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Comparative analysis of pharmacokinetic parameters, bioequivalence, safety, tolerability and immunogenicity of semaglutide-based drug for the treatment of obesity

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One of the new classes of drugs for weight loss in overweight and obesity, the safety and efficacy of which have been proven in large-scale studies, are glucagon-like peptide-1 receptor agonists (GLP-1 agonists). Separately, it is worth highlighting the main representative from the GLP-1 agonists class, semaglutide. At a dose of 2.4 mg, this drug demonstrated clinically significant results in terms of the body weight reduction and improvement of cardiometabolic health.

The aim of the work was to evaluate pharmacokinetic parameters, bioequivalence, safety, tolerability and immunogenicity of the Velgia® (WRYC12301) at doses of 0.25 mg (0.68 mg/mL) and 2.4 mg (3.2 mg/mL) in comparison with the reference drug Wegovy® (Novo Nordisk A/S, Denmark) at the doses of 0.25 mg (0.68 mg/mL) and 2.4 mg (3.2 mg/mL).

Materials and methods. The study was conducted between March and June 2024. The volunteers (*n*=60) were randomised into 4 groups (*n*=15 in each) in a 1:1 ratio to study the semaglutide dosages of 0.25 mg/dose (0.68 mg/mL) in Groups 1, 2 and 2.4 mg/dose (3.2 mg/mL) in Groups 3, 4. The study drug and the reference drug were injected subcutaneously into the anterior abdominal wall. Pharmacokinetic parameters, bioequivalence, safety, tolerability and immunogenicity of semaglutide (solution for subcutaneous administration, JSC Biochemik, Russia) were studied. Some parameters regulating the quality of the active pharmaceutical substance semaglutide, were determined.

Results. The obtained 90% confidence intervals (CIs) for the ratio of C_{max} and $AUC_{(0-t)}$ values of the study and reference drugs (Groups 1, 2) at a dose of 0.25 mg (0, 68 mg/mL) were 85.19–114.36% for C_{max} and 81.35–112.60% for $AUC_{(0-t)}$, respectively, while for Groups 3, 4, at a dose of 2.4 mg (3.2 mg/mL), C_{max} was 83.18–111.3% and $AUC_{(0-t)}$ was 91.70–120.89%, respectively. The obtained 90% CI lies within the established limits, which confirms the bioequivalence of the study and reference drugs. All adverse events registered during the study were of mild severity. According to the results of the immunogenicity parameters analysis, no antibodies to semaglutide were detected in the serum of volunteers.

Conclusion. In the course of the study, the bioequivalence of the study and reference drugs was confirmed. A high safety profile and absence of immunogenicity were demonstrated for the Russian drug Velgia® (WRYC12301, semaglutide, solution for a subcutaneous administration, JSC Biochemik, Russia) in comparison with the reference drug (semaglutide, solution for a subcutaneous administration, Novo Nordisk A/S, Denmark) in doses of 0.25 mg/dose (0.68 mg/mL) and 2.4 mg/dose (3.2 mg/mL).

Keywords: semaglutide; glucagon-like peptide-1 receptor agonist; obesity; subcutaneous administration; safety; tolerability; immunogenicity; pharmacokinetic parameters

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Abbreviations: T2D — type 2 diabetes; MAFLD — metabolic-associated fatty liver disease; GLP-1 — glucagon-like peptide-1; GLP-1 agonists — glucagon-like peptide-1 receptor agonists; HbAlc — glycated haemoglobin; ELISA — enzyme-linked immunosorbent assay; BMI — body mass index; GI — gastrointestinal tract; BAC — biologically active compound; HR — heart rate; RR — respiratory rate; ECG — electrocardiography; AE — adverse event; SAE — serious adverse event; CI — confidence interval; API — active pharmaceutical ingredients.

Сравнительное исследование фармакокинетических параметров, биоэквивалентности, безопасности, переносимости и иммуногенности лекарственного препарата для лечения ожирения на основе семаглутида

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Одним из новых классов препаратов для снижения массы тела при избыточном весе и ожирении, безопасность и эффективность которых доказаны в масштабных исследованиях, являются агонисты рецепторов глюкагоноподобного пептида-1 (АР ГПП-1). Отдельно стоит выделить основного представителя из класса АР ГПП-1 — семаглутид. Данный препарат в дозе 2,4 мг продемонстрировал клинически значимые результаты в отношении уменьшения массы тела и улучшения параметров кардиометаболического здоровья.

Цель. Оценить фармакокинетические параметры, биоэквивалентность, безопасность, переносимость и иммуногенность отечественного лекарственного препарата Велгия® (WRYC12301) в дозировках 0,25 мг/доза (0,68 мг/мл) и 2,4 мг/доза (3,2 мг/мл) в сравнении с референтным препаратом Wegovy® (Ново Нордиск А/С, Дания) в дозировках 0,25 мг/доза (0,68 мг/мл) и 2,4 мг/доза (3,2 мг/мл).

Материалы и методы. Исследование было проведено в период с марта по июнь 2024 года. Добровольцы (*n*=60) были рандомизированы в 4 группы (*n*=15 в каждой) в соотношении 1:1 для исследования дозировки семаглутида 0,25 мг/доза (0,68 мг/мл) — Группа 1, 2 и 2,4 мг/доза (3,2 мг/мл) — Группа 3, 4. Исследуемый препарат и препарат сравнения вводили подкожно в переднюю брюшную стенку. Были изучены фармакокинетические параметры, биоэквивалентность, безопасность, переносимость и иммуногенность исследуемого препарата семаглутида (раствор для подкожного введения, АО «Биохимик», Россия). Определены некоторые показатели, регламентирующие качество активной фармацевтической субстанции семаглутид.

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Результаты. Полученные 90%-ные доверительные интервалы (ДИ) для отношения значений C_{max} и $AUC_{(0-t)}$ исследуемого и референтного препарата (Группа 1, 2) в дозировке 0,25 мг/доза (0,68 мг/мл) составили для C_{max} — 85,19–114,36% и $AUC_{(0-t)}$ — 81,35–112,60%, соответственно, для Группы 3, 4 дозировки 2,4 мг/доза (3,2 мг/мл) — C_{max} составил 83,18–111,3%, а $AUC_{(0-t)}$ — 91,70–120,89%, соответственно. Полученные 90% ДИ лежат в установленных границах, что подтверждает биоэквивалентность исследуемого и референтного препаратов. Все зарегистрированные в ходе исследования нежелательные явления были лёгкой степени тяжести. По результатам анализа параметров иммуногенности у добровольцев не были выявлены антитела к семаглутиду в сыворотке крови.

Заключение. В ходе проведённого исследования была подтверждена биоэквивалентность исследуемого и референтного препаратов. Был продемонстрирован высокий профиль безопасности и отсутствие иммуногенности у российского препарата Велгия® (WRYC12301, семаглутид, раствор для подкожного введения, АО «Биохимик», Россия) в сравнении с зарубежным референтным препаратом (семаглутид, раствор для подкожного введения, Ново Нордиск А/С, Дания) в дозировках 0,25 мг/доза (0,68 мг/мл) и 2,4 мг/доза (3,2 мг/мл).

Ключевые слова: семаглутид; агонист рецепторов глюкагоноподобного пептида-1; ожирение; подкожное введение; безопасность; переносимость; иммуногенность; фармакокинетические параметры

Список сокращений: СД 2 — сахарный диабет 2 типа; МАЖБП — метаболически ассоциированная жировая болезнь печени; ГПП-1 — глюкагоноподобный пептид-1; АР ГПП-1 — агонисты рецепторов глюкагоноподобного пептида-1; HbAlc — гликированный гемоглобин; ИФА — иммуноферментный анализ; ИМТ — индекс массы тела; ЖКТ — желудочно-кишечный тракт; БАД — биологически активная добавка; ЧСС — частота сердечных сокращений; ЧДД — частота дыхательных движений; ЭКГ — электрокардиография; НЯ — нежелательное явление; СНЯ — серьёзное нежелательное явление; ДИ — доверительный интервал; АФС — активная фармацевтическая субстанция.

INTRODUCTION

Obesity has become one of the most pressing public health problems in the world today. According to the World Health Organization (WHO) in 2022, one in eight people on the planet was obese. According to the forecast, by 2025, about 46% of the world's adult population will be overweight [1].

Obesity (body mass index [BMI] >30 kg/m^2) and overweight (BMI=25–29.9 kg/m^2) are chronic diseases characterized by an excessive accumulation of the adipose tissue in the body as a result of an excessive energy value (calories) of the diet over physiological needs of a person. The presence of obesity and excess body weight are considered to be the main risk factors for the development of a number of chronic diseases, including type 2 diabetes (T2D), cardiovascular diseases (CVDs), metabolically associated fatty liver disease (MAFLD), cancer, musculoskeletal diseases, mental health disorders, etc. [2].

A 5–10% reduction in body weight has been shown to improve glycemic control, reduce risk factors for CVDs, as well as an insulin resistance, an arterial hypertension, lipid metabolism disorders, including cholesterol and triglyceride concentrations, inflammatory markers and an endothelial dysfunction. The treatment of obesity and overweight is based on a comprehensive approach, including a proper nutrition, a physical activity, pharmacological therapy and, if necessary, endoscopic procedures or, in some cases, bariatric surgery [3]. At the same time, a lifestyle modification without additional therapy provides clinically significant weight loss only in a small category of patients. According to the statistical studies, only 10% of people manage to maintain the achieved weight after weight loss, while the rest return to their previous habits and initial weight parameters [4, 5]. It should be noted that the treatment of obesity and overweight with bariatric surgery is associated with a number of limitations and possible complications both during and after the surgery [1, 6, 7].

Recent scientific advances in the study of the obesity pathogenesis have made it possible to develop and introduce into clinical practice new promising drugs for reducing excess weight and maintaining the achieved results. Taking into account the role of glucagon-like peptide-1 receptor (GLP-1) in the regulation of glucose metabolism and energy balance, as well as significant effects on other organs and systems, drugs capable of stimulating GLP-1 receptors similar to the native hormone — GLP-1 agonists have been developed [7, 8].

Semaglutide is a 94% homologous analogue of human GLP-1. The half-life of semaglutide (about 1 week) allows its use subcutaneously once a week. Its use in patients with T2D not only contributed to the effective glycaemic control, but also resulted in a significant weight loss and control of CVD risks. Semaglutide was initially approved for the treatment of T2D at a dose of 0.5 or 1.0 mg per week; in 2021, the FDA[1] approved a dosage of 2.4 mg [9, 10].

[1] U.S. Food and Drug Administration. FDA Approves New Drug Treatment for Chronic Weight Management, First Since 2014 (For Immediate Release: June 04, 2021). Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014

The dose-dependent effect of semaglutide on weight loss in patients with T2D was observed in the SUSTAIN clinical trial as well as in real clinical practice. Therefore, phase 2 clinical trials were conducted to evaluate the effect of semaglutide on weight in patients without diabetes, in which effective doses and concentrations of semaglutide corresponding to 1.7 and 2.4 mg have been identified [11].

According to the results of the STEP 1 clinical trial, in the semaglutide group, 9 out of 10 patients achieved a clinically significant weight loss of 5% or more, and every third patient achieved a 20% or more reduction in body weight. The mean weight reduction was 16.9% from baseline (17.2 *vs.* 2.7 kg in the placebo group). The body weight reduction was mainly due to the adipose tissue — minus 10.4 kg in the semaglutide (2.4 mg) group and minus 1.17 kg in the placebo group. Semaglutide therapy at a dose of 2.4 mg had a more favourable effect on the cardiometabolic health: this dosage contributed to a reduction in waist circumference (-15.22 cm), a normalization of lipid profile and blood pressure [12, 13].

The STEP 2 clinical trial evaluated the effect of semaglutide therapy on weight loss (0.25, 0.5, 1.0, 1.7 and 2.4 mg) compared to semaglutide for the treatment of T2D (0.25, 0.5 and 1.0 mg) in patients with diabetes (HbA1c: 7–10%, the diabetes duration averaged 8 years). The study participants receiving semaglutide for the treatment of obesity demonstrated a clinically significant reduction in body weight of 9.64% from baseline compared to 6.99% with a 1.0 mg dose. The proportion of patients achieving a weight reduction of 10% or more was 45.6% in the semaglutide (2.4 mg) group *vs.* 28.7% in the semaglutide (1.0 mg) group. The results of the clinical trial obtained at weeks 8–12, when the patients took the same doses of the drug (0.5–1.0 mg), are noteworthy: the reduction in their body weight has statistical differences (p <0.05) in favour of the obesity drug. This study shows that not only the dose, but also a specially selected and scientifically substantiated concentration determines the dynamics of weight loss, because it allows the drug to overcome physiological barriers and affect GLP-1 receptors as effectively as possible, in particular, in the brain structures of the reward system. This is what determines the pronounced effect of the drug on the formation of the rational eating behaviour and the reduction of cravings for sweet and fatty foods [14].

In the two-year STEP 5 clinical trial, the use of semaglutide for obesity contributed not only to a significant weight loss (-15.2 vs. -2.6%), but also to the maintenance of the achieved result throughout the follow-up period. According to the results of therapy in the cohort of patients receiving semaglutide at a dose of 2.4 mg, 83.3% of the patients reduced weight by ≥5% or more, 67.4% by ≥10%, 56.8% by ≥15%, and 39.4% by ≥20% [15].

In the multicentre randomized placebo-controlled SELECT study involving 17 604 patients from 41 countries, it was demonstrated that the administration of semaglutide at a dose of 2.4 mg to patients with CVDs and obesity / overweight without diabetes leads to a 20% reduction in the risk of Major Adverse Cardiovascular Events (MACEs), including a reduction in fatal outcomes, a reduction in the risk of non-fatal infarctions, which fundamentally changes the scenario of the obesity treatment in the long term [13]. The accumulated data on the use of semaglutide at a dosage of 2.4 mg made it possible to include the drug in clinical guidelines for a stroke prevention, which proves the effectiveness of this type of therapy in achieving the main goal of the obesity treatment — reducing the risks of complications and restoring metabolic health [16, 17].

It is important to note that due to its similarity to physiological hormones, an increase in the dosage does not correlate with an increase in the incidence of side effects. Semaglutide at a dosage of 2.4 mg has a favourable safety profile similar to that of semaglutide 1.0 mg [18, 19].

At a dosage of 2.4 mg for the treatment of obesity and overweight, including in patients with T2D, semaglutide is registered in Europe and the USA under the trade name Wegovy®[2,3]. This drug is not registered in Russia, and until recently, Russian specialists have not been able to use this drug in clinical practice.

Promomed Company has been providing the healthcare system with reliable drugs for the treatment of obesity and overweight with a high level of evidence for more than 20 years, and was the first in the country to develop its own full-cycle technology for GLP-1 agonists (liraglutide, semaglutide) — from the chemical synthesis and isolation of active pharmaceutical substances to the production of a finished dosage form. The preparations based on liraglutide 3.0 mg (Enligria®) and semaglutide 1.0 mg (Quinsenta®) were registered in the second half of 2023 and became full substitutes for their foreign predecessors that had left the market.

[2] Ibid.
[3] EMA. Wegovy. Overview. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/wegovy

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THE AIM of the work was to evaluate pharmacokinetic parameters, bioequivalence, safety, tolerability and immunogenicity of the domestic drug Velgia® (WRYC12301) at doses of 0.25 mg (0.68 mg/mL) and 2.4 mg (3.2 mg/mL) in comparison with the reference drug Wegovy® (Novo Nordisk A/S, Denmark) at the doses of 0.25 mg (0.68 mg/mL) and 2.4 mg (3.2 mg/mL).

MATERIALS AND METHODS

Study design

An open randomized parallel bioequivalence study was conducted in a single subcutaneous administration of the study and reference drugs on an empty stomach in healthy volunteers. The block diagram of the design (duration wise) is shown in Fig. 1.

Randomization

The volunteers who had successfully completed the screening procedure (met the eligibility criteria) were randomized into the clinical trial. Each randomized volunteer was assigned according to the randomization plan using WinPepi 11.65 software (ETCETERA module 3.26) by a random number generation (assigning numbers to volunteers — 01 to 60). The volunteers (*n*=60) were randomized into 4 groups in a 1:1 ratio.

If a volunteer dropped out of the clinical trial before time, their randomization number was not reused and the volunteer could not subsequently re-enter the study.

Study subjects and eligibility criteria

The study randomized 60 healthy male and female volunteers aged between 18 and 65 years inclusive with a body mass index of 25–30 kg/m^2 inclusive, who met all the inclusion criteria and did not meet any of the non-inclusion criteria.

All the participants signed an informed consent form and were able and willing to comply with the study protocol.

The main *inclusion criteria* were:

- men and women aged 18 to 65 years;
- body mass >50 kg;
- BMI=25–30 kg/m^2 inclusive;
- verified diagnosis of “healthy” according to the standard clinical, laboratory and instrumental examination methods;
- negative results of tests for alcohol, psychotropic and narcotic substance use, and willingness to give up an alcohol use during the participation in the study.

The participants were warned to use reliable contraceptive methods and to abstain from a sperm donation throughout the study and for 2 months after the end of the study.

The main *non-inclusion criteria* were:

- presence of an aggravated allergological anamnesis, drug intolerance, chronic diseases of various organ systems;
- mental illnesses;
- hypersensitivity to the study drugs;
- history of use of semaglutide or other human GLP-1 analogues (within less than 6 months before screening);
- taking medications with significant effects on haemodynamics and/or a liver function for less than 2 months prior to screening;
- taking other medications, including herbal and homeopathic preparations, vitamins and/or dietary supplements, for less than 4 weeks prior to screening;
- inability to perform subcutaneous injections;
- any history of difficulties with blood collection or any vasovagal attacks during a blood collection;
- Gastrointestinal Surgical Procedures (except appendectomy).

The participants were also not considered for the study inclusion if they had the following diseases and conditions: a history of medullary thyroid cancer, including a family history; a history of multiple endocrine neoplasia type 2; a severe depression; suicidal thoughts or behaviour, including a history; acute infectious diseases or symptoms of acute respiratory infections for less than 4 weeks prior to screening.

The volunteers were excluded from the study if they refused to participate in the clinical trial, if they were taking illegal drugs and tested positive for the use of alcohol, psychotropic and/or narcotic substances, if there were gross violations of the requirements and procedures of the study protocol, if there were adverse events (AEs), or if during the study, the volunteer developed any diseases or conditions that made their further participation in the study impossible. The research physician may decide to exclude a volunteer in the volunteer’s own interests.

Concomitant therapy and exclusion criteria were

assessed throughout the study. The total duration of the study for each volunteer was no more than 35 days (including the screening period).

Study conditions and duration

The study was conducted on the basis of the state budgetary health care institution of the Yaroslavl Clinical Hospital No. 3 (Yaroslavl, Russia) in the period from March to June 2024.

Characteristics of drugs

The following preparations were used in the investigation — the investigational new drug (Velgia®; WRYC12301; IND; semaglutide, a solution for a subcutaneous administration, JSC "Biochemik", Russia) at doses of 0.25 and 2.4 mg/mL) and a reference drug (Wegovy®; RD; semaglutide, a preparation for a subcutaneous administration, Novo Nordisk A/S, Denmark) at doses of 0.68 and 2.4 mg/mL.

Drug administration

The volunteers received the drugs in the morning on an empty stomach subcutaneously into the anterior abdominal wall. Group 1 (*n*=15) and Group 2 (*n*=15) received the study and reference drugs at a dose of 0.5 mg (a single administration of 2 doses of 0.25 mg/dose), Group 3 (*n*=15) and Group 4 (*n*=15) — 2.4 mg (a single administration of 1 dose of 2.4 mg/dose).

Sample preparation and collection

To assess pharmacokinetic and immunogenicity parameters, after the randomization and before the initial blood sampling, a cubital heparinized catheter was placed in the volunteers and removed after the blood sampling at 12 h point (day 1). After the removal of the catheter, the blood was collected from the volunteers by venipuncture.

Blood samples for the determination of pharmacokinetic parameters were collected at the following time points: 1, 0.5 and 0 h (day 1) before the administration of the IND / RD and then on and off at 2, 8, 12 (day 1), 24 (day 2), 36 (day 2), 48 (day 3), 72 (day 4), 96 (day 5), 144 (day 7), 192 (day 9), 240 (day 11), 360 (day 16) and 480 h (day 21) after the administration of the IND / RD.

The blood samples for immunogenicity were collected from the volunteers receiving the IND at a dosage of 2.4 mg/dose (3.2 mg/mL) (Group 3) and the RD at a dosage of 2.4 mg/dose (3.2 mg/mL) (Group 4) no more than 15 min before the administration of the study/reference drug (baseline (0) sample) and 480 h (day 21) after their administration. The blood samples for the analysis of immunogenicity parameters were collected separately from the blood samples for the estimation of pharmacokinetic parameters.

Thus, the study involved the collection of 16 blood samples for each volunteer (6 mL each) for pharmacokinetic parameters and 2 blood samples for the volunteers from Groups 3 and 4 (6 mL each) to carry out immunogenicity studies.

At the screening, a blood sample of no more than 25 mL was taken for standard clinical, biochemical, serological analyses and a blood glucose level determination using a glucometer.

The blood samples were collected into tubes to obtain serum with a coagulation activator. Then, the samples were gently mixed 5–8 times for a better contact between the blood and clotting activator. The tubes with the blood samples were then left on the table in an upright position at 18–25°C until a complete coagulation (clot formation). After the clot formation, the tubes were centrifuged at 1500 g for 10 min at 18–25°C (Eppendorf 5702 R medical centrifuge No. 0006208, Eppendorf, Germany). The obtained serum was carefully transferred into pre-labelled cryotubes, dividing the serum into three 500 µl aliquots — two for the main assay (aliquots A and B), the third - for repeat assays (aliquot C). The serum samples were frozen immediately after the receipt, transferred to cryotubes and stored at -70°C or less.

Analytical method

Calculations of pharmacokinetic parameters were performed by a serum semaglutide concentration. A quantification of semaglutide was performed by a high-performance liquid chromatography with a tandem mass spectrometry (HPLC-MS/MS). A chromatographic separation and detection were performed on an LC-20 Prominence Nexera XR liquid chromatograph (Shimadzu, Japan) and a LCMS-8040 tandem mass spectrometric detector (triple quadrupole) using a Phenomenex Kinetex C18, 100×3.0 mm, 5 µm column. An enzyme-linked immunosorbent assay (ELISA) was used to determine the immunogenicity parameters.

Immunogenicity was assessed in the volunteers with antibodies to semaglutide. A quantitative determination of antibodies to semaglutide in calibration

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and quality control samples was performed using a HiPo MPR-96 microplate photometer (Biosan, Latvia) with the ELISA kit KRIBIOLISA™ Anti-Semaglutide (Ozempic™) ELISA (competitive) (Krishgen BioSystems, USA).

Safety and tolerability assessment

To assess the safety of the IND, the frequency and severity of the AEs registered according to the data of deviations from normal results of the laboratory tests, physical examination, assessment of basic vital signs, electrocardiogram (ECG); the number of cases of an early participation termination in the study due to the development of AEs and/or serious AEs (SAEs), including those associated with IND / RD, were taken into account. Tolerability of the drug was assessed by the study physician using a Likert scale.

Among the criteria for assessing immunogenicity, the number (%) of the volunteers with detected antibodies to semaglutide were considered.

Ethical approval

The conduct of the study was approved by the Local Ethical Committee of the Yaroslavl Clinical Hospital No. 3 (extract from Minutes No. 202 dated 21 March 2024).

Statistical analysis

Principles of sample size calculation

The calculation was based on the interindividual variability (CV_{inter}) of semaglutide as reported in Clinical Review (S) Semaglutide [1].

As the CV_{inter} value of semaglutide had not been published directly, it was calculated from the submitted data in the R software environment with the PowerTOST package using the "CV from CI" function. The calculation of the required abundance was performed using the PASS 11 programme (PASS 11 PLUS, UK). For standard two-parallel-group design conditions, assuming a 90% CI of 80.00–125.00%, CV_{inter}=17%, α=0.05, the study power of 80%, and the IND / RD ratio of 0.95, the inclusion of at least 26 healthy volunteers (13 in each dose group) who will fully complete the study and be accepted the for statistical analysis, is required.

Methods of statistical data analysis

The aim of the work was to evaluate pharmacokinetic parameters, bioequivalence, safety, tolerability and immunogenicity of the IND at doses of 0.25 mg (0.68 mg/mL) and 2.4 mg (3.2 mg/mL) in comparison with the RD.

The primary database was created in MS Excel 19 (Microsoft Corp., USA) by processing the registration cards received from the research centre. The calculation of pharmacokinetic parameters, a statistical analysis of safety parameters and the presentation of results were performed using statistical packages (StatSoft Statistica version 10.0/13.3, IBM SPSS Statistics 22 and using the R project software (current version, GPL-2/GPL-3 licence) with a bear extension). The following pharmacokinetic variables were calculated: C_{max} — the maximum concentration of the substance in serum; t_{max} — the time to reach C_{max}; $AUC_{(0-t)}$ — the area under the concentration-time curve from the time of a drug administration to the last detectable concentration at time point t; $AUC_{(0-\infty)}$ — the area under the pharmacokinetic curve from time zero to infinity; $AUC_{(0-t)}/AUC_{(0-\infty)}$ — a ratio of $AUC_{(0-t)}$ to $AUC_{(0-\infty)}$; K_{el} — a terminal elimination rate constant; $t_{1/2}$ — elimination half-life; V_d — volume of distribution; $AUC_{(t-\infty)}$ — residual (extrapolated) area under the curve, determined by the formula $AUC_{(0-\infty)}$– $AUC_{(0-t)}/AUC_{(0-\infty)}$. The conclusion about bioequivalence of the compared drugs was made by the ratio of C_{max} and $AUC_{(0-t)}$ parameters of the study drug to the reference drug, which should lie in the range of 80.00–125.00% at the 90% CI.

The following statistical parameters were calculated for all pharmacokinetic parameters: arithmetic mean (Mean), standard deviation of mean (SD), coefficient of variation (CV), median (Me), minimum (Min) and maximum (Max) values, and spread.

To analyze frequency indicators, the fractions using a two-sided version of Fisher's exact test (or the χ^2 (chi-square) criterion), were compared. For the comparison of quantitative continuous indicators, the Students' t-test (in case of a normal distribution) or the Mann-Whitney test (in case of the distribution other than normal) were used. The test for normality of the data distribution was carried out using generally accepted methods (the Shapiro-Wilk test or the Kolmogorov-Smirnov test). The differences at p <0.05 were considered statistically significant.

Quality control of semaglutide active pharmaceutical substance

The appearance of all tested samples of the semaglutide active pharmaceutical ingredient (API) was assessed visually. A specific optical rotation values were determined in accordance with the requirements of the Pharmacopoeia of Eurasian Economic Union (PhEAEU), general monograph (GM) 2.1.2.7 "Optical rotation".

High-resolution mass spectra were recorded on the LCMS-9030 instrument (Shimadzu, Japan) by an electrospray ionization mass spectrometry method (ESI-MS). The following parameters were used: capillary voltage — 4.0 kV; mass scanning range — 500–2000 m/z; external calibration with sodium iodide solution in MeOH / H_2O; drying and heating gases — nitrogen (10 L/min each); atomizing gas — nitrogen (3 L/min); interface temperature — 300°C. Molecular ions in the spectra were analyzed using LabSolutions v.5.114 software (LabSolutions Series, Shimadzu, Japan).

The control method for the indicator "Peptide mapping" included an enzymatic cleavage of proteins to form peptide fragments with their subsequent separation and identification by HPLC (PhEAEU GM 2.1.2.39. "Peptide mapping"). A high-pressure liquid chromatograph with Agilent UV detector (Agilent Technologies, USA) and a 150×4.6 mm column filled with XBridge Peptide BEH C18 sorbent (4.6×150 mm, 3.5 µm) were used for the study; the elution mode was gradient. The detection was performed at a wavelength of 214 nm.

The determination of the quantitative content and the identification of related impurities in the samples of the semaglutide substance was carried out by HPLC (PhEAEU GM 2.1.2.28. "High-performance liquid chromatography"). A high-pressure liquid chromatograph with Agilent UV detector, Kinetex 2.6 µm C18 100 Å column, LC Column 150×4.6 mm, elution mode — gradient, were used for the study. The detection was carried out at a wavelength of 210 nm.

The determination of the acetic and trifluoroacetic acid content was carried out by a HPLC method (PhEAEU GM 2.1.2.28 "High-performance liquid chromatography"). A high-pressure liquid chromatograph with an Agilent UV detector, Luna C18(2) 5 µm 4.6×250 mm column, the elution mode — gradient, were used for the study. The detection was carried out at a wavelength of 210 nm.

The content of bacterial endotoxins evaluated according to PhEAEU GM 2.1.6.8 "Bacterial endotoxins". The total amount of aerobic bacteria, yeasts and moulds was determined according to PhEAEU GM 2.3.1.2 "Requirements for microbiological purity of medicinal preparations, pharmaceutical substances and excipients for their production", and GM 2.1.6.8 "Bacterial endotoxins". The total amount of aerobic bacteria, yeasts and moulds was determined according to PhEAEU GM 2.3.1.2 "Requirements for microbiological purity of medicinal preparations, pharmaceutical substances and excipients for their production".

RESULTS

The primary outcome of the study was to evaluate the pharmacokinetic parameters, bioequivalence, safety, tolerability and immunogenicity of the Velgia® at doses of 0.25 (0.68 mg/mL) and 2.4 mg (3.2 mg/mL) in comparison with the reference drug Wegovy® (Novo Nordisk A/S, Denmark) at doses of 0.25 (0.68 mg/mL) and 2.4 mg (3.2 mg/mL).

Population

Sixty male and female volunteers participated in the study. The main anthropometric characteristics and gender distribution are shown in Table 1.

Bioequivalence assessment

The mean values of basic and additional pharmacokinetic parameters for the study and reference drugs are presented in Table 2.

Fig. 2 shows the averaged pharmacokinetic profiles after the administration of the study and reference drugs at a dosage of 0.25 mg/dose (0.68 mg/mL). As can be seen from the compared curves, the comparability of the nature of the "concentration-time" dependence for the studied drugs is observed.

Figure 3 shows the averaged pharmacokinetic profiles with and without standard deviations after the administration of the study and reference drugs at a dosage of 2.4 mg/dose (3.2 mg/mL). As can be seen from the compared curves, the nature of the "concentration-time" dependence for the compared drugs did not practically differ either.

Time after drug administration, hours

According to the results of the statistical analysis, the obtained 90% CIs for the ratio of C_{max} and $AUC_{(0-t)}$ values of the Velgia® and the reference drug Wegovy® in the dosage of 0.25 mg/dose (0.68 mg/mL) — Group 1, 2 — were for C_{max} — 85.19–114.36% and $AUC_{(0-t)}$ — 81.35–112.60%, respectively; for the dosage of 2.4 mg/dose (3.2 mg/mL) —Group 3, 4 — C_{max} was 83.18–111.3% and $AUC_{(0-t)}$ — 91.70–120.89%, respectively. The obtained confidence intervals lie within the established limits, which confirms the bioequivalence of the studied drugs.

Safety and tolerability assessment

All the volunteers completed the study in full compliance with the approved study protocol. During the study, Group 1 and Group 2 (0.25 mg/dose (0.68 mg/mL)) volunteers did not experience any AEs.

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In Groups 3 and 4 (the dosage of 2.4 mg/dose (3.2 mg/mL)), single cases of AEs, similar in type (nausea or vomiting), frequency of occurrence and severity, were reported in both the study and reference drugs groups. All the AEs registered during the study were of mild severity. The nature and frequency of AEs were consistent with the known profile for semaglutide and did not require withdrawal of therapy.

The tolerability of IND / RD at 0.25 mg/dose (0.68 mg/mL) and at 2.4 mg/dose (3.2 mg/mL) was rated as "good" and "satisfactory" in 100% of cases and was comparable to the reference drug.

No SAEs were observed in the volunteers during the study and after its completion. No deaths were observed. No cases of pregnancy of the sexual partner of the study participant during the study and after its completion were registered. No abnormalities were detected in the results of clinical and biochemical blood tests, blood glucose levels, a general urinalysis, parameters of basic vital signs, a physical examination and ECG.

Immunogenicity evaluation

According to the results of the immunogenicity parameters analysis, no antibodies to semaglutide were detected in the serum of the volunteers, which indicated the absence of immunogenicity of the drug. Unexpected results were not observed in the study, which supports the concept of the advantage of the drug chemical "origin".

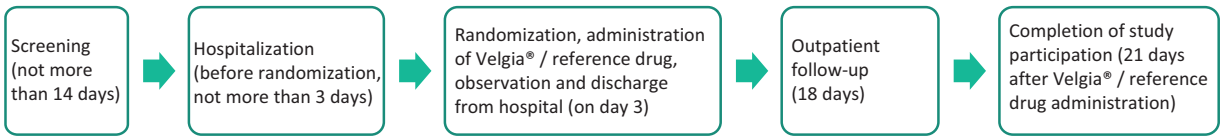

Figure 1 – Study design

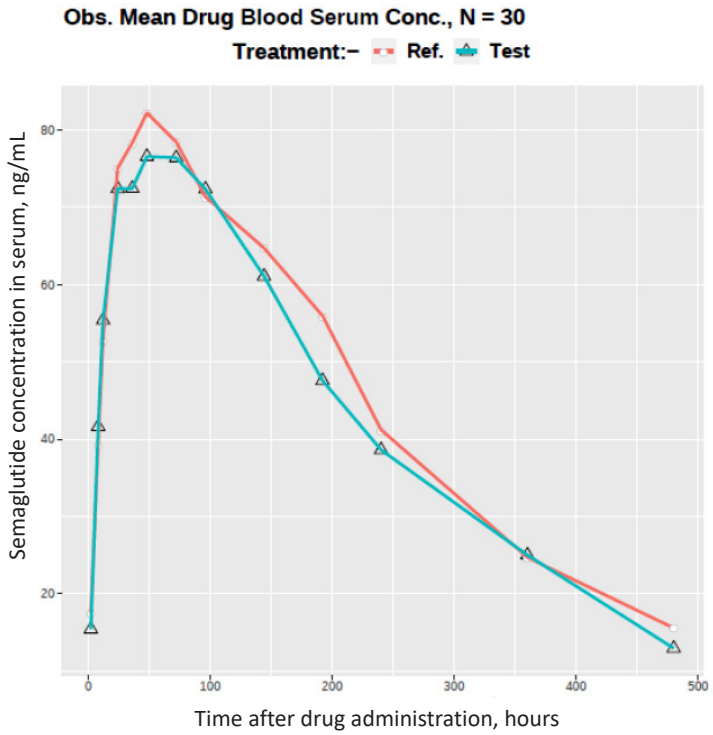

Figure 2 – Averaged pharmacokinetic profiles after administration of the study drug Velgia® and the reference drug Wegovy® at a dosage of 0.25 mg/dose (0.68 mg/mL)
Note: Ref. — reference drug; Test — study drug.

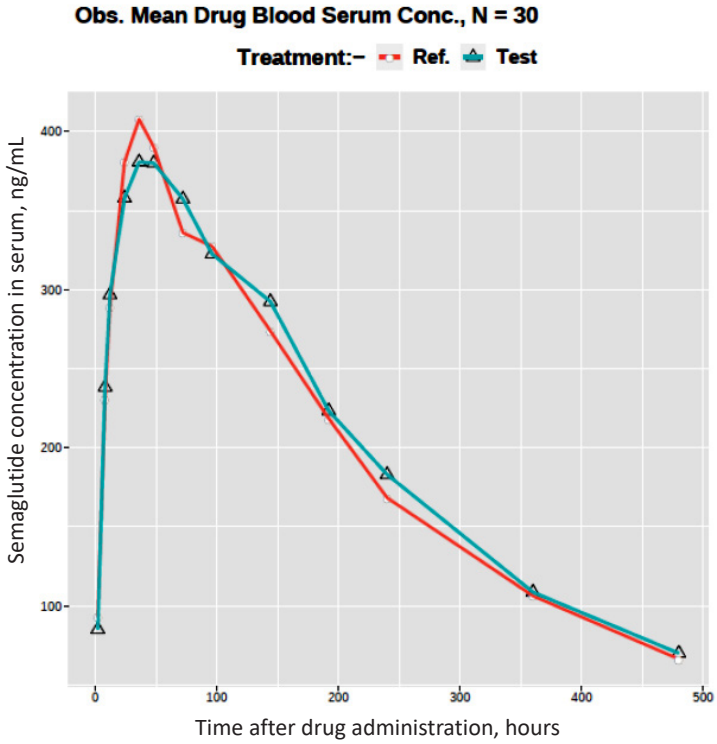

Figure 3 – Averaged pharmacokinetic profiles after administration of the study drug Velgia® and the reference drug Wegovy® at a dosage of 2.4 mg/dose (3.2 mg/mL)
Note: Ref. – reference drug; Test – study drug.

Table 1 – Descriptive characteristics of demographic and anthropometric data of volunteers' study and reference drugs groups

Indicator		0.5 mg dose (2 doses of 0.25 mg/dose), *n*=30			2.4 mg dose, *n*=30		
Gender, *n* (%):							
	Male	8 (26.67%)			21 (70%)		
	Female	22 (72.33%)			9 (30%)		
–		Mean	-95% CI	95% CI	Men	-95% CI	95% CI
Age, full years		45.13	41.76	48.51	43.87	40.60	47.13
Body weight, kg		75.71	73.05	78.37	82.89	80.37	85.41
Height, cm		169.40	166.58	172.21	175.77	172.82	178.71
BMI, kg^2/m		26.35	25.97	26.72	26.81	26.42	27.21

Table 2 – Pharmacokinetic parameters calculated for the studied drugs dosages

Parameter, units	Dose 0.25 mg/dose (0.68 mg/mL), Mean±SD		Dose 2.4 mg/dose (3.2 mg/mL), Mean±SD	
	Velgia®	Wegovy®	Velgia®	Wegovy®
C_{max}, ng/mL	85.63±22.14	86.75±16.12	417.54±83.16	433.85±125.47
$AUC_{(0-t)}$, ng×h/mL	19458.26±5374.17	20330.32±4374.67	94426.48±18947.4	89684.6±21791.3
$AUC_{(0-\infty)}$, ng×h/mL	22168.60±7014.38	23829.36±6296.99	112034.65±25345.73	106204.16±25136.1
k_{el}, h^{-1}	0.005±0.003	0.005±0.001	0.004±0.001	0.004±0.001
t_{max}, h	52.46±35.19	51.47±54.2	40.53±26.24	45.67±22.16
$t_{1/2}$, h	139.7±43.1	149.77±38.16	167.68±43.24	167.77±39.34
$AUC_{(t-\infty)}$, %	9.73±5.51	12.55±7.62	13.99±6.78	14.51±5.8
V_d, L	4.55±1.37	4.53±1.49	5.18±1.55	5.47±1.96
$AUC_{(0-t)}$ / $AUC_{(0-\infty)}$, %	87.77±5.51	85.32±7.62	84.28±6.78	84.45±5.8

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Table 4 – Comparison of norms and actually obtained control results quality of semaglutide (production of JSC "Biochemik", Russia and Zhejiang Peptites Biotech Co., Ltd, China)

Parameter	Semaglutide (JSC Biochemik, Russia)		Semaglutide (Zhejiang Peptites Biotech Co., Ltd, China)	
	Standardised indicator	Control result	Standardised indicator	Control result
Appearance	White or almost white amorphous powder	White amorphous powder	White or almost white powder or a loose lump	Almost white powder
Specific rotation	-2° to -20° in terms of anhydrous and acetic acid free	-14.6°	This indicator is not controlled	
Identification (by HPLC)	In the chromatogram of the standard sample, the retention time of the main peak of the test solution shall correspond to the retention time of the semaglutide peak	Corresponds.	The retention time of the main peak of the test sample should correspond to the retention time of the main peak of the standard sample	Corresponds
Identification (MS)	M.W.: 4113.6±1.0	M.W.: 4112.8	MW: 4113.6±1.0	M.W.: 4112.8
Peptide mapping	The chromatographic profile of the lysate solution of the test sample shall correspond to the chromatographic profile of the lysate solution of the semaglutide standard sample.	Corresponds.	This indicator is not controlled.	
Related impurities (by HPLC method)	Impurity A: Not more than 0.15%	0.02%	G06-IM37: Not more than 0.1%	Not detected
	Impurity A: Not more than 0.15%	0.09%	G06-IM42: Not more than 0.1%	Not detected
	Impurity A: Not more than 0.15%	0.03%	G06-IM10: Not more than 0.1%	Not detected
	Impurity A: Not more than 0.15%	0.02%	G06-IM60: Not more than 0.2%	0.10%
	Any single impurity: Not more than 0.10%	0.03%	G06-IM18: Not more than 0.2%	Not detected
	Total impurities: Not more than 1.0%	0.23%	G06-IM01: Not more than 0.2%	0.07%
			G06-IM59: Not more than 0.2%	0.10%
			G06-IM28: Not more than 0.2%	0.09%
			G06-IM03: Not more than 0.2%	Not detected
			Any single impurity: Not more than 0.10%	Not detected
			Total impurities: Not more than 2.0%	0.36%
Acetic acid	Not more than 0.25 %	0.01%	Not more than 0.5%	0.03%
Trifluoroacetic acid	Not more than 0.25 %	Not detected	Not more than 0.25 %	0.02%
Bacterial endotoxins	Not more than 5 EUs/mg	Less than 5 EU/mg	Less than 10 EUs/mg	Less than 10 EUs/mg
Total aerobic bacteria	Not more than 100 CFUs/g	Absent	Not more than 100 CFUs/g	Less than 10 CFUs/g
Total yeasts and moulds	Not more than 50 CFUs/g	Absent	Not more than 100 CFUs/g	Less than 10 CFUs/g

DISCUSSION

The broad evidence base for the efficacy of semaglutide with respect to the weight loss, a restoration of metabolic health and a reduction of risks of complications presents semaglutide as a priority drug for a widespread use in routine clinical practice for the therapy of obesity and overweight [4, 10, 11, 24]. Moreover, the potential of the molecule is not limited to metabolic diseases. Semaglutide shows positive results in preclinical and clinical studies for the treatment of MAFLD, apnea, Alzheimer's disease, CVD prevention [12, 17], depression, etc. [23, 24, 26]. In 2024, semaglutide was included in the latest Russian clinical guidelines[4] for the treatment of obesity (revision 2024) for a sustained reduction of a body weight and cardiovascular risks in overweight and obese patients. Availability of the above-mentioned medicines for patients in Russia is an important task for the introduction of health-saving technologies into medical practice. An adequate drug supply is critical for achieving the main goals of the healthcare system — preservation and promotion of public health.

At the moment, Velgia® is the only domestic preparation based on semaglutide INN containing all necessary dosages and concentrations of the active substance for the treatment of obesity and overweight, taking into account the need for a proper transition from the first use of the drug through the titration period to the therapeutically effective dosage.

The authors' own original technology of obtaining and purification of the active pharmaceutical substance ensures a high level of quality control of the obtained substance, an exclusion of undesirable impurities and isomerization. As a consequence, it contributes to the achievement of high efficiency and safety of the therapy. The developed technology of the chemical synthesis and product isolation allows Promomed Company to create peptide molecules with precisely defined properties without a spontaneous replacement of amino acids in the peptide structure, the absence of products of producers' life activities (as in case of their production from bacteria or yeast), a high degree of purity, which increases the safety profile of the drug. The literature describes the advantages of the developed technology compared to foreign precursors [14, 15].

Moreover, the production of semaglutide by this method is highly productive, scalable and economically feasible compared to the biotechnological route used by a foreign company, which ensures that the need for the drug is met for a wide range of patients [20, 21, 25, 26]. The registration procedure for the medicinal product Velgia® (semaglutide) was completed on 3 October 2024. Biological, pharmaceutical, functional and consumer characteristics of this drug meet all the requirements for the drugs for the treatment of obesity and overweight:

- high efficacy and safety parameters, taking into account the specifics of a long-term use for the treatment of chronic obesity;
- full range of specially selected dosages and concentrations of the active ingredient to ensure the required dose titration pattern from the first use (0.25 mg/week) to the therapeutic dose (2.4 mg/week);
- syringe pens, which are easy to use and do not require any effort and specialized skills during their use.

The introduction of Velgia® (semaglutide) into the practice of Russian physicians represents an access to the drug therapy proven worldwide, which will reduce the burden of the obesity pandemic and ensure an effective and safe weight loss.

The syringe pen specially designed for this drug does not require specialized skills and is compatible with needles of any manufacturer, which is important in case of a possible decrease in the availability of foreign-made needles.

For the production of semaglutide, Promomed Company uses the solid-phase peptide synthesis (SPPS) method. It allows to automate the process and accurately reproduce the specified structure of the peptide, which mitigates the risks of changes in the obtained substance and, consequently, adverse immune reactions when using the drug.

[4] Clinical Guidelines for Obesity (revised 2024). Available from: https://cr.minzdrav.gov.ru/view-cr/28_3. Russian

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Comparative evaluation of quality indicators of semaglutide active pharmaceutical substance

The main characteristics affecting the quality of semaglutide substance (Biochemik JSC, Russia) and semaglutide substance manufactured by Zhejiang Peptites Biotech Co., Ltd, China, which is a part of one of the medicinal preparations registered in Russia, were analyzed. The indices pledged by both manufacturers for the control of their APIs, were taken into account. The results of the study are presented in Table 4.

The above data show that the semaglutide API produced by Zhejiang Peptites Biotech Co., Ltd, China is not controlled by the indicators “Specific rotation” and “Peptide mapping”. That indicates the lack of a systematic authenticity verification of the obtained preparation and the risk of reducing the effectiveness of the finished drug as a result of, for example, an amino acid substitution. Moreover, in comparison with the semaglutide API produced by JSC Biochemik (Russia), the Chinese manufacturer lays down underestimated quality requirements for the indicators “Sum of impurities”, “Acetic acid content”, “Bacterial endotoxins” and “Total yeast and moulds”. This fact may indirectly indicate a coarser technology of the APIs purification, which may affect the safety parameters and lead to the rejection of the entire series of the finished dosage form according to the indicator “Sterility” and, consequently, interruptions in the supply of the vital drug.

Increased requirements for the API purity of the semaglutide produced by JSC Biochemik, Russia, in particular, reflected the lack of immunogenicity at the stage of clinical trials.

Thus, thanks to the efforts of domestic pharmaceutical companies, in particular Promomed Company, all the most effective tools to combat overweight and obesity are available in our country and the new drug Velgia® will be the next step towards a metabolically healthy society.

CONCLUSION

The study confirmed the bioequivalence of the study drug Velgia® (WRYC12301, semaglutide, a solution for a subcutaneous administration, JSC Biochemik, Russia) and the reference drug (semaglutide, a solution for a subcutaneous administration, Novo Nordisk A/S, Denmark), both at doses of 0.25 mg (0.68 mg/mL) and 2.4 mg (3.2 mg/mL), their high safety profile, good tolerability and lack of immunogenicity.

Velgia® is available in ergonomic syringe pens, in 5 doses, each containing one of the following prescribed doses of semaglutide: 0.25, 0.5, 1, 1.7 and 2.4 mg/dose. Each syringe pen contains four doses of the drug to be used once a week for a month.

A step-by-step titration of Velgia® promotes a safe and effective weight loss. The drug is produced in Russia according to the full cycle — from the chemical synthesis of the substance to the finished dosage form. The prescription of the drug does not require in-depth diagnostics, and can be implemented by doctors of various specialities as an addition to a low-calorie diet and physical activities to reduce a body weight for the indication “obesity and overweight”, which will allow effective and safe therapy of patients regardless of their gender, age and presence of comorbidities.

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The sponsor had no influence on the selection of material
for publication, data analysis and interpretation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Aleksander S. Ametov — development of the clinical study concept, analysis and description of the results, text correction; Kira Ya. Zaslavskaya — analysis and selection of literature sources, writing the text of the article; Ekaterina A. Rogozhina — discussion of the study design and results; Petr A. Bely — implementation of the study design, processing of the study data; Victoria S. Shcherbakova — development of the study design and concept, writing the text of the article; Yurii G. Kazaishvili — development of the clinical study design and concept; Alexey V. Taganov — analyzing and describing the results, searching and analyzing literature sources; Tatiana G. Bodrova, Ekaterina S. Mishchenko, Ksenia N. Koryanova, Larisa I. Shcherbakova — processing the study data, editing the text of the article.

All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet. 2024;403(10431):1027–50. DOI: 10.1016/S0140-6736(23)02750-2
2. Dedov II, Mel'nichenko GA, Shestakova MV, Troshina EA, Mazurina NV, Shestakova EA, Yashkov YuI, Neimark AE, Biryukova EV, Bondarenko IZ, Bordan NS, Dzgoeva FH, Ershova EV, Komshilova KA, Mkrtumyan AM, Petunina NA, Romantsova TI, Starostina EG, Strongin LG, Suplotova LA, Fadeyev VV. Russian national clinical recommendations for morbid obesity treatment in adults. 3rd revision (Morbid obesity treatment in adults). Obesity and metabolism. 2018;15(1):53–70. DOI: 10.14341/omet2018153-70
3. Lingvay I, Cohen RV, Roux CWL, Sumithran P. Obesity in adults. Lancet. 2024;404(10456):972–87. DOI: 10.1016/S0140-6736(24)01210-8
4. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, Wallenstein SOR, Garvey WT; STEP 3 Investigators. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults with Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021;325(14):1403–13. DOI: 10.1001/jama.2021.1831
5. Kaplan LM, Golden A, Jinnett K, Kolotkin RL, Kyle TK, Look M, Nadglowski J, O'Neil PM, Parry T, Tomaszewski KJ, Stevenin B, Lilleøre SK, Dhurandhar NV. Perceptions of Barriers to Effective Obesity Care: Results from the National ACTION Study. Obesity (Silver Spring). 2018;26(1):61–69. DOI: 10.1002/oby.22054
6. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG. Meta-analysis: surgical treatment of obesity. Ann Intern Med. 2005;142(7):547–559. DOI: 10.7326/0003-4819-142-7-200504050-00013
7. Jensen AB, Renström F, Aczél S, Folie P, Biraima-Steinemann M, Beuschlein F, Bilz S. Efficacy of the Glucagon-Like Peptide-1 Receptor Agonists Liraglutide and Semaglutide for the Treatment of Weight Regain After Bariatric surgery: a Retrospective Observational Study. Obes Surg. 2023;33(4):1017–1025. DOI: 10.1007/s11695-023-06484-8
8. Yang XD, Yang YY. Clinical Pharmacokinetics of Semaglutide: A Systematic Review. Drug Des Devel Ther. 2024;18:2555–70. DOI: 10.2147/DDDT.S470826
9. Ard J, Fitch A, Fruh S, Herman L. Weight Loss and Maintenance Related to the Mechanism of Action of Glucagon-Like Peptide 1 Receptor Agonists. Adv Ther. 2021;38(6):2821–2839. DOI: 10.1007/s12325-021-01710-0
10. Amaro A, Skolnik NS, Sugimoto D. Cardiometabolic risk factors efficacy of semaglutide in the STEP program. Postgrad Med. 2022;134(sup1):18–27. DOI: 10.1080/00325481.2022.2147325
11. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, Carson CG, Jepsen CH, Kabisch M, Wilding JPH. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet. 2018;392(10148):637–49. DOI: 10.1016/S0140-6736(18)31773-2
12. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, Lingvay I, McGowan BM, Oral TK, Rosenstock J, Wadden TA, Wharton S, Yokote K, Kushner RF; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022;24(8):1553–64. DOI: 10.1111/dom.14725
13. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989–1002. DOI: 10.1056/NEJMoa2032183
14. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, Lingvay I; STEP 2 Study Group. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet. 2021;397(10278):971–84. DOI: 10.1016/S0140-6736(21)00213-0
15. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, Jódar E, Kandler K, Rigas G, Wadden TA, Wharton S; STEP 5 Study Group. Two-year effects of semaglutide in adults with overweight or

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2024-12-3-231-246

obesity: the STEP 5 trial. Nat Med. 2022;28(10):2083–91. DOI: 10.1038/s41591-022-02026-4

16. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, Lingvay I, Oral TK, Michelsen MM, Plutzky J, Tornøe CW, Ryan DH; SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221–32. DOI: 10.1056/NEJMoa2307563
17. Ryan DH, Lingvay I, Deanfield J, Kahn SE, Barros E, Burguera B, Colhoun HM, Cercato C, Dicker D, Horn DB, Hovingh GK, Jeppesen OK, Kokkinos A, Lincoff AM, Meyhöfer SM, Oral TK, Plutzky J, van Beek AP, Wilding JPH, Kushner RF. Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial. Nat Med. 2024;30(7):2049–57. DOI: 10.1038/s41591-024-02996-7
18. Wharton S, Calanna S, Davies M, Dicker D, Goldman B, Lingvay I, Mosenzon O, Rubino DM, Thomsen M, Wadden TA, Pedersen SD. Gastrointestinal tolerability of once-weekly semaglutide 2.4 mg in adults with overweight or obesity, and the relationship between gastrointestinal adverse events and weight loss. Diabetes Obes Metab. 2022;24(1):94–105. DOI: 10.1111/dom.14551
19. Ghusn W, De la Rosa A, Sacoto D, Cifuentes L, Campos A, Feris F, Hurtado MD, Acosta A. Weight Loss Outcomes Associated with Semaglutide Treatment for Patients with Overweight or Obesity. JAMA Netw Open. 2022;5(9):e2231982. DOI: 10.1001/jamanetworkopen.2022.31982
20. Ametov AS, Shokhin IE, Rogozhina EA, Bodrova TG, Nevretdinova ME, Bely PA, Zaslavskaya KYa, Scherbakova VS, Kurkin DV, Koryanova KN, Mishchenko ES, Kesova EYu, Kozlov ED, Samoshkina ES, Andreev DN, Kazaishvili YuG, Noskov SM, Balykova LA. Comparative analysis of physicochemical properties, bioequivalence, safety and tolerability of the first domestic semaglutide. Pharmacy & Pharmacology. 2023;11(4):324–346. DOI: 10.19163/2307-9266-2023-11-4-324-346
21. Ametov AS, Shokhin IE, Rogozhina EA, Bodrova TG, Nevretdinova ME, Bely PA, Zaslavskaya KYa, Kurkin DV, Koryanova KN, Mishchenko ES, Noskov SM. Russian development for drug independence in endocrinology: comparative analysis of bioequivalence, safety and tolerability of the first domestic liraglutide. Pharmacy & Pharmacology. 2023;11(3):255–76. DOI: 10.19163/2307-9266-2023-11-3-255-276
22. Wang W, Wang Q, Qi X, Gurney M, Perry G, Volkow ND, Davis PB, Kaelber DC, Xu R. Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US. Alzheimers Dement. 2024;20(12):8661–72. DOI: 10.1002/alz.14313
23. Bushnell C, Kernan WN, Sharrief AZ, Chaturvedi S, Cole JW, Cornwell WK 3rd, Cosby-Gaither C, Doyle S, Goldstein LB, Lennon O, Levine DA, Love M, Miller E, Nguyen-Huynh M, Rasmussen-Winkler J, Rexrode KM, Rosendale N, Sarma S, Shimbo D, Simpkins AN, Spatz ES, Sun LR, Tangpricha V, Turnage D, Velazquez G, Whelton PK. 2024 Guideline for the Primary Prevention of Stroke: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2024;55(12):e344–424. DOI: 10.1161/STR.0000000000000475. Erratum in: Stroke. 2024;55(12):e439. DOI: 10.1161/STR.0000000000000482. Erratum in: Stroke. 2025;56(2):e98. DOI: 10.1161/STR.0000000000000486
24. Weghuber D, Barrett T, Barrientos-Pérez M, Gies I, Hesse D, Jeppesen OK, Kelly AS, Mastrandrea LD, Sørrig R, Arslanian S; STEP TEENS Investigators. Once-Weekly Semaglutide in Adolescents with Obesity. N Engl J Med. 2022;387(24):2245–57. DOI: 10.1056/NEJMoa2208601
25. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, Rudofsky G, Tadayon S, Wadden TA, Dicker D; STEP 4 Investigators. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults with Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021;325(14):1414–1425. DOI: 10.1001/jama.2021.3224
26. Phillips A, Clements JN. Clinical review of subcutaneous semaglutide for obesity. J Clin Pharm Ther. 2022;47(2):184–93. DOI: 10.1111/jcpt.13574

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