Multicenter double-blind placebo-controlled parallel group randomized clinical trial of efficacy and safety of MMH-407 in the treatment of acute respiratory viral infection

Phase III

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-407-001**
Version date:	**July 01, 2019**
ClinicalTrials.gov Id:	**NCT04244084**

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, National Standard of the Russian Federation GOST 52379-2005 "Good Clinical Practice", Helsinki Declaration of World Medical Association, 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 MMH-407 in the treatment of acute respiratory viral infection.

Phase: III

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

Protocol No. MMH-407-001

Objective of the study

- To evaluate the efficacy and safety of MMH-407 in the treatment of acute respiratory viral infection (ARVI).

Endpoints

Primary endpoint

1. Time to resolution of ARVI symptoms[1,2] (PCR-confirmed).

Secondary endpoints

1. Severity of ARVI (clinically diagnosed and/or PCR-confirmed); based on the area under the curve (AUC) data for the Total Severity (TS) score[3] on days 1-6 of the observation).
2. Percentage of patients with resolution of ARVI symptoms (clinically diagnosed and/or PCR-confirmed).
3. Time to resolution of ARVI symptoms (clinically diagnosed and/or PCR-confirmed).
4. Percentage of patients with resolution of ARVI symptoms (PCR-confirmed).
5. Dosing frequency of antipyretics on days 1-3 of therapy[4].
6. Percentage of patients requiring administration of antibiotics or hospitalization on 4-14 days of the observation.

[1] Time from enrollment to symptom resolution. **Resolution of ARVI symptoms** is defined if body temperature ≤37.30C within 24 hours (without further increase during observation period) + absence/presence of ARVI symptoms ≤2.
[2] Based on a patient diary.
[3] **Total Disease Index** will be calculated based on the intensity of each ARVI symptom (body temperature, systemic symptoms and nasal/pharyngeal/chest symptoms in points) with further statistical processing of data by OOO "NPF "Materia Medica Holding" experts. To determine total score, absolute values of body temperature measured in Celsius degrees will be converted into relative units (or points) based on the following classification: ≤37.3^{0}C=0; 37.4-38.0^{0}C=1; 38.1-39.0^{0}C=2; ≥39.1^{0}C=3.
[4] Based on a patient diary.

Safety assessment

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

Study design

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

The study will enroll outpatients of either gender aged 18-70 years old with clinical manifestations of ARVI within the first day after the onset of the disease during seasonal ARVI morbidity.

After signing patient information sheet and informed consent form, medical history, thermometry, objective examination, laboratory tests and concomitant medication will be performed. Severity of ARVI symptoms is evaluated with 4-point scale.

The nasopharyngeal swabs for PCR diagnosis and verification of respiratory viruses will be performed prior to therapy to confirm the viral etiology of ARVI.

If a patient meets all inclusion criteria and does not have any exclusion criteria, at Visit 1 (Day 1) he/she will be randomized into one of two groups: the 1st group will take MMH-407 according to the dosage regimen for 5 days; the 2nd group will take Placebo according to MMH-407 dosage regimen for 5 days.

The study will use electronic patient diary for recording morning and evening axillary body temperature (measured using a mercury-free Geratherm Classic thermometer) and disease symptoms (Symptom Severity Score). Besides, antipyretic dosing (if applicable) and any aggravation in a patient's condition (if applicable, for safety evaluation/AE documentation) will also be recorded in a patient diary. The investigator will provide instructions on filling the diary; at Visit 1 the patient together with a doctor will record ARVI symptom severity and body temperature in the diary.

Patient will be observed for 14 days (screening, randomization - Day 1, treatment period − 5 days, follow-up − up to 2 days; deferred "phone visit" − Day 14).

During the treatment and follow-up period the patients or investigators will make 3 visits and the fourth "phone visit" will be scheduled additionally: 1) visits by physician/patient - on Days 1, 5 and 7 (Visits 1, 2 and 3) – in a study center or at home; 2) "phone visit" (Visit 4) – on Day 14.

At Visits 2 and 3, the investigator will perform an objective examination, document changes in the symptoms and concomitant medications to check patient diaries. At Visit 3 compliance will be evaluated and laboratory tests will be performed. "Phone visit" is carried out to interview the

patient about his/her condition, presence/absence of secondary bacterial/viral complications and use of antibiotics.

During the study, symptomatic therapy and therapy for their co-morbidities are allowed with the exception of the drugs indicated in the section "Prohibited Concomitant Treatment".

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of either gender aged 18-70 years.
2. Diagnosis of ARVI based on medical examination: axillary temperature ≥ 38.0°C at examination + total general symptoms score ≥4, nasal/throat/chest symptoms score ≥2.
3. The first 24 hours after ARVI onset[5].
4. Patients giving their consent to use reliable contraception during the study.
5. Signed patient information sheet (informed consent form).

Exclusion criteria

1. Clinical symptoms of severe influenza/ARVI[6] requiring hospitalization.
2. Suspected pneumonia, bacterial infection (including otitis media, sinusitis, urinary tract infection, meningitis, sepsis, etc.) requiring administration of antibiotics from the first day of illness.
3. Suspected initial manifestations of diseases with symptoms similar to ARVI at onset (other infectious diseases, flu-like syndrome at the onset of systemic connective tissue diseases, and other pathology).
4. Patients requiring antiviral medication prohibited within the study.
5. Medical history of primary and secondary immunodeficiency.
6. Medical history/suspicion of oncology of any localization (except for benign neoplasms).
7. Aggravation or decompensation of chronic diseases affecting a patient's ability to participate in the clinical trial.
8. Malabsorption syndrome, including congenital or acquired lactase or other disaccharidase deficiency, galactosemia.
9. Allergy/ hypersensitivity to any component of the study drug.
10. Pregnancy, breast-feeding; childbirth less than 3 months prior to the inclusion in the trial, unwillingness to use contraceptive methods during the trial.

[5] **Time of ARVI onset** is the time of manifestation of fever or febrile illness (axillary temperature ≥37.4^{0}C, oral or tympanic temperature ≥37.6^{0}C, or rectal temperature ≥38.0^{0}C)

[6] **Severe influenza/ARVI** [7] is characterized with abrupt onset, high temperature (> 40°C) with acute intoxication symptoms (strong headache, body ache, insomnia, delirium, anorexia, nausea, vomiting, meningeal symptoms, sometimes encephalitic syndrome); pulse > 120 bpm, weak, sometimes arrhythmia; systolic blood pressure < 90 mm Hg; muffled heart sounds; respiration rate > 28/min. Very severe disease is characterized with fulminant presentation, rapidly developing intoxication signs, potential DIC-syndrome.

11. Course administration of the drug products specified in the section “Prohibited Concomitant Therapy” within two weeks prior to inclusion in the study.
12. Patients who will not fulfill the requirements during the study or follow the order of administration of the studied drug products, from the Investigator's point of view.
13. Medical history of mental diseases, alcoholism or drug abuse that according to the investigator’s opinion will compromise compliance with the study procedures.
14. Participation in other clinical trials for 3 months prior to enrollment in this study.
15. Patients who are related to any of the on-site research personnel directly involved in the study or are an immediate relative of the investigator. ‘Immediate relative’ means husband, wife, parent, son, daughter, brother, or sister (regardless of whether they are natural or adopted).
16. Patients who work for OOO “NPF “MATERIA MEDICA HOLDING” (i.e. the company's employees, temporary contract workers, designated officials responsible for carrying out the research or any immediate relatives of the aforementioned).

Criteria for Withdrawal or Termination

1. Patient failed screening procedure.
2. Inability or refusal of patient to comply the Protocol requirements.
3. Deviation from the schedule of visits 2 and 3 for more than 1 day.
4. Necessity in medicines prohibited within the study.
5. An adverse event requiring the study drug cancellation.
6. Desire of patient to complete the study ahead of schedule due to inefficacy of therapy or any other reason.
7. Pregnancy.
8. Cases not specified by the protocol where the investigator decides that further participation may harm the patient.
9. Incorrect inclusion of ineligible patient.

Number of patients

It is planned to include 240 patients (120 patients in MMH-407 and Placebo groups).

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: MMH-407

Active ingredient: affinity purified antibodies to human interferon gamma – 10000 UMA*, affinity purified antibodies to CD4 – 10000 UMA*, affinity purified antibodies to β1-domain of MHC class II – 10000 UMA*, affinity purified antibodies to β2-microglobulin of MHC class I – 10000 UMA*

* *Units of the Modifying Activity.*

Excipients: Lactose monohydrate – 0.267 g, microcrystalline cellulose – 0.03 g, magnesium stearate – 0.003 g.

Method of administration: Tablet for oral use. One tablet per intake. On day 1, five tablets are taken in the first 2 hours (one tablet every 30 min), followed by three more tablets regularly spaced during the rest of the day. From day 2 through 5, one tablet is administered three times daily. The drug is administered not during meals (i.e. between the meals or 15-30 minutes before meal). The tablet should be held in mouth until complete dissolution.

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: NA

Excipients: Lactose monohydrate – 0.267 g, microcrystalline cellulose – 0.03 g, magnesium stearate – 0.003 g.

Method of administration: Placebo using MMH-407 scheme.

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

MMH-407/Placebo treatment duration is 5 days.

Observation period

Overall the patient will be monitored for 14 days (screening, randomization - up to 1 day, study treatment period − 5 days, follow-up period − up to 2 days; delayed "phone" visit − day 14).

Symptomatic (Standard) treatment

Throughout the study, the patients may receive symptomatic ARVI therapy:

• antipyretic/non-steroidal anti-inflammatory drug (paracetamol/ibuprofen)

and/or

• vasoconstrictive nasal drug – oxymetazoline/naphazoline

and/or

• cough suppressant/expectorant drug – butamirate/ambroxol, bromhexine, guaifenesine, acetylcysteine.

Indications for prescription of antipyretics:

Increased body temperature > 39°C in patients without complications and co-morbidities and > 38°C in patients with co-morbidities (congestive heart failure, hepatic, renal diseases; history of convulsive syndrome).

If antipyretic was taken by the patient on his own (without doctor recommendation) with no indications the patient is not excluded from the study. The patient should record the values of thermometry before taking the drug, its name and dose.

Not considered as prohibited products:

- systemic antihistamines (R06A)
- medication for the treatment of obstructive airway diseases (R03).

Prohibited concomitant therapy

Two weeks before inclusion in the study*, as well as during the study (from signing of the information sheet for patient /informed consent form and initiation of screening) the following medication are not allowed (their ATC group is indicated in brackets):

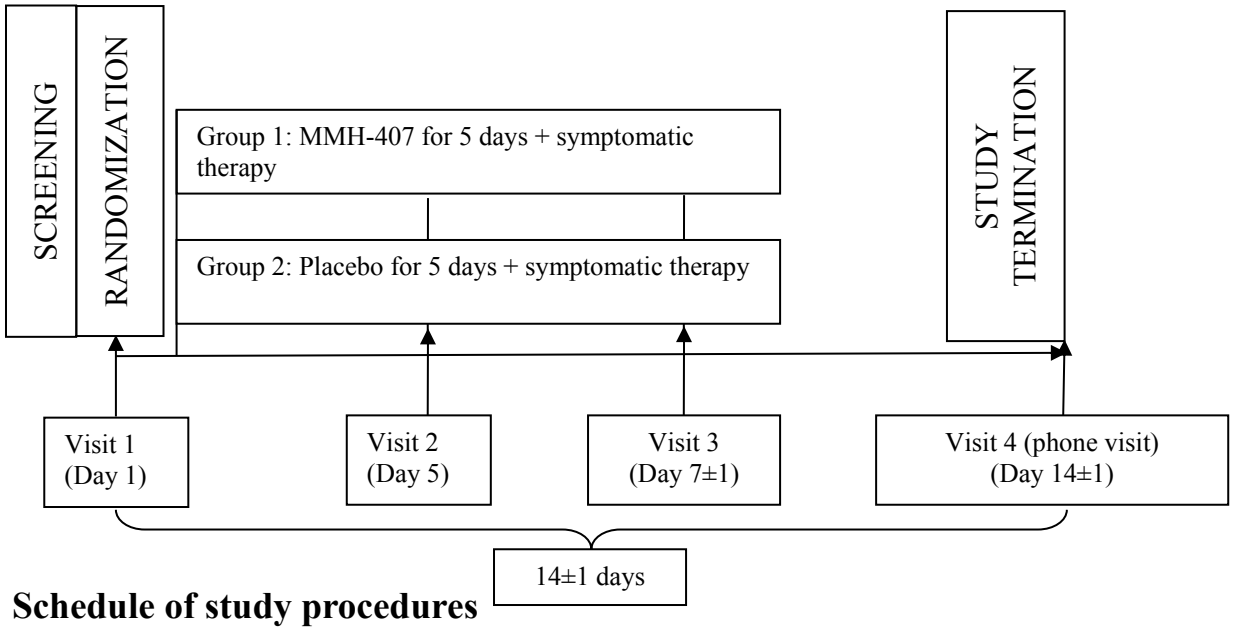
1. Antivirals (J05).
2. Antimicrobials and antiseptics for local treatment of oral diseases (A01AB).
3. Medications for the treatment of throat diseases (R02A).
4. Immunostimulants (L03), including:
    - interferon inducers (acridonoacetic acid, meglumine acridone acetate/cycloferon®, umifenovir/arbidol®, kagocel®, tiloron/amixin®, polyadenyl acid + polyuridylic acid/poludan®, sodium oxodihydroacridinyl acetate/neovir®, lavomax®, tilaxin®, etc.)
    - interferons;

- 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.);
- medication with thymus hormones.

5. Non-steroidal anti-inflammatory drugs (M01, except for ibuprofen).
6. Analgesics and antipyretics (N02A, N02B except for paracetamol).
7. Combination preparations for symptomatic therapy of acute respiratory infections.
8. Homeopathic preparations.
9. Systemic (oral or parenteral) corticosteroids.
10. Immunosuppressants (L04).
11. Antineoplastic agents (L01) and combined (with hormones) antineoplastic endocrine therapy (L02).
12. Immune sera and immunoglobulins (J06).
13. Vaccines (J07).
14. Drugs that previously caused hypersensitivity/ allergic reactions in patient.

** Patients were allowed to take a single dose of prohibited medications (except for 9 - 14) prior to inclusion, if the interval between the medication intake and randomization was more than 12 hours.*

Study design scheme



Schedule of study procedures

Procedure/Visit	Visit 1 (Day 1)	Visit 2 (Day 5)	Visit 3 (Day 7±1)	Visit 4 (Day 14±1)

Informed consent	+			
Registration of a study patient in the IVRS and assignment of patient ID	+			
Collection of complaints	+	+	+	
Medical history	+			
Physical examination	+	+	+	
ARVI symptoms registration	+	+	+	
Patient Diary	+	+	+	+
Pregnancy test	+			
Concomitant therapy	+	+	+	
Eligibility assessment	+			
Nasopharyngeal swabs for PCR	+			
Laboratory tests* (safety evaluation)	+		+	
Randomization	+			
Study drug supply	+			
Study drug accountability and return			+	
Treatment compliance			+	
Evaluation of treatment safety	+	+	+	
Visit completion	+	+	+	
Phone survey				+
Study completion**				+

** Including hematology, urinalysis, biochemistry (total protein, glucose, total bilirubin, creatinine, ALT, AST, cholesterol).*
***In case of early withdrawal the procedure may be performed at visits 1, 2 or 3.*

Statistical Analyses

SAS 9.4 will be used for data processing and statistical calculations.[7]

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 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) the 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.

[7] Licensee: OOO "NPF "Materia Medica Holding", No. 70100045

Per protocol set. This sample includes all patients who have received the complex therapy under the Protocol and completed all the scheduled visits. This sample will be used for the ***Per Protocol analysis (PP- analysis)*** of the study therapy efficacy. 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:

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

Evaluation of sample size

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 the erroneous acceptance of an alternative hypothesis is less than 0.05);
   - 1.3 the statistical criteria used are 2-sided;
   - 1.4 the protocol contains evaluation of minimum detectable effect at fixed: sample size, population variance, type 1 and 2 error values;
   - 1.5 the ratio between the sample sizes of the study drug and placebo groups is 1:1 (1 study drug patient - 1 placebo patient);

[8] 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).

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

$$\mathbf{H_0: M_1\text{-}M_2 = 0}$$

$$\mathbf{H_a: M_1\text{-}M_2 \neq 0}$$

where M1 – the mean time to resolution of all symptoms in the study drug group;

M2 – the mean time to resolution of all symptoms in the placebo group.

Analysis of the expected effect within the fixed sample will be carried out in accordance with the following formulas:

$$\mathbf{n_1 = kn_2}$$

$$\boldsymbol{\varepsilon} = \left(\frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 * (1 + 1/k) * \sigma^2}{\mathbf{n_2}} \right)^{\frac{1}{2}}$$

where $\mathbf{n_1}$, $\mathbf{n_2}$ – the sample size of the study drug and the placebo groups respectively;

$\boldsymbol{\varepsilon} = \boldsymbol{M_1 - M_2}$ – the minimum detectable difference in time in study drug and placebo groups;

k – the coefficient of study drug /placebo sample ratio (k=1);

σ – the standard deviation;

$z_{\alpha/2}$ – a tabulated two-tailed z-test for **α**;

z_{β} – a tabulated one-tailed z-test for **β**.

1.7 effective sample size will be determined using the formula:

$$\mathbf{Npp = N_T * (1 - C_w)},$$

where $\mathbf{N_T}$ – the final sample size;

$\mathbf{N_{PP}}$ – the value calculated in section 1.6, i.e. the expected number of the patients completing the study per protocol;

$\mathbf{C_w}$ – withdrawal coefficient.

2. Assumptions about the expected effects of the clinical study: To evaluate the minimum detectable effect at fixed sample size a priori estimate of population parameters should be performed:

A priori estimates for tested parameter variables in the groups:

Primary endpoint (efficacy criterion)*:*

Time to resolution of ARVI symptoms.

Study drug group:

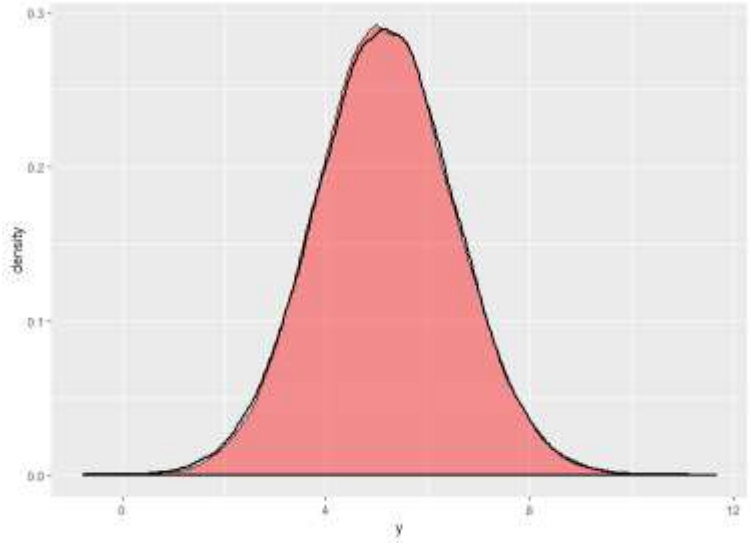
Time to resolution of symptoms was estimated on the basis of the previous studies.

T_{tr}=(<max(N(2.6,1.77), N(5,1.47))>)[9,10]

Where <…> stands for averaging operation, N(x,s) – normally distributed random variable with the mean x and standard deviation s.

corresponds to the Gumbel type I distribution[11]

*for power analysis this empirical distribution is approximated by the normal distribution with characteristics m=5.17, σ=**1.38**.*



Note. Red area is empirical distribution of time to resolution of symptoms in Product group (number of simulation repetitions N=10^5). Red curve is approximate parametric distribution for the groups.

Therefore, given fixed sample (N_{pp}=120) obtained above for population standard deviation (sd=1.38) and levels of errors (**α**=0.05, **β**=0.2), the minimum detectable effect in the study will be **0.71 day**. When planning the study withdrawal rate of 50% patientss was taken[12] (**C_w=0.5**). In total 240 patients will participate in the study.

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

[9] Based on the clinical trial "A study to assess the therapeutic efficacy and safety of Anaferon against influenza and other upper respiratory tract infections in aduls" [11]. Duration distributions for symptom domains are considered independent. 95% confidence interval is taken for the corresponding standard deviations.

[10] The data resulting in major variance evaluation are used.

[11] On the distribution of the maximum of N independent normal random variables: IID and INID cases. SDSSU Multidisciplinary Research Journal Vol. 1 No. 2±2013

[12] This rate is complex: 10% patients will be screening failures or will withdraw for other reasons specified in the relevant protocol section, 44% remaining patient will not have the diagnosis verified by PCR.

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 parameters 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, clarification of the factor and covariance structures of the model is carried out with fit statistics such as AIC (Akaike information criterion).

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

- 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 Generalized Linear Models for studying temporal dynamics (ANOVA, ANCOVA);
- GENMOD – analysis of Generalized Linear Models.
  MIXED – analysis of Generalized Linear Models.

Non-parametric criteria

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

1. To evaluate time changes in the parameters compared – 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. Relevant confidence intervals will also be provided for the data suggesting statistical conclusion. Extreme values (outliers) will be analyzed additionally. The data will be grouped by visits. The categorical variables will be presented as frequency tables by visits.