https://doi.org/10.21518/ms2024-346

Original article

Semaglutide for the treatment of obesity: Results of two open randomized pharmacokinetic studies

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Abstract

Introduction. Obesity is a growing public health issue in Russia, increasing the risk of cardiovascular diseases, type 2 diabetes, and hypertension. Controlling obesity involves lifestyle changes and pharmacotherapy. Semaglutide, an effective obesity treatment, stimulates insulin production and reduces appetite. Developing a generic semaglutide preparation will improve its availability in Russia.

Aim. To study the comparative pharmacokinetics, bioequivalence, safety and tolerability of semaglutide products GP40331 and Wegovy using concentrations of 0.68 and 3.2 mg/mL in healthy volunteers under fasting conditions.

Materials and methods. Bioequivalence studies, conducted per Good Clinical Practice, were open-label, randomized, and involved healthy male volunteers. Subjects received semaglutide at single doses of 0.25 mg (0.68 mg/mL) and 0.5 mg (3.2 mg/mL) under fasting. Bioequivalence was determined by the 90% CI of the ratios of geometric mean values of the primary pharmacokinetic parameters (AUC_{0-t}, C_{max}). Semaglutide concentrations were measured using high-performance liquid chromatography with tandem mass spectrometry.

Results. The 90 % CI values for the ratios of geometric means of the primary PK parameters of semaglutide were 90.22–110.29 and 86.48–108.98% (0.68 mg/mL) and 90.62–115.71 and 92.86–113.51% (3.2 mg/mL). Comparable safety was proven for both concentrations.

Conclusion. GP40331 and Wegovy at 0.68 and 3.2 mg/mL are bioequivalent and equally safe.

Keywords: bioequivalence, diabetes, cardiovascular risk, obesity, glucagon-like peptide-1

Acknowledgments. The study was funded by GEROPHARM LLC.

For citation: Noskov SM, Arefeva AN, Banko VV, Radaeva KS, Gefen ML, Archakova OA, Karnakova PK, Vetrova ES, Karpova PA, Komarov TN, Shohin IE. Semaglutide for the treatment of obesity: Results of two open randomized pharmacokinetic studies. *Meditsinskiy Sovet*. 2024;18(16):216–222. (In Russ.) https://doi.org/10.21518/ms2024-346.

Conflict of interests. Anna N. Arefeva, Veniamin V. Banko, Kseniia S. Radaeva is an employee of Pharm-Holding CJSC (a spin-off of Geropharm LLC). Sergey M. Noskov is an employee of the health-care facility that performed this study under contract with GEROPHARM LLC. That did not affect the results of the study in any way.

INTRODUCTION

Obesity is a multifactorial disease and a leading cause of increased cardiovascular risk, both directly and indirectly by increasing the risk of dyslipidemia, type 2 diabetes mellitus (T2D), arterial hypertension, and sleep disorders. Moreover, the higher the body mass index (BMI), the higher the risk of morbidity and mortality from both cardiovascular disease and other causes. A decrease in BMI reduces the risk of developing T2D, arterial hypertension, acanthosis nigricans, depression, etc. [1].

Some investigators consider obesity to be a global epidemic, given that the worldwide prevalence as of 2016 according to the World Health Organisation was 29 % of the adult population. According to the Russian investigators, the prevalence of obesity increased from 10.8 % in 1993 to 27.9 % in 2017 among men, and from 26.4 % to 31.8 % among women, respectively, thereby representing a worldwide trend [2].

Glucagon-like peptide (GLP-1) secreted by L-cells in the small intestine is an incretin hormone that reduces the blood glucose levels by stimulating dose-dependent insulin secretion. Additional effects include a delay in gastric emptying, decreased appetite and cravings for fatty high-calorie foods, as well as improved control of food portions [1].

In this regard, biosimilar GLP-1 receptor agonists (aGLP-1), which include semaglutide, began to be used in clinical practice. Its features include a long half-life and high resistance to the effect of dipeptidyl peptidase-4. Semaglutide was originally authorised as a hypoglycaemic agent for the treatment of T2D, but its weight-loss benefits have already been discovered during pre-marketing clinical studies. Following extension clinical studies, semaglutide has been authorised with a wide range of concentrations, allowing a higher dose to be administered in order to achieve optimal therapeutic effects on body weight loss. The use of semaglutide at a dose of 2.4 mg (Wegovy) with increased physical activity and a low-calorie diet was associated with a clinically significant and sustained body weight loss by an average of 14.9 % with more than 75 % of subjects achieving at least a 5 % of body weight loss [3]. The use of semaglutide in the 0.25 mg dose is an indispensable part of the titration period prior to reaching a therapeutic dose, as it allows reducing the occurrence and severity of adverse events, in particular, gastrointestinal (GI) adverse events.

Liraglutide is the only product from the aGLP-1 group approved in Russia for the treatment of obesity. Semaglutide was first compared to liraglutide in the STEP 8 study conducted from 2019 to 2021.The results have shown that in overweight or obese patients without diabetes mellitus, therapy with semaglutide caused a greater body weight loss in 68 weeks as compared to liraglutide in combination with recommendations on diet and physical activity [4]. In addition, semaglutide demonstrated higher efficacy in weight loss as compared to other aGLP-1 products (exenatide, dulaglutide) [5], and this effect did not depend on the severity of GI adverse events, which was later confirmed by studies in real-life clinical practice settings [6–8].

The development of a generic medicinal product containing semaglutide in a wide range of concentrations is a relevant step towards better availability of semaglutide medicines in the Russian Federation, as well as significantly more effective control of body weight in patients with obesity and overweight.

The **purpose** of these studies was to investigate the comparative pharmacokinetics (PK) and bioequivalence of semaglutide-containing medicines, GP40331 and Wegovy, at concentrations of 0.68 mg/mL and 3.2 mg/mL, in healthy volunteers. Additionally, the study assessed the safety and tolerability of the investigational products.

MATERIALS AND METHODS

Study population

Each of the studies included healthy Caucasian male volunteers aged 18 to 45 years inclusive, with the BMI of 18.5–29.9 kg/m^2. A "healthy" diagnosis was verified based on personal and family history, physical examination, as well as standard clinical, laboratory, and instrumental examination methods (complete blood count, biochemical blood assay, urinalysis, electrocardiogram (ECG), etc.). The important exclusion criteria included a history (including a family history) of medullary thyroid cancer, multiple endocrine neoplasia type 2, as well as a history of chronic or acute pancreatitis.

Investigational products

Test product 1 (T_1, GP40331-0.68): GP40331, solution for subcutaneous injection, 0.68 mg/mL (OOO "GEROPHARM", Russia); reference product 1 (R_1, Wegovy-0.68): Wegovy, solution for subcutaneous injection, 0.68 mg/mL (Novo Nordisk A/S, Denmark). Test product 2 (T_2, GP40331-3.2): GP40331, solution for subcutaneous injection, 3.2 mg/mL (OOO "GEROPHARM", Russia); reference product 2 (R_2, Wegovy-3.2): Wegovy, solution for subcutaneous injection, 3.2 mg/mL (Novo Nordisk A/S, Denmark).

The volunteers in each study were randomly assigned to one of two groups in a 1:1 ratio. For the 0.68 mg/mL investigational products, each group was prescribed a single injection of T_1 or R_1 in the equal dose of 0.25 mg into the anterior abdominal-wall subcutaneous tissue. For the 3.2 mg/mL investigational products, each group was prescribed a single injection of T_2 or R_2 in the equal dose of 0.5 mg into the anterior abdominal-wall subcutaneous tissue. Doses for each study were selected according to the Summary of Product Characteristics[1], as well as the published PK and safety data for semaglutide [9].

Study design

The studies for each concentration (0.68 mg/mL and 3.2 mg/mL) were conducted in accordance with the protocol, the principles of the Declaration of Helsinki, guidelines of the Good Clinical Practice (ICH GCP), as well as other laws adopted in the Russian Federation and the Eurasian Economic Union (EAEU). A prerequisite for these studies was Authorisation No. 117 of the Russian Ministry of Health dated 27/03/2024 and approval of the study by the Ethics Council (extract from Minutes No. 355 of the Ethics Council meeting dated 12/03/2024) for semaglutide 0.68 mg/mL, and Authorisation No. 118 of the Russian Ministry of Health dated 27/03/2024, and approval of the study by the Ethics Council (extract from Minutes No. 355 of the Ethics Council meeting dated 12/03/2024) for semaglutide 3.2 mg/mL. Prior to initiation of any study procedures, all the volunteers signed the informed consent form.

Both studies were planned as open-label, randomised, parallel group studies in healthy volunteers, with single injections of the investigational products at concentrations of 0.68 mg/mL and 3.2 mg/mL.

The clinical part of each study included the screening, treatment period and out-patient PK follow-up period. The total duration of each study for volunteers was no more than 35 days.

Study endpoints

In accordance with the study purpose, the PK parameters of the investigational semaglutide products were evaluated at concentrations of 0.68 mg/mL and 3.2 mg/mL. The primary endpoints of the studies included:

- C_{max} is the maximum concentration of the active ingredient in the volunteers' blood during the follow-up period;
- AUC_{0-t} is the area under the active ingredient concentration–time curve from time 0 to time t when the last analysable biomaterial was sampled.

The obtained data were used to assess the bioequivalence.

Evaluation of pharmacokinetic parameters

Twenty-three blood samples of 6 mL each were collected during the study to determine the PK parameters (approximately 138 mL). Moreover, additional blood sampling was performed at the screening and final visit (approximately 48 mL). Biological samples were collected within 20 days after dosing of the investigational products.

Concentrations of semaglutide in human serum samples were determined by high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS). The range of the developed procedure for the dose of 0.25 mg (for semaglutide 0.68 mg/mL) was 0.50–200.00 ng/mL, and for the dose of 0.5 mg (for semaglutide 3.2 mg/mL) it was 1.00–800.00 ng/mL. The biological samples were prepared by serum protein precipitation with a mixture of acetonitrile and methanol (70:30). 0.3 % (v) formic acid solutions in water and acetonitrile were selected as the mobile phase eluents. Chromatographic column Phenomenex Kinetex C_{18}, 100 × 3.0 mm, 5 µm (Phenomenex, USA), was used as a stationary phase. Sample separation and analyte and internal standard (liraglutide) detection were performed in the Nexera XR HPLC-MS/MS with LCMS-8040 triple quadrupole (Shimadzu, Japan).

[1] [1] Wegovy Product Information. Available at: https://www.ema.europa.eu/en/documents/ product-information/wegovy-epar-product-information_en.pdf.

The developed HPLC-MS/MS procedure for the assay of semaglutide in human serum was pre-validated in accordance with the Rules for Bioequivalence Studies of Medicinal Products in force in the EAEU (as approved by Decision No. 85 of the Council of the Eurasian Economic Commission dated 03/11/2016)[2], as well as with the FDA[3] and EMA[4] guidelines for validation of bioanalytical methods. The developed procedure was validated for the calibration curve, lower limit of quantification, accuracy, precision, selectivity, reference standard suitability, matrix effect, recovery, carryover, and stability.

Safety assessment

Following the injection of the investigational products and throughout the study, the safety (including local tolerance) of the compared semaglutide products was evaluated at concentrations of 0.68 mg/mL and 3.2 mg/mL. Adverse events were recorded based on the volunteers' complaints, abnormalities in physical examination data, vital signs (blood pressure, respiratory rate, heart rate, axillary body temperature), laboratory and instrumental examinations, and evaluation of injection sites. Laboratory tests included complete blood count, biochemical blood assay, and urinalysis. Instrumental examinations included blood glucose level measurement using a blood glucose meter, and ECG.

Statistical analysis

The conclusion about the bioequivalence of the compared medicinal products was made using a classical approach based on the estimation of 90 % confidence intervals (CI) for geometric mean ratios of PK parameters (AUC_{0-t}, C_{max}) for the active ingredient in the investigational products at concentrations of 0.68 mg/mL and 3.2 mg/mL. The medicinal products were considered bioequivalent if the limits of each estimated CI were within 80.00–125.00 %.

Data analysis was performed using the R statistical programming language (version 4.2.2 or later). Analysis of variance (ANOVA) was carried out for log-transformed AUC_{0-t} and C_{max} at each concentration studied (0.68 mg/mL and 3.2 mg/mL). Descriptive statistics were calculated for the primary and secondary pharmacokinetic endpoints and safety parameters.

RESULTS

Demographic data

Seventy-four healthy male volunteers were screened and randomised for each study. All randomised subjects completed the studies as per the protocol procedures and were included in the bioequivalence analysis set (PP set). None of the volunteers dropped out during the screening procedures or during the studies due to critical protocol violations and occurrence of adverse events (*Fig. 1*).

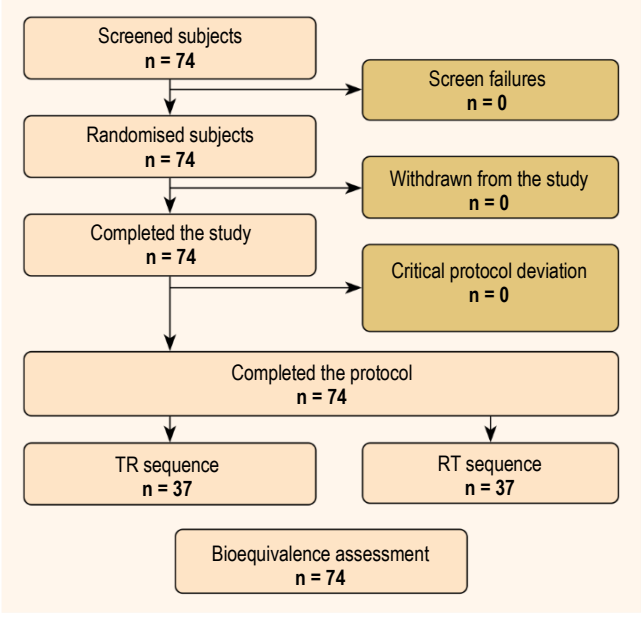
Pharmacokinetics

The PK data analysis and bioequivalence hypothesis testing were performed in the PP set for each study separately. The results of the geometric mean ratio estimation for the PK parameters (AUC_{0-t}, C_{max}) at each semaglutide concentration in the investigational products, as well as 90 % confidence intervals for these ratios, are presented in the *table* below. It was shown that 90 % confidence intervals for the geometric mean ratios of the main PK parameters of semaglutide at concentrations of 0.68 mg/mL and 3.2 mg/mL were within the acceptable limits of 80.00–125.00 % (*Fig. 2*). Averaged PK profiles of semaglutide in linear and semi-log coordinates for the concentrations of 0.68 mg/mL and 3.2 mg/mL are shown in *Fig. 3* and *Fig. 4*, respectively.

Safety

The safety was evaluated in the SAF set (Safety Analysis Set). According to the protocol, the SAF set included volunteers from each study who received at least one dose of the investigational products ($T_{1,2}$ or $R_{1,2}$). The SAF set and PP set were equal for each study and included 74 randomised volunteers. No adverse events, clinically significant abnormalities in blood and urine tests as well as in blood glucose levels were reported during the studies. Vital signs, ECG and physical examination findings stayed within the physiological range. None of the volunteers reported local reactions to injections of the investigational products.

Figure 1. Flow diagram of subjects in clinical trial

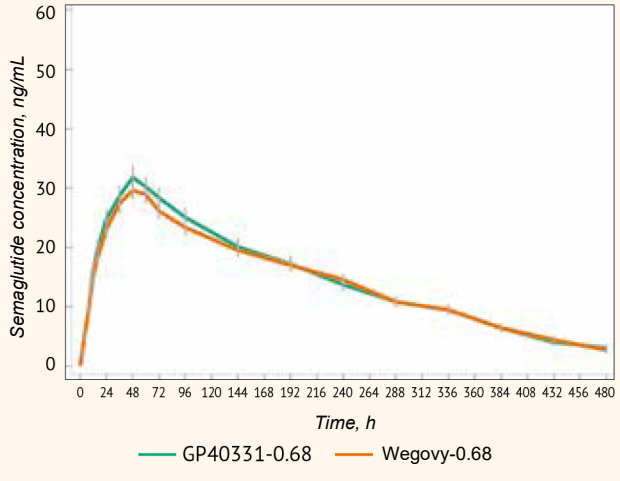


[2] Rules for Bioequivalence Studies of Medicinal Products in the Eurasian Economic Union (approved by Decision No. 85 of the Council of the Eurasian Economic Commission dated 03/11/2016). URL: https://docs.cntd.ru/ document/456026107/.
[3] Bioanalytical Method Validation. Guidance for Industry. U.S. Food and Drug Administration, Center for Drug Evolution and Research (CDER). Available at: https://www.fda.gov/regulatory- information/search-fda-guidance-documents/bioanalytical-method-validation-guidance- industry/.
[4] Guideline on bioanalytical method validation. European Medicines Agency. Committee for medicinal products for human use. Available at: https://www.ema.europa.eu/en/ bioanalytical-method-validation/.

Table. Calculated Confidence Intervals for pharmacokinetic primary endpoints of semaglutide at concentrations of 0.68 and 3.2 mg/mL

Parameter	I/R geometric mean ratio	90 % confidence intervals		Acceptable values, %
		Lower limit, %	Upper limit, %	
$AUC_{0\text{-}t\ 0.68}$	1.00	90.22	110.29	80.00–125.00
$C_{max\ 0.68}$	0.97	86.48	108.98	80.00–125.00
$AUC_{0\text{-}t\ 3.2}$	1.02	90.62	115.71	80.00–125.00
$C_{max\ 3.2}$	1.03	92.86	113.51	80.00–125.00

Figure 3. Arithmetic mean pharmacokinetic profile on linear scale of semaglutide (GP40331 and Wegovy®) in concentration of 0.68 mg/mL



DISCUSSION

GP40331 is a generic medicinal product of Wegovy, a GLP-1 agonist. It contains semaglutide as an active pharmaceutical ingredient. Comprehensive analytical studies conducted by OOO "GEROPHARM" under the semaglutide study programme have shown a high level of comparability between GP40331 and the reference product in terms of characteristics of the active ingredient, impurities and excipients. This Phase I clinical study to investigate the PK and safety of the investigational products has become a direct extension of the programme and was conducted to confirm the bioequivalence in terms of clinical pharmacology.

Figure 2. 90 % Confidence Intervals for pharmacokinetic primary endpoints of semaglutide at concentrations of 0.68 and 3.2 mg/mL

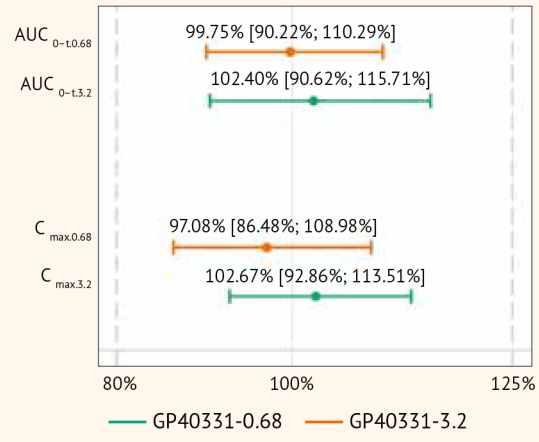
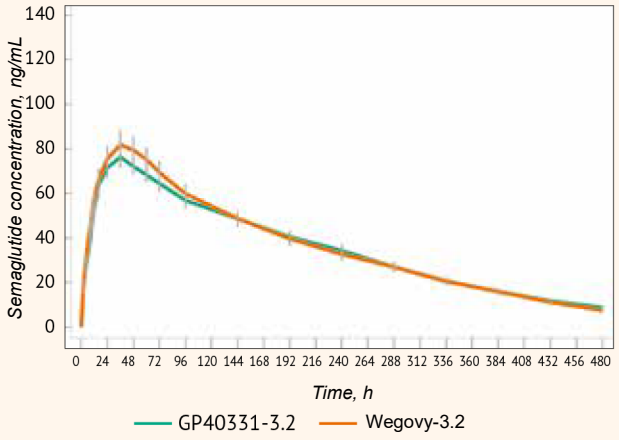


Figure 4. Arithmetic mean pharmacokinetic profile on linear scale of semaglutide (GP40331 and Wegovy®) in concentration of 3.2 mg/mL



The parallel design for these studies was selected due to a long elimination half-life of semaglutide (about 1 week) [10]. A cross-over design requires a wash-out period lasting for 5 or more half-lives[5], i. e. at least 5 weeks, which would significantly extend the study duration and increase the risk of drop-out.

[5] Decision No. 85 of the Council of the Eurasian Economic Commission dated 3 November 2016 "On Approval of the Rules for Bioequivalence Studies of Medicinal Products in the Eurasian Economic Union". URL: https://www.alta.ru/tamdoc/16sr0085/.

The studies were selected to be open-label for both the volunteers and study doctor due to the fact that the primary PK endpoints were sufficiently stable and resistant to the subjectivity of the study subjects. Despite that, the data were additionally blinded for the bioanalytical laboratory staff: test tubes with biological samples had no marks allowing identification of a volunteer and the investigational product received by the volunteer before blood sampling.

In order to prove the bioequivalence of the investigational products and obtain the most reliable data, the population of healthy male volunteers aged 18 to 45 years inclusive was selected. This is a more homogeneous population, which allows the inter-individual variability to be reduced to the optimal levels for bioequivalence studies.

CONCLUSION

Thus, based on the findings of this clinical study, GP40331 (OOO "GEROPHARM", Russia) and Wegovy (Novo Nordisk A/S, Denmark) at concentrations of 0.68 mg/mL and 3.2 mg/mL can be considered bioequivalent and equally safe. The study findings make it possible to recommend GP40331 to be applied to the Ministry of Health of the Russian Federation for a marketing authorisation.

Received 03/07/2024
Revised 09/08/2024
Accepted 11/08/2024

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