumed inter-subject coefficient of variation was based on an earlier study conducted at Azidus Laboratories Limited, Chennai, India.

2.7. Safety assessment

Safety was evaluated from the screening stage through completion of study participation. Safety monitoring included continuous subject well-being assessments, adverse event monitoring, vital signs, physical examination, 12-lead electrocardiogram, clinical laboratory tests, urine analysis, and pregnancy testing for female subjects. Vital signs were recorded at check-in, pre-dose, 3, 9, 32, 54, and 71 h post-dose, during ambulatory visits, at post-study assessment, and whenever clinically indicated. Blood glucose was assessed at 2, 16, 40, 48, and 72 h post-dose. The safety monitoring strategy was consistent with the known clinical safety profile of semaglutide and GLP-1 receptor agonist therapy.¹⁴⁻²¹ Post-study safety evaluation, including laboratory assessment and clinical examination, was performed at the 816-h ambulatory visit.

In long-duration single-dose peptide studies, safety surveillance carries added importance because observation extends well beyond the immediate dosing period.^{2,6-13} The study design therefore appropriately combined early in-clinic monitoring with later ambulatory follow-up, making it possible to capture both early tolerability events and later post-dose safety observations within a single coherent framework. This adds value to the study because it allows safety to be interpreted as an integral part of the study quality rather than as a routine secondary component of the pharmacokinetic assessment.

3. Results

3.1. Subject disposition

A total of 80 healthy adult subjects were enrolled; 78 received study treatment, and 74 were included in the pharmacokinetic and statistical analyses. Discontinuations occurred because of adverse events or withdrawal of consent. [Figure 1](#) summarizes subject enrollment, treatment administration, discontinuations, and inclusion in the pharmacokinetic and statistical analysis sets.

From an analytical perspective, it is useful to distinguish between three populations described in the study materials: the enrolled population, the dosed population, and the pharmacokinetic/statistical analysis population.³³⁻³⁷ Presenting the populations in this way makes the study flow easier to follow and clarifies that

the bioequivalence conclusion was based on subjects with evaluable pharmacokinetic data.³³⁻³⁷

3.2. Demographic characteristics

The demographic characteristics of the evaluable study completers were generally consistent with a healthy adult volunteer population suitable for a phase I comparative pharmacokinetic study.³³⁻³⁷ Among the 74 subjects included in the pharmacokinetic and statistical analyses, the mean age was 35 years, the mean height was 1.664 m, the mean body weight was 67.8 kg, and the mean body mass index was 24.55 kg/m². Overall, these characteristics are consistent with a healthy volunteer population suitable for comparative pharmacokinetic assessment under controlled conditions. Baseline demographic characteristics of the pharmacokinetic analysis set are summarized in [Table 2](#).

The study included both male and female participants, providing a broader healthy volunteer population while remaining within the standard framework used for bioequivalence trials. No meaningful demographic imbalance was evident that would be expected to undermine the pharmacokinetic comparison, and the non-significant group-effect findings further support the internal consistency of the study.

3.3. Pharmacokinetic profile

The pharmacokinetic sampling schedule allowed characterization of semaglutide plasma concentrations from the pre-dose baseline through 816 h after a single subcutaneous injection. The long sampling duration is a clear strength of the study because it allowed both the absorption phase and the prolonged terminal elimination phase to be characterized adequately.^{6-13,33-37} The general concentration–time behavior described in the published semaglutide article—gradual rise to peak exposure followed by slow decline is also consistent with the expectations for semaglutide and supports the appropriateness of the sampling design used in the present study.⁶⁻¹³ Mean plasma semaglutide concentration–time profiles on linear and semi-logarithmic scales are shown in [Figures 2 and 3](#), respectively.

Mean C_{max} was 59.641 ± 12.562 ng/mL for the test formulation and 59.190 ± 9.243 ng/mL for the comparator formulation. Mean AUC_{0-t} values were $15,038.950 \pm 3,253.077$ hr·ng/mL and $14,716.720 \pm 3,004.870$ hr·ng/mL for the test and comparator products, respectively. Mean $AUC_{0-\infty}$ values were $15,958.976 \pm 3,157.561$ hr·ng/mL for the test product and $16,199.783 \pm 2,338.601$ hr·ng/mL for the comparator product. These results indicate close overall agreement in both peak exposure and total systemic exposure between the two formulations.³³⁻³⁷

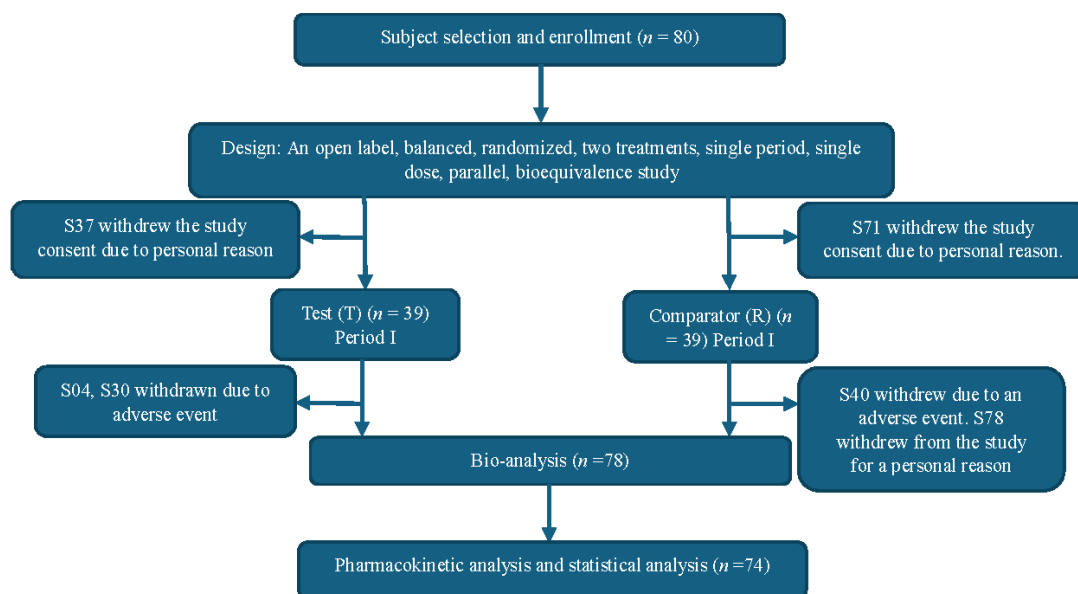


Figure 1. Subject disposition flow diagram

Table 2. Baseline demographic characteristics of subjects included in the pharmacokinetic analysis set

Parameter	Mean	Standard deviation	Minimum	Maximum
Age (years)	35	6	23	45
Height (m)	1.664	0.072	1.520	1.860
Weight (kg)	67.8	8.3	51.5	86.2
Body mass index (kg/m ²)	24.55	3.08	18.78	29.96

Note: Data are presented for subjects included in the pharmacokinetic and statistical analysis set.

Secondary pharmacokinetic parameters also showed broadly comparable behavior. Median $T_{\max}$ was 52 h for the test formulation and 36 h for the comparator formulation, while mean terminal half-life values were 139.675 ± 12.055 h and 143.391 ± 15.561 h, respectively. The elimination rate constant and percentage extrapolated AUC similarly supported an overall comparable disposition profile between formulations. A summary of the primary and secondary pharmacokinetic parameters is presented in Table 3.

The adequacy of the 816-h sampling duration was

supported by the low percentage of extrapolated AUC. Mean $AUC_{\% \text{Extrap_Obs}}$ was 5.965% for the test product and 7.242% for the comparator product, indicating that most systemic exposure was captured within the observed sampling interval and that $AUC_{0-\infty}$ was estimated with limited extrapolation.

3.4. Bioequivalence assessment

The formal bioequivalence comparison showed that the geometric mean ratio (test/reference) was 99.92% for $C_{\max}$, 102.77% for AUC_{0-t} , and 97.76% for $AUC_{0-\infty}$. The corresponding 90% confidence intervals were 93.11%–

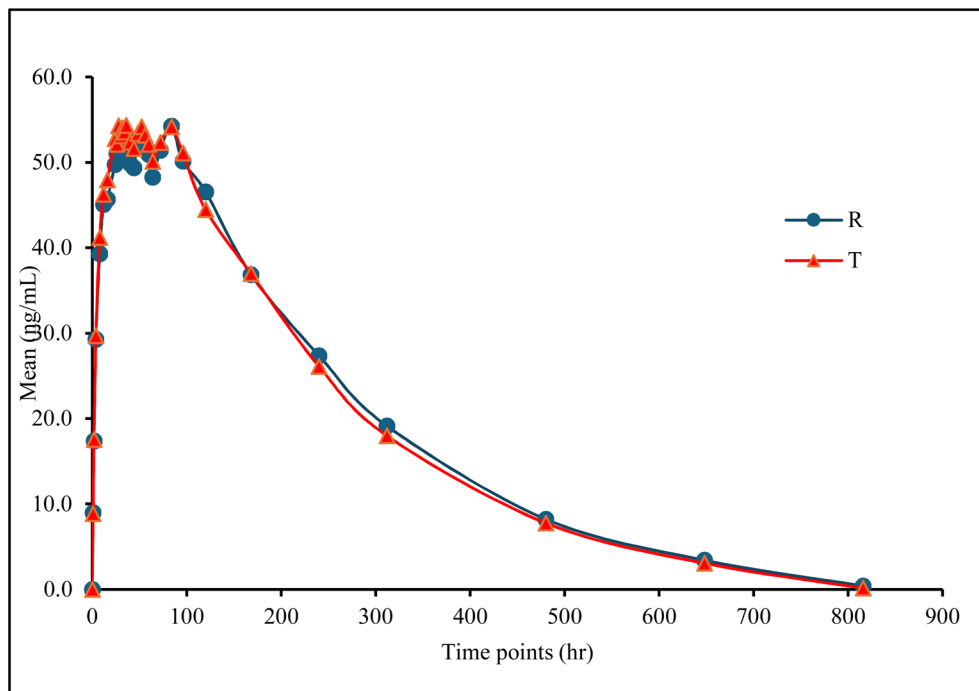


Figure 2. Mean plasma semaglutide concentration–time profile on a linear scale. R refers to the comparator group, and T refers to the test group.

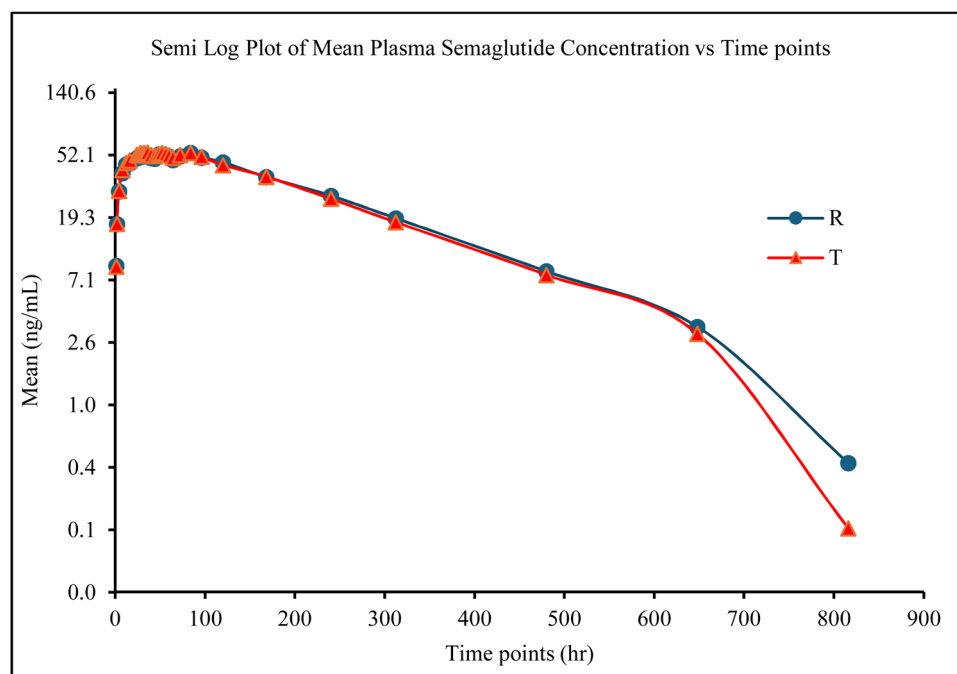


Figure 3. Mean plasma semaglutide concentration–time profile on a semi-logarithmic scale. R refers to the comparator group, and T refers to the test group.

Table 3. Summary of pharmacokinetic parameters of semaglutide following single-dose subcutaneous administration

Parameter	<i>n</i>	Test T (A)	<i>n</i>	Comparator R (B)
C _{max} (ng/mL)	37	59.641 ± 12.562	37	59.190 ± 9.243
AUC _{0-t} (hr·ng/mL)	37	15,038.950 ± 3,253.077	37	14,716.720 ± 3,004.870
AUC _{0-∞} (hr·ng/mL)	37	15,958.976 ± 3,157.561	36	16,199.783 ± 2,338.601
T _{max} (hr), median (range)	37	52.00 (16.00–98.33)	37	36.00 (12.00–120.00)
Terminal half-life (hr)	37	139.675 ± 12.055	36	143.391 ± 15.561
Elimination rate constant (hr ⁻¹)	37	0.005 ± 0.000	36	0.005 ± 0.001
AUC _{-%Extrap_Obs(%)}	37	5.965 ± 5.119	36	7.242 ± 9.793

Note: Data are presented as mean ± standard deviation unless otherwise indicated.

107.22%, 93.76%–112.65%, and 91.48%–104.47%, respectively. All three confidence intervals were fully contained within the predefined bioequivalence range of 80% to 125%, thereby confirming bioequivalence between the test and comparator formulations.³³⁻³⁷ The statistical comparison of the primary pharmacokinetic parameters and the corresponding bioequivalence assessment are summarized in Table 4.

The inter-subject coefficients of variation were 18.36% for C_{max}, 24.02% for AUC_{0-t}, and 17.14% for AUC_{0-∞}, with high associated statistical power. These findings indicate that the study was adequately powered and that the parallel design was sufficiently robust to support a clear bioequivalence conclusion despite the expected inter-subject variability.

3.5. Treatment and group effects

For the actual-time analysis, treatment/formulation effects were statistically insignificant for C_{max}, AUC_{0-t}, and AUC_{0-∞}, with *p*-values of 0.9850, 0.6209, and 0.5712, respectively. Treatment/formulation × group effects were also statistically insignificant, with *p*-values of 0.9104 for C_{max}, 0.7914 for AUC_{0-t}, and 0.7450 for AUC_{0-∞}. These findings indicate that the observed bioequivalence conclusion was not driven by treatment or dosing-group imbalance. This is an important supportive result in a four-group parallel study because it indicates that any meaningful group-related analytical artifact did not drive the observed exposure comparability.³³⁻³⁷ In practical terms, it means that the equivalence conclusion remained stable across

the study's operational grouping structure. These findings support the consistency of the bioequivalence conclusion across the study's dosing groups.

3.6. Safety and tolerability

Safety findings were consistent with expectations for a single-dose semaglutide study conducted in healthy volunteers. A total of 46 non-serious adverse events were reported in 28 subjects. Of these, 29 events occurred after administration of the test product and 17 events occurred after administration of the comparator product, corresponding to event incidences of 74.36% and 43.59%, respectively, based on 39 subjects exposed to each treatment. No serious adverse events, deaths, severe adverse events, or significant adverse events were reported. Fourteen events were mild, and 32 were moderate in severity. Relationship to study drug was assessed as probable for 28 events, possible for 13 events, and unlikely for 5 events. All adverse events resolved without sequelae. Treatment-emergent adverse events by treatment group are summarized in Table 5.

The more commonly reported adverse events included gastrointestinal symptoms and related events such as vomiting, diarrhea, nausea, hypoglycemia, headache, and dizziness. These observations are not unexpected in a semaglutide exposure setting and are consistent with the general tolerability patterns described in the comparator semaglutide literature summarized in the published article.¹⁴⁻²¹ Importantly, the overall safety conclusion was that both formulations were relatively well tolerated at the administered dose level in the selected study population.

Table 4. Statistical comparison of primary pharmacokinetic parameters and bioequivalence assessment

Parameters	Geometric mean		T/R ratio (%)	90% confidence interval	Inter-subject coefficient of variation (%)	Power
	Test product (T)	Comparator (R)				
LN_C _{max}	58.4353	58.4819	99.92	93.11%–107.22%	18.36	0.9997
LN_AUC _{0-t}	14,715.688	14,318.691	102.77	93.76%–112.65%	24.02	0.9902
LN_AUC _{0-∞}	15,674.891	16,034.108	97.76	91.48%–104.47%	17.14	0.9999

Note: Bioequivalence was concluded because the 90% confidence intervals for all primary pharmacokinetic parameters were within the predefined acceptance interval of 80% to 125%.

Table 5. Summary of treatment-emergent adverse events by treatment group (Safety population: 39 subjects exposed to each treatment)

System organ class / preferred term	Test product (n = 39)	Comparator product (n = 39)
Nervous system disorders		
Headache	2	1
Dizziness	2	1
Gastrointestinal disorders		
Vomiting	12	4
Nausea	3	2
Diarrhea	7	5
Gastritis	0	1
Metabolism and nutrition disorders		
Hypoglycemia	3	1
Respiratory, thoracic and mediastinal disorders		
Upper respiratory tract infection	0	1
Injury, poisoning and procedural complications		
Accidental injury	0	1
Total number of reported adverse events	29 (74.36%)	17 (43.59%)

Note: Values are presented as number of reported adverse events. No serious adverse events or deaths were observed during the study. All reported adverse events were mild or moderate in severity and resolved without sequelae.

A small number of post-study laboratory abnormalities were observed in a few subjects, with outcomes remaining unknown in those lost to follow-up. However, these findings did not alter the overall study conclusion and were not classified as serious adverse events.

Post-study laboratory abnormalities were observed in five subjects. These included decreased sodium in S01, increased bilirubin parameters in S04, decreased platelet count and increased bilirubin parameters in S53, increased triglycerides in S75, and increased triglycerides, urine glucose, and random blood sugar in S78. These subjects were clinically normal at the time of examination and were advised to return for repeat testing; however, they did not report despite follow-up attempts and were considered lost to follow-up according to site procedures. Outcomes for these laboratory abnormalities therefore remained unknown. These findings were not classified as serious adverse events and did not alter the overall safety conclusion.

4. Discussion

The present study demonstrated that semaglutide 0.5 mg solution for injection developed by Dr. Reddy's Laboratories Limited was pharmacokinetically bioequivalent to the innovator semaglutide product when administered as a single subcutaneous dose under fasting conditions in healthy adult subjects.³³⁻³⁷ The 90% confidence intervals for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ all fell well within the accepted bioequivalence interval of 80% to 125%, and the closeness of the point estimates further supports the conclusion that the two products provided comparable systemic exposure. These findings directly address the main study objective and support the conclusion that the two formulations were pharmacokinetically equivalent under the conditions tested.

The study design was aligned with comparative pharmacokinetic principles used for products intended to demonstrate comparable systemic exposure.³³⁻³⁷ The design included single-dose administration, prespecified primary pharmacokinetic endpoints, sampling across absorption and terminal elimination phases, validated bioanalytical quantification, log-transformed analysis of variance, and evaluation of 90% confidence intervals against the 80%–125% bioequivalence criterion. For peptide-based injectable products, confidence in clinical substitution should be based on the totality of evidence. In addition to pharmacokinetic bioequivalence, this includes active ingredient sameness, formulation and product-quality comparability, manufacturing control, stability, storage and handling conditions, delivery-system performance

where applicable, and post-approval pharmacovigilance. The present study contributes the clinical pharmacokinetic component of this evidence package.

The study was conducted in healthy adults to reduce variability related to disease status, concomitant medications, and heterogeneous clinical conditions, thereby allowing a sensitive comparison of formulation-related pharmacokinetic differences.³³⁻³⁷ The findings should therefore be interpreted as evidence of comparable systemic exposure after single-dose administration under controlled conditions, rather than as an independent demonstration of long-term efficacy or safety in patients with type 2 diabetes mellitus. Translation to the patient population relies on the regulatory principle that comparable systemic exposure can support therapeutic equivalence when combined with appropriate product quality, formulation, and regulatory evidence.^{12,14-21,33-37}

A major strength of the study lies in the fit between the drug's pharmacokinetic properties and the selected study design. Semaglutide is a long-acting peptide, and the decision to use a single-dose parallel-group design was methodologically sound because it avoided the extended washout demands that would have accompanied a crossover study.^{6-13,33-37} The extended 816-h sampling schedule was similarly appropriate and ensured that the comparison was not confined to early exposure alone, but instead captured the full exposure profile sufficiently to support reliable $AUC_{0-\infty}$ estimation. In this respect, the study illustrates how the choice of design was well aligned with the pharmacological and pharmacokinetic characteristics of semaglutide.

The close alignment of C_{max} and AUC values between formulations suggests comparability in both the rate and extent of semaglutide exposure following subcutaneous administration.^{6-13,33-37} Secondary parameters such as terminal half-life and T_{max} were likewise directionally similar, supporting the conclusion that the overall disposition profile of semaglutide was preserved across formulations. For a product such as semaglutide, where the exposure profile is closely linked to therapeutic performance, this broader pharmacokinetic similarity strengthens the primary bioequivalence finding.

Safety findings were consistent with what would be expected in a healthy volunteer semaglutide study.¹⁴⁻²¹ The reported adverse events were non-serious, mild or moderate, and largely gastrointestinal or related symptoms commonly associated with semaglutide exposure. No serious adverse events or deaths occurred, and all reported events resolved without sequelae. Although a numerically higher number of adverse events was reported in the test

arm, the overall tolerability profile remained acceptable, and no clinically meaningful divergence between formulations was evident.

Beyond meeting formal bioequivalence criteria, the study also adds useful evidence for the development of a generic injectable semaglutide formulation with comparable pharmacokinetic performance.³⁰ In this way, the findings are relevant not only to regulatory evaluation, but also to the broader goal of improving access to long-acting GLP-1 receptor agonist therapy.

At the same time, it is important to preserve the standard limitations inherent to bioequivalence trials. The study was conducted in healthy adults rather than patients with type 2 diabetes mellitus, and it used a single-dose design rather than repeated dosing at steady state. These features are entirely appropriate for a bioequivalence study and are consistent with established regulatory practice³³⁻³⁷, but they should still be acknowledged as part of transparent scientific reporting. The purpose of the study was not to re-establish clinical efficacy or long-term safety of semaglutide, but to demonstrate that the test formulation provides comparable systemic exposure to the reference product under controlled conditions.

Another limitation is that, like many long-duration phase I studies, the trial involved ambulatory follow-up across extended post-dose time points, and some samples were uncollected because certain subjects did not return for all scheduled visits. However, the pharmacokinetic and statistical analyses were performed on the defined evaluable population, the study retained sufficient power, and the resulting data consistently supported the bioequivalence conclusion.

Taken together, the findings support equivalence of exposure, confirm the suitability of the study design, and highlight the potential value of the product in improving access to therapy. This perspective helps place the results within a broader clinical and developmental context beyond numerical confirmation of bioequivalence alone.

In summary, the study succeeded not only because the formal bioequivalence criteria were met, but because the evidence was generated through a design that was appropriate for semaglutide, executed with sufficient analytical robustness, and interpreted within a clinically meaningful context. Taken together, these features make the study relevant not only from a regulatory standpoint but also as a useful scientific contribution.

From a healthcare perspective, a pharmacokinetically comparable semaglutide formulation may help improve treatment access where cost or supply constraints limit

long-term use of innovator products.^{31,32} Improved availability of clinically suitable alternatives may support continuity of therapy, which is important in chronic disease management. However, adherence, economic impact, prescribing behavior, and uptake within public or private healthcare systems were not directly evaluated in this study and require separate real-world and pharmacoeconomic assessment.

5. Conclusion

In this randomized, single-dose, open-label, parallel-group study conducted under fasting conditions, semaglutide 0.5 mg solution for injection developed by Dr. Reddy's Laboratories Limited was demonstrated to be pharmacokinetically bioequivalent to the innovator semaglutide product. The predefined bioequivalence criteria were met for C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$, and the overall pharmacokinetic profiles of the two formulations were closely aligned. Both treatments were generally well tolerated, with no serious adverse events reported during the study.

These findings support the pharmacokinetic comparability of the generic and innovator semaglutide formulations under the studied conditions. More broadly, they also illustrate how carefully designed bioequivalence studies can contribute to the evidence base needed to expand access to complex injectable therapies without compromising scientific rigor.

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Conflict of interest

All authors are employees of Dr. Reddy's Laboratories Ltd. and were involved in the design and conduct of the bioequivalence study. The authors declare no other competing interests.

Author contributions

Conceptualization: All authors

Formal analysis: All authors

Investigation: All authors

Methodology: All authors

Writing–original draft: All authors

Writing–review & editing: All authors

Ethics approval and consent to participate

The study protocol AZBE052311 (version 1.0 dated June 2, 2023) and the informed consent documents were reviewed and approved on June 24, 2023, by the Independent Ethics Committee (IEC) (#132/1) of Tamil Nadu, India. Erratum 1.0 to the approved protocol was approved on March 21, 2024, and Erratum 2.0 was approved on June 24, 2024. Written informed consent was obtained from each volunteer before screening and again before enrollment into the study.

Consent for publication

Consent for publication was obtained as part of the informed consent process. The manuscript does not contain participant-identifying information.

Availability of data

The data supporting the findings of this study are contained within the clinical study documentation and are available from the corresponding author on reasonable request, subject to applicable confidentiality and data-sharing restrictions.

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