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MODERN DIRECTED ANTIVIRAL COVID-19 THERAPY: RESULTS OF MULTICENTER CLINICAL EFFECTIVENESS AND SAFETY STUDY OF FIXED NIRMATRELVIR+RITONAVIR COMBINATION

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The article presents the data from an open, two-stage, multicenter study on the efficacy and safety evaluation of a combined drug (a fixed combination of nirmatrelvir 300 mg and ritonavir 100 mg) in the complex therapy in COVID-19 patients.

The aim of the study was to assess the safety, tolerability and pharmacokinetic parameters of the fixed combination of nirmatrelvir 300 mg and ritonavir 100 mg in healthy volunteers, the efficacy and safety assessment of the drug in the combination therapy compared with the standard therapy in COVID-19 patients.

Material and methods. An open two-stage multicenter clinical study to assess the main pharmacokinetic parameters, safety, and efficacy against COVID-19 of the drug nirmatrelvir 300 mg and ritonavir 100 mg combination (Skyvira® PROMOMED RUS LLC, Russia) in the adult population, included 2 stages. At stage 1, safety, tolerability and pharmacokinetic parameters were evaluated in healthy volunteers (over 18 years of age) in order to confirm their comparability with the literature data known for a set of active substances. Phase 2 assessed efficacy and safety in COVID-19 patients. As a part of the second stage, the study involved 264 patients (men and women aged 18 to 80 years), who had been divided into two groups. The first group patients (n=132) received the study drugs (nirmatrelvir 300 mg and ritonavir 100 mg) – 1 tablet twice a day with an interval of 12±2 hours for 5 days in combination with pathogenetic and symptomatic therapy. The second group patients (n=132) received standard therapy in accordance with the approved Temporary Guidelines for the Prevention and Treatment of Novel Coronavirus Infection (Version 15 dated February 22, 2022).

Results. During the study, none of the patients from the (nirmatrelvir + ritonavir) group experienced a transition of the COVID-19 course to a heavier severity level, in contrast to the patients in the standard therapy group. The study participants included patients with comorbidities (68% of the general population), with risk factors for COVID-19 progression to a heavier severity level and the risk of hospitalization (75% of the general population). There were no cases of COVID-19 progression

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to a heavier severity level in the study drug group. By the 6th day, in the nirmatrelvir + ritonavir group, the proportion of the patients who had achieved a complete recovery was twice more and amounted to 35.61% (p=0.0001), and the proportion of the patients with a negative RNA analysis to SARS-CoV-2 was 20% higher than in the comparison group, and amounted to 82.58% (p=0.0001). The fixed nirmatrelvir + ritonavir combination therapy has a favorable safety profile comparable to the standard therapy. The identified adverse reactions were transient in nature and did not require discontinuation of therapy or changes in the treatment regimen.

Conclusion. The fixed nirmatrelvir + ritonavir combination has a favorable safety profile in COVID-19 patients, comparable to the standard therapy. The data obtained demonstrate a clinical and pharmacoeconomic feasibility of including the fixed (nirmatrelvir + ritonavir) combination in the COVID-19 treatment regimen.

Keywords: coronavirus; COVID-19; nirmatrelvir; ritonavir; Skyvira®; adverse events

Abbreviations: RDS – respiratory distress syndrome; WHO – World Health Organization; FDA – Food and Drug Administration (USA); SBP – systolic blood pressure; EMA – European Medicines Agency; AE – adverse event; DBP – diastolic blood pressure; HR – heart rate; RR – respiratory rate; BMI – body mass index; SAE – serious adverse events; IG – Interim Guidelines "Prevention, diagnosis and treatment of a new coronavirus infection"; Cmbs – comorbidities; NAAT – nucleic acid amplification test; NSAIDs – non-steroidal anti-inflammatory drugs; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ULN – upper limit of normal; MedDRA (Medical Dictionary for Regulatory Activities) – medical dictionary of terms of international medical terminology; EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) – assessment of protease inhibition in COVID-19 in patients at high risk; CI – confidence interval; SARS-CoV-2 – severe acute respiratory syndrome coronavirus; COVID-19 – CoronaVIrus Disease 2019; CTs – clinical trials; IWRS – Interactive web randomization system.

СОВРЕМЕННАЯ НАПРАВЛЕННАЯ ПРОТИВОВИРУСНАЯ ТЕРАПИЯ COVID-19: РЕЗУЛЬТАТЫ МНОГОЦЕНТРОВОГО КЛИНИЧЕСКОГО ИССЛЕДОВАНИЯ ЭФФЕКТИВНОСТИ И БЕЗОПАСНОСТИ ФИКСИРОВАННОЙ КОМБИНАЦИИ, СОДЕРЖАЩЕЙ НИРМАТРЕЛВИР И РИТОНАВИР

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В статье представлены данные открытого двухэтапного многоцентрового исследования по оценке эффективности и безопасности комбинированного препарата (фиксированная комбинация нирматрелвир 300 мг и ритонавир 100 мг) в комплексной терапии у пациентов с COVID-19.

Цель. Оценить безопасность, переносимость и фармакокинетические параметры фиксированной комбинации нирматрелвир 300 мг и ритонавир 100 мг у здоровых добровольцев, эффективность и безопасность применения препарата в комплексной терапии в сравнении со стандартной терапией у пациентов с COVID-19.

Материал и методы. Открытое двухэтапное многоцентровое клиническое исследование по оценке основных фармакокинетических параметров, безопасности, а также эффективности в отношении COVID-19 лекарственного препарата нирматрелвир 300 мг и ритонавир 100 мг (Скайвира® ООО «ПРОМОМЕД РУС», Россия) у взрослой популяции включало 2 этапа. На I этапе оценивалась безопасность, переносимость и фармакокинетические параметры у здоровых добровольцев (старше 18 лет) с целью подтверждения их сопоставимости с литературными данными, известными для набора действующих веществ. На II этапе оценивалась эффективность и безопасность у пациентов с COVID-19. В рамках II этапа в исследовании участвовало 264 пациента (мужчины и женщины в возрасте от 18 до 80 лет), которые были распределены на две группы. Пациенты первой группы (n=132) получали исследуемый препарат (нирматрелвир 300 мг и ритонавир 100 мг) по 1 таблетке 2 раза в день с интервалом 12±2 ч в течение 5 дней в комплексе с патогенетической и симптоматической терапией. Пациенты второй группы (n=132) получали стандартную терапию в соответствии с утвержденными Временными методическими рекомендациями по профилактике и лечению новой коронавирусной инфекции, утвержденными Министерством здравоохранения Российской Федерации (Версия 15 от 22.02.2022).

Результаты. За время исследования ни у одного пациента из группы (нирматрелвир + ритонавир) не наблюдалось перехода течения COVID-19 в более тяжелую степень в отличие от пациентов группы стандартной терапии. Среди участников исследования были пациенты с сопутствующими заболеваниями (68% от общей популяции), с факторами риска прогрессирования COVID-19 до тяжелого течения и риска госпитализации (75% от общей популяции). В группе исследуемого препарата не было ни одного случая перехода COVID-19 в более тяжелую степень течения. К 6-му дню в группе (нирматрелвир + ритонавир) доля пациентов, достигших полного выздоровления, была больше в 2 раза и составляла 35,61% (p=0,0001), а доля пациентов с отрицательным анализом РНК к SARS-CoV-2 была на 20% выше, чем у группы сравнения и составила 82,58% (p=0,0001). Терапия фиксированной комбинацией (нирматрелвир + ритонавир) характеризуется благоприятным профилем безопасности, сопоставимым со стандартной терапией. Выявленные нежелательные реакции носили транзиторный характер и не требовали отмены терапии или изменения схемы лечения.

Заключение. Фиксированная комбинация (нирматрелвир + ритонавир) характеризуется благоприятным профилем безопасности у пациентов с COVID-19, сопоставимым со стандартной терапией. Полученные данные свидетельствуют о клинической и фармакоэкономической целесообразности включения фиксированной комбинации нирматрелвира с ритонавиром в схему лечения COVID-19.

Ключевые слова: коронавирус; COVID-19; нирматрелвир; ритонавир; Скайвира®; нежелательные явления

Список сокращений: РДС – респираторный дистресс-синдром; ВОЗ – Всемирная организация здравоохранения; FDA – Управление по санитарному надзору за качеством пищевых продуктов и медикаментов (США); САД – систолическое артериальное давление; EMA – Европейское агентство лекарственных средств; НЯ – нежелательное явление; ДАД – диастолическое артериальное давление; ЧСС – частота сердечных сокращений; ЧДД – частота дыхательных движений; ИМТ – индекс массы тела; СНЯ – серьёзные нежелательные явления; ВМР – Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции»; СЗ – сопутствующие заболевания; МАНК – метод амплификации нуклеиновых кислот; НПВП – нестероидные противовоспалительные препараты; АЛТ – аланинаминотрансферазы; АСТ – аспартатаминотрансфераза; ВГН – верхняя граница нормы; MedDRA – медицинский словарь терминов международной медицинской терминологии; EPIC-HR – оценка ингибирования протеазы при COVID-19 у пациентов с высоким риском; ДИ – доверительный интервал; SARS-CoV-2 – коронавирус, возбудитель COVID-19; COVID-19 – коронавирусная инфекция; КИ – клинические исследования; IWRS – модуль рандомизации пациентов.

INTRODUCTION

COVID-19 can follow several scenarios – from asymptomatic carrier state to pneumonia of varying severity with the development of acute respiratory distress syndrome (ARDS). Despite the alleged “weakening” of SARS-CoV-2 new variants, the medical community has come to the consolidated opinion that without targeted antiviral therapy and vaccination, the COVID-19 pandemic may “approach” the scale of the 1894 plague (12 million deaths) and the flu pandemic A(H1N1) 1918 (50 million deaths) [1].

To date, the spread of the coronavirus disease (COVID-19) is still unstoppable (the number of confirmed cases and deaths continues to rise). The World Health Organization (WHO) reported the detection of cases in 216 different countries, which dictates the need to find new treatment strategies that can withstand the pandemic [2, 3].

The unprecedented global spread of SARS-CoV-2 has created serious challenges for the healthcare system. The global research community calls for the development of effective treatment protocols with the inclusion of new drugs with a high efficacy and safety profile that can significantly affect the containment and elimination of the COVID-19 pandemic [3, 4].

Currently, along with a standard supportive care, therapeutic approaches for the treatment of COVID-19 include the use of drugs that interfere with the life cycle of SARS-CoV-2 and block viral replication. At the moment, according to the medical community, the most promising is the combination of nirmatrelvir and ritonavir. It has been established that nirmatrelvir (PF-07321332) stops the spread of COVID-19 in animal models, and ritonavir slows down its metabolism and helps maintain therapeutic plasma concentrations. Despite frequent mutations in the SARS-CoV-2 genome, nirmatrelvir exhibits an effective antiviral effect against recent mutations and variants of coronavirus [5].

All coronaviruses, including SARS-CoV-2, encode two proteases required for the processing of the PP1A and PP1AB polyproteins. The main protease 3CL (chemotrypsin-like) gives rise to the formation of NSP11/16 proteins. The 3CL protease was chosen as one of the possible therapeutic targets for the development of antiviral drugs against SARS-CoV-2 due to its highly conserved sequence and structure. Nirmatrelvir (PF-00835231) has a high inhibitory activity against this particular protease. The antiviral activity of the drug was detected during the SARS-CoV-1 epidemic [6, 7].

Subsequently, a high antiviral activity of the nirmatrelvir and ritonavir combination against SARS-CoV-2 has been demonstrated [8]. Pharmacokinetic studies have shown off a significant increase in the systemic exposure of nirmatrelvir when co-administered with the CYP3A4 inhibitor ritonavir, consistent with the predominant role of CYP3A4 in the metabolism of nirmatrelvir [9, 10].

Further, in a number of clinical studies, the effectiveness of the nirmatrelvir + ritonavir combination was confirmed. Nirmatrelvir + ritonavir showed a greater reduction in the risk of hospitalization and death than molnupiravir compared with placebo. The both drugs were prescribed in the first five days after the onset of symptoms [11, 12].

In the EPIC-HR study, the use of the nirmatrelvir + ritonavir combination in the patients with a coronavirus infection resulted in an 88% reduction in hospitalization or mortality among unvaccinated outpatients with early COVID-19. The overall risk of hospitalization was 45% lower among the patients treated with nirmatrelvir + ritonavir [13]. An interim analysis demonstrated an 89% reduction in the risk of hospitalization or deaths from any cause associated with COVID-19 compared with placebo in the patients starting treatment within three days of the symptom onset (the primary endpoint) [14].

In a double-blind (randomized) study, unvaccinated, non-hospitalized adults at high risk of progression to the severe disease of COVID-19 were given nirmatrelvir (300 mg) + ritonavir (100 mg) every 12 hours for 5 days [15–16]. The primary aim of the study was to evaluate the efficacy of nirmatrelvir + ritonavir by comparing the percentage of patients with hospitalization or deaths from any cause related to COVID-19 within 28 days in the two groups.

A total of 2246 patients were randomized; 1120 patients received nirmatrelvir+ritonavir (a nirmatrelvir group) and 1126 patients received placebo (a placebo group). The incidence of hospitalizations or deaths associated with COVID-19 by day 28 in the nirmatrelvir group was 6.32% lower than in the placebo group (95% confidence interval (CI), –9.04 to –3.59; p <0.001, the reduction in the relative risk of hospitalization was 89.1%). All 13 deaths occurred in the placebo group.

The frequency of adverse events (AEs) was similar in the two groups (any AE: nirmatrelvir + ritonavir group/ placebo group – 22.6%/23.9%; serious AEs – 1.6%/6.6%; AEs leading to the drug withdrawal –2.1%/4.2%). Dysgeusia (5.6% vs 0.3%) and diarrhea (3.1% vs 1.6%) were more common in the groups treated with nirmatrelvir + ritonavir than with placebo. The treatment with nirmatrelvir in combination with ritonavir resulted in an 89% reduction in the risk of progression to severe COVID-19 compared with placebo and was characterized by a favorable safety profile [15–18].

In the study by Najjar-Debbiny R. et al. (2022), it was also proved that in the “Era of Omicrons”, nirmatrelvir in combination with ritonavir was very effective in reducing the risk of severe COVID-19 and/or mortality [19].

It is important to notify that the main target (3CL) is practically not amenable to mutations and modifications, and therefore nirmatrelvir in combination with ritonavir will be effective regardless of SARS-CoV-2 strains, which was also proven in a number of studies [20, 21].

The combination (nirmatrelvir + ritonavir) received a conditional approval in the United Kingdom in December 2021 for the treatment of adults at a high risk of progressing to severe COVID-19 patients who do not require supplemental oxygen. In January 2022, the nirmatrelvir + ritonavir combination was approved in the European Union to be used in adults and children over 12 years of age for the same indication and also has been approved for an emergency use in the USA [22, 23].

Due to the rapid spread of the Omicron SARS-CoV-2 virus variant worldwide, the Food and Drug

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Administration (FDA, USA) has issued an emergency use authorization of the nirmatrelvir + ritonavir combination for the outpatient treatment of mild to moderate COVID-19 patients who are susceptible to risk of progression [15, 24–25]. Nirmatrelvir is included in the WHO guidelines for the COVID-19 treatment [26].

THE AIM of the study was to assess the safety, tolerability and pharmacokinetic parameters of the fixed combination of nirmatrelvir and ritonavir in healthy volunteers, the efficacy and safety assessment of the drug in the combination therapy compared with the standard therapy in COVID-19 patients.

MATERIAL AND METHODS

An open two-stage multicenter study has been conducted to assess the main pharmacokinetic parameters and safety, as well as to evaluate the effectiveness of the drug Skyvira® (LLC PROMOMED RUS, Russia) against COVID-19 in the adult population.

This study was conducted with the aim of registering the drug in the Russian Federation, and included an assessment of the main pharmacokinetic parameters, safety, and efficacy against COVID-19[1].

The present study included 2 stages. At Stage 1, the safety, tolerability and pharmacokinetic parameters of the drug were evaluated in healthy volunteers (n=16), at Stage 2, the efficacy and safety of the drug were evaluated in COVID-19 patients.

The study was conducted in accordance with the principles of good clinical practice from February 17, 2021 to June 1, 2022 in 8 cities of the Russian Federation (Moscow, Saransk, Kirov, Ivanovo, Smolensk, St. Petersburg, Ryazan, Yaroslavl), on the basis of 12 medical institutions involved in the treatment of patients with a novel coronavirus infection.

Stage 1, research centers of clinical trials:

1. "Clinical Hospital No. 3" (Yaroslavl);
2. Analytical laboratory: LLC Center for Pharmaceutical Analytics (Moscow).

Stage 2, research centers of clinical trials:

1. Clinical Hospital No. 3 (Yaroslavl);
2. Spasokukotsky City Clinical Hospital, Moscow City Health Department (Moscow);
3. National Research Ogarev Mordovia State University, (Saransk);
4. Clinical Hospital No. 1 (Smolensk);
5. Ivanovo Clinical Hospital n. a. after the Kuvaevs (Ivanovo);
6. Ryazan Pavlov State Medical University (Ryazan);
7. Kirov State Medical University (Kirov);
8. Smolensk State Medical University (Smolensk);
9. LLC "Aurora MedFort" (St. Petersburg);
10. OrKli Hospital Limited Liability Company (St. Petersburg);
11. LLC "Uromed" (Smolensk).

Research objectives

Stage 1 of the study included a non-randomized cohort design. All volunteers were screened and then hospitalized per cohort (the volunteers of cohort 2 were invited to hospitalization after the completion of participation in the study of cohort 1volunteers, subject to approval of a further study by the Expert Council for Drug Safety).

At this stage of the study, after the use of a fixed combination of nirmatrelvir + ritonavir, the following factors were evaluated in healthy volunteers: drug tolerability, basic vital signs, physical examination data, ECG, laboratory parameters (a clinical blood test, a biochemical blood test, a clinical urinalysis), the frequency and the AE severity. The pharmacokinetic parameters of the active substances (nirmatrelvir + ritonavir) after single and multiple uses of the drug were also studied.

Inclusion criteria for Stage I:

1. Possession of a signed and dated informed consent form, as well as the ability and willingness to comply with all the requirements of the study protocol;
2. Men between 18 and 45 years old (inclusive) at the time of signing the informed consent form;
3. A verified diagnosis of "healthy" according to the standard clinical, laboratory and instrumental methods of examination;
4. Hemodynamic parameters: systolic blood pressure (SBP) 100–130 Mmhg, diastolic blood pressure (DBP) 60–85 Mmhg, heart rate (HR) 60–90 beats per minute, respiratory rate (RR) 16-20 breaths per minute;
5. Negative test results for human immunodeficiency virus (HIV), syphilis, hepatitis B (HbsAg), and hepatitis C (HCV);

[1] Open two-stage multicenter study has been conducted to assess the main pharmacokinetic parameters and safety, as well as to evaluate the effectiveness of the drug Skyvira® (LLC PROMOMED RUS, Russia) against COVID-19 in the adult population film-coated tablets (LLC PROMOMED RUS, Russia). Research sponsor LLC PROMOMED RUS, Russia. Study protocol: No. NR-012022. Phase of clinical development: I–III phase. Stage I – open incompare cohort. Stage II – open, randomized multicenter comparative. Dates of the study: 2021 Feb 17 – 2022 Jan 06. Contract research organization: SOLYUR-PHARM LLC, office 2, room 1, floor 3, Bldg 2, 4, Ivana Franko Str., Moscow, Russia, 121108.

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6. Negative test results for the use of alcohol, narcotic drugs and psychotropic substances.

7. Body mass index (BMI): 18.5–30 kg/m^2;

8. Willingness to abstain from alcohol within 72 hours prior to screening and during the study period;

9. A volunteer's consent to use reliable methods of contraception during the study period, within 3 weeks after its completion.

Criteria for non-inclusion, Stage 1:

1. Aggravated allergological anamnesis, drug intolerance. Hypersensitivity to the components of the study drug;

2. Lactase deficiency, lactose intolerance, glucose-galactose malabsorption;

3. Impossibility to install a venous catheter for blood sampling;

4. Difficulties in swallowing tablets;

5. Donation or loss of blood (≥450 ml of blood or plasma) less than 3 months prior to screening;

6. Acute and chronic diseases of the cardiovascular, bronchopulmonary, endocrine and nervous systems, including organic diseases of the central nervous system (CNS), as well as diseases of the gastrointestinal tract (GIT), liver, kidneys, blood;

7. Any deviations from normal values during laboratory and/or instrumental examinations.

8. Surgical interventions on the gastrointestinal tract (with the exception of appendectomy) in anamnesis;

9. Acute infectious diseases or symptoms of SARS less than 4 weeks before the screening visit;

10. Detection of SARS-CoV-2 RNA or SARS-CoV-2 antigen within 6 months prior to the screening;

11. Presence of at least one of the epidemic signs:

- return from an overseas travel 14 days prior to the screening and no test results for SARS-CoV-2 RNA or SARS-CoV-2 antigen;
- close contact with a person under observation for COVID-19 who subsequently became ill, in the past 14 days prior to the screening;
- close contact with a laboratory confirmed case of COVID-19 in the past 14 days prior to the screening;
- professional contacts with individuals who have a suspected or confirmed case of COVID-19 in the last 14 days prior to the screening.

12. Regular intake of medications, including herbal and homeopathic preparations, vitamins and/or dietary supplements (BASs) less than 4 weeks before the screening visit;

13. Taking medications that have a pronounced effect on hemodynamics and/or liver function (barbiturates, omeprazole, cimetidine, etc.) less than 2 months before the screening visit;

14. Special diet (e.g., vegetarian, salt-restricted) less than 2 months prior to the screening visit;

15. Special lifestyle (night work, an extreme physical activity) less than 2 months prior to the

16. Alcohol ingestion in anamnesis: 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 hard liquor), or anamnestic data on alcoholism, drug addiction, drug abuse;

17. Smoking more than 10 cigarettes per day at the time of the screening visit;

18. Performing piercing procedures, tattooing/ tattooing less than 1 month before screening procedures and throughout the study;

19. Mental, physical and other reasons that do not allow the volunteer to adequately assess their behavior and correctly fulfill the conditions of the Research Protocol;

20. Participation in another clinical trial less than 3 months before the screening visit;

21. Other reasons that do not allow the volunteer, in the opinion of the research physician, to take part in this study.

Duration of Stage I

The total duration of a volunteer's participation in the study was no more than 11 days, herewith, the screening duration was no more than 7 days, the duration of a hospital stay was no more than 3.5 days, the duration of the study drug was no more than 3 days.

Assessed safety indicators for Stage I:

1. The frequency and severity of AEs registered on the basis of complaints, changes in the well-being of volunteers according to abnormal results of laboratory tests, physical examinations, assessment of vital signs, ECG;

2. Number of cases of participants' early termination in the study due to the development of AEs and/or SAEs, including those related to the investigated drug;

3. Assessment of the overall tolerability of the investigated drug on the Likert scale by the investigator.

Method of application in Stage I

It was supposed to include 2 cohorts of 8 healthy volunteers each: Cohort 1 – 300 mg + 100 mg once; Cohort 2 – 300 mg + 100 mg every 12 hours, 5 doses in total.

The study began with the use of the drug by Cohort 1 volunteers. Taking the drug by the volunteers Cohort 2

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was started only after assessing the safety of the drug by the volunteers of Cohort 1.

The decision on the possibility of switching to the multiple use of the drug within Cohort 2 was made by the Expert Council for Drug Safety based on the assessment of AE/SAE. The transition to Cohort 2 could be stopped if at least one of the following stopping criteria was found in Cohort 1 of the volunteers. These criteria are as follows: the development of a serious adverse reaction with a possible, probable or definite connection with the study drug in ≥1 healthy volunteers; the development of a severe adverse reaction with a possible, probable or definite connection with the use of the study drug in ≥2 healthy volunteers, regardless of whether they belong to the same class of organ systems or not.

Randomization of Stage II

Randomization was performed using the IWRS (Interactive web randomization system) built into a patient's electronic individual registration card. At Stage 2 of the study, 264 patients who had finished the study all over in accordance with the approved protocol were randomized.

In the group of the drugs combination nirmatrelvir + ritonavir (group 1), 84 female patients (63.64%) and 48 male patients (36.36%) were randomized, in the standard therapy group – 82 female patients (62.12%) and 50 male patients (37.88%). Subgroup 1–1 (n=33) was without any presence of a risk factor for the development of a severe COVID-19 course. Subgroup 1–2 (n=99) was characterized by the presence of at least one risk factor for the development of a severe COVID-19 course.

The mean age of patients in the fixed combination (nirmatrelvir + ritonavir) group was 46.61±15.75 years (from 19 to 79 years of age), the mean body weight was 80.69±14.31 kg (from 49.0 to 116 .0 kg), the height was 170.44±7.78 cm (from 152 to 190 cm), BMI – 27.81± 4.89 kg/m^2 (from 18.37 to 40.90 kg/m^2).

The mean age of patients in the standard therapy group was 46.62±15.97 years (from 18 to 77 years old), the mean body weight was 79.32±14.57 kg (from 50.0 to 122.0 kg), the mean height – 170.01±7.74 cm (from 148 to 193 cm), the mean BMI – 27.45±4.81 kg/m^2 (from 17.71 to 43.74 kg/m^2).

The first group (n=132) received 1 tablet of the study drug (nirmatrelvir + ritonavir) twice a day with an interval of 12±2 hours for 5 days in combination with pathogenetic and symptomatic therapy, presented in the Interim Guidelines "Prevention, diagnosis and treatment of novel coronavirus infection" (IG)[2], valid at the time of the study.

The second group (n=132) received standard therapy in accordance with the IGs in force at the time of the study[3].

Each group included 2 subgroups depending on the presence/absence of at least one risk factor for the development of severe COVID-19 in the ratio of 3:1.

Inclusion criteria for Stage 2:

1. Availability of an informed consent form signed and dated by the patient;

2. Men and women aged from 18 to 80 years old inclusive at the time of signing the informed consent form;

3. A confirmed case of COVID-19 at the screening time: a positive laboratory test for the presence of SARS-CoV-2 RNA using nucleic acid amplification methods (NAAT) or SARS-CoV-2 antigen using an immunochromatographic analysis[4];

4. A mild or moderate infection caused by SARS-CoV-2;

5. At the time of screening and randomization, there is at least one of the following symptoms characteristic of COVID-19: nasal congestion or a running nose, a sore throat, shortness of breath on exertion, cough, fatigue, muscle or body pain, headache pain, chills, fever (body temperature >38°C), nausea, vomiting, diarrhea, loss of smell (anosmia), loss of taste sensation (ageusia).

6. The onset of the disease (appearance of the first symptom) no more than 5 days before randomization;

7. A patient is willing and able to take oral medications;

8. A patient's consent to use reliable methods of contraception throughout the study and for 3 weeks after the end of the study.

The study could also include the women who are unable to bear children (anamnesis: hysterectomy, tubal ligation, infertility, menopause for more than 10 years), as well as men with infertility or anamnesis of vasectomy.

[2] Interim guidelines "Prevention, diagnosis and treatment of a new coronavirus infection" (COVID-19), version 16 (2022 Aug 18), approved by the Ministry of Health of Russian Federation.
[3] Interim guidelines "Prevention, diagnosis and treatment of a new coronavirus infection" (COVID-19), version 15 (2022 Feb 22), approved by the Ministry of Health of Russian Federation.
[4] SARS-CoV-2 test results obtained up to 5 days prior to randomization could be considered if supporting documentation was available.

Criteria for non-inclusion, Stage 2:

1. Hypersensitivity to the components of the study drug;

2. Lactase deficiency, lactose intolerance, glucose-galactose malabsorption;

3. Use of direct-acting antivirals within 10 days prior to the screening;

4. At the screening time, the use of the drugs, clearance of which is highly dependent on the CYP3A isoenzyme, or which are strong inducers of CYP3A (for more information, see the section "Prohibited Therapy");

5. The need for the use of drugs from the list of prohibited therapies;

6. The need for oxygen therapy at the time of screening;

7. The need for hospitalization at the time of screening, or expecting the need for hospitalization caused by COVID-19 within 48 hours of randomization, other than the need for hospitalization in an observatory for social reasons (e.g., living in a hostel, cohabiting with people, including risk factors for severe COVID-19, who, after a contact with a patient, have a negative result in SARS-CoV-2 RNA/antigen, etc.);

8. Availability of criteria for severe and extremely severe course of the disease at the time of screening;

9. Vaccination less than 4 weeks prior to the screening;

10. Presence of a probable or confirmed case of moderate COVID-19 within 6 months prior to the screening;

11. Presence of a probable or confirmed case of severe and extremely severe COVID-19 in anamnesis;

12. Patients with the established moderate to severe renal insufficiency (the estimated glomerular filtration rate (GFR) <60 ml/min/1.73m^2 according to the CKD-EPI formula) or receiving renal replacement therapy at the screening time;

13. A severe liver failure (class C in Child-Pugh's classification) at the moment of screening or anamnesis (within 6 months prior to the screening) of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.5 upper limit of normal (ULN)), and/or total bilirubin ≥2 ULN (≥3 ULN in Gilbert's syndrome);

14. A positive result of the analysis for the presence of HIV, syphilis, hepatitis B and/or C at the screening;

15. Alcohol, pharmacological and/or drug dependence in anamnesis and/or at the screening time;

16. Schizophrenia, schizoaffective disorder, a bipolar disorder or other psychiatric pathology in anamnesis or suspicion of their presence at the screening time;

17. Any anamnestic data that, in the opinion of the investigator, may complicate the interpretation of the results of the study or create any kind of an additional risk for a patient as a result of his participation in the study;

18. Unwillingness or inability of a patient to comply with the procedures of the Protocol (according to the investigator);

19. Pregnant or lactating women or women planning a pregnancy;

20. Participation in another clinical study within 3 months prior to the enrollment in the study;

21. Other conditions that prevent the inclusion of the patient in the study.

Duration of Stage 2

The total duration of a patient's participation in the study was no more than 31 days (Table 1).

Criteria for safety assessment, Stage II:

1. Total number of AEs stratified by severity and frequency.

2. Frequency of adverse events.

3. Frequency of SAEs, including those associated with study drug/standard therapy.

4. Proportion of patients with at least one AE.

5. Percentage of patients interrupting the treatment due to AE/SAE.

Criteria for evaluating effectiveness at Stage 2:

Primary efficacy criterion:

Incidence of patients with COVID-19 progressing to a more severe Interim Guidelines from baseline at visit 4 (Day 16).

Secondary efficacy criteria:

1. Dynamics of clinical status on a categorical ordinal scale of clinical improvement;

2. Frequency of worsening clinical status on a categorical ordinal scale of clinical improvement by ≥1 category at visits 2, 3 and 4;

3. Frequency of patients with category 0 on the categorical ordinal scale of clinical improvement at visits 2, 3 and 4;

4. Rate of SARS-CoV-2 RNA negative patients at visits 2, 3 and 4;

5 Symptom scores for Visits 2–6 on the COVID-19 Major Symptom Rating Scale.

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Statistical processing of research results

For the statistical analysis, software with validated algorithms for performing statistical analyzes and proper documentation StatSoft Statistica 10.0., IBM SPSS Statistics 22 (current version, GPL-2/GPL-3 license) was used.

Descriptive statistics is presented for all indicators of efficacy, safety, tolerability, and pharmacokinetic parameters collected during the study.

Continuous (quantitative) data are presented using a number of observations, arithmetic mean, 95% confidence interval (CI) for mean, standard deviation, median, interquartile range (25^{th} and 75^{th} centiles), minimum and maximum (if not specified otherwise).

Ordinal, categorial, and qualitative data are presented as absolute frequencies (a number of observations), relative frequencies (percentage), and 95% CI (unless noted otherwise).

Checking for the normality of the distribution was carried out by one of the generally accepted methods (the Shapiro-Wilk test, the Kolmogorov-Smirnov test). In case of a non-Gaussian distribution, non-parametric estimation methods were used to compare indicators.

To assess the parameters represented by ordinal values, non-parametric methods of the analysis were used. The Mann-Whitney test was used to compare indicators between the groups; to assess the dynamics of an indicator within each group, the Friedman criterion for several dependent variables was used; to compare between the start and the end points within each group, the Wilcoxon test for two dependent variables was applied. If all the expected values in the cells of the contingency table for this analysis were 5 or more, the Fisher's exact test or the chi-square test χ^2 could be also used for the analysis,

For the comparison between the groups of continuous quantitative indicators, the Student's t-test or Mann-Whitney test was used (depending on the conclusion about the nature of the distribution). Between the start and the end points of the assessment within each group, a paired t-test or the Wilcoxon test for two dependent variables (depending on the accepted conclusion about the nature of the distribution) were used.

In the case of estimating the time to the event (time-to-event), taking into account censored observations, the Kaplan-Meier method and the construction of survival tables could be used as descriptive methods of the analysis; the Cox-Mentel or Log-rank test.

The differences were considered statistically significant at $p < 0.05$.

Significance levels and confidence intervals were calculated as two-tailed, statistical significance of the differences was by default two-tailed and referred to a significance level of 0.05 (unless indicated otherwise).

For Stages I and II of the study, demographic data (age, sex), baseline data are presented as absolute frequencies (numbers of observations), relative frequencies (percentage) or using the arithmetic mean, 95% CI for the mean, standard (root mean square) deviation, median, interquartile range (25^{th} and 75^{th} centiles), minimum and maximum depending on the type of the variable.

At Stage 2, to test the hypothesis about the homogeneity of the study groups, the null hypotheses (about the absence of differences between groups) using the Student's t-test (for interval indicators with a normal distribution in the study population) were tested. The Mann-Whitney test (for ordinal indicators or for interval indicators with a distribution other than normal) or the Fisher's exact test and the χ^2 test (for qualitative traits) were also used.

In the case of finding statistically significant differences between the groups, the magnitude of the differences between the study groups was assessed using CI.

RESULTS AND DISCUSSION

Results of study, Stage 1

As a part of the first stage of the investigation, the safety of the studied combination was initially confirmed and its pharmacokinetic profile was studied (Fig. 1, 2).

During the first phase of the study, the comparability of the main pharmacokinetic parameters of the studied fixed combination with the literature data [8, 9, 16] for both nirmatrelvir and ritonavir was shown, both with a single and multiple administration.

Nirmatrelvir

Cohort 1 (a single administration): the median time to reach the maximum concentration (C_{max} = 1988.92±1109.65 ng/ml) of nirmatrelvir was T_{max} = 1.75 hours. Nirmatrelvir was eliminated from blood plasma with a mean of $T_{1/2}$ = 5.80 ± 1.96 hours. The $AUC0_{-\infty}$ and AUC_{0-t} values were 15354.88±6258.84 ng×h/ml and 13105.22±5656.34 ng×h/ml, respectively. The total clearance (Cl) was 23.18 ± 11.21 l/h. The volume of the drug distribution corresponded to the value of V_d = 189.08±98.03 liters. The value of the mean retention time of the drug substance in the blood plasma was MRT = 8.82±3.00 hours.

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Table 1 – Schedule of patients' visits at Stage 2 of the study

Visit No.	Interval (hours/days)	Study status
0	No more than 48 hours	Screening
1	1 day*	Randomization
2	6–7 day	–
3	11–12 days	–
4	14–15 days**	–
5	21±1 days**	–
6	28±1 days**	Completion

Note: * – visit 1 may have coincided with visit 0. If visit 1 and visit 0 were the same, then physical examinations, vital signs, registration of concomitant therapy, pulse oximetry with SpO_2 measurement, symptom scores using the COVID-19 Symptom Scale were not repeated, inclusion and non-inclusion criteria were assessed immediately before randomization, and exclusion criteria were assessed after drug administration. ** – the visit could be carried out both in person and by a phone call. In case of a phone call visit, and in the presence of a positive SARS-CoV-2 RNA test at the previous visit, medical personnel were sent to collect a swab from the nasopharynx and/or oropharynx for SARS-CoV-2 RNA analysis.

Table 2 – Risk factors in patients in study drug and standard therapy group

Risk factors	Main group (n=132)	Comparison group (n=132)
BMI 30 or more kg/m^2	36.36%	37.12%
Heart diseases	31.06%	30.30%
Age over 60 years	22.73%	21.97%
Chronic kidney diseases	3.03%	6.82%
Chronic lung diseases	2.27%	6.82%
Diabetes mellitus	0.76%	1.52%
Active malignancy	0.76%	–

Table 3 – Analysis of adverse reactions frequency according to WHO classification associated with taking nirmatrelvir + ritonavir combination

System organ class and preferred MedDRA term	Number of events (abs/%)		p-value (Fisher's criterion)
	Nirmatrelvir + ritonavir (n=132)	Standard therapy (n=132)	
Gastrointestinal disorders			
Diarrhea	1 (0.8%) (infrequent)	1 (0.8%) (infrequent)	1.0000
Dry mouth	1 (0.8%) (infrequent)	Not observed	1.0000
Nausea	Not observed	2 (1.5%) (frequent)	0.4981
Laboratory and instrumental data			
Increased ALT levels	3 (2.3%) (frequent)	2 (1.5%) (frequent)	1.0000
Increased AST levels	3 (2.3%) (frequent)	2 (1.5%) (frequent)	1.0000
Skin and subcutaneous tissue disorders			
Erythema	Not observed	1 (0.8%) (infrequent)	1.0000
Nervous System Disorders			
Dysgeusia	3 (2.3%) (frequent)	Not observed	0.2472

Note: The frequency of adverse reactions occurrence is defined as follows: very often (≥1/10), often (≥1/100, but <1/10), infrequently (≥1/1000, but <1/100), rarely (≥ 1/10,000 but <1/1000), very rarely (<1/10,000), not known (cannot be established based on available data). ALT – alanine aminotransferase, AST – aspartate aminotransferase.

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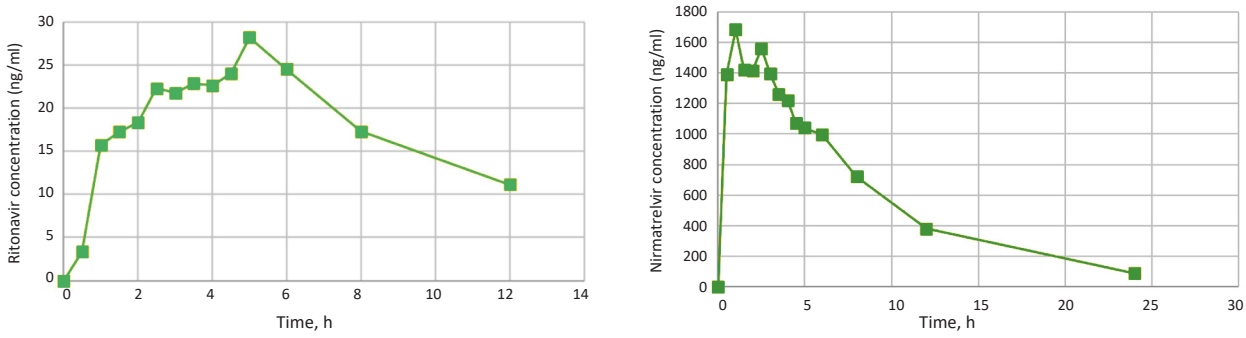
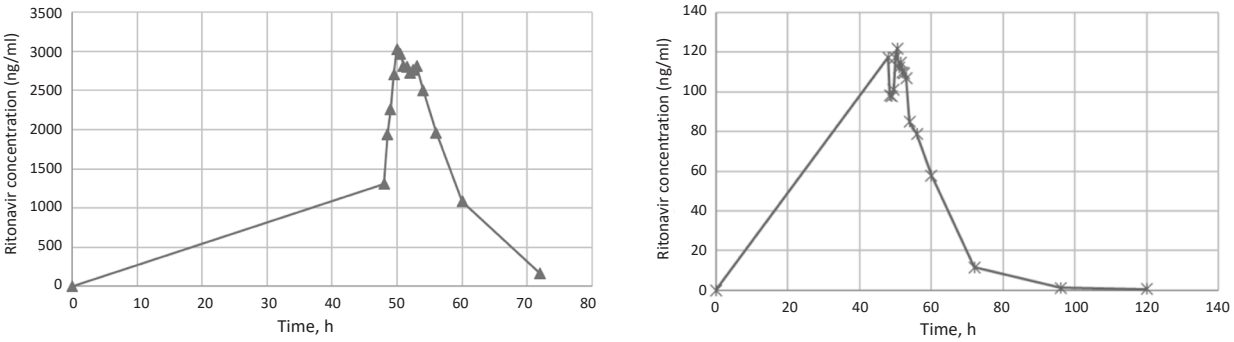


a) b)

Figure 1 – Pharmacokinetic profile of average concentration values of nirmatrelvir a) and ritonavir b) over time (in a linear transformation) after a single dose of the study drug



a) b)

Figure 2 – Pharmacokinetic profile of average concentration values of nirmatrelvir a) and ritonavir b) over time (in a linear transformation) after multiple doses of the study drug

Cohort 2 (a repeated administration): the value of the maximum nirmatrelvir concentration in the volunteers' blood plasma was $C_{max,\ ma}$ = 3442.52±1078.88 ng/ml. The value of the minimum nirmatrelvir concentration in the blood plasma of volunteers was $C_{min,\ ma}$ = 246.30± 174.85 ng/ml. The $AUC_{48-\tau}$ value was 33334.03± 9770.52 ng×h/ml.

Ritonavir

Cohort 1 (a single administration): the value of the median time to reach the maximum concentration (C_{max} = 25.74±20.98 ng/ml) of ritonavir was T_{max} = 5 hours. Ritonavir was eliminated from the blood plasma with a mean of $T_{1/2}$ = 8.13 ± 3.08 hours. $AUC_{0-\infty}$ and AUC_{0-t} values were 652.80 ± 264.85 ng×h/ml and 183,89± 206,42 ng×h/ml, respectively. The total clearance (Cl) was 173.84±78.32 l/h. The volume of the drug distribution corresponds to the value of V_d = 1991.30± 1049.61 liters. The value of the mean retention time of the drug substance in the blood plasma was MRT = 13.39±4.12 hours.

Cohort 1 (a repeated administration): the value of the maximum ritonavir concentration in the volunteers' blood plasma was $C_{max,\ ma}$ = 148.15±92.80 ng/ml. The value of the minimum ritonavir concentration in the volunteers' blood plasma was $C_{min,\ ma}$ = 16.78±9.48 ng/ml. The $AUC_{48-\tau}$ value was 1542.89±1207.18 ng×h/ml.

Since the results of the clinical trials (CTs) Stage 1 showed a favorable safety profile and a good tolerability in single and multiple oral administrations of the combination in the form of film-coated tablets, nirmatrelvir 300 mg and ritonavir 100 mg, during the Stage 1 study, no criteria for stopping the CTs were identified, and comparability of the obtained pharmacokinetic data for nirmatrelvir and ritonavir with the available literature data was demonstrated. The Ethics committee of the Ministry of Health[5] of Russian Federation considered it possible to proceed to the second stage of the study. It should be notified that the data obtained confirm the possibility and expediency of combining the active substances in the form of the fixed combination, which reduces polypharmacy and increases the convenience of use for patients.

Results of study, Stage 2

182 (68.94%) of 264 patients had MedDRA-classified comorbidities (Cmbs).

[5] Study protocol: No. NR-012022. Contract research organization: SOLYUR-PHARM LLC, office 2, room 1, floor 3, Bldg 2, 4, Ivana Franko Str., Moscow, Russia, 121108.

The most common Cmbs were obesity (36.32%) and hypertension (32.48%), kidney diseases (15%), other Cmbs (11%), respiratory diseases (7%), etc. The groups were comparable in terms of the Cmbs presence. In the study drug group, it is interesting to notify the presence of patients with oncological diseases and anamnestic data on atrial fibrillation, i.e., the patients for whom a high safety profile of the drug is especially important.

A total of 264 patients including 198 patients with risk factors (99 (75%) patients in each group) were observed in the study (Stage 2). Of these, with the risk factor of "the age over 60 years" there were 30 patients (22.73%) in the study drug group and 29 patients (21.97%) in the comparison drug group; with the risk factor of "obesity (BMI 30 or more kg/m^2)" – 48 patients (36.36%) in the study drug group and 49 patients (37.12%) in the comparison drug group; with the risk factor of "diabetes mellitus" – 1 patient (0.76%) in the study drug group and 2 patients (1.52%) in the comparison drug group; with a risk factor of "a heart disease" – 41 patients (31.06%) in the study drug group and 40 patients (30.30%) in the comparison drug group; with the risk factor of "chronic lung diseases" – 3 patients (2.27%) in the study drug group and 9 patients (6.82%) in the comparison drug group; with the risk factor of "chronic kidney diseases" – 4 patients (3.03%) in the study drug group and 9 patients (6.82%) in the comparison drug group; with the risk factor of "active malignant neoplasm" – 1 patient (0.76%) in the study drug group. Information on the frequency of risk factors occurrence in the patients in the study drug group and a standard therapy group is presented in Table 2.

The intergroup analysis showed that the study groups were comparable in terms of demographic and clinical characteristics.

During the study, none of the patients in the nirmatrelvir + ritonavir group experienced a transition of the COVID-19 course to a heavier severity level, более тяжелую степень тяжести in contrast to the patients in the standard therapy group.

In the drug group (nirmatrelvir + ritonavir), the proportion of patients with the transition of the course of COVID-19 to a heavier severity level, более тяжелую степень тяжести compared to the initial state by day 16, was 0.00% (0/132), 95% CI [0.0000; 0.0352], in the standard therapy group – 6.06% (8/132), 95% CI [0.0285; 0.1198]. The difference in proportions between the drug groups (nirmatrelvir + ritonavir) and the standard therapy group was 0.0606 (6.06%), 95% CI [0.0129; 0.1198].

Hypothesis testing for the final statistical analysis was carried out at a one-sided significance level of 0.0275. As a result of a comparative analysis of the patients' frequency with the transition of the course of COVID-19 to a heavier severity level compared to the initial state by day 16, statistically significant differences were revealed between the drug group (nirmatrelvir + ritonavir) and the standard therapy group (p = 0.0035, i.e. p <0.0275).

Thus, the hypothesis of the therapy superiority with nirmatrelvir + ritonavir over the standard therapy can be considered proven. It has been also concluded that fixed combination therapy reduces the risk of deterioration in the patients' clinical condition and improves the prognosis of the disease course.

Due to the fact that among the study participants there were patients with Cmbs (68% of the general population), with risk factors for the progression of COVID-19 to a heavier severity level and the risk of hospitalization (75% of the total population), we can conclude that the therapy was highly effective (nirmatrelvir + ritonavir), regardless of the risk factors presence for an aggravated course of the disease.

Thus, the therapy under consideration is reasonable, clinically and pharmacoeconomically effective.

The dynamics of the mean value (Mean ± SD) of the clinical status on the categorical ordinal scale of the clinical improvement in the study drug group (nirmatrelvir and ritonavir) on the 6th day of the observation was 1.30±1.01 points compared to the standard therapy 1.76±0.79 (p=0.0001). This demonstrates the advantage of the fixed combination over the standard regimen in terms of reducing the severity of COVID-19 symptoms and improving the clinical condition of the patients and accelerating their recovery.

The frequency of patients with category 0 on the categorical ordinal scale of clinical improvement by the 6th day of observation in the drug group (nirmatrelvir and ritonavir) was 2 times more and amounted to 35.61% (47/132), compared to the standard therapy group – 14.39% (19/132) (p=0.0001). The data obtained indicate a high efficiency of the fixed combination (nirmatrelvir + ritonavir) and its significant advantages over the comparison group in terms of the improvement rate in the clinical status of the patients and the reduction of their recovery time.

The frequency of patients with a negative SARS-CoV-2 RNA analysis by the 6th day in the study drug group, was 20% higher than in the control group (82.58% of patients (109/132) and 61.36% of patients (81/132), respectively), which indicates the effective antiviral effect of the fixed combination (nirmatrelvir + ritonavir), characterized by a reduction in the elimination of the SARS-CoV-2 virus compared to the standard therapy. That leads to a faster disappearance of the infectious

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disease symptoms and reduces the risk of developing COVID-19 complications.

As a result of a comparative analysis of the patients' frequency with varying severity symptoms by day 6, statistically significant differences were found between the drug group (nirmatrelvir and ritonavir) and the standard therapy group in terms of symptoms: nasal congestion or a running nose (p = 0.0027), a sore throat (p=0.0016), cough (p=0.0424), fatigue (p=0.0003), as well as the presence of cough symptoms at visit 4 (p=0.0016), indicating the effectiveness of the fixed combination in COVID-19 patients.

The assessment of the total score on the scale of the main COVID-19 symptoms shows that the average value of the total score for all the symptoms in the group taking the combination of nirmatrelvir + ritonavir (Mean ± SD) by day 6 (p <0.0001), was 1.39 ± 1.45 points (at screening – 5.43±2.16), in the standard therapy group – 2.21±1.77 points (at screening – 5.80 ± 2.46). I.e., in the study drug group, positive dynamics for all the symptoms occurred 60% faster than in the comparison group, and the changes were more pronounced. Thus, the use of the considered combination provides an improvement in the general condition and relief of the main symptoms of the disease.

Additionally, according to the WHO classification, an analysis of the adverse reactions frequency including AEs with a certain, probable and possible connection with the drugs nirmatrelvir + ritonavir (Table 3), was made.

The results of the comparative analysis also showed that taking the study drug contributed to a more effective decrease in the body temperature, which led to a decrease in the need for taking non-steroidal anti-inflammatory drugs (NSAIDs) and an increase in the therapy safety in general.

The incidence of patients in the study drug group with reported AEs was 7.58% (10/132). In total, 14 AEs were notified in 10 patients of the nirmatrelvir + ritonavir group. Among the reported AEs, 92.86% (13/14) were of a mild severity, 7.14% (1/14) were of a moderate severity. According to the study physicians, a causal relationship with the study drug therapy was assessed as "possible" in 71.43% (10/14) of cases, as "not related" in 14.29% (2/14) of cases, as "probable" in 7.14% (1/14) of cases, as "doubtful" in 7.14% (1/14) of cases. The analysis of the AEs outcomes frequency in the patients showed that in the group of patients who had received the study drug, "recovery without consequences" was notified in 100% (14/14) of cases.

The frequency of patients in the standard therapy group with reported cases of AEs was 6.06% (8/132). A total of 10 AEs were notified in 8 patients of the standard therapy group. Among the registered AEs, 90.00% (9/10) were of a mild severity, 10.00% (1/10) were of a moderate severity.

According to the investigators, a causal relationship with standard therapy was assessed as "possible" in 70.00% (7/10) of cases, as "not related" in 10.00% (1/10) of cases, as "probable" in 10.00% (1/10) of cases, as "doubtful" in 10.00% (1/10) of cases.

As a result of the AEs comparative analysis in terms of their presence, severity, causal relationship with the therapy and outcomes, no statistically significant differences were found between the observation groups. It was shown that taking the study drug does not adversely affect the ECG and other vital functions (BP, heart rate, etc.). No serious AEs, including deaths, were reported during the study.

In the nirmatrelvir + ritonavir group, the following adverse events classified by frequency, were identified: increased ALT levels – 3 (2.3%), increased AST levels – 3 (2.3%), dysgeusia – 3 (2.3%), diarrhea – 1 (0.8%), dry mouth – 1 (0.8%). In the standard therapy group, the following adverse events were identified: nausea 2 (1.5%), increased ALT levels – 3 (2.3%), increased AST levels – 3 (2.3%), diarrhea 1 (0.8%), erythema – 1 (0.8%).

The carried out analysis of adverse events in the therapy groups showed no statistically significant differences between the drug group (nirmatrelvir + ritonavir) and the standard therapy group.

CONCLUSION

Thus, it can be argued that therapy with a fixed combination of nirmatrelvir + ritonavir is characterized by a favorable safety profile comparable to standard therapy. The identified adverse events were transient in nature and did not require discontinuation of therapy or changes in the treatment regimen.

The unique technology developed in the Russian Federation, which made it possible to combine both active substances into one fixed dosage form, reduces a number of tablets used, by 6 times compared to the American analogue, which reduces polypharmacy and increases adherence and safety of therapy in general [27].

As a result of the clinical study "Open-label two-stage multicenter study on evaluation of main pharmacokinetic parameters, safety, and efficacy against COVID-19 of drug Skyvira® in adult population", the advantage of therapy with a fixed nirmatrelvir (300 mg) + ritonavir (100 mg) combination was demonstrated over the standard therapy in COVID-19 patients, as well as the comparability of the pharmacokinetic profile of the drug with the available data on the components.

The advantage of Skyvira® therapy over standard

therapy in COVID-19 patients has been demonstrated in terms of reducing the risk of a heavier severity level of the disease and hospitalization, the rate of the virus elimination, the dynamics of reducing the symptoms severity of the infectious disease, improving the general condition of patients and their clinical status, reducing the risks of complications development in the course of COVID-19 in both patients without and those with risk factors for the progression of COVID-19 to a heavier severity level.

The results of the study demonstrated a favorable efficacy and safety profile of Skyvir (fixed combination: nirmatrelvir 300 mg + ritonavir 100 mg) when used in COVID-19 patients. The data obtained indicate a clinical and pharmacoeconomic feasibility of the therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

LAB – development and implementation of research design, text writing and editing; NMS – study design implementation, data processing; EIG – study design implementation, data processing, OISh – study design implementation, data processing; NVK – study design implementation, processing of the obtained data; ENS – study design implementation, processing of the obtained data; KBK – study design development and implementation, research design implementation, text editing; DYuP – study design development and implementation, results analysis, text editing; DNZ – literary sources analysis, results analysis; KYaZ – research design development, text editing, literary sources analysis; SMN – study design implementation, processing of the obtained data; AVT – research data processing, results analysis; PAB – research design development, text editing.

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