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Molnupiravir in the treatment of patients with influenza or acute respiratory viral infections: a multicenter comparative randomized double-blind placebo-controlled trial

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The aim. To evaluate the efficacy and safety of molnupiravir compared to placebo in patients with influenza and/or ARVI.

Materials and methods. The study involved 300 patients. The study included patients aged 18 to 80 years with clinical signs of influenza/ARVI (duration no more than 48 hours): elevated body temperature ≥37.5°C and the presence of at least 2 symptoms of moderate severity (chills, headache, myalgia, sore throat, nasal congestion, runny nose, sneezing, cough, with laboratory-confirmed diagnosis of influenza/ARVI at the time of screening), meeting the selection criteria for the study. Group 1 (n = 150) received the investigational medicine molnupiravir (Esperavir®, Promomed Rus LLC, Russia) 800 mg (4 capsules) 2 times/day (daily dose 1600 mg) for 5 days; Group 2 (n = 150) received placebo 4 capsules 2 times/day for 5 days, then patient observation was carried out until day 14 (4 visits after screening). The effectiveness of therapy was assessed according to primary and secondary efficacy criteria. The primary efficacy criterion was the time (in days) to clinical recovery. Safety was assessed by considering the number and severity of adverse events (AEs) and serious adverse events (SAEs). For the analysis of qualitative indicators, an intergroup comparison of proportions was performed using a two-sided version of Fisher's exact test, or the χ^2 ("chi-square") test. For quantitative indicators — using the non-parametric Mann–Whitney test. Differences were considered statistically significant at $p < 0.05$.

Results. According to the results of the assessment of the primary efficacy criterion, it was shown that molnupiravir therapy statistically significantly reduces the time to clinical recovery compared with placebo (p = 0.000039). According to secondary efficacy criteria, a statistically significant advantage of therapy with the investigational medicine compared with placebo was also demonstrated in terms of the frequency of patients who achieved clinical recovery at Visits 2 and 3 p = 0.0110, p = 0.0070), the frequency of virus elimination. Even on the 3rd day of therapy, the frequency of virus elimination in the investigational drug group was 64.7% compared with 40% in the placebo group ($p < 0.0001$). Statistically significant differences were also shown between the groups in the frequency of patients with the development of ARVI/influenza complications (bronchitis, acute sinusitis, pneumonia, tonsillitis, tracheitis, tracheobronchitis) by Visits 2–4 (Day 3–14) ($p < 0.0001$), which proves the validity of using targeted antiviral therapy in relation to achieving surrogate therapy endpoints. Therapy with the investigational medicine was characterized by a favorable safety profile. The registered AEs in the molnupiravir and placebo groups belong to the category of expected and did not require drug withdrawal. No SAEs were observed during the study.

Conclusion. As a result of the phase III clinical study, the efficacy of molnupiravir (Esperavir®, Promomed Rus LLC, Russia) in the treatment of influenza and/or ARVI and the prevention of the risk of developing complications compared with placebo was proven: patients achieved clinical recovery as early as on the 3rd day of therapy. A favorable safety profile was shown, corresponding to the general characteristics of the medicine.

Keywords: molnupiravir; Esperavir; influenza; acute respiratory viral infection; ARVI; clinical study; infectious diseases; pulmonology

List of abbreviations: ARVI - acute respiratory viral infection; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration Formula; COVID-19 — Coronavirus disease 2019; GCP — Good clinical practice; ICH — The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; NHC — β-D-N4-hydroxycytidine; IWRS — Interactive web randomization system; NYHA — New York Heart Association; RdRP — RNA-dependent RNA polymerase; SARS-CoV-2 — Severe acute respiratory syndrome-related coronavirus 2; BD — blood pressure; ULN — upper limit of normal; HIV — human immunodeficiency virus; WHO — World Health Organization; CI — confidence interval; PIL — patient information leaflet; BMI — body mass index; LEC — local ethics committee; AE — adverse event; RNA — ribonucleic acid; SAE — serious adverse event; FC — functional class.

Молнупиравир в лечении пациентов с гриппом или ОРВИ: многоцентровое сравнительное рандомизированное двойное слепое плацебо-контролируемое исследование

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Цель. Оценить эффективность и безопасность применения препарата молнупиравира в сравнении с плацебо у пациентов с гриппом и/или ОРВИ.
Материалы и методы. В исследовании приняли участие 300 пациентов в возрасте от 18 до 80 лет с наличием клинических признаков гриппа/ОРВИ (длительностью не более 48 ч): повышенной температурой тела ≥37,5°С и наличием не менее 2 симптомов средней степени тяжести (озноб, головная боль, миалгия, боль в горле, заложенность носа, насморк, чихание, кашель, с лабораторно подтверждённым на момент скрининга диагнозом грипп/ОРВИ), соответствующие критериям включения в исследование. 1 группа (n=150) получала исследуемый препарат молнупиравира (Эсперавир®, ООО Промомед Рус, Россия) по 800 мг (4 капсулы по 200 мг) 2 р/сут (суточная доза 1600 мг) в течение 5 дней; 2 группа (n=150) получала плацебо по 4 капсулы 2 р/сут в течение 5 дней, далее до 14 дня проводилось наблюдение пациента (4 визита после скрининга). Оценку эффективности терапии осуществляли по первичным и вторичным критериям эффективности. В качестве первичного критерия эффективности оценивалось время (в днях) до наступления клинического выздоровления. Оценку безопасности проводили, учитывая количество и выраженность нежелательных явлений (НЯ) и серьезных нежелательных явлений (СНЯ). Для анализа качественных показателей проведено межгрупповое сравнение долей при помощи двустороннего варианта точного критерия Фишера, или критерия χ^2 («хи-квадрат»). Для количественных показателей — при помощи непараметрического критерия Манна–Уитни. Статистически достоверными считались различия при p <0,05.
Результаты. По результатам оценки первичного критерия эффективности было показано, что терапия препаратом молнупиравир (Эсперавир®) статистически значимо сокращает время до наступления клинического выздоровления по сравнению с плацебо (p=0,000039). По вторичным критериям эффективности также было продемонстрировано

статистически значимое преимущество терапии исследуемым препаратом по сравнению с плацебо в отношении частоты пациентов, достигших клинического выздоровления на Визитах 2 и 3 (p=0,0110, p=0,0070), частоты элиминации вируса. Уже на 3 день терапии частота элиминации вируса в группе исследуемого препарата составила 64,7% по сравнению с 40% в группе плацебо (p <0,0001). Также были показаны статистически значимые различия между группами по частоте пациентов с развитием осложнений ОРВИ/гриппа (бронхит, острый синусит, пневмония, тонзиллит, трахеит, трахеобронхит) к Визитам 2–4 (День 3–14) (p <0,0001), что доказывает обоснованность применения направленной противовирусной терапии в отношении достижения суррогатных точек терапии.

Терапия исследуемым препаратом характеризовалась благоприятным профилем безопасности.

Нежелательные явления (НЯ): головокружение, головная боль, диарея, тошнота, диспепсия, крапивница, зарегистрированные в группе исследуемого препарата молнупиравира (Эсперавир®), соответствуют изученному профилю безопасности зарегистрированного препарата Эсперавир® и могут быть отнесены к категории предвиденных с сопоставимой частотой. В ходе исследования не наблюдалось возникновения СНЯ.

Заключение. В результате проведённого клинического исследования III фазы была доказана эффективность препарата молнупиравира (Эсперавир®, ООО Промомед Рус, Россия) при лечении гриппа и/или ОРВИ и предотвращение рисков развития осложнений в сравнении с плацебо: уже на 3 сутки терапии пациенты достигали клинического выздоровления. Показан благоприятный профиль безопасности, соответствующий общей характеристике лекарственного препарата.

Ключевые слова: молнупиравир; грипп; острая респираторная вирусная инфекция; ОРВИ; клиническое исследование; инфекционные болезни; пульмонология; Эсперавир®

Список сокращений: CKD-EPI — формула оценки почечной функции (Chronic Kidney Disease Epidemiology Collaboration Formula); COVID-19 — Новая коронавирусная инфекция (Coronavirus disease 2019); GCP — надлежащая клиническая практика (Good clinical practice); ICH — Международная конференция по гармонизации технических требований к регистрации лекарственных препаратов для применения у человека; NHC — β-D-N4-гидроксицитидин; IWRS — интерактивная on-line система рандомизации; NYHA — Нью-Йоркская ассоциация кардиологов (New York Heart Association); RdRP — РНК-зависимая РНК-полимераза (RNA-dependent RNA polymerase); SARS-CoV-2 — острое респираторное заболевание, вызванное коронавирусом; АД — артериальное давление; ВГН — верхняя граница нормы; ВИЧ — вирус иммунодефицита человека; ВОЗ — Всемирная организация здравоохранения; ДИ — доверительный интервал; ИЛП — информационный листок пациента; ИМТ — индекс массы тела; ЛЭК — локальный этический комитет; НЯ — нежелательное явление; РНК — рибонуклеиновая кислота; СНЯ — серьезное нежелательное явление; ФК — функциональный класс.

INTRODUCTION

Acute respiratory viral infections (ARVIs) are a leading cause of overall morbidity in the population. ARVI also holds a leading position among other pathogens of infectious diseases. For example, in the Moscow region in 2020–2021, ARVI accounted more than 85% of all registered cases of diagnosed infectious and parasitic diseases [1].

Influenza is a highly contagious acute viral disease characterized by seasonality, with the peak incidence of influenza occurring in the autumn-winter period[1]. The most common complications of influenza are bronchitis, pneumonia, sinusitis, and otitis. Influenza viruses account for 6.2–12.6% of all cases of ARVI[2].

In Russia, 27.3–41.2 million cases of influenza and ARVI are registered annually. At the same time, the economic damage caused annually by ARVI and influenza is the maximum compared to other infectious diseases. For example, in the Russian Federation in 2021, the economic damage from ARVI amounted to more than 750 billion rubles, and the economic damage from influenza epidemics often amounts to more than 10 billion rubles per year[3] [1].

Risk factors for the development of ARVI and influenza include a decrease in the protective properties of the body against the background of frequent hypothermia and stress, the presence of chronic somatic diseases, etc.[4] [2, 3].

The “seasonal” complex of ARVI pathogens includes dozens of simultaneously circulating viruses (> 200 genetic groups from 6 families and 10 genera). At the same time, the clinical picture of the disease caused by various respiratory viruses consists of the same symptoms, which do not differ either in severity or in the duration of their course [4].

Molnupiravir is a targeted antiviral agent from the group of isopropyl ether derivatives. The mechanism of action is characterized by targeted suppression of viral RNA replication by incorporation into the viral genome and disruption of its structure. As a prodrug, molnupiravir is cleaved in human plasma to the active

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nucleoside analog β-D-N4-hydroxycytidine (NHC). NHC is subsequently converted to 5'-triphosphate (NHC-triphosphate). NHC-triphosphate interacts with the virus-encoded RNA-dependent RNA polymerase (RdRp) and is incorporated into the structure of RdRp. In the future, the resulting modified RNA is used as a template for the synthesis of viral RNA, which leads to the accumulation of mutations and the loss of its virulent properties by the viral RNA [5, 6].

The results of studies have shown that molnupiravir is active against a number of viruses, including influenza A and B viruses, coronaviruses, respiratory syncytial virus, norovirus, chikungunya virus, Venezuelan equine encephalitis virus, and Ebola virus [7–9].

Currently, molnupiravir preparations are registered in the Russian Federation for the indication "treatment of new coronavirus infection (COVID-19), mild and moderate severity in adult patients with an increased risk of disease progression to severe and not requiring additional oxygen therapy"[5]. It is worth noting that, in accordance with the Interim Guidelines for the Treatment of New Coronavirus Infection, it is recommended to include drugs based on molecules with direct antiviral activity against viral RNA polymerase in treatment regimens before confirming the etiological diagnosis and based on the clinical picture, taking into account the similarity of the clinical symptoms of mild forms of COVID-19 with seasonal ARVI, to prevent the risk of the disease transitioning to a more severe course in patients with initial symptoms of ARVI[6]. Due to annual seasonal outbreaks of influenza and ARVI, there is a need to introduce effective drugs for the treatment of these respiratory viral infections into clinical practice. Based on the mechanism of action [5, 6], as well as the research data available in the literature [8–10] and real clinical practice, it can be concluded that molnupiravir is potentially a highly effective medicine for solving the above problem.

To assess the efficacy and safety of molnupiravir in patients with influenza and/or ARVI in accordance with regulatory documents[7, 8], a Phase III clinical trial was conducted: "A double-blind, placebo-controlled, randomized, multicenter, comparative study to evaluate the efficacy and safety of molnupiravir (Esperavir®, PROMED RUS LLC, Russia) in patients with influenza and/or ARVI."

THE AIM. To evaluate the efficacy and safety of molnupiravir compared to placebo in patients with influenza and/or ARVI.

MATERIALS AND METHODS

Study design

The study is a Phase III clinical trial and is a double-blind, placebo-controlled, randomized, multicenter, comparative study.

This clinical study included the following stages: screening — no more than during 30 hours; randomization — no more than 1 day; therapy — for 5 days; follow-up — up to day 14. The total duration of the study for each patient was no more than 16 days. A scheme of the study design is shown in Figure 1.

Study duration and setting

The study was conducted from November 28, 2024 to March 18, 2025 in 11 research centers in the Russian Federation: Kirov State Medical University; Clinical Hospital No. 1 (Smolensk, Russia); City Clinical Hospital No. 24 (Mosco, Russia); OrKli Hospital (St. Petersburg, Russia); Aurora MedFort (St. Petersburg, Russia); National Research Ogarev Mordovia State University (Saransk, Russia); Ivanovo Clinical Hospital named after Kuvaev (Ivanovo, Russia); Smolensk State Medical University (Smolensk, Russia); Consultative and diagnostic polyclinic No. 121 (Moscow, Russia); two clinical centers of Eco-Safety Research Center (St. Petersburg, Russia). Scientific consulting and coordination of the study was carried out by specialists from the National Medical Research Center for Therapy and Preventive Medicine (Moscow, Russia) under the leadership of Academician of the Russian Academy of Sciences, Chief Visiting Specialist in Therapy and General Medical Practice of the Ministry of Health of Russia Oksana M. Drapkina.

Ethics approval

This clinical study was approved by the Ministry of Health of Russia (RCI No. 534 dated November 08, 2024), and also approved by the Ethics Council of the Ministry of Health of Russia (Extract from Protocol No. 367 dated September 17, 2024).

[5] Encyclopedia of medicines. Molnupiravir. Available from: https://www.rlsnet.ru/drugs/molnupiravir-88133. Russian
[6] Interim guidelines "Prevention, diagnosis and treatment of novel coronavirus infection (COVID-19)". Version 19 (dated May 27, 2025)" (approved by the Ministry of Health of Russia).
[7] Federal Law No. 61-FZ "On the Circulation of Medicines". Russian
[8] Recommendations of the Council of the Eurasian Economic Commission dated July 17, 2018 No. 11 "On guidelines on general issues of clinical trials". Russian

Population selection

The study included male and female patients aged 18 to 80 years including those who had influenza and/or ARVI.

The population was selected based on the studied mechanism of action and the expected therapeutic effect of the medicine, based on the results of preclinical studies.

The complex of pathogens of "seasonal" acute respiratory viral infections includes dozens of simultaneously circulating viruses (> 200 genetic groups from 6 families and 10 genera). At the same time, the clinical picture of the disease caused by infection with various strains (types) of respiratory viruses will include the same symptoms, both in terms of severity and duration of their course.

The spectrum of ARVI pathogens that annually cause epidemics in the world in the autumn-winter period includes representatives of virus families whose genome is represented by [4]:

— **RNA molecule:**

- *orthomyxoviruses* — influenza A viruses (Influenza A virus — A(H1N1)pdm09, A(H3N2), etc.) and Influenza virus B (Influenza B virus);
- *paramyxoviruses*, including:
  - pneumoviruses — respiratory syncytial virus (HRSV (RSV) or Human Respiratory syncytial virus),
  - human metapneumovirus (HMPV or Human Metapneumovirus),
  - 4 types of parainfluenza viruses from 2 genera Rubulavirus (HPIV-2, -4 or Human Parainfluenza virus 2- and 4-) and Respirovirus (HPIV-1, -3);
- *coronaviruses* — Human Coronavirus 229E, Human Coronavirus OC43, Human Coronavirus NL63, Human Coronavirus HKUI) and
- *picornaviruses* — human rhinovirus (HRV or Rhinovirus), types A, B, C, >152 serotypes (genus Enterovirus D of human or HEV-D) and

– **DNA molecule,** 2 families:

- 54 serotypes of 7 human adenoviruses (HAdV or Human mastadenovirus) and
- parvoviruses — human bocavirus (HBV or Human bocavirus).

All of the above noted viruses cause ARVI among all age groups, with the exception of human bocavirus, which infects only children[9, 10].

The most common pathogens of respiratory diseases are rhinoviruses (up to 50% of all ARVI), coronaviruses, influenza and parainfluenza viruses. Less common are respiratory syncytial virus, adenoviruses and reoviruses [7, 10].

From the above, it follows that in 95% of all diagnosed ARVI, the pathogens of infection are RNA viruses. At the same time, molnupiravir is an antiviral medicine, which is aimed to suppress the replication of RNA viruses by incorporating into the genome exclusively of the virus and disrupting the structure of this genome by inducing a viral error / mutation [5, 6].

Randomization

Randomization of patients was carried out through an interactive web randomization system (iWRS) integrated into an electronic individual registration card (e-IRC), in accordance with the randomization plan.

Before the beginning of the study, each physician-researcher who was delegated the responsibility of transferring data to the e-IRC was given an access code (a combination of username and password) to the e-IRC, as well as detailed written instructions on how to work with the e-IRC, including detailed instructions on the randomization procedure.

Randomization was carried out according to the following algorithm. Each patient who met all the inclusion criteria and did not meet any of the non-inclusion criteria was assigned a three-digit randomization number using the IWRS system. The patient's randomization number and other relevant data were entered by the physician-researcher into the Journal of Clinical Trial Participants in Screening / Randomization.

If a patient prematurely discontinued participation in the study, his randomization number was not reused, and the patient could no longer participate in the study.

This study was double-blind, so neither the patient nor the physician-researcher knew what therapy the patient was receiving.

Participants

It was planned to randomize up to 300 patients into the study. Taking into account the possible exclusion of patients at the screening stage, the maximum number of patients who signed the informed consent form of the patient information leaflet (PIL) and involved in screening could not exceed 430 people. In the study,

[9] Acute respiratory viral infection (ARVI). Children. Available from: https://www.pediatr-russia.ru/information/%D0%9E%D0%A0%D0%92%D0%98_%D0%B4%D0%B5%D1%82%D0%B8_%D0%BE%D0%B4%D0%BE%D0%B1%D1%80%D0%B5%D0%BD%D1%8B_%D0%9D%D0%9F%D0%A1_%D1%83%D1%82%D0%B2%D0%B5%D1%80%D0%B6%D0%B4%D0%B5%D0%BD%D1%8B.pdf

[10] Clinical guidelines. Acute respiratory viral infections (ARVI) for adults; 2024. Available from: https://rnmot.org/video/repository/klinicheskie_rekomendacii_orvi_10102023_801a37eb.pdf

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331 patients underwent screening procedures, of which 300 patients were randomized, all patients completed the study completely in accordance with the approved study protocol. Patients received symptomatic therapy with the following groups of drugs: antipyretic, antibacterial, analgesic, expectorant, antitussive, diuretics, vasoconstrictors, etc., depending on the needs of a particular patient.

Inclusion criteria: a signed and dated Informed Consent Form PIL by the patient; men and women aged 18 to 80 years inclusive; a diagnosis of influenza and/or ARVI confirmed at the time of screening, caused by RNA viruses, based on the results of laboratory diagnostics[11]; the presence of both clinical signs of influenza/ARVI (the presence of body temperature ≥ 37.5 °C at the time of screening or within 6 hours before screening in the case of taking antipyretic drugs; the presence of at least 2 symptoms of moderate severity: chills, headache, myalgia, sore throat, nasal congestion, runny nose, sneezing, cough); the duration of symptoms of the disease is no more than 48 hours before taking the study drug / placebo (assessed at Visit 1 [Day 1]); uncomplicated course of influenza / ARVI; the patient's consent and ability to take oral medications; the patient's consent to use reliable methods of contraception throughout the entire participation in the study and for 3 months after the end of therapy.

The following could participate in the study: women who have a negative pregnancy test and use contraception, women who are unable to bear children (in history: hysterectomy, bilateral oophorectomy, bilateral tubal ligation, infertility, menopause for more than 2 years); men with preserved reproductive function who use contraception, with infertility or a history of vasectomy.

Non-inclusion criteria: hypersensitivity to molnupiravir, other components of the study drug; the use of direct-acting antiviral drugs within 7 days before screening; the use of immunostimulants and immunomodulators within 7 days before screening; a diagnosis of ARVI confirmed at the time of screening, caused exclusively by DNA viruses, based on the results of laboratory diagnostics; a diagnosis of COVID-19 or co-infection with COVID-19 confirmed at the time of screening based on the results of laboratory diagnostics; vaccination against influenza less than 3 weeks before screening; clinical signs of pneumonia, for example, shortness of breath, hypoxemia, crepitation (visualization was not required); the presence in the anamnesis of chronic respiratory diseases (COPD, chronic bronchitis, diffuse panbronchiolitis, bronchiectasis, pulmonary emphysema, pulmonary fibrosis, tuberculosis, etc.), with the exception of bronchial asthma, not requiring therapy at the time of screening; patients with established severe renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 according to the CKD-EPI formula) or receiving renal replacement therapy at the time of screening; primary biliary cirrhosis of the liver class C according to the Child-Pugh classification in history or the presence in history (within 6 months before screening) and/or at the time of screening of ALT and/or AST levels ≥ 3 ULN and/or total bilirubin ≥ 2 ULN (≥ 3 ULN in case of Gilbert's syndrome); chronic heart failure III–IV FC according to the functional classification of the New York Heart Association (NYHA); autoimmune diseases in history; the presence of HIV, syphilis, hepatitis B and/or C in history; the presence of malignant neoplasms in history, with the exception of patients in whom the disease has not been observed for the last 5 years, patients with completely cured basal cell skin cancer or completely cured carcinoma in situ; alcohol, pharmacological and/or drug addiction in history and/or at the time of screening; schizophrenia, schizoaffective disorder, bipolar disorder or other mental pathology in history or suspicion of their presence at the time of screening; any history data that, in the opinion of the physician-researcher, may lead to complications in the interpretation of the study results or create additional risk for the patient as a result of his participation in the study; the patient's unwillingness or inability to comply with the Protocol procedures (in the opinion of the physician-researcher); pregnant or lactating women, or women planning pregnancy during participation in a clinical study or within 3 months after the end of therapy; participation in another clinical study within 3 months before inclusion in the study; other conditions that prevent the patient from being included in the study.

Duration of treatment and dosage regimen

Male and female patients (*n* = 300) aged 18 to 80 years inclusive with influenza and/or ARVI who met the inclusion criteria and did not meet the non-inclusion criteria were randomized into 2 groups in a 1:1 ratio:

[11] The detection of influenza/ARVI viruses, as well as the determination of SARS-CoV-2 RNA / antigen, was carried out using immunochromatographic methods and/or PCR. Russian

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- Group 1 (n = 150) received molnupiravir (Esperavir®, Promomed Rus LLC, Russia) 800 mg (4 capsules) 2 per day (daily dose 1600 mg) for 5 days;
- Group 2 (n = 150) received placebo 4 capsules 2 per day for 5 days.

The studied drug / placebo was used on an outpatient basis. The interval between doses was 12 ± 2 h. The use of the studied drug / placebo was allowed in conjunction with pathogenetic and symptomatic therapy used in the treatment of influenza / ARVI.

Rules for the use of the studied drug / placebo was taken regardless of food intake; it was desirable to use the medicine/placebo at the same time; the capsules had to be swallowed without chewing and washed down with bottled or boiled water; the duration of use of the medicine was 5 days (a total of 10 doses of 800 mg). In case of missing a dose, the patient was guided by the following rules: if ≤ 10 h have passed since the missed dose, it was necessary to take the missed dose and continue taking the medicine in accordance with the previous schedule; if > 10 h have passed since the missed dose, the patient should not have taken the missed dose, he had to carry out the next dose at the scheduled time without increasing the dose.

The duration of the study for one patient was no more than 16 days, of which the duration of therapy was 5 days and the follow-up period was no more than 8 days.

Visits: visit 0 (screening, no more than 30 hours); visit 1 (randomization, Day 1)[12]; visit 2 (Day 3–4)[13]; visit 3 (Day 6–7); visit 4 (Day 13–14).

Efficacy criteria

The effectiveness of therapy was assessed according to the following endpoints:

Primary efficacy criterion: time (in days) to clinical recovery (clinical recovery from influenza (achieving 0–1 points for each symptom of ARVI / Influenza);

- body temperature < 37.5°C without taking antipyretic drugs and without subsequent increase in body temperature.

Secondary efficacy criteria:

- Frequency of patients who achieved clinical recovery by Visits 2–4 (Day 3–14).
- Frequency of patients with virus elimination by Visits 2 (Day 3–4) and 3 (Day 6–7).
- Assessment of symptom severity by Visits 2–4 (Day 3–14) using the Likert scale[14].
- Time (in hours) to achieve body temperature < 37.5°C without taking antipyretic drugs and without subsequent increase in body temperature.
- Frequency of patients who achieved body temperature < 37.5°C without taking antipyretic drugs and without subsequent increase in body temperature, by Visits 2–4 (Day 3–14).
- Frequency of patients with the development of complications of ARVI / influenza (bacterial infections of the upper and lower respiratory tract) by Visits 2–4 (Day 3–14).
- Frequency of patients who required hospitalization due to worsening of the course of influenza / ARVI.

Additional points: frequency of patients with the need for antipyretic drugs in the number of days.

Safety criteria

Safety was assessed according to the following criteria: total number of adverse events (AEs), stratified by severity and frequency; frequency of adverse reactions; frequency of serious adverse events (SAEs), including those associated with the use of the studied medicine/placebo; frequency of patients who registered at least one AE; frequency of patients who discontinued treatment due to the occurrence of AE / SAE. An analysis was carried out of AEs registered according to the WHO classification, with a cause-and-effect relationship with studied medicine/placebo — definite, probable, possible with the determination of frequency in the population.

Statistical analysis

Sample size calculation

The time (in days) to clinical recovery was chosen as the primary endpoint.

Clinical recovery meant (compliance with both criteria):

— relief / disappearance of symptoms of ARVI / influenza (achieving 0–1 points for each symptom of ARVI / influenza);

[12] Visit 1 could coincide with Visit 0. If Visit 1 and Visit 0 coincided, then a physical examination, vital signs assessment, registration of concomitant therapy, and assessment of the severity of symptoms were not repeated, the inclusion and non-inclusion criteria were evaluated immediately before randomization, and exclusion criteria were evaluated after drug administration. Russian

[13] The visit was conducted at home or research center.

[14] 0 — no, 1 — mild symptoms, 2 — moderate, 3 — severe.

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— body temperature < 37.5°C without taking antipyretic drugs and without subsequent increase in body temperature.

The sample calculation was based on data from a meta-analysis of studies of the antiviral drug riamilovir, which assessed the efficacy of riamilovir when used as etiotropic therapy for influenza [11]. According to the study, the duration of catarrhal syndrome in the groups of the drug riamilovir (TN: Triazavirin 500 mg/day or 750 mg/day and placebo) was (Mean ± SD) 6.84 ± 3.15 days, 5.41 ± 2.94 days and 8.84 ± 2.94 days, respectively. The time to normalization of temperature was shorter compared to the duration of catarrhal syndrome in all three groups: (Mean ± SD) 2.92 ± 1.14 days, 2.59 ± 0.93 days and 6.41 ± 2.55 days for the groups of riamilovir 500 mg/day, Triazavirin 750 mg/day and placebo, respectively. The minimum clinically significant difference with placebo was 2 days. With a conservative assessment, in the planned study, it can be expected to achieve a difference in the average of the drug with placebo in 1 day (d)), and a standard deviation (SD) of about 3 days.

The sample size was calculated using the following formula [12]:

$$N = 2 \times (Z_{\frac{\alpha}{2}} + Z_{\beta}) / (d / SD)^2,$$

where N is the required number of subjects in one group; $Z_{\frac{\alpha}{2}}$ and Z_{β} are the values of the normal distribution of probability α/2 and β, respectively; d — clinically significant difference in group means (expected difference in means); SD — root mean square (standard deviation); d/SD — effect size (ES, effect size).

With a planned study power of 80% (0.80) and a significance level of 0.05, the numerator of the formula takes the value:

$$2 \times (Z_{\frac{\alpha}{2}} + Z_{\beta})^2 = 2 \times (1,96 + 0,84)^2 = 15,68$$

The calculation according to the formula with *ES=d/SD=1/3=0.33(3)* gave the value of the required number for statistical analysis of 142 patients in each study group.

Taking into account the possible dropout during the study, it was necessary to randomize 150 patients in each group, the total number of randomized patients was 300 people.

Statistical methods

Statistical analysis was carried out in accordance with the requirements of ICH E9, the Rules of Good Clinical Practice approved by the Eurasian Economic Commission, and other applicable requirements and laws.

For statistical analysis, certified statistical software with validated algorithms for performing statistical analyses and proper documentation of StatSoft Statistica, version 13 (TIBCO Software Inc. Statistica, version 13) was used.

The data were tested for normality of distribution using the generally accepted method (Shapiro–Wilk test), and in the case of a distribution other than normal, non-parametric methods of assessment were used. The data were presented as absolute values (*n*) and proportions (%), mean (M) and standard error (SD).

To test the hypothesis about the homogeneity of the study groups in the initial period, testing was carried out for the absence of differences between the groups using the Mann–Whitney test and the χ^2 test. In the case of statistically significant differences between the groups, these differences were illustrated using box diagrams, which were presented by the median, minimum and maximum values, 25 and 75 percentiles, depending on the nature of the data distribution.

For the analysis of qualitative indicators, an intergroup comparison of proportions was carried out using a two-sided version of Fisher's exact test (or the chi-square test). For quantitative indicators, taking into account the assumption about the nature of the distribution, the comparison was carried out using the non-parametric Mann–Whitney test.

To compare ordinal indicators, a two-sided version of Fisher's exact test (or the χ^2 test ("chi-square") was used, if all expected values in the cells of the contingency table for this analysis were 5 or more.

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

RESULTS

Baseline characteristics of participants

The study included patients aged 18 to 80 years, with clinical signs of influenza / ARVI (lasting no more than 48 hours) — elevated body temperature ≥ 37.5°C and the presence of at least 2 symptoms of moderate severity: chills, headache, myalgia, sore throat, nasal congestion, runny nose, sneezing, cough, with a laboratory-confirmed diagnosis of influenza / ARVI at the time of screening, corresponding to the selection criteria in the study. The characteristics of the study participants are presented in Table 1.

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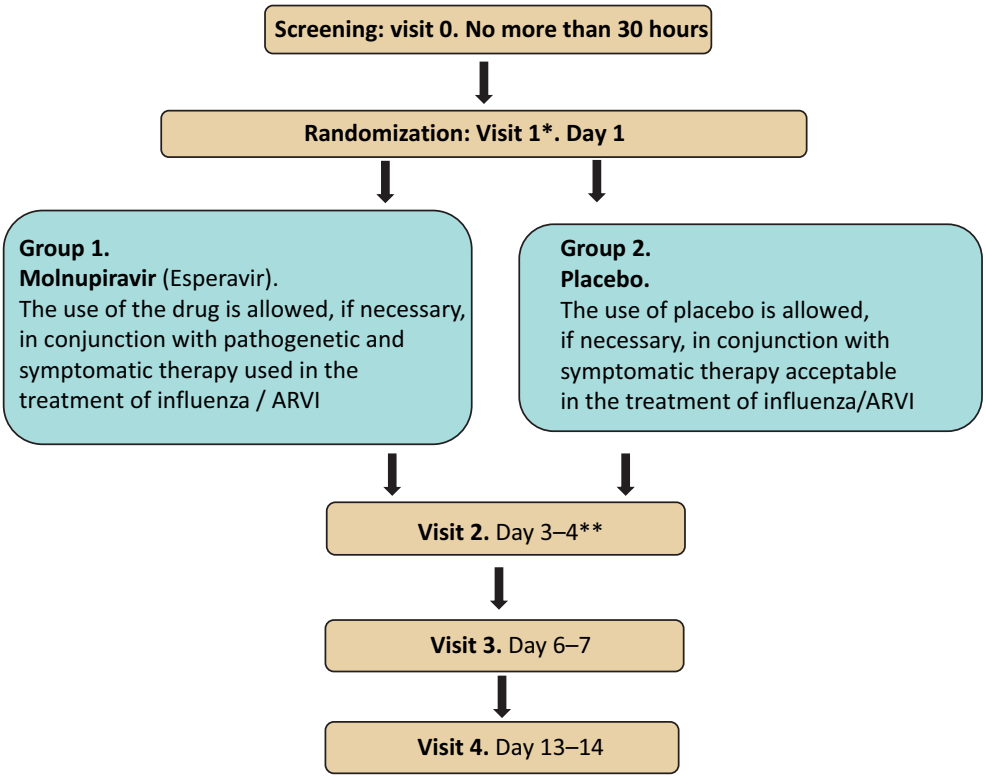

Figure 1 – Graphical scheme of the study design.

Note: * — Visit 1 could coincide with Visit 0. If Visit 1 and Visit 0 coincided, then a physical examination, assessment of vital signs, registration of concomitant therapy, and assessment of symptom severity were not repeated, inclusion and non-inclusion criteria were assessed immediately before randomization, and exclusion criteria were assessed after drug administration; ** — The visit was carried out at home or in the research center. The patient was monitored in accordance with the clinical practice of the research center.

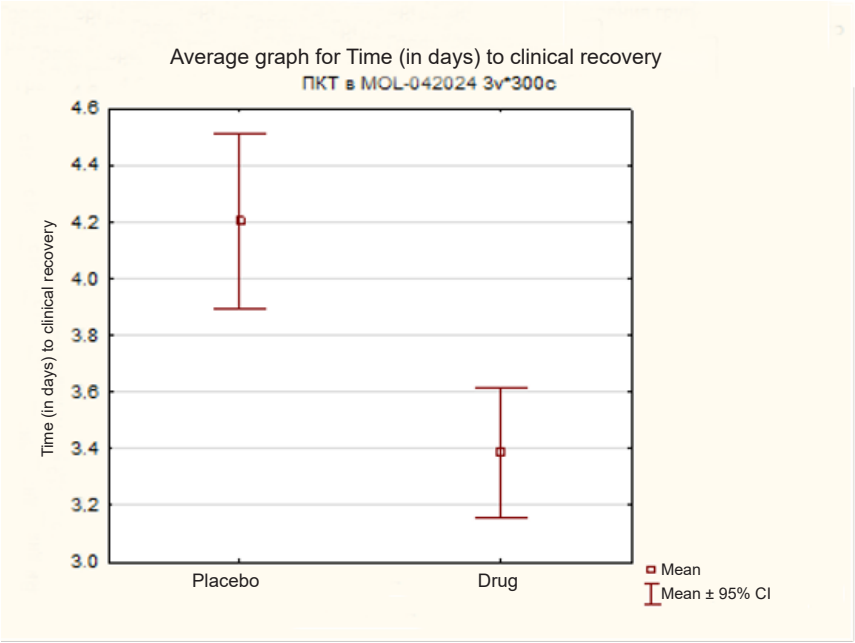

Figure 2 – Graph of average values and 95% confidence interval of time (in days) to clinical recovery.

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Table 1 – Baseline characteristics of participants

Indicator		Molnupiravir	Placebo	*p**
Demographic and anthropometric data				
Gender, *n* (%)	Female	81 (54%)	87 (58%)	0.4853
	Male	69 (46%)	63 (42%)	
Average age, M ± SD, years		39.00 ± 13.35	42.76 ± 14.68	0.0356
Body weight, M ± SD, kg		75.73 ± 11.79	74.98 ± 11.83	0.6465
Height, M ± SD, cm		172.38 ± 7.38	171.65 ± 7.30	0.4400
BMI, M ± SD, kg/m^2		25.43 ± 3.20	25.40 ± 3.45	0.9358
Frequency of patients with influenza, ARVI and mixed infection, *n* (%)				
Influenza		73 (48.67%)	76 (50.67%)	0.9402
ARVI		73 (48.67%)	70 (46.67%)	
Mixed infection		4 (2.67%)	4 (2.67%)	
Concomitant diseases		80 (53.33%)	82 (54.67%)	0.9078

Note: BMI — body mass index; * — significance level (differences were considered statistically significant at $p < 0.05$).

Table 2 – Summary results for primary and secondary efficacy criteria between groups: molnupiravir and placebo

Indicators / Visits			Molnupiravir (*n* = 150)	Placebo (*n* = 150)	*p*
Mean time to clinical recovery, M ± SD, days			3.39 ± 1.42	4.20 ± 1.92	0.000039
Frequency of patients achieving clinical recovery, *n* (%)					
Visit 2 (Day 3–4)			63 (42.00%)	42 (28.00%)	0.0110
Visit 3 (Day 6–7)			140 (93.33%)	125 (83.33%)	0.0070
Visit 4 (Day 13–14)			150 (100%)	150 (100%)	–
Frequency of patients with virus elimination by Visits 2 (Day 3–4) and 3 (Day 6–7), *n* (%)					
Visit 2 (Day 3–4)			97 (64.67%)	60 (40.00%)	0.0001
Visit 3 (Day 6–7)			141 (94.00%)	128 (85.33%)	0.0137
Assessment of symptom severity by Likert scale at Visits 2–4 (Day 3–14), *n* (%)					
Visit 2 (Day 3–4)	Chills	Absent	82 (54.67%)	65 (43.33%)	0.0004
		Mild	54 (36.00%)	44 (29.33%)	
		Moderate	13 (8.67%)	41 (27.33%)	
		Severe	1 (0.67%)	0 (0.00%)	
Visit 3 (Day 6–7)		Absent	145 (96.67%)	130 (86.67%)	0.0068
		Mild	5 (3.33%)	19 (12.67%)	
		Moderate	0 (0.00%)	1 (0.67%)	
		Severe	0 (0.00%)	0 (0.00%)	
Visit 2 (Day 3–4)	Headache	Absent	78 (52.00%)	61 (40.67%)	0.0394
		Mild	52 (34.67%)	53 (35.33%)	
		Moderate	19 (12.67%)	36 (24.00%)	
		Severe	1 (0.67%)	0 (0.00%)	
Visit 3 (Day 6–7)	Sore throat	Absent	131 (87.33%)	105 (70.00%)	0.0008
		Mild	19 (12.67%)	43 (28.67%)	
		Moderate	0 (0.00%)	2 (1.33%)	
		Severe	0 (0.00%)	0 (0.00%)	
Indicators of achieving a body temperature < 37.5°C without antipyretic drugs and without subsequent temperature increase					
Meantime, M ± SD, h			59.61 ± 29.90	80.15 ± 43.59	<0.0001
Visit 2 (Day 3–4), *n* (%)			96 (64.00%)	60 (40.00%)	<0.0001
Visit 3 (Day 6–7), *n* (%)			149 (99.33%)	137 (91.33%)	0.0015
Frequency of patients with the development of ARVI / influenza complications (bacterial infections of the upper and lower respiratory tract), *n* (%)					
Visit 2 (day 3–4)			1 (0.67%)	22 (14.67%)	<0.0001
Visit 3 (day 6–7)			4 (2.67%)	26 (17.33%)	<0.0001
Visit 4 (day 13–14)			4 (2.67%)	26 (17.33%)	<0.0001
Frequency of patients requiring hospitalization due to worsening of influenza / ARVI, n (%)					
Patient frequency			0 (0.00%)	0 (0.00%)	–
Frequency of patients with the need for antipyretic drugs, M ± SD, days					
Patient frequency			1.94 ± 1.81	2.18 ± 2.21	0.5347

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Table 3 – Adverse events, distributed in accordance with SOC, registered with a causal relationship with the study drug / placebo — definite, probable, possible with the determination of frequency in the population in accordance with WHO

System Organ Class and Preferred Term MedDRA	Number of events, *n* (%)*	
	Molnupiravir (*n* = 150)	Placebo (*n* =1 50)
Gastrointestinal disorders		
Abdominal pain	1 (0.7%) (uncommon)	not reported
Diarrhea	2 (1.3%) (common)	not reported
Dyspepsia	1 (0.7%) (uncommon)	not reported
Nausea	3 (2%) (common)	5 (3.3%) (common)
Infections and infestations		
Bacterial bronchitis	1 (0.7%) (uncommon)	2 (1.3%) (common)
Laboratory and instrumental data		
Increased aspartate aminotransferase	not reported	1 (0.7%) (uncommon)
Respiratory, thoracic and mediastinal disorders	not reported	1 (0.7%) (uncommon)
Respiratory, thoracic and mediastinal disorders		
Hiccups	not reported	1 (0.7%) (uncommon)
Skin and subcutaneous tissue disorders		
Urticaria	1 (0.7%) (uncommon)	not reported
Nervous system disorders		
Headache	1 (0.7%) (uncommon)	not reported
Dizziness	1 (0.7%) (uncommon)	2 (1.3%) (common)

Note: * — the frequency of each adverse event is presented relative to the number of subjects exposed to the medicine.

As a result of a comparative analysis of demographic and anthropometric data of patients, no statistically significant differences were found, with the exception of the parameter “age in years” (p = 0.0356). These differences were considered insignificant due to the fact that all patients met the inclusion criteria and did not meet the non-inclusion criteria.

As a result of a comparative analysis of the frequency of patients with influenza, ARVI and mixed infection, no statistically significant differences were found between the study groups (p = 0.9402). The list of identified RNA viruses at screening in the study population: influenza A viruses, including H1N1, H3N2, influenza B, rhinovirus, RS virus, coronaviruses of the species E229, NL63, OC43, HKUI, parainfluenza viruses 1–4 types, metapneumovirus.

The following concomitant diseases were diagnosed in the study subjects: endocrine system (impaired glucose tolerance, impaired fasting glycemia, hypothyroidism, goiter, obesity, type 2 diabetes mellitus, hepatic steatosis); cardiovascular diseases (atherosclerosis, hypertension, hypercholesterolemia, peripheral vascular disease, varicose veins, mitral valve prolapse, sinus tachycardia, angina pectoris, essential hypertension); gastrointestinal diseases (biliary dyskinesia, gastroesophageal reflux disease, duodenal ulcer, dyspepsia, colitis, chronic pancreatitis, chronic gastritis, hiatal hernia); gynecological diseases (adenomyosis, endometrial hyperplasia, uterine leiomyoma, cervical dysplasia, salpingoophoritis, fibrocystic breast disease); diseases of the liver and kidneys (nephrolithiasis, chronic pyelonephritis, renal cyst, Gilbert’s syndrome, cholelithiasis, cholecystectomy, chronic cholecystitis); diseases of the musculoskeletal system (carpal tunnel syndrome, osteoarthritis, osteochondrosis, pathology of intervertebral discs, protrusion of the intervertebral disc, synovitis); ENT organs (allergic rhinitis, chronic sinusitis; chronic tonsillitis) and other diseases that do not contradict the non-inclusion criteria (anemia, astigmatism, metabolic dysfunction-related asthma, iron deficiency anemia, calculus in the urinary tract, hemorrhoids, non-proliferative retinopathy, gout, presbyopia, myopia, benign prostatic hyperplasia, prostatitis, autonomic nervous system regulation disorder, type V hyperlipidemia).

As a result of a comparative analysis of the frequencies of patients with concomitant diseases/ conditions at screening between the studied drug group and the placebo group, no statistically significant differences were found.

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Results of efficacy evaluation

The evaluation of the effectiveness of the therapy in the drug group and the placebo group was based on a statistical analysis of primary and secondary endpoints.

Primary efficacy criterion

Analysis of the primary efficacy criterion showed that the average time (in days) to clinical recovery in the molnupiravir (Esperavir®) group (Mean ± SD) was 3.39 ± 1.42 days and in the placebo group (Mean ± SD) — 4.20 ± 1.92 days (Fig. 2). The difference in the average time (in days) to clinical recovery between the molnupiravir and placebo groups was -0.82 days, the 95% CI for the difference in means was [-1.20; -0.43] days. As a result of a comparative analysis of the time (in days) to clinical recovery (Table 2), a statistically significant advantage of molnupiravir therapy in terms of accelerating recovery was proven (p = 0.000039).

The majority of patients — 88.67% (133 / 150) in the molnupiravir group started therapy on the second day after the onset of symptoms of the disease. Thus, the effectiveness and expediency of molnupiravir therapy is shown even with a delayed start of taking the drug. The study showed the effectiveness of molnupiravir therapy in patients with risk factors (age over 65 years, the presence of cardiovascular diseases, bronchial asthma, diabetes mellitus, obesity), in patients with cardiovascular diseases, as well as in patients over 65 years: the average time (in days) to clinical recovery in the molnupiravir group (Mean ± SD) in patients with risk factors was 3.67 ± 1.43 days (p = 0.0035), including in patients with cardiovascular diseases 3.43 ± 1.52 days (p = 0.0166), as well as in patients over 65 years — 2.70 ± 0.64 days (p = 0.0134).

Thus, it can be concluded that Esperavir® therapy is highly effective in patients with influenza and/or ARVI, in terms of reducing the time to achieve clinical recovery, including in groups at high risk of complications and hospitalization, which proves the clinical effectiveness and pharmacoeconomic feasibility of the proposed therapy.

Secondary efficacy criteria

The frequency of patients with virus elimination in the study drug group by Visit 2 (Day 3–4) was 64.67% (97 / 150) and by Visit 3 (Day 6–7) — 94.00% (141 / 150), while in the placebo group the frequency of patients with virus elimination by Visit 2 (Day 3–4) was — 40.00% (60 / 150) and by Visit 3 (Day 6–7) — 85.33% (128 / 150), respectively. A comparative analysis of the frequency of patients with virus elimination showed statistically significant differences between the study groups both by Visit 2 (Day 3–4) (p < 0.0001) and by Visit 3 (Day 6–7) (p = 0.0137), which confirms the advantage of molnupiravir therapy in terms of virus elimination compared to placebo already by the 3rd day of therapy.

The frequency of patients who achieved clinical recovery in the molnupiravir group by Visit 2 (day 3–4) was 42.00% (63 / 150) and by Visit 3 (Day 6–7) — 93.33% (140 / 150), while in the placebo group the frequency of patients who achieved clinical recovery by Visit 2 (Day 3–4) was — 28.00% (42 / 150) and by Visit 3 (Day 6–7) — 83.33% (125 / 150), respectively. A comparative analysis of the frequency of patients who achieved clinical recovery showed statistically significant differences between the molnupiravir and placebo groups by Visit 2 (Day 3–4) (p = 0.0110) and by Visit 3 (Day 6–7) — p = 0.0070. By Visit 4 (Day 13–14), all patients in both the study drug group and the placebo group had achieved clinical recovery.

It was shown that molnupiravir therapy can significantly reduce the time to achieve a decrease in body temperature up to normalization. The average time (in hours) to achieve body temperature < 37.5°C without taking antipyretic drugs in the molnupiravir group was 59.61 ± 29.90 hours, while in the placebo group — 80.15 ± 43.59 hours. In the molnupiravir group, by Visit 2 (Day 3–4), the frequency of patients who achieved body temperature < 37.5°C was 64.00% (96 / 150) and by Visit 3 (Day 6–7) — 99.33% (149 / 150), while in the placebo group, by Visit 2 (Day 3–4), the frequency of patients who achieved body temperature < 37.5°C was 40.00% (60 / 150) and by Visit 3 (Day 6–7) — 91.33% (137 / 150). Thus, a comparative analysis of the frequency of patients who achieved body temperature < 37.5°C showed statistically significant differences between the study groups by Visit 2 (Day 3–4) — p < 0.0001 and by Visit 3 (Day 6–7) — p = 0.0015. The results obtained prove the advantage of molnupiravir therapy in terms of reducing body temperature up to normalization without taking antipyretic drugs already by the 3 day of therapy.

The main symptoms of influenza / ARVI that were registered in patients in the study were: chills,

headache, myalgia, sore throat, nasal congestion, runny nose, sneezing, cough. The severity of symptoms was assessed using the Likert scale. According to the results of the analysis, statistically significant differences were found between molnupiravir and placebo by Visit 2 (Day 3–4) and Visit 3 (Day 6–7) in the severity of symptoms such as: chills, headache, sore throat (Table 2). The data obtained indicate the high effectiveness of molnupiravir and significant advantages compared to placebo in terms of the dynamics of the disappearance of symptoms of influenza / ARVI, improving the condition and improving the quality of life of patients.

During the clinical study, bacterial infections of the upper and lower respiratory tract were registered as complications of ARVI / influenza: bronchitis, acute sinusitis, pneumonia, tonsillitis, tracheitis, tracheobronchitis. Analysis of the frequency of ARVI / influenza complications in the groups showed that in the molnupiravir group, by Visit 2 (Day 3–4), the frequency of patients with ARVI / influenza complications was 0.67% (1 / 150), while in the placebo group, the frequency of patients with ARVI / influenza complications was 14.67% (22 / 150), and by Visit 3 (Day 6–7), the frequency of patients with ARVI / influenza complications in the molnupiravir and placebo groups was 2.67% (4 / 150) and 17.33% (26 / 150), respectively. By Visit 4 (Day 13–14), complication rates remained at the level of Visit 3 (Day 6–7). Comparative analysis of the frequency of patients with ARVI / influenza complications showed statistically significant differences between the study groups by Visit 2 (Day 3–4), Visit 3 (Day 6–7), and Visit 4 (Day 13–14) ($p < 0.0001$ for each Visit), which confirms the significant efficacy of molnupiravir in reducing the risks of ARVI / influenza complications.

During the study, no patients required hospitalization due to worsening of influenza / ARVI, neither in the molnupiravir group nor in the placebo group.

Summary data on secondary efficacy criteria are presented in Table 2.

Safety assessment

The frequency of patients with registered cases of adverse events (AEs) was 23.67% (71 / 300): in the molnupiravir group — 18.00% (27 / 150), in the placebo group — 29.33% (44 / 150). In total, 71 patients had 104 AEs: 27 patients in the study drug group had 32 AEs, and 44 patients in the placebo group had 72 AEs.

As a result of the comparative analysis of AEs, statistically significant differences were found between the study groups ($p = 0.021$).

As a result of the comparative analysis of AEs by severity, association of AEs with therapy, and outcomes, no statistically significant intergroup differences were found.

No cases of SAEs were registered during the study.

The smaller number of AEs in the molnupiravir group compared to the placebo group indirectly suggests that molnupiravir therapy leads to a reduction in the risks of developing complications of the underlying disease and a smaller number of adverse events that may develop against the background of complications.

AEs registered according to the WHO classification with a causal relationship with the study drug / placebo — definite, probable, possible with the determination of frequency in the population were also analyzed (Table 3).

Registered AEs had a profile and frequency comparable to the placebo group. Such AEs as: dizziness, headache, diarrhea, nausea, dyspepsia, urticaria, registered in the molnupiravir study drug group, corresponded to the studied safety profile of Esperavir® and can be classified as expected with a comparable detection frequency.

Abdominal pain (1 case in the IP group), bacterial bronchitis (1 case in the IP group) were registered for the first time as isolated cases, therefore they can be classified as new data that require confirmation, in particular, registration of similar cases in the future when using the medicine in routine practice. It is worth noting that the development of AEs in the study drug group did not require discontinuation of therapy, which further confirms the favorable benefit/risk ratio for molnupiravir.

The development of bacterial bronchitis may be a consequence of the underlying disease; it was registered both in the study drug group and in the placebo group.

Thus, in the clinical study, AEs were registered that were identified when using the study drug molnupiravir, which belong to the category of expected.

The study showed that molnupiravir therapy is characterized by a favorable safety profile and good tolerability, corresponding to the information in the

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summary of product characteristics for molnupiravir (Esperavir®).

DISCUSSION

The search for rational and effective pharmacotherapy for ARVI and influenza, which allows not only to quickly relieve the main symptoms and reduce the duration of diseases, but also to reduce the risks of developing serious complications, is an urgent problem for healthcare professionals in all countries.

PROMOMED RUS LLC has developed a medicine containing molnupiravir as an active substance [(2R,3S,4R,5R)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl] methyl 2-methylpropanoate. Currently, the medicine is registered and approved for use in the treatment of new coronavirus infection (COVID-19), mild and moderate in adults patients with an increased risk of disease progression to severe and not requiring additional oxygen therapy[15].

Molnupiravir is an antiviral medicine, the mechanism of which is aimed to suppress the replication of RNA viruses by incorporating into the viral genome and disrupting the structure of the genome by inducing viral error / mutation. Showing activity against the RNA-dependent RNA polymerase of one type of RNA virus, molnupiravir will also be active against other RNA viruses, moreover, when the virus mutates and the strain changes seasonally, resistance to the medicine will not develop, the effectiveness will remain at the required level [8, 13–15].

A series of preclinical studies have shown the antiviral activity of the medicine against influenza viruses and respiratory syncytial virus in various animal models: mice, guinea pigs, Javan macaques and ferrets [16–18].

Being an analogue of ribonucleoside, molnupiravir is known for its effect on the replication and function of mitochondria. However, in *in vitro* studies, the medicine did not cause significant mitochondrial toxicity and did not impair their function [19]. After seven days of treatment with molnupiravir (EIDD-2801), no significant changes in the rate of transmission of nuclear or mitochondrial signals were observed in the lung tissue of ferrets [17].

An important advantage of molnupiravir in the elimination of RNA-containing viruses is that molnupiravir does not affect the replicative apparatus of human cells due to the absence of its own RdRp in the human body. A series of scientific publications convincingly shows that the low toxicity of nucleoside analogs (molnupiravir) in the elimination of RNA-containing viruses is due to the absence of its own RdRp in the human body, which ensures selectivity of action against viral targets and safety of therapy — the drug acts only on “infected cells” [8, 13–15, 20]. Available data indicate that NHC has an antiviral effect, selectively introducing mutations only into viral RNA, leaving the host RNA intact, which indicates high genetic resistance to the development of resistance to NHC [21, 22].

According to literature data, the minimum effective dose of molnupiravir in *in vivo* studies in humans for the treatment of RSV and seasonal influenza was 580–625 mg. These tests indicate that even minimal pharmaceutical intervention (a dose of 187.5 mg in human equivalent) in RSV replication can lead to significant changes in RSV disease markers in a mouse model. Effective suppression of influenza virus transmission (delay) between individuals was noted [23]. Toots et al. in their work determined the minimum concentration effective for influenza therapy and equal to 160–350 mg 2 per day in human equivalent [17, 18].

The results of a clinical study showed a favorable safety profile of molnupiravir, both with a single dose (50–1600 mg) and with multiple doses (50–800 mg 2 per day).

Most subjects reported AEs after placebo administration than after molnupiravir administration; all adverse events were mild in severity; the most common adverse events were headache with single administration and diarrhea with multiple administration [24], but its use is not recommended during pregnancy or breastfeeding due to reproductive toxicity observed in animals exposed to high doses (exceeding human doses by 2–6 times). It is worth noting that therapy with most registered antiviral drugs is characterized by a warning about contraindications for pregnant women, which is associated with insufficient evidence base on the safety of this type of therapy [25].

As part of a clinical study of molnupiravir, the following dosage regimen was studied: 800 mg 2 per day (daily dose 1600 mg) for 5 days.

In accordance with the data of the State Register of Medicines of the Russian Federation[16] of the registered

[15] Esperavir®. State Register of Medicines of the Russian Federation. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=6d34e8f9-9267-4125-b461-2ee715c4b6c0

[16] Ibid.

Esperavir®, capsules, the course of therapy is 5 days. In this regard, the duration of therapy (5 days) was justified in the study and fully proved its effectiveness. Clinical recovery while taking molnupiravir occurred on average already on the 3rd day of therapy, and in 64.7% of patients, complete elimination of the virus was observed two days after taking the drug. More than 60% of patients already on the 3 day of therapy reached a body temperature below subfebrile, up to complete normalization, which is important from the point of view of reducing the need for antipyretics and the risk of developing complications. A significant advantage of molnupiravir therapy in relieving other symptoms of ARVI and influenza (chills, sore throat, runny nose, etc.) was proven. It is important to note that during the week in the group of the study drug, only 4 patients developed complications of the disease, while in the placebo group there were 6 times more such patients.

Thus, the effectiveness of therapy with the molnupiravir (Esperavir®) in achieving clinical and surrogate endpoints of therapy was proven, while a high safety profile was noted as a result of taking the drug.

Study limitations

This clinical study was conducted only with adults, since the evaluation of the efficacy and safety of molnupiravir in children was not planned as part of this work. It is also worth noting that this study was conducted only on the territory of the Russian Federation, therefore, the researchers did not have the opportunity to obtain data on adherence to treatment in subjects depending on race, nationality and other factors.

CONCLUSION

As a result of the clinical study, the high efficacy of therapy with Esperavir® (molnupiravir) in patients with influenza and/or ARVI was proven in terms of reducing the time to achieve clinical recovery (observed already 2 days after the start of taking the medicine), eliminating viruses, reducing the severity of symptoms of the disease, reducing the time to achieve subfebrile body temperature values without the need for antipyretic drugs, preventing the development of bacterial complications and, as a result, reducing the need for antibacterial drugs and fewer adverse events that may develop against the background of complications. Already on the second day of taking molnupiravir, a significant relief of symptoms of ARVI and influenza occurred, which indicates an improvement in the quality of life of patients. The results of the clinical study prove the clinical efficacy and safety of molnupiravir therapy and determine the prospects for including Esperavir® in clinical guidelines and protocols for the treatment of influenza and other viral infections.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Oksana M. Drapkina — development and implementation of research design, writing and editing of text; Aleksander Y. Gorshkov — processing of the received data, implementation of the research design; Tatyana I. Chudinovskikh — implementation of research design; Elena N. Simakina — implementation of research design, processing of the obtained data; Grigory V. Rodoman — implementation of research design; Varvara V. Popova — text editing, analysis of literary sources; Igor V. Balaban — development of research design, text editing; Natalia M. Selezneva — analysis of results; Larisa A. Balykova — development and implementation of research design, text editing; Natalia V. Kirichenko — processing of research data, analysis of results; Roman S. Kozlov — processing of received data; Dmitrii A. Bystritskii — research data processing; Vasiliy B. Vasilyuk — research design implementation, data processing; Kira Ya. Zaslavskaya — research design development and implementation, results analysis; Petr A. Bely — research design development, text editing; Ksenia N. Koryanova — research design implementation; Ekaterina S. Mishchenko — data processing, analysis of literary sources; Victoria S. Scherbakova, Lyudmila A Pochaevets — analysis of literary sources; Alexey V. Taganov — implementation of research design. All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

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