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Post-exposure prophylaxis of COVID-19: results of double-blind, placebo-controlled, multicenter clinical study evaluation of efficacy and safety of double-stranded sodium salt RNA drug

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The aim of the study was to evaluate the efficacy and safety of an RNA double-stranded sodium salt drug, a lyophilisate for a solution preparation for an intramuscular and subcutaneous administration, as a means of post-exposure COVID-19 prophylaxis in comparison with placebo.

Material and methods. A double-blind, placebo-controlled, multicenter, randomized phase III clinical trial was conducted to evaluate the efficacy and safety of a double-stranded sodium salt RNA drug (RADAMIN®VIRO), a lyophilisate for preparing a solution for intramuscular and subcutaneous administration as a means of post-exposure prophylaxis of COVID-19. The study was conducted in 10 research centers in the Russian Federation from May 31, 2022 to January 17, 2023. The study included

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men and women aged ≥18 years who cohabitate with a person with a documented COVID-19 diagnosis and do not have symptoms characteristic of COVID-19. At the randomization stage, the subjects were assigned to one of two groups: group 1 (*n*=400) received a study drug RADAMIN®VIRO 5 mg (1 vial) intramuscularly once a day; group 2 (*n*=400) received placebo 1 vial intramuscularly once a day. The total duration of the study for each subject was no more than 30 days.

Results. By day 10–11, in the double-stranded sodium salt RNA drug group, the proportion of the subjects with confirmed COVID-19 and at least 1 symptom characteristic of COVID-19 was 5.76% (23/399), and in the placebo group – 11.03% (44/399). The difference in proportions between the study drug and placebo groups was 0.0526 (5.26%), the 95% confidence interval (CI) for the difference in proportions between the groups was [0.0123;0.0937]). More than 94% of single-dose subjects did not become infected with COVID-19 with any symptoms during the 11 days of the follow-up. As a result of a comparative analysis, it was shown that the infection frequency in the study drug group was statistically significantly (almost twice) less than in the comparison group, which indicates a high efficiency and expediency of using the double-stranded sodium salt RNA drug as a means of the post-exposure COVID-19 prophylaxis.

Conclusion. Thus, regardless of the vaccination availability, the effectiveness and feasibility of using the study double-stranded sodium salt RNA drug as a means of the post-exposure COVID-19 prophylaxis was demonstrated not only in medical institutions (outpatient clinics and hospitals), but also in caregivers and/or the persons in contact with COVID-19 patients. The situation was the same in the organizations and enterprises in case of evolution of a mass infection threat and the availability of appropriate medical personnels.

Keywords: coronavirus; COVID-19; RNA double-stranded sodium salt; RADAMIN©VIRO; prophylaxis; interferon inducer

Abbreviations: WHO – World Health Organization; AE – adverse events; SAE – serious adverse events; IG – Interim guidelines "Prevention, diagnosis and treatment of a new coronavirus infection"; CCs – comorbid conditions; ARI – acute respiratory infection; NAAT – nucleic acid amplification test; NSAIDs – non–steroidal anti–inflammatory drugs; MedDRA – Medical Dictionary for Regulatory Activities; CI – confidence interval; COVID–19 – coronavirus disease; SARS-CoV-2 – coronavirus, the causative agent of COVID–19; CTs – clinical trials, IWRS – Interactive Web Randomization System; eIRC – electronic individual registration card; GFR – glomerular filtration rate.

Постконтактная профилактика COVID-19: результаты двойного слепого плацебо-контролируемого многоцентрового клинического исследования по оценке эффективности и безопасности применения препарата РНК двуспиральной натриевой соли

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Цель. Оценка эффективности и безопасности применения препарата РНК двуспиральной натриевой соли, лиофилизат для приготовления раствора для внутримышечного и подкожного введения, в качестве средства постконтактной профилактики COVID-19 в сравнении с плацебо.

Материал и методы. Проведено двойное слепое плацебо-контролируемое многоцентровое рандомизированное клиническое исследование III фазы по оценке эффективности и безопасности применения препарата РНК двуспиральной натриевой соли (РАДАМИН®ВИРО), лиофилизат для приготовления раствора для внутримышечного и подкожного введения в качестве средства постконтактной профилактики COVID-19. Исследование проведено в 10 исследовательских центрах на территории РФ в период с 31.05.2022 г. по 17.01.2023 г. В исследование включались мужчины и женщины в возрасте ≥18 лет, совместно проживающие с лицом с документально подтвержденным диагнозом COVID-19 и не имеющие симптомов, характерных для COVID-19. На этапе рандомизации субъекты распределялись в одну из двух групп: 1 группа (*n*=400) получала исследуемый препарат РАДАМИН®ВИРО по 5 мг (1 флакон) внутримышечно однократно; 2 группа (*n*=400) получала плацебо по 1 флакону внутримышечно однократно. Общая продолжительность исследования для каждого субъекта составляла не более 30 дней.

Результаты. В группе препарата РНК двуспиральной натриевой соли доля субъектов с подтвержденным COVID-19 и наличием как минимум 1 симптома, характерного для COVID-19, к 10–11 сут составила 5,76% (23/399), а в группе плацебо – 11,03% (44/399). Разница в долях между группами исследуемого препарата и плацебо составила 0,0526 (5,26%), 95% доверительный интервал (ДИ) [0,0123; 0,0937]. Более чем у 94% субъектов, которым однократно вводили лекарственный препарат, не наблюдалось заражение COVID-19 с проявлением каких-либо симптомов в течение 11 дней наблюдения. В результате сравнительного анализа было показано, что частота заражения в группе исследуемого препарата была статистически значимо (практически в 2 раза) меньше, чем в группе сравнения, что говорит о высокой эффективности и целесообразности применения препарата РНК двуспиральной натриевой соли в качестве средства постконтактной профилактики COVID-19.

Заключение. Таким образом, была продемонстрирована эффективность и целесообразность применения исследуемого препарата РНК двуспиральной натриевой соли в качестве средства постконтактной профилактики COVID-19 вне зависимости от наличия вакцинации не только в медицинских учреждениях (амбулаториях и стационарах), но и у субъектов, осуществляющих уход и/или контактировавших с больными COVID-19, а также в организациях и на предприятиях при возникновении угрозы массового заражения и наличия соответствующего медицинского персонала.

Ключевые слова: коронавирус; COVID-19; РНК двуспиральной натриевая соль; РАДАМИН®ВИРО; профилактика; индуктор интерферонов

Список сокращений: ВОЗ – Всемирная организация здравоохранения; НЯ – нежелательное явление; СНЯ – серьёзные нежелательные явления; АПФ2 – ангиотензинпревращающий фермент 2; ВМР – Временные методические рекомендации «Профилактика, диагностика и лечение новой коронавирусной инфекции»; ОРВИ – острая респираторная вирусная инфекция; СЗ – сопутствующие заболевания; МАНК – метод амплификации нуклеиновых кислот; НПВП – нестероидные противовоспалительные препараты; MedDRA – медицинский словарь терминов международной медицинской терминологии; ДИ – доверительный интервал; COVID-19 – коронавирусная инфекция; SARS-CoV-2 – коронавирус, возбудитель COVID-19; КИ – клинические исследования; IWRS – модуль рандомизации пациентов; э-ИРК – электронная индивидуальная регистрационная карта; СКФ – скорость клубочковой фильтрации.

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INTRODUCTION

The COVID-19 pandemic has damaged many aspects of society, but at the same time has had a powerful driver on the development of the pharmaceutical industry, in particular, the development and implementation of effective drugs for the treatment and prevention of coronavirus infection. During the pandemic, clinical trials were accelerated and the procedure for registering new drugs was simplified, careful monitoring, but at the same time, permanent monitoring of the drugs safety and efficacy was observed [1, 2].

The new coronavirus infection (COVID-19) turned into a pandemic in March 2020 and was characterized by high contagiousness, damage not only to the lungs, but also to other organs and systems (digestive tract, cardiovascular system, kidneys) and a lethality of about 2%[1]. SARS-CoV-2 is RNA single-stranded virus, which, binds with ACE2, entering at the human body through the cell membrane, penetrates the cell, multiplies with the release of new virions from the infected cell, the development of a local and systemic inflammatory response, with damage to target organs [3].

Despite the fact that at present there are the signs of the COVID-19 pandemic subsiding and the epidemiological situation has switched on to a "managed" mode, due to virus mutations (decrease in virulence), increases of collective immunity and number of COVID-19 vaccinated and recovering, the risk of infection, especially with new sublines of SARS-CoV-2 persists, and the search for new means and methods of treatment and prevention of a new coronavirus infection is relevant now [4–6]. Social distancing (self-isolation, breakup, public places and enterprises; the cancellation of mass events), quarantine measures limited to the recording of disease cases, isolation of severely ill patients in a hospital, mild cases at home and contact tracing[2], have historically been the first approaches to prevention of COVID-19, but had a limited effect [7] and, unfortunately, have not made the spread of the infection possible to take complete control of it[3].

The presence of niches where the SARS-CoV-2 virus circulates both during the peaks of the pandemic and outside the pandemic waves, which include asymptomatic carriers and/or mild cases with symptoms of seasonal acute respiratory infection (ARI) [8, 9] explained the low effectiveness of social prevention measures and the need for immunization and other ways to prevent infection [10, 11]. However, the problems of vaccination against a new coronavirus infection remain unresolved [12, 13]. One of the reasons for this is a high contagiousness of SARS-CoV-2 "Omicron" and its subvariants[4]. Moreover, the virus has a reduced "recognition" of post-infection and post-vaccination antibodies [14].

Some patients (including vaccinated) carry a new coronavirus infection asymptomatically or in a mild form, but the spread of the virus by humans continues [15]. No "superinfectors" should be disregarded: to the high replication of the virus in the oral cavity, nasopharynx and oropharynx, they can release large concentrations of the virus during close contacts in sneezing and coughing [16, 17].

Despite the unprecedented lockdown measures, families always have the members involved in the process flow production (doctors, pharmacists, employees of law enforcement agencies, emergency services, transport), forced to be at the workplace all the time. In this regard, it is possible that the disease of one family member poses a threat of infection not only to all their family members, but also to those around them [18]. The search for methods of drug prevention that affect the signaling pathways of interferon, which have an immunomodulatory and early antiviral effect after contact with patients with COVID-19, is extremely relevant and especially significant for controlling morbidity in contact persons in the family, in labor collectives, crowded places and among medical workers [19].

Nonspecific prophylactic measures aimed at the infection source, include an early diagnosis and an active detection of the infected, including those who are asymptomatic, the isolation of patients and persons with a suspected disease, and the prescription of the etiotropic therapy [20, 21]. Cytokines are regulatory peptides produced by body cells that play one of the main roles in individual reactivity associated with clinical manifestations.

The antiviral response mediated by interferons has a direct relationship with the viral load, which depends on the infecting dose and the degree of the immune replication control [22].

In the early stages of infection, the use of the drugs based on the RNA double stranded sodium salt can act as a factor determining the virus replication control and, at the same time, maintain the endogenous control mechanism of the interferons content in the body no higher than protective concentrations [23].

In the Russian Federation, a medicinal product based on the RNA double-stranded sodium salt (LS-000381 dated Dec 27. 2021) RADAMIN©VIRO is registered for the treatment and prevention of influenza and other ARIs, as well as in the prevention and treatment of other infectious and inflammatory diseases, including caused by herpes zoster, genital, simplex, and chlamydia viruses.

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THE AIM of the study was to evaluate the efficacy and safety of an RNA double-stranded sodium salt drug as a means of a post-exposure COVID-19 prophylaxis in comparison with placebo.

MATERIALS AND METHODS

The efficacy and safety of using the RNA double-stranded sodium salt (lyophilizate for the preparation of a solution for intramuscular and subcutaneous administrations) as a means of a post-exposure COVID-19 prophylaxis, was studied in a double-blind, placebo-controlled, randomized, multicenter, comparative phase III clinical trial (RCT No. 263 dated 12 Apr 2022).

The research was conducted from May 31, 2022 to January 17, 2023 on the basis of 10 research centers in the Russian Federation:

1. LLC "Eco-Safety" Research & Development center, St. Petersburg;
2. LLC OrKli Hospital Company, St. Petersburg;
3. Kirov State Medical University;
4. LLC "Professor's Clinic", Perm;
5. LLC Aurora MedFort, St. Petersburg;
6. National Research Ogarev Mordovia State University, Saransk;
7. Smolensk State Medical University, Smolensk;
8. City Clinical Hospital named after S.I. Spasokukotsky, Moscow City Health Department;
9. Ivanovo Clinical Hospital;
10. Smolensk Clinical Hospital No. 1.

This study was conducted in accordance with the rules of Good Clinical Practice of the International Conference on Harmonization (ICH GCP), the ethical principles set forth in the Declaration of Helsinki of the World Medical Association (Fortaleza, 2013) and the requirements of the Russian legislation.

The study protocol, the Investigator's Brochure, the Subject Information Sheet with the Informed Consent Form for Participation in the Study, were approved by the Ethics Council prior to the inclusion of subjects in the study (Protocol No. 307 dated 04.05.2022). The subjects consented to participate in this study by signing the Informed Consent Form.

Randomization of study subjects into groups

The study screened 804 subjects, 800 subjects of which were randomized (4 subjects were not randomized due to the non-inclusion criteria; Fig. 1).

The subjects were randomized using an interactive on-line randomization system (Interactive web randomization system, IWRS) embedded in an electronic individual registration card (eIRC). Before the start of the study, each investigator-physician who had been delegated the responsibility of transferring the data to the eIRC was provided with an access code (a combination of a username and password) to the eIRC, as well as detailed written instructions for working with the eIRC, including detailed instructions for the randomization procedure. The randomization was carried out according to the following algorithm. Each subject that had met all of the inclusion criteria and had not met any of the exclusion criteria was assigned a three-digit randomization number by the IWRS system. The subject randomization number and other relevant data were entered by the investigator into the Subject Screening/Randomization Journal. If a subject had terminated participation in the study prematurely, their randomization number was not reused and the subject was subsequently unable to participate in the study. Neither the investigator nor the subject knew what therapy the subject was receiving.

Study design

The study included men and women (*n*=800) aged 18 to 80 years who cohabited with a person with a documented COVID-19 diagnosis and had symptoms characteristic of COVID-19, meeting the inclusion criteria and not meeting the non-inclusion criteria. Subjects were screened and randomized into 2 groups in the ratio of 1:1. The choice of drug for patients was carried out in accordance with the randomization number assigned to patients at the time of randomization.

Depending on the randomization, the study subjects received either the study RNA sodium double-stranded drug or placebo. During the randomization phase, the subjects were assigned to 1 of the 2 groups:

Group 1 (*n*=400) received the study RNA double-stranded sodium salt drug (RADAMIN®VIRO, JSC "Biochemist", series 010122) 5 mg (1 vial) intramuscularly once;

Group 2 (*n*=400) received a placebo (sodium chloride, JSC "Biochemist", Russia, series 010122) 1 vial intramuscularly once.

The study drug/placebo was administered by the study center medical staff in the upper outer quadrant of the buttock. The study provides for a single intramuscular RADAMIN® VIRO injection at the dose of 5 mg[5]. This is due to its dosage form and dosing regimen approved by the current instructions for the prevention and treatment of influenza and SARS. A placebo was used as a reference drug, which made it possible to obtain objective results of this study. The study participants who were diagnosed with COVID-19 during the course of the study could receive standard therapy in accordance with the IGs in force at the time of the research. Due to the lack of the approved COVID-19 post-exposure prophylaxis, the drugs that could be used as comparators, and to avoid the data collection/evaluation bias during the study, placebo was used as the study comparator.

[5] Russian State Register of Medicines. Instructions for the medical use of RADAMIN®VIRO. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=2e3ad776-6616-4e43-99c1-3133cd95b280

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The clinical study included the following steps (Fig. 2):

- screening – no more than 24 h;
- randomization – no more than 1 day;
- study drug/placebo therapy – 1 day;
- post-observation – 28 days.

The duration of the study for the subjects was no more than 30 days, herewith, the study drug/placebo treatment period was 1 day. If a subject had been diagnosed with COVID-19 during the course of the study based on the results of SARS-CoV-2 RNA analyses using the NAAT, the standard therapy presented in the current version of the IG, could be prescribed to the subject at the discretion of the investigator.

Depending on the COVID-19 severity, its treatment could be carried out both at home and in a hospital setting. At Visits 2 and 3, regardless of the presence/absence of COVID-19 symptoms, nasopharyngeal and/or oropharyngeal swabs were collected from the subjects for the SARS-CoV-2 RNA determination by the NAAT to detect COVID-19.

In addition, if a study subject had experienced the symptoms consistent with COVID-19 prior to day 29 after the administration of the study drug/placebo, he was given a COVID-19 Confirmation Visit. However, if the subject developed the symptoms consistent with COVID-19 after being diagnosed with COVID-19 based on the NAAT SARS-CoV-2 RNA results, the COVID-19 Confirmation Visit was not conducted.

If a subject did not need to be hospitalized due to the COVID-19 development, he was not withdrawn from the study, and continued to be monitored. If a subject needed to be hospitalized during the course of the study, he was excluded from the study.

If a subject had been diagnosed with COVID-19, additional procedures outside the Protocol could be performed at the discretion of the investigator physician in accordance with the clinical practice of the research center.

Selection of subjects for analysis

Primary and secondary efficacy outcomes were analyzed using a dataset of the study participants selected according to the protocol compliance, i.e., all the patients who had completed the study in accordance with the Study Protocol. A participant was excluded from the data set if he had met the exclusion criteria. The safety data set included all randomized patients who had been exposed to the study drug, regardless of the degree of adherence to the Protocol during the study. The study screened 804 subjects, 800 of which were randomized. 4 subjects were not randomized due to the non-inclusion criteria. During the course of the study, 1 subject was excluded from the RNA double-stranded sodium salt drug group due to the meeting the exclusion criterion No. 4 “Invalid inclusion of a subject not meeting the inclusion criteria and/or meeting the non-inclusion criteria”, i.e., living with 2 or more persons with documented COVID- 19 at the time of screening. One subject in the placebo group was tested positive for SARS-CoV-2 RNA by the NAAT at screening.

Inclusion Criteria

The subjects meeting the following inclusion criteria were included in the study:

1. Men and women aged 18 to 80 inclusive (subjects) at the time of signing the Informed Consent Form.

2. The subject is living with a person with documented COVID-19 who meets both of the following criteria:

– the first positive result of a laboratory test for the presence of SARS-CoV-2 RNA using nucleic acid amplification tests (NAATs) or SARS-CoV-2 antigen using an immunochromatographic analysis within 72 hours before the randomization of the subject participating in this study;

– the presence of at least 1 of the symptoms characteristic of COVID-19, with the onset of symptoms no more than 5 days before the randomization of the subject participating in this study.

3. A negative result for the presence of SARS-CoV-2 antigen using an immunochromatographic analysis.

4. The absence of the symptoms characteristic of COVID-19.

5. The subject is expected to continue to live with a person with documented COVID-19 for the duration of the participation in the clinical study, no need for hospitalization of a person;

6. A subject’s consent to use reliable methods of contraception throughout the study and for 3 weeks after the end of the study. Reliable means of contraception are: sexual abstinence, the use of a condom in combination with spermicide. The study may also include the women who are unable to bear children (history: hysterectomy, tubal ligation, infertility, menopause for more than 2 years), as well as the men with infertility or a history of vasectomy.

7. An availability of an Informed Consent Form signed and dated by the subject.

8. An availability of a signed and dated by a person documented COVID-19 Informed Consent Form for the collection of information on COVID-19.

Exclusion Criteria

The subjects meeting at least one of the following non-inclusion criteria were not included in the study:

1. Hypersensitivity to the components of the study drug, procaine.

2. The presence of contraindications for intramuscular injections.

3. Contact with 2 or more individuals with documented COVID-19 within 1 month prior to screening, or living with 2 or more individuals with documented COVID-19 at the time of screening.

4. Shared accommodation with > 10 people.

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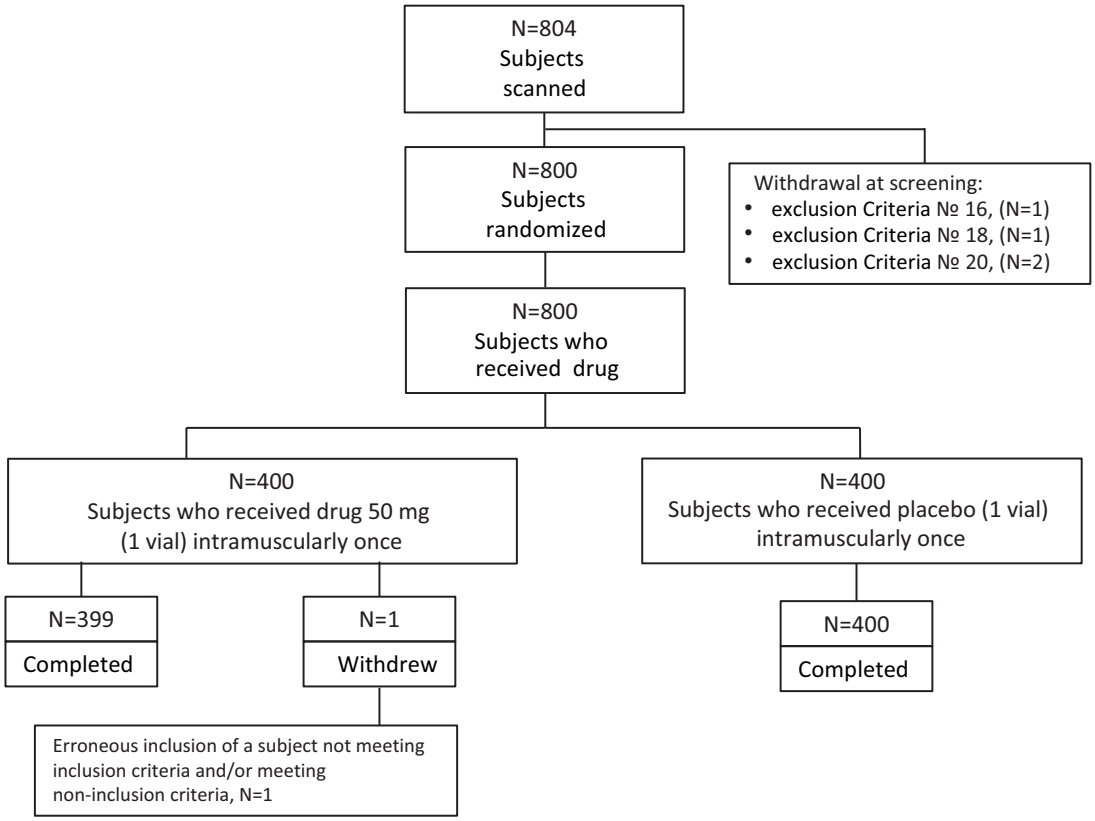

Figure 1 – Randomization of study subjects into groups

Table 1 – Criteria for effectiveness evaluation

No.	Effectiveness criterion	End point
	Primary effectiveness criterion	
1.	Frequency of subjects with confirmed COVID-19 and at least 1 symptom consistent with COVID-19*	Visit 3
	Secondary effectiveness criteria	
2.	Frequency of subjects with confirmed COVID-19 and at least 1 symptom consistent with COVID-19**	Visits 2, 4, 5
3.	Frequency of subjects with confirmed COVID-19 and no symptoms consistent with COVID-19**	Visits 2, 3.
4.	Frequency of Subjects with Confirmed COVID-19 with and without Symptoms of COVID-19**	Visits 2–5
5.	Time till exposure to COVID-19* Infection was understood as the moment of the onset of a symptom characteristic of COVID-19, or the moment of SARS-CoV-2 RNA by NAAT detection, depending on what had been previously detected.	–
6.	Assessment of the severity of symptoms characteristic of COVID-19* Assessment was performed only for the subjects who had developed symptoms of COVID-19 during the study up to and including Visit 3.	Visits 2–5
7.	Duration of symptoms characteristic of COVID-19** Assessment was performed only for subjects who had developed symptoms of COVID-19 during the study up to and including Visit 3. The score was presented for symptoms that had ended before the end of the subject's participation in the study.	–
8.	Estimated severity of COVID-19**. Assessment was performed only for subjects who had tested positive for COVID-19.	To visits 2–5
9.	Frequency of subjects requiring hospitalization due to development of COVID-19.	–

Note: * – Analysis includes subjects with a negative SARS-CoV-2 RNA assay by NAAT selected at screening; ** – Assessment was performed with and without subjects who were positive for SARS-CoV-2 RNA by NAAT at the time of screening. The assessment included subjects who had a COVID-19 confirmation visit between visits and found positive SARS-CoV-2 RNA by NAAT.

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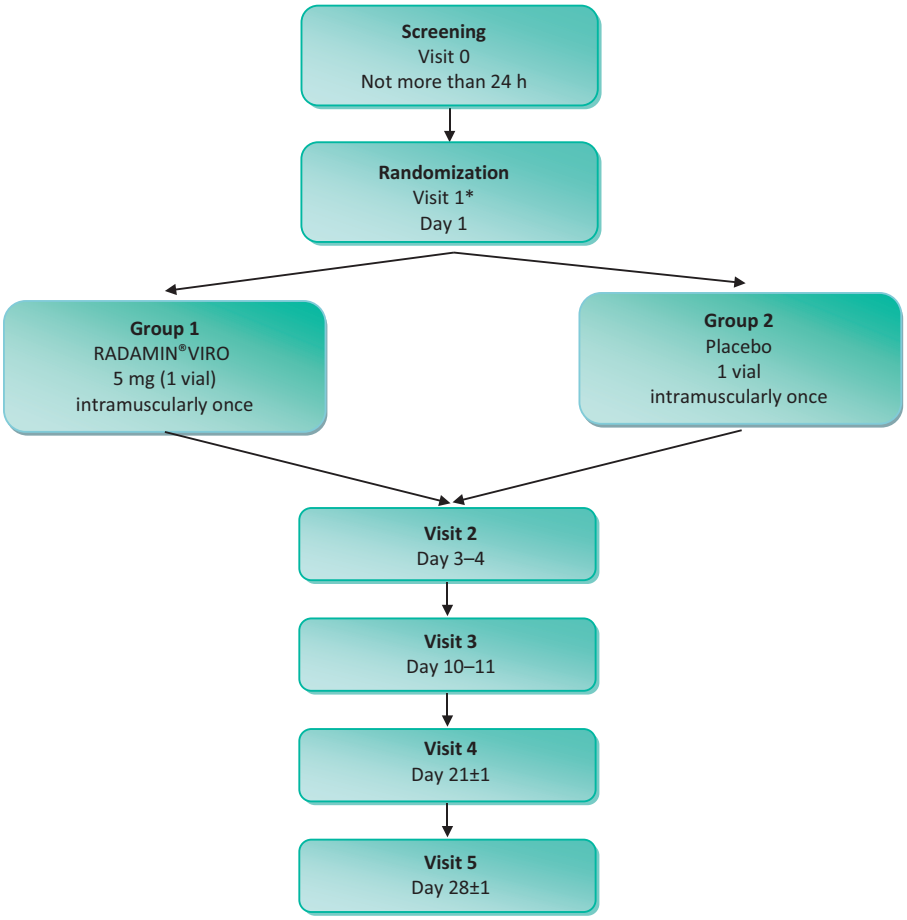

Figure 2 – Study design

Note: * – Visit 1 could be the same as Visit 0. If Visit 1 and Visit 0 were the same, then a physical examination, a pulse oximetry with SpO_2 measurement, a vital signs assessment, concomitant therapy registration was not re-assessed, the inclusion and non-inclusion criteria had been evaluated immediately before randomization, and the exclusion criteria were assessed after the drug use. The visits could take place at the study center or at home. If a subject had experienced the symptoms consistent with COVID-19 before day 29 after the study drug/placebo administration, that subject was eligible for a COVID-19 Confirmation Visit. The visit was carried out as soon as possible, but not later than 3 days after the development of the first COVID-19 symptom.

Table 2 – Baseline demographic, anthropometric and clinical characteristics of patients

Characteristics		RNA double-stranded sodium salt, *n*=400	Placebo, *n*=400
Age, years (M±SD)		44.68±15.60	45.96±14.86
Gender:	males, *n* (%)	169 (42.25%)	174 (43.50%)
	females, *n* (%)	231 (57.75%)	226 (56.50%)
Weight, kg (M±SD)		74.80±13.39	75.84±13.71
Height, cm (M±SD)		171.41±8.00	171.44±8.18
BMI, kg/m^2 (M±SD)		25.41±4.00	25.74±3.99
Comorbid conditions, including:		121 (30.33%)	128 (32.00%)
	obesity	45 (11.28%)	52 (13.00%)
	arterial hypertension	81 (20.30%)	90 (22.50%)
Vaccination against COVID-19		284 (71%)	291 (72.75%)

Note: BMI – body mass index.

Table 3 – Generalized data of comparative evaluation of RNA double-stranded sodium salt efficacy

Checkpoint	Groups	
	Placebo	RNA double stranded sodium salt
Primary criterion		
Frequency of subjects with confirmed COVID-19 and at least 1 symptom consistent with COVID-19*		
Visit 3	11.03% (44/399)	5.76% (23/399)
Secondary efficacy criteria		
Frequency of subjects with confirmed COVID-19 and at least 1 symptom consistent with COVID-19**		
Visit 2	7.00% (28/400)	3.51% (14/399)
Visit 4	11.50% (46/400)	6.02% (24/399)
Visit 5	11.50% (46/400)	6.27% (25/399)
Frequency of subjects with confirmed COVID-19 and no symptoms consistent with COVID-19**		
Visit 2	0.25% (1/400)	0.75% (3/399)
Visit 3	0.00% (0/400)	0.50% (2/399)
Frequency of subjects with confirmed COVID-19 with and without symptoms consistent with COVID-19**		
Visit 2	7.25% (29/400)	4.26% (17/399)
Visit 3	11.25% (45/400)	6.27% (25/399)
Visit 4	11.50% (46/400)	6.52% (26/399)
Visit 5	11.50% (46/400)	6.77% (27/399)
Frequency of COVID-19 infection by day 11 of the study**		
Visit 3	11.25% (45/400)	6.27% (25/399)
Frequency of subjects with COVID-19 symptoms prior to Visit 3*		
Visit 2-5	9.02% (36/399)	17.04% (68/399)
Duration of symptoms characteristic of COVID-19**		
Sore throat, days	4.68±2.53	3.06±1.25
Smell Change	2.25±1.26	11.13±6.45
Severity assessment of COVID-19**		

Checkpoint	Mild illness	Asymptomatic/ completed case	Mild illness	Asymptomatic/ completed case
Visit 2	100% (28/28)	0.00% (0/28)	94.12% (16/17)	5.88% (1/17)
Visit 3	47.73% (21/44)	52.27% (23/44)	64.00% (16/25)	36.00% (9/25)
Visit 4	17.78% (8/45)	82.22% (37/45)	23.08% (6/26)	76.92% (20/26)
Visit 5	15.56% (7/45)	84.44% (38/45)	22.22% (6/27)	77.78% (21/27)
Frequency of subjects requiring hospitalization due to COVID-19 development.				
Visits 1-5	0.00% (0/45)		0.00% (0/27)	

Note: * – The analysis includes subjects with a negative SARS-CoV-2 RNA assay by NAAT selected at screening; ** – The evaluation was carried out with and without the subjects who were positive for SARS-CoV-2 RNA by NAAT at the time of screening. The evaluation included the subjects who had a COVID-19 confirmation visit between the visits and a positive SARS-CoV-2 RNA was found out by NAAT.

Table 4 – Severity of symptoms characteristic of COVID-19

Checkpoint	Placebo			RNA sodium double-stranded		
	Severity of symptoms			Severity of symptoms		
	Absence	Moderate	Severe	Absence	Moderate	Severe
			Sore throat			
Visit 2	94.99% (379/399)	4.76% (19/399)	0.25% (1/399)	97.49% (389/399)	2.51% (10/399)	0.00% (0/399)
Visit 3*	97.24% (388/399)	2.76% (11/399)	0.00% (0/399)	99.25% (396/399)	0.75% (3/399)	0.00% (0/399)
Visit 4	99.75% (398/399)	0.25% (1/399)	0.00% (0/399)	100% (399/399)	0.00% (0/399)	0.00% (0/399)
Visit 5	100% (399/399)	0.00% (0/399)	0.00% (0/399)	100% (399/399)	0.00% (0/399)	0.00% (0/399)
			Fatigue			
Visit 2	94.24% (376/399)	4.76% (19/399)	1.00% (4/399)	96.49% (385/399)	2.76% (11/399)	0.75% (3/399)
Visit 3**	96.24% (384/399)	3.76% (15/399)	0.00% (0/399)	98.50% (393/399)	1.50% (6/399).	0.00% (0/399)
Visit 4	99.75% (398/399)	0.25% (1/399)	0.00% (0/399)	100% (399/399)	0.00% (0/399)	0.00% (0/399)
Visit 5	100% (399/399)	0.00% (0/399)	0.00% (0/399)	100% (399/399)	0.00% (0/399)	0.00% (0/399)
			Chills			
Visit 2***	98.25% (392/399)	1.75% (7/399)	0.00% (0/399)	99.75% (398/399)	0.25% (1/399)	0.00% (0/399)
Visit 3	99.25% (396/399)	0.75% (3/399)	0.00% (0/399)	99.50% (397/399)	0.50% (2/399)	0.00% (0/399)
Visit 4	100% (399/399)	0.00% (0/399)	0.00% (0/399)	100% (399/399)	0.00% (0/399)	0.00% (0/399)
Visit 5	100% (399/399)	0.00% (0/399)	0.00% (0/399)	100% (399/399)	0.00% (0/399)	0.00% (0/399)

Note: * – statistically significant difference between groups; p=0.0314; ** – statistically significant difference between groups, p=0.0472; *** – statistically significant difference between groups; p=0.0191.

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Table 5 – Description of total number of reported AEs in subjects in study groups

AEs (RT* according to MedDRA)	Number of AEs, absolute value (% of AEs total number)		
	Total (*n*=400)	Placebo group (*n*=200)	RADAMIN®VIRO group (*n*=200)
Asthenia	3 (4.92%)	3 (7.14%)	0 (0.00%)
Pain	1 (1.64%)	1 (2.38%)	0 (0.00%)
Pain at injection site	2 (3.28%)	2 (4.76%)	0 (0.00%)
Pain in oropharynx (oropharyngeal)	1 (1.64%)	1 (2.38%)	0 (0.00%)
Viral infection of respiratory tract	6 (9.84%)	2 (4.76%)	4 (21.05%)
Headache	14 (22.95%)	10 (23.81%)	4 (21.05%)
Nasal congestion	6 (9.84%)	3 (7.14%)	3 (15.79%)
Cough	3 (4.92%)	2 (4.76%)	1 (5.26%)
Oropharyngeal discomfort	1 (1.64%)	1 (2.38%)	0 (0.00%)
Sore throat	2 (3.28%)	2 (4.76%)	0 (0.00%)
Pyrexia	4 (6.56%)	3 (7.14%)	1 (5.26%)
Rhinitis	3 (4.92%)	3 (7.14%)	0 (0.00%)
Rhinorrhea	2 (3.28%)	1 (2.38%)	1 (5.26%)
Tension headache	1 (1.64%)	0 (0.00%)	1 (5.26%)
Nausea	1 (1.64%)	1 (2.38%)	0 (0.00%)
Induration at infection site	2 (3.28%)	2 (4.76%)	0 (0.00%)
Fatigue	7 (11.48%)	3 (7.14%)	4 (21.05%)
Erythema at infection site	2 (3.28%)	2 (4.76%)	0 (0.00%)
TOTAL	61 (100%)	42 (100%)	19 (100%)

Table 6 – Frequency of adverse effects according to WHO classification

System organ class and preferred MedDRA term	Number of events (absolute value, %)		*p* value (Pearson's chi-squared test)
	RADAMIN®VIRO (*n*=400)	Placebo (*n*=400)	
Infections and invasions			
Viral infection of respiratory tract	0 (0)	1 (0.3) infrequent	0.3170
Nervous system disorders			
Headache	0 (0)	1 (0.3) infrequent	0.3170
General disorders and reactions at injection site			
Erythema	0 (0)	2 (0.5) infrequent	0.1568
Pain	0 (0)	2 (0.5) infrequent	0.1568
Induration	0 (0)	2 (0.5) infrequent	0.1568

5. Within 6 months prior to the randomization, presence of a laboratory-confirmed COVID-19 case.

6. The subjects vaccinated against COVID-19 less than 4 weeks prior to screening.

7. The use or need to use drugs from the prohibited list at the time of screening.

8. The use of immunostimulating, immunomodulatory or immunosuppressive drugs within 3 months prior to screening.

9. The subjects on the renal replacement therapy or with a history of a severe renal failure (the estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 calculated using the CKD-EPI formula within 6 months prior to screening).

10. Child-Pugh class C primary biliary cirrhosis or history of chronic or active hepatitis B or C.

11. A positive test result for the presence of HIV, syphilis, hepatitis B and/or C at screening.

12. A chronic heart failure (III–IV FC) according to the functional classification of the New York Heart Association (NYHA).

13. A history of malignancy, excluding the subjects with no history of disease in the past 5 years, the subjects with completely healed basal cell skin cancer or completely healed carcinoma *in situ.*

14. A history of alcohol, pharmacological and/or drug dependence and/or at the time of screening.

15. A history of or suspected schizophrenia, schizoaffective disorder, bipolar disorder, or other psychiatric disorder at screening.

16. Any history data that, in the opinion of the investigator, may complicate the interpretation of the results of the study or create additional risk for the subject as a result of his participation in the study.

17. Unwillingness or inability of the subject to comply with Protocol procedures (in the opinion of the investigator).

18. Pregnant or lactating women or women planning a pregnancy.

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

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20. Other conditions that prevent the subject from being included in the study.

Exclusion Criteria

A decision to exclude a subject from the study was made by the investigator. The subject was withdrawn from the study immediately if any of the following situations occurred:

1. The occurrence during the course of the study of any diseases or conditions that worsen the prognosis of the subject, and make it impossible for the subject to continue participation in the clinical study. If a subject was diagnosed with COVID-19 based on the results of SARS-CoV-2 RNA analyses using the NAAT, selected both at the screening stage and after it, and there was no need for hospitalization of the subject, he was not excluded from the study, he continued to be monitored. If a subject needed to be hospitalized during the course of the study, the subject was excluded from the study.
2. Taking drugs of prohibited therapy or the need to prescribe them.
3. Pregnancy (for study participants).
4. Invalid inclusion of a subject that does not meet the inclusion criteria and/or meets the non-inclusion criteria.
5. Other violations of the Protocol which, in the opinion of the investigator, are significant.
6. Refusal of the subject to participate in the study.
7. Other administrative reasons.

Criteria for evaluating effectiveness

The primary endpoint for this study was selected based on the FDA's Guidelines for Drug Development[6] for the Treatment and Prevention of COVID-19. The primary efficacy endpoint analysis included COVID-19 cases prior to Visit 3 (days 10–11). A case of COVID-19 in this study was defined as the absence of a positive SARS-CoV-2 RNA test by the NAAT at the screening stage, the appearance of at least one symptom characteristic of COVID-19 during the study, and the detection of a positive result for RNA during the SARS-CoV-2 study by the NAAT. The primary outcome was assessed prior to Visit 3 (Days 10–11), which was sufficient time to reliably evaluate the efficacy of a single RADAMIN®VIRO dose, taking into account the SARS-CoV-2 incubation period. At the same time, the study subjects were monitored for 28 days after the use of the drug. As a part of the secondary efficacy endpoints, the following indicators were assessed: the incidence of COVID-19 cases with and without symptoms during the entire period of a subject's participation in the study, the severity of the developed COVID-19 disease, the frequency of hospitalizations due to COVID-19, the assessment of the severity and duration of symptoms. The selection of these criteria was also based on the FDA Drug Development Guidelines for the Treatment and Prevention of COVID-19.

The endpoints for evaluating the effectiveness of therapy are presented in Table 1.

Criteria for safety assessment

- Total number of AEs stratified by severity and frequency;
- Frequency of adverse reactions;
- Frequency of SAEs, including those associated with the study drug/standard therapy;
- Proportion of patients with at least one AE.

Statistical analysis

For a statistical analysis, software with validated algorithms for performing statistical analyzes and a proper documentation was used (StatSoft Statistica 13.3).

Descriptive statistics is presented for all efficacy and safety measures collected during the study. Continuous (quantitative) data are presented using the number of the observations, arithmetic mean, a 95% confidence interval (CI) for the mean, a standard deviation, median, an interquartile range (25^{th} and 75^{th} percentiles), minimum and maximum.

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

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

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

Demographic data (age, sex), baseline data are presented for the safety population as absolute frequencies (number of observations), relative frequencies (percentage) or using the arithmetic mean, a 95%CI for the mean, standard (root mean square) deviation, median, an interquartile range (25^{th} and 75^{th} percentiles), minimum and maximum depending on the type of the variable. To test the hypothesis about the homogeneity of the study groups in the initial period, null hypotheses were tested (about the absence of differences between the groups) using the Mann-Whitney test (for ordinal indicators or for interval indicators with a distribution that differs from normal) or the χ^2 test (for qualitative signs). In case of finding statistically significant differences between the groups, the magnitude of the differences between the study groups was assessed using confidence intervals.

[6] COVID-19: Developing Drugs and Biological Products for Treatment or Prevention,Guidance for Industry / U.S. Department of Health and Human Services Food and Drug Administration, 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention

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For the analysis of secondary efficacy parameters, represented by qualitative values, an intergroup comparison of shares was used using a two-tailed version of Fisher's exact test (or χ^2 ("chi-square") test, if all the expected values in the cells of the contingency table for this analysis were 5 or more). To assess the parameters represented by ordinal values, non-parametric methods of the analysis were used: to compare indicators between the groups, the Mann-Whitney test was used; the Wilcoxon test was used for two dependent variables. The Fisher's exact test or the χ^2 ("chi-square") test could be also used for the analysis, if all the expected values in the cells of the contingency table for this analysis are 5 or more.

For comparison between the groups of continuous scores, the Student's *t*-test or the Mann-Whitney test (depending on the conclusion about the nature of the distribution) will be used.

To estimate the time to the event (time-to-event), taking into account censored observations, the Kaplan-Meier method and the construction of survival tables were used as descriptive methods of analysis, and the Cox-Mantel criterion was used to compare the time between the study groups. The differences were considered statistically significant at $p < 0.05$.

For all safety indicators collected during the study, descriptive statistics is presented (means, scatter measures, frequency, 95% confidence intervals, median, quartiles, minimum and maximum values or absolute frequencies (number of observations), relative frequencies (percentage)). The comparison of groups in terms of frequency indicators was carried out using the Fisher's exact test or the chi-square test, depending on the expected value in the cells of the contingency table. For quantitative laboratory results, comparisons between the groups at the respective visits were made using the Mann-Whitney test. The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Baseline Patient Characteristics

The study involved 800 male and female subjects. The average age of the subjects in the population was 45.32±15.24 years (from 18 to 80 years), the average body weight was 75.32±13.55 kg (from 44.70 to 130 kg), the average height was 171.42± 8.08 cm (from 150 to 192 cm), the average body mass index (BMI) was 25.58±3.99 kg/m^2 (from 16.16 to 46.87 kg/m^2).

As a result of a comparative analysis of the demographic and anthropometric data of the subjects, no intergroup statistical differences were found out (Table 2).

It is worth noting that the average BMI of the population indicates that the majority of patients were overweight, which means they had an increased risk of contracting a new coronavirus infection and a complicated course of the disease.

A total of 575 subjects vaccinated against the novel coronavirus infection participated in the study: 284 vaccinated subjects in the study drug group and 291 subjects in the placebo group.

344 subjects (43.00%) had comorbidities. In the study drug group, the frequency of subjects with comorbidities was 174 (43.50%), in the placebo group – 170 (42.5%).

A total of 249 subjects with comorbid conditions such as obesity, type 2 diabetes mellitus, hypertension, chronic pyelonephritis, chronic bronchitis, cystitis, impaired glucose tolerance, prostatitis, chronic tonsillitis, rheumatoid arthritis, psoriasis, chronic sinusitis, angina pectoris, a chronic heart failure, asthma, a chronic obstructive pulmonary disease, diabetic neuropathy, dyslipidemia, a non-alcoholic fatty liver disease, herpes virus often recurrent lesions of the genital mucosa (no relapses were recorded during the observation period). In the study drug group, the frequency of the subjects with these diseases was 121 (30.33%), in the placebo group – 128 (32.00%).

Among the identified pathologies, the conditions such as hypertension and obesity were most frequently observed. In the RNA double-stranded sodium salt drug group, the frequency of the subjects with hypertension was 81 (20.30%), in the placebo group – 90 (22.50%). In the study drug group, the incidence of obese subjects was 45 (11.28%), in the placebo group – 52 (13.00%).

Primary efficacy criterion

The analysis included subjects (*n*=798) with a negative SARS-CoV 2 RNA assay by NAAT selected at screening: the RNA double-stranded sodium salt drug group (*n*=399) and the placebo group (*n*=399).

In the double-stranded sodium salt RNA drug group, the proportion of subjects with confirmed COVID-19 and at least 1 symptom characteristic of COVID-19 at Visit 3 was 5.76% (23/399), and in the placebo group it was 11.03% (44/399). The difference in proportions between the RNA double-stranded sodium salt drug and placebo groups was 0.0526 (5.26%), the 95%CI [0.0123; 0.0937]). The comparison of the frequency of subjects with confirmed COVID-19 and at least 1 symptom of COVID-19 at Visit 3 (Day 10-11) between the study drug and placebo groups showed statistically significant differences between study groups (*p*=0.0074).

Despite a close contact with a patient with a confirmed novel coronavirus infection, a single dose of the RNA sodium double-stranded study drug prevented the infection and symptoms in more than 94% of the subjects during 11 days of follow-up. As a result of a comparative analysis, it was shown that the infection frequency in the group of the study drug was statistically significantly (almost twice) less than in the comparison

group, which indicates a high efficiency and expediency of using the RNA double-stranded sodium salt drug as a means of the post-exposure COVID-19 prophylaxis.

Additionally, a primary endpoint analysis was performed taking into account the factor of vaccination.

A total of 575 subjects vaccinated against the novel coronavirus infection participated in the study: 284 vaccinated subjects in the study drug group, 291 subjects in the placebo group. In the RNA double-stranded sodium salt drug group, the proportion of vaccinated subjects with confirmed COVID-19 and at least 1 symptom characteristic of COVID-19 at Visit 3 was 5.28% (15/284), and in the placebo group it was 10.65% (31/291). The analysis revealed statistically significant differences between the studied groups (p=0.017).

Thus, the effectiveness and expediency of using the RNA studied double-stranded sodium salt drug as a means of the post-exposure COVID-19 prophylaxis, regardless of the presence of vaccination, was demonstrated.

Secondary efficacy criteria

The frequency of subjects with confirmed COVID-19 and at least 1 symptom consistent with COVID-19. As a result of a comparative analysis of the frequency of the subjects with confirmed COVID-19 and the presence of at least 1 symptom characteristic of COVID-19, statistically significant differences had been revealed between the study groups by Visit 2 (p=0.0270), by Visit 4 (p=0.0061), by Visit 5 (p=0.0093). A statistically significant decrease in the incidence of COVID-19 infection in the study drug group compared to the placebo group, both in the short term (3-4 days of follow-up) and in the long term (28 days of the follow-up), allow us to make a conclusion about the effectiveness and validity of the studied method of preventing infection with a new coronavirus infection.

Frequency of subjects with confirmed COVID-19 and no symptoms consistent with COVID-19. In the RADAMIN®VIRO group, the frequency of subjects with symptoms of COVID-19 that had appeared before Visit 3 inclusive, was 9.02% (36/399), in the placebo group – 17.04% (68/399). No statistically significant differences between the study groups were found between the frequency of subjects with "confirmed COVID-19" and no symptoms "consistent with COVID-19" at Visits 2 and 3 in the RNA sodium double-stranded drug and placebo groups.

The frequency of subjects with confirmed COVID-19 with and without symptoms consistent with COVID-19. A comparative analysis of the frequency of confirmed COVID-19 subjects with and without COVID-19 symptoms in the RNA sodium double-stranded drug and placebo groups had shown statistically significant differences between the study groups by Visit 3 (p=0.0127), by Visit 4 (p=0.0139), by Visit 5 (p=0.0203). Thus, it was shown that the subjects who had received the study RNA sodium double-stranded drug as a means of the post-exposure COVID-19 prophylaxis, were not only significantly less likely to test positive for COVID-19, but also showed fewer symptoms of the disease, which indicates a decrease in its severity course. This may be associated with the development of an adequate immune response against the background of the use of the studied drug.

Time till COVID-19 infection. As a result of the analysis, it was shown that by day 11 (Visit 3) in the RNA sodium double-stranded drug group, the infection occurred in 6.27% (25/399) of the subjects, and in the placebo group – in 11.25% (45/400). In addition, among all infected subjects in the study drug group, 75% were infected before day 7, while in the placebo group it was before day 5. Thus, the subjects treated with placebo were shown to become infected earlier than the subjects treated with the RNA sodium double-stranded drug. The median time till the exposure to COVID-19 in the study drug group and placebo group was 3 days. A comparative analysis revealed statistically significant differences in time to the COVID-19 infection between the RNA sodium double-stranded drug and placebo groups (p=0.0249). As a result of the analysis, it was shown that when using the study drug, there is a delay in the infection of subjects undergoing the COVID-19 prophylaxis, which may be important in terms of reducing the level of the viral load at the time of infection and reducing the risk of developing a complicated course of the disease.

Assessment of symptoms severity characteristic of COVID-19. The assessment was performed only for the subjects who had developed symptoms of COVID-19 during the study up to and including Visit 3. In the RNA sodium double-stranded drug group, the frequency of subjects with symptoms of COVID-19 that had appeared up to and including Visit 3, was 9.02% (36/399), in the placebo group it was 17.04% (68/399). A comparative analysis of the frequency of subjects with COVID-19 symptoms prior to and including Visit 3, regardless of the presence of laboratory-confirmed COVID-19, showed statistically significant differences between the RNA sodium double-stranded drug group and the placebo group (p=0.0008), which indicates a high efficiency of the study drug in preventing the infection with a novel coronavirus infection and reducing the severity of the disease. In the population, there were statistically significant differences between the study drug group and the placebo group in the frequency of the subjects with the COVID-19 symptoms onset up to and including Visit 3 (p=0.0006); by the frequency of the subjects with varying degrees of severity of the Sore Throat symptom at Visit 3 (p=0.0314); by the frequency of the subjects with different severity of the “Fatigue” symptom by Visit 3 (p=0.0472) by the frequency of the subjects with different severity of the “Chills” symptom by Visit 2 (p=0.0191) (Table 4). In terms of symptoms (a nasal congestion and a runny nose,

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shortness of breath or shortness of breath during the exertion, cough, pains in the muscles and throughout the body, a headache, a fever (body temperature >38°C), a sense of smell in the last 24 h), there were no statistically significant differences between the groups. At the same time, none of the groups showed symptoms such as: vomiting, diarrhea, changes in the taste sensitivity.

Duration of symptoms characteristic of COVID-19. As a result of the comparative analysis, statistically significant differences between the groups were revealed in the duration of symptoms characteristic of COVID-19, namely "Sore throat" (p=0.0173) and the symptom "Smell in the last 24 h» (p=0.0214). There were no statistically significant differences between the groups in the duration of the following symptoms: nasal congestion or runny nose, shortness of breath or shortness of breath with an exertion, cough, fatigue, muscle or whole-body pains, a headache, chills, a fever (body temperature >38°C).

Assessing COVID-19 severity. The assessment was performed only for the subjects who had tested positive for COVID-19 during the course of the study. There were no significant differences in the severity of COVID-19 between the study groups (p ≥0.05).

Frequency of subjects requiring hospitalization due to COVID-19 development. There were no cases of hospitalization of the subjects due to the development of COVID-19 during the study.

Safety Assessment Results

The frequency of subjects with reported cases of AEs was 5.13% (41/800). A total of 61 AEs were noted in 41 subjects. The frequency of the subjects in the RNA sodium double-stranded drug group with reported AEs was 4.0% (16/400). A total of 19 AEs were observed in 16 subjects of the RNA sodium double-stranded drug study group. The incidence of the subjects in the placebo group with reported AEs was 6.25% (25/400). A total of 42 AEs were observed in 25 subjects in the placebo group. All reported AEs in the subjects in the study drug and placebo groups were of a mild severity (Table 5).

According to the investigators, the causal relationship with the study drug therapy was assessed as "not related" in 26.32% (5/19) of cases, as "doubtful" in 73.68% (14/19) of cases; a causal relationship with placebo was assessed as "not related" in 52.38% (22/42) of cases, as "doubtful" in 28.57% (12/42) of cases, as "probable" in 7.14% (3/42) of cases, as "possible" – in 11.90% (5/42) of cases.

An analysis of the frequency of AE outcomes in the subjects treated with the study RNA sodium double-stranded drug showed that "a recovery without consequences" was noted in 94.74% (18/19) of cases and "an improvement" in 5.26% (1/19) cases; the subjects treated with placebo in all cases had "a recovery without consequences".

An analysis of the interventions for AEs frequency in the subjects who received the study drug of the RNA sodium double-stranded drug showed that "no treatment was carried out" in 52.63% (10/19) of cases, "local therapy" was required in 15.79% (3/19) cases and "systemic therapy" was required in 31.58% (6/19) of cases; in the subjects receiving placebo, "not treated" – in 59.52% (25/42) of cases, "topical therapy" was required in 21.43% (9/42) of cases, and "systemic therapy" was required in 19, 05% (8/42) of cases.

There were no statistically significant differences between the study groups in terms of the presence of AEs (p ≥0.05). As a result of the analysis, statistically significant differences were found between the treatment groups in terms of the association of AEs with the drug (p=0.0078), with a predominance of drug-related AEs in the placebo group.

It should be noted that against the background of pharmacotherapy with the study drug, there were no relapses of chronic, as well as previously transferred diseases. In some articles, the COVID-19 infection has been associated with the coinfection or reactivation of human herpesviruses [24, 25]. Thus, it is known that the COVID-19 infection can cause reactivation of the latent human herpes simplex viruses, including urogenital, by enhancing the expression of lytic genes and supporting the antegrade movement of the activated viruses to the epithelial tissues [24]. At the same time, in the course of this study, there were no cases of relapse in the patients with a history of urogenital herpes.

In the course of the study, no adverse events associated with the use of the RNA sodium double-stranded study drug were registered.

In the course of the study, there was not a single confirmed case of pyrogenicity (increased body temperature) occurring with the use of this group of drugs. This effect is associated with an innovative technology for obtaining an active active substance, in which special attention is paid to the purification of the resulting substance from protein components and impurities formed during the microbiological synthesis of double-stranded RNA [26–28].

No cases of SAEs were reported during the course of the study.

In the course of the study, there were no cases of pregnancy of the subject/sexual partner of the study participant.

Additionally, an analysis was made of possible adverse effects associated with the use of study drugs (Table 6).

The analysis of both groups included AEs with a definite, probable and possible drug association. Thus, no adverse reactions associated with the use of the study drug were identified. The study drug based on the RNA double-stranded sodium salt has a high favorable and predictable safety profile.

CONCLUSION

Features of the immune response during viral infection, in particular, the penetration of SARS-CoV-2, determine both the risk of initiating a disease with clinical manifestations and the severity of the infection, including the complications risk. The results of the placebo-controlled study convincingly prove the effectiveness of RADAMIN®VIRO in preventing diseases with a novel coronavirus infection, regardless of the fact of vaccination, gender, age, and concomitant diseases, including such as an overweight and obesity. At the same time, in case of the COVID-19 infection, the symptoms of the disease developed less frequently than in the placebo group patients. A decrease in the frequency of development, duration and severity of the symptom complex characteristic of COVID-19, indicates a high efficiency of the preventive effect, a decrease in the risk of a complicated course of the disease, an acceleration of recovery, and a positive effect of RADAMIN®VIRO on the quality of patients' lives. Thus, it is appropriate to include the studied drug in the schemes for the prevention of a novel coronavirus infection used in medical institutions or at enterprises when cases of the disease are detected and there is a high risk of its mass prevalence.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Larisa A. Balykova – research design development and implementation, text writing and editing; Olga A. Radaeva – study design development, results analysis, text editing; Kira Ya. Zaslavskaya – research design development, text editing, literary sources analysis; Alexey V. Taganov – study design implementation, data processing; Petr A. Bely – study design development, results analysis, text editing; Konstantin A. Zakharov – research design implementation, data processing; Varvara V. Popova – research design implementation, data processing; Tatyana I. Chudinovskikh – research design implementation, data processing; Svetlana V. Teplykh – research design implementation, data processing; Igor V. Balaban – research design implementation, data processing;, Roman S. Kozlov – research design implementation, data processing; Natalya V. Kirichenko – research design implementation, data processing; Elena N. Simakina – study design implementation, data processing; Ksenia N. Koryanova – collection of sources, data processing, article writing; Dmitry Yu. Pushkar – research design development, research design implementation, data processing.

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