



## EFFECTIVENESS AND SAFETY OF FAVIPIRAVIR INFUSION IN PATIENTS HOSPITALIZED WITH COVID-19

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Research in the development of new therapeutic agents with a wide spectrum of the antiviral activity and a low ability to develop resistance remains the main dimension in combating the global threat to public health. The need for a parenteral form of favipiravir was dictated by the necessity to increase the efficacy of therapy in COVID-19 inpatients. This dosage form has expanded the possibilities of drug therapy in the inpatients, for whom a therapeutic effect acceleration and a high safety profile of the drugs used are especially important.

**The aim** of the article is the evaluation of the efficacy and safety of a medicinal product containing favipiravir for the parenteral administration against the background of pathogenetic and symptomatic therapy, in comparison with standard therapy in hospitalized COVID-19 patients.

**Materials and methods.** An open, randomized, multicenter comparative study was conducted in 6 research centers in the Russian Federation to evaluate the efficacy and safety of favipiravir, a lyophilisate for the preparation of a concentrate for the infusion solution administered to the patients hospitalized with COVID-19. Screening procedures and randomization were completed in 217 patients, 209 of which had completed the study in accordance with the protocol.

**Results.** Between the study groups, statistically significant differences have been found out, making it possible to consider the hypothesis of the drug Areplivir (favipiravir) superiority for the parenteral administration over the standard therapy, which included favipiravir (p. o.) and remdesivir. A comparative analysis has shown that a course of therapy with the paren-

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teral favipiravir drug leads to a significant improvement in the condition of patients with COVID-19, significant benefits in terms of the speed and frequency of improvement in the clinical status of patients, as well as a reduction in the hospital stay length. It has been proven that therapy with a drug containing favipiravir for the parenteral administration does not adversely affect the parameters of clinical and biochemical blood tests, urinalysis, coagulograms, vital signs and ECG, which indicates the therapy safety. The study drug is characterized by a high safety profile and tolerability.

**Conclusion.** The versatility and resistance to mutations of RNA-dependent RNA polymerase make it possible to consider it as the main target for combating the most common RNA viruses that cause ARVI, that determines the need further studies of favipiravir to expand the range of its indications.

**Keywords:** favipiravir; COVID-19; SARS-CoV-2; novel coronavirus infection; areplivir

**Abbreviations:** COVID-19 – novel coronavirus infection (Coronavirus disease 2019); AV – Artificial ventilation; GIT – gastrointestinal tract; ECMO – Extracorporeal membrane oxygenation; ITT – population of all included (Intent-to-treat) patients; PP – the population of patients who completed the study according to the protocol (Per protocol); NAATs – nucleic acid amplification techniques; NYHA – New York Heart Association; e-IRK – electronic individual registration card; ARDS – Acute Respiratory Distress Syndrome; CRP – c-reactive protein; ESR – erythrocyte sedimentation rate; NAATs – Nucleic Acid Amplification Techniques; GIT – gastrointestinal tract; HR – heart rate; AspAT – aspartate transaminase; ALT – alanine aminotransferase; ULN – upper limit of normal; UDE – undesirable effects; IGS – Interim Guidelines; NSAIDs – non-steroidal anti-inflammatory drugs; GGT – gamma-glutamyl transpeptidase; CK – creatine kinase.

## ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ИНФУЗИОННОГО ВВЕДЕНИЯ ФАВИПИРАВИРА У ПАЦИЕНТОВ, ГОСПИТАЛИЗИРОВАННЫХ С COVID-19

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Основным направлением по борьбе с глобальной угрозой здоровью населения остаются исследования в области создания новых терапевтических средств с широким спектром противовирусной активности и низкой способностью к развитию резистентности. Потребность в парентеральной форме фавипиравира была продиктована необходимостью повышения эффективности терапии у стационарных больных с COVID-19. Данная лекарственная форма расширила возможности медикаментозной терапии у стационарных пациентов, для которых особенно важно ускорение наступления терапевтического эффекта и высокий профиль безопасности применяемых препаратов.

**Цель.** Оценка эффективности и безопасности применения лекарственного препарата, содержащего фавипиравир для парентерального введения на фоне патогенетической и симптоматической терапии в сравнении со стандартной терапией у пациентов, госпитализированных с COVID-19.

**Материалы и методы.** В 6 исследовательских центрах на территории России проведено открытое рандомизированное многоцентровое сравнительное исследование по оценке эффективности и безопасности применения фавипиравира, лиофилизат для приготовления концентрата для приготовления раствора для инфузий у пациентов, госпитализированных с COVID-19. Процедуры скрининга и рандомизации прошли 217 пациентов, из них 209 завершили исследование полностью в соответствии с протоколом.

**Результаты.** Выявлены статистически значимые различия между исследуемыми группами, позволяющие считать доказанной гипотезу превосходства препарата Арепливив (фавипиравир) для парентерального введения над стандартной терапией, которая включала фавипиравир (перорально) и ремдесивир. Сравнительный анализ показал, что курс терапии лекарственным препаратом фавипиравир для парентерального применения приводит к существенному улучшению состояния пациентов с COVID-19, значимым преимуществам в отношении скорости и частоты улучшения клинического статуса пациентов, а также сокращению длительности пребывания в стационаре. Доказано, что терапия лекарственным препаратом, содержащим фавипиравир для парентерального введения, не оказывает негативного влияния на показатели клинического и биохимического анализа крови, общего анализа мочи, коагулограммы, на показатели жизненно важных функций и ЭКГ, что свидетельствует о безопасности проводимой терапии. Исследуемый препарат характеризуется высоким профилем безопасности и хорошей переносимостью.

**Заключение.** Универсальность и устойчивость к мутациям РНК-зависимой-РНК-полимеразы позволяют рассматривать ее как основную мишень для борьбы с наиболее распространенными РНК-вирусами – возбудителями ОРВИ, что определяет необходимость проведения дальнейших исследований фавипиравира для расширения спектра его показаний.

**Ключевые слова:** фавипиравир; COVID-19; SARS-CoV-2; новая коронавирусная инфекция; Арепливив

**Список сокращений:** COVID-19 – новая коронавирусная инфекция; ИВЛ – искусственная вентиляция легких; ЖКТ – желудочно-кишечный тракт; ЭКМО – экстракорпоральная мембранная оксигенация; ИТТ – популяция всех включенных пациентов; РР – популяция пациентов, завершившая исследование согласно протоколу; МАНК – метод амплификации нуклеиновых кислот; NYHA – Нью-Йоркская ассоциация кардиологов; э-ИРК – электронная индивидуальная регистрационная карта; ОРДС – острый респираторный дистресс-синдром; СРБ – с-реактивный белок; СОЭ – скорость оседания эритроцитов; МАНК – методы амплификации нуклеиновых кислот; ЖКТ – желудочно-кишечный тракт; ЧСС – частота сердечных сокращений; АСТ – аспартатаминотрансфераза; АЛГ аланинаминотрансфераза; ВГН – верхняя граница нормы; НЯ – нежелательное явление; ВМП – временные методические рекомендации; НПВП – нестероидные противовоспалительные препараты; ГГТ – гамма-глутамилтранспептидаза; КФК – креатинкиназа.

## INTRODUCTION

Coronavirus infection (SARS-CoV-2), first recorded in December 2019 in Wuhan (China), is currently the cause of the ongoing COVID-19 pandemic. This disease is characterized by damage to the lungs tissue, the development of acute respiratory distress syndrome, kidney damage, the formation of thromboembolic complications, the development of multiple organ failure, septic shock, and deaths [1]. Most patients have a mild or moderate severity of the disease, however, in 5–10% of patients, COVID-19 acquires a severe and even life-threatening course [2, 3]. Since December 2019, SARS-CoV-2 has infected hundreds of millions of people around the world, claiming millions of lives. Thus, according to the published data of Worldometers.info<sup>1</sup> as of February 8, 2022, 398,671,423 cases of SARS-CoV-2 infection were registered in 225 countries of the world,

5,771,021 of which were fatal. As for Russia, on February 8, 2022, 13,147,666 cases of coronavirus infection were registered, and the number of deaths reached 336,721.

A new disease is putting an unprecedented loading on the global health system, leading to massive increases in hospitalizations. In November 2021, a new strain of Omicron was first identified in southern Africa, becoming the dominant variant of SARS-CoV-2 in most parts of the world, including Russia. It has been notified that the protection of modern vaccines in relation to the new strain is significantly reduced [4–6]. In addition, there is a huge pool of immunocompromised patients in whom vaccination is not effective enough [7, 8]. According to the Interim Guidelines of the Ministry of Health of the Russian Federation for the Prevention, Diagnosis and Treatment of the Novel Coronavirus Infection, regardless of their version, the main approach to the treatment of COVID-19 should be preemptive before the development of a full symptom complex of life-threatening conditions,

<sup>1</sup> Worldometer – real time world statistics. Available from: <https://www.worldometers.info/coronavirus/#countries>.

i. e. pneumonia, ARDS, sepsis<sup>2</sup>. The international medical community agrees that an early control of the viral RNA replication and the use of targeted antiviral therapy is the most important element in improving the prognosis of the disease by reducing the increasing viral load and preventing the development of complications [9–11]. At the same time, the data from the observational studies confirm that during bronchoscopy in critically ill and/or ventilated patients, a high level of SARS-CoV-2 viral load is determined; in these patients, this is the main predictor of death from COVID-19. The authors conclude that in order to improve the prognosis of patients hospitalized with COVID-19, the priority should be the therapy aimed at reducing a virus replication [12].

A number of antiviral drugs are currently under investigation and have not been approved for the treatment of COVID-19. Therefore, today it is obvious that the further development and study of specific antiviral therapy is of paramount importance for the treatment and prevention of a new coronavirus infection [13].

One of the promising drugs used for antiviral therapy of coronavirus infection is favipiravir, a selective RNA polymerase inhibitor, a synthetic antiviral drug that is active against a wide range of different RNA-containing viruses. The active form of the drug (favipiravir-RTF) acts on the RNA-dependent RNA polymerase of the virus. The first mechanism of action of the drug on the virus is the inclusion in the viral RNA chain or binding to the preserved polymerase domains, which leads to the prevention of the viral RNA replication and ultimately leads to the disappearance of the viral genome, as well as a decrease in the infection transmission. The second is the inclusion of favipiravir-RTF into the replicating viral RNA, which leads to lethal mutagenesis, which accelerates the elimination of the viral agent [14]. Thus, we can say that favipiravir has a targeted effect on the life processes of the virus in the body, and this explains the versatility of its application in the treatment of various diseases caused by RNA-containing viruses, including influenza and coronavirus infection.

The possibility of using favipiravir for the treatment of COVID-19 was proposed in February 2020. Currently, it is the most studied molecule for the targeted antiviral COVID-19 therapy with proven efficacy and a high safety profile. Analyzing the publication activity of scientific articles indexed in PubMed and ScienceDirect, mentions of the favipiravir molecule are the most frequent, which may indicate a high interest in this molecule from the medical community, especially in the context of the COVID-19 pandemic. On the multidisciplinary platform ScienceDirect (Elsevier publishing house) on request (INN + COVID-19, period 2020–2022), indexed publications: Oseltamivir – 203, Favipiravir – 686,

Molnupiravir – 129, Remdesivir – 85. In the database of medical and biological publications PubMed, on request (INN+COVID-19, period 2020–2022), indexed publications: Oseltamivir – 197, Favipiravir – 672, Molnupiravir – 113, Remdesivir-13. The keywords for the search were INNs and “COVID-19”. The search was carried out during the period from 2020 to 2022. As a result, the following numbers of publications were indexed on the ScienceDirect multidisciplinary platform (Elsevier publishing house)<sup>3</sup>: Oseltamivir – 203, Favipiravir – 686, Molnupiravir – 129, Remdesivir – 85. In the PubMed database<sup>4</sup>, the numbers of the indexed publications were as follows: Oseltamivir – 197, Favipiravir – 672, Molnupiravir – 113, Remdesivir – 13.

At the moment, clinical studies have proven the efficacy and safety of using the tablet form of favipiravir for the SARS-CoV-2 treatment and prevention [14–19]. Moreover, according to the latest data, Omicron strains are sensitive to favipiravir [20].

One of the ways to increase the treatment efficacy is to increase the bioavailability of the drug, which affects the efficacy and safety profile. In COVID-19, lesions of the gastrointestinal tract such as an increase in the activity of gastrointestinal enzymes, are known in more than 20% of patients. The development of pseudomembranous colitis against the background of the disease, the violation of the intestinal microflora when using combinations of antibiotics, lead to a change in the pharmacokinetic parameters of oral drugs, and hence, reducing their effectiveness [21]. The international medical community has recognized the need to develop and use intravenous favipiravir to improve the therapy efficacy of the hospitalized COVID-19 patients [22, 23].

The first drug containing favipiravir and registered in the Russian Federation, the molecule with a proven activity against SARS-CoV-2, was Areplivir® (the oral form). Later, in 2020, the world's first original Areplivir® was developed and registered in the Russian Federation in the form of a dosage form for the parenteral administration (RU LP-007598).

Phase 1 clinical<sup>5</sup> studies have shown that favipiravir for the parenteral administration has improved pharmacokinetic parameters compared to the oral form, i.e., it provides achieving a 100% bioavailability, a faster and uniform penetration and distribution of the drug in the cells. A decrease in the “Time to reach maximum concentration” indicator, combined with an increase in the area under the pharmacokinetic curve, indicates a lon-

<sup>2</sup> Interim guidelines “Prevention, diagnosis and treatment of a new coronavirus infection COVID-19 (version 13.1. dated 11/17/2021, version 14 dated 12/28/2021

<sup>3</sup> ScienceDirect Search Results—Keywords (favipiravir covid-19). Available from: <https://www.sciencedirect.com/search?q=favipiravir%20covid-19>.

<sup>4</sup> Favipiravir, covid 19 – Search Results. Available from: <https://pubmed.ncbi.nlm.nih.gov/?term=Favipiravir%2C+covid+19>.

<sup>5</sup> An open non-randomized clinical study to assess the safety, tolerability and pharmacokinetic parameters of various doses of AREPLIVIR, a lyophilisate for the preparation of a concentrate for solution for infusion (OOO PROMOMED RUS, Russia) in healthy volunteers. RCT No. 226 dated April 26, 2021 Protocol No. FAV-012021. Available from: <https://grlsbase.ru/clinicaltrails/clintrail/11428>.

ger maintenance of a therapeutic concentration in the body while reducing the toxicological load due to the absence of favipiravir peak concentrations, which increases the safety profile of the drug. It should be notified that favipiravir for the parenteral administration is convenient for patients with gastrointestinal symptoms of COVID-19 (nausea, vomiting), as well as with difficulties in swallowing or in a stable prone position.

Parenteral therapy has advantages over the oral route of the drug delivery. It can be used in the situations where a patient is in a serious condition or unconscious, has a difficulty in swallowing or might be in conditions that prevent it (this can be important for gastrointestinal symptoms of COVID-19) and other situations where an oral administration is difficult (incl. ALV, ECMO, etc.). An intravenous route of the drug administration is used for a quick and pronounced result, since the drug immediately enters the bloodstream, the bioavailability is faster and more predictable, and there is no interaction with food or digestive enzymes [24–26].

**THE AIM** of the article is the evaluation of the efficacy and safety of favipiravir for the intravenous administration in COVID-19 inpatients.

#### MATERIALS AND METHODS

In accordance with the Recommendation of the Council of the Eurasian Economic Commission dated July 17, 2018 No.11 “On guidelines for general issues of clinical trials”, the rules of Good Clinical Practice of the International Conference on Harmonization (ICH GCP), the ethical principles set forth in the Helsinki Declaration of the World Medical Association (Fortaleza, 2013) and the requirements of the Russian legislation (Federal Law No. 61-FZ dated April 12, 2010 “On the Circulation of Medicines”), a phase III clinical trial was conducted. It comprised the following: “An open randomized multicenter comparative study to evaluate the efficacy and safety of Areplivir®, a lyophilisate for the preparation of a concentrate for the preparation of an infusion solution (LLC Promomed RUS, Russia) in the patients hospitalized with COVID-19. The study was approved by the Ministry of Health of the Russian Federation RCT No. 440 (08/11/2021) FAV052021, and was also peer-reviewed in the international registry of clinical trials [clinicaltrials.gov](https://clinicaltrials.gov) (NCT05185284)<sup>6</sup>.

1. The research took place from 08/11/2021 to 12/15/2021 on the basis of six research centers in the Russian Federation:
2. Smolensk Clinical Hospital No. 1, Smolensk, Russia;
3. Ivanovo Clinical Hospital n. a. the Kuvaevs”, Ivanovo, Russia;
4. Regional Clinical Hospital, Ryazan, Russia;

5. Municipal Clinical Hospital No. 24”, Moscow City Health Department, Russia;

6. Moscow State Medical and Dental University n. a. A.I. Evdokimov Moscow, Russia;

7. National Research Mordovian State University n. a. N.P. Ogarev, Saransk, Russia.

The inclusion criteria for this study were: male and female patients aged 18 to 80 years hospitalized with moderate COVID-19; the COVID-19 diagnosis was confirmed by NAATs; obligatory clinical signs were changes at CT, typical for a viral lesion (the volume of the lesion was minimum or medium; CT was 1–2). An additional clinical sign was compliance with 1 of the following criteria: body temperature > 38°C; RR > 22/min; breath shortness during physical exertion; SpO<sub>2</sub> < 95%; Serum CRP > 10 mg/l; consent of the patient to use reliable methods of contraception (sexual rest, use of a condom in combination with spermicide) throughout the study and for 1 month for women and 3 months for men after its completion; for men (optional): consent to avoid sexual contact with pregnant women throughout the study and for 3 months after its completion; the women who are unable to bear children, as well as men with infertility or a history of vasectomy.

The criteria for exclusion from the study were: hypersensitivity to favipiravir, remdesivir and/or other components of the study drug; the impossibility of performing a CT procedure; the vaccination history against COVID-19; the presence of a previous probable or confirmed case of COVID-19 of a moderate, severe and extremely severe course; the use of favipiravir or remdesivir within 10 days prior to screening; the need to use the drugs from the list of prohibited therapies; the presence of criteria for severe and extremely severe courses of the disease; the need for treatment in the intensive care unit; abnormal liver function (AST and / or ALT ≥ 2 ULN and / or total bilirubin ≥ 1.5 ULN) at the time of screening; the impaired renal function (GFR < 60 ml/min) at the time of screening; gout in past medical history; a positive test for HIV, syphilis, hepatitis B and / or C; chronic heart failure (III–IV FC) according to the NYHA functional classification; a history of malignant neoplasms; history of alcohol, pharmacological and/or drug dependence at the time of screening and/or in past medical history; schizophrenia, schizoaffective disorder, bipolar disorder, or other psychiatric disorder in past medical history or suspicion of their presence at the time of screening; severe, decompensated or unstable somatic diseases; any history data that, in the opinion of the investigator, may complicate the interpretation of the results of the study or create an additional risk for the patient as a result of his participation in the study; unwillingness or inability of the patient to comply with the procedures of the Protocol (in the opinion of the investigator); pregnant or lactating women, or women planning a pregnancy; participation in another clinical trial within 3 months prior to the enrollment in the study;

<sup>6</sup> Randomized Multicenter Study on the Efficacy and Safety of Favipiravir for Parenteral Administration Compared to Standard of Care in Hospitalized Patients With COVID-19. Promomed, LLC. 11 Jan 2022. Available from: <https://clinicaltrials.gov/ct2/show/NCT05185284>.

other conditions that, in the opinion of the investigator, prevent the inclusion of the patient in the study.

If any diseases or conditions appeared during the study that worsened the patient's prognosis, made it impossible for the patient to continue participating in the clinical trial, and if it was necessary to prescribe prohibited concomitant therapy/procedures, the patient was excluded from the study.

### Study design

The evaluation of the efficacy and safety of the drug was carried out in comparison with the standard therapy provided by the IGs, version 11 dated 05/07/2021 or valid at the time of the study, i.e. the drugs containing favipiravir in the tablet form, the drug containing remdesivir in the form of a lyophilisate for the preparation of a concentrate for an infusion solution.

Patients were randomized using an interactive on-line system (Interactive web randomization system – IWRS) built into the e-RCI. The population of all included patients (Intent-to-treat) – ITT in the study was 214 (106 patients in the study drug favipiravir group + 108 patients in the standard therapy group). The population of patients who completed the study according to the protocol (Per protocol) – PP was 209 (102 patients in the study drug favipiravir group + 107 patients in the standard therapy group). This met the requirements for the minimum number of patients required for a clinical study – 200 patients (100 patients per group). The groups were comparable in anthropometric, laboratory and clinical baseline parameters (Table 1).

The most common comorbidities were arterial hypertension and other cardiovascular diseases, obesity, type 2 diabetes mellitus, gastrointestinal diseases, etc. Thus, the study included the patients with a high risk of developing life-threatening conditions and worsening prognosis. A comparative analysis of comorbidities and the general condition of patients also did not reveal intergroup differences.

The 1<sup>st</sup> group received the study drug Areplivir® (favipiravir) for the parenteral administration against the background of pathogenetic and symptomatic therapy presented in the IGs, version 11 (07.05.2021) or valid at the time of the study.

Pharmacotherapy was carried out in hospital according to the following scheme: the 1<sup>st</sup> day – 1600 mg twice a day; the 2<sup>nd</sup>–10<sup>th</sup> days – 800 mg twice a day. The administration of the drug was carried out intravenously by drop infusion for 2 hours.

The 2<sup>nd</sup> group received standard therapy in accordance with the IGs, version 11 (05/07/2021). (Table 2) or valid at the time of the study.

Discharge from the hospital was carried out in accordance with the local practice of the research center in compliance with the current sanitary and epidemiological regime.

The patients in the study drug group could not

additionally receive other etiotropic drugs, as well as monoclonal antibodies with a virus-neutralizing effect (bamlanivimab in monotherapy or in combination with etesevimab, casirivimab in combination with imdevimab), or anti-covid plasma.

The study consisted of the following stages: screening – no more than 24 hours; randomization – not more than 1 day; therapy – 10 days; post-observation – not more than 19 days.

The total duration of each patient's study for was not more than 30 days. The patient's condition was monitored during 6 visits to the research center.

In case of the development of acute respiratory distress syndrome and the need to transfer the patient to the artificial lung ventilation, the use of the study drug was canceled, the patient was not excluded from the study. The patient was followed up to Visit 6, and the data obtained were taken into account to evaluate the efficacy in the ITT population.

### Parameters under study

Among the studied parameters there were: a clinical status of patients on the categorial ordinal scale of clinical improvement, the degree of lung damage according to CT, virus elimination, inflammatory markers (CRP, ESR). The presented approach is consistent with the FDA Guidelines on the Development of Drugs for the Treatment and Prevention of COVID-19<sup>7</sup> and the Guidelines of the WHO Working Group on the Clinical Characterization and Treatment of COVID-19 Infection [27].

The primary points for evaluating efficacy were: the frequency of improvement in clinical status on a categorial ordinal scale of clinical improvement by 2 or more categories after 10 days of therapy, as well as the time (in days) to the improvement in clinical status on a categorial ordinal scale of clinical improvement (Table 3).

Additionally, the clinical status at each study visit, the proportion of patients who had achieved clinical status 0 / 1 at the study visits, the degree of lung damage (according to the CT data, according to the "empirical" scale), the rate of the virus elimination (a negative result of a laboratory test for the presence of SARS-CoV-2 RNA by NAATs), SpO<sub>2</sub>, clinical (hemoglobin, hematocrit, erythrocytes, leukocytes, platelets, ESR, leukocyte formula) and biochemical (AST, ALT, GGT, CPK, triglycerides, total protein, creatinine, urea, uric acid, total bilirubin, glucose, CRP, ferritin, lactate) blood parameters, were assessed. The degree of lung damage was assessed in accordance with the IGs of the Ministry of Health of the Russian Federation for the prevention, diagnosis and treatment of a new coronavirus infection using the scale presented in Table 4.

<sup>7</sup> COVID-19: Developing Drugs and Biological Products for Treatment or Prevention. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention>.

**Table 1 – Initial indices**

Indices	Favipiravir drug group	Standard therapy group
Average age of patients	48.56±12.25 years (from 24 to 76 years)	48.70±13.21 years (from 22 to 74 years)
Average body weight	80.57±15.84 kg (from 50 to 120 kg)	81.03±16.73 kg (from 54 to 153 kg)
Average height	170.37±7.93 cm (from 153 to 194 cm)	170.85±8.38 cm (from 149 to 190 cm)
Comorbidities (95 patients)	47.17%	46,67%

Note: among the randomized patients, there were 113 female patients (52.80%) and 101 male patients (47.20%). The groups were also comparable in terms of gender composition.

**Table 2 – Recommended treatment regimens according to IGs, version 11 (07.05.2021)**

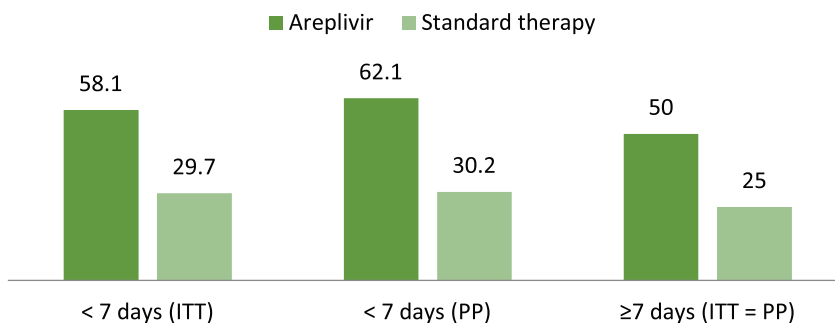
	No.	Drug	Dosing regimen
Scheme 1	1	Favipiravir	For patients weighing <75 kg: 1600 mg twice daily on the 1 <sup>st</sup> day and then 600 mg twice daily from the 2 <sup>nd</sup> to the 10 <sup>th</sup> days.  For patients weighing 75 kg or more: 1800 mg twice daily on the 1 <sup>st</sup> day, then 800 mg twice daily from the 2 <sup>nd</sup> to the 10 <sup>th</sup> days.
	2	Baricitinib	4 mg once daily for 7–14 days
		<i>or</i>	
		Tofacitinib	10 mg twice daily for 7–14 days
		<i>or</i>	
		Netakimab	120 mg in the form of two subcutaneous injections of 1 ml (60 mg) each. Administered once a week on weeks 0, 1 and 2.
	3	Anticoagulant drug for parenteral administration	
	4	NSAIDs according to indications	
Scheme 2	1	Remdesivir	Day 1: 200 mg (in a 0.9% sodium chloride solution) given as a single dose, intravenously. From the 2 <sup>nd</sup> day: 100 mg intravenously once daily. The general course is no more than 10 days.
	2	Baricitinib	4 mg once daily for 7–14 days
		<i>or</i>	
		Netakimab	120 mg in the form of two subcutaneous injections of 1 ml (60 mg) each. Administered once a week on weeks 0, 1 and 2.
	3	Anticoagulant drug for parenteral administration	
	4	NSAIDs according to indications	
Scheme 3	1	<u>Favipiravir</u>	<u>For patients weighing &lt;75 kg:</u> <u>1600 mg twice daily on the 1<sup>st</sup> day and then 600 mg twice daily from the 2<sup>nd</sup> to the 10<sup>th</sup> days.</u> <u>For patients weighing 75 kg or more:</u> <u>1800 mg twice daily on the 1<sup>st</sup> day, then 800 mg twice daily from the 2<sup>nd</sup> to the 10<sup>th</sup> days.</u>
	2	Olokizumab	160 mg/ml – 0.4 ml subcutaneously / 0.8 ml as a single dose, intravenously.
		<i>or</i>	
		Levilimab	324 mg (two pre-filled syringes of 162 mg/0.9 ml each) subcutaneously/as a single dose, intravenously.
	3	Anticoagulant drug for parenteral administration	
	4	NSAIDs according to indications	
Scheme 4	1	Remdesivir	Day 1: 200 mg (in a 0.9% sodium chloride solution) as a single dose, intravenously. From the 2 <sup>nd</sup> day: 100 mg daily as a single dose, intravenously. The general course is no more than 10 days.
	2	Olokizumab	160 mg/ml – 0.4 ml subcutaneously / 0.8 ml as a single dose, intravenously.
		<i>or</i>	
		Levilimab	324 mg (two pre-filled syringes of 162 mg/0.9 ml each) subcutaneously/as a single dose, intravenously.
	3	Anticoagulant drug for parenteral administration	
	4	NSAIDs according to indications	
	5	In fever (t > 38°C) for longer than 3 days in a moderate course, antibiotic therapy is prescribed according to indications	

**Table 4 – “Empirical” visual scale for assessing the degree of lung damage according to CT data in accordance with the IGs of the Ministry of Health of the Russian Federation for the diagnosis and treatment of COVID-19, version 11 (05/07/2021)**

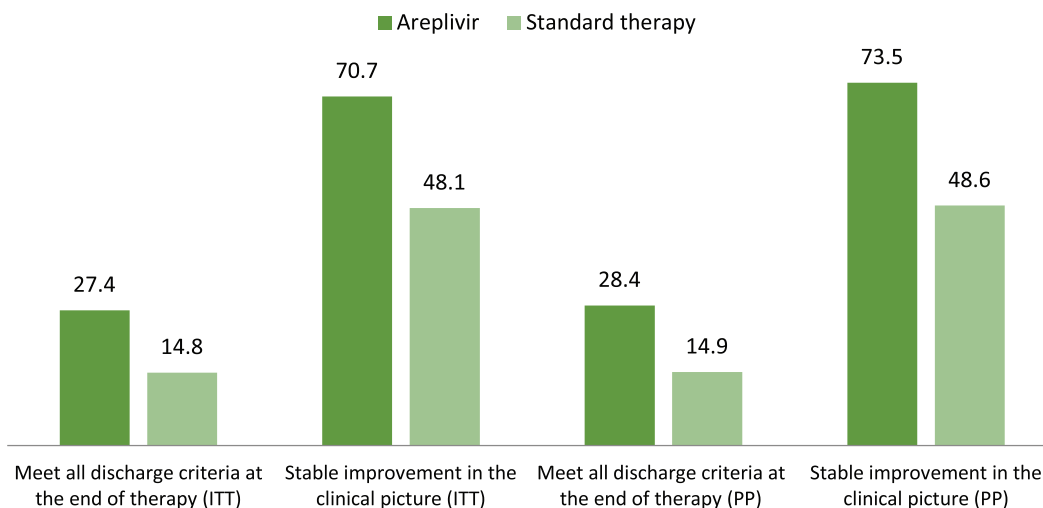
Description	Value
1. Absence of characteristic manifestations	KT-0
2. Minimum volume/prevalence < 25% lung volume	KT-1
3. Average volume/prevalence 25–50% of lung volume	KT-2
4. Significant volume/prevalence 50–75% of lung volume	KT-3
5. Critical volume/extent > 75% lung volume	KT-4

**Table 3 – Categorical scale for determining patients’ clinical condition**

Patient’s condition	Description	Category
Uninfected	No clinical / virological signs of infection	0
Outpatient	No activity restrictions	1
	Activity restrictions	2
Hospitalized: – mild course of the disease	Hospitalized, no oxygen therapy	3
	Oxygenation with mask or nasal cannula	4
	– severe disease	Non-invasive ventilation or high-flow oxygen therapy
– severe disease	Intubation or mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, renal replacement therapy, extracorporeal membrane oxygenation (ECMO)	7
	Deceased	Death



**Figure 1 – Frequency (% of patients) of improvement in clinical status by 2 points or more with duration of symptoms before therapy < than 7 days and ≥ than 7 days**



**Figure 2 – Comparative analysis of patients’ frequency meeting discharge criteria for current IGs at the end of therapy**



To determine the clinical condition of the patient, the characteristics of the infection course and the safety of the therapy prescribed for all patients, the information on complaints and symptoms was collected daily. The vital signs (body temperature, saturation, blood pressure, heart rate, respiratory rate) were measured at screening, then on the 5<sup>th</sup> and on the 11<sup>th</sup> days; clinical and laboratory studies (clinical and biochemical blood tests, coagulogram, urinalysis) and ECG monitoring were performed. ECG diagnostics, clinical and laboratory analyzes were performed at screening, then on the 5<sup>th</sup> and 11<sup>th</sup> days. In addition, the frequency and severity of adverse events (AEs) and serious AEs, as well as the frequency of any AEs that led to the discontinuation of the study drugs, the frequency of significant changes in vital signs and clinical and laboratory parameters, the need for non-invasive oxygen support or mechanical ventilation, as well as the incidence of deaths were assessed.

### Statistical processing of results

A statistical analysis was carried out in accordance with the requirements of ICH 9, the Rules of Good Clinical Practice approved by the Eurasian Economic Commission and other applicable requirements and laws. Statistical processing of the data at the end of the study was carried out by the employees not associated with the management of patients participating in the study in order to create conditions for an independent assessment of the results obtained. For the statistical analysis, certified statistical software with validated algorithms for performing statistical analyzes and proper documentation was used Statistica version 13 (TIBCO Software Inc.). Checking for the normality of the distribution was carried out by one of the generally accepted methods (Shapiro-Wilk test). In case of a non-Gaussian distribution, non-parametric evaluation methods were used to compare efficacy and safety indicators. Significance levels and confidence intervals were calculated as two-tailed; the statistical significance of differences is two-tailed by default and refers to a significance level of 0.05 (unless otherwise indicated).

To analyze the parameter "frequency of improvement in clinical status on a categorical ordinal scale of clinical improvement by 2 or more categories at Visit 3", an intergroup comparison of shares was used with the help of a two-tailed version of Fisher's exact test (or a two-tailed version of the  $\chi^2$  («chi-square») test, in case all the expected values in the cells of the contingency table for this analysis were 5 or more). The difference in proportions between treatment groups and a 95% two-sided confidence interval for the difference in proportions were calculated using the Newcomb-Wilson method.

Student's t-test for independent samples was used to compare the efficacy between the groups in terms of "time (in days) till the improvement in clinical status on a categorical ordinal scale of clinical improvement". For

a comparative assessment of the time (in days) till the improvement in the clinical status of the patient between the study groups, the Gehan-Wilcoxon test, the Cox-Mentel test, or the Log-rank test were used. The primary efficacy analyzes were performed in the ITT population (the primary analysis) and in the PP population (the additional analysis).

## RESULTS

### Efficacy evaluation

The efficacy evaluation of the studied drug was based on a statistical analysis of primary and secondary endpoints.

The rate of improvement in the clinical status on a categorical ordinal scale of clinical improvement by 2 or more categories in the ITT population in the Areplivir® (favipiravir) parenteral group was 54.72%, and in the standard therapy group it was 27.78% ( $p=0.0001$ ). The difference in proportions between the favipiravir drug group and the standard therapy group (pa-pb) was 0.2694 (26.94%), 95% CI [0.1313; 0.3942]. In the PP population, in the favipiravir group, the proportion of patients with an improvement in the clinical status by 2 or more categories was 56.86%, in the standard therapy group it was 28.04 ( $p<0.0001$ ). The difference in proportions between the favipiravir group and the standard therapy group (pa-pb) was 0.2883 (28.83%), 95% CI [0.1480;0.4139] ([14.80%;41.39%]). There were statistically significant differences in the proportions of patients between the study groups in both the ITT population ( $p=0.0001$ ) and the PP population ( $p<0.0001$ ). Compared with the group receiving only standard therapy for COVID-19, in the group of injectable favipiravir, almost twice more patients were recorded with an improvement in the clinical status by 2 or more points on a categorical ordinal scale.

The median time (in days) till the improvement in clinical status (in the ITT and PP populations) was 5 days in the favipiravir group and 7 days in the standard therapy group ( $p=0.0184$  and  $p=0.0048$ , respectively).

Thus, by both primary endpoints established by the study protocol, Areplivir® showed an advantage in terms of efficacy compared with standard therapy.

Additionally, for both ITT and PP populations, a comparative analysis was performed taking into account the duration of the symptoms presence before the start of therapy (< than 7 days and  $\geq 7$  days) (Fig. 1).

The proportion of patients with an improvement in the clinical status by 2 or more points in the ITT population in the Areplivir® group was 58% (< than 7 days) and 50% ( $\geq 7$  days), which was twice higher than in the standard therapy group (29.7% – < than 7 days and 25% –  $\geq 7$  days). A similar trend is observed in the PP population. Statistically significant differences in the proportions of ITT patients are:  $p=0.0013$ , PP:  $p=0.0004$  (< than 7 days) and  $p=0.0154$  ( $\geq 7$  days). The data obtained confirm a high efficacy of the parenteral etiotropic drug

and the expediency of prescribing it even in a delayed start of treatment. Moreover, the efficacy of the therapy under consideration was analyzed in patients depending on the presence of risk factors for a severe course of a coronavirus infection (the age over 60 years, the presence of concomitant diseases, such as obesity, type 2 diabetes, etc.). As a result of a comparative analysis of the improvement cases frequency in clinical status by 2 or more categories, statistically significant differences were revealed between the study groups ( $p=0.0027$ ). Thus, in the Areplivir® group, every second patient with risk factors for complications after a course of therapy achieved an improvement in clinical status by 2 points or more.

The rate of improvement in clinical status and the possibility of reducing the patients' stay length of in hospital is an important factor in assessing the appropriateness of a particular therapy, given the enormous economic burden of coronavirus infection. The study showed that in the favipiravir group, the proportion of patients with a clinical status of < than 4 which corresponds to the status of "outpatient" after a course of therapy, was 66.04% (70/106). There were statistically significant differences between the study groups ( $p=0.0121$ ) for this indicator. Moreover, in the study drug group, one in four patients (25.47%) achieved a clinical status of 0 and 1 on a categorial ordinal scale, corresponding to complete recovery. In the standard therapy group, this figure was only 6.48%.

The presence of positive dynamics in the disease course in the form of a decrease in the degree of lung damage in the favipiravir group according to CT data, is evidenced by the results of an intragroup analysis. Thus, a statistically significant difference was found between Visits 1 (beginning of the therapy) and 4 (Day 14 of the observation) (ITT:  $p=0.0191$ , PP:  $p=0.0004$ ). However, there was no statistically significant difference between Visits 1 and 4 in the standard therapy group (ITT:  $p=0.1025$ , PP:  $p=0.0733$ ). It is also worth noting that by the end of therapy, 75.47% of the patients in the favipiravir group in the ITT population and 77.45% of patients in the PP population, had achieved improvement in the lungs condition (the degree of the lungs involvement was CT-1 and CT-0), up to complete disappearance of the disease symptoms.

An analysis of the patients' frequency with the SARS-CoV-2 virus elimination (a negative laboratory test for the presence of SARS-CoV-2 RNA by the NAATs method) showed that in the group of patients who were receiving the study drug favipiravir, the elimination of the virus occurred earlier than in the standard therapy group. On the 5th day of therapy, the elimination of the virus was observed in 73.58% of patients in the main group.

An improvement in the clinical picture is an efficacy marker of etiotropic therapy, since even in the absence of a pathogen in the oropharynx, progression of pneumonia and worsening of the general condition may occur. Against the background of the therapy, there was

a pronounced positive trend in the parameters of the biochemical blood test, including such important markers of inflammation as CRP (45.5 mg/l at the screening visit, 11.3 mg/l after 5 days of therapy and 7.1 mg/l after the course of therapy); CPK (146.7 u/l at the screening visit and 78.8 u/l after the course of therapy) and ESR (20.9 mm/h at the screening visit and 9.99 mm/h after 10 days of therapy). There was normalization of body temperature and the level of blood oxygen saturation already on the 3-5th days of treatment, which indicates a decrease in the risk of developing complications of the disease and an improvement in its prognosis.

A comparative analysis of the patients frequency meeting discharge criteria on the basis of active IGs at the end of therapy showed that in the ITT population, the number of patients receiving favipiravir (27.36%) was twice the percentage of the standard therapy patients (14.81%) who had met all the discharge criteria by the end of therapy. In the favipiravir group, a stable improvement in the clinical picture was observed in 70.75%, in the standard therapy group it was 48.15%. A similar trend was observed in the PP population (Fig. 2).

A significant advantage over standard therapy in terms of achieving such "surrogate" endpoints as a faster onset of clinical improvement, shorter time to hospital discharge, and faster recovery indicates not only the clinical but also the pharmaco-economic efficacy of Areplivir for parenteral administration and the feasibility of the chosen drug therapy in patients hospitalized with COVID-19.

### Safety assessment

In this study, the analysis of all safety parameters was performed in a safety population that coincided with the ITT population of 214 patients (106 patients in the favipiravir group + 108 patients in the standard therapy group). The frequency of patients in the group of the drug favipiravir for the parenteral administration with reported cases of UDEs was 26.42%. A total of 46 UDEs was notified in 28 patients in the favipiravir group. The frequency of patients in the standard therapy group with reported cases of UDEs was 23.15%. There were no significant intergroup differences in the frequency and severity of UDEs.

Among the main UDEs, one can distinguish: an increase in ALT (39.22% in the main group, 45.45% in the comparison group), an increase in AST (15.69% in the main group, 20.45% in the comparison group), an increase in gamma-GTT (7.84% in the main group, 4.55% in the comparison group), bradycardia (3.95% and 4.95% in the main and control groups, respectively). Dizziness, hyperglycemia, and pyrexia can be distinguished out of the single UDEs, the frequency of which did not exceed 1%.

Among the reported UDEs in the favipiravir group patients, 93.48% were mild, 4.35% were moderate; in patients of the standard group therapy, 82.93% were

mild, 17.07% – moderate. According to the physicians' study, the causal relationship with the study drug therapy was assessed as "not related" in 6.52%, "possible" in 63.04%, "doubtful" in 21.74%, "probable" – in 6.52%, "conditional" – in 2.17% of cases; a causal relationship with standard therapy was assessed as "not related" in 2.44%, "possible" in 73.17%, "doubtful" in 14.63%, "probable" in 9.76% of cases.

The analysis of the frequency of UDEs outcomes in patients showed that in the group of the study drug favipiravir, significantly more UDEs ended in "recovery without consequences" ( $p=0.096$ ) and "improvement" ( $p=0.049$ ). In the study drug group, most UDEs were transient, and no treatment discontinuation or dose changes due to UDEs were reported in the study drug group. There were no ventilator requirements, deaths, or serious adverse events associated with the study medication, consistent with the predictable high safety profile of parenteral favipiravir in patients with coronavirus infection.

It has been shown that favipiravir therapy does not adversely affect the parameters of clinical and biochemical blood tests, urinalysis, coagulograms, vital signs and ECG. The study physicians assessed that the study drug was well tolerated by the patients. It should be emphasized that the parenteral administration of favipiravir does not have a local irritating effect on the gastrointestinal tract, which is especially important for COVID-19 patients, taking into account both the negative impact of the virus itself and the polypharmacy characteristic of this disease treatment [28].

## DISCUSSION

Compared to the group receiving only standard therapy for COVID-19, in the parenteral favipiravir group, almost 2 times more people were recorded with an improvement in clinical status by 2 or more points on a categorial ordinal scale, which indicates a high efficacy and the feasibility of the therapy. The revealed statistically significant differences in the proportions of patients between the study groups in both the ITT population ( $p=0.0001$ ) and the PP population ( $p<0.0001$ ) prove the hypothesis of the Areplivir® superiority over standard therapy.

A comparative analysis of the patients' frequency with a clinical status of 0 and 1 on a categorial ordinal scale of clinical improvement in both populations (ITT, PP), both at Visit 3 (the end of therapy) and at Visit 4 (Day 14 of follow-up), showed statistically significant differences (Pearson's Chi-square,  $p=0.0001$ ) in favor of the Areplivir® drug group.

The median time (in days) till the improvement in clinical status (in the ITT and PP populations) was 5 days in the favipiravir group and 7 days in the standard therapy group ( $p=0.0184$  and  $p=0.0048$ , respectively). The revealed statistically significant differences in the time till improvement of the patients' clinical status prove the

hypothesis of the superiority of the drug favipiravir over standard therapy.

Even with a delayed start of treatment, therapy with parenteral favipiravir is effective and reasonable. These data prove the efficacy of parenteral favipiravir in terms of increasing the rate and frequency of a pronounced improvement in the clinical status in the vast majority of patients hospitalized with COVID-19: statistically significant differences in the proportions of patients ITT:  $p=0.0013$ , PP:  $p=0.0004$  (< than 7 days) and  $p=0.0154$  ( $\geq 7$  days).

In the group of patients who received the study drug favipiravir, the elimination of the virus occurred earlier than in the standard therapy group. Already by Visit 2, virus clearance had been observed in 73.58% of patients in the ITT population and in 76.47% of patients in the PP population. The data obtained indicate a more rapid decrease in the viral load when using the parenteral form of the drug favipiravir, which helps to reduce the risks of aggravating the condition and improve the prognosis.

In the ITT population, the number of patients treated with favipiravir (27.36%) was twice the percentage of the patients on standard therapy (14.81%) who met all discharge criteria at the end of therapy. The comparative analysis revealed statistically significant differences between the study groups in terms of the frequency of patients meeting all discharge criteria at the end of therapy (ITT:  $p=0.0244$ , PP:  $p=0.0178$ ), as well as the achievement of a stable improvement in the clinical picture (ITT:  $p=0.0008$ , PP:  $p=0.0002$ ).

Therapy with the study drug favipiravir is accompanied by a significant improvement in the condition of the lungs according to CT, up to the complete disappearance of the disease symptoms.

Based on the statistical analysis of the data obtained, it can be argued that therapy with favipiravir for the parenteral administration significantly improves the condition of patients, accelerates recovery and reduces the time of hospital stay compared to standard therapy.

The analysis of the UDEs outcomes frequency in patients showed that in the group of the study drug favipiravir, significantly more UDEs ended in "recovery without consequences" ( $p=0.096$ ) and "improvement" ( $p=0.049$ ). In the study drug group, most UDEs were transient, and no treatment discontinuation or dose changes due to UDEs were reported in the study drug group. No UDEs or deaths associated with the use of favipiravir have been reported.

It has been shown that favipiravir therapy does not adversely affect laboratory parameters such as clinical and biochemical blood tests, urinalysis, coagulogram, vital signs and ECG, which indicates the safety of the therapy. During the study, the patients treated with the study drug showed positive changes in laboratory parameters, such as C-reactive protein, D-dimer, CPK, as well as a smaller increase in ALT and AST levels, which indicates a decrease in the intensity of inflammatory processes in

the body and the onset of a convalescence period. The study physicians assessed that the study drug was well tolerated by the patients.

### CONCLUSION

The results of a comparative assessment of the parenteral favipiravir therapy efficacy in COVID-19 patients compared with standard therapy, made it possible to establish significant advantages of using the drug in terms of the speed and frequency of a pronounced improvement onset in clinical parameters. That contributed to a faster transfer of patients from hospital to the outpatient stage of observation or achieving complete clinical recovery (4 times more patients in the main group than in the comparison group). It has been shown that the use of favipiravir in the form for the parenteral administration, due to favorable pharmacokinetic parameters, makes a faster and more pronounced therapeutic effect mediated by achieving complete elimination of the virus, possible.

That determines the reduction in the risk of developing a severe course and entering the ICU, and also helps to speed up the discharge of patients and improve the prognosis.

It can be argued that therapy with Areplivir® for the parenteral administration is characterized by a favorable safety profile, comparable, and in some cases, superior to that of standard therapy.

Taking into account the established reliable clinical benefits and data on the favipiravir effectiveness, regardless of a new coronavirus infection strain, the new original development of Areplivir® for the parenteral administration opens up additional opportunities to combat complicated forms of the disease and reduce the clinical and economic burden of COVID-19. The versatility and resistance to mutations of RNA-dependent RNA polymerase make it possible to consider it as the main target for combating the most common RNA viruses that cause ARVI, that determines the need further studies of favipiravir to expand the range of its indications.

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### CONFLICT OF INTEREST

The clinical study was organized by LLC Promomed RUS. LLC "Promomed RUS" is a member of the Promomed group of companies. LLC "Promomed RUS" is the holder of the registration certificate for the drug "Areplivir" LP-007598 dated 11/12/2021, LP-007660 dated 12/03/2021, LP-007681 dated 12/14/2021. The manufacturer of the drug "Areplivir" is JSC "Biochemist", which is a part of the group of companies of the state corporation "Promomed". Zaslavskaya K.Ya. is the Director of new products of LLC "Promomed DM".

### AUTHORS' CONTRIBUTION

Larisa A. Balykova – development and implementation of research design, research, writing and editing the text; Kira Ya. Zaslavskaya – research design development, text writing and editing; Vera F. Pavelkina – implementation of the study design, study data processing; Nikolai A. Pyataev – implementation of the study design, study data processing; Natalya M. Selezneva – implementation of the study design, study data processing;

Natalya V. Kirichenko – implementation of the study design, study data processing; Anastasia Yu. Ivanova – implementation of the study design, processing of research results; Grigory V. Rodoman – implementation of the study design, study data processing; Konstantin B. Kolontarev – development and implementation of research design, text editing; Konstantin S. Skrupsky – implementation of the study design, study data processing; Elena N. Simakina – implementation of the study design, study data processing; Olga A. Mubarakshina – analysis of the research results, writing and editing the text; Aleksey V. Taganov – data collection, analysis of the research results; Dmitry Yu. Pushkar – development and implementation of research design, analysis of results, text editing.

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