Multicenter double-blind placebo-controlled parallel group randomized clinical study of efficacy and safety of Raphamin in the treatment of coronavirus disease 2019 in outpatient subjects

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-407-006**
Version date:	**February 09, 2022**
ClinicalTrials.gov Id:	**NCT05364671**

Protocol Summary

This document represents the protocol summary for the study on human patients. The study will be carried out in accordance with ICH GCP, Helsinki Declaration of World Medical Association, Rules of good clinical practice, approved by order of the Ministry of Health of the Russian Federation dated April 1, 2016 N 200n, , relevant requirements of the regulatory authorities as well as the study procedures.

Title of Study

Multicenter double-blind placebo-controlled parallel group randomized clinical trial of efficacy and safety of Raphamin in the treatment of coronavirus disease 2019 in outpatient subjects.

Phase: III

Sponsor: OOO «NPF "MATERIA MEDICA HOLDING», Moscow, Russia

Protocol No. MMH-407-006

Objective of the study

- To evaluate the efficacy and safety of Raphamin in the treatment of Coronavirus Disease 2019 in outpatient subjects.

Endpoints

Primary endpoint

1. Frequency of progression of COVID-19 to a more severe level by observation day 28[1].

Secondary endpoints

1. Time to sustained clinical recovery[2] from the new coronavirus infection COVID-19.
2. Proportion of patients hospitalized during 28 days of follow-up.

Additional endpoints

1. Time to COVID-19 progression to more severe level within 28-day follow-up period.

[1] **Severity of COVID-19** will be assessed in accordance with the criteria presented in the current 14th version dated 27.12.2021 Temporary Guidelines on Prevention, Diagnosis and Treatment of New Coronavirus Disease (COVID-19) (COVID-19)" of the Ministry of Health of the Russian Federation:
Mild: temperature < 38.0°C, cough, chest congestion, sore throat, nasal congestion/moderate rhinorrhea, cough, weakness, headache, muscle pain, nausea, vomiting, diarrhea, taste loss and olfaction loss, lack of laboured breathing/lack of dyspnea, SpO2≥95%, lack of criteria of moderate or severe form of the disease.
Moderate: body temperature >38.0°C; breathing rate >22/min; shortness of breath during exercise; CT (X-ray) changes, typical for viral lesions; SpO2 <95%; serum CRP >10 mg/L.
Severe: HR >30/min; SpO2 ≤93%; PaO2 /FiO2 ≤300 mm Hg; reduced consciousness; agitation; unstable hemodynamics (systolic BP < 90 mm Hg or diastolic BP < 60 mm Hg, diuresis < 20 mL/hour); lung changes on CT (X-ray), typical for viral changes; arterial blood lactate >2 mmol/L; qSOFA >2.

[2] **Stable clinical recovery** is determined as the first day of stable clinical improvement (at least 4 consecutive days, the improvement day is the first of the 4) to grade 1 or 0 (for rhinitis/nasal congestion, sore throat, weakness/fatigue, muscle pain/body ache, headache, chill, fever, nausea, diarrhea), to grade 0 (for dyspnea/laboured breathing and vomiting) to grade ≤ 2 (for cough) and lack of new symptoms grade 1 using 4-point scale ("Assessment of 14 Common COVID-19 Related Symptoms", Appendix 1); in this case, the axillary temperature should be ≤37.3^{0}C.

2. Proportions of patients with negative PCR test for SARS-CoV-2 on days 6 and 10 of observation.

Safety assessment

1. Adverse events (AEs) during the therapy, AEs severity and relation to the study drug, and AEs outcomes.
2. Changes in vital signs during the treatment.
3. Percentage of patients with clinically relevant laboratory abnormalities.

Study design

Study design: multicenter, double blind, placebo-controlled, parallel group randomized clinical trial.

The study enrolls outpatients of either gender aged 18-75 years with increased body temperature > 37.5°C and other symptoms of upper respiratory infection (cough, chest congestion, sore throat, nasal congestion/moderate rhinorrhea). The investigator should specify the patient's status of vaccination for COVID-19, influenza and other infections. Patients within the first four weeks after any vaccination/booster vaccination are not considered as candidates to participate in the study.

Nasopharyngeal swabs and rapid COVID-19 test are made after signing informed consent (two versions are used: 1) for patients consented for laboratory tests; 2) for patients without the consent). Patients with a positive rapid test and presence of mild COVID-19 (symptoms of upper respiratory infection, no symptoms of moderate or severe levels) within 24 hours after manifestation of the first symptoms of disease are considered as candidates for the study. Oxygen saturation (SpO2) is measured by pulse oximetry in all patients (pulse oximeters are provided by the study sponsor). If SpO2 is ≥95%, a patient may be selected for the study. Baseline severity of COVID-19 symptoms is evaluated using the scoring system «Assessing of 14 Common COVID-19-Related Symptoms» (FDA, 2020). This scoring system assesses the follows symptoms:

1. Stuffy or runny nose.
2. Sore throat.
3. Shortness of breath (difficulty breathing).
4. Cough.
5. Low energy or tiredness.
6. Muscle or body aches.
7. Headache.
8. Chills or shivering.
9. Feeling hot or feverish.

10. Nausea (feeling like you wanted to throw up).
11. Vomiting.
12. Diarrhea.
13. Sense of smell.
14. Sense of taste.

Each symptom is scored individually using the following scoring values:

- Items 1–10: None = 0; Mild = 1; Moderate = 2; and Severe = 3;
- Items 11 and 12: Not at all = 0; 1–2 times = 1; 3–4 times = 2; 5 or more times = 3;
- Items 13 and 14: Sense of smell/taste same as usual = 0; Sense of smell/taste less than usual = 1; No sense of smell/taste = 2.

The minimal baseline score for COVID-19-related symptoms is defined as follows: at least two symptoms with a score of 2 or higher, with the exception of taste and smell where subjects may have a score of 1 or higher, and the absence of shortness of breath (difficulty breathing).

If more severe symptoms are presented, the patient is not included in the study. The therapeutic approach is determined by the current edition of the clinical recommendations of the Ministry of Health of the Russian Federation «Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19)».

At visit 1 (Day 1), in addition to rapid COVID-19 test and SpO2 measurement, the investigator collects complaints and medical history of the patient, performs objective examination including vital signs (blood pressure, heart rate and breathing rate), records concomitant diseases and concomitant therapy, performs nasopharyngeal swabs for PCR (for detection SARS-CoV-2), laboratory tests (if the patient gave his/her consent for blood and urine sampling).

Patients who meet all the inclusion criteria and do not have exclusion criteria at Visit 1 (Day 1) are randomized into one of two groups: patients in group 1 receive Raphamin for 5 days; patients in group 2 receive placebo according to the Raphamin regimen.

If positive PCR test is received (confirmation of new coronavirus disease COVID-19), the patient continues to participate in the study. If PCR result is negative, the patient completes participation in the study ahead of schedule, and his further therapy is determined by the investigator in accordance with the standards of care.

Electronic patient diary (EPD) is utilized in the study, in which morning and evening axillary temperature records are made with the time of measurement. The sponsor provides a classical mercury-free thermometer to each patient. In addition, presence and severity of the disease symptoms according to the scoring system «Assessment of 14 Common COVID-19-Related Symptoms», antipyretics administration and probable worsening of disease duration should also be recorded in EPD. All patients are provided with paracetamol. The physician instructs the patient

how to fill in the diary. The EPD is available for filling in within 28 days of participation in the study.

Overall, patients are observed for 28 days (screening and randomization up to 1 day, treatment for 5 days, follow-up till 28th day).

During the study, six visits are planned: on days 1, 3, 6, 10, 21, and 28 (visits 1, 2, 3, 4, 5, and 6). Visits 1, 3, and 4 are in person (visits to the patient or visits to the medical center) when the physician examines the patient and monitors EPD records. At visit 3, the patient's adherence to treatment is assessed and laboratory tests are performed. Visits 2, 5 and 6 are phone surveys to determine the patient's condition, presence/absence of complaints. In case of worsening of disease duration, the physician makes an extra visit. Patients with COVID-19 progression to more severe level as well as hospitalized patients are considered as reaching the study endpoints and terminate participation in the study ahead of schedule. The therapeutic approach is determined by the current edition of the clinical recommendations of the Ministry of Health of the Russian Federation «Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19)».

During the study, the use of paracetamol and medicines for the treatment of concomitant diseases is allowed, with the exception of the drugs specified in the section «Prohibited concomitant treatment».

Inclusion and exclusion criteria

Inclusion criteria

1. Male and female patients aged 18-75 years old.
2. Diagnosis of new coronavirus infection COVID-19 based on medical examination: axillary temperature >37.5°C, symptoms of upper respiratory infection, SpO2 ≥ 95%, no symptoms of moderate or severe levels.
3. The minimal baseline score for COVID-19-related symptoms defined as follows: at least two symptoms with a score of 2 or higher, with the exception of taste and smell where subjects may have a score of 1 or higher, and the absence of shortness of breath (difficulty breathing).
4. Positive rapid test for SARS-CoV-2 (COVID-19).
5. The first 24 hours from the disease onset.
6. Patients giving their consent to use reliable contraception during the study.
7. Signed patient information sheet (informed consent form).

Exclusion criteria

1. Moderate and severe COVID-19.
2. The first four weeks after any vaccination/revaccination, including against COVID-19, influenza, pneumococcal and other infections.

3. Suspected pneumonia, bacterial infection (including otitis media, sinusitis, urinary tract infection, meningitis, sepsis, etc.).
4. Patients requiring medications prohibited within the study.
5. Medical history or previously diagnosed primary and secondary immunodeficiency.
6. Medical history/suspicion of oncology of any localization (except for benign neoplasms).
7. Exacerbation or decompensation of chronic diseases affecting the patient's ability to participate in the clinical study.
8. Malabsorption syndrome, including congenital or acquired lactase or disaccharidase deficiency, galactosemia.
9. Allergy/hypersensitivity to any of the components of the medications used in the treatment.
10. Pregnancy, breast-feeding; childbirth less than 3 months prior to the inclusion in the trial, unwillingness to use contraceptive methods during the study.
11. Use of medications listed in “Prohibited concomitant therapy” within 4 weeks before the study entry.
12. Patients who, from the investigator's point of view, will fail to comply with the observation requirements of the trial or with the intake regimen of the study drugs.
13. Medical history of mental diseases, alcoholism or drug abuse which, according to the investigator's opinion, will interfere with the study procedures.
14. Participation in other clinical trials within 3 months prior to enrollment in this study.
15. The patient is related to the study center staff directly involved in the trial or is the immediate family member of the investigator. Immediate family is defined as a spouse, parents, children or siblings, whether natural or adopted.
16. The patient works for OOO "NPF "MATERIA MEDICA HOLDING” i.e. is the company's employee, part-time employee under contract or appointed official in charge of the trial, or their immediate family.

Criteria for Withdrawal or Termination

1. Screening failure.
2. Negative PCR test for SARS-CoV-2.
3. Failure or refusal of the patient to follow the protocol.
4. Deviation from personal visit schedule by more than 1 day.
5. The necessity to use medications not permitted in the study.
6. An adverse event requiring discontinuation of the study drug.
7. Patient’s decision to withdraw early for lack of efficacy or other reasons.
8. Pregnancy.

9. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.
10. Eligibility error.
11. Participation in any other clinical study.
12. Unblinding.

Number of patients

It is planned to include 838 patients, 798 of them will be randomized which is expected to yield at least 712 patients (356 per Raphamin and Placebo groups) completing all the protocol procedures.

Interim analysis

The protocol does not schedule unblinded interim analyses. At the sponsor's decision, blinded interim analysis may be carried out to specify population parameters and potential further specification of sample size (increase only).

Treatment

Group 1

Name of the medicinal product: Raphamin

Active ingredient: affinity purified antibodies to human interferon-gamma – 10 000 UMA*,
affinity purified antibodies to CD4 – 10 000 UMA,
affinity purified antibodies to β2-microglobulin major histocompatibility complex class I – 10 000 UMA,
affinity purified antibodies to β1-domain of major histocompatibility complex class II – 10 000 UMA

* *UMA – Units of Modifying Activity.*

Excipients: lactose monohydrate, microcrystalline cellulose, magnesium stearate

Method of administration: Per os without food. The tablet should be held in mouth until completely dissolved. On the first day of treatment, take 8 tablets according to the following scheme: 1 tablet every 30 minutes for the first 2 hours (total 5 tablets in 2 hours), then during the same day take another 1 tablet 3 times at equal intervals. On the 2nd day and beyond, take 1 tablet 3 times a day. The duration of treatment is 5 days.

Dosage form: Tablet for oral use.

Description: Flat, cylinder-shaped, scored beveled edge, white to off-white tablets.

Storage conditions: At temperature below 25ºC. Keep out of the reach of children.

Group 2

Name of the medicinal product: Placebo

Active ingredient: N/A

Excipients: lactose monohydrate, microcrystalline cellulose, magnesium stearate

Method of administration: Per os without food. The tablet should be held in mouth until completely dissolved. On the first day of treatment, take 8 tablets according to the following scheme: 1 tablet every 30 minutes for the first 2 hours (total 5 tablets in 2 hours), then during the same day take another 1 tablet 3 times at equal intervals. On the 2nd day and beyond, take 1 tablet 3 times a day. The duration of treatment is 5 days.

Dosage form: Tablet for oral use.

Description: Flat, cylinder-shaped, scored beveled edge, white to off-white tablets.

Storage conditions: At temperature below 25ºC. Keep out of the reach of children.

Treatment duration

Raphamin/Placebo treatment duration is 5 days.

Observation period

Overall, the patient will be monitored for 28 days (screening, randomization - up to 1 day, treatment - 5 days, follow-up - up to 28 days).

Symptomatic (Standard) treatment

Throughout the study the patients may receive an antipyretic medication Paracetamol (provided by the sponsor) and other symptomatic medications (vasoconstrictive nasal agents, antitussive agents).

Dosage regimens

Paracetamol (at body temperature ≥ 38.0 ºC)

Orally, with plenty of liquid, 1-2 hours after eating.

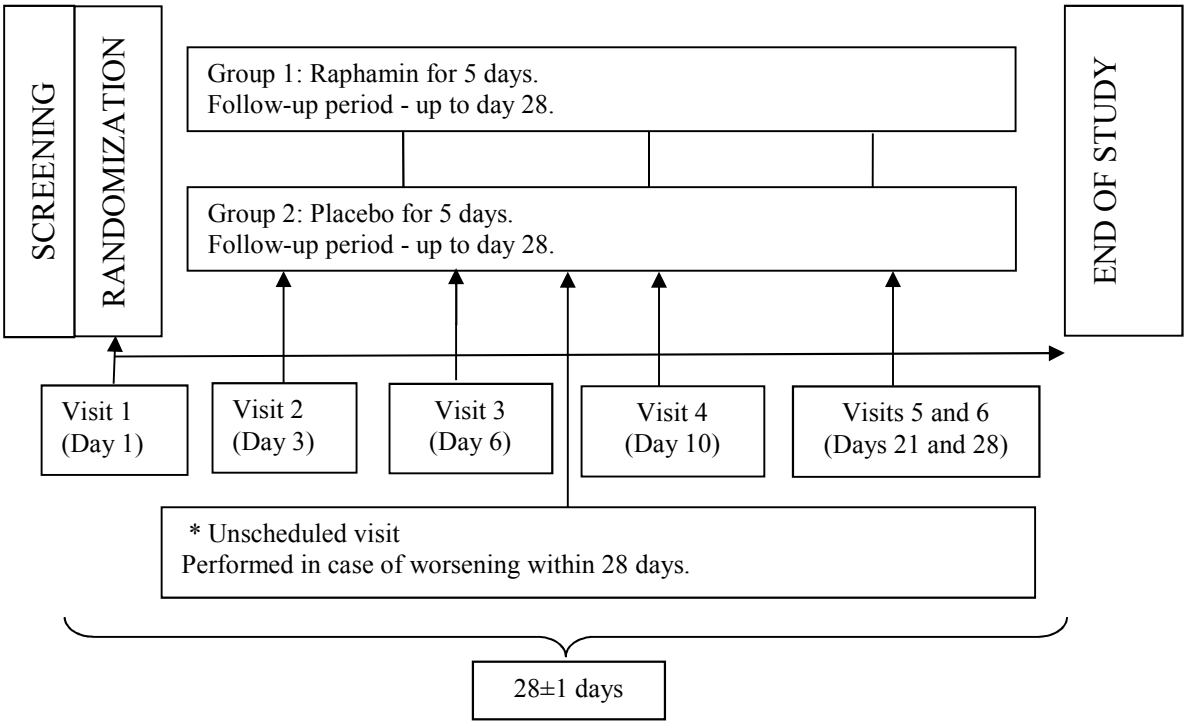
Single dose is 500 (1 tablet). The maximum single dose is 1 g (2 tablets). The maximum daily dose is 4 g (8 tablets). The interval between doses is at least 4 hours. The patient should record thermometry values in EPD before taking the antipyretic drug, its name and dose.

Prohibited concomitant therapy

Four weeks prior to the enrollment as well as during the study (from signing of the patient information sheet and initiation of screening) the following medications are not allowed (ATC index is indicated in brackets):

1. Antiviral drugs (J05), as well as remdesivir, synthetic small interfering ribonucleic acid (siRNA) [double-stranded] (MIR 19), molnupiravir, nirmatrelvir + ritonavir, recombinant monoclonal antibodies (includinh sotrovimab, regdanvimab, bamlanivimab + etesivimab; casirivimab + imdevimab).
2. Systemic antimicrobial agents (J01).
3. Immunostimulants, including:
    - interferon inducers (acridonoacetic acid, meglumine acridone acetate/cycloferon, umifenovir/arbidol, kagocel, tiloron/amixin, polyadenyl acid + polyuridylic acid/poludan, sodium oxodihydroacridinyl acetate/neovir, lavomax, tilaxin, etc.);
    - interferons including recombinant interferon-alpha;
    - bacterial immunomodulators (including ribomunyl, sodium ribonucleate/ridostin, etc., sodium deoxyribonucleate/derinat, etc., IRS-19, imudon, broncho-munal, etc.);
    - pidotimod/immunorix;
    - interleukins;
    - synthetic immunostimulants (levamisole, alpha-glutamyl-tryptophan/thymogen, etc.);
    - medications containing thymus hormones.
4. Preventive anti-inflammatory therapy of COVID-19 including baricitinib, tofacitinib, netakimab, olokizumab, levilimab, tocilizumab, sarilumab, canakinumab, anakinra, methylprednisolone, dexamethasone, hydrocortisone.
5. Homeopathic medicines for the treatment of acute respiratory tract infections.
6. Systemic (oral or parenteral) corticosteroids.
7. Immunosuppressants (L04) including anakinra.
8. Antineoplastic agents (L01) and antineoplastic hormonal agents (L02).
9. Immune sera and immunoglobulins (J06) including anti-COVID plasma, human immunoglobulin against COVID-19.
10. Vaccines (J07).
11. Any unauthorised medicinal product.
12. Drugs that previously caused hypersensitivity/ allergic reactions in patient.

Study design scheme



Schedule of study procedures

Procedure/Visit	Visit 1 (Day 1)	Visit 2* (Day 3)	Visit 3 (Day 6)	Visit 4 (Day 10)	Visit 5* (Day 21±1)	Visit 6* (Day 28±1)	Unscheduled visit**
Informed consent	+						
Registration of a study patient in the IVRS[1] and assignment of patient ID	+						
Complaints collection	+	+	+	+	+	+	+
Medical history	+						
Demographic data (gender and year of birth of the patient)	+						
Physical examination	+		+	+			+
Thermometry	+		+	+			+
Evaluation of 14 Symptoms Associated with COVID-19	+		+	+			+
SARS-CoV-2 rapid test	+						
Nasopharyngeal swabs for PCR	+		+	+			
Pulsoxymetry (SpO2)	+		+	+			+
Electronic patient diary	+	+	+	+	+	+	+
Concomitant diseases and conditions	+	+	+	+	+	+	+
Concomitant therapy	+	+	+	+	+	+	+

Procedure/Visit	Visit 1 (Day 1)	Visit 2* (Day 3)	Visit 3 (Day 6)	Visit 4 (Day 10)	Visit 5* (Day 21±1)	Visit 6* (Day 28±1)	Unscheduled visit**
Pregnancy test	+						
Inclusion/exclusion criteria	+						
Laboratory tests*** (for safety evaluation)	+		+				+****
Randomization	+						
Study drug supply	+						
Antipyretic drug and thermometer supply	+						
Study drug accountability and return			+				+****
Treatment compliance			+				+****
Safety evaluation	+	+	+	+	+	+	+
Visit completion	+	+	+	+	+	+	+
Study completion*****						+	+

[1] Interactive Voice Responsible System with Web Access
** Phone survey*
*** Unscheduled visit will be performed in case of aggravation (based on EPD), at the investigator's discretion and in case of early withdrawal (e.g. at the patient's option).*
**** Include complete blood analysis and urinalysis, serum chemistry (total protein, total bilirubin, creatinine, ALT, AST, cholesterol, C-reactive protein). Performed with availability of signed PIS and ICF including the patient's consent for blood and urine sampling.*
***** If unscheduled visit is made before visit 3.*
****** In case of early withdrawal the procedure may be carried out at Visits 1-5 or at unscheduled visit.*

Statistical Analyses

SAS-[9.4].[3] will be used for data processing and statistical calculations.

Samples

Total set: all patients who have signed ICF. This sample will consider all the recorded AEs, including those occurred prior to the study therapy.

Safety population: all included and randomized patients who received at least one dose of the study drug. This sample will be used for ***analysis of the study treatment safety and tolerability***, as all adverse events identified after the study drug administration will be recorded.

Full Analysis Set. This sample includes all enrolled patients, except for those who met at least one of the following events:

1) non-compliance with inclusion / exclusion criteria;
2) patient did not take a single dose of the study drug;
3) lack of any data about the patient after administration of the study drug.

This sample, the most consistent with the "Intention-to-treat" principle**,** will be used for the ***Intention-to-treat analysis (ITT analysis)*** of the study therapy efficacy.

[3] Holder of license: OOO "NPF "MATERIA MEDICA HOLDING", No. 70100045.

Per protocol set. This sample includes all patients who completed the therapy as per the study protocol and completed all the scheduled visits. This set will be used for the ***Per Protocol analysis (PP analysis)*** of the study therapy efficacy. *PP set* will not include the patients with their data completely or partially invalid for analysis due to a protocol deviation.

The list of deviations that may result in complete or partial invalidity of data is developed by a medical expert jointly with a biostatistician according to the study design.

The deviations that may result in partial or complete invalidation of the study subject's data.

1. Inappropriate distribution/supply of the study drug.
2. Prescription of prohibited therapy.
3. Increase or decrease in the study drug dosing by ≥ 25%.
4. Inability to assess the patient's compliance using the formula (e.g. loss of pack with the product).
5. Major discrepancies between source documents and CRF identified during monitoring or another authorized inspection.
6. Violation of the procedure of obtaining informed consent.
7. Non-compliance with the clinical study protocol procedures.
8. Inability to collect all the patient's data used for evaluation of the study endpoints[4] (e.g. lack of records in source documents required for verification of inclusion/exclusion criteria, safety and efficacy criteria).
9. Any other protocol deviations covered by the term “major deviation”.

Evaluation of sample size

It is expected that out of 798 patients randomized[5] 712 patients will complete the study per protocol. Taking into consideration the expected screening failures, the informed consent should be obtained from 838 patients.

The sample size was assessed on the basis of the following rules and assumptions:

1. Statistical provisions.
   - 1.1 the power of the statistical tests “P = (1 - β)” is assumed to be 80% (the probability of correct rejection of the null hypothesis is 0.8);
   - 1.2 the probability of a type I error “α” is allowed to be less than 5% (the probability of false acceptance of an alternative hypothesis is less than 0.05);
   - 1.3 the study **does not plan** unblinded interim analysis;

[4] If, considering the lack of some data in primary endpoint variable, the fact of reaching the primary endpoint by the patient can still be determined, the patient will be eligible for PP analysis (e.g. the diary lacks some records but the time of recovery can still be determined).

5 No more than 5% patients who signed PIS and ICF are expected to be screening failures for various reasons.

1.4 the applied statistical tests for group comparisons are two-sided, unless stated otherwise;

1.5 the sample size is calculated based on the assumptions on the expected effect declared in the primary endpoint of this protocol;

1.6 the ratio between the sample sizes of the study drug and placebo groups is 1:1 (1 study drug patient - 1 placebo patient);

1.7 statistical hypotheses: null and alternative hypotheses about the superiority of the study drug over placebo using the applied dosing regimen:

primary endpoint[6]:

$$\mathbf{H_0: OR_{12} = 1}$$

$$\mathbf{H_a: OR_{12} \neq 1}$$

where : OR12 – is odds ratio for an event occurrence in Raphamin and Placebo groups (the lower, the better).

The following SAS program code was used to determine the required sample size:

SAS code performed:

```
proc power;
twosamplefreq test=lrchi
OR=0.5
refp=0.15
power=.8
alpha=.04
npergroup=.;
run;
```

1.8 Full sample size is determined using the formula:

$$\mathbf{N = Npp / (1 - R_w)},$$

where **N** – the final sample size;

$\mathbf{N_{PP}}$ – result of calculation in cl. 1.7, i.e. scheduled number of the patients completing the study per protocol;

$\mathbf{R_w}$ – withdrawal rate.

2. Assumptions on expected effects of the clinical study: Odds ratio for the event occurrence in Raphamin and Placebo groups is expected to be no more than **0.5** at population event frequency of at least **0.15**[7] [32-34].

[6] The analysis stipulates for obligatory assessment and accounting for effects of additional factors: history of vaccination and age/age groups of the subjects.

[7] In assumption of reduced proportion of severe form in case of strain change (to Omicron) and based on the following sources:

Therefore, the number needed to compare study drug and placebo will be **712** patients for both groups. Given potential withdrawal of at least 15% [8] patients **(Rw = 0.15)** during the study for various reasons, at least **838** subjects will be required to sign informed consent allowing to randomize **798** patients with **399** subjects per group (see cl. 1.8).

Statistical criteria

All the statistical calculations will be performed using two groups of statistical criteria:

- parametric – to obtain effective evaluations for parameters of random values, if the relevant conditions of applicability of methods/models are not violated (e.g. sphericity, normality, proportionality of risks, etc.);
- non-parametric – in any other cases.

Parametric criteria

The application of parametric criteria will be accompanied by a check of models for applicability (e.g. Kolmogorov-Smirnov test, Shapiro-Wilk test, etc.).

The following parametric tests and approaches are to be used:

1. To evaluate the differences of continuous variables obtained in one group at two different visits – Student's test for matched samples.
2. To evaluate the temporal dynamics of the compared indicators – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.
3. In case of multiple comparisons between the groups will apply a variety of corrections for multiplicity (Dunnett, Tukey, Scheffe, Holm adaptive test), etc.
4. In case of abnormal data distribution, approaches with the Generalized Linear Models and / or Mixed Linear Models will be used.
5. Selection of the type of distribution, specification of the factor and covariance structures of the model will be made using fit-statistics such as AIC[9] (Akaike information criterion).

To perform the above-mentioned statistical tests and techniques, it is assumed that the following SAS procedures are used:

1) Weekly epidemiological update: Omicron variant of concern (VOC) – week 2 (data as of 13 January 2022) EU/EEA https://www.ecdc.europa.eu/en/news-events/weekly-epidemiological-update-omicron-variant-concern-voc-week-2-data-20-january-2022
2) Wolter N, Jassat W, Walaza S. et al Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet 2022; 399: 437-46. DOI: https://doi.org/10.1016/S0140-6736(22)00017-4
3) Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods - United States, December 2020-January 2022. MMWR Morb Mortal Wkly Rep 2022; 71(4):146-152. DOI: http://dx.doi.org/10.15585/mmwr.mm7104e4

[8] This coefficient was complex: 5% patients will be screening failures.
[9] Akaike information criterion (AIC).

- UNIVARIATE – check for normality of the compared distributions;
- CORR, MEANS – calculation of descriptive statistics;
- TTEST – Student t-test with all the modifications;
- GLM – analysis of General Linear Models for studying temporal dynamics (ANOVA, ANCOVA);
- GENMOD – analysis of Generalized Linear Models;
- MIXED – analysis of Mixed Linear Models.

Non-parametric criteria

Below, there are the main types of possible comparisons with the respective criteria:

1. To evaluate the temporal dynamics of the compared indicators – Friedman test, nonparametric analogue of repeated measures analysis of variance.
2. For the frequency analysis of 2×2 cross tables – χ^2-test (if the compared frequencies are greater than 5) or Fisher exact test (if one of the compared frequencies is less than 5).
3. For the frequency analysis of cross tables with independent strata – Cochran–Mantel–Haenszel test (modification of the χ^2-test for multiple comparisons).
4. For the frequency analysis of data on the presence / absence of an event or outcome during repeated measures (cross tables with dependent strata) – survival analysis.

To perform the above-mentioned non-parametric statistical analysis options, it is assumed that the following SAS procedures are used:

- FREQ – Friedman test, χ^2-test and / or Fisher exact test; Cochran–Mantel–Haenszel test
- LIFETEST, PHREG – survival analysis
- NPAR1WAY – Mann-Whitney U-test.

Safety parameters

Adverse events recorded during the study will be grouped into frequency tables by severity, seriousness and relationship with the study drug.

Data presentation

Descriptive statistics will be provided for each study continuous / interval variable. Numerical data will be presented by mean, standard deviation, min and max values (other measures of central tendency and variance may be provided where applicable). The data suggesting statistical conclusion will have the relevant confidence intervals. Extreme values (outliers) will be analyzed additionally. The data will be pooled according to visits. Categorical variables will be presented as per-visit frequency tables.

Appendix 1 *

Table 1. Example of an Assessment of 14 Common COVID-19-Related Symptoms: Items and Response Options

Example items *For items 1–10, sample item wording could be: "What was the severity of your [**insert symptom**] at its worst over the last 24 hours?"*	**Example response options and scoring***
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you **vomit (throw up)** in the last **24 hours**?**	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3

continued

Table 1, continued

12. How many times did you have **diarrhea (loose or watery stools)** in the last **24 hours**?**	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of **smell** in the last **24 hours**	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of **taste** in the last **24 hours**	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

* Note: Score values are included in the table for ease of reference. FDA cautions against including the score values within the response options presented to trial subjects to avoid confusing subjects.
** The response options shown for items 11 and 12 are intended only for use with a 24-hour recall period.

* Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment. FDA. Guidance for Industry. September 2020.