A REPRODUCED COMBINATION OF IVACAFTOR AND LUMACAFTOR, CFTR PROTEIN MODULATORS. ETHICAL AND PHARMACOKINETIC ASPECTS

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The lack of effective and affordable therapies for rare diseases is an important ethical issue. One example is cystic fibrosis (CF), a chronic, progressive disease characterized by an impaired function of all exocrine glands. The combination of ivacaftor and lumacaftor (CFTR potentiator and corrector) should lead to a sufficient level of protein on the cell surface and to an increase in its activity, thereby correcting the impaired function. Development of a generic drug containing ivacaftor and lumacaftor as active pharmaceutical substances will increase the availability of this medication and improve patient survival. To study comparative pharmacokinetics and bioequivalence of drugs containing ivacaftor and lumacaftor in healthy volunteers. It was conducted as an open-label, randomized, crossover bioequivalence study involving a single intake of the drug during each period under fed condition in healthy male and female volunteers. The conclusion about bioequivalence was made if 90% confidence interval for primary pharmacokinetic parameters (C_{max}, AUC_{0-t}) fell within the accepted bioequivalence limits of 80–125%. According to the results of the study, it was shown that the values of 90% CI of the geometric mean of the main pharmacokinetic parameters for ivacaftor and lumacaftor fall within the acceptance limits for bioequivalence. According to the applied criteria, the drugs are bioequivalent, which makes it possible to recommend the investigational drug to the Ministry of Health of the Russian Federation for obtaining the registration status.

Key words: bioequivalence, cystic fibrosis, CFTR, pharmacokinetics, ethics

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Author contribution: Arefeva AN and Radaeva KS conceived of the presented article. Arefeva AN conceived and planned the trial. Radaeva KS wrote the manuscript with input from all authors. Arefeva AN and Noskov SM collected and processed data. Radaeva KS conducted a comprehensive review of the existing literature on the topic. Arefeva AN analysed data. All authors edited the paper and contributed to the final manuscript.

Compliance with ethical standards: the condition for conducting the clinical trial was authorization from the Ministry of Health of the Russian Federation No. 212 dated 04/17/2023 and approval of the study by Independent Ethics Committee (excert from the meeting protocol of the Ethics Committee No. 325 dated 01/17/2023). All the essential trial documents (protocol GP30511-P4–01–01, Investigator’s Brochure, written information given to trial subjects and informed consent form, volunteer life and health insurance certificate) were provided and approved by the Independent Ethics Committee (IEC) of the research center according to the procedures of this committee. The researchers are obliged not to disclose personal and medical data of the subjects. Prior to the start of any trial procedures, an informed consent procedure was carried out in accordance with the principles of the Declaration of Helsinki, ICH recommendations and national regulatory standards. Each volunteer included in the study was insured and must have received an original insurance certificate.

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ВОСПРОИЗВЕДЕННАЯ КОМБИНАЦИЯ МОДУЛЯТОРОВ БЕЛКА CFTR — ИВАКАФТОРА И ЛУМАКАФТОРА. ЭТИЧЕСКИЕ И ФАРМАКОКИНЕТИЧЕСКИЕ АСПЕКТЫ

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Отсутствие эффективной и доступной терапии для редких заболеваний является важной этической проблемой. Одним из примеров является муковисцидоз (МВ) — хроническое, прогрессирующее заболевание, характеризующееся нарушением функции всех экзокринных желез. Комбинация ивакафтора и лумакафтора (потенциатора и корректора CFTR) должна приводить к достаточному уровню белка на поверхности клетки и к увеличению его активности, тем самым корректируя нарушенную функцию. Разработка воспроизведенного препарата, содержащего в качестве активных фармацевтических субстанций ивакафтор и лумакафтор, позволит увеличить доступность данного препарата и улучшить выживаемость пациентов. Изучение сравнительной фармакокинетики и биоэквивалентности препаратов, содержащих ивакафтор и лумакафтор у здоровых добровольцев. Данное исследование проводилось как открытое, рандомизированное, перекрестное исследование биоэквивалентности с однократным приемом препарата после еды у здоровых добровольцев обоих полов. Вывод о биоэквивалентности был сделан, если при оценке 90% доверительных интервалов для первичных фармакокинетических параметров (C_{max}, AUC_{0-t}) они находились в принятых границах биоэквивалентности 80–125%. По результатам исследования было показано, что значения 90% ДИ для отношений геометрических средних основных фармакокинетических параметров для ивакафтора и лумакафтора укладываются в допустимые пределы биоэквивалентности. Согласно применяемым критериям, препараты являются биоэквивалентными, что позволяет рекомендовать тестируемый препарат в МЗ РФ для получения регистрационного статуса.

Ключевые слова: биоэквивалентность, муковисцидоз, CFTR, фармакокинетика, этика

Финансирование: исследование финансировалось ООО «ГЕРОФАРМ».

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Соблюдение этических стандартов: условием для проведения клинического исследования являлись Разрешение МЗ РФ № 212 от 17.04.2023 и одобрение исследования Советом по этике (выписка из протокола заседания Совета по этике № 325 от 17.01.2023). Все основные документы исследования (протокол GP30511-P4-01-01, брошюра исследователя, информационный листок здорового добровольца и форма информированного согласия, документы по страхованию жизни и здоровья добровольцев) были предоставлены и одобрены Независимым этическим комитетом (НЭК) исследовательского центра, согласно процедурам этого комитета. Исследователи взяли на себя обязанность неразглашения личных и медицинских данных субъектов. До начала любых процедур исследования была проведена процедура получения информированного согласия, которая соответствовала принципам Хельсинской декларации, правилам ICH и национальным регуляторным стандартам. Каждый доброволец, включенный в исследование, был застрахован и обязательно получил оригинал полиса страхования.

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One of the important ethical dilemmas is the lack of effective and safe therapy for orphan diseases [1]. Although rare diseases occur individually with a low frequency, they collectively affect a significant part of the population. Due to the low prevalence, patients with orphan diseases experience many difficulties related to both the severity of the disease and the lack or low availability of appropriate treatment. When combined, these factors infringe on the right of such patients to receive qualitative medical care and thereby exacerbate inequality and vulnerability of affected patients, which is unacceptable from the perspective of medical ethics. Cystic fibrosis (CF) is an example of such a disease. CF is a chronic, progressive autosomal recessive disorder associated with impaired transport and secretion of chlorine ions, which leads to a change in the electrolyte composition and dehydration of the secretion of the endocrine glands. CF is characterized by damage to all exocrine glands and other vital organs and systems. Currently, one in 9,000 newborns in the Russian Federation (RF) is diagnosed with CF and, according to the registry, there are about 4,000 patients with this pathology in the RF [2].

The disease is developed due to mutations in the gene of the *Cystic Fibrosis Transmembrane Conduction Regulator (CFTR)* protein. More than 2,000 types of mutations have been currently identified. The most prevalent mutation in the RF is a deletion within the reading frame, leading to the loss of phenylalanine at position 508 in the *CFTR* — F508del *protein*. This mutation occurs in 52.79% of cases and, according to some data, at least one copy of it has been registered in about 90% of patients with cystic fibrosis [3]. This mutation belongs to type II mutations and results in abnormalities in protein processing, localization and transport to the apical membrane of cells [3, 4].

Conventional approaches of CF therapy are mainly focused on addressing the underlying symptoms. Pancreatic insufficiency is well compensated by enzyme substitution therapy and adherence to a specialized high-calorie diet [5]. The bronchopulmonary process is treated with antibacterial, including inhaled kinesitherapy methods, used to improve the drainage of secretions in the distal parts of respiratory tract, mucolytic drugs, inhaled bronchodilators, and in some cases — hormonal therapy with glucocorticosteroids are also used. The discovery of molecules that modulate the CFTR activity marked a new era in the treatment of CF, since this is the first option to therapeutically target a defective CFTR protein, rather than treating complications caused by the absence or reduced CFTR function [6].

The combination of CFTR modulators ivacaftor and lumacaftor belongs to the drugs of pathogenetic therapy of CF. Ivacaftor, which is a *CFTR* potentiator, increases the activity of the protein delivered to the cell surface, which enhaces ion transport. Lumacaftor, which is a *CFTR* corrector, facilitates cellular processing and *CFTR* transportation that increase the amount of protein on the cell surface. The combination should lead to a sufficient level of protein on the cell surface and increase in its activity. Thus, these effects are intended to correct disorders caused by the F508del mutation. It is believed that if the combination has a sufficiently strong effect on *F508del*, then the presence of at least one such allele will be sufficient to obtain a significant clinical benefit [7].

Pathogenetic therapy is aimed to address the unmet needs of patients with cystic fibrosis. However, ethical concerns emerge due to excessively high prices of novel drugs for orphan diseases, making life-saving medicines inaccessible to patients [8]. Although high prices may be justified by the cost of new drug development and the limited market size in case of rare diseases, this circumstance is associated with a decreased adherence to treatment and leads to significant inequalities in access to the drugs. This violates the fundamental principle of medical ethics that consists in ensuring equality and justice in the provision of medical care. Like patients with more common diseases, patients with rare diseases benefit from lower prices for medicines due to appearance of generics. Generic drugs are about 80–85% cheaper than innovative ones, so their proper administration by clinical specialists can significantly reduce the cost of treating patients in need [9]. However, generic drugs will be affordable only if a sufficient number of drugs enter the market to ensure strong price competition. According to previous researches, introduction of one generic competitor to the market leads to a reduction in the price of drugs by about 10–15%. At the same time, in order to reduce the price by 50 percent or more, 4 or more generic drugs should be available on the market [10]. Drugs for the treatment of orphan diseases may not sufficiently compete with generics, since manufacturers of reproduced drugs often prefer drugs for the treatment of more common diseases. In this regard, development of as many generic drugs as possible to treat rare diseases makes a significant contribution to solving the ethical problem of limited patient access to therapy.

In addition, there is no need in an extensive program of preclinical and clinical trials (CT) similar to those conducted with respect to the original drug in order to register reproduced drugs. This approach is more ethical, as it reduces the number of subjects required for the study and duration of their participation in CT. Also, the reduced number of the conducted CT is justified from the perspective of economic efficiency. It ensures the maximum reduction of time required for registration and market launch of the drug. This makes it possible to ensure and maintain rapid access of patients to effective and safe therapy. It also reduces the risks associated with the possible termination of the original drug supply in the case of foreign manufacturers.

GP30511 tested in this study belongs to the reproduced drug (generics) containing ivacaftor and lumacaftor as active pharmaceutical substances. Today, patients and representatives of the medical community have prejudices about the lower effectiveness and safety of generic drugs in relation to original ones, and manufacturing companies sometimes use unethical ways to promote original drugs on the market. Despite this, the reproduced medicines can help meet existing medical needs by increasing the availability of drugs, which is correct from an ethical point of view [11, 12]. Increased access to effective and safe medicines will lead to an increase in the number of patients receiving appropriate treatment, earlier initiation of therapy in accordance with clinical recommendations, and a more reliable continuity of treatment.

The aim of this study was to investigate the comparative pharmacokinetics and bioequivalence of drugs containing ivacaftor and lumacaftor in healthy volunteers. Additionally, safety and tolerability of the studied drugs were evaluated as part of the study.

Clinical research is necessary to develop medical knowledge and improve the quality of patient care. By publishing the results of clinical trials, researchers contribute to the collective understanding of treatment methods and the results of their application. This sharing of information allows other researchers to rely on the existing knowledge and improve the

overall standards of research and patient care. Publishing the results of clinical trials is an ethical imperative that supports development of medical science, promotes transparency and prioritizes patients safety and well-being.

PATIENTS AND METHODS

The study population

Since the main objective of this study was to study the pharmacokinetic parameters of the tested drugs in order to prove their bioequivalence, a homogeneous population of healthy volunteers was selected to ensure the experimental purity and to obtain the most reliable data. The study population included healthy male and female volunteers aged 18–45 years with a body mass index of 18.5–29.9 kg/m^2, who agreed to comply with adequate method of contraception and restrictions imposed by the study protocol. Compliance with the criteria was established based on the collection of a medical history, physical examination and instrumental and laboratory examinations, which included electrocardiography, complete blood count, biochemical blood assay, urinalysis and serological tests for hepatitis C (antibodies) and hepatitis B (surface antigen and antibodies), HIV (antibodies to HIV-1/2) and syphilis (antibodies to *Treponema pallidum*). Also, all subjects underwent tests for pregnancy (for female participants), alcohol, cotinine, drug use and abuse of potent medicinal substances. During their stay at the research center, the volunteers had a monotonous diet. No strenuous activities, nicotine-containing products, medicines and bioactive additives, vitamins, foods and beverages that can affect metabolism were allowed during the entire study period. Before being included in the study, all subjects were explained all the restrictions imposed by the study and their rights, the volunteers were familiarized with the information sheet of the study subject and signed an informed consent form.

Investigational drugs

The investigational drug GP30511, containing ivacaftor and lumacaftor in the dose of 125 and 200 mg consequently as film-coated tablets, was produced by GEROPHARM LLC, Russia. The reference drug was the same dose of Orkambi®, produced by Vertex Pharmaceuticals Limited, Ireland. The investigational drugs were taken orally by subjects at a dose of 250+400 mg (2 film-coated tablets each) after a standardized high-calorie breakfast with 200 ml of still water at room temperature. Administration of the investigational drugs at the indicated doses is safe for subjects, does not exceed the maximum single and therapeutic doses and allows to provide the concentrations of ivacaftor and lumacaftor necessary for assessment of pharmacokinetic profiles with a minimal risk for healthy volunteers. This correlates with the literature data on already conducted studies of the combination and does not contradict the instructions for medical use of this drug [13].

Trial design

The bioequivalence study was an open-label, randomized, 2-period crossover study involving a single intake of the drug in each period (test or reference drug) in fed conditions. The study was conducted in one research center (Clinical Hospital No. 3, Yaroslavl). After hospitalization of the subjects and before the first administration of the drug, randomization was performed using the IWRS electronic system. The subjects were randomized into two groups: group 1 (TR) received the tested drug during the 1st period of the study and the reference drug during the 2nd; group 2 (RT) received the reference drug during the 1st period and the tested one during the 2nd period.

All hospitalization procedures were identical in all study periods. Hospitalization of the subjects started approximately 12 hours before each drug intake and lasted approximately 36 hours. After hospitalization, the researchers collected complaints, the subjects were interviewed to ensure compliance with the limitations of the study, a physical examination and assessment of vital signs were performed, alcohol breath tests were performed using an alcometer, drug and cotinine tests in urine were done using test strips, female volunteers also had a pregnancy test. On the day of hospitalization, subjects had a standard dinner according to the hospital's meal schedule followed by a restriction of the food intake. On the day of the drug administration, the volunteers were given a high-calorie breakfast, which they had to eat completely. The next meal was no earlier than 6 hours later. Before blood sample collection, vital signs were evaluated at –10 min and an intravenous peripheral catheter was placed in the ulnar vein to take blood samples for up to 12 hours after taking the drug, inclusive, with blood sampling at subsequent time points by direct venipuncture. The subject's hospitalization was completed following blood sampling at 24 hours after the drug was administered. Subsequently, the subjects were invited to outpatient visits at 48 and 72 hours after taking the investigational drug. During the outpatient visit, blood samples were taken for a biochemical blood test 72 hours after taking the drug in period 1. In the 2nd period of the study, a blood sample was taken for clinical and biochemical blood analysis and a urine sample was taken for urinalysis 72 hours after administration of the drug during the outpatient visit. Throughout the study, safety parameters were evaluated and adverse events were recorded.

The washout period in this study was 14 days, during it, the subjects continued to comply with all the limitations of the study. The total duration of this study was no more than 36 days for each volunteer.

Study endpoints

The pharmacokinetic parameters were evaluated in accordance with the purpose of the study. The total area under the plasma concentration of active drug -time curve (AUC) from zero to the collection of the last blood sample with the determined concentration of active substances of drugs at time point t (AUC_{0-t}) and the maximum observed concentration of active substances in the blood plasma of subjects during the observation period (C_{max}) were selected as the primary pharmacokinetic endpoints. Bioequivalence was assessed based on the data obtained.

Assessment of pharmacokinetic parameters

To assess the pharmacokinetic parameters during the study, blood samples were collected from subjects at 21 point in each period: –10 min predose and at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1 hour 30 minutes, 2 hours, 2 hours 30 minutes, 3 hours, 3 hours 30 minutes, 4 hours, 4 hours 30 minutes, 5 hours, 5 hours 30 minutes, 6 hours, 8hours, 10 hours, 12 hours, 24 hours, 48 hours and 72 hours postdose.

Quantative determination of the concentrations of the active substances of the investigational drugs in blood plasma was performed using high-performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) according to a developed and validated technique. Validation was performed in accordance with the OECD, the Principles of Good Laboratory Practice (GLP), national and international standards. Validation was carried out according to the main characteristics of the technique: the degree of extraction of compounds from plasma, the matrix effect, the Lower Limit of Quantification (LLQ), calibration curves, precision and accuracy, selectivity, stability of compounds and sample transfer.

Safety assessment

The safety parameters were evaluated from the moment of the investigational drug first intake until participation in the study was completed. The assessment was carried out according to the occurrence and dynamics of adverse events, registered on the basis of complaints from subjects, according to physical examination, vital signs (blood pressure, heart rate, RR and body temperature) and laboratory and instrumental methods (complete blood count and biochemical blood tests, urinalysis and electrocardiography).

Statistical analysis

After completion of the study, the pharmacokinetic parameters were evaluated. The drugs were considered bioequivalent if 90% of the CI of the geometric mean AUC and C_{max} for both active substances were in the range of 80–125%.

The data analysis was performed using R Statistical Software (v 4.2.2). Statistical analysis of the main PK parameters was performed assuming their lognormal distribution. After the logarithmic transformation, an analysis of variance (ANOVA) was performed for the parameters AUC_{0-t} and C_{max} of the active substances of the investigational drugs. Descriptive statistics were calculated for primary and secondary pharmacokinetic parameters, as well as for safety parameters. To assess comparability, a PP population was analyzed, which included all volunteers who completed two study periods in accordance with the protocol. The safety assessment was carried out on the SAF population, which included all volunteers who received at least one dose of the drug.

THE RESULTS OF THE STUDY

Demographic data

A total of 60 subjects, TR (n = 30) and RT (n = 30), were included and randomized in the study. All participants completed the study in accordance with the protocol and were included in PP population. Not a single subject dropped out of the clinical part of the study. No serious deviations from the study protocol were observed (Fig. 1). The baseline characteristics of the study participants are presented in Table 1.

Pharmacokinetics

The analysis of pharmacokinetic data was carried out on the PP population. The obtained data on pharmacokinetic parameters for the investigational drugs are presented in Table 2. No significant differences were found between the tested and the reference drugs. A graphical representation of these concentrations of ivacaftor and lumacaftor demonstrates the matching shapes of the averaged pharmacokinetic profiles of the tested drug and the reference drug (Fig. 2, 3).

The results of the evaluation of the ratio of geometric mean pharmacokinetic parameters AUC_{0-t}, C_{max} of velpatasvir and sofosbuvir of the studied drugs and 90% CI for these ratios are presented in Tables 3 and 4. All parameters fell within the specified bioequivalence limits.

Safety

No adverse events were reported during the clinical trial.

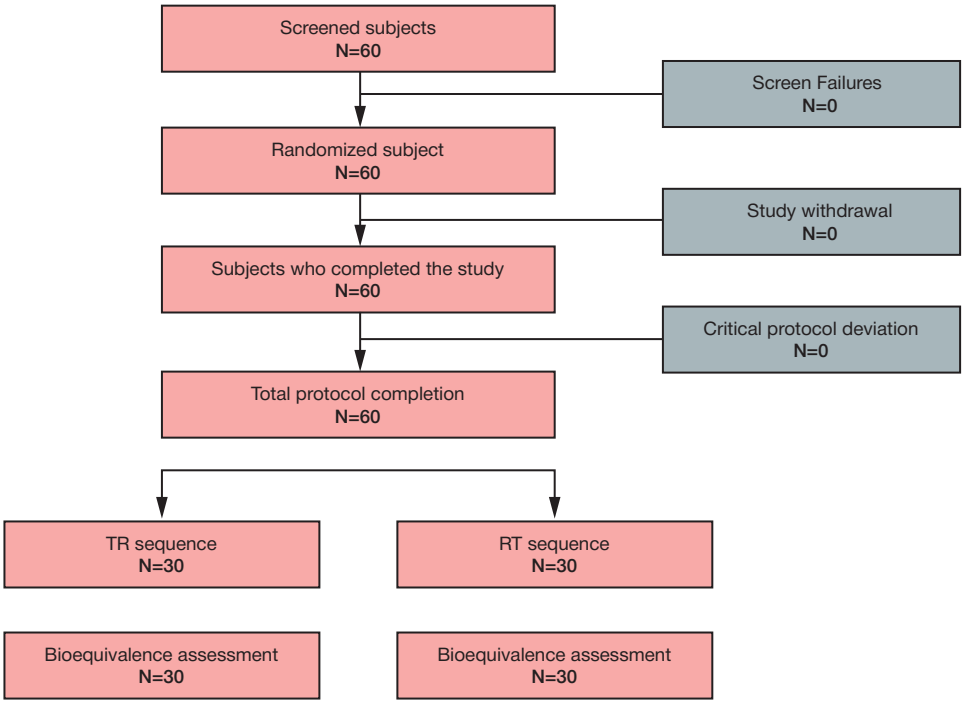

Fig. 1. Flow diagram of the distribution of subjects in a clinical trial

Table 1. Baseline characteristics of the study participants

Parameter		N=60
		Subject (% of N)/mean ± SD
Age, years		34.7±6.6
Gender	Male	28 (46.7)
	Female	32 (53.3)
Race (Caucasian)		60 (100)
BMI, kg/m^2		24.0±1.8
Weight, kg		70.4±8.6
Height, cm		170.8±6.0
Smoking – yes – no – history of smoking		– 0 – 60 (100) – 0
Alcohol – yes – no history of alcohol intake		– 8 (13.3) – 52 (86.7) – 0

Note: BMI is for body mass index, SD is for a standard deviation, N is for the number of randomized subjects.

Table 2. The obtained pharmacokinetic parameters after taking the tested and reference drug (N = 60)

Parameter	Ivakaftor			Parameter	Lumakaftor		
	The tested drug (mean ± SD)	The reference drug (mean ± SD)	The geometric mean ratios (90% CI)		The tested drug (mean ± SD)	The reference drug (mean ± SD)	The geometric mean ratios (90% CI)
AUC_{0-T} (ng/ml)/h	15415 ± 4359	15631 ± 4932	1.00	AUC_{0-T} (ng/ml)/h	392 ± 105	389 ± 99	1.00
C_{max} ng/ml	1575 ± 384	1609 ± 402	0.98	C_{max} mcg/ml	22 ± 3.5	22 ± 3.1	1.00
$AUC_{0-\infty}$ (ng/ml)/h	15602 ± 4386	15819 ± 4962	1.00	$AUC_{0-\infty}$ (μg/ml)/h	472 ± 168	463 ± 153	1.01
t_{max}, h	3.1 ± 0.9	3.1 ± 0.8	1.01	t_{max}, h	3.1 ± 1.0	3.1 ± 0.9	1.00
t1/2, h	8.3 ± 2.0	8.1 ± 2.0	1.02	$t_{1/2}$, h	27.6 ± 9.7	27.3 ± 8.6	1.00

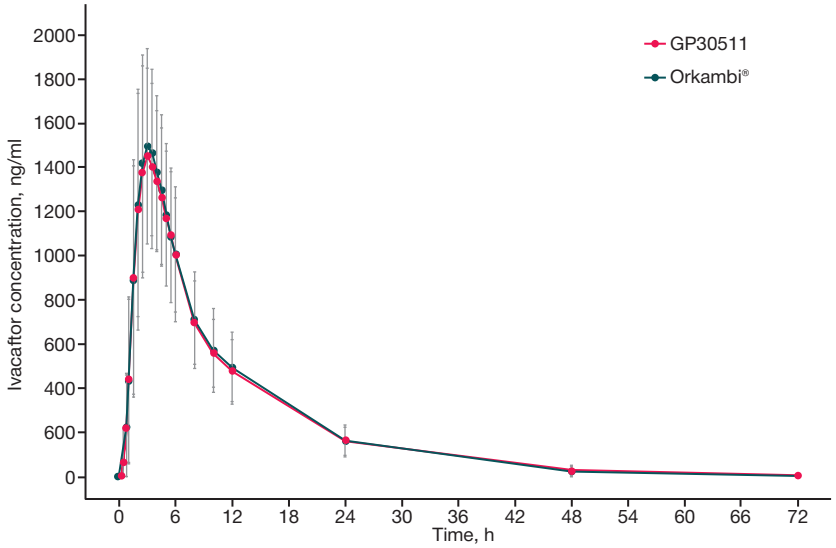

Fig. 2. Averaged pharmacokinetic profiles of ivacaftor in linear coordinates (mean ± SD, N = 60)

DISCUSSION OF THE RESULTS

Lumacaftor and ivacaftor are oral bioavailable peroral CFTR modulators, and their combination is the first drug combining a CFTR corrector and a potentiator. The lumacaftor-ivacaftor combination was developed for the treatment of patients with cystic fibrosis (CF) homozygous for the f508del-CFTR mutation [14]. Lumacaftor-ivacaftor is administered per os. It has shown effectiveness in improving the lung function and reducing the number of pulmonary exacerbations in patients with CF. Studies

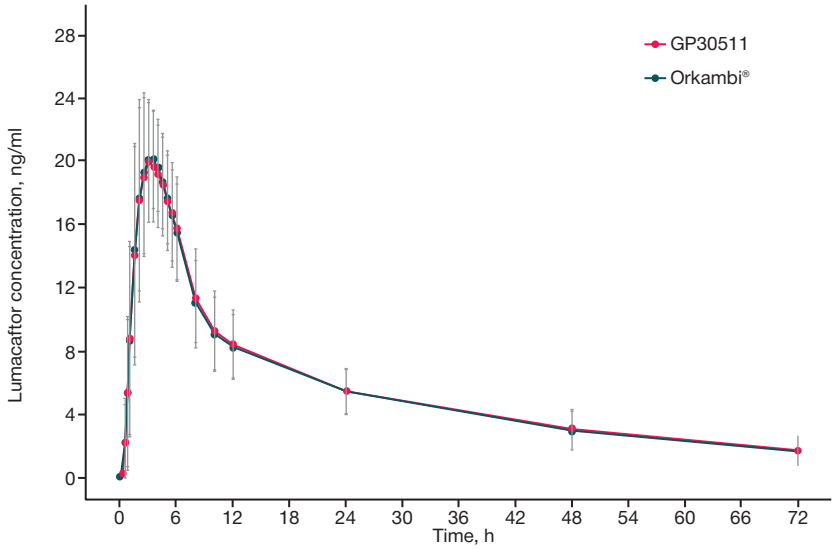

Fig. 3. Averaged pharmacokinetic profiles of lumacaftor in linear coordinates (mean ± SD, N = 60)

Table 3. The values of calculated confidence intervals for primary endpoints of ivacaftor pharmacokinetics (N = 60)

Parameter	The geometric mean ratio T/R	90% confidence interval		Estimated parameters for 90% CI	CV
		Lower limit	Upper limit		
AUC_{0-t}	1.00	95.92%	103.32%	80% — 125%	12.22%
C_{max}	0.98	94.71%	101.65%	80% — 125%	11.61%

Table 4. The value of calculated confidence intervals for primary endpoints of lumacaftor pharmacokinetics (N = 60)

Parameter	The geometric mean ratio T/R	90% confidence interval		Estimated parameters for 90% CI	CV
		Lower limit	Upper limit		
AUC_{0-t}	1.00	97.67%	103.08%	80% — 125%	8.84%
C_{max}	1.00	97.89%	102.35%	80% — 125%	7.31%

have shown that combination therapy gives a greater clinical effect compared with each of the drugs separately [15–17]. In addition, the combination of drugs can improve the condition of liver fibrosis in children and adolescents with CF, which indicates potential benefits in the treatment of CF-associated liver diseases [18].

According to the results of this study, the comparable pharmacokinetics and safety of the tested and reference drug were proved. The open nature of the study for volunteers and the researcher was chosen based on the fact that the primary pharmacokinetic points are sufficiently stable and resistant to the subjectivity of the study participants. In order to prove the bioequivalence of the studied drugs and to obtain the most reliable data, a population of healthy volunteers was chosen, since such a population is the most homogeneous one, which allows to reduce the intra-individual variability for bioequivalence research to the optimal level. This study was conducted in accordance with ethical principles designed to ensure the safety of the volunteers involved and to prevent any restriction of the rights of the subjects of the study. For this purpose, the study had a crossover design with the inclusion of the minimum number of subjects necessary to demonstrate the comparability of drugs, based on published literature data [19]. The dose of the drug, which was minimally sufficient for a reliable assessment of PK profiles, was also selected. It was acceptable from the perspective of safety and did not lead to the development of adverse events in the study.

60 healthy male and female volunteers were randomized and completed their participation in the studie according to the protocol, the analysis of pharmacokinetic parameters was carried out on the PP population, which included all randomized subjects. The results showed that the confidence intervals for the ratio of the geometric mean values of the pharmacokinetic parameters AUC_{0-t} and C_{max} of ivacaftor and lumacaftor in the PP population fell within the established acceptance limits of bioequivalence. Thus, this study made it possible to prove the bioequivalence of the studied drugs in a short time and in compliance with all requirements to ensure the safety of CT subjects for subsequent registration of GP30511.

CONCLUSIONS

Thus, based on the results of this study of GP30511 (GEROPHARM LLC) and Orkambi® (Vertex Pharmaceuticals Limited, Ireland), it can be concluded that the drugs are bioequivalent and have similar safety profiles. Entering the generic drug market will increase the availability of the combination of ivacaftor and lumacaftor for many patients with cystic fibrosis, which, in turn, will allow more effective management of the disease and improve patient survival. The implementation of GP30511 is an important step towards ensuring equal access of patients to modern treatment.

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