



Comparative analysis of bioequivalence, safety, and tolerability of semaglutide (tablets): results of an open-label randomized crossover comparative study

A.S. Ametov¹, L.A. Balykova², K.Ya. Zaslavskaya², I.E. Shokhin³, T.G. Bodrova⁴, L.A. Zorina⁵, V.S. Shcherbakova⁶, D.V. Kurkin^{4,7}, K.N. Koryanova^{1,8}, E.S. Mishchenko⁸, M.L. Maksimov¹, A.V. Matveev¹, L.I. Shcherbakova⁸, I.N. Dyakova⁸, E.D. Kozlov², D.N. Andreev⁴, Yu.G. Kazaishvili⁶, S.M. Noskov^{9,10}, P.A. Bely⁴

¹ Russian Medical Academy of Continuing Professional Education,
Bld. 1, 2/1, Barrikadnaya Str., Moscow, Russia, 125993

² National Research Ogarev Mordovia State University,
68, Bolshevistskaya Str., Saransk, Russia, 430005

³ Limited Liability Company "Center for Pharmaceutical Analytics",
8, Simferopolsky Blvd, Moscow, Russia, 117638

⁴ Russian University of Medicine,
4, Dolgorukovskaya Str., Moscow, Russia, 127006

⁵ Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies,
28 Orekhovy Blvd, Russia, Moscow, 115682

⁶ Tver State Medical University,
4 Sovetskaya Str., Tver, Russia, 170100

⁷ Volgograd State Medical University,
1 Pavshikh Bortsov Sq., Volgograd, Russia, 400066

⁸ Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University,
11 Kalinin Ave., Pyatigorsk, Russia, 357532

⁹ Yaroslavl State Medical University,
5 Revolutionary Str., Yaroslavl, Russia, 150000

¹⁰ Clinical Hospital No. 3,
61 Mayakovskogo Str., Yaroslavl, Russia, 150007

E-mail: Victoria_kaptar@mail.ru

Received 26 Dec 2025

After peer review 18 May 2026

Accepted 30 June 2026

The aim. To conduct a comparative evaluation of the physicochemical properties, biological activity, bioequivalence, and safety, including tolerability and immunogenicity, of the drug Semaltara® (semaglutide, tablets 3 and 14 mg (Biochemik, Russia) and the drug Rebelas® (semaglutide, tablets in dosages of 3 and 14 mg (Novo Nordisk A/S, Denmark) when administered to healthy volunteers.

Materials and Methods. To assess the bioequivalence of the investigational drug Semaltara® (semaglutide, tablets 3 and 14 mg (Biochemik, Russia) with a chemically synthesized active substance to the original (reference) drug Rebelas® (semaglutide, tablets in dosages of 3 and 14 mg (Novo Nordisk A/S, Denmark), an open-label randomized crossover

For citation: A.S. Ametov, L.A. Balykova, K.Ya. Zaslavskaya, I.E. Shokhin, T.G. Bodrova, L.A. Zorina, V.S. Shcherbakova, D.V. Kurkin, K.N. Koryanova, E.S. Mishchenko, M.L. Maksimov, A.V. Matveev, L.I. Shcherbakova, I.N. Dyakova, E.D. Kozlov, D.N. Andreev, Yu.G. Kazaishvili, S.M. Noskov, P.A. Bely. Comparative analysis of bioequivalence, safety, and tolerability of semaglutide (tablets): results of an open-label randomized crossover comparative study. *Pharmacy & Pharmacology*. 2026;14(4):387-409. DOI: 10.19163/2307-9266-2026-14-4-387-409

© А.С. Аметов, Л.А. Балькова, К.Я. Заславская, И.Е. Шохин, Т.Г. Бодрова, Л.А. Зорина, В.С. Щербакова, Д.В. Куркин, К.Н. Корянова, Е.С. Мищенко, М.Л. Максимов, А.В. Матвеев, Л.И. Щербакова, И.Н. Дьякова, Е.Д. Козлов, Д.Н. Андреев, Ю.Г. Казашвили, С.М. Носков, П.А. Белый, 2026

Для цитирования: А.С. Аметов, Л.А. Балькова, К.Я. Заславская, И.Е. Шохин, Т.Г. Бодрова, Л.А. Зорина, В.С. Щербакова, Д.В. Куркин, К.Н. Корянова, Е.С. Мищенко, М.Л. Максимов, А.В. Матвеев, Л.И. Щербакова, И.Н. Дьякова, Е.Д. Козлов, Д.Н. Андреев, Ю.Г. Казашвили, С.М. Носков, П.А. Белый. Сравнительный анализ биоэквивалентности, безопасности и переносимости семаглутида (таблетки): результаты открытого рандомизированного перекрестного сравнительного исследования. *Фармация и фармакология*. 2026;14(4):387-409. DOI: 10.19163/2307-9266-2026-14-4-387-409

comparative study ($n = 110$) was conducted. Patients were randomized into 4 groups: Group 1 ($n = 25$) — patients received the investigational drug Semaltara® and the comparator drug Rebelas® daily once a day at a dose of 3 mg (1 tablet) for 28 days; Group 2 ($n = 25$) — the comparator drug Rebelas® and the investigational drug Semaltara® daily once a day at a dose of 3 mg (1 tablet) for 28 days; Group 3 ($n = 30$) — the investigational drug Semaltara® and the comparator drug Rebelas® daily once a day at a dose of 14 mg (1 tablet) for 28 days; Group 4 ($n = 30$) — the comparator drug Rebelas® and the investigational drug Semaltara® daily once a day at a dose of 14 mg (1 tablet) for 28 days. The concentration of semaglutide was determined in serum samples using a pre-validated enzyme-linked immunosorbent assay (ELISA) method. The conclusion on bioequivalence of the compared drugs was made based on the assessment of 90 % confidence intervals for the ratios of geometric mean values of $C_{\max}$ and $AUC_{(0-t)}$ parameters of semaglutide in the original units of measurement.

Results. The results of the clinical study demonstrated the bioequivalence of the investigational drug and the comparator drug. The pharmacokinetic parameters of the drugs were comparable: Based on statistical analysis, the obtained 90 % confidence intervals for the ratio of $C_{\max,ss}$ and $AUC_{(0-t)ss}$ values of semaglutide 3 mg were 96.57–120.94 % and 94.37–120.06 %, respectively. For the 14 mg dosage, the 90 % confidence intervals for the ratio of $C_{\max,ss}$ and $AUC_{(0-t)ss}$ values of semaglutide were 91.79–109.68 % and 91.47–112.80 %, respectively. The tolerability of the drugs in volunteers was noted as good. No serious adverse events were registered during the entire study. Thus, the investigational drug Semaltara®, tablets, and the comparator drug Rebelas®, tablets, have a similar safety profile, including tolerability, at both the 3 mg and 14 mg dosages.

Conclusion. The conducted study demonstrated the bioequivalence and similar safety profile, as well as tolerability of the Russian drug Semaltara® (semaglutide 3 and 14 mg, tablets, Promomed LLC, Russia) in comparison with the foreign drug Rebelas® (semaglutide, tablets in dosages of 3 and 14 mg (Novo Nordisk A/S, Denmark).

Keywords: glucagon-like peptide-1; bioequivalence; pharmacokinetics; semaglutide; type 2 diabetes mellitus; physicochemical properties; safety profile; biological activity; tablets

List of Abbreviations: T2DM — type 2 diabetes mellitus; HbA1c — glycated hemoglobin; GLP-1 — glucagon-like peptide-1; BMI — body mass index; BP — blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; ECG — electrocardiography; AE — adverse event; SAE — serious adverse event; CI — confidence interval.

Сравнительный анализ биоэквивалентности, безопасности и переносимости семаглутида (таблетки): результаты открытого рандомизированного перекрестного сравнительного исследования

А.С. Аметов¹, Л.А. Балыкова², К.Я. Заславская², И.Е. Шохин³, Т.Г. Бодрова⁴,
Л.А. Зорина⁵, В.С. Щербакова⁶, Д.В. Куркин^{4,7}, К.Н. Корянова^{1,8}, Е.С. Мищенко⁸,
М.Л. Максимов¹, А.В. Матвеев¹, Л.И. Щербакова⁸, И.Н. Дьякова⁸, Е.Д. Козлов²,
Д.Н. Андреев⁴, Ю.Г. Казайшвили⁶, С.М. Носков^{9,10}, П.А. Белый⁴

¹ Федеральное государственное автономное образовательное учреждение дополнительного профессионального образования «Российская медицинская академия непрерывного образования» Министерства здравоохранения Российской Федерации, Россия, 125993, г. Москва, ул. Баррикадная, д.2/1, стр.1

² Федеральное государственное бюджетное образовательное учреждение высшего образования «Национальный исследовательский Мордовский государственный университет имени Н.П. Огарёва» Россия, 430005, г. Саранск, ул. Большевикская, д.68

³ Общество с ограниченной ответственностью «Центр Фармацевтической Аналитики» (ООО «ЦФА»), Россия, 117638, г. Москва, Симферопольский бульвар, д.8

⁴ Федеральное государственное бюджетное образовательное учреждение высшего образования «Российский университет медицины» Министерства здравоохранения Российской Федерации, Россия, 127006, г. Москва, ул. Долгоруковская д.4

⁵ Федеральное государственное бюджетное учреждение «Федеральный научно-клинический центр специализированных видов медицинской помощи и медицинских технологий Федерального медико-биологического агентства России», Москва, Россия Россия, 115682, г. Москва, Ореховый бульвар, д.28

⁶ Федеральное государственное бюджетное образовательное учреждение высшего образования «Тверской государственный медицинский университет Министерства здравоохранения Российской Федерации, Россия, 170100, г. Тверь, ул. Советская, д.4

⁷ Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 400066, г. Волгоград, пл. Павших Борцов, д.1

⁸ Пятигорский медико-фармацевтический институт – филиал федерального государственного бюджетного образовательного учреждения высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 357532, г. Пятигорск, пр-кт Калинина, д.11

⁹ Федеральное государственное бюджетное образовательное учреждение высшего образования «Ярославский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 150000, г. Ярославль, ул. Революционная, д.5

¹⁰ Государственное бюджетное учреждение здравоохранения Ярославской области «Клиническая больница № 3», Россия, 150007, г. Ярославль, ул. Маяковского, д.61

E-mail: Victoria_kaptar@mail.ru

Получена 26.12.2025

После рецензирования 18.05.2026

Принята к печати 30.06.2026

Цель. Провести сравнительную оценку физико-химических свойств, биологической активности, биоэквивалентности и безопасности, включая переносимость и иммуногенность, лекарственного препарата Семальтара (семаглутид, таблетки 3 и 14 мг (АО «Биохимик», Россия) и препарата Ребелсас® (семаглутид, таблетки в дозировках 3 и 14 мг (Ново Нордиск А/С, Дания) при применении здоровыми добровольцами.

Материалы и методы. Для оценки биоэквивалентности исследуемого препарата Семальтара® (семаглутид, таблетки 3 и 14 мг (АО «Биохимик», Россия) с химически синтезированным активным веществом оригинальному (референтному) препарату Ребелсас® (семаглутид, таблетки в дозировках 3 и 14 мг (Ново Нордиск А/С, Дания) проведено открытое рандомизированное перекрестное сравнительное исследование ($n=110$). Пациенты путём рандомизации распределены на 4 группы: 1 группа ($n=25$) — пациенты получали исследуемый препарат Семальтара® и препарат сравнения Ребелсас® ежедневно 1 раз в сут в дозе 3 мг (1 таблетка) в течение 28 дней; 2 группа ($n=25$) — препарат сравнения Ребелсас® и исследуемый препарат Семальтара® ежедневно 1 раз в день в дозе 3 мг (1 таблетка) в течение 28 дней; 3 группа ($n=30$) — исследуемый препарат Семальтара® и препарат сравнения Ребелсас® ежедневно 1 раз в сут в дозе 14 мг (1 таблетка) в течение 28 дней; 4 группа ($n=30$) — препарат сравнения Ребелсас® и исследуемый препарат Семальтара® ежедневно 1 раз в день в дозе 14 мг (1 таблетка) в течение 28 дней. Концентрацию семаглутида определяли в образцах сыворотки крови с помощью предварительно валидированного метода иммуноферментного анализа (ИФА). Вывод о биоэквивалентности сравниваемых препаратов делали по оценке 90% доверительных интервалов для отношений средних геометрических значений параметров $C_{\max}$, $AUC_{(0-t)}$ семаглутида в исходных единицах измерения.

Результаты. Результаты клинического исследования продемонстрировали биоэквивалентность исследуемого препарата и препарата сравнения. Фармакокинетические параметры препаратов были сопоставимы между собой: По результатам статистического анализа полученные 90% доверительные интервалы для отношения значений $C_{\max}$, ss и $AUC_{(0-t)ss}$ семаглутида 3 мг составили 96,57–120,94% и 94,37–120,06%, соответственно. Для в дозировки 14 мг 90% доверительные интервалы для отношения значений $C_{\max}$, ss и $AUC_{(0-t)ss}$ семаглутида составили 91,79–109,68% и 91,47–112,80%, соответственно. Переносимость препаратов у добровольцев отмечена как хорошая. В течение всего исследования не зарегистрировано ни одного серьёзного нежелательного явления. Таким образом, исследуемый препарат Семальтара®, таблетки и препарат сравнения Ребелсас®, таблетки, имеют сходный профиль безопасности, включая переносимость как в дозировке 3 мг, так и в дозировке 14 мг.

Заключение. В ходе проведённого исследования показана биоэквивалентность и сходный профиль безопасности, а также переносимость российского препарата Семальтара® (семаглутид 3 и 14 мг, таблетки, ООО «Промомед», Россия) в сравнении с зарубежным препаратом Ребелсас® (семаглутид, таблетки в дозировках 3 и 14 мг (Ново Нордиск А/С, Дания).

Ключевые слова: глюкагоноподобный пептид-1; биоэквивалентность; фармакокинетика; семаглутид; сахарный диабет 2-го типа; физико-химические свойства; профиль безопасности; биологическая активность; таблетки

Список сокращений: СД 2 — сахарный диабет 2 типа; HbA1c — гликированный гемоглобин; ГПП-1 — глюкагоноподобный пептид-1; ИМТ — индекс массы тела; АД — артериальное давление; САД — систолическое артериальное давление; ДАД — диастолическое артериальное давление; ЧСС — частота сердечных сокращений; ЭКГ — электрокардиография; НЯ — нежелательное явление; СНЯ — серьёзное нежелательное явление; ДИ — доверительный интервал.

INTRODUCTION

According to the latest data from the NCD Risk Factor Collaboration (2022), the number of people with diabetes mellitus (DM) has reached 828 million, of whom more than 95% suffer from type 2 DM [1]. Statistics show that the prevalence of DM will continue to grow, however, this figure is likely higher due to varying estimates of current diabetes prevalence [1–3]. Type 2 DM is a complex, multisystem metabolic disorder characterized by high blood glucose levels resulting from progressive defects in insulin secretion or insulin resistance of tissues¹ [4]. Type 2 DM is a common and heterogeneous disorder characterized by varying degrees of beta-cell dysfunction and insulin resistance.

There is a strong link between obesity and type 2 DM, affecting pathways regulated by the central nervous system. These pathways control food intake and energy expenditure by integrating signals from peripheral organs and the environment [5]. It should also be noted that type 2 DM does not only affect older people; in recent years, a twofold or threefold increase in the incidence of type 2 DM in young people (< 40 years) has been observed [6].

Glucagon-like peptide-1 (GLP-1) receptor agonists are recently approved drugs for the treatment of DM and obesity. GLP-1 has physiological effects on various organs. Like incretin, it enhances glucose-dependent insulin secretion by pancreatic β -cells, promotes β -cell neogenesis, inhibits β -cell apoptosis, and suppresses glucagon secretion by α -cells (shown in rodent studies). Furthermore, GLP-1 affects other tissues and organs, including the stomach—slowing gastric emptying, the heart—exerting cardioprotective effects, as well as adipose tissue and skeletal muscles—improving glucose uptake, and also acts centrally on hypothalamic neurons, inducing satiety [7–9]. GLP-1 receptor agonist therapy suppresses appetite, leading to weight loss, which in turn has a broad impact on improving patients' quality of life and reducing the risk of cardiovascular and renal complications [10]. Various GLP-1 receptor agonists are approved for the treatment of type 2 DM, including exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide. These drugs are characterized by subcutaneous administration, although an oral form of semaglutide is also available [10]. Scientific studies have shown that

GLP-1 analogs improve glycemic control in patients with type 2 DM and additionally contribute to a reduction in systolic blood pressure (BP). Long-acting preparations of this class are associated with more effective glucose reduction and exhibit fewer gastrointestinal side effects compared to their short-acting counterparts [11–14].

Scientific developments in recent years have allowed for a detailed study of the role of incretin hormones in regulating carbohydrate metabolism in the human body and their effect on β -cells, as well as the creation of a new direction in pharmacotherapy. One of the representatives of incretin mimetics is semaglutide [15, 16].

Semaglutide reduces total body weight and fat mass by decreasing energy intake. The mechanism of action of semaglutide contributes to appetite reduction by enhancing satiety signals and weakening hunger signals, as well as improving control over food intake volume and reducing cravings for it. As a consequence, insulin resistance decreases due to weight loss. In addition, semaglutide reduces the preference for high-fat foods [17, 19].

The company LLC “PROMMOMED RUS” has developed a drug with the active substance semaglutide, Semaltara®, in tablet form.

For the semaglutide (tablets), the reference product is Rybelsus® (INN: semaglutide), tablets—an original drug from Novo Nordisk A/S, registered in Denmark, where the level of pharmaceutical market regulation requirements is not lower than that established in the EAEU.

In the reference product Rybelsus®, the active substance semaglutide is obtained by a biotechnological method from recombinant DNA of *Saccharomyces cerevisiae*, whereas in the investigated product Semaltara®, the active substance is obtained by chemical synthesis [17].

Current international requirements allow the use of an accelerated registration procedure for drugs such as semaglutide without conducting comparative efficacy studies, considering them redundant [18].

To establish equivalence, it is sufficient for the applicant to demonstrate using modern analytical methods (HPLC-MS, NMR, etc.) that the active ingredient in the proposed synthetic peptide is the same as in the reference drug—comparable physicochemical characteristics, biological activity,

¹ International Diabetes Federation. IDF Diabetes Atlas 10th Edition; 2021. Available from: <https://diabetesatlas.org/>

and an identical impurity profile². According to FDA guidance (ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin, 2021), information on the safety and efficacy of the original drug, in the case of a similar dosage form, route of administration, dosage, and conditions of use, is sufficient to establish equivalence of the drug³.

Thus, conducting a bioequivalence study is relevant and applicable for confirming the reproducibility of the investigated semaglutide drug⁴.

THE AIM is to conduct a comparative analysis of the physicochemical properties, biological activity, bioequivalence, and safety, including tolerability and immunogenicity, of the medicinal product Semaltara® (semaglutide, tablets 3 mg and 14 mg (JSC "Biokhimik", Russia) and the reference product Rybelsus® (semaglutide, tablets in dosages of 3 mg and 14 mg (Novo Nordisk A/S, Denmark) used to healthy volunteers.

MATERIALS AND METHODS

Study Design

A single-center, open-label, randomized, crossover bioequivalence study with multiple administrations of the study drug and reference drug was conducted.

The total duration of the study for each volunteer was no more than 71 days.

The study included the following stages:

1. Screening—no more than 14 days.

2. Randomization.

3. Period I—volunteers in groups 1 and 3 received the study drug Semaltara® (T1 or T2), volunteers in groups 2 and 4 received the reference drug Rybelsus® (R1 or R2). The duration of the period was no more than 28 days (outpatient visits on days 1, 15, 25, 26, 27; hospitalization in the evening on day 27 at least 10 hours before drug intake for up to 26 hours after drug intake on day 28, blood sampling within 24 hours after drug intake on day 28).

4. Period II—volunteers in groups 1 and 3 received the reference drug Rybelsus® (R1 or R2), volunteers in groups 2 and 4 received the study drug

Semaltara® (T1 or T2). The duration of the period was no more than 28 days (outpatient visits on days 29, 43, 53, 54, 55; hospitalization in the evening on day 55 at least 10 hours before drug intake for up to 26 hours after drug intake on day 56, blood sampling within 24 hours after drug intake on day 56).

5. Completion of study participation.

Considering the variability data of semaglutide drugs, a crossover design with multiple administrations of the study drug / reference drug in each period is provided. Given that steady-state concentration of semaglutide is achieved after 4–5 weeks of once-daily administration, each period includes a duration of 28 days of study drug / reference drug intake [6].

Considering that the study involved the investigation of steady-state concentration of the drug with multiple administrations, a washout period is not provided in the present study.

A graphical scheme of the study design is presented in Figure 1.

Study subjects and eligibility criteria

The study was conducted with healthy male and female volunteers aged 18 to 65 years inclusive, who met all inclusion criteria and none of the exclusion criteria.

Inclusion criteria: signing the informed consent form ICF, as well as the ability and willingness to comply with all Protocol requirements; women of non-childbearing potential and men aged 18 to 65 years inclusive at the time of signing the ICF; body mass index (BMI) 25–30 kg/m² inclusive; verified diagnosis of "healthy" based on standard clinical, laboratory, and instrumental examination methods; hemodynamic parameters: systolic blood pressure (SBP) 100–130 mmHg, diastolic blood pressure (DBP) 60–90 mmHg, heart rate (HR) 60–90 bpm, respiratory rate (RR) 16–20 breaths/min; negative results for human immunodeficiency virus (HIV), syphilis, hepatitis B (HBsAg), and hepatitis C (HCV); negative results for alcohol, psychotropic, and narcotic substance use; willingness to abstain from alcohol consumption during study participation. Women of non-childbearing potential (history of hysterectomy, bilateral oophorectomy, tubal ligation, infertility, absence of menstruation for 12 consecutive months prior to screening), and men; the absence of treatment upon diagnosis of "infertility" prior to study enrollment, as well as planned treatment throughout the study and for

² ANDAs for certain highly purified synthetic peptide drug products that refer to listed drugs of rDNA origin. Available from: <https://collections.nlm.nih.gov/catalog/nlm:nlmuid-9918350982606676-pdf>

³ Ibid.

⁴ National Center for Biotechnology Information (2023). PubChem Compound Summary for CID 56843331, Semaglutide. Retrieved May 15, 2023. Available from: <https://pubchem.ncbi.nlm.nih.gov/compound/Semaglutide>

2 months after its completion (both standard, surgical, and non-traditional or experimental treatments); consent of male volunteers to use reliable methods of contraception (abstinence, barrier method (condom or occlusive cap (diaphragm or cervical / vault cap)) or dual barrier method of contraception (condom or occlusive cap (diaphragm or cervical / vault cap) plus spermicide (foam / gel/ film / cream / suppository)) throughout their participation in the study and for 2 months after its completion.

Exclusion Criteria: history of allergies, drug intolerance; hypersensitivity to semaglutide or any of the excipients of the study drug / reference drug, to therapeutic proteins; women of childbearing potential; use of medicinal products: history of semaglutide use; other analogs of human GLP-1—within less than 6 months prior to screening; medicinal products with a significant impact on hemodynamics and/or liver function (barbiturates, omeprazole, cimetidine, etc.)—within less than 2 months prior to screening; other medicinal products (including those used for weight loss), including herbal and homeopathic preparations, vitamins and/or dietary supplements (DSs)—within less than 4 weeks prior to screening; inability to insert a cubital heparinized catheter; difficulty swallowing tablets; tendency for frequent bowel movements, diarrhea within less than 2 weeks prior to screening /at the time of screening / randomization; any difficulties with blood collection in history or any vasovagal episodes during blood collection that, in the opinion of the investigator, could significantly interfere with blood sampling for the study; donation or loss of blood (≥ 450 mL of blood or plasma) within less than 3 months prior to screening; planned donation of blood / plasma/blood components or surgical intervention during study participation; any deviations from normal values in laboratory and/or instrumental examination; history of severe cardiovascular, bronchopulmonary, endocrine, central nervous system, gastrointestinal diseases, malignant oncological or hematological diseases; gastrointestinal surgery (except appendectomy) in history; history of medullary thyroid carcinoma, including familial; history of multiple endocrine neoplasia type 2; diabetes mellitus; history of pancreatitis; severe depression, suicidal thoughts or behavior, including in history; acute infectious diseases or symptoms of ARVI within less than 4 weeks prior to screening; special diet (e.g., vegetarian, vegan, low-salt, low-calorie, etc.) within less

than 2 months prior to screening procedures; special lifestyle (night work, extreme physical exertion) within less than 2 months prior to screening procedures; alcohol consumption within 72 hours prior to any screening procedures; history of consuming more than 10 units of alcohol per week (1 unit of alcohol is equivalent to 500 mL of beer, 200 mL of wine, or 50 mL of spirits) or history of alcoholism, drug addiction, substance abuse; smoking more than 10 cigarettes per day at the time of screening; undergoing piercing, tattooing /tattooing procedures within less than 1 month prior to screening or planning to undergo them during study participation; inability or incapacity to comply with necessary contraceptive measures; pregnancy (positive pregnancy test in women) or breastfeeding period; mental, physical, and other reasons that prevented the volunteer from adequately assessing their behavior and correctly following the study Protocol; participation in another clinical study within less than 3 months prior to screening; other reasons that, in the opinion of the investigator, prevented the volunteer from participating in this study.

Exclusion Criteria: the principal investigator could exclude a volunteer from the study for the following reasons: volunteer's refusal to participate in the clinical study; the investigator decided that the volunteer needed to be excluded in the volunteer's best interest; erroneous enrollment of a volunteer who did not meet the inclusion criteria and/or met the exclusion criteria; positive test for alcohol, psychotropic and/or narcotic substances; variability (positive pregnancy test in women); missed two or more blood draws for pharmacokinetic parameter determination consecutively within one study period or three blood draws for pharmacokinetic parameter determination within one study period; volunteer's use of vitamins, DS, drugs, including herbal and/or homeopathic, except for the study drug / reference drug; development of any diseases or conditions during the study that make further participation impossible; volunteer refuses to cooperate, is undisciplined, does not comply with the study participation rules.

Randomization Procedure

Each volunteer who met all inclusion criteria and did not meet any exclusion criteria was assigned a randomization number according to the randomization plan prepared for this study in the WinPepi 11.65 program (module ETCETERA 3.26) using

a random number generation method. The volunteer's randomization number was entered by the investigator into the Clinical Trial Participant Registration Log for screening / randomization. If a volunteer prematurely discontinued study participation, their randomization number was not reused, and the volunteer could not subsequently return to the study.

Study conditions and duration

The study was conducted from August 9, 2024, to March 21, 2025, at the Research Center of the Clinical Hospital No. 3 (Yaroslavl, Russia). The total duration of the study for each volunteer was no more than 71 days (including the screening period). All randomized volunteers completed the study fully in accordance with the approved Study Protocol.

Description of Procedures and Methodology

Drug Administration

A total of 110 volunteers who met the inclusion criteria and had no exclusion criteria were randomized into 4 groups:

3 mg Dosage

Group 1 ($n = 25$) received the study drug Semaltara® (T1) in Period I of the study and the reference drug Rybelsus® (R1) in Period II (T1R1 sequence). The drugs were administered orally once daily at a dose of 3 mg (1 tablet) for 28 days.

Group 2 ($n = 25$) received the reference drug Rybelsus® (R1) in Period I of the study and the study drug Semaltara® (T1) in Period II (R1T1 sequence). The drugs were administered orally once daily at a dose of 3 mg (1 tablet) for 28 days.

14 mg Dosage

Group 3 ($n = 30$) received the study drug Semaltara® (T2) in Period I of the study and the reference drug Rybelsus® (R2) in Period II (T2R2 sequence). The drugs were administered orally once daily at a dose of 14 mg (1 tablet) for 28 days.

Group 4 ($n = 30$) received the reference drug Rybelsus® (R2) in Period I of the study and the study drug Semaltara® (T2) in Period II (R2T2 sequence). The drugs were administered orally once daily at a dose of 14 mg (1 tablet) for 28 days.

Volunteers took the study drug / reference drug orally in the morning on an empty stomach, at least 30 minutes before food and additional fluids/drinks. Tablets should be swallowed whole, without chewing, dissolving, crushing, or breaking them, with 120 mL of still water.

Sample preparation and collection

Blood sampling times for pharmacokinetic parameter assessment:

Day 1: no more than 15 minutes before administration of the study drug / reference drug (corresponds to time 0 h in Tables 59–62; this point is not included in pharmacokinetic profile construction).

Days 25 and 53: no more than 15 minutes before administration of the study drug / reference drug (corresponds to time 576 h in Tables 59–62 and time -72 h in pharmacokinetic profiles).

Days 26 and 54: no more than 15 minutes before administration of the study drug / reference drug (corresponds to time 600 h in Tables 59–62 and time -48 h in pharmacokinetic profiles).

Days 27 and 55: no more than 15 minutes before administration of the study drug / reference drug (corresponds to time 624 h in Tables 59–62 and time -24 h in pharmacokinetic profiles).

Days 28 and 56: no more than 5 minutes before administration of the study drug / reference drug and then at 10 min, 20 min, 30 min, 40 min, 50 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 12 h, 24 h after administration of the study drug / reference drug on days 28 and 56 (correspond to times 648 h, 648.17 h, 648.33 h, 648.5 h, 648.67 h, 648.83 h, 649 h, 649.5 h, 650 h, 651 h, 652 h, 654 h, 660 h, and 672 h in Tables 59–62 and times 0 h, 0.17 h, 0.33 h, 0.5 h, 0.67 h, 0.83 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 12 h, and 24 h in pharmacokinetic profiles).

Thus, 35 blood samples were collected for each volunteer (15 mL each) for pharmacokinetic parameter assessment. A total of 3850 blood samples were collected for pharmacokinetic parameter assessment in 110 volunteers, assuming each volunteer completed the study. 7700 blood samples were transferred to the analytical center for pharmacokinetic parameter assessment (aliquots A and B) in 110 volunteers.

During the screening, blood was collected in a volume of no more than 25 mL for clinical, biochemical, and serological analyses, determination of glycated hemoglobin, and blood glucose level determination using a glucometer.

During the hospital stage, upon discharge from the inpatient facility (in periods I and II), blood was collected for clinical and biochemical analyses, determination of glycated hemoglobin, and blood glucose level determination using a glucometer, with a total volume not exceeding 15 mL in each period.

Analytical Method

Pharmacokinetic parameters were assessed based on semaglutide concentration in serum by HPLC using a triple quadrupole tandem mass spectrometric detector. For this purpose, the following pharmacokinetic variables were calculated: $AUC_{(0-t)ss}$ is area under the “concentration–time” curve during the dosing interval at steady state (corresponding to AUC_{0-24} on Days 28 and 56); $C_{max, ss}$ is maximum serum drug concentration at steady state (corresponding to C_{max} on Days 28 and 56); $C_{min, ss}$ is minimum serum drug concentration at steady state (corresponding to C_{min} on Days 28 and 56); $T_{max, ss}$ is time to reach maximum serum drug concentration at steady state.

Additional pharmacokinetic calculations could be performed if necessary.

Sample Preparation

Sample preparation was performed by protein precipitation using a methanol–acetonitrile mixture (70 : 30). To 100 μ L of serum sample placed in 2 mL Eppendorf centrifuge tubes, 10 μ L of semaglutide working standard solution was added, followed by 300 μ L of precipitant. The mixture was vortexed for 10 sec and then centrifuged for 15 minutes at 12,300 g. Subsequently, 320 μ L of the supernatant was transferred to a well of a 96-well plate and placed in the chromatograph autosampler.

Chromatographic Separation and Detection Conditions

Chromatographic separation and detection were performed on a Nexera XR high-performance liquid chromatograph and an LCMS-8040 triple quadrupole tandem mass spectrometric detector. Raw data processing was carried out using LabSolutions Ver. 5.91 software (Shimadzu Corp., Japan). Chromatographic separation and detection conditions are presented in Tables 1 and 2.

Method Validation

The developed method was validated according to the following parameters: selectivity, system suitability, matrix effect, calibration curve, accuracy, precision, recovery, lower limit of quantification, sample transfer, short-term stability (“bench-top” and “post-preparative”), stability upon three freeze-thaw cycles, stability of stock and working standard solutions, long-

term analyte stability in matrix, and absence of sample dilution effect.

Within 1–3 validation cycles, the method was fully validated in December 2024. The confirmed analytical range of the method was **1.00–300.00 ng/mL** in serum for semaglutide.

During the analytical stage of the study according to protocol No. 13101-SR, version 1.0 dated June 07, 2024, “Open randomized cross-over comparative study of pharmacokinetic parameters, bioequivalence, safety, and tolerability of the drug WTBC13101 (PROOMED RUS LLC, Russia) in healthy volunteers,” a discrepancy was found between the obtained results and the expected concentration range, based on which the analytical range of the method for semaglutide was selected. In this regard, a decision was made to change the analytical range of the method for semaglutide such that the LLOQ does not exceed 5% of the minimum C_{max} value.

In December 2024, as part of the 4 validation cycle, partial validation of the method for quantitative determination of semaglutide in human serum was conducted to expand the analytical range for semaglutide towards reducing the method’s LLOQ from 1.00 ng/mL to 0.50 ng/mL (Rules for conducting bioequivalence studies of medicinal products within the Eurasian Economic Union, approved by Decision No. 85 of the Council of the Eurasian Economic Commission dated 03.11.2016, Annex VI, Sections 2 and 3, paragraphs 48 and 50). The following validation parameters were assessed: selectivity, calibration curve, accuracy, precision, lower limit of quantification. The confirmed analytical range of the method was **0.50–300.00 ng/mL** in serum for semaglutide.

Bioequivalence Assessment

Bioequivalence of the studied drugs was assessed based on semaglutide concentration in serum. The conclusion on the bioequivalence of the compared drugs was formed using an approach based on the assessment of 90% confidence intervals (CIs) for the ratios of the geometric mean values of $AUC_{(0-t)ss}$ and $C_{max, ss}$ parameters of semaglutide in original units of measurement. The 90% CI limits were rounded to two decimal places. The drugs were considered bioequivalent if the limits of the estimated confidence interval for $AUC_{(0-t)ss}$ and $C_{max, ss}$ of semaglutide were within 80.00–125.00%.

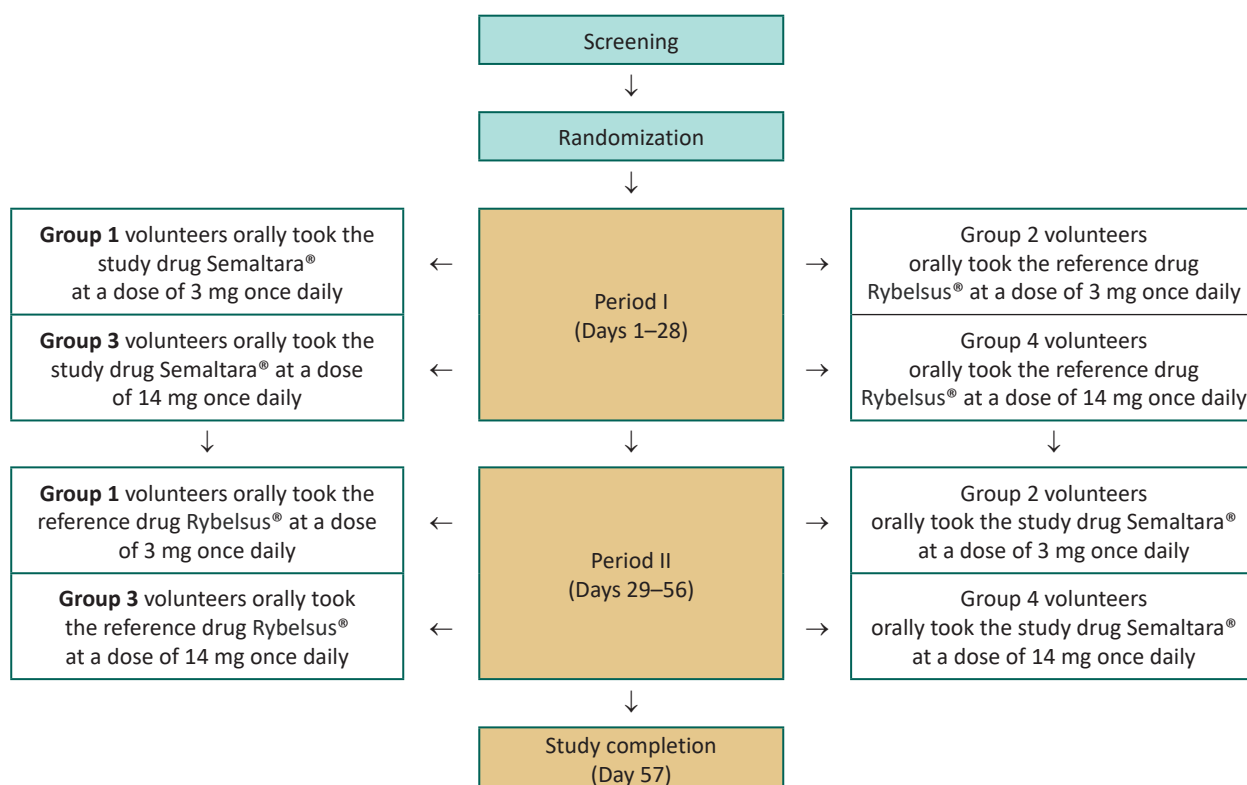


Figure 1 — Study Design.

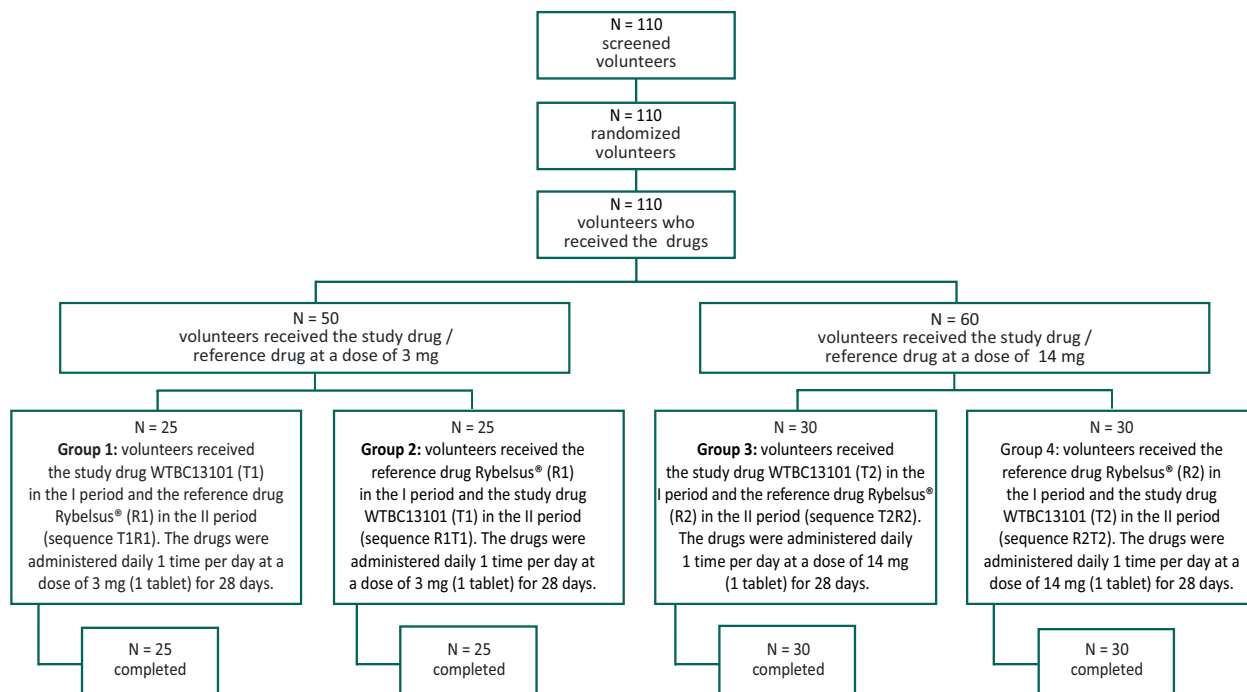


Figure 2 — Distribution of Volunteers.

Table 1 — Chromatographic conditions

Chromatographic conditions			
Column		Phenomenex Luna C18, 100A, 50×2.00 mm, 5 μm	
Pre-column		Phenomenex C18, 4×3.0 mm	
Column thermostat temperature		50°C	
Mobile phase	Eluent A	0.3 % formic acid solution in water (by volume)	
	Eluent B	0.3 % formic acid, 7% ethyl acetate, 5% methanol in acetonitrile (by volume)	
Gradient of the mobile phase	Time, min	% content of eluent B	Flow rate of the mobile phase, mL/min
	0.00	5.0	1.50
	0.50	5.0→100.0	
	1.31	100.0	
	1.99	100.0	2.00
	2.00	100.0	
	2.05	5.0	
	2.50	5.0	1.50
	2.70	100.0	
	3.00	100.0	
	3.01	100.0	2.00
	3.99	100.0	
	4.00	100.0	
	4.05	5.0	1.50
	5.50	5.0	
Volume of the injected sample		20 μL	
Retention time of semaglutide		about 1.1 min	
Liraglutide retention time		about 1.1 min	
Time of registration of the chromatogram		0.00–5.50 min	

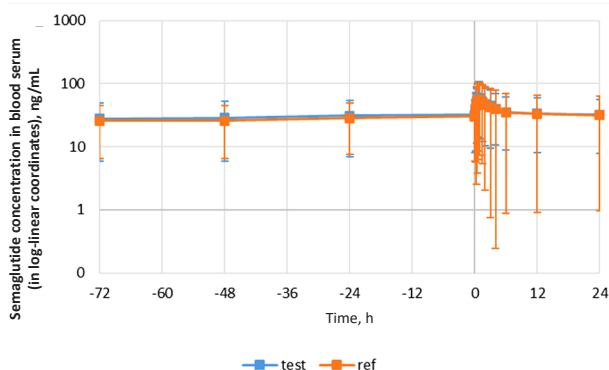
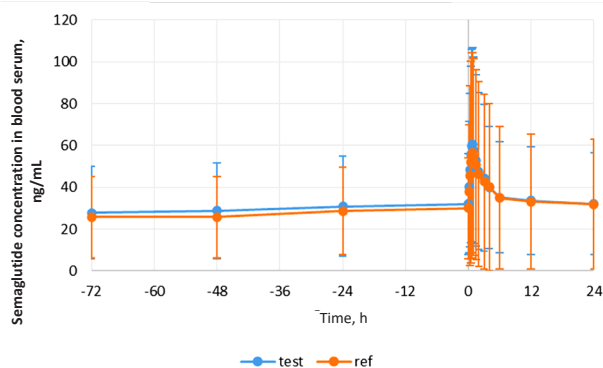
Table 2 — Mass spectrometric detection conditions

Mass spectrometric detection conditions							
Parameters of an electrospray ionization							
Sheath gas	Auxiliary Gas	Heating unit	Desolvation line	Needle voltage		Ionization mode	
				SEM	LIR	SEM	LIR
3 L/min	20 L/min	400 °C	250 °C	5.0 κB	5.0 κB	+	+
Semaglutide detection conditions, m/z							
1029.10→1302.30		1028.90→1109.65		1029.10→1237.60		1029.40→1359.10	
Liraglutide detection conditions, m/z z							
938.35→1128.30			938.35→1063.75				

Table 3 — Average values of the main pharmacokinetic parameters for the study drug and the reference drug

Parametr	Dose 3 mg		Dose 14 mg	
	Semaltara® (T1)	Rybelsus® (R1)	Semaltara® (T2)	Rybelsus® (R2)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
C _{max, ss} , ng/mL	51.30 ± 48.06	47.36 ± 52.55	171.10 ± 77.70	171.90 ± 97.43
C _{min, ss} , ng/mL	20.81 ± 18.70	19.77 ± 23.38	107.57 ± 57.92	105.42 ± 66.01
T _{max, ss} , h	0.74 ± 0.23	0.74 ± 0.29	0.79 ± 0.17	0.81 ± 0.12
AUC _{(0-t)ss} , ng×h/mL	670.43 ± 649.14	628.67 ± 818.19	3246.81 ± 1593.14	3226.51 ± 1974.19
ln(C _{max, ss})	3.88 ± 0.69	3.80 ± 0.67	5.12 ± 0.46	5.12 ± 0.52
ln(AUC _(0-t))	6.47 ± 0.73	6.40 ± 0.74	8.07 ± 0.54	8.05 ± 0.62

3 mg Dosage



14 mg Dosage

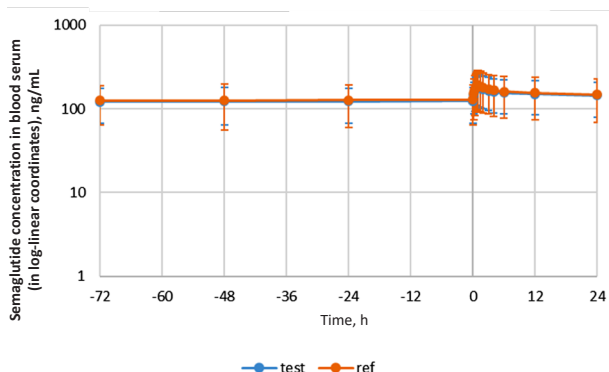
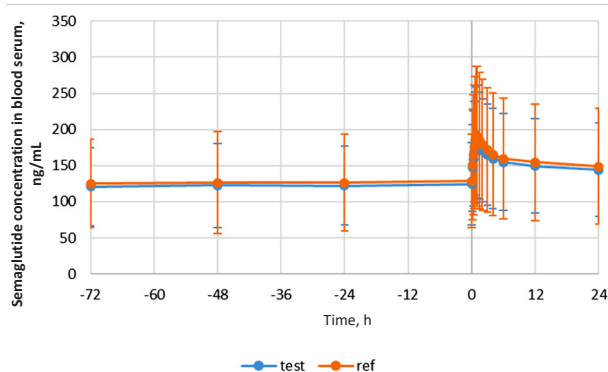


Figure 3 — Pharmacokinetic profiles of semaglutide drugs by concentration and time.

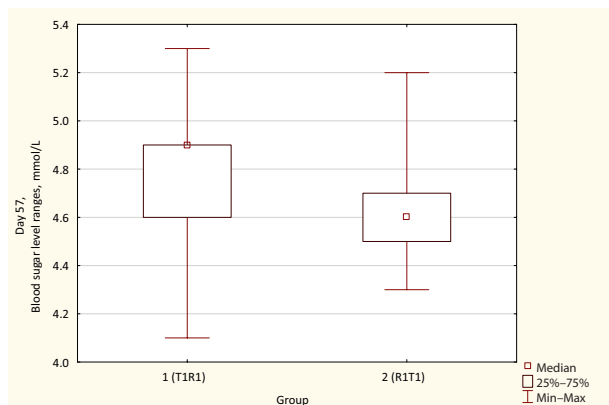
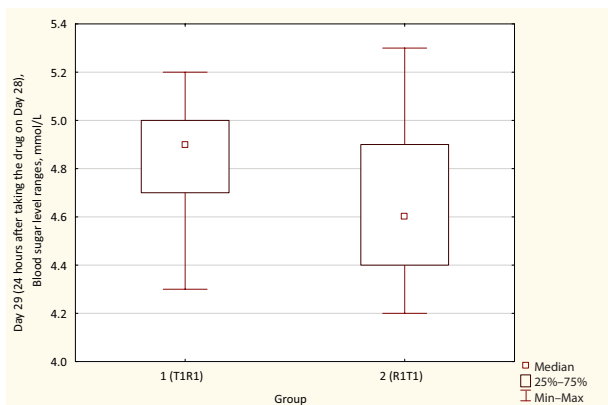
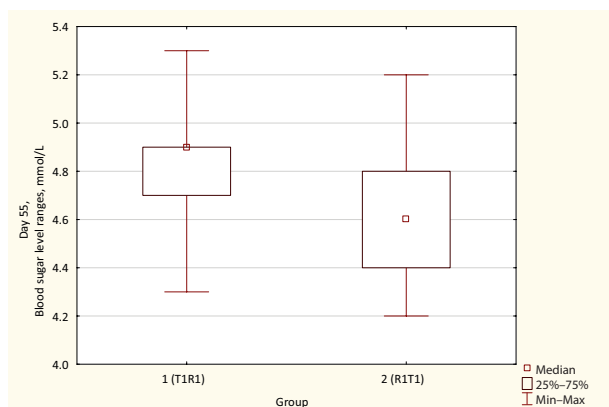
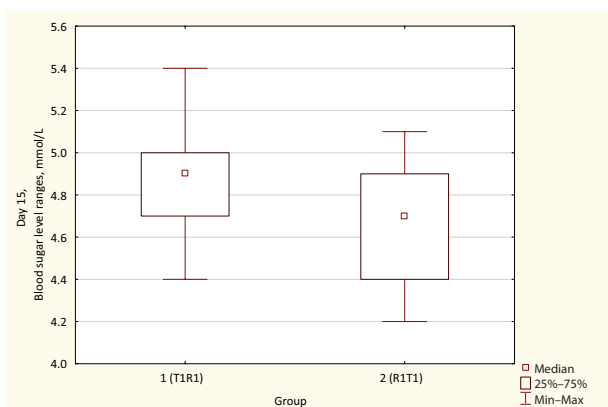


Figure 4 — Comparative analysis of blood glucose levels at hospital and outpatient stages in volunteers.

Safety and Tolerability Assessment

To assess the safety and tolerability of the study drug semaglutide, the following criteria were evaluated:

- Frequency and severity of adverse events (AEs) recorded based on deviations from normal laboratory test results, physical examination, assessment of vital signs, and ECG.
- Number of cases of premature discontinuation from the study due to the development of AEs and/or serious adverse events (SAEs), including those related to the study drug / reference drug.

The investigator's assessment of the overall tolerability of the study drug / reference drug was performed using a Likert scale.

Ethics Approval

The study complied with the ethical principles set forth in the Declaration of Helsinki as revised, the Good Clinical Practice rules of the Eurasian Economic Union, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH E6 GCP R2) Good Clinical Practice guidelines, and other applicable legislation. The clinical study protocol was approved by the Ethics Council of the Ministry of Health of Russia (Extract from the minutes of meeting No. 363 of the Ethics Council of the Ministry of Health of the Russian Federation dated July 23, 2024), as well as by the Local Independent Ethics Committee at the Research Center of the Clinical Hospital No. 3 (extract from the minutes of meeting No. 213 dated August 29, 2024).

Statistical Analysis

Sample Size Calculation

The required number of participants was calculated based on data on intra-individual variability coefficients (CV_{intra}) of key pharmacokinetic parameters in similar studies. The Assessment report Rybelsus [1] presents data indicating that CV_{intra} for $AUC_{(0-t)ss}$ does not exceed 33%. The sample size calculation was performed using PASS 11 software (USA). Considering that the 90% CI was 80.00–125.00%, $AUC_{(0-t)ss}/C_{max, ss}$ was 33%, $\alpha = 0.05$, study power was 80%, and the expected T / R ratio was 0.95, at least 46 healthy volunteers were required to fully complete the study and be included in the statistical analysis. Accounting for potential

dropouts during the study, 50 healthy volunteers were randomized into the 3 mg dosage study (25 volunteers per group) and 60 healthy volunteers (30 volunteers per group) into the 14 mg dosage study. Thus, the total number of randomized volunteers was 110.

Statistical Analysis

Pharmacokinetic parameters, statistical analysis of safety and tolerability indicators, and results reporting were performed using statistical packages (StatSoft Statistica version 13.3, and R project (version 4.1.3, GPL-2/GPL-3 license) with the “bear” extension, version 2.9.1⁵). For all pharmacokinetic parameters, the following statistical parameters were calculated: arithmetic mean, geometric mean, standard deviation of the mean, coefficient of variation, median, minimum and maximum values, range. Statistical analysis was conducted assuming a log-normal distribution for C_{max} , ss and $AUC_{(0-t)ss}$, and a normal distribution for other pharmacokinetic parameters. After logarithmic transformation, these parameters were analyzed using analysis of variance (ANOVA).

The conclusion on the bioequivalence of the compared drugs was made using an approach based on the assessment of 90% CI for the ratios of the geometric mean values of $AUC_{(0-t)ss}$ and $C_{max, ss}$ parameters of semaglutide in original units of measurement. The 90% CI limits were rounded to two decimal places. The drugs were considered bioequivalent if the limits of the estimated confidence interval for $AUC_{(0-t)ss}$ and $C_{max, ss}$ of semaglutide were within 80.00–125.00%.

For all safety and tolerability indicators collected during the study, descriptive statistics are presented as mean and standard deviation (Mean $\pm$ SD), 95% confidence interval for the mean (M [95% CI]), median (Me), interquartile range [Q1 ; Q3], minimum (min) and maximum (max), or as frequencies and percentages (n , %) depending on the variable type.

For the analysis of frequency indicators, proportions were compared using the two-sided exact Fisher's test (or the χ^2 (“chi-squared”) test, if all expected values in the contingency table cells for this analysis were 5 or more). For the comparison of continuous quantitative indicators, the Student's t-test (in case of normal distribution) or the Mann-Whitney

⁵ R project. bear (BE/BA for R) v2.9.6. Available from: <https://www.pkpd168.com/bear>

U test was used (in case of distribution different from normal).

Differences were considered statistically significant at $p < 0.05$.

RESULTS

Bioequivalence and comparability of safety and tolerability profile

Population

The study included 110 male and female volunteers who received the study drugs / reference drugs at doses of 3 mg and 14 mg. The mean age of volunteers in the population was 46.82 ± 8.93 years (range 23 years to 64 years), body weight was 83.26 ± 8.62 kg (range 66.50 kg to 97.20 kg), height was 172.91 ± 7.18 cm (range 162 cm to 189 cm), and the mean BMI was 27.78 ± 1.30 kg/m² (range 25.05 kg/m² to 29.83 kg/m²).

Among the volunteers who received the study drugs / reference drugs at doses of 3 mg and 14 mg, there were 58 (52.73%) male volunteers and 52 (47.27%) female volunteers.

Pharmacokinetics and bioequivalence

3 mg Dose

Based on the statistical analysis, the obtained 90% CIs for the ratio of $C_{\max,ss}$ and $AUC_{(0-t),ss}$ values of semaglutide were 96.57–120.94% and 94.37–120.06%, respectively. The obtained confidence intervals fall within the limits established by regulatory documentation and the Study Protocol (80.00–125.00% for $C_{\max,ss}$, $AUC_{(0-t),ss}$), indicating that the bioequivalence of the study drugs at a dose of **3 mg** in this sample of subjects is statistically proven (Table 3).

The obtained intra-individual variation coefficients for the pharmacokinetic parameter $C_{\max,ss}$ were 34.46%, and for the parameter $AUC_{(0-t),ss}$ they were 37.03%.

The statistical power of the study for the pharmacokinetic parameter $C_{\max,ss}$ was 80.32%, and for the pharmacokinetic parameter $AUC_{(0-t),ss}$ it was 74.70% (Table 3).

14 mg Dose

Based on the statistical analysis, the obtained 90% CIs for the ratio of $C_{\max,ss}$ and $AUC_{(0-t),ss}$ values of semaglutide were 91.79–109.68% and 91.47–112.80%, respectively. The obtained confidence intervals fall within the limits established by regulatory documentation and the Study Protocol (80.00–125.00% for $C_{\max,ss}$, $AUC_{(0-t),ss}$), indicating that the bioequivalence of the study drugs at a dose of **14 mg** in this sample of subjects is statistically proven (see Table 3).

The obtained intra-individual variation coefficients for the pharmacokinetic parameter $C_{\max,ss}$ were 29.74%, and for the parameter $AUC_{(0-t),ss}$ they were 35.28%.

The statistical power of the study for the pharmacokinetic parameter $C_{\max,ss}$ was 93.92%, and for the pharmacokinetic parameter $AUC_{(0-t),ss}$ it was 85.44%.

Figure 3 presents the averaged pharmacokinetic profiles over time (in linear and log-linear transformations, with and without standard deviations) after administration of the study drug and the reference drug at doses of 3 mg and 14 mg. As can be seen from the compared curves, the concentration-time relationship for the compared drugs is practically indistinguishable.

Complete Blood Count

As a result of the comparative analysis of clinical blood count parameters, no intergroup differences were found, except for differences in “Leukocytes, 10⁹/L” ($p = 0.0073$) at the outpatient stage on day 29 between groups 1 and 2, “Hemoglobin, g/L” ($p = 0.0270$), “Erythrocytes, 10¹²/L” ($p = 0.0114$), “Platelets, 10⁹/L” ($p = 0.0032$), “Color Index/MCH, pg” ($p = 0.0324$) at the outpatient stage on day 29 between groups 3 and 4, “Hemoglobin, g/L” ($p = 0.0313$), “Hematocrit, %” ($p = 0.0371$), “Erythrocytes, 10¹²/L” ($p = 0.0042$), and “Platelets, 10⁹/L” ($p = 0.0040$) at the inpatient stage on day 57 between groups 3 and 4. Differences in these parameters were deemed clinically insignificant because all volunteers had these parameters within the reference ranges.

Urinalysis

Based on the comparative analysis of urinalysis parameters, no significant differences were found, except for differences in “pH, units” ($p = 0.0245$) at the outpatient stage between groups 1 and 2, and “pH, units” ($p = 0.0239$) at the inpatient stage between groups 1 and 2. Differences in these parameters were deemed clinically insignificant because all volunteers had them within the reference ranges.

Biochemical Blood Analysis

Based on the comparative analysis of biochemical blood analysis parameters, no intergroup differences were found, except for differences in “AST, U/L” ($p = 0.0478$) at the outpatient stage, “Total Bilirubin, $\mu\text{mol/L}$ ” ($p = 0.0456$), and “AST, U/L” ($p = 0.00298$)

at the inpatient stage, between groups 1 and 2. Differences in these parameters were deemed clinically insignificant because all volunteers had these parameters within the reference ranges.

Differences were also found in "Total Cholesterol, mmol/L" ($p = 0.0443$) at the inpatient stage between groups 3 and 4. Differences in these parameters were deemed clinically insignificant because all volunteers had these parameters within the reference ranges.

Blood Glucose Level

Based on the comparative analysis of blood glucose level parameters, no intergroup differences were found, except for differences in "Blood Glucose Level, mmol/L" ($p = 0.0126$) at the outpatient stage on day 15, "Blood Glucose Level, mmol/L" ($p = 0.0132$) at the outpatient stage on day 29 (24 hours after drug administration on day 28), "Blood Glucose Level, mmol/L" ($p = 0.0031$) at the outpatient stage on day 55, and "Blood Glucose Level, mmol/L" ($p = 0.0032$) at the inpatient stage on day 57, between groups 1 and 2. Differences in these parameters were deemed clinically insignificant because all volunteers had these parameters within the reference ranges.

Blood Pressure Parameters

Based on the comparative analysis of vital signs, no intergroup differences were found between groups 1 and 2, except for differences at the outpatient stage on day 55 for SBP ($p = 0.0340$), on day 1 (0 h, before randomization) for DBP ($p = 0.0363$), on day 43 for RR ($p = 0.0337$), and at the inpatient stage: on day 56 for DBP ($p = 0.0103$), and on day 27 for RR ($p = 0.0100$). Differences in these parameters were deemed clinically insignificant because all volunteers had these parameters within the normal range. No AEs were recorded for these parameters.

Based on the comparative analysis of vital signs, no intergroup differences were found between groups 3 and 4, except for differences at the outpatient stage on day 29 (4 h) for DBP ($p = 0.0272$), on day 53 for DBP ($p = 0.0276$), on day 15 for HR ($p = 0.0159$), on day 53 for HR ($p = 0.0019$), on day 53 for temperature ($p = 0.0292$), on day 1 (0 h, before randomization) for RR ($p = 0.0495$), on day 1 (4 hours after drug administration) for RR ($p = 0.0183$), on day 29 (4 hours after drug administration) for RR ($p = 0.0431$), and at the inpatient stage: on day 27 for HR ($p = 0.0252$).

Differences in these parameters were deemed clinically insignificant because all volunteers had these parameters within the normal range. No AEs were recorded for these parameters.

Safety and tolerability

Safety and tolerability were assessed for all 110 volunteers who received a dose of the drug.

In groups 1 and 2 (3 mg dose), no cases of AEs were recorded. In groups 3 and 4 (14 mg dose), nausea was reported as an AE in 6 volunteers.

A total of 6 AEs were recorded in 6 volunteers during the study: 3 AEs were noted in 3 volunteers in group 3 (T2), and 3 AEs were noted in 3 volunteers in group 4 (R2).

All AEs recorded during the study were of mild severity. According to the investigators, the causal relationship with the use of the study drug / reference drug was assessed as "probable" in all cases. Analysis of the frequency of AE outcomes in volunteers showed that by the end of the study, "recovery without sequelae" was observed in all cases. In all cases of volunteers with recorded AEs, no treatment was administered.

All volunteers completed the study fully in accordance with the approved study protocol.

The investigator's assessment of the overall tolerability of the study drug / reference drug was conducted using a Likert scale. Tolerability of the study drug / reference drug at a dose of 3 mg was assessed as "good" in 100% of cases. Tolerability of the study drug / reference drug at a dose of 14 mg was also assessed as "good" in 90% of cases and "satisfactory" in 10% of cases. Tolerability of the study drug / reference drug at a dose of 14 mg on day 1 was assessed as "good" in 90% of cases and "satisfactory" in 10% of cases. On days 29 (24 hours after drug administration on day 28 and 4 hours after drug administration) and day 57, tolerability was assessed as "good" in 100% of cases.

No SAEs were identified during or after the study. There were no deaths.

No cases of pregnancy in study participants / sexual partners of study participants were recorded during or after the study.

Thus, the study drug Semaltara®, tablets (T), and the reference drug Rybelsus®, tablets (R), have a similar safety profile, including tolerability, at both the 3 mg and 14 mg doses.

DISCUSSION

The structure of semaglutide resembles native human GLP-1 with three key modifications: 1) substitution of alanine with alpha-aminoisobutyric acid at position 8, rendering it resistant to DPP-4 degradation; 2) addition of an 18-carbon chain to lysine at position 26, enhancing albumin binding and increasing half-life; 3) substitution of lysine with arginine at position 34, improving stability [20]. These modifications create a potent, long-acting GLP-1 analog. Oral administration of semaglutide faces bioavailability challenges due to its size and susceptibility to enzymatic degradation. Co-administration with SNAC improves absorption by buffering gastric pH, reducing pepsin activity, and increasing the lipophilicity of semaglutide itself. This allows semaglutide to cross the gastric membrane and enter the systemic circulation, functioning similarly to the subcutaneous form [21, 22].

Unlike most oral drugs, semaglutide is absorbed in the stomach, and its absorption is dependent on the amount of *N*-(8-[2-hydroxybenzoyl]amino) caprylate sodium (SNAC). Studies indicate that 300 mg of SNAC provides the highest plasma levels of semaglutide. Semaglutide and SNAC concentrations are highest near the absorption site in the stomach, decreasing significantly beyond 3 cm. This supports the local buffering effect of SNAC and the need for co-formulation and co-development of the drug product [21]. Oral semaglutide has lower bioavailability and higher inter-individual variability compared to the subcutaneous form, necessitating higher doses to achieve comparable results [23].

Clinical trial program results showed that oral doses of semaglutide 7 mg and 14 mg led to more pronounced improvements in Hb_{A1c} levels compared to sitagliptin, while the 3 mg dose did not show clinically significant benefit [24]. Food, rather than water, significantly reduces semaglutide absorption [21, 25]. Therefore, patients should fast before taking the medication and refrain from eating for at least 30 min after administration [21].

Semaglutide is metabolized via proteolytic cleavage by DPP-4 and neutral endopeptidases, followed by beta-oxidation of its fatty acid side chain [26]. The breakdown products are excreted in urine and feces, indicating renal and hepatic impairment [26, 27].

Pharmacokinetic studies show that oral semaglutide in combination with 300 mg SNAC has

similar pharmacokinetics to the subcutaneous form, irrespective of the presence of renal or hepatic insufficiency [23, 28].

Numerous clinical studies, including the SUSTAIN and PIONEER programs, have been conducted to evaluate the efficacy and safety of injectable and oral semaglutide in patients with diabetes. The SUSTAIN clinical trial program included Phase IIIA randomized controlled trials (SUSTAIN 1–5) to assess the efficacy and safety of weekly subcutaneous semaglutide administration in various groups of patients with type 2 DM, from drug-naïve individuals to those on oral antidiabetic drugs and/or insulin [29–33]. Additionally, SUSTAIN 7 compared semaglutide with dulaglutide, and SUSTAIN 6 focused on cardiovascular safety [34, 35]. The primary outcome in SUSTAIN 1–5 was the change in Hb_{A1c} from baseline to end of treatment. Semaglutide demonstrated significant and sustained reductions in Hb_{A1c} across all studies, ranging from -1.2% to -1.5% at a dose of 0.5 mg and -1.5% to -1.8% at a weekly dose of 1 mg. In SUSTAIN 7, semaglutide reduced Hb_{A1c} by -1.5% and -1.8% at doses of 0.5 mg and 1 mg, respectively, while dulaglutide reduced it by -1.1% and -1.4% at doses of 0.75 mg and 1.5 mg, respectively.

SUSTAIN 8 compared semaglutide (1.0 mg weekly) to canagliflozin (300 mg daily) in 788 patients over 52 weeks. Semaglutide resulted in a greater reduction in Hb_{A1c} (-1.5% vs. -1.1%) and more significant weight loss (-4.7 kg vs. -3.2 kg), demonstrating its superior efficacy in glycemic control and weight management [36].

SUSTAIN 9 evaluated the efficacy of semaglutide in 302 patients on insulin over 30 weeks. Hb_{A1c} levels decreased by -0.8% with semaglutide compared to placebo (+0.1%), and weight decreased by -2.0 kg compared to +0.2 kg with placebo. This study confirmed the role of semaglutide as an effective add-on therapy for patients on insulin [37].

SUSTAIN 10 compared semaglutide (1.0 mg weekly) to liraglutide (1.2 mg daily) in 577 patients over 30 weeks. Semaglutide provided a greater reduction in Hb_{A1c} (-1.7% vs. -1.0%) and more significant weight loss (-5.8 kg vs. -1.9 kg), highlighting its superior efficacy among GLP-1 receptor agonists [38].

Building on the success of injectable semaglutide trials, various clinical studies have been conducted to evaluate the efficacy and safety of oral semaglutide, providing valuable insights into its role as an innovative treatment option for patients with type 2 DM.

A Phase I study by C. Granhall et al. assessed

the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of oral semaglutide and the absorption enhancer SNAC in healthy volunteers and individuals with type 2 DM [39]. In a single-ascending dose study, various combinations of oral semaglutide (2–20 mg) and SNAC were tested to optimize absorption. Results showed that oral semaglutide exposure increased in a dose-dependent manner, with 300 mg of SNAC being the optimal dose. AEs, primarily gastrointestinal disorders and headaches, were mild but more frequent in the semaglutide group compared to placebo [39]. In a multiple-ascending dose study, 107 subjects (healthy and with type 2 DM) were given semaglutide (up to 40 mg) in conjunction with SNAC. Oral semaglutide exposure was similar in healthy individuals and patients with type 2 DM, leading to a significant reduction in Hb_{A1c} (1.5%) and body weight (up to 7.2 kg) after 10 weeks ($p < 0.001$). Most adverse events were mild, with gastrointestinal disorders being the most common [39]. Further pharmacokinetic studies found no consistent pattern of change in semaglutide exposure in patients with renal impairment, except for those with severe renal impairment, where exposure was lower [23].

A Phase II study by M. Davies et al. evaluated the efficacy of oral semaglutide compared to subcutaneous semaglutide for glycemic control in 632 patients with type 2 DM [40]. Participants were randomized into 9 groups, including various doses of oral semaglutide (2.5 mg to 40 mg), placebo, and subcutaneous semaglutide. The primary endpoint, Hb_{A1c} reduction, was achieved: with oral semaglutide 40 mg, the reduction was 1.8% compared to 0.3% in the placebo group ($p < 0.001$). Hb_{A1c} reduction was dose-dependent across all oral semaglutide groups, ranging from 0.4% to 1.6%. At 26 weeks, more participants achieved an Hb_{A1c} level below 7% with oral semaglutide, with rates increasing from 44% in the 2.5 mg group to 90% in the 40 mg group ($p < 0.001$ for all). All groups receiving oral semaglutide also experienced significant weight loss compared to placebo, with the 40 mg dose leading to a reduction of 6.9 kg ($p < 0.001$). No notable difference in weight loss was observed between the oral semaglutide 20 mg and 40 mg groups and the subcutaneous semaglutide group.

The global Phase III clinical trial program for oral semaglutide, PIONEER, comprises 12 clinical trials and involves 9542 patients with type 2 DM. The PIONEER program used two criteria for efficacy assessment:

the treatment policy criterion, which includes patients regardless of drug discontinuation or rescue medication use, and the study drug efficacy criterion, which assumes all patients continued treatment without rescue medication.

PIONEER 1, completed in February 2020, evaluated the safety and efficacy of oral semaglutide versus placebo in patients with type 2 DM treated with diet and exercise alone [41]. Participants (mean age 55 years, Hb_{A1c} = 7.0–9.5%) were randomized to receive 3 mg, 7 mg, or 14 mg of oral semaglutide or placebo for 26 weeks. All semaglutide doses significantly reduced Hb_{A1c} compared to placebo ($p < 0.001$). More participants achieved an Hb_{A1c} value $< 7\%$ with semaglutide (55.1%, 68.8%, 76.9%) compared to placebo (31%) ($p < 0.001$ for all). Reductions in fasting plasma glucose and body weight were more pronounced with semaglutide, particularly at the 14 mg dose, which showed a weight loss difference of -2.3 kg ($p < 0.001$). Higher doses also significantly increased lipase levels and heart rate.

In the PIONEER 2, oral semaglutide (14 mg once daily) was compared with empagliflozin (25 mg once daily) for 52 weeks in patients with type 2 DM with Hb_{A1c} levels from 7.0% to 10.5%, all of whom were taking metformin (≥ 1500 mg/day). At 26 weeks, oral semaglutide showed a greater reduction in Hb_{A1c} (-1.3%) compared to empagliflozin (-0.9%, $p < 0.0001$), with 47.4% of patients achieving an Hb_{A1c} level of $\leq 6.5\%$ vs. 17.2% in the empagliflozin group. These effects were maintained up to and including 52 weeks. Oral semaglutide also resulted in a significantly greater reduction in body weight ($> 10\%$) at both 26 weeks (12.5% vs 6.8%) and 52 weeks (15.0% vs 7.8%, $p = 0.0028$), confirming its superiority regarding Hb_{A1c} and weight reduction [42].

In the 78-week PIONEER 3, oral semaglutide (3 mg, 7 mg and 14 mg) was compared with sitagliptin (100 mg) in 1864 patients with type 2 DM not controlled by metformin, with or without sulfonylurea (mean age 58 years, Hb_{A1c} 7.0–10.5%). At 26 weeks, Hb_{A1c} reduction was more significant with oral semaglutide 14 mg (-1.3%) compared to sitagliptin (-0.8%), with 55% of patients in the 14 mg group achieving an Hb_{A1c} level of $< 7.0\%$ ($p < 0.001$). Fasting plasma glucose also improved with semaglutide 14 mg (-30.5 mg/dL) compared to sitagliptin (-15.4 mg/dL). By 78 weeks, semaglutide demonstrated a more significant reduction in fasting plasma glucose and body weight:

30% of the 14 mg group achieved $\geq 5\%$ weight loss by 26 weeks ($p < 0.001$) compared to 10% with sitagliptin, and 33% versus 12% by 78 weeks [24].

The PIONEER 4 was the first to compare oral semaglutide with another GLP-1 receptor agonist, subcutaneous liraglutide, in patients with type 2 DM treated with metformin, with or without an SGLT-2 inhibitor (mean age 55 years, Hb_{A1c} 7.0–9.5%). Dose escalation was performed in both groups. At 52 weeks, oral semaglutide showed a greater reduction in Hb_{A1c} (-1.6%) compared to liraglutide (-1.1% , $p = 0.0002$) and placebo (-0.2% , $p < 0.0001$). Furthermore, 43% of patients taking oral semaglutide achieved an Hb_{A1c} level of $\leq 6.5\%$, compared to 33% with liraglutide ($p = 0.0084$) and 4% with placebo ($p < 0.0001$). Oral semaglutide also led to greater weight loss than liraglutide or placebo, with 14% and 16% of patients achieving $\geq 10\%$ weight loss at 26 and 52 weeks, respectively. Semaglutide showed a more significant reduction in fasting plasma glucose compared to placebo ($p < 0.0001$), although no statistically significant difference was observed compared to liraglutide [43].

The PIONEER 5 and PIONEER 6 evaluated the efficacy of oral semaglutide in patients with type 2 DM and renal impairment, and assessed its cardiovascular safety in patients with type 2 DM with established cardiovascular disease, chronic kidney disease, or high cardiovascular risk.

The PIONEER 7 compared the safety and efficacy of flexible-dose oral semaglutide and sitagliptin in patients with type 2 DM ($Hb_{A1c} = 7.5$ – 9.5%). The study included 504 participants randomized to receive either dose-adjusted oral semaglutide (3 mg, 7 mg, or 14 mg) or sitagliptin 100 mg. At 52 weeks, 58% of patients in the semaglutide group achieved an Hb_{A1c} level of $< 7\%$ compared to 25% in the sitagliptin group ($p < 0.0001$). A significantly greater weight loss was observed with semaglutide, averaging -2.9 kg compared to -0.8 kg with sitagliptin ($p = 0.0065$). Fewer patients required additional therapy with semaglutide (3.2%) compared to sitagliptin (15.9%, $p < 0.0001$). Semaglutide outperformed sitagliptin in both Hb_{A1c} reduction and weight loss [44].

The PIONEER 8 evaluated the efficacy, safety, and tolerability of oral semaglutide (3 mg, 7 mg, 14 mg) compared to placebo in patients with type 2 DM receiving stable insulin therapy. At 26 weeks, semaglutide significantly reduced Hb_{A1c} by -0.6% ,

-0.9% , and -1.3% for the 3 mg, 7 mg, and 14 mg doses, respectively, compared to -0.1% in the placebo group ($p < 0.0001$). A greater proportion of patients achieved an Hb_{A1c} level of $< 7\%$ with semaglutide (58.4% at the 14 mg dose) compared to the placebo group (6.8%). Weight loss was dose-dependent, with a maximum reduction of -3.7 kg at the 14 mg dose ($p < 0.0001$). Symptomatic rescue medication use was less frequent in the semaglutide groups, and fewer patients required additional glucose-lowering agents compared to the placebo group. Additionally, semaglutide improved fasting lipid profiles and led to a slight increase in heart rate [45].

The PIONEER 9 evaluated the safety and efficacy of oral semaglutide versus subcutaneous liraglutide in Japanese patients with type 2 DM. The study included 243 patients randomized to receive oral semaglutide (3 mg, 7 mg or 14 mg), liraglutide (0.9 mg), or placebo. At 26 weeks, oral semaglutide resulted in Hb_{A1c} reductions of -1.1% , -1.6% , and -1.8% compared to -1.4% with liraglutide and -0.4% with placebo. At 52 weeks, an Hb_{A1c} level of $< 7.0\%$ was achieved by 80% of patients taking semaglutide 14 mg, compared to 49% with liraglutide. Greater weight loss was observed with semaglutide 14 mg (-2.8 kg) than with liraglutide ($+0.4$ kg) or placebo (-1.0 kg). Heart rate slightly increased in all GLP-1 receptor agonist groups [46].

In the PIONEER 10, an open-label, 52-week trial in Japan, oral semaglutide (3 mg, 7 mg, 14 mg) was compared to subcutaneous dulaglutide (0.75 mg) in patients with type 2 DM whose blood sugar was not controlled by a single oral antihyperglycemic agent. After 52 weeks, semaglutide 14 mg led to a greater reduction in Hb_{A1c} (-1.8%) compared to dulaglutide (-1.3%). An Hb_{A1c} level of $< 6.5\%$ was achieved by 21%, 43%, and 58% of patients taking semaglutide at doses of 3 mg, 7 mg, and 14 mg, respectively, vs. 41% of patients taking dulaglutide. Semaglutide 14 mg also resulted in greater weight loss (-1.9 kg), while dulaglutide caused weight gain ($+1.1$ kg) [47].

The PIONEER 11 evaluated the efficacy and safety of oral semaglutide versus placebo in a predominantly Chinese population with type 2 DM inadequately controlled by diet and exercise alone. The study was conducted across 52 centers, with 521 participants randomized to receive oral semaglutide (3 mg, 7 mg and 14 mg) or placebo for 26 weeks. The primary endpoint was the change in Hb_{A1c} , and the secondary endpoint was body weight. Semaglutide

significantly reduced Hb_{A1c} compared to placebo for all doses, with reductions ranging from -1.0% to -1.5% ($p < 0.001$). Weight loss was also significant for the 7 mg and 14 mg doses. Adverse events, primarily gastrointestinal, were more frequent in the semaglutide group but were mostly mild to moderate in severity. Similar results were observed in the Chinese subpopulation, which comprised 74.9% of the study participants [48].

The PIONEER 12 compared oral semaglutide with sitagliptin in Chinese patients with type 2 DM inadequately controlled by metformin for 26 weeks. Oral semaglutide (3 mg, 7 mg, and 14 mg) resulted in significantly greater reductions in Hb_{A1c} and body weight compared to sitagliptin. Hb_{A1c} reductions were -0.2%, -0.7%, and -1.0% for the semaglutide doses, while body weight reductions were -0.9 kg, -2.3 kg, and -3.3 kg. Most AEs with semaglutide were mild to moderate gastrointestinal disorders. Similar results were noted in the Chinese subpopulation [49]. However, it is likely that oral semaglutide demonstrated safety and non-inferior efficacy compared to subcutaneous semaglutide and other GLP-1 agonists in clinical trials. As the first oral GLP-1 receptor agonist, it offers an alternative for patients with type 2 DM who are apprehensive about injectable medications but struggle to achieve target Hb_{A1c} levels with existing oral agents.

In summary, the listed studies have demonstrated the efficacy and safety of oral semaglutide across diverse patient populations, including those with type 2 DM and various comorbidities, treatment regimens, and geographic regions. The SUSTAIN and PIONEER clinical trial programs provide extensive evidence of semaglutide's efficacy and safety, regardless of its administration route, whether

injectable or oral. The SUSTAIN studies showed significant reductions in Hb_{A1c} and weight loss with notable superiority over references such as dulaglutide and liraglutide. Semaglutide consistently outperformed alternative treatments in improving glycemic control, particularly in patient groups ranging from those with cardiovascular risk factors to those on insulin therapy. The PIONEER program further validated the effectiveness of oral semaglutide, offering a promising alternative to injectable therapy, especially for patients unwilling to use injections but needing to achieve glycemic targets. Both programs underscore semaglutide's potential to enhance treatment adherence, lower Hb_{A1c} levels, and promote weight loss across various patient profiles, thereby solidifying its role as a key advancement in type 2 DM management.

Study Limitations

The small sample size, due to the single-center design of the study, significantly increases the probability of underestimating the real clinical effect during the statistical interpretation of the results. Continuation of this clinical study, as well as conducting additional clinical and observational studies involving a larger number of patients and an increased observation period, will enhance the representativeness of the results of semaglutide use.

CONCLUSION

Thus, the clinical study conducted confirmed the bioequivalence and demonstrated a similar safety profile, including tolerability, of the study drug Semaltara®, tablets, and the reference drug Rybelsus®, tablets, at both 3 mg and 14 mg dosages.

FUNDING

The clinical study was supported by LLC PROMOMED RUS (Russia). 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

Alexander S. Ametov, Larisa A. Balykova — conceptualization, data analysis, writing—review & editing; Igor E. Shokhin — investigation, data analysis, visualization; Kira Ya. Zaslavskaya — investigation, data analysis, visualization, writing—original draft; Ekaterina A. Rogozhina — methodology, investigation, data analysis;

Tatiana G. Bodrova — investigation data analysis, writing—original draft; Larina A. Zorina — conceptualization, data analysis, writing—original draft; Victoria S. Scherbakova — data analysis, writing—original draft; Denis V. Kurkin — data analysis, writing—original draft; Ksenya N. Koryanova — data analysis, writing—original draft; Ekaterina S. Mishchenko — working with data, writing—original draft; Maxim L. Maksimov — data analysis, writing—original draft; Alexander V. Matveev — data analysis, writing—original draft; Larisa I. Shcherbakova — data analysis, writing—original draft; Irina N. Dyakova — data analysis, writing—original draft; Evgeny D. Kozlov — data analysis, writing—review & editing; Dmitry N. Andreev — conceptualization, writing—original draft; Yuri G. Kazaishvili — conceptualization, writing—original draft; Sergey M. Noskov — conceptualization, writing—original draft. Petr A. Bely — conceptualization, working with data, writing—original draft.

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 diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet*. 2024;404(10467):2077–2093. DOI: 10.1016/S0140-6736(24)02317-1. Erratum in: *Lancet*. 2025;405(10485):1146. DOI: 10.1016/S0140-6736(25)00620-8
2. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2023;402(10397):203–34. DOI: 10.1016/S0140-6736(23)01301-6 Erratum in: *Lancet*. 2023;402(10408):1132. DOI: 10.1016/S0140-6736(23)02044-5 Erratum in: *Lancet*. 2025;405(10474):202. DOI: 10.1016/S0140-6736(25)00053-4
3. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr*. 2010;8:29. DOI: 10.1186/1478-7954-8-29
4. Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. *Lancet Diabetes Endocrinol*. 2018;6(1):69–80. DOI: 10.1016/S2213-8587(17)30186-9
5. Abel ED, Gloyn AL, Evans-Molina C, Joseph JJ, Misra S, Pajvani UB, Simcox J, Susztak K, Drucker DJ. Diabetes mellitus-Progress and opportunities in the evolving epidemic. *Cell*. 2024;187(15):3789–3820. DOI: 10.1016/j.cell.2024.06.029
6. Strati M, Moustaki M, Psaltopoulou T, Vryonidou A, Paschou SA. Early onset type 2 diabetes mellitus: an update. *Endocrine*. 2024;85(3):965–78. DOI: 10.1007/s12020-024-03772-w.
7. Farilla L, Hui H, Bertolotto C, Kang E, Bulotta A, Di Mario U, Perfetti R. Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. *Endocrinology*. 2002;143(11):4397–408. DOI: 10.1210/en.2002-220405
8. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab*. 2016;18(4):317–32. DOI: 10.1111/dom.12596
9. Lim GE, Huang GJ, Flora N, LeRoith D, Rhodes CJ, Brubaker PL. Insulin regulates glucagon-like peptide-1 secretion from the enteroendocrine L cell. *Endocrinology*. 2009;150(2):580–91. DOI: 10.1210/en.2008-0726
10. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes. *Circulation*. 2022;146(24):1882–94. DOI: 10.1161/CIRCULATIONAHA.122.059595
11. Nauck MA, Meier JJ. MANAGEMENT OF ENDOCRINE DISEASE: Are all GLP-1 agonists equal in the treatment of type 2 diabetes? *Eur J Endocrinol*. 2019;181(6):R211–R234. DOI: 10.1530/EJE-19-0566
12. Dungan KM, Povedano ST, Forst T, González JG, Atisso C, Sealls W, Fahrbach JL. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349–57. DOI: 10.1016/S0140-6736(14)60976-4. Erratum in: *Lancet*. 2014;384(9951):1348.
13. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, Annett MP, Aroda VR. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care*. 2018;41(2):258–66. DOI: 10.2337/dc17-0417
14. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab*. 2020;46(2):100–9. DOI: 10.1016/j.diabet.2019.101117
15. Shestakova MV. Liraglutid – возможности комплексного терапевтического подхода в терапии SD 2 типа. *Diabetes mellitus*. 2009;12(5):3–6. DOI: 10.14341/2072-0351-5807. EDN: QIZFNH

16. Kurkin DV, Bakulin DA, Morkovin EI, Petrov VI, Strygin AV, Koryanova KN, Gorbunova YuV, Kolosov YuA, Ivanova OV, Pavlova EV, Dzhavakhyan MA, Zaborovsky AV, Saparova VB, Makarenko IE, Draï RI, Chumachenko AN. Physiology and pharmacology of glucagon-like peptide-1 receptor. *Pharmacy & Pharmacology*. 2023;11(4):347–80. DOI: 10.19163/2307-9266-2023-11-4-347-380. EDN: XFDHKA
17. Ametov AS, Shokhin IE, Rogozhina EA, Bodrova TG, Nevretdinova ME, Bely PA, Zaslavskaya KYa, Scherbakova VS, Kurkin DV, Koryanova K.N, 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):324–46. DOI: 10.19163/2307-9266-2023-11-4-324-346. EDN: PABLBC
18. Chincholkar A, Khobragade D, Pathak S. US FDA Regulatory Framework for Generic Peptides Referring to rDNA Origin Reference Products. *J Pharm Res Int*. 2022;34(41A):44–9. DOI: 10.9734/jpri/2022/v34i41A36276
19. Młynarska E, Czarnik W, Dzieża N, Jędraszak W, Majchrowicz G, Prusinowski F, Stabrawa M, Rysz J, Franczyk B. Type 2 Diabetes Mellitus: New Pathogenetic Mechanisms, Treatment and the Most Important Complications. *Int J Mol Sci*. 2025;26(3):1094. DOI: 10.3390/ijms26031094
20. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, Madsen K, Knudsen LB, McGuire J, Steensgaard DB, Strauss HM, Gram DX, Knudsen SM, Nielsen FS, Thygesen P, Reedtz-Runge S, Kruse T. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. *J Med Chem*. 2015;58(18):7370–80. DOI: 10.1021/acs.jmedchem.5b00726
21. Buckley ST, Bækdal TA, Vegge A, Maarbjerg SJ, Pyke C, Ahnfelt-Rønne J, Madsen KG, Schéele SG, Alanentalo T, Kirk RK, Pedersen BL, Skyggebjerg RB, Benie AJ, Strauss HM, Wahlund PO, Bjerregaard S, Farkas E, Fekete C, Søndergaard FL, Borregaard J, Hartoft-Nielsen ML, Knudsen LB. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. *Sci Transl Med*. 2018;10(467):eaar7047. DOI: 10.1126/scitranslmed.aar7047
22. Twarog C, Fattah S, Heade J, Maher S, Fattal E, Brayden DJ. Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C₁₀). *Pharmaceutics*. 2019;11(2):78. DOI: 10.3390/pharmaceutics11020078
23. Granhall C, Søndergaard FL, Thomsen M, Anderson TW. Pharmacokinetics, Safety and Tolerability of Oral Semaglutide in Subjects with Renal Impairment. *Clin Pharmacokinet*. 2018;57(12):1571–80. DOI: 10.1007/s40262-018-0649-2
24. Rosenstock J, Allison D, Birkenfeld AL, Blicher TM, Deenadayalan S, Jacobsen JB, Serusclat P, Violante R, Watada H, Davies M; PIONEER 3 Investigators. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. *JAMA*. 2019;321(15):1466–80. DOI: 10.1001/jama.2019.2942
25. Bækdal TA, Breitschaft A, Donsmark M, Maarbjerg SJ, Søndergaard FL, Borregaard J. Effect of Various Dosing Conditions on the Pharmacokinetics of Oral Semaglutide, a Human Glucagon-Like Peptide-1 Analogue in a Tablet Formulation. *Diabetes Ther*. 2021;12(7):1915–27. DOI: 10.1007/s13300-021-01078-y
26. Jensen L, Helleberg H, Roffel A, van Lier JJ, Bjørnsdóttir I, Pedersen PJ, Rowe E, Derving Karsbøl J, Pedersen ML. Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. *Eur J Pharm Sci*. 2017;104:31–41. DOI: 10.1016/j.ejps.2017.03.020
27. Jensen L, Kupcova V, Arold G, Pettersson J, Hjerpstet JB. Pharmacokinetics and tolerability of semaglutide in people with hepatic impairment. *Diabetes Obes Metab*. 2018;20(4):998–1005. DOI: 10.1111/dom.13186
28. Bækdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, Safety, and Tolerability of Oral Semaglutide in Subjects With Hepatic Impairment. *J Clin Pharmacol*. 2018;58(10):1314–23. DOI: 10.1002/jcph.1131
29. Sorli C, Harashima SI, Tsoukas GM, Unger J, Karsbøl JD, Hansen T, Bain SC. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(4):251–60. DOI: 10.1016/S2213-8587(17)30013-X
30. Ahrén B, Masmiquel L, Kumar H, Sargin M, Karsbøl JD, Jacobsen SH, Chow F. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol*. 2017;5(5):341–54. DOI: 10.1016/S2213-8587(17)30092-X
31. Ahmann AJ, Capehorn M, Charpentier G, Dotta F, Henkel E, Lingvay I, Holst AG, Annett MP, Aroda VR. Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial. *Diabetes Care*. 2018;41(2):258–266. DOI: 10.2337/dc17-0417
32. Aroda VR, Bain SC, Cariou B, Piletič M, Rose L, Axelsen M, Rowe E, DeVries JH. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol*. 2017;5(5):355–66. DOI: 10.1016/S2213-8587(17)30085-2
33. Rodbard HW, Lingvay I, Reed J, de la Rosa R, Rose L, Sugimoto D, Araki E, Chu PL, Wijayasinghe N, Norwood P. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial. *J Clin Endocrinol Metab*. 2018;103(6):2291–301. DOI: 10.1210/jc.2018-00070

34. Pratley RE, Aroda VR, Lingvay I, Lüdemann J, Andreassen C, Navarria A, Viljoen A; SUSTAIN 7 investigators. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol.* 2018;6(4):275–86. DOI: 10.1016/S2213-8587(18)30024-X
35. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834–44. DOI: 10.1056/NEJMoa1607141
36. Lingvay I, Catarig AM, Frias JP, Kumar H, Lausvig NL, le Roux CW, Thielke D, Viljoen A, McCrimmon RJ. Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2019;7(11):834–44. DOI: 10.1016/S2213-8587(19)30311-0
37. Zinman B, Bhosekar V, Busch R, Holst I, Ludvik B, Thielke D, Thrasher J, Woo V, Philis-Tsimikas A. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2019;7(5):356–367. DOI: 10.1016/S2213-8587(19)30066-X Erratum in: *Lancet Diabetes Endocrinol.* 2019;7(5):e5. DOI: 10.1016/S2213-8587(19)30109-3. Erratum in: *Lancet Diabetes Endocrinol.* 2019;7(8):e20. DOI: 10.1016/S2213-8587(19)30220-7 Erratum in: *Lancet Diabetes Endocrinol.* 2019;7(11):e22. DOI: 10.1016/S2213-8587(19)30323-7
38. Capehorn MS, Catarig AM, Furberg JK, Janez A, Price HC, Tadayon S, Vergès B, Marre M. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1-3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). *Diabetes Metab.* 2020;46(2):100–9. DOI: 10.1016/j.diabet.2019.101117
39. Granhall C, Donsmark M, Blicher TM, Golor G, Søndergaard FL, Thomsen M, Bækdal TA. Safety and Pharmacokinetics of Single and Multiple Ascending Doses of the Novel Oral Human GLP-1 Analogue, Oral Semaglutide, in Healthy Subjects and Subjects with Type 2 Diabetes. *Clin Pharmacokinet.* 2019;58(6):781–91. DOI: 10.1007/s40262-018-0728-4
40. Davies M, Pieber TR, Hartoft-Nielsen ML, Hansen OKH, Jabbour S, Rosenstock J. Effect of Oral Semaglutide Compared With Placebo and Subcutaneous Semaglutide on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. *JAMA.* 2017;318(15):1460–1470. DOI: 10.1001/jama.2017.14752
41. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, Jeppesen OK, Christiansen E, Hertz CL, Haluzik M; PIONEER 1 Investigators. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. *Diabetes Care.* 2019;42(9):1724–32. DOI: 10.2337/dc19-0749
42. Rodbard HW, Rosenstock J, Canani LH, Deerochanawong C, Gumprecht J, Lindberg SØ, Lingvay I, Søndergaard AL, Treppendahl MB, Montanya E; PIONEER 2 Investigators. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. *Diabetes Care.* 2019;42(12):2272–81. DOI: 10.2337/dc19-0883
43. Pratley R, Amod A, Hoff ST, Kadowaki T, Lingvay I, Nauck M, Pedersen KB, Saugstrup T, Meier JJ; PIONEER 4 investigators. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet.* 2019;394(10192):39–50. DOI: 10.1016/S0140-6736(19)31271-1 Erratum in: *Lancet.* 2019;394(10192):e1. DOI: 10.1016/S0140-6736(19)31519-3
44. Pieber TR, Bode B, Mertens A, Cho YM, Christiansen E, Hertz CL, Wallenstein SOR, Buse JB; PIONEER 7 investigators. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes Endocrinol.* 2019;7(7):528–539. DOI: 10.1016/S2213-8587(19)30194-9 Erratum in: *Lancet Diabetes Endocrinol.* 2019;7(9):e21. DOI: 10.1016/S2213-8587(19)30247-5
45. Zinman B, Aroda VR, Buse JB, Cariou B, Harris SB, Hoff ST, Pedersen KB, Tarp-Johansen MJ, Araki E; PIONEER 8 Investigators. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. *Diabetes Care.* 2019;42(12):2262–71. DOI: 10.2337/dc19-0898
46. Yamada Y, Katagiri H, Hamamoto Y, Deenadayalan S, Navarria A, Nishijima K, Seino Y; PIONEER 9 investigators. Dose-response, efficacy, and safety of oral semaglutide monotherapy in Japanese patients with type 2 diabetes (PIONEER 9): a 52-week, phase 2/3a, randomised, controlled trial. *Lancet Diabetes Endocrinol.* 2020;8(5):377–91. DOI: 10.1016/S2213-8587(20)30075-9
47. Yabe D, Nakamura J, Kaneto H, Deenadayalan S, Navarria A, Gislum M, Inagaki N; PIONEER 10 Investigators. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. *Lancet Diabetes Endocrinol.* 2020;8(5):392–406. DOI: 10.1016/S2213-8587(20)30074-7
48. Wang W, Bain SC, Bian F, Chen R, Gabery S, Huang S, Jensen TB, Luo B, Yuan G, Ning G; PIONEER 11 investigators. Efficacy and safety of oral semaglutide monotherapy vs placebo in a predominantly Chinese population with type 2 diabetes (PIONEER 11): a double-blind, Phase IIIa, randomised trial. *Diabetologia.* 2024;67(9):1783–99. DOI: 10.1007/s00125-024-06142-3
49. Ji L, Agesen RM, Bain SC, Fu F, Gabery S, Geng J, Li Y, Lu Y, Luo B, Pang W, Tao Y; PIONEER 12 investigators. Efficacy and safety of oral semaglutide vs sitagliptin in a predominantly Chinese population with type 2 diabetes uncontrolled with metformin: PIONEER 12, a double-blind, Phase IIIa, randomised trial. *Diabetologia.* 2024;67(9):1800–16. DOI: 10.1007/s00125-024-06133-4

AUTHORS

Alexander S. Ametov — Doctor of Sciences (Medicine), Professor, Head of the Department of Endocrinology, Head of the UNESCO Network Department on the topic “Bioethics of Diabetes Mellitus as a global problem”, Russian Medical Academy of Continuing Professional Education; Honored Scientist of the Russian Federation. ORCID ID: 0000-0002-7936-7619. E-mail: alexander.ametov@gmail.com

Larisa A. Balykova — Doctor of Sciences (Medicine), Professor, Head of the Department of Pediatrics, Corresponding Member of the Russian Academy of Sciences, Director of the Medical Institute, National Research Ogarev Mordovia State University; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0002-2290-0013. E-mail: larisabalykova@yandex.ru

Kira Ya. Zaslavskaya — Assistant of the Department of Biological and Pharmaceutical Chemistry with the course of organization and management of pharmacy, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-7348-9412. E-mail: kiryonok@yandex.ru

Igor E. Shokhin — Doctor of Sciences (Pharmacy), General Director, Center for Pharmaceutical Analytics LLC, Moscow, Russia. ORCID ID: 0000-0002-1185-8630. E-mail: i.shohin@cpha.ru

Ekaterina A. Rogozhina — PhD candidate of the Department of Biotechnology and Industrial Pharmacy of MIREA, Russian Technological University. ORCID ID: 0000-0002-3325-2605. E-mail: e.kate.rogozhina@gmail.com

Tatiana G. Bodrova — PhD candidate of the Scientific and Educational Institute of Pharmacy n.a. K.M. Lakin, Russian University of Medicine. ORCID ID: 0009-0001-0881-4880. E-mail: btatg@mail.ru

Larisa A. Zorina — Candidate of Sciences (Medicine), clinical pharmacologist, obstetrician-gynecologist, dietitian, lecturer of the Department of Therapy, Geriatrics, and Anti-Aging Medicine, Federal Scientific and Clinical Center for Specialized Types of Medical Care and Medical Technologies. ORCID ID: 0009-0006-4544-5486. E-mail: slarisa@bk.ru

Victoria S. Scherbakova — Candidate of Sciences (Biology), Assistant Professor of the Department of Pharmacology, Tver State Medical University. ORCID: 0000-0002-7251-8744. E-mail: victoria_kaptar@mail.ru

Denis V. Kurkin — Doctor of Sciences (Pharmacy),

Assistant Professor, Director of the Scientific and Educational Institute of Pharmacy n.a. K.M. Lakin, Russian University of Medicine; Professor of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University. ORCID ID: 0000-0002-1116-3425. E-mail: strannik986@mail.ru

Ksenia N. Koryanova — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Pharmacy, Faculty of Postgraduate Education of the Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University; Assistant Professor of the Department of Pharmacy, General Pharmacology and Pharmaceutical Consulting of the Russian Medical Academy of Continuing Professional Education. ORCID ID: 0000-0003-1571-9301. E-mail: kskor-16@mail.ru

Ekaterina S. Mishchenko — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Toxicological and Analytical Chemistry, Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University. ORCID ID: 0000-0001-7778-8391. E-mail: ekaterina-mischenko1809@mail.ru

Maxim L. Maximov — Doctor of Sciences (Medicine), Professor, Dean of the Faculty of Preventive Medicine and Healthcare Organization, Head of the Department of Pharmacy, General Pharmacology and Pharmaceutical Consulting, Russian Medical Academy of Continuing Professional Education. ORCID ID: 0000-0002-8979-8084. E-mail: maksim_maksimov@mail.ru

Alexander V. Matveev — Candidate of Sciences (Medicine), Assistant Professor, Assistant Professor of the Department of Clinical Pharmacology and Therapy named after Academician B. E. Votchal, Russian Medical Academy of Continuous Professional Education. ORCID ID: 0000-0002-6636-3950. E-mail: avmcsmu@gmail.com

Larisa I. Shcherbakova — Candidate of Sciences (Pharmacy), Assistant Professor, Deputy Director for Educational Work, Head of the Department of Inorganic, Physical and Colloidal Chemistry, Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University. ORCID ID: 0000-0002-7806-2805. E-mail: shcherbakovali@mail.ru

Irina N. Dyakova — Candidate of Sciences (Pharmacy), Assistant Professor, Head of the Department of Biology and Physiology, Acting Dean of the Faculty of Postgraduate Education, Pyatigorsk Medical and Pharmaceutical Institute — branch of

Volgograd State Medical University. ORCID ID: 0009-0002-9522-7605. E-mail: irochkadyakova@mail.ru

Evgeny D. Kozlov — senior lecturer of the Department of Outpatient Therapy of the Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0000-0001-8373-6109. E-mail: dr.kozlov@yandex.ru

Dmitry N. Andreev — Candidate of Sciences (Medicine), Assistant Professor, Assistant Professor of the Department of Propaedeutics of Internal Diseases and Gastroenterology, Russian University of Medicine. ORCID ID: 0000-0002-4007-7112. E-mail: dna-mit8@mail.ru

Yuri G. Kazaishvili — Candidate of Sciences

(Biology), Assistant Professor of the Department of Pharmacology, Tver State Medical University. ORCID ID: 0000-0003-0826-4177. E-mail: ykaza87@icloud.com

Sergey M. Noskov — Doctor of Sciences (Medicine), Professor, Head of the Department of Hospital Therapy, Yaroslavl State Medical University; internist, Chief Researcher, Clinical Hospital No. 3, Yaroslavl, Russia. ORCID ID: 0000-0003-3456-9409. E-mail: Noskov03@gmail.com

Petr A. Bely — Doctor of Sciences (Medicine), Professor of the Department of Internal Medicine and Gastroenterology, Russian University of Medicine. ORCID ID: 0000-0001-5998-4874. E-mail: pbely@ncpharm.ru