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RESEARCH ARTICLE

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PreKinetix: web application for pharmacokinetic analysis in preclinical drug research

P.M. Rezvanov[1], N.E. Moskaleva[1], K.M. Shestakova[1], V.V. Tarasov[1], E.A. Smolyarchuk[1], D.A. Kudlay[1, 2, 3], S.A. Apollonova[1]

[1] Sechenov First Moscow State Medical University (Sechenov University),
2 Trubetskaya Str., Bldg 8, Moscow, Russia, 119991
[2] Lomonosov Moscow State University,
1 Leninskie Gory, Moscow, Russia, 119991
[3] State Research Center Institute of Immunology,
24 Kashirskoe Hwy, Moscow, 115522, Russia

E-mail: rezvanov_p_m@staff.sechenov.ru

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The aim. Development and validation of domestic software for non-compartmental analysis (NCA) of pharmacokinetic data, comparable in accuracy and functionality to the recognized foreign software Phoenix WinNonlin (USA).

Materials and methods. The PreKinetix web application is implemented in the Python programming language using the Streamlit framework. Algorithms for calculating pharmacokinetic parameters (maximum concentration [C_{max}], area under the pharmacokinetic curve [AUC], half-life [$T_{1/2}$], mean residence time [MRT], etc.) are based on the methods of the reference software Phoenix WinNonlin (Certara, USA), used for comparison and are widely used in international practice. Three models of single drug administration are supported: intravenous bolus, intravenous infusion, and extravascular administration. Literary and experimental data covering more than 450 pharmacokinetic profiles were used for verification.

Results. Calculations performed using PreKinetix showed complete agreement with the results of Phoenix WinNonlin with a relative error of less than 0.0001% for all main parameters. The program stably processes zero and missing values, automatically excludes incorrect records, visualizes pharmacokinetic profiles in linear and semi-logarithmic scales, and generates reports in .xlsx* and .docx* formats. The application interface allows it to be used not only by specialists but also by less trained users.

Conclusion. PreKinetix is a domestic tool for NCA that combines accuracy, automation, accessibility, and convenience. It can be used in preclinical and early phases of clinical trials, as well as in educational settings for training specialists in pharmacokinetics and biopharmaceutics.

Keywords: pharmacokinetic analysis; preclinical studies; non-compartmental analysis; pharmacokinetics; biopharmaceutical research; software; pharmaceutical development

List of abbreviations: adjusted R^2 — adjusted coefficient of determination; ADME — absorption, distribution, metabolism, excretion; AUC — area under the concentration–time curve; AUMC — area under the first moment curve; C_0 — initial concentration (for bolus administration only); Cmax — maximum drug concentration in blood; C_{max}/D — C_{max} to dose ratio; GLP — Good Laboratory Practice; GUI — graphical user interface; $K_{el/\lambda z}$ — terminal elimination rate constant; MRT — mean residence time of the drug in the body; PBPK — physiologically based pharmacokinetics; RE/REi — relative error; sparse sampling — sparse sampling; $T_{1/2}$ — half-life; T_{max} — time to reach maximum concentration; NCA — non-compartmental analysis; PK — pharmacokinetics/pharmacokinetic.

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ОРИГИНАЛЬНАЯ СТАТЬЯ
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PreKinetix: веб-приложение для проведения фармакокинетического анализа в доклинических исследованиях лекарственных препаратов

П.М. Резванов[1], Н.Е. Москалева[1], К.М. Шестакова[1], В.В. Тарасов[1], Е.А. Смолярчук[1], Д.А. Кудлай[1, 2, 3], С.А. Апполонова[1]

[1] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский Университет), Россия, 119991, г. Москва, ул. Трубецкая, д. 8, стр. 2
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Московский государственный университет имени М.В. Ломоносова», Россия, 119991, г. Москва, Ленинские горы, д. 1
[3] Федерального государственного бюджетного учреждения «Государственный научный центр “Институт иммунологии”» Федерального медико-биологического агентства, Россия, 115522, г. Москва, Каширское шоссе, д. 24

E-mail: rezvanov_p_m@staff.sechenov.ru

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Цель. Разработка и валидация отечественного программного обеспечения для некомпартментного анализа (НКА) фармакокинетических данных, сопоставимого по точности и функциональности с признанным зарубежным программным обеспечением Phoenix WinNonlin (США).

Материалы и методы. Веб-приложение PreKinetix реализовано на языке программирования Python с использованием фреймворка Streamlit. Алгоритмы расчёта фармакокинетических параметров (максимальная концентрация [C_{max}], площадь под фармакокинетической кривой [AUC], период полувыведения [$T_{1/2}$], среднее время пребывания [MRT] и др.) основаны на методиках референсного программного обеспечения Phoenix WinNonlin (Certara, США), использованного для сравнения и широко применяемого в международной практике. Поддерживаются три модели однократного введения лекарственного средства: внутривенное болюсное, внутривенная инфузия и внесосудистое введение. Для верификации использованы литературные и экспериментальные данные, охватывающие более 450 фармакокинетических профилей.

Результаты. Расчёты, выполненные с помощью PreKinetix, показали полное совпадение с результатами Phoenix WinNonlin с относительной ошибкой менее 0,0001% по всем основным параметрам. Программа устойчиво обрабатывает нулевые и пропущенные значения, автоматически исключает некорректные записи, визуализирует фармакокинетические профили в линейной и полулогарифмической шкалах, формирует отчёты в форматах .xlsx* и .docx*. Интерфейс приложения позволяет использовать его не только специалистам, но и менее подготовленным пользователям.

Заключение. PreKinetix представляет собой отечественный инструмент для НКА, объединяющий точность, автоматизацию, доступность и удобство. Он может применяться в доклинических и ранних фазах клинических исследований, а также в образовательных целях для подготовки специалистов в области фармакокинетики и биофармацевтики.

Ключевые слова: фармакокинетический анализ; доклинические исследования; некомпартментный анализ; фармакокинетика; биофармацевтические исследования; программное обеспечение; фармацевтическая разработка

Список сокращений: adjusted R^2 — скорректированный коэффициент детерминации; ADME — абсорбция, распределение, метаболизм, экскреция; AUC — площадь под кривой «концентрация–время»; AUMC — площадь под кривой первого момента времени; C_0 — начальная концентрация (только для болюсного введения); C_{max} — максимальная концентрация препарата в крови; C_{max}/D — отношение C_{max} к дозе; GLP — надлежащая лабораторная практика; GUI — графический пользовательский интерфейс; $K_{el/\lambda z}$ — терминальная константа скорости элиминации; MRT — среднее время пребывания препарата в организме; PBPK — физиологически обоснованная фармакокинетика; RE/REi — относительная ошибка; $T_{1/2}$ — период полувыведения; T_{max} — время достижения максимальной концентрации; ЛС – лекарственное средство; НКА — некомпартментный анализ; ПО — программное обеспечение; ФК — фармакокинетика/фармакокинетический.

INTRODUCTION

The main aim of pharmacokinetic (PK) studies is to study the kinetic properties of drugs, including the processes of absorption, distribution, metabolism, and excretion (ADME — absorption, distribution, metabolism, excretion) [1]. One of the simplest and most effective methods for studying these processes is non-compartmental analysis (NCA). NCA includes various approaches for calculation of the area under the pharmacokinetic curve (AUC — area under the curve) — a graph of the dependence of the concentration of drugs in a biological material on the sampling time [1–4]. The non-compartmental approach includes calculation of key PK parameters, such as the maximum observed drug concentration (C_{max}), AUC, time to reach peak concentration (T_{max}), half-life ($T_{1/2}$), area under the first moment curve (AUMC — area under the first moment curve), and others[1] [1, 3].

PK studies are increasingly faced with the need to work with sparse sampling, especially in preclinical and phase trials, where multiple sampling enquiries may be ethically and logistically difficult. At low density of time points, classical NCA demonstrates high error in estimation of key pharmacokinetic parameters, such as $T_{1/2}$ and AUC exposure, which can negatively affect the accuracy of pharmacotherapeutic decisions [5]. This necessitates reliable tools for processing sparse data, while maintaining the accuracy of calculations even with limited measurements.

At the same time, there is a noticeable increase in the preference for open-source software in pharmacokinetics and physiologically based modeling (PBPK). According to the works of Rajput et al. (2023) and Aldibani et al. (2023), the proportion of publications using open-source platforms has significantly increased due to their transparency, flexibility, and the ability to be expanded by research groups [6, 7]. However, most existing tools focus on compartmental analysis or PBPK modeling, and available NCA toolkits remain either commercial or require significant programming skills. This underscores the importance of developing user-friendly, verifiable, and user-oriented domestic software, such as PreKinetix, capable of ensuring the independence and reproducibility of PK studies.

Modern software solutions for PK analysis using the NCA method are represented by both commercial (e.g., Phoenix WinNonlin, CPhaMAS, PKanalix) and freely distributed tools (PKSolver, Pkweb, R-packages NonCompart and ncar). However, free software has a number of limitations. For example, the NonCompart and ncar packages lack a graphical user interface, which makes them difficult to use by non-specialists. In addition, some PKSolver algorithms (in particular, the estimation of the elimination rate constant — λz) are unstable and give discrepancies in results compared to commercial solutions. Moreover, most free software does not meet the validation requirements established by regulatory authorities [1, 2, 8]. Commercial solutions for NCA are currently represented mainly by foreign software; similar products are not yet offered on the territory of the Russian Federation[2], [3] [9]. In this regard, the development of domestic software is relevant, which would ensure the technological independence of research organizations in the field of PK analysis.

In response to this need, we have developed the PreKinetix web application, focused on conducting NCA in preclinical and phase I clinical PK studies. The current version supports the analysis of a single dose administration with modeling of three main methods of administration: intravenous bolus, intravenous infusion, and extravascular administration, using data on the concentration of the drug in the blood. Algorithms for calculating and visualizing the results of studies of absolute and relative bioavailability, the distribution of drugs in the organs and tissues of laboratory animals, dose linearity, etc. have also been implemented. Thus, **THE AIM** of this work was to create and initially validate the PreKinetix program and present its capabilities for PK analysis.

MATERIALS AND METHODS

Software development

The Python programming language was chosen to implement the web application, as it is one of the most popular languages in scientific research due to its simplicity, flexibility, and extensive ecosystem of tool libraries. Python is widely used in various fields — from data analysis to modeling and visualization — which is confirmed by many works [10–12]. The Streamlit[4] framework (open-source Python framework) was used to speed up the development of the web interface and simplify testing the application with data.

The main computational logic of PreKinetix is implemented using a number of Python libraries: pandas (version 1.5.3) [13], numpy (1.24.2) [14], matplotlib (3.7.1) [15], seaborn (0.12.2) [16], SciPy (1.10.1) [17], scikit-learn (1.3.1) [18], statsmodels (0.14.0) [19], cycler (0.11.0)[5], python-docx (0.8.11)[6],

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networkx (3.4.2) [20] and pyvis (0.3.2)[7]. The Visual Studio Code software platform (version 1.99.3)[8] was used as the development environment.

Microsoft Excel 2016 (Microsoft Office package, Microsoft Corporation, USA)[9] was used to build certain graphs and diagrams when analyzing data for vizualization of the comparative analysis results described below.

Reference software

The Phoenix WinNonlin program (version 8.3.4.295, Certara, USA) was applied as a reference system used for comparison.

Data sets for comparative analysis

450 PK profiles were analyzed as part of the initial scientific testing of the PreKinetix web application. Three data groups were used to assess the correctness of calculations: open reference sets of PK data from the PKanalix software distribution (version 2024R1, Lixoft, France[10]; PKanalix data were obtained by downloading statistical collections) and the Rdatasets collection prepared by Arel-Bundock et al.[11, 12], experimental data obtained in our scientific organization, as well as specially constructed examples for verifying individual boundary cases.

The following medicines M2000, cefamandole[13] and indomethacin[14] were randomly selected as demonstration examples for calculating statistical parameters, NCA, visualizing the obtained results of comparing Prekinetix and Phoenix WinNonlin (Table 1).

Algorithm for calculating of statistical parameters

To implement the algorithms for calculating statistical parameters, principles similar to Phoenix WinNonlin were used according to the documentation of the reference software[15].

The criterion of compliance was the relative difference between the values of each statistical parameter calculated by the two systems, in which the maximum deviation did not exceed 10^{-6}. Thus, in all tested cases, the calculations of PreKinetix and Phoenix WinNonlin showed complete coincidence of results, confirming the correctness of the algorithmic implementation.

Algorithm for calculating of pharmacokinetic parameters

To implement the algorithms for calculating NCA, principles similar to Phoenix WinNonlin were used according to the documentation of the reference software[16].

PreKinetix calculates a complete set of PK parameters based on the results of NCA, similar to Phoenix WinNonlin. The designations of key parameters used in our software and their correspondence to the designations of Phoenix WinNonlin are given in Table 2 with a brief description of each indicator.

As you can see, most parameters have identical designations in both software, and some differ slightly (for example, $AUC_{0\to t}$ as AUC_{last}, etc.).

The criterion of compliance was the relative difference between the values of each PK parameter calculated by the two systems, in which the maximum deviation did not exceed 10^{-6}. Thus, in all tested cases, the calculations of PreKinetix and Phoenix WinNonlin showed complete coincidence of results, confirming the correctness of the algorithmic implementation.

Visualization of results of comparative analysis

To assess the accuracy of the coincidence of PreKinetix results with the reference software, we used an approach similar to that described in [9]. The relative error of determining the i-th parameter (RE_i — Relative Error,%) was introduced, calculated by the formula:

$$RE_i = \left(\frac{P_i - R_i}{R_i} \right) \times 100\%$$

where Pi is the value of the parameter obtained by the tested algorithm; and Ri is the corresponding value calculated using Phoenix WinNonlin.

This indicator allows you to quantitatively assess the accuracy of the developed algorithm and identify possible systematic bias in the calculation of one or another pharmacokinetic indicator. Negative RE values indicate a slight underestimation of the PreKinetix result relative to Phoenix, positive values indicate an overestimation. The criterion of acceptability was a relative error of less than 0.0001% for most parameters.

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[16] Ibid.

Visualization of pharmacokinetic profiles

In addition PreKinetix provides convenient tools for vizualization of PK profiles. The application's user interface allows to customize the display of graphs: change the scale of the axes, the division step, the location of the legend, and other parameters.

To build graphs of PK profiles using the developed software, data from subject No. 271 of the M2000[17] drug were used (Table 1).

RESULTS

Software implementation results

The PreKinetix web application was developed and designed for conducting NCA in preclinical studies and phase I clinical trials. The current version supports the analysis of PK data after a single administration of a drug with three main methods of administration: intravenous bolus, intravenous infusion, and extravascular administration, based on measurements of drug concentration in the blood. In addition to calculating standard NCA parameters, the system implements algorithms for evaluating and visualizing the results of studies of absolute and relative bioavailability, the distribution of a drug in the organs and tissues of laboratory animals, checking dose linearity, and other PK analysis tasks.

Python scripts with open-source code are available at https://github.com/FimaLab/prekinetix.

Calculation of pharmacokinetic parameters

The general principles and sequence for calculation statistical indicators and PK parameters in the developed software were based on the algorithms of the commercially available validated software Phoenix WinNonlin (version 8.3.4.295), which is considered as the "gold standard" in the international market of PK analysis[18]. In particular, PreKinetix implements standard methods for calculating AUC and AUMC. There are several main methods for calculating AUC / AUMC: the linear trapezoid method, the log-linear trapezoid method, as well as a combined method involving linear interpolation at the stage of increasing concentration and logarithmic interpolation at the stage of decreasing[19] [3, 21]. PreKinetix includes two of the most popular approaches: linear trapezoidal and combined methods for calculating the area under the curve [21, 22].

[17] Lixoft. PKanalix. Available from: https://pkanalix.lixoft.com/
[18] Certara. Phoenix WinNonlin User Guide – Noncompartmental Analysis. Available from: https://onlinehelp.certara.com/phoenix/8.2/topics/nca.htm
[19] Ibid.

Assessment of the terminal constant elimination (λz)

The terminal elimination constant λz (K_{el}) is estimated using linear regression on the final section of the PK profile, corresponding to a monoexponential decrease in concentration [21]. PreKinetix implements an automatic algorithm for estimating λz according to the approach used in Phoenix WinNonlin. Automatic Kel estimation in Phoenix is performed by the best fit method, sequentially iterating through different sized sets of points on the terminal section of the curve. In our software, this algorithm is implemented as follows:

1. Linear regression of the dependence of the logarithm of concentration on time is performed, starting from the last 3 positive points (from 2 points for the bolus model).
2. The number of points used in the regression is gradually increased to 4, 5, etc., excluding in each such analysis data up to the time of reaching C_{max}, the C_{max} point itself (for non-bolus models), as well as points with C_0.
3. For the intravenous infusion model, points before the end of the drug administration are additionally excluded if C_{max} is observed earlier than the end of the infusion.
4. For each regression performed, the adjusted coefficient of determination (adjusted R^2) is calculated. The option with the maximum value of this indicator is selected. If several options give close values (difference ≤ 0.0001), preference is given to the option with a larger number of points.
5. The minimum number of points for calculating λz is 3 for non-bolus models and 2 for bolus administration. The condition for the correctness of the result is a negative value of the angular coefficient (i.e., a negative slope of the regression line)[20].

Correction of the initial concentration

The calculation of the initial concentration C_0 is performed only for the intravenous bolus administration model. The initial concentration is taken equal to the first observed concentration value if it is measured at the time of drug administration; otherwise, C_0 is calculated by back extrapolation using linear regression. This indicator affects the calculation of a number of PK parameters (AUC and AUMC) in the bolus administration model, so the user is given the opportunity to include the back extrapolation algorithm if necessary for correct accounting of C_0 in calculations[21].

[20] Ibid.
[21] Ibid.

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Features of calculation with infusion administration

For the intravenous infusion model, it is necessary to take into account the infusion time when calculating some parameters. For example, when calculating the mean residence time of the drug in the body (MRT — mean residence time), the duration of the infusion affects the result[22] [23]. The value of the infusion time is entered by the user through the corresponding interface field, and it is used by the program when calculating MRT and related parameters.

The developed algorithms for calculating statistical indicators and PK parameters stably process zero concentration values that may be present in the initial data array. Records with missing time or concentration values are automatically excluded from the analysis[23]. This ensures the correctness of the results even if there are missing or zero points in the pharmacokinetic profile.

Statistical parameters

First, the correctness of calculating basic statistical indicators was checked. When comparing the values of statistical parameters calculated by PreKinetix with the corresponding results of Phoenix WinNonlin, it was shown that the differences were less than 10^{-6}. Table 3 shows data on a number of such indicators using the example of calculating the elimination constant λz of M2000[24], cefamandole, and indomethacin.

It may be concluded that both software products give identical values for all statistical parameters (number of observations, mean, standard deviation, etc.).

Pharmacokinetic parameters

To assess the correctness of the calculation of PK parameters in general, as well as to check for the absence of systematic deviations, a series of comparative calculations were performed on various data sets. Table 4 shows the results of calculating the main PK parameters for some of these data sets (using the example of the M2000, cefamandole, and indomethacin)[25].

In this example, the analysis was performed for the intravenous bolus administration model (single dose). As in the case of statistical indicators, the difference in the values of all PK parameters calculated by PreKinetix compared to Phoenix WinNonlin was less than 10^{-6}.

The results of the comparative analysis of PK parameters were demonstrated by calculating the RE and constructing the corresponding graphs. Figure 1 reflects the relative error (RE_i,%) for the main calculated PK parameters (according to Table 4).

All detected discrepancies between the programs were random and extremely small in magnitude (less than 0.0001% for most parameters). This indicates that the developed tool does not introduce systematic errors in calculations and can reproduce results at the accuracy level of the reference software. The results of comparing NCA calculations using intravenous infusion and intravascular administration methods were also satisfying.

Visualization of pharmacokinetic profiles

Figures 2 and 3 show an example of a graphical representation of an individual PK profile in the blood, constructed by PreKinetix using the example of the drug M2000: in linear coordinates (Fig. 2) and in semi-logarithmic coordinates (Fig. 3).

Such graphs are generated automatically and can be included in a .docx* report, which facilitates data presentation and interpretation.

It should be noted that all graphic materials created by the program can be saved by the user for its subsequent application in reports or scientific publications and help to improve the clarity of the results, as well as the convenience of their analysis.

DISCUSSION

The development and validation of the PreKinetix program were aimed to confirm its equivalence with the generally accepted means of NCA of PK data. Phoenix WinNonlin (Phoenix 64, version 8.3.4.295) is historically known as the “gold standard” for NCA and is widely used for scientific and regulatory purposes. PreKinetix calculations for 3 experimental drugs (M2000, cefamandole, indomethacin) showed almost complete agreement with the results obtained using Phoenix WinNonlin. All major pharmacokinetic parameters — maximum concentration (C_{max}), time to maximum (T_{max}), area under the curve (AUC), half-life ($T_{1/2}$), elimination rate constant (λz), etc. — were identical when using both software tools, with a relative difference of less than 0.0001%. For example, for bolus intravenous administration of M2000, PreKinetix and Phoenix give the same absence of time delay in reaching Cmax (T_{max}=0 h) at a high initial concentration (C_{max}≈2950 ng/mL), while for extravascular administration of indomethacin, both tools show the expected delay in reaching the peak (T_{max}≈0.25 h) at a comparatively smaller C_{max} value (≈1.5 μg/mL). The complete match of parameters throughout the profile (including, for example,

[22] Ibid.
[23] Ibid.
[24] Lixoft. PKanalix. Available from: https://pkanalix.lixoft.com/
[25] Ibid.

AUC_{0-t}=4126.36 for M2000, 3740.5 for cefamandole and 1.741 for indomethacin; $T_{1/2}$=6.40, 56.04 and 4.38 h, respectively) indicates the correctness of PreKinetix algorithms and the absence of systematic error in calculations. As can be seen in Figure 1, a graphical analysis of relative errors did not reveal a systematic bias, which confirms the correctness of the algorithms implemented in PreKinetix. Thus, PreKinetix provides calculation accuracy at the level of the reference software, which confirms the successful verification of the developed tool using the example of drugs with different PK properties.

The results obtained are consistent with similar publications of recent years devoted to the validation of various NCA tools. For example, in a recent study by Zang et al. (2010) presented the PKSolver add-in for Microsoft Excel, the calculation results of key PK parameters of which showed a satisfactory degree of correspondence to the results of Phoenix WinNonlin [2]. In the work of Kim et al. (2018) compared calculations between Phoenix and the R-package NonCompart, which underlies the online tool PKWeb, which also confirmed the identity of the output parameters [1]. In addition, a recent article by Kyang et al. (2024) presented the CPhaMAS cloud platform, designed for the analysis of PK data, including NCA and bioequivalence; the authors showed that CPhaMAS calculations are in close agreement with Phoenix WinNonlin results in *in vivo* modeling and parameter analysis [9]. The totality of these independent validations confirms that when using the same algorithmic approaches, different NCA software tools give practically indistinguishable results.

Table 1 – Part of the initial data of M2000, cefamandole and indomethacin with information about ID (subject), dose, time and concentration

M2000				cefamandole				indomethacin			
ID	Dose (mg)	Time (h)	Concentration (ng/mL)	ID	Dose (mg)	Time (min)	Concentration (μg/mL)	ID	Dose (mg)	Time (h)	Concentration (μg/mL)
271	100	0	2950	1	15	0	0	1	50	0	0
271	100	0.17	2164	1	15	10	127	1	50	0.25	1.5
271	100	0.25	1884	1	15	15	80	1	50	0.5	0.94
271	100	0.5	1366	1	15	20	47.4	1	50	0.75	0.78
271	100	1	844	1	15	30	39.9	1	50	1	0.48
271	100	1.5	625	1	15	45	24.8	1	50	1.25	0.37
271	100	2	478	1	15	60	17.9	1	50	2	0.19
271	100	4	256	1	15	75	11.7	1	50	3	0.12
271	100	6	147	1	15	90	10.9	1	50	4	0.11
271	100	8	88	1	15	120	5.7	1	50	5	0.08
271	100	10	58	1	15	150	2.55	1	50	6	0.07
271	100	12	48	1	15	180	1.84	1	50	8	0.05
271	100	16	26	1	15	240	1.5	–	–	–	–
271	100	24	13	1	15	300	0.7	–	–	–	–
–	–	–	–	1	15	360	0.34	–	–	–	–

Table 2 – Key pharmacokinetic parameters: correspondence of designations in PreKinetix and Phoenix WinNonlin

PreKinetix	WinNonlin	Description
C_{max}	C_{max}	Maximum observed concentration
T_{max}	T_{max}	Needed time to reach C_{max}
AUC_{0-t}	AUC_{last}	Area under the pharmacokinetic curve from the time of dosing to the last measured concentration (T_{last})
K_{el}	Lambda_z	Terminal elimination rate constant, estimated from the final part of the pharmacokinetic profile
$T_{1/2}$	HL_Lambda_z	Half-life in the terminal phase
Cl (Cl/F)	Cl_obs (Cl_F_obs)	Total drug clearance
Vz (Vz/F)	Vz_obs (Vz_F_obs)	Volume of distribution in the terminal phase (for non-stationary data)
$AUMC_{0-t}$	AUMClast	Area under the concentration×time curve to T_{last}
$MRT_{0\to t}$	MRTlast	Mean residence time of the drug in the body to T_{last}
V_{ss}	Vss_obs	Volume of distribution at steady state (for non-stationary data)

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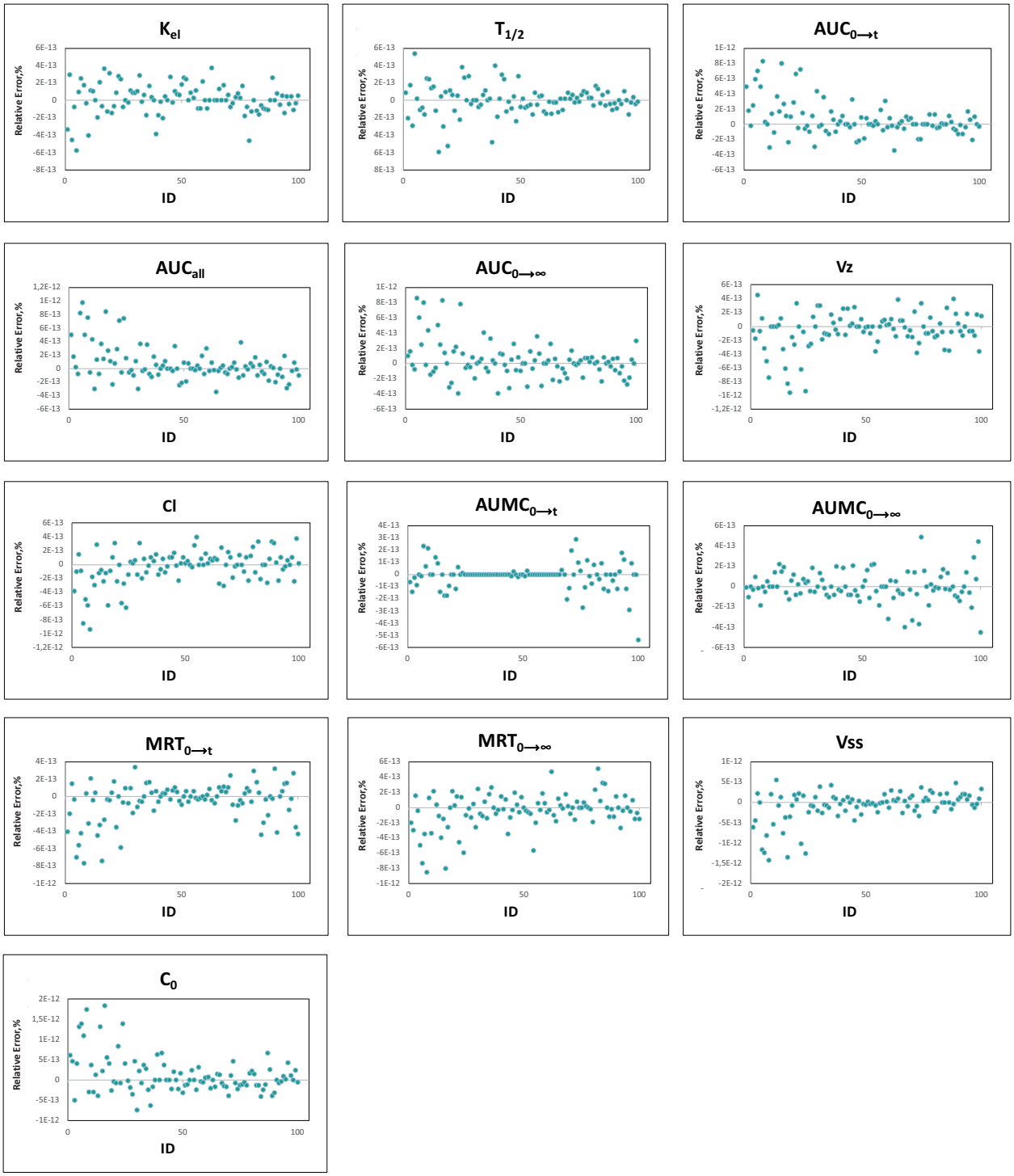

Figure 1 – Relative error (RE_i,%) for a number of key pharmacokinetic parameters calculated using PreKinetix algorithms (intravenous bolus administration model, single dose, linear trapezoidal method, without extrapolation of initial concentration) compared to Phoenix WinNonlin results.

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Table 3 – Comparison of the results of calculating statistical parameters (using the example of the λz parameter of M2000, cefamandole, and indomethacin)

Medicine		M2000		Cefamandole		Indomethacin	
Parameter	Description	WinNonlin	PreKinetix	WinNonlin	PreKinetix	WinNonlin	PreKinetix
N	Number of non-missing observations	12	12	6	6	6	6
NMiss	Number of observations with missing data	0	0	0	0	0	0
NObs	Number of observations	12	12	6	6	6	6
Mean	Arithmetic mean	0.11888	0.11888	0.011296	0.011296	0.324034	0.324034
SD	Standard deviation	0.016801	0.016801	0.00083	0.00083	0.11021	0.11021
SE	Standard error	0.00485	0.00485	0.000339	0.000339	0.044993	0.044993
Variance	Unbiased sample variance	0.000282	0.000282	0.000001	0.000001	0.012146	0.012146
CVPercent	Coefficient of variation	14.132647	14.132647	7.34997	7.34997	34.011658	34.011658
Min	Minimum value	0.10525	0.10525	0.01004	0.01004	0.15832	0.15832
Median	Median — based on the results of calculating percentiles, the 50th percentile	0.110571	0.110571	0.011238	0.011238	0.3279	0.3279
Max	Maximum value	0.156808	0.156808	0.012369	0.012369	0.455445	0.455445
Range	Sample range (difference between the maximum and minimum values)	0.051558	0.051558	0.002329	0.002329	0.297125	0.297125
MeanLog	Arithmetic mean of natural logarithms of observations	-2.13801	-2.13801	-4.485572	-4.485572	-1.184033	-1.184033
SDLog	Standard deviation of natural logarithms of observations	0.132149	0.132149	0.074198	0.074198	0.388093	0.388093
GeometricMean	Geometric mean	0.117889	0.117889	0.01127	0.01127	0.306042	0.306042
GeometricSD	Geometric standard deviation of natural logarithms of observations	1.141278	1.141278	1.07702	1.07702	1.474167	1.474167
GeometricCVPercent	Geometric coefficient of variation	13.272787	13.272787	7.430046	7.430046	40.31756	40.31756
CI95PercentLower	Lower limit of the 95% confidence interval for the data	0.081901	0.081901	0.009162	0.009162	0.040732	0.040732
CI95PercentUpper	Upper limit of the 95% confidence interval for the data	0.155858	0.155858	0.01343	0.01343	0.607337	0.607337
CI95PercentLowerMean	Lower limit of the 95% confidence interval for the arithmetic mean value	0.108205	0.108205	0.010425	0.010425	0.208377	0.208377
CI95PercentUpperMean	Upper limit of the 95% confidence interval for the arithmetic mean value	0.129555	0.129555	0.012167	0.012167	0.439692	0.439692
CI95PercentLowerVar	Lower limit of the 95% confidence interval for the variance	0.000142	0.000142	0	0	0.004733	0.004733
CI95PercentUpperVar	Upper limit of the 95% confidence interval for the variance	0.000814	0.000814	0.000004	0.000004	0.073063	0.073063
CIGEO95PercentLower	Lower limit of the 95% confidence interval for the logarithmized data, reduced to the original scale	0.088137	0.088137	0.009313	0.009313	0.112854	0.112854
CIGEO95PercentUpper	Upper Upper limit of the 95% confidence interval for the logarithmized data, reduced to the original scale	0.157686	0.157686	0.013639	0.013639	0.829936	0.829936
CI95PercentLowerGEOMean	Lower limit of the 95% confidence interval for the geometric mean value	0.108395	0.108395	0.010426	0.010426	0.203658	0.203658
CI95PercentUpperGEOMean	Upper limit of the 95% confidence interval for the geometric mean value	0.128215	0.128215	0.012183	0.012183	0.459897	0.459897
P1	P-th percentile divides the distribution into points in such a way that P percent of the distribution is below this point.	0.10525	0.10525	0.01004	0.01004	0.15832	0.15832
P2.5		0.10525	0.10525	0.01004	0.01004	0.15832	0.15832
P5		0.10525	0.10525	0.01004	0.01004	0.15832	0.15832
P10		0.105356	0.105356	0.01004	0.01004	0.15832	0.15832
P25		0.107117	0.107117	0.010662	0.010662	0.229141	0.229141
P50		0.110571	0.110571	0.011238	0.011238	0.3279	0.3279
P75		0.130099	0.130099	0.012109	0.012109	0.430281	0.430281
P90		0.152636	0.152636	0.012369	0.012369	0.455445	0.455445
P95		0.156808	0.156808	0.012369	0.012369	0.455445	0.455445
P97.5		0.156808	0.156808	0.012369	0.012369	0.455445	0.455445
P99		0.156808	0.156808	0.012369	0.012369	0.455445	0.455445
IQR	Interquartile range (difference between the first and third quartiles).	0.022982	0.022982	0.001448	0.001448	0.20114	0.20114

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Table 4 — Comparison of the results of non-compartmental analysis for the intravenous bolus administration model (single dose, linear trapezoid method, without extrapolation of the initial concentration) using the example of M2000, cefamandole and indomethacin

Drug	M2000		Cefamandole		Indomethacin	
Parameter	WinNonlin	PreKinetix	WinNonlin	PreKinetix	WinNonlin	PreKinetix
N_Samples	14	14	15	15	12	12
Dose	100000000	100000000	15000	15000	50000	50000
Rsq	0.984143	0.984143	0.999758	0.999758	0.997067	0.997067
Rsq_adjusted	0.976215	0.976215	0.999516	0.999516	0.994133	0.994133
Corr_XY	-0.99204	-0.99204	-0.999879	-0.999879	-0.998532	-0.998532
No_points_lambda_z	4	4	3	3	3	3
K_{el}	0.108265	0.108265	0.012369	0.012369	0.15832	0.15832
Lambda_z_intercept	5.116786	5.116786	3.367347	3.367347	-1.724211	-1.724211
Lambda_z_lower	10	10	240	240	5	5
Lambda_z_upper	24	24	360	360	8	8
$T_{1/2}$	6.402296	6.402296	56.039261	56.039261	4.378127	4.378127
Span	2.186716	2.186716	2.141356	2.141356	0.685225	0.685225
T_{max}	0	0	10	10	0.25	0.25
C_{max}	2950	2950	127	127	1.5	1.5
C_{max}/D	0.00003	0.00003	0.008467	0.008467	0.00003	0.00003
C_0	2950	2950	0	0	0	0
T_{last}	24	24	360	360	8	8
C_{last}	13	13	0.34	0.34	0.05	0.05
AUC_{0-t}	4126.36	4126.36	3740.5	3740.5	1.74125	1.74125
AUC_{0-t}/D	0.000041	0.000041	0.249367	0.249367	0.000035	0.000035
AUC_{all}	4126.36	4126.36	3740.5	3740.5	1.74125	1.74125
$AUC_{0\to\infty}$	4246.435284	4246.435284	3767.988172	3767.988172	2.057065	2.057065
$AUC_{0\to\infty}/D$	0.000042	0.000042	0.251199	0.251199	0.000041	0.000041
AUC_%Extrap	2.827673	2.827673	0.729519	0.729519	15.352703	15.352703
AUC_%Back_Ext	0	0	0	0	0	0
Vz	217513.271517	217513.271517	321.84641	321.84641	153527.034923	153527.034923
Cl	23549.163784	23549.163784	3.980904	3.980904	24306.47423	24306.47423
$AUMC_{0-t}$	14317.575	14317.575	190453.5	190453.5	3.27125	3.27125
$AUMC_{0-\infty}$	18308.464419	18308.464419	202571.593629	202571.593629	7.792554	7.792554
AUMC_%Extrap	21.798057	21.798057	5.982129	5.982129	58.020826	58.020826
$MRT_{0\to t}$	3.469783	3.469783	50.916589	50.916589	1.878679	1.878679
$MRT_{0\to\infty}$	4.31149	4.31149	53.761207	53.761207	3.78819	3.78819
V_{ss}	101531.990574	101531.990574	214.018217	214.018217	92077.554608	92077.554608

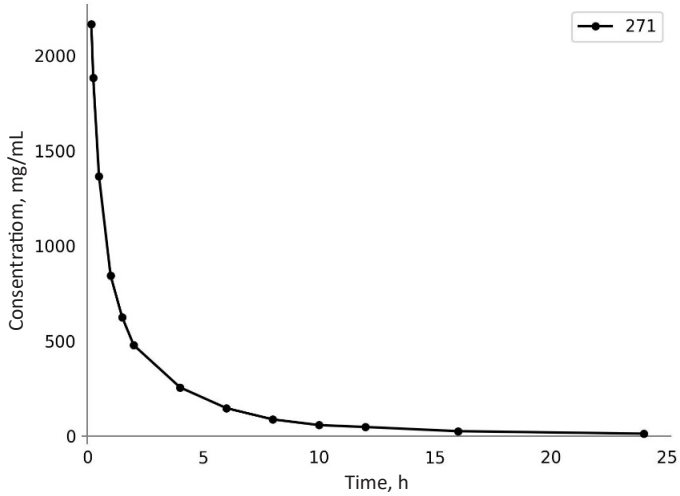

Figure 2 — Individual pharmacokinetic profile in blood (in linear scale), after intravenous bolus administration of M2000.

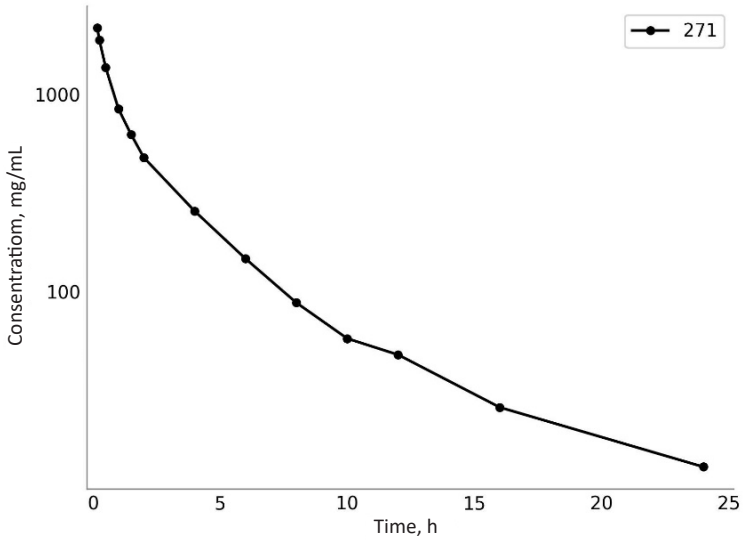

Figure 3 — Individual pharmacokinetic profile in blood (in semi-logarithmic scale) after intravenous bolus administration of M2000.

It should be noted that the fundamental algorithms for calculating PK parameters implemented in PreKinetix correspond to industry-accepted approaches similar to Phoenix WinNonlin. In particular, the area under the curve (AUC) is calculated using the trapezoidal method, if necessary, in a combined mode — with linear interpolation at the stage of increasing concentration and logarithmic at the stage of decreasing. The estimation of the elimination rate constant λz and the associated $T_{1/2}$ in PreKinetix is performed by automatically selecting the points of the terminal phase based on maximizing the coefficient of determination R^2 (usually for the last sequential points with decreasing concentration), which is similar to the built-in Phoenix WinNonlin algorithm. In our calculations, all programs (PreKinetix, Phoenix, etc.) showed the same $T_{1/2}$ values with high statistical quality of approximation of the terminal section, which confirms the equivalence of the methods. As for missing points or concentrations below the limit of quantification, PreKinetix processes them according to generally accepted practice: such values are excluded from the AUC calculation (i.e., do not contribute to the area under the curve) or, if necessary, replaced by conditional zeros — similar to the default settings in Phoenix WinNonlin. Thus, the choice of algorithms for integrating the "concentration–time" profile and estimating λz in PreKinetix is consistent with the approaches implemented in recognized NCA tools, which ensures comparability of results even in non-standard cases.

In numerous studies, Phoenix WinNonlin is used as a reliable tool for NCA calculations on in vivo data. Thus, in the analysis of the PK of the monoclonal antibody WBP216, the authors report that all PK parameters were calculated using Phoenix WinNonlin and used in dose establishment and exposure assessment [24]. The use of Phoenix in early-phase clinical trials confirms its practical significance and compliance with regulatory standards. In addition, a number of other publications describe the use of Phoenix for NCA in the analysis of the effect of food on the PK of various drugs [25]. Thus, the use of Phoenix WinNonlin in this study as a reference for comparing the results obtained using PreKinetix is methodologically justified and consistent with international practice for validating pharmacokinetic software.

From a practical point of view, PreKinetix has a number of advantages. First, the application has an intuitive web interface, which favorably distinguishes it from some existing freely distributed solutions (for example, R-packages without GUI) and facilitates its use by a wide range of users. Secondly, the program integrates a full cycle of PK data analysis — from loading and statistical processing of raw data to calculating PK parameters and visualizing profiles. The results are automatically formatted as easy-to-read reports (Excel tables and Word documents with graphs), which reduces the researcher's labor costs for data formatting. Finally, PreKinetix is based on open technologies (Python, Streamlit, etc.), which provides flexibility in refining and expanding functionality in the future. At the same time, the existing analogues of PreKinetix software that use a similar methodology for calculating PK still have a number of disadvantages.

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Comparison of PreKinetix with other available solutions shows that our application successfully overcomes a number of limitations inherent in them. Unlike tools without a graphical interface [1], our web application provides interactivity and clarity. In terms of the set of implemented models and parameters, PreKinetix is at the level of modern commercial packages (Phoenix, PKanalix, etc.), while being more accessible. Thus, PreKinetix can be used as a reliable alternative to commercial software for NCA tasks in preclinical studies, and also fills a significant gap in the market of software tools for pharmacokinetic analysis in Russia and can contribute to strengthening technological sovereignty in this area.

Study limitations

The limitations of this study include the focus of the current version of PreKinetix primarily on the analysis of PK data with a single administration of the drug. Support for multiple dosing, as well as the possibility of conducting population PK analysis, has not yet been implemented. In addition, the validation of algorithms was carried out mainly on literary and local experimental data, without the involvement of external independent centers, which may require additional confirmation of reproducibility in multicenter studies. Also, at the time of preparation of the article, the application had not undergone official certification or registration as a software tool for use in conditions regulated by the standards of good laboratory practice (GLP). Visualization and export of graphs are implemented with limited flexibility, which may require refinement when used in complex reporting formats.

Further prospects

Modern studies demonstrate a growing interest in hybrid approaches that combine traditional NCA and machine learning methods. Thus, in the work of Hughes et al. (2024) [26] it was shown that MAP-Bayesian methods can significantly increase the accuracy of busulfan dosing compared to classical NCA, despite the close AUC values. In addition, the Deep-NCA model [3], based on deep learning algorithms, demonstrated improved accuracy in predicting C_{max} and AUC compared to classical methods.

This underscores the prospect of expanding PreKinetix in the future by adding machine learning modules to improve the accuracy of algorithms and adapt to large and complex data.

CONCLUSION

During the work, a new web application PreKinetix was created and tested for conducting statistical and NCA PK data. The program supports the main types of preclinical PK experiments (bolus intravenous administration, intravenous infusion, extravascular single-dose administration) and calculates a wide range of PK parameters that fully comply with international standards. The results of the comparative analysis showed that PreKinetix provides high calculation accuracy, not inferior in this respect to the recognized commercial software Phoenix WinNonlin. The introduction of PreKinetix into practice will allow Russian research organizations to reduce the time and financial costs of PK data analysis, automate routine calculations and visualize results with high quality. Thus, PreKinetix is an effective and accessible tool that has great potential for use in preclinical and clinical PK studies, as well as in the educational process for training specialists in the field of biopharmaceutical analysis.

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The authors declare that there is no conflict of interest.

AUTHORS’ CONTRIBUTION

Pavel M. Rezvanov — software development, statistical processing of the results, writing of the draft of the manuscript; Natalia E. Moskaleva — conducting the experiment, statistical processing of the results; Ksenia M. Shestakova — creation of software architecture, statistical processing of the results; Vadim V. Tarasov — analysis of the results with interpretation and conclusions, approval of the final version of the manuscript; Elena A. Smolyarchuk — analysis of literature data on the study aim and results; Dmitry A. Kudlay — analysis of the results with their interpretation and conclusions, approval of the final version of the manuscript; Svetlana A. Appolonova — development of the concept, approval of the final version of the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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AUTHORS

Pavel M. Rezvanov — graduate student, junior researcher at the Laboratory of Bioinformatics and Pharmacological Modeling of the Center for Biopharmaceutical Analysis and Metabolic Research at the Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0009-0006- 8806-6902. E-mail: rezvanov_p_m@staff.sechenov.ru

Natalia E. Moskaleva — Candidate of Sciences (Biology), Deputy Head of the Center for Biopharmaceutical Analysis and Metabolic Research at the Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-7309-8913. E-mail: moskaleva_n_e@staff.sechenov.ru

Ksenia M. Shestakova — Candidate of Sciences (Pharmacy), Head of the Laboratory of Bioinformatics and Pharmacological Modeling of the Center for Biopharmaceutical Analysis and Metabolic Research at the Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0001-6554-3936. E-mail: shestakova_k_m@staff.sechenov.ru

Vadim V. Tarasov — Doctor of Sciences (Pharmacy), Director of the Institute of Translational Medicine and Biotechnology, Vice-Rector for Scientific and Technological Development, I.M. Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-9394-7994. E-mail: echeno_v_v_2@staff.sechenov.ru

Elena A. Smolyarchuk — Candidate of Sciences (Medicine), Assistant Professor, Head of the Department of Pharmacology at the A.P. Nelyubin Institute of Pharmacy, I.M. Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-2615-7167. E-mail: smolyarchuk_e_a@staff.sechenov.ru

Dmitry A. Kudlay — Doctor of Sciences (Medicine), Professor of the Department of Pharmacology at the A.P. Nelyubin Institute of Pharmacy, I.M. Sechenov First Moscow State Medical University (Sechenov University); Deputy Dean for Scientific and Technological Development of the Faculty of Bioengineering and Bioinformatics, Senior Researcher at the Faculty of Bioengineering and Bioinformatics, Lomonosov Moscow State University; Leading Researcher at the Laboratory of Personalized Medicine and Molecular Immunology No. 71, State Research Center Institute of Immunology; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0003-1878-4467. E-mail: kudlay_d_a@staff.sechenov.ru

Svetlana A. Appolonova — Candidate of Sciences (Chemistry), Head of the Center for Biopharmaceutical Analysis and Metabolic Research at the Institute of Translational Medicine and Biotechnology, I.M. Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-9032-1558. E-mail: appolonova_s_a@staff.sechenov.ru

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Assessment of potential risks at the pharmaceutical development stage of minitablets

Ya.S. Novikov, S.N. Egorova

Kazan State Medical University,
49, Butlerova str., Kazan, Russia, 420012

E-mail: svetlana.egorova@kazangmu.ru

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The production of mini tablets (MTs) differs significantly from the production of regular-sized tablets and involves certain risks. The article analyzes scientific publications on the topic of MTs development and production, and based on the data obtained, assesses the risks associated with it.

The aim: To conduct a risk assessment during the pharmaceutical development of MTs.

Materials and methods. The research materials were based on the ICHQ8 guidelines for pharmaceutical development and ICHQ9 guidelines for quality risk management, State Pharmacopoeia of the Russian Federation XV edition, scientific publications on the pharmaceutical development and production of MTs. The study was conducted using the PHA (preliminary hazard analysis) method. The following were considered as critical quality attributes (CQAs) of MTs: disintegration, dissolution, uniformity of dosage units, uniformity of mass, crushing strength, and friability. Hazards were identified using the Ishikawa diagram method. Risk analysis was performed based on data from scientific publications on the development and production of MTs. Articles were searched for between 1990 and 2024 in the ScienceDirect, PubMed, Google Scholar, and elibrary.ru databases. Based on the information presented in these articles and using a logical method, the probability of occurrence and severity (consequences) of the risks were determined. Risk assessment was carried out using a risk matrix.

Results. Among the parameters of the MTs production process, the compression and mixing stages pose a danger. The compression is associated with a high risk for the following CQAs: dissolution, uniformity of dosage units, uniformity of mass, and crushing strength. Mixing is critical to ensuring dosage uniformity. Parameters of the active pharmaceutical ingredient (API), such as particle size and shape, significantly affect dissolution. In addition, the compressibility and flowability of the API are risk factors for ensuring the uniformity of dosage and MTs mass. The choice of excipients (EPs) is of great importance in the development of MTs. The type and content of the filler are of the greatest risk to the studied MTs. An irrational choice of disintegrant and anti-friction EPs can lead to impaired disintegration and dissolution of MTs.

Conclusion. As a result of the risk assessment, hazards were identified, and key risks associated with the pharmaceutical development of MTs were analyzed and evaluated. Particular attention was paid to the main groups of hazards — the influence of the properties of API, EPs, and production process parameters on MTs CQAs. It was found that during the development of MTs, the shape and size of the API particles, the compressibility and flowability of the powder mixture, the type and content of the filler and disintegrant, as well as such technological process parameters as pressing and mixing, pose a particular risk.

Keywords: mini-tablets, risk assessment, quality by design, dosage forms for children.

Abbreviations: DF — dosage form; EP — excipient; SPh XV — State Pharmacopoeia of the Russian Federation XV edition; MT — mini-tablet; PHA — Preliminary Hazard Analysis; CQA — critical quality atribute; API — active pharmaceutical ingredient.

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Оценка возможных рисков на этапе фармацевтической разработки мини-таблеток

Я.С. Новиков, С.Н. Егорова

Федеральное государственное бюджетное образовательное учреждение высшего образования
«Казанский государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 420012, г. Казань, ул. Бутлерова, д. 49

E-mail: svetlana.egorova@kazangmu.ru

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Производство мини-таблеток (МТ) значительно отличается от выпуска таблеток обычного размера и сопряжено с определёнными рисками. В статье проведён анализ научных публикаций на тему разработки и производства МТ, и на основе полученных данных оценены связанные с этим риски.

Цель. Провести оценку рисков при фармацевтической разработке МТ.

Материалы и методы. В качестве материалов исследования за основу были взяты руководства по фармацевтической разработке ICHQ8 и управлению рисками для качества ICHQ9, рекомендации Государственной фармакопеи РФ XV издания, научные публикации по фармацевтической разработке и производству МТ. Исследование проводили методом PHA (предварительного анализа опасностей). В качестве критических показателей качества (КПК) МТ были рассмотрены: распадаемость, растворение, однородность дозирования, однородность массы, прочность на раздавливание, истираемость. Идентификация опасностей проводилась методом построения диаграммы Исикавы. Анализ рисков проводился на основании данных научных публикаций на тему разработки и производства МТ. Поиск статей осуществлялся за период с 1990 по 2024 год в базах данных ScienceDirect, PubMed, Академия Google и elibrary.ru. На основании сведений, представленных в этих статьях, и логическим методом были определены вероятность возникновения и тяжесть (последствия) рисков. Оценивание рисков проводилось с использованием матрицы рисков.

Результаты. Среди параметров технологического процесса производства МТ представляют опасность стадии прессования и смешивания. Прессование связано с высоким риском для следующих КПК: растворение, однородность дозирования, однородность массы и прочность МТ на раздавливание. Смешивание критически важно для обеспечения однородности дозирования. Параметры активной фармацевтической субстанции (АФС), такие как размер и форма частиц, существенно влияют на растворение. Кроме того, прессуемость и сыпучесть АФС являются рискообразующими факторами для обеспечения однородности дозирования и массы МТ. Огромное значение при разработке МТ имеет выбор вспомогательных веществ (ВВ). Наибольший риск воздействия на изучаемые КПК представляет тип и содержание наполнителя. Нерациональный выбор дезинтегранта и антифрикционного ВВ может привести к нарушению распадаемости и растворения МТ.

Заключение. В результате оценки рисков были идентифицированы опасности, проанализированы и оценены ключевые риски, связанные с фармацевтической разработкой МТ. Особое внимание было уделено основным группам опасностей — влиянию свойств АФС, ВВ и параметрам производственного процесса на КПК МТ. Выявлено, что при разработке МТ особый риск представляет форма и размер частиц АФС, прессуемость и сыпучесть порошковой смеси, тип и содержание наполнителя и дезинтегранта, а также такие параметры технологического процесса, как прессование и смешивание.

Ключевые слова: мини-таблетки; оценивание рисков; качество через дизайн; лекарственные формы для детей

Список сокращений: ЛФ — лекарственная форма; ЛП — лекарственный препарат; ВВ — вспомогательное вещество; МТ — мини-таблетка; PHA — предварительный анализ рисков (Preliminary Hazard Analysis); КПК — критический показатель качества; АФС — активная фармацевтическая субстанция.

INTRODUCTION

The lack of special dosage forms (DFs) with reduced dosage for children is an important problem in modern pediatric pharmacotherapy. To a large extent, medicines developed only for adults are used in pediatrics outside the approved indications (off-label) [1]. For example, angiotensin-converting enzyme inhibitors (captopril, enalapril), angiotensin II receptor blockers (losartan, valsartan), β-blockers (carvedilol), diuretics (spironolactone, hydrochlorothiazide, furosemide), cardiac glycosides (digoxin), etc. are used to treat heart failure in children [2]. Often, there are no

specially developed DFs for children of these medicines on the pharmaceutical market, which forces their usage intended for adults. This approach entails increased risks associated with the lack of reliable data on the safety and efficacy of medicines for the children's body [3].

In the context of current problems in pediatric pharmacotherapy, the task of developing new DFs for children is relevant. However, the process of creating specialized drugs for children is associated with certain difficulties. Solid DFs, including tablets and capsules, can cause swallowing problems in children, which negatively affects adherence to the prescribed course of treatment. Liquid DFs, such as solutions and suspensions, are more preferable, but they also have disadvantages: short shelf life, risk of microbial contamination, the presence of non-indifferent excipients (EPs), as well as inaccurate dosing [4, 5].

A promising DF for children is mini-tablets (MTs). The number of publications on the topic of MT development has increased significantly recently [6]. At the same time, orodispersible MTs, which combine the advantages of liquid DFs and conventional tablets, are of great interest [7]. According to Lennartz and Mielck, MTs are tablets with a diameter of 2–3 mm or less [8]. MTs have a number of advantages: easy swallowing, flexible dosing, ensuring accurate dosing, high stability compared to liquid DFs [9]. Unlike pellets, MTs have a constant shape and size, a smooth surface, a low degree of porosity and high mechanical strength, which together facilitates the application of a coating on MTs [10].

MTs are a suitable DF for children of different ages. Klingmann et al. studied the acceptability of uncoated MTs in newborns. The study involved 151 children, with an average age of 4.07 days. The study participants received 2 mm diameter and 7 mg MT-placebo. As a result, 82.2% of children completely swallowed the MT, and none of the newborns experienced severe complications in the form of aspiration [11]. In another study, also conducted by Klingmann et al., the effect of coated and uncoated MT-placebo on children aged 6 months to 5 years was studied. The MT was placed on the child's tongue, after which he was offered to swallow them, drinking with a selected drink (no more than 3 sips). 306 children took part in the study. No child experienced aspiration problems as a result of taking uncoated MTs. Only two cases of coughing were recorded after taking coated MTs among children aged 0.5 to 1 year, but these cases were not clinically significant [12].

In accordance with the ICH Q8 guideline[1], one of the stages of pharmaceutical development is risk assessment. Risk assessment is a valuable scientific process used in quality risk management to identify material indicators and process parameters that potentially affect the critical quality attributes (CQA) of a drug. Risk assessment is usually carried out at an early stage of the pharmaceutical development process and is repeated as more information becomes available and more knowledge is gained[2]. At the same time, in accordance with the ICH Q9 guideline[3] on quality risk management, risk assessment consists of identifying hazards, analyzing and evaluating risks [14]. In the process of pharmaceutical development of MTs, conducting a risk assessment is a critical step to ensure the high quality of the final product. Risk assessment is necessary to identify all potential elements with an increased level of risk and their subsequent detailed study as part of the planning of experimental studies.

THE AIM. Assessment of potential risks at the pharmaceutical development stage of MTs for children.

MATERIALS AND METHODS

The research materials were based on the ICH Q8[4] guidelines for pharmaceutical development and ICH Q9[5] guidelines for quality risk management, recommendations of the State Pharmacopoeia of the Russian Federation XV edition (SPh XV)[6], scientific publications on pharmaceutical development and production of MTs.

The following were considered as CQA MTs: disintegration, dissolution, uniformity of dosage, uniformity of mass, crushing strength, abrasion.

Hazard identification

At the first stage of risk assessment, the PHA (Preliminary Hazard Analysis)[7] method was used to identify hazards — the systematic use of information to identify hazards related to the issue regarding risk or problem description [13, 14]. The Ishikawa diagram ("fishbone") was used to assess cause-and-effect relationships. It is a graphical tool for organizing and presenting knowledge and ideas generated as a result of the collective analytical process of the

[1] International Conference on Harmonisation, Guideline ICH Q8 (R1); Pharmaceutical Development, Step 4; November 2008.

[2] Ibid.

[3] International Conference on Harmonisation, Guideline ICH Q9; Quality Risk Managemen; 2005.

[4] International Conference on Harmonisation, Guideline ICH Q8 (R1); Pharmaceutical Development, Step 4; November 2008.

[5] International Conference on Harmonisation, Guideline ICH Q9; Quality Risk Managemen; 2005.

[6] State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/. Russian

[7] International Conference on Harmonisation, Guideline ICH Q9; Quality Risk Managemen; 2005.

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research team. Causes are classified according to their significance or level of detail, resulting in a hierarchical structure similar to a fish skeleton, where the main categories of causes are represented as "bones" connected to the "spine" [15, 16]. Using this method, the main groups of hazards were logically identified. The most significant groups were located closer to the top of the fish.

Risk analysis and measurement

At the second stage, the analysis and measurement of risks associated with the identified hazards[8] was carried out. For this purpose, data from scientific publications on the development and production of MTs were used. The search for articles was carried out for the period from 1990 to 2024 in the ScienceDirect, PubMed and Google Scholar databases using the keywords: "minitablets", "minitablets", "minitablets development", "minitablets manufacturing", and in elibrary.ru using the keywords "mini-tablets". The initial search identified 82 publications; after removing duplicates, 52 unique articles remained, which were evaluated by titles and abstracts for relevance. For a detailed analysis of risks according to established criteria (publications 1990–2024, focus on MTs development / production, availability of full text), 15 of the most relevant articles containing experimental data on the composition and technology of MTs production were selected. Based on the information presented in these articles, and by logical method, the probability of occurrence and severity (consequences) of risks were determined.

The probability of a risk occurring was assessed on a scale: A — almost certainly (1:2), B — likely (1:10), C — possible (1:100), D — unlikely (1:1000), E — rare (1:10000). The severity of the risk was assessed on a 5-point scale: 1 — insignificant, 2 — stopping the technological process, 3 — rejection of the batch, 4 — non-compliance with the specification, 5 — detected only by the patient [17].

Risk assessment

At the last stage, risk assessment was carried out — comparing the identified and analyzed risk with the specified risk criteria [14]. For this, a risk matrix described by N. Baker was used (Table 1). Risks were divided into low, medium and high [17].

RESULTS AND DISCUSSION

Hazard identification

At the first stage, the main groups of hazards affecting CQA were identified: properties of the active pharmaceutical substance (API), type and content of EP, equipment used, parameters of the technological process, packaging, quality control, staff, environment[9] (Fig. 1).

As shown in Figure 1, the main hazards associated with API are the shape and size of particles, flowability and compressibility properties, hygroscopicity. The choice of the main groups of EPs, such as fillers, disintegrants, anti-friction and binding substances, is important in the development of MTs. The main parameters of the technological process, such as speed, time and degree of grinding and mixing, pressing pressure affect the quality indicators of MTs. The choice of equipment, namely a mixer, grinder, type of tablet press and a set of press tools, also poses a hazard.

The choice of packaging type, material of primary and secondary packaging and quality control of MTs is also important[10]. Hazards associated with personnel and the environment are general in nature and are also important in the development of MTs.

At the second stage, the influence of the most significant hazards in pharmaceutical development[11] (API, EP, parameters of the production process) on CQA was analyzed. Other risks (equipment, packaging, personnel and environment) were excluded from the analysis, since their role is manifested at later stages of MT production.

Mass and dosage uniformity

Mass uniformity and dosage uniformity are important CQA for low-dose DFs. Alalaiwe et al. report that the risk of dosage and mass non-uniformity increases as the tablet size decreases. One way to reduce the risk is to reduce the particle size. However, reducing the size can lead to a deterioration in the flowability of the powder due to particle adhesion and segregation, which can ultimately reduce the uniformity of dosage and mass of MTs obtained by direct compression [18].

As part of a study conducted by I. Stoltenberg et al., the development of 2 mm diameter orodispersible MTs containing hydrochlorothiazide at a dosage of 1 mg was carried out. The manufacturing process was carried out by direct compression using various EP, including Ludiflash, Parteck ODT, Pearlitol Flash, Pharmaburst 500 and Prosolv ODT. The final MTs were characterized by an average weight in the range from 6.41 to 6.61 mg. The authors of the study emphasize the critical role of the pressing process in ensuring the uniformity of dosage and mass of tablets. It was found

[8] Ibid.

[9] Ibid.

[10] International Conference on Harmonisation, Guideline ICH Q8 (R1); Pharmaceutical Development, Step 4; November 2008.

[11] Ibid.

that parameters such as the flowability of the mixture, the size and shape of particles do not have a noticeable effect on the uniformity of dosage [19].

Khan et al. note that to ensure a constant tablet weight and dosage uniformity, it is necessary to ensure good powder flowability. This ensures that the required amount of powder enters the matrix. The authors studied the effect of mixing parameters of a powder mixture of carvedilol with various EPs on the dosage uniformity of MTs. In addition to carvedilol (0.5 and 2 mg), the MTs included EP such as mannitol, microcrystalline cellulose and magnesium stearate. It was assumed that increasing the mixing time contributes to improving the uniformity of dosage, however, extending the mixing to 15 min led to segregation of carvedilol particles, as a result of which heavier particles sank to the bottom of the mixture. As a result, the authors determined the optimal mixing mode: 5 minutes at a speed of 250 rpm, followed by the addition of microcrystalline cellulose [20].

In their study, Lura and Breitkreutz investigated the effect of various press tools used to form tablets on the mass uniformity of MTs. The authors obtained 2 and 3 mm MTs using punches with 1, 7 and 19 tips on the Styl'OneEvo tablet compactor. As a result, the greatest differences in mass are observed in the zones in which the matrix holes were constantly under the shoe (feeder) and in the holes located closer to the edges of the matrix. The researchers note that the process of filling the matrix is a critical process in the production of MTs, and the mass uniformity of MTs depends on the system of press tools and mechanisms for filling the matrix [21].

The data presented indicate that in the pharmaceutical development of MTs, the flowability of the powder mixture, pressing pressure, type and content of the filler have a significant impact on the uniformity of dosage and mass of MTs. Pressing pressure probably (B) affects the listed CQA and can lead to rejection of the batch (3) (Table 2). Particular attention should be paid to the mixing process. Insufficient or excessive mixing time probably (B) can lead to settling of large API particles or uneven distribution of the lubricant, which will lead to non-uniformity of MT dosage and rejection of the batch (3) (Table 2). Almost certainly (A) poor flowability of the API and filler mixture will lead to problems filling the matrix and ultimately — to stopping the technological process (2) or rejection of the batch (3) (Tables 3 and 4).

Abrasion

Abrasion is the damage to tablets under the influence of mechanical shock or abrasion during processing (shaking, vibration, etc.)[12]. In a study conducted by Alalaiwe et al., 3 mm diameter sildenafil MTs were obtained on a rotary tablet press at a pressing pressure of 8 kN. The authors of the study determined the effect of EP, namely pregelatinized starch (Starch 1500) and microcrystalline cellulose (Avicel PH 105), on the abrasion of tablets. During 9 tests, the abrasion of MTs ranged from 0.65% to 1.22%. It was found that with an increase in the concentration of microcrystalline cellulose (from 10 to 40%) and pregelatinized starch (from 2% to 10%), the abrasion of tablets decreased, with pregelatinized starch having the greatest impact on this indicator [18].

Mitra et al. in their study examined the effect of particle size and ibuprofen content in MTs with a diameter of 1.2, 1.5, 2 and 2.5 mm on the abrasion index. The researchers did not find a statistically significant effect of variables such as particle size and ibuprofen content on the abrasion of MTs. Nevertheless, it was found that smaller MTs (1.2 mm) showed higher abrasion rates, ranging from 0.8% to 1.1%, compared to larger diameter tablets (2.5 mm), in which this indicator was from 0.1% to 0.2% [22].

In the study Stoltenberg et al. applied a modified method for studying the abrasion of orodispersible MTs of hydrochlorothiazide. 1 g of MTs in a closable vial were shaken using a Universalshaker SM 25 mechanical shaker (EdmundBühler, Hechingen, Germany) for 1 hour at a frequency of 200 rpm. Then the samples were dedusted using an air jet sieve with a mesh size of 125 µm and a pressure of 600 Pa for 1 min. Samples were weighed before and after processing. All samples obtained at a pressing pressure of 5 kN to 10 kN had an abrasion of less than 1%. In addition, the authors noted that the abrasion of MTs does not always correlate with their crushing strength. The Prosolv® ODT composition, pressed at 3 kN, showed higher crushing strength compared to the Pearlitol® Flash composition, pressed at 5.5 kN, which in turn had satisfactory abrasion. Based on these results, the authors concluded that it is necessary to apply a pressing pressure of at least 5.5 kN to achieve optimal tablet strength [19].

Taking into account the above, it was concluded that the presence of EP, the size of MTs and the pressing pressure affect the abrasion index in MTs. Often, with an increase in pressing pressure, the abrasion of tablets decreases. Almost certainly (A) insufficient pressure can lead to non-compliance of MTs with the specification (4) (Table 2). The type and

[12] GPhM.1.1.1.0015 Abrasion. State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-1/1-1-2/istiraemost-tabletok/

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content of the filler probably (B) can also lead to non-compliance with the specification (4) (Table 3). The effect of API should be considered only with its high content in MTs. It is worth noting that the method for determining abrasion, intended for conventional tablets, is not sensitive enough, therefore, for MTs, it is advisable to consider other methods, for example, the method for determining abrasion for granules and spheroids [23].

Crushing strength

The crushing strength of tablets (tablet resistance to pressure) shows the force required to destroy tablets[13]. In a study conducted by Stolnberg et al., the dependence of the strength of orodispersible MTs of hydrochlorothiazide on the pressing pressure and incoming EP was evaluated. It was found that a crushing strength of more than 7 N is achieved in compositions with Parteck ODT at a pressing pressure of 5.5 kN (7.4 N) and 8 kN (11.8 N), Ludiflash at a pressure of 8 kN (8.1 N), and Pharmaburst at a pressure of 8 kN (8 N). At the same time, compositions with Proslov ODT at a pressure of 5.5 kN and 8 kN, as well as Pearlitol Flash at a pressure of 8 kN and 10 kN, showed a crushing strength of less than 7 N [19].

Alalaiwe et al. studied the crushing strength of sildenafil MTs. The strength of the obtained MTs varied from 2.86 kiloponds (28 N) to 5.31 kiloponds (52 N). In addition, the crushing strength increased with increasing content of MCC and pregelatinized starch [18].

In a study by Cho et al., the effect of fillers and lubricants on the strength and ejection force of MTs was studied. The authors obtained acyclovir MTs on a STYL'OneEvo compactor using a set of punches with 29 tips. MCC 101 (from 24.25% to 97%) and pregelatinized starch (from 24.25% to 97%) were selected as fillers for comparison, and magnesium stearate (0.5% and 2%) was used as lubricants. Granules were pre-obtained by wet granulation. The authors claim that pregelatinized starch was more effective in reducing the ejection force of MTs. Increasing the amount of magnesium stearate also led to a decrease in the ejection force. However, the researchers draw attention to the fact that the use of lubricants in high quantities is undesirable due to the decrease in the mechanical strength of MTs [24].

Thus, one of the main factors to pay attention to when developing MTs is the pressing pressure (Table 2). Almost certainly (A) non-optimal pressing pressure will lead to non-compliance with the specification in terms of MT crushing strength (4). The choice of the appropriate filler will probably (B) ensure good adhesion of the particles of the powder mixture and, therefore, sufficient strength of the MT, which prevents serious consequences in the production of MTs (4) (Table 4). Also, special equipment may be needed to measure the crushing strength of MTs [18].

Dissolution

Dissolution is used to determine the amount of active substance that is released into the dissolution medium from the medicine in a solid dosage over a certain period of time[14]. In a study conducted by Mitra et al., the effect of particle size and ibuprofen content, as well as the diameter of MTs on release was studied. A USP I type dissolution apparatus was used for the tests. The researchers indicate that MTs with 3% ibuprofen content show a higher release rate compared to MTs containing 25% ibuprofen: 80% and 45% in 30 min, 90% and 65% — 60 min, respectively, while complete dissolution is achieved after 90 min. The authors also note that with an increase in the diameter of MTs (from 1.2 mm to 2.5 mm) with 25% ibuprofen content and a particle size of 60 µm, a decrease in the release rate is observed. In addition to this, it was found that the particle size affects the release efficiency: MTs with 25% ibuprofen content and a particle size of 60 µm showed a faster release compared to those with a particle size of 100 µm, with results of 74% and 61% in 30 min, and 91% and 83% — 60 min, respectively [22].

[13] GPhM.1.1.1.0017 Crushing strength. State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-1/1-1-2/prochnost-tabletok-na-razdavlivanie/

[14] Ibid.

Table 1 — Risk matrix

		Severity				
		1	2	3	4	5
Probability	A					
	B					
	C					
	D					
	E					

Note: risks: — low, — medium, — high.

Table 2 — Risks of critical quality attributes due to technological process parameters

Critical quality attributes	Technological process parameters			
	Sieving	Mixing	Lubrication	Pressing
Disintegration	Low	Low	Low	Medium
Dissolution	Low	Low	Low	High
Dosage uniformity	Low	High	Low	High
MT mass uniformity	Low	Low	Low	High
Crushing strength	Low	Low	Medium	High
Abrasion	Low	Low	Low	Low

Table 3 — Risks of critical quality attributes due to pharmaceutical-technological properties of active pharmaceutical ingredient

Critical quality attributes	Pharmaceutical-Technological Properties of active pharmaceutical ingredient			
	Flowability	Particle Size and Shape	Compressibility	Solubility
Disintegration	Low	Low	Medium	Medium
Dissolution	Low	High	Medium	High
Dosage uniformity	High	Medium	High	Low
Mass uniformity	High	Medium	High	Low
Crushing Strength	Low	Low	Low	Low
Abrasion	Low	Low	Low	Low

Table 4 — Risks of critical quality attributes due to the type and content of excipients

Critical quality attributes	Groups of excipients (type and content)			
	Fillers	Disintegrants	Binders	Antifriction
Disintegration	Medium	High	Medium	Medium
Dissolution	Medium	High	Medium	High
Dosage uniformity	High	Low	Low	Medium
Mass uniformity	High	Low	Low	Low
Crushing strength	High	Medium	Medium	Medium
Abrasion	High	Medium	Medium	Medium

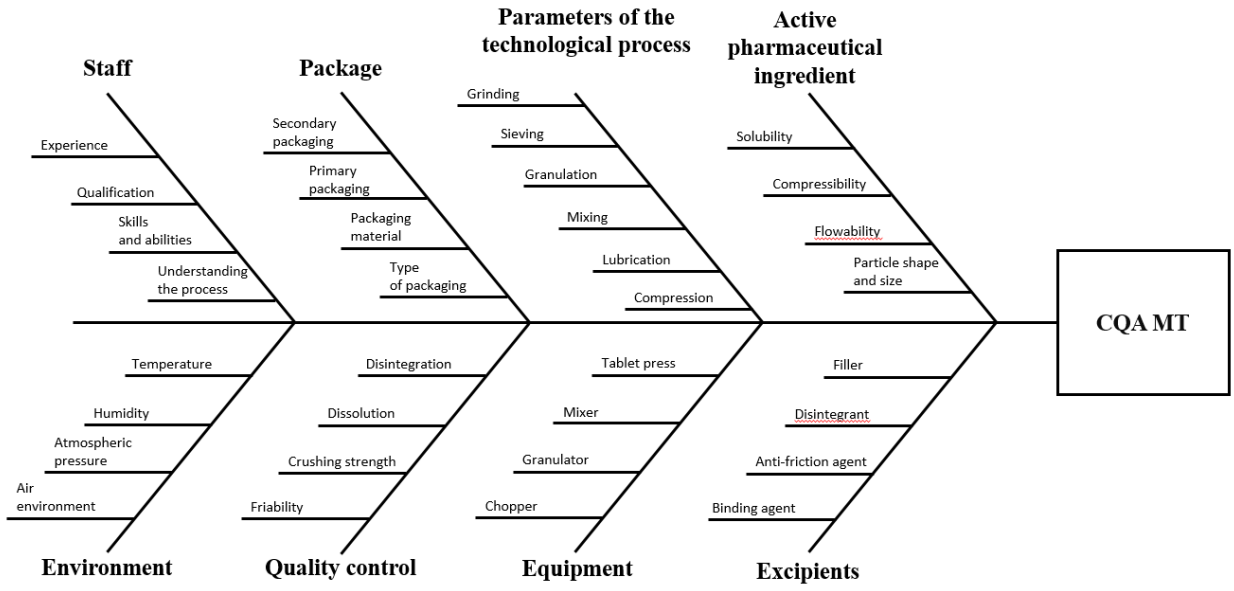

Figure 1 – Factors affecting the critical quality indicators of mini-tablets.

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In a study by Alalaiwe et al. it was shown that the release of sildenafil from MTs was more influenced by the content of pregelatinized starch. With an increase in the content of pregelatinized starch (from 2% to 10%), the percentage of sildenafil released increased from 76.49% to 89.31% during the 30-minute test [18].

At the same time, it should be borne in mind that standard methods for determining dissolution may not be suitable for MTs, and in some cases modified methods are required. One such method is described by Hellberg et al. The study used a modified method for determining the dissolution of ODT MTs of sodium salicylate using a mini-vessel of 250 mL, mini-blades 1/3 the size of standard blades and different rotation speeds of the mini-blades. The authors conclude that this method proved useful for testing MTs, however, similar results can be obtained using standard equipment [25].

Thus, API and EP have a significant impact on the dissolution of MTs. Almost certainly (A) the wrong choice of disintegrant or lubricant will lead to a deviation of the specified CQA and a decrease in the effectiveness of the drug, which can only be detected by the patient (5).

Disintegration

According to PhM.1.4.1.0015 “Tablets”, if the pharmacopoeial article provides for a test for the “Dissolution” indicator, then it is allowed not to conduct a test for the “Disintegration” indicator [15]. Nevertheless, this indicator (the ability of solid dosage DFs to disintegrate in a liquid medium over a certain period of time)[15], in our opinion, is very important and necessary in the pharmaceutical development of MTs.

In a study conducted by Subh et al., it was demonstrated that the disintegration of tablets largely depends on the type and content of EP. The authors obtained 5 mm paracetamol MTs with a dosage of 40 mg by direct compression. During the experiment, the effect of the content of various EP on the disintegration time of MTs was evaluated: Pharmaburst (from 10 MG to 70 mg), sodium starch glycolate (from 1 MG to 10 mg) and magnesium stearate (from 1 MG to 6 mg). It was found that the content of magnesium stearate has the greatest impact on the rate of disintegration, which is confirmed by its influence coefficient, equal to 11.10, while for Pharmaburst and sodium starch glycolate the coefficients were –0.4 and –0.6, respectively [9].

As part of a study conducted by Warnken et al., 2 mm diameter MTs containing 50% clofazimine were obtained by direct compression. Clofazimine is poorly soluble in water and has a small particle size. The paper emphasizes that the process of pressing clofazimine is associated with difficulties due to the formation of intermolecular bonds between small particles, which prevents the disintegration of tablets. The authors added various EP, including 1% sodium stearyl fumarate and 5% croscarmellose sodium. The greatest decrease in disintegration time was recorded when using croscarmellose sodium, which, without dissolving in water, is able to swell, thereby ensuring rapid disintegration of tablets. To reduce the interfacial interaction between the tablet matrix and the powdered substance, it was proposed to use 1% sodium stearyl fumarate and 1% sodium lauryl sulfate. The use of the widely used glidant magnesium stearate was recognized as impractical, since it can create a hydrophobic layer that prevents the disintegration and dissolution of tablets [26].

In the study Stolnderg et al. characterized the negative effects associated with the use of lubricants, which lead to a decrease in wetting and an increase in the disintegration time of ODT MTs of hydrochlorothiazide. The authors compared the effectiveness of magnesium stearate and sodium stearyl fumarate, used as lubricating additives in concentrations from 2% to 5%. The results showed that sodium stearyl fumarate provides faster disintegration of MTs, even at higher content, which indicates its advantages as a lubricant compared to magnesium stearate [19].

However, in a study by Sabbatini et al. it is argued that the presence of a lubricant does not affect the kinetics of water absorption in the presence of a disintegrant. The authors studied the disintegration of tablets depending on the amount of croscarmellose sodium (from 0% to 5%) with a constant amount (3%) of different lubricants, such as magnesium stearate, sodium stearyl fumarate and sodium lauryl sulfate. The disintegration time depended only on the concentration of the disintegrant, and the type of lubricant had no effect. Tablets without disintegrant remained intact for more than 15 min, but with the addition of croscarmellose sodium, the time decreased to less than 20 s [27].

Based on this, when developing MTs, special attention should be paid to the choice of lubricants, since they significantly affect the disintegration index (Table 4). If possible, the addition of magnesium stearate should be avoided, since it probably (B) forms a hydrophobic layer and thereby reduces disintegration,

[15] GPhM.1.4.2.0013 Disintegration. State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-4/1-4-2/raspadaemost-tvyerdykh-lekarstvennykh-form-/

leading to non-compliance with the specification (4). Almost certainly (A) disintegration depends on the type and content of the disintegrant (Table 4). Its choice is one of the key factors in the development of orodispersible MTs (A). Pressing pressure also has a noticeable effect (C), reducing the disintegration of MTs (3) (Table 2). In addition, for orodispersible MTs, it is necessary to consider conducting a wettability test [23].

At the final stage, a risk assessment of the parameters of the technological process (Table 2), API (Table 3) and EP (Table 4) on the CQA MTs was carried out using a risk matrix.

As a result of the risk assessment, it was found that among the parameters of the technological process (Table 2), the processes of pressing and mixing pose a hazard. Pressing is associated with a high risk for the following CQA: dissolution, uniformity of dosage and uniformity of mass of MTs and crushing strength of MTs. Mixing is critical to ensure dosage uniformity. API parameters (Table 3), such as particle size and shape, significantly affect dissolution. In addition, the compressibility and flowability of API poses a hazard in ensuring the uniformity of dosage and mass of MTs. The choice of EP is of great importance in the development of MTs (Table 4). The greatest risk to the studied CQA is the type and content of the filler. An irrational choice of disintegrant and antifriction EP can lead to a violation of the disintegration and dissolution of MTs.

Study limitations

The limitations of the study include the lack of experimental data on the pharmaceutical development and industrial production of MTs. Further experimental studies on the pharmaceutical development of MTs for pediatric practice are recommended, taking into account the identified risk factors.

CONCLUSION

Thus, hazards were identified, key risks associated with the pharmaceutical development of MTs were analyzed and assessed. Special attention was paid to the main groups of hazards — the influence of API properties, EP and parameters of the production process on the CQA MTs. It was revealed that in the development of MTs, the shape and size of API particles, the compressibility and flowability of the powder mixture, the type and content of the filler and disintegrant, as well as such parameters of the technological process as pressing and mixing, pose a particular risk. These pharmaceutical factors must be taken into account in pharmaceutical development

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

Yaroslav S. Novikov — the concept and methodology, study conducting, draft writing a of the manuscript, writing the manuscript (reviewing and editing), visualization; Svetlana N. Egorova — the concept, scientific guidance, writing the manuscript (reviewing and editing). All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept and preparation of the article, read and approved the final version before publication).

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AUTHORS

Yaroslav S. Novikov — Assistant Lecturer at the Institute of Pharmacy, Kazan State Medical University. ORCID ID: 0009-0005-2916-3756. E-mail: yaroslav.novikov@kazangmu.ru

Svetlana N. Egorova — Doctor of Sciences (Pharmacy), Professor, Deputy Director for Educational Affairs at the Institute of Pharmacy, Kazan State Medical University. ORCID ID: 0000-0001-7671-3179. E-mail: svetlana.egorova@kazangmu.ru

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Diagnostic and pharmacological correction of cardiovascular system changes in children, adolescents, and young adults with long COVID: comparative randomized clinical trial in parallel groups

L.A. Balykova[1], M.V. Shirmankina[1], A.V. Krasnopolskaya[1], A.A. Stradina[2], S.A. Ivyansky[1], T.M. Duvayarova[1], D.S. Rodionov[1]

[1] National Research Ogarev Mordovia State University,
68 Bolshevistskaya Str., Saransk, Russia, 430005
[2] Children's Polyclinic No. 4,
92 Volgogradskaya str., Saransk, Russia, 430009

E-mail: larisabalykova@yandex.ru

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The aim. To evaluate the effectiveness of L-carnitine in the complex correction of cardiovascular and autonomic manifestations of long COVID in children, adolescents, and young adults.

Materials and methods. Within the framework of an open, simple, randomized, parallel-group comparative clinical study, the effectiveness of L-carnitine at a dose of 50–75 mg/kg per day in 2 doses for 6 weeks in addition to standard therapy in children and adolescents aged 10 to 17 years, as well as young people aged 18–25 years with long COVID (n = 45) was studied in comparison with the standard therapy (n = 45) using clinical and anamnestic, electrophysiological, echocardiographic and other methods. The statistical processing of the results was carried out by the variational method, and correlation and regression analysis using Student's t-test for dependent samples, as well as the McNemar chi-square test.

Results. The most frequent clinical manifestations of long COVID were: high fatigue, headaches and muscle weakness — in 66.7–100%. After 6 weeks of treatment, the absence of complaints and normalization of objective status were noted in 93.3% of patients in the main group and 66.7% in the comparison group ($p < 0.05$). Repolarization abnormalities and rhythm disturbances, initially registered in 43.3% of patients, were not observed after 6 weeks of therapy in the main group, while they persisted in more than 50% in the comparison group. By the 6 weeks of treatment, there were no changes in Echo in the main group, while in the comparison group (slight dilatation of the left ventricle) persisted in 9 out of 12 patients. In the main group, according to Holter monitoring, restoration of heart rate, normalization of its autonomic regulation, reduction in the representation of bradyarrhythmias and "density" of extrasystoles were achieved.

Conclusion. The effectiveness of L-carnitine for the correction of the frequency and severity of autonomic and cardiac disorders in the subjects with long COVID has been shown.

Keywords: L-carnitine; long COVID; cardiovascular system; children; adolescents; young adults

List of abbreviations: HR — heart rate; LA — left atrium; LVEDD — left ventricular end-diastolic diametr; LV — left ventricle; LVEF — left ventricular ejection fraction; DMSVS — Paediatric multisystem inflammatory syndrome; CVS — cardiovascular system; BP — blood pressure; HM — Holter monitor; AEs — adverse effects; SAEs — serious adverse effects; HR — heart rate; AST — active stand test; HRV — heart rate variability.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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Возможности диагностики и фармакологической коррекции изменений сердечно-сосудистой системы у детей, подростков и лиц молодого возраста с постковидным синдромом: сравнительное параллельное рандомизированное клиническое исследование

Л.А. Балыкова[1], М.В. Ширманкина[1], А.В. Краснопольская[1], А.А. Страдина[2], С.А. Ивянский[1], Т.М. Дуваярова[1], Д.С. Родионов[1]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Национальный исследовательский Мордовский государственный университет им. Н.П. Огарёва», Россия, 430000, г. Саранск, ул. Большевистская, д. 68
[2] Государственное бюджетное учреждение здравоохранения Республики Мордовия «Детская поликлиника № 4», Россия, 430009, г. Саранск, ул. Волгоградская, д. 92

E-mail: larisabalykova@yandex.ru

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Цель. Оценка эффективности препарата L-карнитина в комплексной коррекции кардиоваскулярных и вегетативных проявлений постковидного синдрома ПКС у детей, подростков и лиц молодого возраста.
Материалы и методы. В рамках открытого простого рандомизированного сравнительного клинического исследования в параллельных группах изучена эффективность L-карнитина в дозе 50–75 мг/кг в сутки в 2 приёма в течение 6 нед в добавлении к стандартной терапии у детей и подростков в возрасте от 10 до 17 лет, а также молодых людей 18–25 лет с ПКС (*n*=45) в сравнении со стандартной терапией (*n*=45) с использованием клинико-анамнестических, электрофизиологических, эхокардиографических методов. Статистическая обработка результатов была проведена методом вариационного и корреляционно-регрессионного анализа с использованием критерия Стьюдента для зависимых выборок, а также хи-квадрата МакНемара.
Результаты. Наиболее частыми клиническими проявлениями ПКС были повышенная утомляемость, головные боли и мышечная слабость — у 66,7–100%. Через 6 нед лечения отсутствие жалоб и нормализация объективного статуса отмечались у 93,3% пациентов основной группы и 66,7% в группе сравнения (p <0,05). Аномалии реполяризации и нарушения ритма, зарегистрированные исходно у 43,3% пациентов, через 6 нед терапии в основной группе не отмечались, а в группе сравнения сохранялись более, чем в 50%. К 6 нед лечения в основной группе изменения ЭхоКГ отсутствовали, тогда как в группе сравнения (незначительная дилатация левого желудочка) сохранялись у 9 из 12 пациентов. В основной группе по данным холтеровского мониторирования достигнуто восстановление частоты ритма, нормализация его вегетативной регуляции, сокращение количества брадиаритмий и «плотности» экстрасистолии.
Заключение. Показана эффективность L-карнитина для коррекции частоты и выраженности вегетативных и кардиальных нарушений у исследуемых с ПКС.
Ключевые слова: L-карнитин; постковидный синдром; сердечно-сосудистая система; дети; подростки; лица молодого возраста
Список сокращений: ЧСС — частота сердечных сокращений; ЛП — левое предсердие; КДР ЛЖ — конечный диастолический размер левого желудочка; ПКС — постковидный синдром; ЛЖ — левый желудочек; ФВЛЖ — фракция выброса левого желудочка; ДМСВС — детский мультисистемный воспалительный синдром; ССС — сердечно-сосудистая система; АД — артериальное давление; ХМ — холтеровское мониторирование; НЯ — нежелательные явления; СНЯ — серьёзные нежелательные явления; ЧСС — частота сердечных сокращений; АОП — активная ортостатическая проба; ВСР — вариабельность ритма сердца.

INTRODUCTION

Despite the relatively low incidence and predominance of mild forms of the new coronavirus infection among children and adolescents, the consequences of the pandemic for children's health have yet to be assessed [1]. At the beginning of the pandemic more attention was paid to the acute period of COVID-19, then at the moment the vector of interest has shifted towards the subacute and chronic phases of the coronavirus infection — the so-called "long COVID", in which, according to the recommendations of the National Institute for Health and Care Excellence (NICE) of Great Britain, persistent symptomatic (ongoing) COVID (4–12 weeks from the onset of the disease) and post-COVID syndrome (after 12 weeks)[1] are

[1] COVID-19 rapid guideline: managing the long-term effects of COVID-19. London: National Institute for Health and Care Excellence (NICE). – 2024. Available from: https://pubmed.ncbi.nlm.nih.gov/33555768/

distinguished. A special form of long-term COVID-19 in pediatric practice is the multisystem inflammatory syndrome in children (MIS-C), characterized by the development of a systemic inflammatory response with multi-organ lesions 2–6 weeks after the disease [2].

The prevalence of long-term consequences of COVID-19 varies widely — from 1.6 to 70.0% due to the lack of unified approaches to classification and diagnosis[2] [3]. The frequency of post-COVID syndrome (PCS) in the pediatric population, according to a meta-analysis by Jiang et al., was 16.2% [4]. The clinical manifestations of PCS have much in common in children and adults, with a predominance of asthenic syndrome and other disorders of the nervous system, changes in the gastrointestinal tract (GIT), bronchopulmonary and cardiovascular disorders. Symptoms of post-COVID asthenia in children and adolescents are manifested by cognitive and psychological disorders: in a third, the quality of life decreases, and more than half cannot attend school for a full school day or participate in extracurricular activities [5].

Some patients with PCS have involvement of the cardiovascular system (CVS) with blood pressure (BP) instability, heart rhythm and conduction disorders, valvular dysfunction, pericardial effusion, etc. [6]. Abnormal results of cardiac MRI an average of 2.5 months after COVID-19 infection were observed in 78% of convalescents: late gadolinium enhancement, pericardial enhancement, lower left ventricular ejection fraction (LVEF), higher left ventricular (LV) volumes, higher LV myocardial mass in combination with elevated troponin levels and active lymphocytic inflammation according to endomyocardial biopsy in severe cases [7]. Therefore, cardiac symptoms in patients who have had a coronavirus infection require the exclusion of classical myopericarditis, including coronary arteritis, endocarditis, myocardial infarction, rhythm and conduction disorders, pulmonary embolism, etc. [8, 9], and only then persistent symptoms can be considered as manifestations of PCS.

Unified approaches to the diagnosis and treatment of post-COVID disorders have not been defined [10, 11]. It can be partly explained by the complex and multicomponent nature of the pathogenesis of PCS and its cardiac manifestations, which are based on increased thrombosis, mainly in the vessels of the microcirculatory bed with the development of local ischemia, endothelial dysfunction, oxidative stress, mitochondrial dysfunction, viral persistence[3] [5]. L-carnitine has shown its effectiveness in leveling the manifestations of asthenic syndrome in various diseases [12]. In addition, it has a cardioprotective effect, reduces the severity of autonomic disorders, and corrects endothelial dysfunction [13–15], which determined the choice of L-carnitine as a drug for the complex therapy of PCS in children and adolescents.

THE AIM. To evaluate the effectiveness of L-carnitine in the complex correction of vegetative and cardiovascular manifestations of post-COVID syndrome in children, adolescents, and young adults.

MATERIALS AND METHODS

Study design

An open (unblinded) controlled, comparative randomized clinical trial in parallel groups included 90 individuals who had a new coronavirus infection 12 or more weeks ago, with clinical manifestations of PCS, and 30 practically healthy individuals who made up the control group.

Patients with post-COVID syndrome (30 children — 10–14 years old, 30 adolescents — 15–17 years old and 30 young people — 18–25 years old) were randomized according to age into two groups in a 1:1 ratio: the main group (n = 45), whose treatment plan, in addition to standard therapy, included L-carnitine (PIC-Pharma LLC, Russia) at a dose of 50–75 mg/kg per day in 2 doses, selected on the basis of previous studies [16, 17] for 6 weeks, and the comparison group (n = 45), whose patients received standard therapy — group or individual psychotherapy, massage, therapeutic exercises. The obtained results were compared with the corresponding indicators of individuals in the control group (n = 30), similar to the study subjects in terms of gender and age.

Study setting and duration

The work was performed on the clinical bases of Pediatrics of the Children's Polyclinic No. 4 (Saransk, Russia) and the Center for Medicine "MEDiZ" of the National Research Ogarev Mordovia State University (Saransk, Russia). The study was conducted from February 2022 to May 2024; the duration of the intervention was 6 weeks.

Randomization

All patients included in the study were divided into groups using simple randomization (the "heads" and "tails" method).

Eligibility criteria

Inclusion criteria for the study group: children and adolescents aged 10 to 17 years 11 months and 29 days, as well as young people 18–25 years of male and female sex with a history of 4 or more weeks ago and laboratory-confirmed new coronavirus

[2] Ibid.
[3] Ibid.

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infection; PCS diagnosed by a pediatrician or therapist in children, adolescents and young adults according to the Methodological Recommendations "Features of the course of Long-COVID infection. Therapeutic and rehabilitation measures" [2]; manifestations of PCS from 2 or more organs and systems, including the CVS and nervous system, in the form of objective changes and/or pathological results of laboratory and instrumental methods of examination; written informed consent of parents (legal representatives) of a child under 14 years of age and/or an adolescent 15–17 years of age or a patient 18–25 years of age to participate in the study.

Exclusion criteria for patients in the study: children under 10 years of age; pregnant women; children with previously established chronic diseases of the CVS, respiratory, central nervous, endocrine systems; children receiving metabolic drugs (L-carnitine, phosphocreatine, mildronate, trimetazidine) for 3 months before the start of this study.

Exclusion criteria from the study: refusal to participate in the study at any stage; failure to perform study procedures; the occurrence of serious adverse events during the study.

The control group was formed in accordance with the following criteria: the first and second health groups according to the results of the medical examination; no history of a new coronavirus infection and negative ELISA results for specific antibodies against Sars-CoV-2; absence of objective and laboratory-instrumental manifestations from the CVS, central nervous system, autonomic nervous system and psychological disorders characteristic of PCS; signed informed consent.

Outcomes registration

- Clinical and anamnestic method with assessment of the severity of the infection, the presence of comorbid conditions, complaints and general condition during of examination;
- Physical examination, blood pressure measurement (auscultatory method on peripheral arteries, according to the draft clinical guidelines "Diagnosis and treatment of arterial hypertension in children and adolescents") [18];
- Standard ECG on a SHILLER AT-5 device (Switzerland) at a tape speed of 50 mm/s;
- Echo-CG to assess the morphofunctional state of the myocardium on a Xario model SSA-66 device from TOSHIBA (Japan);
- Holter monitoring (HM) of ECG with assessment of heart rate variability (with calculation of temporal parameters [pNN50, rMSSD, SDNN] using the hardware-software complex "Cardiotechnika-04" NAO "Institute of Cardiological Technology" (Russia);
- Determination of the initial vegetative tone (according to the tables of Vein, modified by N.A. Belokon);
- Active orthostatic test, which was carried out according to the recommendations specified in the guide for doctors Belokon et al[4]. Pathological types of reactions: orthostatic tachycardia, orthostatic hypotension, orthostatic hypertension were determined according to the criteria of foreign authors [19–21].
- Assessment of the severity of PCS symptoms using a visual analog scale (VAS).
- Determination of quality of life (PedsQL™).

Primary outcome of the study

The presence of signs of PCS after 6, 12 and 24 weeks of follow-up.

Safety

In the process of the study, safety was also assessed: the total number of adverse events (AEs), stratified by severity and frequency; the frequency of adverse reactions; the frequency of serious adverse events (SAEs), including those associated with the use of the study drug/placebo; the proportion of subjects who registered at least one AE.

Ethics approval

The study was approved by the Local Ethics Committee of the Medical Institute of the National Research Ogarev Mordovia State University (Protocol No. 93 dated May 28, 2021). Inclusion in the study was carried out in accordance with the approved criteria upon receipt of signed informed voluntary consent for examination from the parent or legal representative of the child and the child who has reached the age of 15 years[5].

Statistical analysis

For statistical data processing the IBM SPSS Statistics v.25 was used. Compliance with the law of normal distribution was checked using the Shapiro–Wilk and Kolmogorov–Smirnov tests. For indicators with a distribution close to normal, the arithmetic mean (M) and standard deviation (SD), 95% confidence interval (CI) were calculated. The statistical significance of differences was determined for two groups using Student's t-test, for three groups — using one-way analysis of variance (ANOVA). The direction and

[4] Belokon NA, Kuberger MB. Diseases of the heart and blood vessels in children. Moscow: Medicine; 1987. 446 p. Russian
[5] Federal Law No. 323-FZ dated November 21, 2011 "On the Basics of Public Health Protection in the Russian Federation". Russian

strength of the correlation between two quantitative indicators were assessed using Pearson's correlation coefficient. Qualitative indicators are presented both in absolute and relative values. To calculate the statistical significance of differences in qualitative characteristics, Pearson's χ^2 test was used. If the number of observations in any of the cells of the table was 10 or more, Yates› correction for continuity was used; if the number of observations was from 5 to 9, with the number of observations less than 5 in any of the cells — Fisher's exact test. The reliability of differences in the data obtained was established at the level of $p < 0.05$.

RESULTS

Baseline characteristics of patients

At the preliminary stage, we analyzed the data of medical records of 461 children, residents of Saransk aged 10–17 years (average age 13.8 ± 1.9 years), who underwent laboratory-confirmed COVID-19 during 2021–2022. 154 (33.4%) revealed indications of the appearance of new / persistence of existing symptoms of the acute phase 4 weeks after the coronavirus infection in the absence of established causes. In 29 of them (6.3% of the total number of children who underwent COVID-19), autoimmune or demyelinating diseases were diagnosed during the year with further in-depth examination, in 47 (10.2%) — cardiovascular, bronchopulmonary, uro-nephrological diseases, blood diseases, gastrointestinal tract, etc. were detected for the first time.

In 13 children and adolescents out of 78 with a diagnosis of exclusion of PCS, established according to the criteria of the Russian Scientific Medical Society of Internal Medicine and NICE, complaints disappeared after 12 weeks, and in 65 symptoms persisted for more than 12 weeks and there was actually PCS, the prevalence of which in the population of minor residents of Saransk was 14.1%. The prevalence of long-term COVID symptoms among 2634 students of Ogarev Moscow State University — residents of Saransk aged 18–25 years, was higher than among children and adolescents and amounted to 49.4% (1300 people) and 761 (28.9% of the total number of those who had been ill) were diagnosed with PCS.

Participation in the clinical study was offered to 98 patients aged 10–25 years with PCS who signed informed consent, of which 90 people met the inclusion criteria. Patients in the main group and the comparison group did not differ in age (14.5 ± 2.6 years and 15.6 ± 1.9 years, respectively) and gender composition (21 [46.7%] male and 24 [53.3%] female patients in the main group and 19 (42.2%) and 26 (57.8%) in the comparison group, respectively). Most often, the new coronavirus infection in children was mild, a moderate course was registered in 10 (23.3%) patients, and 13 patients underwent MIS-C.

Dynamics of clinical manifestations post-COVID syndrome against the background of complex therapy

The main clinical manifestations of PCS were comparable in the main group and the comparison group and were characterized by increased fatigue, headaches and muscle weakness — in 66.7–100% of the study subjects in the main group (Table 1). Less often (in 40.0–57.7%) there were appetite disorders / abdominal syndrome, sleep disorders, cognitive impairments (impaired memory, attention) and anxiety-depressive symptoms, cardialgia, these manifestations were recorded significantly more often in the main group compared with the control group ($p = 0.00$). A third of patients complained of decreased tolerance to physical activity, subfebrile temperature. Complaints of arthralgia, anosmia, hand tremor and hair loss were registered much less frequently. In the control group, only 3.3–6.7% of the examined individuals of the corresponding gender and age noted complaints, most often of increased fatigue and periodic headaches, which were relieved on their own.

The dynamics of clinical manifestations of PCS against the background of complex therapy are presented in Table 1. After 6 weeks of treatment, 42 (93.3%) patients in the main group had no complaints. In the remaining 3 (6.7%) patients in the main group and 15 (33.3%) patients in the comparison group, PCS symptoms were relieved by 12 weeks of follow-up. Symptoms of asthenia and dysosmia persisted longer.

Assessment of the severity of post-COVID syndrome symptoms using a visual analog scale

The results of assessing the severity of some PCS symptoms using VAS are presented in Figure 1.

In the main group, by 6 weeks of treatment, the severity of all symptoms decreased by 1.9–1.7 times ($p = 0.00$). Complaints of a cardiac nature of minimal severity remained only in 2 (4.4%) adolescents by the end of the active intervention, while for children, adolescents and young adults in the comparison group, a similar dynamic was registered only after 12 weeks of treatment. By 24 weeks of follow-up, clinical symptoms were completely absent in all groups.

Dynamics of changes in blood pressure

Initially, normal blood pressure values for the corresponding age, gender and height were recorded in 43.3% of children, adolescents and young adults in the main group. Hypotension was determined in the same percentage of children, and almost

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2 times less often hypertension of the 1 degree and high normal blood pressure. A similar picture was observed in the comparison group. After a course of treatment, hypotension was recorded in only 16.7% of children and adolescents ($p < 0.05$), and the number of examined individuals with high normal blood pressure decreased by almost 2 times ($p > 0.05$). In the comparison group, the representation of children and adolescents with hypotension also decreased in dynamics (from 46.7 to 33.3%, $p > 0.05$).

ECG dynamics

The initial heart rate (HR) according to the standard ECG in the study groups varied widely (Fig. 2): sinus bradyarrhythmia/sinus node dysfunction (migration of the rhythm driver, atrial rhythm) was recorded in 24.4–26.7% of the examined individuals, sinus tachycardia — in 28.9–31.1%. Sinus respiratory arrhythmia was detected in 11.1% of the examined individuals in the main group and 13.3% in the comparison group. By the end of the active intervention period in the main group, there was a significant (from 33.3% to 80%, $p = 0.00$) increase in the proportion of children, adolescents and young adults with sinus rhythm with normal HR (in the comparison group — from 31.1% to 38.9%). Restoration of sinus rhythm and normalization of HR occurred mainly due to improved sinus node function, while in the comparison group bradyarrhythmia/sinus node dysfunction persisted in 17.8%, tachycardia — in 20% and respiratory arrhythmia — in 11.1% of the examined individuals ($p > 0.05$). Although pathological HR values (increase > 98 percentile or decrease < 2 percentile) were not recorded in any of the examined individuals.

Determination of the initial vegetative tone

When determining the initial vegetative tone (modified tables of Vein), sympathicotonia and vagotonia were recorded in 8 (17.8%) and 21 (46.7%) of the examined individuals in the main group. In the comparison group, eutonia in 21 (46.7%) and vagotonia — in 15 (33.3%) predominated.

At the end of the course of treatment, both groups showed positive shifts in vegetative tone in the form of an increase in the representation of eutonia and a reduction in vagotonia and sympathicotonia. However, in the comparison group, the frequency of eutonia increased slightly (up to 57.8%), not reaching the corresponding values of the control group (70%), and sympathicotonia in 5 out of 9 patients changed to vagotonia. Whereas in the main group, complex therapy with L-carnitine significantly reduced the frequency of vagotonia — to 12 (26.7%) and sympathicotonia to 1 (2.2%), contributing to the normalization of vegetative tone in the absolute majority of patients — 32 (71.1%).

Results of the active orthostatic test

Patients in the main group and the comparison group were dominated by normal types of reaction (53.3% and 48.9%, respectively) to AST (classification of Belokon), but they were recorded less often than in the control group (76.7%). Hypersympathicotonic, hyperdiastolic and asympathicotonic types of reaction were noted in 6.7–24.4% and 8.9–28.9% of the examined individuals in the main group and the comparison group, respectively, while sympathoasthenic and asthenosympathetic variants were not found in our population. After 6 weeks of therapy in the main group, there was a significant decrease in the proportion of pathological and an increase in the normal type of reaction to AST (up to 91.1%, $p = 0.00$), hyperdiastolic and asympathicotonic types were not found, and the frequency of the hypersympathicotonic variant of the reaction decreased by 3 times. In the comparison group, the frequency of normal reaction to AST also increased, but less significantly, since all pathological types of reaction persisted, especially hyperdiastolic (Fig. 3).

Specific types of reaction: orthostatic hypertension, orthostatic hypotension, postural orthostatic tachycardia were noted in 3–11 (6.7–24.4%) and 2–13 (4.4–28.9%) patients in the main group and the comparison group, respectively, with a clear predominance of orthostatic postural tachycardia. After 6 weeks of therapy in the main group, postural orthostatic tachycardia syndrome persisted only in 1 adolescent girl (2.2%), while in the comparison group, despite the positive dynamics, there were 8 such patients (17.8%).

Echo-CG results

According to Echo-CG data presented in Table 2, mild LV dilatation (average value of left ventricular end-diastolic diameter (LVEDD) 1.5 (1.1; 1.8) Z-score) was noted in 6 (13.3%) patients, regurgitation on the mitral/tricuspid valve of the 1st degree was detected in 3 (6.7%), minor pericardial effusion — in 3 (6.7%) and dilatation of the coronary arteries — in 1 (2.2%) of the main group (mostly — in children and adolescents who underwent MIS-C). Comparable data were also typical for children, adolescents and young adults in the comparison group. By 6 weeks of treatment in the main group, there were no pathological changes, while in the comparison group, minor LV dilatation persisted in 6 out of 8 patients. In all patients in the main group, the ejection fraction increased within normal values. The values of the thickness of the posterior wall of the LV, the interventricular septum and the size of the right atrium did not have significant differences in the analyzed groups.

Table 1 – Clinical manifestations of post-COVID syndrome in the study groups, *n* (%)

Clinical manifestations	Control (*n* = 30)	Main group (*n* = 45)		Comparison group (*n* = 45)	
		before treatment	6 weeks of therapy	before treatment	6 weeks of therapy
Increased fatigue	2 (6.7%)	45 (100%)* (*p* = 0.00)	3 (6.7%)# (*p* = 0.00)	45 (100%)* (*p* = 0.00)	12 (40.0%)# (*p* = 0.00)
Headaches	2 (6.7%)	40 (88.9%)* (*p* = 0.00)	1 (2.2%)# (*p* = 0.00)	42 (93.3%)* (*p* = 0.00)	14 (31.1%)# (*p* = 0.00)
Muscle weakness	0	30 (66.7%)* (*p* = 0.00)	2 (4.4%)# (*p* = 0.00)	32 (71.1%)* (*p* = 0.00)	13 (28.9%)# (*p* = 0.01)
Appetite disorder / abdominal syndrome	1 (3.3%)	26 (57.7%) * (*p* = 0.00)	1 (2.2%) # (*p* = 0.00)	24 (53.3%)* (*p* = 0.00)	12 (26.7%)# (*p* = 0.01)
Sleep disorder	0	25 (55.6%) * (*p* = 0.00)	0# (*p* = 0.00)	21 (46.7%)* (*p* = 0.00)	7 (15.6%)# (*p* = 0.00)
Cognitive impairments	0	22 (48.9%) * (*p* = 0.00)	1 (2.2%)# (*p* = 0.00)	21 (46.7%)* (*p* = 0.00)	6 (13.3%)# (*p* = 0.00)
Anxiety-depressive symptoms	0	16 (35.6%) * (*p* = 0.00)	0# (*p* = 0.00)	17 (37.8%)* (*p* = 0.00)	5 (11.1%)# (*p* = 0.00)
Emotional lability	1 (3.3%)	17 (37.8%)* (*p* = 0.00)	0# (*p* = 0.00)	18 (40.0%)*	9 (20%)# (*p* = 0.01)
Cardialgia	1 (3.3%)	18 (40.0%)* (*p* = 0.00)	0# (*p* = 0.00)	17 (37.7%)* (*p* = 0.00)	5 (11.1%)# (*p* = 0.00)
Subfebrile condition	0	14 (31.1%) (*p* = 0.00)	0# (*p* = 0.00)	15 (33.3%)* (*p* = 0.00)	3 (6.7%)# (*p* = 0.00)
Decreased tolerance to physical activity	0	16 (35.6%)* (*p* = 0.00)	0# (*p* = 0.00)	15 (33.3%)* (*p* = 0.00)	4 (8.9%)# (*p* = 0.00)
Anosmia / dysosmia	0	14 (31.1%)* (*p* = 0.00)	0# (*p* = 0.00)	13 (28.9%)* (*p* = 0.00)	2 (4.4%)# (*p* = 0.00)
Hand tremor	0	6 (13.3%)* (*p* = 0.03)	0# (*p* = 0.04)	5 (13.3%) (*p* = 0.05)	1 (2.2%) (*p* = 0.13)
Hair loss	0	6 (13.3%)* (*p* = 0.03)	0# (*p* = 0.04)	7 (15.6%)* (*p* = 0.02)	2 (4.4%) (*p* = 0.07)
Arthralgia	0	4 (8.9%) (*p* = 0.08)	0 (*p* = 0.13)	3 (6.7%) (*p* = 0.13)	1 (2.2%) (*p* = 0.48)
Feeling of palpitations	0	9 (20.0%)* (*p* = 0.01)	0# (*p* = 0.01)	8 (17.7%)* (*p* = 0.01)	6 (6.7%) (*p* = 0.48)

Note: * — differences from the corresponding indicators of children in the control group at $p < 0.05$; # — differences from the corresponding indicators of children in the main group/comparison group before and after treatment at $p < 0.05$ (according to McNemar's chi-square test).

Table 2 – Sizes of heart cavities and indicators of central hemodynamics in patients with post-COVID syndrome and children of the control group

Patient groups	LA, mm		LVEDD LV, mm		LVEF,%	
	before	after	before	after	before	after
Main group 10–14 years	22.5 ± 1.2	22.4 ± 1.1 (*p* = 0.46)	46.5 ± 3.4	44.0 ± 1.8* (*p* = 0.02)	70.2 ± 3.0	71.1 ± 2.2 (*p* = 0.66)
Comparison group 10–14 years	22.7 ± 1.6	22.5 ± 1.7 (*p* = 0.60) / (*p* = 0.89)	44.1 ± 4.8	43.4 ± 4.1 (*p* = 0.69) / (*p* = 0.71)	69.8 ± 3.0	69.1 ± 3.3 (*p* = 0.71) / (*p* = 0.16)
Main group 15–17 years	25.2 ± 3.3	23.9 ± 1.6* (*p* = 0.01)	47.1 ± 2.1	46.1 ± 1.2 (*p* = 0.10)	68.9 ± 2.3	68.4 ± 2.5 (*p* = 0.69)
Comparison group 15–17 years	24.4 ± 2.6	24.1 ± 1.9 (*p* = 0.81) / (*p* = 0.84)	47.4 ± 3.7	46.7 ± 3.2 (*p* = 0.64) / (*p* = 0.43)	69.1 ± 3.3	69.8 ± 3.0 (*p* = 0.80) / (*p* = 0.08)
Main group 18–25 years	25.1 ± 2.9	24.1 ± 1.5 (*p* = 0.05)	48.1 ± 2.1	47.1 ± 1.8 (*p* = 0.08)	67.7 ± 2.3	68.3 ± 2.2 (*p* = 0.75)
Comparison group 18–25 years	25.4 ± 2.4	24.8 ± 2.4 (*p* = 0.77) / (*p* = 0.56)	49.3 ± 4.3	48.3 ± 3.4 (*p* = 0.13) / (*p* = 0.29)	68.6 ± 2.1	68.8 ± 2.0 (*p* = 1.00) / (*p* = 0.12)

Note: LA — left atrium; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction. * — differences from the corresponding indicators of children in the main group/comparison group before and after treatment at $p < 0.05$ (according to Student's test); ** — differences from the corresponding indicators of children in the main group and the comparison group after treatment at $p < 0.05$.

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Table 3 – Some indicators of Holter monitoring in children, adolescents and young adults with post-COVID syndrome

Indicators	Duration of the average daily QTc interval, ms	Frequency of detection:		
		episodes of supraventricular rhythm accelerated/ replacement	supraventricular/ ventricular extrasystole	episodes of migration of the rhythm driver/ sino-atrial blockade
Main group before treatment	422.8 ± 12.8	19 (42.2%)	6 (13.3%) / 1 (2.2%)	23 (51.1%)
Main group after 6 weeks	401.8 ± 19.7* (p = 0.01)	1 (2.2%)* (p = 0.00)	0	9(20%)* (p = 0.00)
Comparison group before treatment	418.3±13.8	20 (44.4%)	5 (11.1%) / 2 (4.4%)	26 (57.8%)
Comparison group after 6 weeks	401.4 ± 16.8* (p = 0.02) / (p = 0.70)	12 (26.7%)* (p = 0.01) / (p = 0.00)**	5 (11.1%) / 2 (4.4%)	17 (37.8%)* (p = 0.01) / (p = 0.06)

Note: * — differences from the corresponding indicators before treatment are significant at $p < 0.05$; ** — differences from the corresponding indicators of children in the main group and the comparison group after treatment at $p < 0.05$.

Table 4 – Some indicators of Holter monitoring in children, adolescents and young adults with post-COVID syndrome

Indicator	Age					
	10–14 years		15–17 years		18–25 years	
	Post-COVID	Healthy peers	Post-COVID syndrome	Healthy peers	Post-COVID syndrome	Healthy peers
pNN50	25.7 ± 5.7 (p = 0.97)	25.8 ± 5.1	24.0 ± 3.0 (p = 0.01)*	28.6 ± 7.2	23.3 ± 8.0 (p = 0.01)*	30.0 ± 3.5
rMSSD	51.4 ± 8.1 (p = 0.01)*	59.6 ± 6.1	57.4 ± 6.7 (p = 0.02)*	62.5 ± 3.5	55.5 ± 8.9* (p = 0.03)	68.2 ± 3.6
SDNN	141.7 ± 14.7 (p = 0.11)	155.0 ± 16.2	139.3 ± 16.1* (p = 0.02)	160.1 ± 12.8	144.6 ± 19.2* (p = 0.01)	170.8 ± 16.2

Note: * — differences from the corresponding indicators of children in the control group at $p < 0.05$.

Table 5 – Dynamics of life quality indicators in children, adolescents and young adults with post-COVID syndrome during treatment

Indicator	Main group		Comparison group		Control group
	Before treatment	After	Before treatment	After	
Physical functioning	87.5 ± 5.7* (p = 0.00)	97.8 ± 2.5# (p = 0.00)	88.8 ± 5.3* (p = 0.00)	92.8 ± 4.6# (p = 0.01)** / (p = 0.003)	99.4 ± 1.0
Emotional functioning	65.33 ± 17.9* (p = 0.00)	95.5 ± 4.2# (p = 0.00)	67.4 ± 6.3* (p = 0.00)	91.5 ± 6.9# (p = 0.00) / (p = 0.33)	98.8 ± 1.4
Social functioning	89.8 ± 8.3* (p = 0.00)	96.7 ± .5# (p = 0.00)	88.9 ± 9.2* (p = 0.00)	92.0 ± 6.5 (p = 0.48) / (p = 0.07)	98.4 ± 1.8
School functioning	69.3 ± 6.5* (p = 0.00)	84.6 ± 7.6# (p = 0.00)	71.1 ± 4.5* (p = 0.00)	84.3 ± 6.3# (p = 0.00) / (p = 0.52)	98.3 ± 1.9

Note: * — differences from the corresponding indicators of children in the control group at $p < 0.05$; # — differences from the corresponding indicators of children in the main group and the comparison group before and after treatment at $p < 0.05$; ** — differences from the corresponding indicators of children in the main group and the comparison group after treatment at $p < 0.05$.

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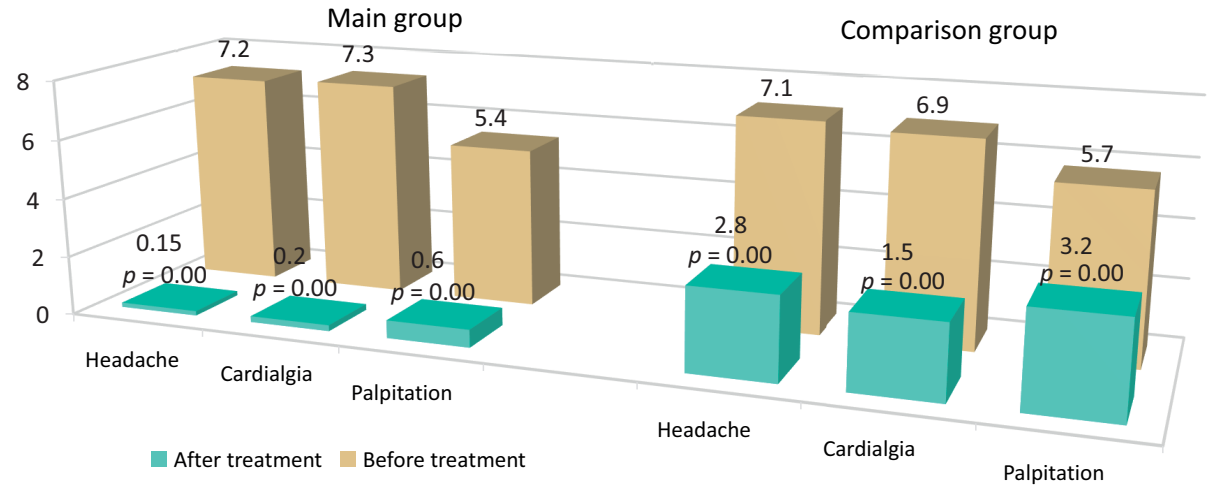

Figure 1 – Dynamics of the severity of headaches, cardialgia, palpitations during treatment in children of the main group.

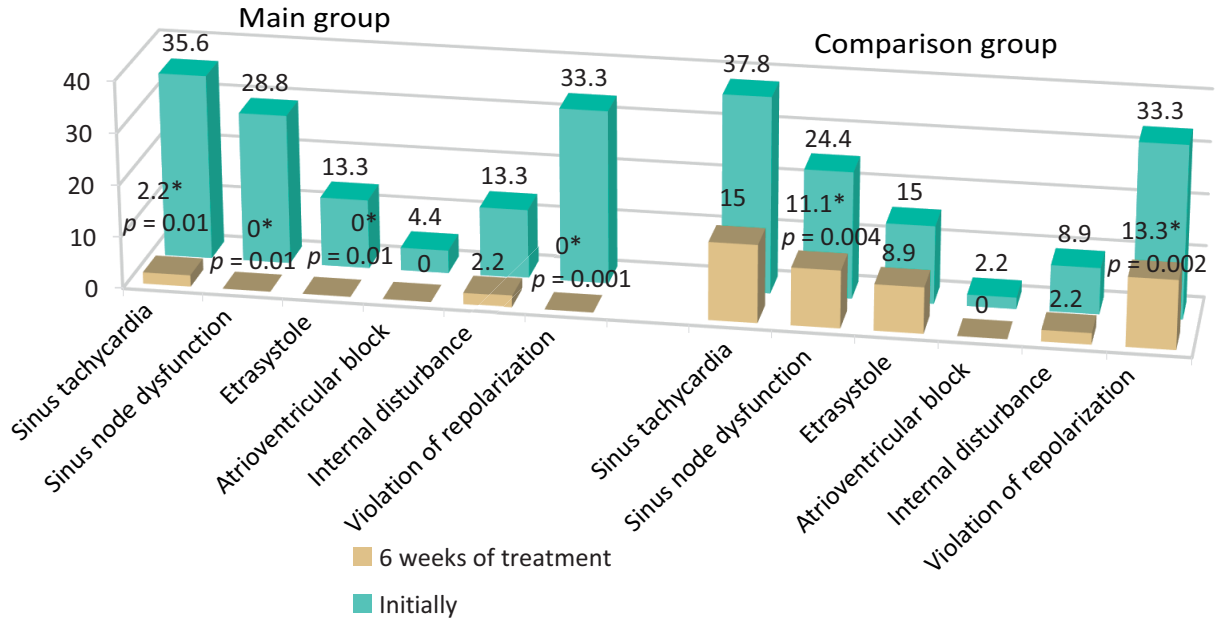

Figure 2 – Dynamics of ECG disorders in children, adolescents and young adults in the main group and the comparison group during treatment.

Note: * — differences from the corresponding indicators of children in the comparison group at $p < 0.05$.

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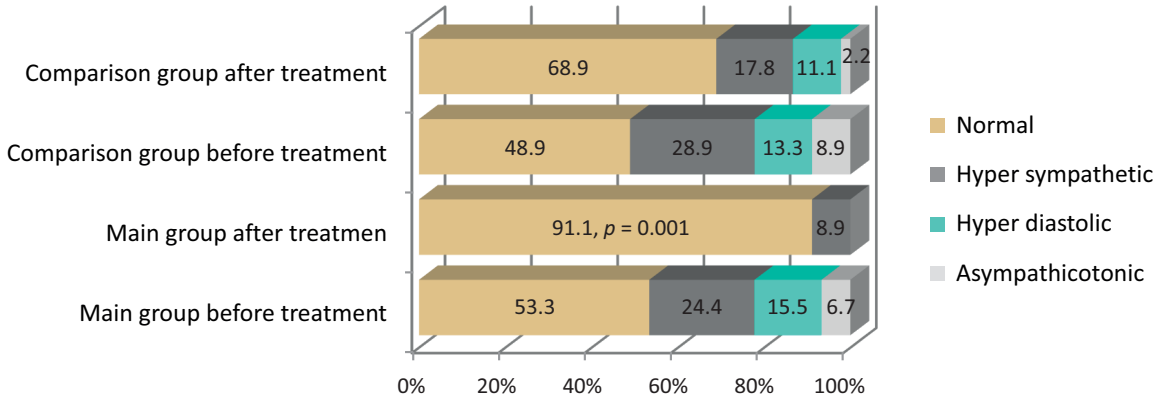

Figure 3 – Representation of types of reaction to the orthostatic test in individuals of the main group and the comparison group during therapy.

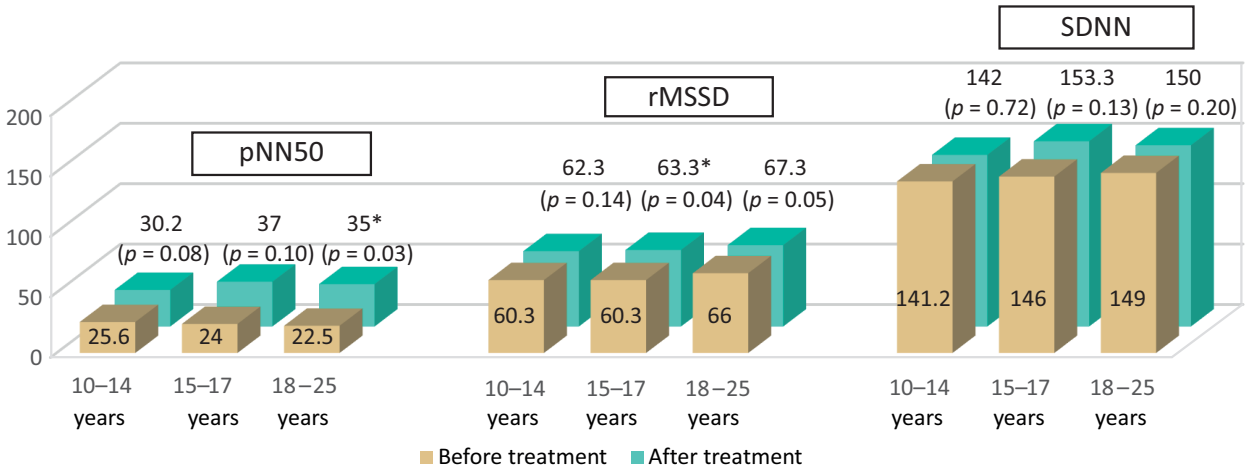

Figure 4 – Indicators of temporal analysis of heart rate variability in dynamics in patients of the main group.

Holter ECG monitoring with assessment of heart rate variability

The initial HR values (during the day and at night) during HM ECG in the main group and the comparison group did not differ significantly and tended to bradycardia (in comparison with children and adolescents in the control group), more pronounced in patients 10–14 years old — 72.7 ± 9.9 vs 79.5 ± 7.5 per min. Patients with PCS registered single extrasystole (atrial in 13.3%, ventricular — in 2.2%) with a frequency of 1385.6 ± 97.3 and 1513.8 ± 102.3 per day for patients in the main group and the comparison group (which in most patients was monomorphic and only in 2 — polymorphic in nature and in 1 adolescent episodes of allorhythmia of the trigeminy type were detected). In 32–36 patients in each group (71.1–77.8%), signs of sinus node dysfunction were detected (episodes of migration of the rhythm driver, sinoatrial blockade, supraventricular replacement rhythm), and clinically significant rhythm pauses (1432–1692 ms) were recorded in 3 (6.7%) patients with PCS (Table 3).

The inclusion of L-carnitine in addition to standard therapy led to the restoration of HR, a reduction in the frequency of registration of bradyarrhythmias and a decrease in the "density" of extrasystole ($p = 0.01$). The representation of ectopic complexes and the number of episodes of non-sinus rhythm in the comparison group changed insignificantly.

The average daily value of the QTc interval according to HM was initially higher in children, adolescents and young adults who had a new coronavirus infection — 429.1 ± 11.6 ms vs healthy peers — 399.3 ± 18.8 ($p = 0.01$). Non-specific repolarization disorders were leveled out by 6 weeks in both study groups. One 10-year-old child who underwent MIS-C with myocarditis and coronary arteritis had flattening of the T wave and ST depression up to 150 μV according to HM ECG, which were leveled out after a course of complex therapy with the additional use of L-carnitine.

Indicators of temporal analysis of heart rate variability (HRV) according to HM in all age categories

were initially reduced in 26 (57.8%) patients in the main group and 27 (60%) individuals in the comparison group (Table 4), and the average SDNN values regardless the age were lower in patients with PCS compared to healthy peers. By 6 weeks of treatment, the average group values of pNN50, rMSSD, SDNN significantly increased in all children, adolescents and young adults in the main group, approaching the indicators of healthy peers. A similar dynamic was observed in the comparison group, but the differences did not reach statistical significance. By the end of the observation, the main indicators of temporal analysis of HRV corresponded to reference values in 39 (86.7%) and only in 14 (31.1%) patients in the main group and the comparison group, respectively (p = 0.00) (Fig. 4).

Quality of Life Assessment (PedsQL™)

Cardiac disorders in patients with PCS were associated with psychological problems and a decrease in quality of life according to the PedsQL™ questionnaire. At the same time, emotional and social functioning was more reduced in adolescents aged 15–17 years, and physical and school functioning — in children aged 10–14 years. When assessing physical functioning, we identified statistically significant differences depending on the presence of rhythm and conduction disturbances (p = 0.013). As follows from the data presented in Table 5, there was a statistically significant increase in quality of life indicators in all areas (physical, emotional, social, school functioning) in patients of the main group, while in the comparison group, the indicator of emotional and school functioning significantly improved.

In general, after 6 weeks of treatment, the therapy with the additional use of L-carnitine led to the absence of complaints, normalization of objective status, laboratory and instrumental data in 42 (93.3%) patients of the main group, and in the comparison group, similar results were obtained in 66.7% ($p < 0.05$).

Adverse events

No adverse events requiring drug withdrawal, significant deterioration of clinical, instrumental and biochemical parameters (ALT, AST, urea, creatinine, glucose) during drug administration were registered.

DISCUSSION

Despite the lower rates of morbidity, severity and mortality, health problems after a new coronavirus infection could not but affect the population of children and adolescents. According to the literature, the prevalence of long COVID (including ongoing symptomatic COVID) and PCS varies from 1.6 to 78% (depending on age and diagnostic criteria) [22]. The prevalence of PCS in our study was 14.1% among minors and 28.9% among individuals aged 18–25 years, which corresponds to the age trends in the formation of PCS, but is generally somewhat lower than according to Russian studies [23, 24], but, at the same time, higher than according to the results of the meta-analysis by Wulf Hanson et al., which established that 3 months after a new coronavirus infection, 2.8% of the subjects under 20 years of age had at least 1 symptom of PCS [3].

The likelihood of developing PCS practically does not correlate with the severity of acute COVID-19, but is higher in seropositive patients [5, 25]. Our study included only patients with laboratory-confirmed new coronavirus infection, but only 23.3% of them had a moderate course of the disease in the acute period, the rest had a mild or asymptomatic course. Although, it should be noted that 13 patients out of 45 patients included in the study with a diagnosis of U09.9 — Condition after COVID-19, had a history of MIS-C associated with a new coronavirus infection [26].

According to the literature, it is the lesion of the CVS, along with the involvement of the gastrointestinal tract, that is the leading organ manifestation of MIS-C and often determines the life prognosis [27]. At the same time, repolarization disorders on the ECG, arrhythmias and conduction blocks, increased activity of cardio-specific enzymes, myocardial dysfunction, pericardial effusion and dilatation of the coronary arteries, which are determined in 67–90% of children with MIS-C, can persist for more than 12 weeks from the moment of infection manifestation [28] and “result” in the development of independent nosological forms — myocarditis, pericarditis, arterial hypertension, coronary artery aneurysms.

Adult patients after a coronavirus infection have a 1.6 times higher risk of developing a new cardiovascular disease, including rhythm disorders, non-ischemic / ischemic cardiomyopathy, cerebrovascular and thrombotic diseases [29]. Similar information for the pediatric population was first presented in a recent review by Zhang et al. [30], who demonstrated that after a new coronavirus infection in children and adolescents, there is an increased risk of developing arterial hypertension, rhythm disorders, myocarditis, heart failure, cardiomyopathy and thromboembolic disorders. Moreover, patients aged

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5–20 years demonstrated a higher risk of developing cardiovascular disorders (especially arrhythmias) compared with children under 5 years of age. In our study, the presence of certain cardiovascular diseases was an exclusion criterion, but the frequency of cardiac manifestations of PCS (chest pain, palpitations, syncope) was 1.71%, which fully corresponded to the data of the review [30].

CVS damage in long-term COVID in children, in contrast to MIS-C, is described in a small number of studies, according to which cardiovascular consequences occurred in 8.7–14.5 patients [31–33]. The most common symptoms were increased or decreased blood pressure and postural tachycardia syndrome. According to our data, arterial hypo- and hypertension at rest and abnormal reactions to orthostasis were detected in 3–16 patients (6.7–24.4%). Among electrophysiological abnormalities, sinus tachy- and bradycardia, repolarization disorders are most often described [34]. The work of Delogu et al. also presents data on a slight prolongation of QTc (within the normal range) in the long-term COVID group, as well as a change in heart rate variability with a predominance of parasympathetic activity [34].

However, in general, the examined children, adolescents and young adults with PCS, were dominated by complaints of an asthenic nature, which is fully consistent with the known literature data, about the most frequent detection in children and adolescents with long-term COVID-19 of increased fatigue (up to 87%) and headache (up to 80%) [32, 35]. Although severe headache may be due to a decrease or increase in blood pressure, and increased fatigue and decreased tolerance to physical activity, in part, is mediated by myocardial dysfunction and the development of rhythm disorders. This is confirmed by the presence of a direct moderate correlation between symptoms from the CVS and a decrease in quality of life: in particular, the number of extrasystoles and impaired physical functioning (r = 0.469).

Given the complex nature of pathogenesis, the treatment of PCS is currently only being developed [36]. In adult patients, tranquilizers of the benzodiazepine group, antidepressants (tricyclic and serotonin reuptake inhibitors), nootropics, vitamins (especially groups B, C and D), antioxidants, and energy-tropic drugs are used. In children, the protective effect of aminoacetic acid (glycine) and its combinations with glutamic acid and L-cysteine (eltacin) has been shown [37].

L-carnitine has demonstrated its effectiveness in the acute period of COVID-19, providing antioxidant, immunomodulatory, suppressing TNF-α, IL-6, and IL-1, as well as cardioprotective effects [38]. In a study by Scaturro et al., it was found that the combination of physical exercises with L-acetylcarnitine therapy in patients with PCS can significantly improve the quality of life and eliminate the manifestations of depression [39]. We have previously shown the ability of L-carnitine to correct psychological disorders that are part of the clinical spectrum of PCS manifestations [40].

Study limitations

The limitations of this study include the lack of a preliminary calculation of the sample size, due to the limited number of children who have had laboratory-confirmed COVID-19. In addition, a possible limitation of this work is the lack of comparative analysis in groups (depending on age), which is an independent task and the subject of another publication.

CONCLUSION

The effectiveness of L-carnitine in correcting the frequency and severity of the main manifestations of PCS — vegetative, cardiovascular, psychoneurological disorders and asthenic disorders in children, adolescents and young adults has been demonstrated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Larisa A. Balykova, Marina V. Shirmankina, Anna V. Krasnopolskaya — data collection and processing, writing of the text; Stanislav A. Ivyansky, Anna A. Stradina, Tatyana M. Duvayarova, Daniil S. Rodionov — data collection and processing, editing of the text of the article. All the authors confirm that their authorship meets the ICMJE international criteria (all the authors have made substantial contributions to the conceptualisation, research and preparation of the article, and have read and approved of the final version before the publication).

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AUTHORS

Larisa A. Balykova – Doctor of Sciences (Medicine), Professor, Vice-Rector for Innovation in the field of Biotechnology and Medicine, National Research Ogarev Mordovia State University; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0002-2290-0013. E-mail: larisabalykova@yandex.ru

Marina V. Shirmankina – Assistant Lecturer of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-9049-5662. E-mail: shirmankina99@mail.ru

Anna V. Krasnopolskaya – Candidate of Sciences (Medicine), Assistant Professor of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 000-0003-3990-9353. E-mail: abalykova@mail.ru

Stanislav A. Ivyansky – Candidate of Sciences (Medicine), Assistant Professor of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0000-0003-0087-4421. E-mail: stivdoctor@yandex.ru

Anna A. Stradina – Pediatrician of Children's Polyclinic No. 4 (Saransk, Russia). ORCID ID: 0000-0003-1208-9949. E-mail: gofj@mail.ru

Tatyana M. Duvayarova – Assistant Lecturer of the Department of Pediatrics with a course in Dietetics of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0009-0008-0564-9534. E-mail: zolnickova.tatjana@yandex.ru

Daniil S. Rodionov – 6th-year student of Medical Institute, National Research Ogarev Mordovia State University. ORCID ID: 0009-0009-6773-0124. E-mail: Daniil.serg.rod@gmail.com

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The use of sonidegib in the treatment of patients with locally advanced basal cell carcinoma of the skin: an analysis of the impact on the Russian healthcare budget

M.Yu. Frolov[1], V.A. Rogov[1], O.I. Ivakhnenko[1], V.V. Ryazhenov[2]

[1] Volgograd State Medical University,
1 Pavshikh Bortsov Sq., Volgograd, Russia, 400066
[2] Sechenov First Moscow State Medical University (Sechenov University),
2 Trubetskaya Str., Bldg 8, Moscow, Russia, 119991

E-mail: clinpharmrussia@yandex.ru

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Budget Impact Analysis (BIA) is a key step in justifying the inclusion of new medicines in the list of vital and essential medicines (VED). It allows you to predict the financial consequences of the introduction of therapy and evaluate the effectiveness of resource allocation, which is of particular importance when using innovative antitumor drugs.

The aim. Implementation of the BIA of Healthcare of the Russian Federation of the use of sonidegib to assess the feasibility of inclusion in the list of VEDs for the treatment of patients with locally advanced basal cell carcinoma (laBCCs).

Materials and methods. In the pharmacoeconomic model developed for use in the Russian Federation, the BIA was conducted for healthcare in the Russian Federation based on comparative modeling of two scenarios: basic (all patients receive vismodegib) and alternative (phased introduction of sonidegib with an increase in the share to 50% by the third year). The time horizon is 3 years. Direct medical costs, price data from VED registers, government procurement, regulatory allowances, demographic and epidemiological parameters are taken into account. Additionally, a one-way sensitivity analysis was performed in the range of ±10% of key variables

Results. An analysis of the impact on the healthcare budget of the Russian Federation showed that the inclusion of sonidegib in the list of VED will lead to a 3.15% reduction in budget costs for the treatment of patients with laBCCs (-37,270,334 rubles or -387,440.81 USD) within the modeled patient population. The presented BIA results remain stable with changes in the price of comparison drugs, the total population size and the distribution of patient flow over the years, with a deviation from the baseline value of ±10%.

Conclusion. Modeling shows that the inclusion of the drug sonidegib in the list of VED leads to a reduction in the costs of the healthcare system with a possible increase in the tolerability of therapy and an expansion of the therapeutic arsenal for the treatment of laBCCs, i.e. it is justified from the point of view of clinical and economic consequences. The results obtained confirm its pharmacoeconomic validity as an alternative to vismodegib in the treatment of laBCCs.

Keywords: basal cell carcinoma of the skin; sonidegib; budget impact analysis; vital and essential medicines; targeted

Abbreviations: BCC — basal cell carcinoma; MNs — malignant neoplasms; BIA — budget impact analysis; VED — vital and essential medicines; laBCCs — locally advanced basal cell carcinoma; SmPC — summary of product characteristics; VEN List — List of Vital and Essential Medicines; MSP — manufacturer's selling price.

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Применение препарата сонидегиб при лечении пациентов с местно распространённым базальноклеточным раком кожи: анализ влияния на бюджет здравоохранения России

М.Ю. Фролов[1], В.А. Рогов[1], О.И. Ивахненко[2], В.В. Ряженов[2]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Волгоградский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, Россия, 400066, г. Волгоград, пл. Павших Борцов, д. 1

[2] Федеральное государственное автономное образовательное учреждение высшего образования «Первый Московский государственный медицинский университет имени И.М. Сеченова» Министерства здравоохранения Российской Федерации (Сеченовский университет), Россия, 119048, г. Москва, ул. Трубецкая, д. 8, стр. 2

E-mail: clinpharmrussia@yandex.ru

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Анализ влияния на бюджет (АВБ) является ключевым этапом обоснования включения новых лекарственных препаратов в перечень жизненно необходимых и важнейших лекарственных препаратов (ЖНВЛП). Он позволяет прогнозировать финансовые последствия внедрения терапии и оценивать эффективность распределения ресурсов, что имеет особое значение при применении инновационных противоопухолевых средств.

Цель. Проведение АВБ здравоохранения РФ применения сонидегиба для оценки целесообразности включения в перечень ЖНВЛП для терапии пациентов с местно распространённым базальноклеточным раком кожи (мрБКРК).

Материалы и методы. В разработанной для применения в условиях РФ фармакоэкономической модели проведён АВБ для здравоохранения РФ на основе сравнительного моделирования двух сценариев: базового (все пациенты получают висмодегиб) и альтернативного (поэтапное внедрение сонидегиба с ростом доли до 50% к третьему году). Временной горизонт — 3 года. Учтены прямые медицинские затраты, данные о ценах из реестров ЖНВЛП, государственные закупки, нормативные надбавки, демографические и эпидемиологические параметры. Дополнительно выполнен односторонний анализ чувствительности в диапазоне ±10% ключевых переменных

Результаты. АВБ здравоохранения РФ показал, что включение сонидегиба в перечень ЖНВЛП приведёт к снижению бюджетных затрат на лечение пациентов с мрБКРК на 3,15% (-37 270 334 руб. или -387 440,81 USD) в рамках моделируемой совокупности пациентов. Представленные результаты АВБ сохраняют устойчивость при изменении цены препаратов сравнения, размеров популяции в сумме и распределения пациентопотока по годам, при отклонении от базового значения ±10%.

Заключение. Моделирование показывает, что включение лекарственного препарата сонидегиб в перечень ЖНВЛП приводит к снижению затрат системы здравоохранения при возможном повышении переносимости терапии и расширении терапевтического арсенала для лечения мрБКРК, т.е. является обоснованным с точки зрения клинико-экономических последствий. Полученные результаты подтверждают его фармакоэкономическую обоснованность в качестве альтернативы висмодегибу в терапии мрБКРК.

Ключевые слова: базальноклеточный рак кожи; сонидегиб; анализ влияния на бюджет; ЖНВЛП; таргетная терапия

Список сокращений: БКРК — базальноклеточный рак кожи; ЗНО — злокачественные новообразования; ЛП — лекарственный препарат; АВБ — анализ влияния на бюджет; ЖНВЛП — жизненно необходимые и важнейшие лекарственные препараты; мрБКРК — местно распространенный базальноклеточный рак кожи; ОХЛП — общая характеристика лекарственного препарата; ГР ЖНВЛП — Государственный реестр жизненно необходимых и важнейших лекарственных препаратов; ОЦП — отпускная цена производителя.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer. According to expert estimates, it accounts for up to 80% of all non-melanoma malignant neoplasms (MNs) of the skin [1–4]. In the Russian Federation, BCC also has a leading position among skin MNs[1] [4], considering it as part of non-melanoma skin tumors. According to the National Cancer Registry, the incidence of BCC in the country has been steadily increasing over the past decades, which is associated

[1] Clinical Guidelines Basal cell carcinoma of the skin. Available from: https://cr.minzdrav.gov.ru/view-cr/467_3. (accessed July 20, 2025). Russian

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with both improved diagnostics and an increase in life expectancy: the total incidence of skin cancer in the Russian Federation is more than 50 cases per 100 thousand population, with BCC accounting for up to 70–80% of them[2]. According to 2022 data, the total number of new cases of non-melanoma skin cancer in Russia amounted to 79,399, while the standardized incidence rate was 26.49 per 100,000 population[3]. In the vast majority of patients, the disease is diagnosed at localized stages, when radical treatment is effective. However, a certain proportion of patients develop a locally advanced process that is not amenable to surgical or radiation treatment, which necessitates the use of systemic therapy [2, 4]. The proportion of patients with unresectable and recurrent forms of BCC, potential candidates for systemic therapy, is estimated by experts to reach 1–2% of the total population of patients [5].

Despite the relatively low potential of BCC for metastasis, some patients develop a locally advanced, recurrent, or unresectable course of the disease, which requires systemic targeted therapy [2]. Modern treatment strategies for advanced forms of BCC include the use of targeted therapy, which today represents a breakthrough in the treatment of metastatic, locally advanced, and unresectable forms of BCC [6, 8, 9]. Its mechanism is based on targeted effects on key molecular pathways involved in the development of the tumor, which makes the therapy highly effective and relatively safe. The main focus is on inhibiting the Hedgehog signaling pathway, which plays a key role in the pathogenesis of BCC. Thus, the use of medicines vismodegib and sonidegib provides an objective tumor response and control over its growth in cases where surgical or radiation treatment is impossible [6, 8, 10]. In particular, the BOLT study demonstrated the high efficacy of sonidegib in patients with unresectable disease [9], and the STEVIE study confirmed the stability of the effect of vismodegib with long-term therapy [11].

A comparative analysis of the pharmacokinetic and clinical properties of medicines indicates a number of differences that are potentially important for the healthcare system. Sonidegib has a longer half-life, which helps to reduce the frequency of visits to the doctor and potentially reduces the costs associated with monitoring treatment [9, 12]. In addition, the safety profile of sonidegib, according to the BOLT study, is characterized by a lower frequency of certain adverse events, such as alopecia and muscle cramps [13], which is also confirmed by real-world clinical practice studies in different countries [14].

Available pharmacoepidemiological data currently allow us to estimate the potential size of the target population for these medicines and to conduct economic assessments of their use. In 2025, an important publication by Orlova et al. was published, dedicated to the use of sonidegib in patients with locally advanced basal cell carcinoma (laBCC) in real clinical practice in the Russian Federation [15]. This multicenter prospective observational study makes it possible to adjust key parameters for budget impact analysis using local data reflecting current medical practice.

To assess the financial consequences of introducing sonidegib into the treatment of laBCC and the impact on the healthcare budget, a budget impact analysis (BIA) is required. This type of analysis complements the cost-effectiveness assessment and is of practical importance for healthcare authorities involved in the formation of the list of vital and essential drugs (VED) and in making decisions on financing new drugs[4, 5]. In this logic, our joint team of researchers in 2025 has already completed a study to assess the clinical and economic feasibility of using sonidegib in widespread clinical practice, which showed the clinical and economic advantages of its use in the 1-line therapy of patients with laBCC [17].

In the context of limited healthcare resources, the assessment of the budgetary consequences of introducing sonidegib into the system of preferential drug provision in the Russian Federation is of particular importance. Such an analysis allows not only to justify the medical feasibility of expanding the therapeutic arsenal for the treatment of laBCC, but also to demonstrate the economic sustainability of the solution, which is critical for its practical implementation[6].

Currently, there are no published data on the analysis of the impact on the budget of the Russian Federation of the use of sonidegib in the treatment of patients with locally advanced basal cell carcinoma of the skin, which determines the novelty of this study.

[2] Malignant neoplasms in Russia in 2023 (morbidity and mortality); Kaprin AD, Starinsky VV, Shakhzadova AO, editors. Moscow: Herzen Moscow Medical Research Institute – branch of the NMITS of Radiology; 2024. 276 p. Available from: https://oncology-association.ru/wp-content/uploads/2024/08/zis-2023-elektronnaya-versiya.pdf. Russian

[3] Ibid.

[4] Decree of the Government of the Russian Federation dated Aug 28, 2014 No. 871 (amended at July 25, 2024) "On Approval of the Rules for the Formation of Lists of medicines for medical use and the minimum range of medicines required for medical care". Russian

[5] Guidelines for assessing the impact on the budget within the framework of the implementation of the program of state guarantees of free medical care to citizens, approved by Order No. 242-od of the Russian Ministry of Health dated December 29, 2018. Russian

[6] Ibid.

The present study is based on the hypothesis that the inclusion of sonidegib in the list of VED and its use within the state healthcare system of the Russian Federation for the treatment of patients with laBCC will expand therapeutic options in the 1-line of systemic treatment due to a clinically comparable, and in some parameters more preferable in terms of tolerability profile, targeted medicines; reduce the total direct medical costs of medicine therapy for this category of patients in a limited budget, and also support the implementation of the principles of personalized medicine by choosing the most suitable drugs, taking into account the individual characteristics of the patient, the profile of adverse events, and the treatment regimen. It is assumed that the partial replacement of vismodegib with sonidegib in the treatment of laBCC, subject to regulatory pricing conditions and procurement volumes, will not have a negative impact on the healthcare budget and will increase the clinical and economic efficiency of treatment.

THE AIM. To conduct an analysis of the impact on the healthcare budget of the Russian Federation of the use of sonidegib to assess the feasibility of inclusion in the list of VED for the treatment of patients with laBCC in the Russian Federation.

MATERIALS AND METHODS

Methodology

To achieve the objectives of the study, the following tasks were set:

1. To form basic and modeled scenarios for the use of drug therapy in patients with laBCC;
2. To determine the number of the target population of patients with laBCC potentially in need of therapy with drugs inhibiting the HH pathway;
3. To estimate the direct medical costs of drug treatment of patients in each of the scenarios;
4. To conduct a sensitivity analysis to assess the stability of the results while varying the key parameters of the model.

The BIA was performed taking into account the provisions of current regulatory documents and recommendations[7, 8].

The BIA was carried out using domestic data on morbidity, the cost of drug therapy and medical services, as well as the projected volume of medicine consumption. A feature of the BIA in the Russian Federation is the mandatory reliance on official sources (State Price Registers, Statistics from the Ministry of Health and RosStat) and the analysis of budgetary consequences in the context of approved standards of drug provision, which ensures the comparability of calculations and allows them to be integrated into the process of state pricing and procurement planning[9].

Uncertainty of input parameters was taken into account by performing a one-way scenario sensitivity analysis in the range of ± 10% of key variables. The format of presentation of results (absolute amounts and relative changes, year-by-year breakdown and difference by cost items) corresponds to the current Russian methodological requirements for BIA[10] and international practice (ISPOR [18], EUnetHTA[11]).

The model was developed in Microsoft Excel 2019 pro. It simulates the costs of the healthcare system of the Russian Federation in the treatment of patients with laBCC using vismodegib (basic scenario) and sonidegib (modeled scenario with phased implementation).

The analysis period is 3 calendar years (2026–2028). The scenarios were compared from the position of the state budget, including only direct medical costs for drug treatment of patients in the 1-line of therapy.

Description of the general structure and input parameters of the model

The model includes two scenarios:

1. Basic scenario: all patients receive vismodegib;
2. Modeled scenario: sonidegib is gradually introduced into therapeutic practice, starting from 10% in 2026 and up to 50% in 2028.

The input parameters of the pharmacoeconomic model are shown in Table 1. All data are normalized per one year of therapy per patient. A cohort approach is used without differentiation by outcomes, since the compared medicines belong to the same class and are comparable in clinical efficacy.

Cost estimation

The assessment of the impact on the healthcare budget of the Russian Federation of the use of sonidegib in widespread clinical practice in the event of the inclusion of the medicine in the list of VED was carried out taking into account only direct medical

[7] Requirements for the methodological quality of clinical and economic research of a medicines and research using the analysis of the impact on budgets of the budgetary system of the Russian Federation. Appendix No. 5.1 to the Rules for the Formation of Lists of medicines for medical use and the Minimum range of medicines required for Medical Care, approved by Decree of the Government of the Russian Federation dated August 28, 2014 No. 871. Russian

[8] Guidelines for assessing the impact on the budget within the framework of the implementation of the program of state guarantees of free medical care to citizens, approved by Order No. 242-od of the Russian Ministry of Health dated December 29, 2018. Russian

[9] Ibid.

[10] Ibid.

[11] EUnetHTA. Guidelines for Budget Impact Analysis of Health Technologies in the European Union. 2015. Available from: https://health.ec.europa.eu/health-technology-assessment/behind-hta-regulation_en

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costs for drug treatment in patients in the target population. It should be noted that the experience of researchers shows that additional costs incurred by the healthcare system are associated with the introduction of medicine, monitoring the patient, correcting side effects, etc. in drug of this pharmacotherapeutic group are not only practically identical, but also extremely low in the healthcare system of the Russian Federation. The above facts determine the choice of this approach to the selection of cost categories for BIA.

The calculation of the costs of therapy with vismodegib for the interventions under consideration was carried out on the basis of information on the methods of use and dosage regimens indicated in the SmPC[12] and clinical guidelines[13, 14]. As a source of information on the volume of purchases of the comparator vismodegib, data from IQVIA on monitoring public procurement for state and municipal needs for the period 2021–2025, provided by the company free of charge, were used.

As a source of information on prices for vismodegib, information on the current maximum selling price of the manufacturer (MSP) posted in the State Register of Registered Prices (as of March 13, 2025)[15] was used. Data on the MSP of sonidegib, planned for registration for the proposed medicine for inclusion, were provided by the manufacturing company, information on the methods of use and dosage regimens corresponds to the package leaflet — information for the patient[16] on the State Register of Medicines of the Russian Federation website[17]. The duration of 1 month was taken as 30.44 days. The calculations took into account the allowances established by the legislation of the Russian Federation (VAT 10%). Thus, the main parameters for calculating the costs of conducting 1 line of therapy for laBCC in the Russian Federation are shown in Table 2.

Number of patients

Data on the number of patients in the study group were obtained by calculation. For this purpose, an analysis of IQVIA data on purchases of vismodegib for the period from 2021 to 2025 was carried out. These data are presented in Table 3.

Table 2 shows that 1 369 packages of vismodegib were sold in 2021, 1 388 packages in 2022, 1 452 packages in 2023, 1 605 packages in 2024, and 2 023 packages in 2025.

Thus, it was found out the total number of courses of vismodegib purchased for the treatment of the study group of patients. Next, the number of patients that can be treated with this amount of medicine each year was calculated. We proceeded from the fact that the drug package contains 28 capsules, and the patient needs 365 capsules per year. The calculation results are also presented in Table 2. Based on the data obtained, a trend equation was calculated (using MS Excel 2019 pro).

The graph describing the trend and the trend equation is shown in Figure 1. Based on the trend equation, the forecast values of the total sales volume of vismodegib for the forecast period were calculated. The forecast data are presented in Table 2.

Thus, from the data in Figure 1 and Table 2, it can be seen that the forecast values of the number of patients, based on the expected purchase volume for the next 3 years, are 155, 167 and 179 patients, respectively.

It should be noted that the indicated number of patients includes patients with metastatic and unresectable BCC. At the same time, during the literature search, the most convincing data on the ratio of the number of patients with locally advanced and metastatic forms are presented in the work of Orlova et al., according to the Blokhin National Medical Research Center of Oncology [15]. This medical institution is one of the largest in the Russian Federation in the field of providing oncological care, respectively, we consider it possible to transfer their data to the general population of patients. The work notes that among all cases of BCC, 94 (3.4%) cases of the forms of the disease under consideration were registered: with a locally advanced form of BCC — 78 (2.8%) patients and a metastatic form — 16 (0.6%) patients. Thus, the proportion of patients with a locally advanced form is — 82.98% (78 out of 94 patients). Based on this, the number of patients in the model in the forecast period will be:

1. In 2025 / 26, 82.98% of 155 patients will be 129 patients
2. In 2026 / 27, 82.98% of 167 patients will be 139 patients
3. In 2027 / 28, 82.98% of 155 patients will be 149 patients.

[12] General characteristics of the Erivage, 150 mg, capsules. Corresponds to the expert report dated October 19, 2022 No. 24523 (sequence 0007). Available from: https://lk.regmed.ru/Register/EAEU_SmPC. Russian

[13] Clinical Guidelines Basal cell carcinoma of the skin.

[14] General characteristics of the Erivage, 150 mg, capsules. Corresponds to the expert report dated October 19, 2022 No. 24523 (sequence 0007).

[15] Vismodegib. State Register of Registered Prices. Available from: https://grls.minzdrav.gov.ru/PriceLims.aspx

[16] Leaflet; information for the patient Odomzo, 200 mg, capsules. Corresponds to the expert report dated July 02, 2025 No. 16397 (sequence 0005). Available from: https://lk.regmed.ru/Register/EAEU_SmPC

[17] Sonidegib. State Register of Medicines of the Russian Federation. Available from: https://grls.rosminzdrav. ru/Grls_View_v2.aspx?routingGuid=e000a8be-5db8-41a8-8c06- 0c06d4f83b05

Table 1 — Input parameters of the pharmacoeconomic model

Parameter	Value	Source
Period of time	3 years (2026–2028)	Own calculations
Population	Patients with laBCC suitable for systemic therapy	Section 5
Object of analysis	Costs of targeted therapy (vismodegib, sonidegib)	SmPC, VED List dated July 29, 2025
Price sources	VED List (vismodegib), manufacturer data (sonidegib)	[16], manufacturer
Model type	Deterministic cohort Excel model	Own development

Note: SmPC — summary of product characteristics; VED — List of Vital and Essential Drugs; laBCC — locally advanced basal cell carcinoma.

Table 2 — The cost of drugs used in accounting for the costs of drug therapy of 1-line of locally advanced basal cell carcinoma of the skin in the Russian Federation

INN	form, dosage	VEN List price without VAT, rubles (USD)	Price per capsule without / with VAT, rubles (USD)	Costs per 1 month of therapy, rubles with VAT (USD)	Costs per 1 year of therapy, rubles (USD)	Difference Δ
Vismodegib	Capsules 150 mg, No. 28	198,051.61 (2058.83)*	7 073.27 / 7780.60 (73.53 / 80.88)*	236,817.11 (2461.81)*	2 841,804.88 (29 541.76)*	–
Sonidegib	Capsules 200 mg, No. 30	189,158.00 (1966.38)*	6 305.28 / 6935.80 (65.55 / 72.10)*	211,104.20 (2194.52)*	2 533,249.96 (26 334.20)*	-10.86%

Note: * — the average exchange rate of the dollar against the ruble was used in the calculations: 96.1962 rubles per 1 USD for October 2024; ** — costs per 1 administration, rubles *** — in the calculations, the duration of 1 month was taken as 30.44 days in accordance with Federal Law No. 107-FZ of 06/03/2011 "On Calculating Time". INN — international nonproprietary name; VED List — List of Vital and Essential Drugs.

Table 3 — The volume of purchases of the vismodegib according to IQVIA for the period 2021–2025

Indicator	05.20–05.21	05.21–05.22	05.22–05.23	05.23–05.24	05.24–05.25	1 forecast year (2025 / 26)	2 forecast year (2026 / 27)	3 forecast year (2027 / 28)
Number of vismodegib packages purchased during the period	1 369	1 388	1 452	1 605	2 023	2025	2177	2330
Number of annual courses	105	106	111	123	155	155	167	179

Table 4 — Structure of the flow of patients receiving 1-line therapy for locally advanced basal cell carcinoma of the skin in the Russian Federation, used in the BIA model, *n* (%)

Medicine	Basic scenario		
	1 year	2 year	3 year
Sonidegib	0 (0%)	0 (0%)	0 (0%)
Vismodegib	129 (100%)	139 (100%)	149 (100%)
	Modeled scenario		
	1 year	2 year	3 year
Sonidegib	13 (10%)	42 (30%)	75 (50%)
Vismodegib	116 (90%)	97 (70%)	75 (50%)
Total	129 (100%)	139 (100%)	150 (100%)

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Table 5 – Results of the BIA of patients receiving 1-line therapy for locally advanced basal cell carcinoma of the skin in the Russian Federation, taking into account the full cost of therapy per year, rubles (USD)

Basic scenario				
Medicine	1 year	2 year	3 year	Total
Sonidegib	0.00	0.00	0.00	0.00
Vismodegib	366 592,829.34 (3 810 886.81)*	395 010,878.13 (4 106,304.39)*	423 428,926.92 (4 401,721.969)*	1 185 032,634.39 (12 318,913.16)*
Total	366 592,829.34 (3 810,886.81)*	395 010,878.13 (4 106,304.39)*	423 428,926.92 (4 401,721.969)*	1 185 032,634.39 (12 318,913.16)*
Modeled scenario				
	1 year	2 year	3 year	Total
Sonidegib	32 932,250 (342,344.60)*	106 396,498 (1 106,036.40)*	189,993 747 (1 975,064.96)*	329 322,495 (3 423,445.99)*
Vismodegib	329 649,366 (3 426,843.95)	275 655,073 (2 865,550.54)*	213 135,366 (2 215,631.86)*	818 439,805 (8 508,026.36)*
Total	362 581,615 (3 769,188.55)	382 051,572 (3 971,586.94)*	403 129,113 (4 190,696.86)*	1 147 762,300 (11 931,472.35)*
Difference Δ	-4 011,214 (-41,698.26)*	-12 959,306 (-134,717.4463)*	-20 299,814 (-211,025.11)*	-37 270,334 (-387,440.81)*
Difference Δ,%	-1.09%	-3.28%	-4.79%	-3.15%

Note: * — the average exchange rate of the dollar against the ruble was used in the calculations: 96.1962 rubles per 1 USD for October 2024.

Table 6 – Results of the sensitivity analysis of the results of the BIA of the healthcare system of the Russian Federation of the use of the sonidegib in the treatment of patients with locally advanced basal cell carcinoma of the skin

Dynamic parameter	Value of the changed parameter,%			BIA result (savings over 3 years, rubles)	
	Baseline	-10%	10%	-10%	10%
Price of sonidegib	189.158.00 (1 966.38)*	170.242.46 (1 769.74)*	208,074.12 (2 163.02)*	-70 202,584 (-729,785.41)*	-4 338,084 (-45,096.21)*
Price of vismodegib	198 051.61 (2 058.83)*	178246.44 (1 852.95)*	217,856.77 (2 264.71)*	-611,217 (-6 353.86)*	-73 889,145 (-768,108.77)*
Number of the target population for 3 years, people.	417	375	459	-34 093,209 (-354413.26)*	-42 938,995 (-446,368.93)*
Proportion of patients switched to sonidegib in year 1,%	10.0%	9.0%	11.0%	-36 941,793 (-384,025.49)*	-37 558,569 (-390,437.14)*
Proportion of patients switched to sonidegib in year 2,%	30.0%	27.0%	33.0%	-32 007,589 (-332,732.36)*	-33 857,916 (-351,967.29)*
Proportion of patients switched to sonidegib in year 3,%	50.00%	45.0%	55.0%	-37 623,309 (-391,110.13)*	-42 249,125 (-439,197.45)*

Note: * — the average exchange rate of the dollar against the ruble was used in the calculations: 96.1962 rubles per 1 USD for October 2024.

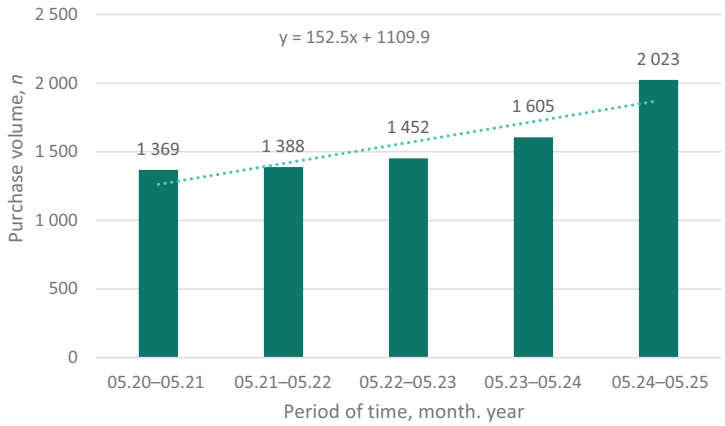

Figure 1 – Dynamics of the purchase volume of the vismodegib (150 mg No. 28) according to IQVIA for the period from 2021 to 2025 with a trend equation.

RESULTS

As part of the BIA model prepared by us, the calculation of expenses for the basic scenario, which includes vismodegib capsules 150 mg, 1 capsule 1 per day for the entire period under consideration, as part of the 1-line of therapy for laBCC, was performed.

At the same time, the modeled scenario includes the use of sonidegib in the 1-line of therapy in the mode of capsules 200 mg, 1 capsule 1 per day for the entire period under consideration.

The calculation of the costs of drug therapy with vismodegib for the interventions under consideration was carried out on the basis of information on the methods of use and dosage regimens indicated in the SmPC[18] and clinical guidelines "Basal cell carcinoma of the skin"[19].

The number and mechanism of calculation of the studied population of patients are described in the previous section "Number of patients".

Analysis of the literature data showed that the new medicine has high efficacy [6, 7] against the background of a significantly lower price per similar course of therapy compared to the competitor, which creates market prerequisites for a rapid replacement of vismodegib with sonidegib. Based on this, in Table 4 we see that in the basic scenario, all patients are on vismodegib therapy throughout the entire study period, while in the modeled scenario, starting from year 1, the proportion of sonidegib is rapidly increasing, reaching 50% by year 3, i.e. replaces half of the share of compared medicines. This distribution is an empirical assumption of the research team and is an assumption of the study.

Based on the forecast number of patients presented above in the "Number of patients" section, as well as the basic and modeled scenarios of their distribution presented in Table 4, we have the following structure of the patient flow, presented in Table 4.

Based on the available data on the structure and number of patients (see Table 4), as well as the cost of annual courses of therapy with compared medicines (see Table 2), a calculation was made of the amount of budget expenditures required for the treatment of patients in the study group under the basic and modeled scenarios. The results are presented in Table 5.

From the data in Table 5, it can be seen that the use of sonidegib in the 1-line therapy of laBCC provides savings to the healthcare budget of 3.15% (-37 270,334 rubles or -387,440.81 USD)

Sensitivity analysis of the results obtained

The stability of the results obtained was confirmed by the method of one-way sensitivity analysis. The parameters that were changed during the analysis, as well as the degree of their change, are presented in Table 6.

Thus, the presented results of the BIA remain stable even with the changes of the price of compared medicines, the size of the population in total, and the distribution of patient flow by year, with a deviation from the base value of ± 10%.

DISCUSSION

The obtained results of the BIA of the healthcare system of the Russian Federation when using sonidegib in the treatment of laBCC confirm its pharmacoeconomic validity as an alternative to vismodegib. Especially, taking into account the reduction of total budget expenditures by 3.15%, the transfer of some patients to sonidegib therapy may be a rational step in the framework of expanding therapeutic options.

The key argument in favor of sonidegib is its clinical profile. The BOLT study demonstrated that sonidegib has high efficacy in patients with unresectable BCC, achieving an objective response in more than 56% of patients with a disease control duration of up to 22 months [9]. At the same time, the tolerability profile was recognized as acceptable, with a lower frequency of pronounced side effects, including muscle cramps and alopecia [6, 12]. It is important that, assessing this clinical study [9], the respondent doctors expressed their opinion that these data were extremely significant for choosing the treatment of patients with laBCC [19].

The pharmacokinetic features of sonidegib also deserve attention. The medicine is characterized by a longer half-life (approximately 28 days) [20], which may reduce the frequency of visits to the doctor and the need for dosage adjustment compared to vismodegib [2, 7]. This may have a positive impact on patient loyalty to therapy and reduce indirect costs. Regarding the assessment of the safety of the compared medicines, information continues to be accumulated, the different spectrum of toxicity is the subject of close study and serves as the basis for choosing between them with individual patients [4, 21].

Earlier studies of the efficacy and safety of vismodegib showed stable control over the disease with long-term use, but were accompanied by a significant frequency of adverse events [9, 10, 22]. In particular, in one of the studies [6], the frequency

[18] General characteristics of the Erivage, 150 mg, capsules. Corresponds to the expert report dated October 19, 2022 No. 24523 (sequence 0007).

[19] Clinical Guidelines Basal cell carcinoma of the skin.

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of objective response to vismodegib therapy was 47.6% (95% CI: 35.5–60.6), and when patients were transferred to sonidegib due to toxicity, clinical efficacy was maintained: the frequency of objective response reached 56%, disease control — 75%, with a more favorable tolerability profile. Data from a multicenter retrospective study in China [4] clarify that adverse events during sonidegib therapy occurred in 89% of patients, but were predominantly mild and moderate in severity, no serious complications were noted, and the median duration of treatment was 28 weeks. An additional comparative analysis of adverse event profiles based on the FAERS database [23] showed that muscle spasms and dysgeusia (taste distortion) were most often recorded for both Hedgehog inhibitors, but the differences between vismodegib and sonidegib concerned lesions of the nervous system, gastrointestinal tract, skin, and urinary system. These results confirm the clinical relevance of individual drug selection and indicate the potential advantages of sonidegib in case of vismodegib intolerance. Similar results were obtained as a result of the analysis of actual data from the French national register CARADERM[20] [24].

In addition, tumor resistance to Hedgehog inhibitor therapy may be associated with mutations in the *SMO* gene, which requires a strategy of changing the drug as part of an individualized treatment selection [1, 3, 25].

It is important to note that the inclusion of new medicines in the drug provision system should be accompanied by an analysis of real clinical efficacy and cost assessment. As real-world clinical practice data on the use of sonidegib in the Russian Federation accumulate, a more accurate assessment of its impact on the overall costs of the healthcare system, as well as on the survival and quality of life of patients, will become possible. At the same time, it is important to take into account that the clinical studies underlying the registration of the medicine were conducted on a selected population and under controlled protocols [5, 7, 23], which may differ somewhat from routine clinical practice. Such studies on the use of sonidegib are being conducted in different countries [23, 26, 27], supplementing information from randomized clinical trials.

Available sources note the potential of sonidegib as a 2nd line medicine in patients forced to discontinue vismodegib therapy due to intolerance. It was previously shown [9] that among patients who discontinued vismodegib treatment due to toxicity, switching to sonidegib was accompanied by the maintenance of clinical efficacy: the frequency of objective response reached 56%, and disease control was recorded in 75% of patients with a more favorable tolerability profile.

Thus, expanding access to sonidegib may be strategically justified, given the clinical and pharmacological advantages, possible reduction of side effects, improvement of patients' quality of life, and potential reduction of indirect costs associated with hospitalizations, treatment of complications, and palliative care [7, 9, 14].

Study limitations

Like any pharmacoeconomic modeling, the study has a number of limitations that must be taken into account when interpreting the results obtained. Some of the limitations are related to the availability and completeness of data. The number of the target population was calculated on the basis of available epidemiological data and mathematical modeling, since official statistics on the proportion of patients with locally advanced and unresectable BCC in the Russian Federation are not publicly available. The study is based on data from international clinical trials (BOLT [9], STEVIE [11], etc.), since there are no large post-registration studies in the Russian Federation reflecting the clinical efficacy and safety of the medicine in real clinical practice. In such cases, differences in the population characteristics of patients and adherence to treatment are always possible, which may affect the reproducibility of the results obtained. Direct medical costs were estimated on the basis of available prices in the VEN List and data provided by the manufacturer of sonidegib. Actual purchase prices in various subjects of the Russian Federation may differ depending on contractual terms, regional allowances, and the level of competition at auctions. The analysis did not include indirect costs (indirect expenses), such as productivity losses, care and rehabilitation costs. Only direct medical costs for drug therapy were taken into account, as is customary in the framework of the BIA, carried out in accordance with the provisions of the current version of the Decree of the Government of the Russian Federation No. 871[21] for the purposes of inclusion in the list of VED.

[20] CARADERM . Available from: https:// www.caraderm.org/

[21] Decree of the Government of the Russian Federation dated August 28, 2014 No. 871 (amended at July 25, 2024) "On Approval of the Rules for the Formation of Lists of medicines for medical use and the minimum range of medicines required for medical care". Russian

CONCLUSION

Modern methods of treatment of metastatic and BCC are focused on the use of targeted therapy aimed at inhibiting the Hedgehog signaling pathway. The main medicines are vismodegib and sonidegib, which have proven their efficacy in clinical studies, providing control over tumor growth and improving survival in patients for whom traditional methods of treatment, such as surgery and radiation therapy, are not available.

Sonidegib has a number of advantages over vismodegib. First of all, it has a longer half-life, which allows less frequent dosage adjustments and potentially reduces the frequency of visits to the doctor. This may reduce the overall medical expenses associated with monitoring therapy. In addition, clinical studies show that sonidegib may be better tolerated, characterized by a lower frequency and severity of some side effects, such as alopecia and muscle cramps, which contributes to a better quality of life for patients during long-term treatment.

An analysis of the impact on the healthcare budget showed that the inclusion of sonidegib in the list of VED will lead to a reduction in budget expenditures for the treatment of patients with laBCC by 3.15% (-37 270,334 rubles or -387,440.81 USD) within the framework of the modeled population of patients. Analysis of the literature data showed that expanding therapeutic options through the introduction of sonidegib can increase the effectiveness of treatment and improve the quality of life of patients, which will lead to a reduction in indirect costs associated with complications, hospitalizations, and palliative care. The results of the study can serve as a clinical and economic justification for the inclusion of sonidegib in the list of VED, which will expand the availability of targeted therapy and improve the quality of medical care for patients with locally advanced basal cell carcinoma of the skin.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS’ CONTRIBUTION

Maksim Yu. Frolov — design development, collection and critical analysis of literature and regulatory legal documents, data collection and analysis, modeling and interpretation of results, writing, draft editing, final approval of the article; Vladimir A. Rogov — critical analysis of literature, making comments of intellectual content, draft editing; Vasily V. Ryazhenov — critical analysis of literature, making comments of intellectual content, draft editing; Oksana I. Ivakhnenko — critical analysis of literature, making comments on intellectual content, draft editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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AUTHORS

Maxim Yu. Frolov — Candidate of Sciences (Medicine), Assistant Professor of the Department of Clinical Pharmacology and Intensive Care of the Volgograd State Medical University. ORCID ID: 0000-0002-0389-560X. E-mail: clinpharmrussia@yandex.ru

Vladimir A. Rogov — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Pharmaceutical Business Organization, Pharmaceutical Technology and Biotechnology of the Volgograd State Medical University. ORCID ID: 0000-0002-2164-2323. E-mail: var85@ya.ru

Oksana I. Ivakhnenko – Assistant of the Department of Regulatory Relations in the field of circulation of medicines and medical devices of the Sechenov First Moscow State Medical University (Sechenov University); Master of Law. ORCID ID: 0000-0002-9483-3171. E-mail: oii@hta-expert.ru

Vasily V. Ryazhenov — Doctor of Sciences (Pharmacy), Head of the Department of Regulatory Relations in the Field of Circulation of Drug Products and Medical Devices of the Sechenov First Moscow State Medical University (Sechenov University). ORCID ID: 0000-0002-1278-5883. E-mail: 5052568@mail.ru

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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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

O.M. Drapkina[1], A.Yu. Gorshkov, T.I. Chudinovskikh[2], E.N. Simakina[3], G.V. Rodoman[4], V.V. Popova[5], I.V. Balaban[6], L.A. Balykova[7], N.M. Selezneva[7], N.V. Kirichenko[8], R.S. Kozlov[9], D.A. Bystritskii[10], V.B. Vasilyuk[11], K.Ya. Zaslavskaya[7], P.A. Bely[12], K.N. Koryanova[13, 14], E.S. Mishchenko[13], A.V. Taganov[14], L.A Pochaevets[15], V.S. Scherbakova[15]

[1] National Medical Research Center for Therapy and Preventive Medicine,
10 Petroverigsky Ln., Bldg 3, Moscow, Russia, 101990
[2] Kirov State Medical University,
112 Karl Marks Str., Kirov, Russia, 610027
[3] Clinical Hospital No. 1,
40 Frunze Str., Smolensk, Russia, 214006
[4] City Clinical Hospital No. 24,
10 Pistsovaya Str., Moscow, Russia, 127015
[5] OrKli Hospital,
48/27 Sredny Ave., St. Petersburg, Russia, 199178
[6] Aurora MedFort,
28 Novorossiysk Str., room 2, St. Petersburg, Russia, 194156
[7] National Research Ogarev Mordovia State University,
68 Bolshevistskaya Str., Saransk, Russia, 430005
[8] Ivanovo Clinical Hospital named after Kuvaev,
52/2 Ermak Str., Ivanovo, Russia, 153025
[9] Smolensk State Medical University,
28 Krupskaya Str., Smolensk, Russia, 214019
[10] Consultative and diagnostic polyclinic No. 121,
87 Yuzhnobutovskaya str., Moscow, 117042, Russia
[11] Eco-Safety Research Center,
65 Yuri Gagarin Ave., Zvezdnoye Municipal District, Saint Petersburg, Russia, 196143
[12] Russian University of Medicine,
4 Dolgorukovskaya Str., Moscow, Russia, 127006
[13] Pyatigorsk Medical and Pharmaceutical Institute – branch of Volgograd State Medical University,
11 Kalinin Ave., Pyatigorsk, Russia, 357532
[14] Russian Medical Academy of Continuous Professional Education,
2/1 Barrikadnaya Str., Bldg 1, Moscow, Russia, 125993
[15] Tver State Medical University,
4 Sovetskaya Str., Tver, Russia, 170100

E-mail: kiryonok@yandex.ru

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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

О.М. Драпкина[1], А.Ю. Горшков[1], Т.И. Чудиновских[2], Е.Н. Симакина[3], Г.В. Родоман[4], В.В. Попова[5], И.В. Балабан[6], Л.А. Балыкова[7], Н.М. Селезнева[7], Н.В. Кириченко[8], Р.С. Козлов[9], Д.А. Быстрицкий[10], В.Б. Василюк[11], К.Я. Заславская[7], П.А. Белый[12], К.Н. Корянова[13, 14], Е.С. Мищенко[13], А.В. Таганов[14], Л.А. Почаевец[15], В.С. Щербакова[15]

[1] Федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр терапии и профилактической медицины» Министерства здравоохранения Российской Федерации, Россия, 101990 г. Москва, Петроверигский пер., д. 10, стр. 3

[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Кировский государственный медицинский университет» Министерства здравоохранения Российской Федерации, Россия, 610027, г. Киров, ул. Карла Маркса, д. 112

[3] Областное государственное бюджетное учреждение здравоохранения «Клиническая больница № 1», Россия, 214006, г. Смоленск, ул. Фрунзе, д. 40

ОРИГИНАЛЬНАЯ СТАТЬЯ
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[4] Государственное бюджетное учреждение здравоохранения города Москвы
«Городская клиническая больница № 24» Департамента здравоохранения города Москвы,
Россия, 127015, г. Москва, ул. Писцовая, д. 10
[5] Общество с ограниченной ответственностью «Госпиталь ОрКли»,
Россия, 199178, г. Санкт-Петербург, ул. В.О. Средний проспект, д. 48/27, помещение 20 Н, литер А
[6] Общество с ограниченной ответственностью «Аврора МедФорт»,
Россия, 194156, г. Санкт-Петербург, ул. Новороссийская, д. 28
[7] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Национальный исследовательский мордовский государственный университет им. Н.П. Огарёва»,
Россия, 430005, г. Саранск, ул. Большевистская, д. 68
[8] Областное бюджетное учреждение здравоохранения
«Ивановская клиническая больница имени Куваевых»,
Россия, 153025, г. Иваново, ул. Ермака, д. 52/2
[9] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Смоленский государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 214019, г. Смоленск, ул. Крупской, д. 28
[10] Государственное бюджетное учреждение здравоохранения города Москвы
«Консультативно-диагностическая поликлиника № 121»
Департамента здравоохранения города Москвы,
Россия, 117042, г. Москва, ул. Южнобутовская, д. 87
[11] Общество с ограниченной ответственностью «Научно-исследовательский центр Эко-безопасность»,
Россия, 196143, Санкт-Петербург, проспект Юрия Гагарина, д.65
[12] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Российский университет медицины»
Министерства здравоохранения Российской Федерации,
Россия, 127006, г. Москва, ул. Долгоруковская, д. 4
[13] Пятигорский медико-фармацевтический институт – филиал федерального государственного
бюджетного образовательного учреждения высшего образования
«Волгоградский государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 357532, г. Пятигорск, пр-кт Калинина, д. 11
[14] Федеральное государственное бюджетное образовательное учреждение
дополнительного профессионального образования «Российская медицинская академия непрерывного
профессионального образования» Министерства здравоохранения Российской Федерации,
Россия, 125993, г. Москва, ул. Баррикадная, д. 2/1, стр. 1
[15] Федеральное государственное бюджетное образовательное учреждение высшего образования
«Тверской государственный медицинский университет»
Министерства здравоохранения Российской Федерации,
Россия, 170100, г. Тверь, ул. Советская, д. 4

E-mail: kiryonok@yandex.ru

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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

[1] WHO. Influenza (seasonal); dated February 28, 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

[2] Popova AY. On the epidemiological situation of influenza and acute respiratory viral infections and measures to ensure the preparedness of the subjects of the Russian Federation for the upcoming epidemic season. Proceedings of the All-Russian Interdepartmental Conference on the prevention of respiratory diseases during the rise in the incidence of influenza and ARVI in the 2016-2017. Available from: https://rospotrebnadzor. ru/upload/iblock/af4/prezentatsiya_-popova-a.yu.-14.11.2016.pdf. Russian

[3] Smorodintsev AA. Research Institute of Influenza. Up-to-date information about influenza and other acute respiratory viral infections, information about medications. Available from: https://survey.influenza.spb.ru/shablon_stranici/. Russian

4 Acute respiratory infections. Available from: https://gb-1.ru/zozh/ostryerespiratornye-virusnye-infekcii/. Russian

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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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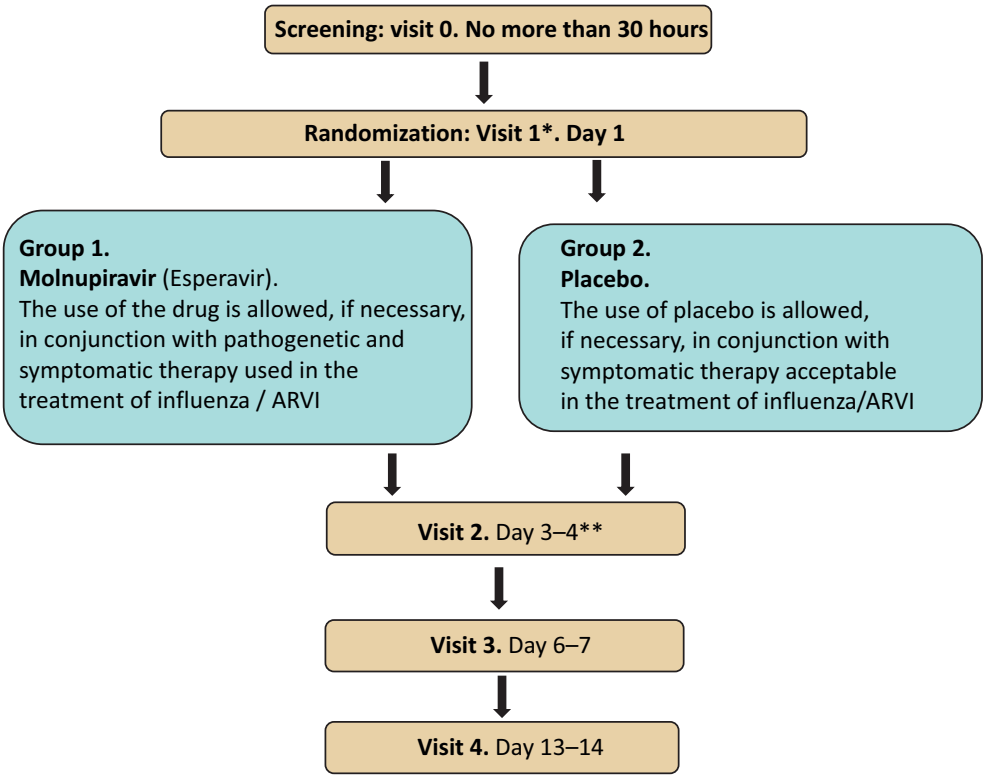

Figure 1 – Graphical scheme of the study design.

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.

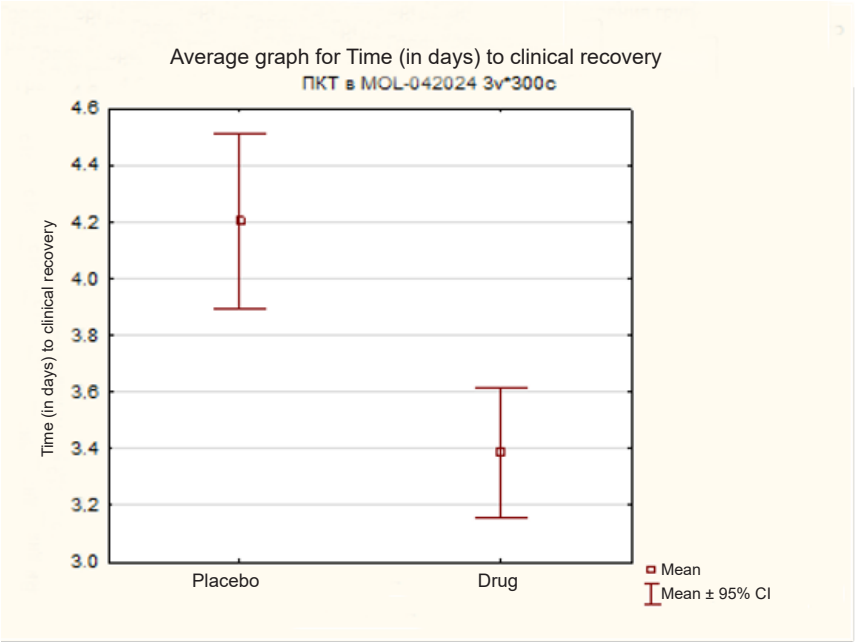

Figure 2 – Graph of average values and 95% confidence interval of time (in days) to clinical recovery.

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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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AUTHORS

Oksana M. Drapkina — Doctor of Sciences (Medicine), Professor, Director of the National Medical Research Center for Therapy and Preventive Medicine, Chief freelance specialist in Therapy and General Medical Practice of the Ministry of Health of the Russian Federation; Honored Doctor of the Russian Federation; Academician of the Russian Academy of Sciences. ORCID ID: 0000-0002-4453-8430. E-mail: ODrapkina@gnicpm.ru

Aleksander Yu. Gorshkov — Candidate of Sciences (Medicine), Deputy Director for Scientific and Outpatient Work of the National Medical Research Center for Therapy and Preventive Medicine. ORCID ID: 0000-0002-1423-214X. E-mail: AGorshkov@gnicpm.ru

Tatyana I. Chudinovskikh — Candidate of Sciences (Medicine), Assistant Professor of the Department of Hospital Therapy of the Kirov State Medical University. ORCID: 0000-0002-7515-2215. E-mail: tanuha_07@mail.ru

Elena N. Simakina — infectious disease doctor, Head of the Infectious Diseases Department of Clinical Hospital No. 1, Smolensk, Russia. ORCID ID: 0000-0002-5709-8913. E-mail: e.simakina@mail.ru

Grigory V. Rodoman — Doctor of Sciences (Medicine), Chief Physician of Municipal Clinical Hospital No. 24, Moscow, Russia. ORCID ID: 0000-0001-6692-1425. E-mail: generalsurgery24@mail.ru

Varvara V. Popova — Candidate of Medical Sciences, Head of the Clinical Research Department; OrKli Hospital LLC, St. Petersburg, Russia. ORCID ID: 0000-0001-6524-1575. E-mail: varvara-pa@mail.ru

Igor V. Balaban — psychiatrist, narcologist, Chief Specialist, Aurora MedFort LLC, St. Petersburg, Russia. E-mail: igorbalaban.81@mail.ru

Larisa A. Balykova — Doctor of Sciences (Medicine), Professor, Vice Rector for Innovation in Biotechnology and Medicine of the National Research Ogarev Mordovia State University; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0002-2290-0013. E-mail: larisabalykova@yandex.ru

Natalia M. Selezneva — Candidate of Sciences (Medicine), Assistnt Professor of the Department of Hospital Therapy of the National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-3004-2063. E-mail: nata_rm@mail.ru

Natalia V. Kirichenko — Deputy Chief Medical Officer, Ivanovo Clinical Hospital, Ivanovo, Russia. E-mail: doctor-kirichenko@mail.ru

Roman S. Kozlov — Doctor of Sciences (Medicine), Professor, Rector of the Smolensk State Medical University; Corresponding Member of the Russian Academy of Sciences. ORCID ID: 0000-0001-8728-1113. E-mail: roman.kozlov@antibiotic.ru

Dmitrii A. Bystritskii — specialist of the organizational and methodological Department of the Moscow Department of Health for Infectious Diseases, infectious disease specialist, methodologist, Head of the Department for paid medical services, Consultative and diagnostic polyclinic No. 121, Moscow, Russia. ORCID ID: 0000-0001-9253-9684. E-mail: bistritskiyda@ikb1.ru

Vasiliy B. Vasilyuk — Doctor of Sciences (Medicine), Managing Director of Eco-Safety Research Center LLC. ORCID ID: 0000-0003-2503-4402. E-mail: vasilyuk_vb@ecosafety.ru

Kira Ya. Zaslavskaya — Assistant of the Department of Biological and Pharmaceutical Chemistry with the course of organization and management of pharmacy of the National Research Ogarev Mordovia State University. ORCID ID: 0000-0002-7348-9412. E-mail: kiryonok@yandex.ru

Petr A. Bely — Doctor of Sciences (Medicine), Senior Laboratory Assistant of Department of Internal Medicine and Gastroenterology of the Russian University of Medicine. ORCID ID: 0000-0001-5998-4874. E-mail: pbely@ncpharm.ru

ОБЗОР
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Ksenia N. Koryanova — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Pharmacy, Faculty of Postgraduate Education of the Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University; Assistant Professor of the Department of Pharmacy, General Pharmacology and Pharmaceutical Consulting of the Russian Medical Academy of Continuing Professional Education. ORCID ID: 0000-0003-1571-9301. E-mail: kskor-16@mail.ru

Ekaterina S. Mishchenko — Candidate of Sciences (Pharmacy), Assistant Professor of the Department of Toxicological and Analytical Chemistry, Pyatigorsk Medical and Pharmaceutical Institute — branch of Volgograd State Medical University. ORCID ID: 0000-0001-7778-8391. E-mail: ekaterina-mischenko1809@mail.ru

Alexey V. Taganov — Doctor of Sciences (Medicine), Professor, Professor of the Department of Infectious Diseases of Russian Medical Academy of Continuous Professional Education. ORCID ID: 0000-0001-5056-374X. E-mail: matis87177@yandex.ru

Lyudmila A Pochaevets — Assistant Professor at the Department of Pharmacology of the Tver State Medical University. ORCID: 0009-0003-4187-8768. E-mail: l.pochaevets@mail.ru

Victoria S. Scherbakova — Candidate of Sciences (Biology), Assistant Professor of the Department of Pharmacology, Tver State Medical University. ORCID: 0000-0002-7251-8744. E-mail: victoria_kaptar@mail.ru

EDITORIAL

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CORRIGENDUM: Assessment of the allergenic and immunotoxic properties of the recombinant non-immunogenic staphylokinase in preclinical and clinical trials. [Pharmacy & Pharmacology. 2025;13(1):31-44. DOI: 10.19163/2307-9266-2025-13-1-31-44]

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We hereby inform readers that
changes have been made to the final version of the article in Russian and English.

In the published article "Assessment of the allergenic and immunotoxic properties of the recombinant non-immunogenic staphylokinase in preclinical and clinical trials" the authors found an error: randomly, due to a technical error and without any malicious intent, in the "Results" section, subsection "Clinical study of the effect of recombinant non-immunogenic staphylokinase on the formation of specific antibodies and neutralizing activity of patient plasma" (p. 37, second column, 4th paragraph from the top), erroneous numerical indicators were indicated: "In the study of specific antibody titers in patients with STEMI who were administered recombinant non-immunogenic staphylokinase, it was found that **30 (30%)** patients did not have specific antibodies. In **70 (70%)** patients, specific antibodies were detected with a low titer — in the range of 1/100–1/800."

Correct version:

"In the study of specific antibody titers in patients with STEMI who were administered recombinant non-immunogenic staphylokinase, it was found that **70 (70%)** patients did not have specific antibodies. In **30 (30%)** patients, specific antibodies were detected with a low titer — in the range of 1/100–1/800."

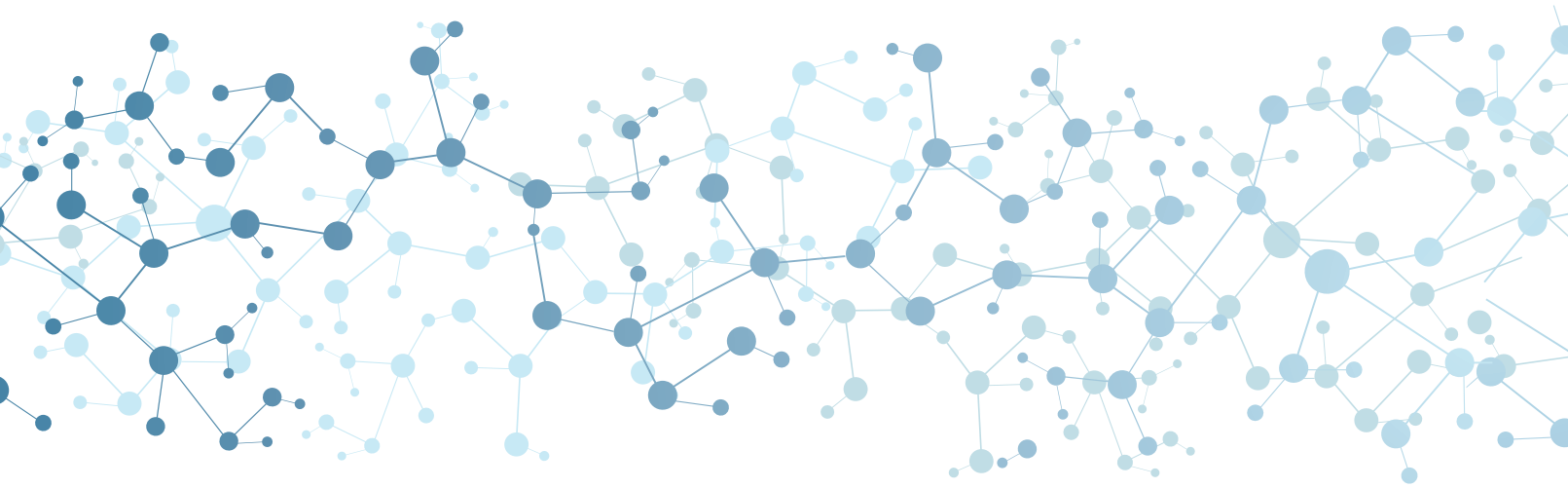
This error is technical in nature, because the abstract text displays correct data, and further in the text of the article correct data are shown: "...neutralizing activity of blood plasma of patients with STEMI who were administered recombinant non-immunogenic staphylokinase revealed that samples from 70 (70%) patients did not have neutralizing activity...".

The error does not change the essence of the data presented in the article, does not violate their perception by readers or interpretation.

The authors would like to apologize for any inconvenience.

The authors declare no conflict of interest.

The original article has been updated in the online version: https://www.pharmpharm.ru/jour/article/view/1674

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