Comparative Parallel-group Randomized Clinical Trial of Efficacy and Safety of Ergoferon Versus Oseltamivir in the Treatment of Influenza

Phase IV

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-ER-003**
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Protocol Summary

This document represents the protocol summary for the study on human subjects. 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.

Official Title

Comparative Parallel-group Randomized Clinical Trial of Efficacy and Safety of Ergoferon Versus Oseltamivir in the Treatment of Influenza

Phase: IV
Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia
Protocol No. MMH-ER-003

Study purposes

- To assess the efficacy of Ergoferon in the treatment of influenza.
- To compare the efficacy of Ergoferon and Oseltamivir in the treatment of influenza.
- To assess the safety of Ergoferon in the treatment of influenza.

Outcome Measures

Primary Outcome Measure

1. Proportion of patients with recovery/improvement in health[1] on days 2-7 − according to the patient's diary; on days 3 and 7 – according to objective examination conducted by a physician

Secondary Outcome Measures

2. Fever changes over time (body temperature change on days 2-7 compared to baseline).
3. Average duration of fever[2].
4. Proportion of subjects with normal body temperature (below $37,0^0$C) on days 2-7.
5. Severity of clinical manifestations of influenza (fever[3], general symptoms and nasal/ throat/chest symptoms) in scores on day 1-7 − according to the patient's diary; on days 1, 3 and 7 – according to objective examination by the investigator.

[1] **Recovery criteria:** body temperature <37.0^0C + no symptoms.
Improvement criteria: body temperature ≤37.2^0C + total symptom score (except for fever index) ≤2 scores.
[2] Criteria of no fever - body temperature lower than 37.0° C for 24 hours.

6. Duration of the major clinical symptoms of influenza (fever, general symptoms and (nasal/throat/chest symptoms) in days (according to the patient diary).
7. Severity of influenza course (based on area under curve for total influenza severity score on days 1-7 − according to the patient diary; on days 1, 3 and 7 – according to objective examination by the physician).
8. Proportion of patients, who used antipyretics on days 1, 2, 3, 4 and 5 of the treatment.
9. Proportion of patients with complications requiring antibiotics, aggravation of the disease (severe influenza).
10. Proportion of patients with negative results of virology assay on days 3, 5 and 7 (based on PCR of nasopharyngeal swabs).
11. Dynamics of Parameters of Immune Status (T-cell and B-cell Immune Response) on days 1, 3 and 7 of the observation:
    - Concentration of regulators of the T-cell immune response (IL2, IFN -γ, IL-18), and regulators of B-cell immune response (IL-4, IL-16).
12. Dynamics of Parameters of Immune Status (IFN-α and IFN-γ Production) on days 1, 3 and 7 of the observation:
    - Level of spontaneous and induced production of IFN-α and IFN-γ by leukocytes (in vitro).
13. Dynamics of Parameters of Immune Status (Absolute Number of Each Type of White Blood Cells and Different Lymphocyte Phenotypes) on days 1, 3 and 7 of the observation:
    - The absolute number of each type of white blood cells (WBC): Absolut Count (AC) of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and CD3, CD4, CD8, CD4/CD8, CD16, CD119 leukocytes.
14. Dynamics of Parameters of Immune Status (relative percentage of each type of white blood cells and different lymphocyte phenotypes) on days 1, 3 and 7 of the observation:
    - The relative percentage of each type of white blood cells (WBC): Relative Count (AC) of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and CD3, CD4, CD8, CD4/CD8, CD16, CD119 leukocytes.

Safety assessment

- Presence and nature of adverse events during the therapy, their association with the drug administration and other features.

[3] Temperature scoring to determine total disease score will be made at the statistical analysis by OOO "NPF "Materia Medica Holding" personnel. To do this, absolute body temperatures (in degrees Celsius) will be converted to points (or scores) using the following scale: $\leq 37.2^0$C=0 points; 37.3-38.0^{0}C=1 point; 38.1-39.0^{0}C=2 points; $\geq 39.1^0$C=3 points.

Study design

Study design: an open-label, comparative, randomized, parallel group clinical study to evaluate efficacy of the study treatment.

The study will enroll outpatient subjects of either gender aged 18-70 years old inclusively with clinical manifestations of influenza during seasonal morbidity seeking medical advice within the first two days of the disease.

After signing informed consent to participate in the clinical study baseline examination will be initiated including nasal swab for rapid diagnosis and verification of influenza as the cause of the disease. In case of positive result of immunochromatographic test the patient will be enrolled. In case of negative result of rapid test the patient will be enrolled provided that (1) he/she has clinical manifestations of typical influenza; (2) the history evidences contact with a patient with influenza; (3) the region has influenza epidemics. Additionally, at the screening (Day 1) all patients regardless of the results of rapid test will provide nasopharyngeal wabs for further PCR diagnosis and identification of RNA of influenza A and B virus, thermometry, history collection, evaluation of vital signs, physical examination will be performed and concomitant therapy will be recorded. Females of childbearing potential will undergo pregnancy test. If inclusion criteria are met and non-inclusion criteria are absent (Day 1) the patient will be enrolled in the trial and randomized into one of the two groups: group 1 will receive Ergoferon as per the selected dosing regimen for 5 days; group 2 will be treated with Oseltamivir at 75 mg twice a day for 5 days.

At Day 1 visit the patient will receive the study product and an antipyretic product approved by the study protocol.

The patient will receive the diary in which he/she will have to record axillary body temperature (measured by non-mercuric Geratherm Classic thermometer) in the morning and evening as well as intensity of the disease symptoms and number of doses of the antipyretic product. The investigator will train the patient concerning the diary filling.

In total 3 visits (Days 1, 3 and 7) will be made by the patient/investigator during the treatment and follow-up period, on day 5 an additional visit will be made for nasopharyngeal swabs.

At Day 1, Day 3 and Day 7 visits blood sampling will be made for immunological tests at the investigator's discretion. At Day 3 and Day 7 visits the investigator will collect complaints, document examination findings, intensity of influenza symptoms in scores, control the prescribed and concomitant medications, assess safety of the study therapy and check the patient's diary. Furthermore, nasopharyngeal swabs (Days 1, 3, 5, 7) and blood samples (Days 1, 3, 7) will be made for lab tests. The total observation period will be 7 weeks (screening, randomization – 1 day, treatment – 5 days, follow-up – 2 days). The patient will keep diary throughout the whole 7-day observation period.

Symptomatic therapy of influenza and co-morbidities will be allowed except for the products specified in "Forbidden concomitant therapy" section.

Inclusion and exclusion criteria

Inclusion criteria

1. Patients aged from 18 to 70 years.
2. Patients who were admitted to hospital within 48 hours from the onset of influenza signs.
3. Patients with body temperature ≥37.8°C when visiting a doctor + severity of influenza symptoms ≥4 scores (presence of at least one general symptom ≥2 scores and 1 nasal/throat/chest symptom ≥2 scores or greater number of symptoms with the severity ≥1 point).
4. Diagnosed influenza confirmed by rapid diagnostic test (OSOM Influenza A&B Test).
5. The possibility to start therapy after the onset of the first symptoms of influenza.
6. Usage of contraceptive methods by both gender patients of reproductive age during the trial and within 30 days after ending the participation in the trial.
7. Availability of signed patient information sheet (Informed Consent form) for participation in the clinical trial.

Exclusion criteria

1. Suspected pneumonia, bacterial infection or the presence of a severe disease requiring usage of antibacterial drugs (including sulphanilamides) starting from Day 1 of the disease.
2. Severe influenza[4] with indications for hospitalization.
3. Suspected early manifestations of diseases that have symptoms similar to influenza symptoms (other acute respiratory and infectious diseases, influenza-like syndrome at the onset of systemic connective tissue disorders, hematologic neoplasms and other pathology).
4. Patients requiring concurrent antiviral products forbidden by the study.
5. Medical history of primary and secondary immunodeficiencies. a) lymphoid immunodeficiencies (T-cell and/or B-cell, immunodeficiencies with predominant antibody deficit); b) phagocytic deficits; c) complement factor deficit; d) combined immunodeficiencies including AIDS secondary to HIV infection; toxic, autoimmune,

[4] Severe influenza criteria (RF MoH, 2009; WHO 2014; CDC 2009-2014): Extreme degree of general intoxication syndrome (toxic shock III, vomiting, dehydration symptoms, reduced diuresis/anuria, restlessness or abrupt weakness up to complete adynamia, tachypnea, tachycardia inconsistent with temperature, convulsions, meningism symptoms), cognitive disorders, hemorrhagic syndrome (epistaxis, dermal and mucosa petechiae), hemodynamic instability, expressed obstructive disorders (stenosing laryngotracheitis, bronchial obstruction syndrome), acute respiratory failure, primary and secondary pneumonia. Risk factors for severe influenza and complications: chronic cardiovascular, respiratory diseases, diabetes mellitus, immunodeficiencies, oncology.

infectious, radiation panleukopenic syndrome; total lymphocytopenic syndrome; polyclonal lymphocyte activation syndrome; postsplenectomic syndrome; congenital asplenia; abnormal immune complex syndrome associated with infectious, autoimmune and allergic diseases.

6. Medical history of sarcoidosis
7. An oncological disease/suspected oncological disease.
8. Exacerbated or decompensated chronic diseases affecting a patient's ability to participate in the clinical trial.
9. Medical history of polyvalent allergy.
10. Allergy/intolerance to any of the components of the product used for influenza therapy.
11. Impaired glucose tolerance, type 1 and type 2 diabetes mellitus.
12. Malabsorption syndrome, including congenital or acquired lactose deficiency or another disaccharide deficiency.
13. Pregnancy, breast-feeding.
14. Consumption of narcotics, alcohol > 2 alcohol units per day, mental diseases.
15. Use of any medicine listed in the section "Prohibited concomitant treatment" within 30 days preceding the inclusion in this study.
16. Patients who, from the investigator's point of view, will fail to comply with the observation requirements of the trial or with the regimen of the study drugs.
17. Participation in other clinical studies within 1 month prior to enrollment in the current trial.
18. Patients related to the research staff of the clinical trial site who are directly involved in the trial or are the immediate family member of the researcher. The immediate family members include husband/wife, parents, children or brothers (or sisters), regardless of whether they are natural or adopted.
19. Patients employed with OOO "NPF "MATERIA MEDICA HOLDING" (i.e., the company's employee, part-time employee under contract, or appointed official in charge of the trial, or their immediate family).

Discontinuation criteria

1. Participant's failure or decline to comply with the protocol requirements.
2. Deviation from the schedule of examinations and sampling for lab tests by ≥ 1 day.
3. The necessity to use medications not permitted in the study.
4. An adverse event requiring discontinuation of the study drug.
5. Patients who decide to withdraw early from the study due to lack of treatment efficacy or for any other reason.

6. Cases not stipulated in the protocol where the investigator decides that further participation may harm the patient.
7. Eligibility error.

Number of patients

198 Informed consent forms are supposed to be signed and expected to yield at least 158 patients (79 x 2 groups (Ergoferon and Oseltamivir)) completing all the protocol procedures (withdrawal index 1,2).

Treatment

Group 1

Name: Ergoferon

Active ingredient: affinity purified antibodies to human interferon-gamma – 0.006 g*, affinity purified antibodies to histamine – 0.006 g*, affinity purified antibodies to CD4 - 0.006 g*

** applied onto lactose as a mixture of three active water-alcohol solutions of the API diluted 100^{12}, 100^{30}, 100^{50} times, respectively.*

Excipients: Lactose monohydrate, microcrystalline cellulose, magnesium stearate.

Dosage: Per os. Dose per administration - 1 tablet (without food) hold in the mouth until complete dissolution.

Dosing scheme: One dose every 30 minutes for the first 2 hours, followed by three more doses spaced regularly during the rest of the day. From day 2 to 5: 1 tablet 3 times a day.

Dosage form: Orally disintegrating tablets.

Description: White to off-white, circular, flat faced, beveled edge tablets, scored on one side. Each tablet is debossed with MATERIA MEDICA on the scored side and ERGOFERON on the other flat side.

Storage conditions: Store in a place protected from light at a temperature below 25ºC. Keep out of the reach of children.

Group 2

Name: Tamiflu

Active ingredient: Oseltamivir 75 mg (as oseltamivir phosphate 98.5 mg)

Excipients: Pregelatinized starch, povidone K30, croscarmellose sodium, talc, sodium stearyl fumarate.

Dosage: Per os, with or without food. Dosage scheme: Adult patients - 1 capsule (75 mg) twice daily. Treatment period - 5 days.

Dosage form: Capsules

Description: Hard, gelatinised capsules, size 2. Grey opaque body; light yellow opaque cap. Capsule contents - white to yellowish-white powder. The capsule is engraved with "Roche" (body) and "75 mg" (cap) in light blue ink.

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

Treatment period

Ergoferon/Tamiflu® treatment period is 5 days.

Observation period

Overall the patient was observed in the study for 7 days (screening/randomization/prescription of treatment - Day 1, study therapy − days 1-5, follow-up − days 6-7).

Basic therapy

Throughout the study the patients may receive symptomatic therapy for influenza based on the treatment standards including detoxication agents, vitamins, antitussive drugs and expectorants, mucolytics, vasoconstrictive nasal drops, where applicable* - antipyretics** except for antiviral, antihistamine, immunomodulating and other drugs included into "Forbidden concomitant therapy".

* *Indications for antipyretic therapy:*

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; mental diseases, diabetes mellitus, history of convulsive syndrome).

Given that congestive heart failure, mental disorders, diabetes mellitus are exclusion criteria for this clinical study, these indications need not be considered.

If antipyretic product was administered by the patient on his/her own (without medical prescription) with no indications thereto the patient will not be withdrawn from the study. The patient should record thermometry values in the diary before the product administration as well as its name and dose.

** *Products approved as antipyretics (ATC group is specified in brackets):*

1. Paracetamol (N02BE01).

2. Ibuprofen (M01AE01).

3. Metamizole sodium (N02BB02) – for hyperthermia uncontrolled by paracetamol/ibuprofen as an emergency drug.

The product shall be chosen by the investigator issuing the antipyretic to the patient at Visit 1.

Prohibited concomitant therapy

Within one month prior to enrollment* and throughout the study (beginning with signing Informed Consent and initiation of screening) patients cannot use any of the following medications (ATC group is specified in brackets):

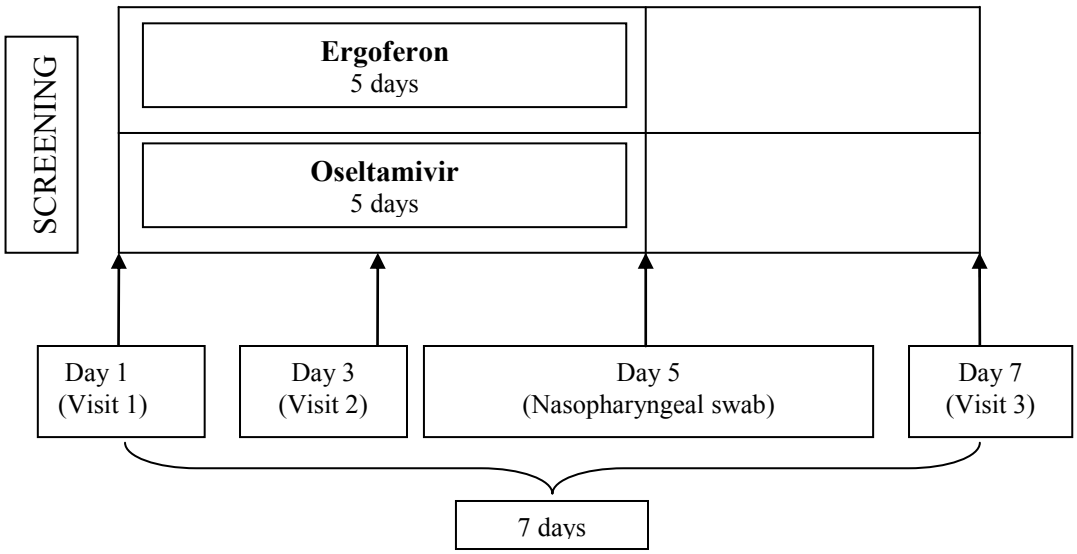
1. Antiviral drugs (J05) except for Ergoferon and oseltamivir prescribed within the study.

2. Immune sera and immunoglobulins (J06).
3. Vaccines (J07).
4. Antitumour drugs (L01) and antitumour hormonal products (L02).
5. Immunostimulants (L03) including:
    - Colony-stimulating factors (L03AA) – filgrastim, molgramostim, lenograstim, pegfigrastim.
    - Interferons (L03AB) – interferon alpha, interferon gamma, interferon alpha-2a, interferon alpha-2b, interferon alpha-n1, interferon beta-1a, interferon beta-1b, peginterferon alpha-2b, peginterferohn alpha-2a.
    - Interleukins (L03AC) – aldesleukin.
    - Other immunostimulants (L03AX) – BCG vaccine; pidotimod; glatiramer acetate.
    - Interferon inducers (acridonacetic acid, meglumine acridonacetate, complex of polyadenylic acid and polyuridylic acid, methylphenylthiomethyl-dimethylaminomethyl-hydroxybromindole carboxylic acid ethyl ether, oxodihydroacridinylacetate sodium, kagocel, tilorone).
    - The products containing thymus hormones (alpha-thymosin, alpha-glutamyl-triptophan, thymus extract, thymoptin).
    - B-activin.
    - Synthetic immunostimulants (levamisole, alpha-glutamyl-triptophan).
    - Bacterial immunomodulators (ribomunyl, ribonucleate sodium, deoxyribonucleate sodium)
6. Immunodepressants (L04).
7. Fenspiride (R03DX03), omalizumab (R03DX05).
8. Antihistamine drugs (R06).
9. Anaferon (L03AX), epigam, rengalin (R05DB).
10. Combined products for symptomatic therapy of acute respiratory diseases containing acetylsalicylic acid, diclofenac, propifenazone, metamizole, phenylephrine, H1-histamine blockers (including phenyramine, chlorphenamine).
11. Drugs known to have caused allergic reactions.
12. Products forbidden as antipyretic products:
    - Butylpyrazolidones (M01AA) including phenylbutazone.
    - Acetic acid derivatives (M01AB) including indometacin, diclofenac, ketorolac, aceclofenac.
    - Oxicams (M01AC) including piroxicam, meloxicam, tenoxicam, lornoxicam.

- Propionic acid derivatives (M01AE).
- Coxibs (M01AH).
- Niflumic acid (M01AX02).
- Nimesulide (M01AX17)
- Acetylsalicylic acid (N02BA01) including in combination with other products.
- Pyrazolones (N02BB) including in combination with other products (except for metamizole sodium).

** If a single dose of any of the products from the list "Forbidden concomitant therapy" was administered within 12 hours prior to the enrollment to the study (except for the products specified in cl. 2-4, 6), it is not an exclusion criteria.*

Study design scheme



Schedule of study procedures

Procedure/visit	Day 1	Day 3	Day 5	Day 7
Obtaining informed consent (signing informed consent by the patient)	+			
Collection of complaints	+	+		+
Collection of medical history data	+			
Objective examination	+	+		+
Recording influenza symptoms in scores	+	+		+
Collection of nasal swabs and isolation of influenza agent antigens	+			
Collection of nasopharyngeal swab for PCR diagnosis	+	+	+	+
Pregnancy test	+			
Information on concomitant medicines	+	+		+

Inclusion/exclusion criteria	+			
Randomization and prescription of study therapy	+			
Antipyretic drug dispensing	+			
Blood sampling for immunological tests	+	+		+
Dispensing of the study drug	+			
Drug accountability and return, assessment of compliance				+
Distribution of diaries	+			
Evaluation of correct diary filling		+		+
Diary return				+
Evaluation of therapeutic safety		+		+

Statistical Analyses

Samples

Total set comprised all enrolled patients whose parents/adopters had signed the informed consent form for participation of a patient in the trial. This sample will consider all adverse events throughout the study, including those occurred prior to the study therapy. Any medically unfavourable events (conditions) recorded in patients from Total set after signing informed consent but before administration of the study product will be considered as concomitant conditions.

Sample of the patients receiving at least one dose of the study product will be used for the study drug safety assessment (Safety population), as any adverse events emerging after administration of the product will be recorded.

Full Analysis Set This sample will consist of all enrolled patients, except for those who met at least one of the following criteria:

1) failure to meet inclusion/non-inclusion criteria;

2) patient failing to take any dose of the study drug;

3) absence of any data on the patient after randomization.

This was the best set for the Intention-to-treat method, so it will be used in the Intention-to-treat efficacy analysis of the test therapy.

Unavailable/missing data (parameters/variants) will be completed by the Last Observation Carried Forward method (LOCF).

Per Protocol set. This sample includes all patients who completed the therapy as per the study protocol, without any missing visits or major protocol deviations. This set will be used in the Per Protocol efficacy analysis of the test therapy.

Evaluation of sample size

The sample size was assessed in accordance with the following rules and assumptions:

1. Statistical assumptions:

1.1 Lack of clinically relevant superiority of reference product (oseltamivir) over test product (Ergoferon) is assumed, thus statistically meeting Non-Inferiority design:

$$\mathbf{H_0: Ef_{control} - Ef_{test} \geq \delta}$$

$$\mathbf{H_A: Ef_{control} - Ef_{test} < \delta,}$$

where $\mathbf{Ef_{control}}$ – effect of reference product (oseltamivir), $\mathbf{Ef_{test}}$ – effect of test product (Ergoferon), **δ** –clinically relevant difference;

1.2 Clinically relevant difference value "δ" is considered to be equal to 20% (i.e. Ergoferon effect is supposed to be comparable to the one of oseltamivir if the effect of test product is superior to or inferior to the effect of reference product by no more than 20%);

1.3 The power of statistical tests 'P = (1 − β)' is 80% (the probability of correct rejection of the null hypothesis is 0.8);

1.4 The probability of type 1 error 'a' is less that 5% (the probability of false acceptance of the alternative hypothesis is less than 0.05);

1.5 Therefore, sample size will be calculated taking into account:

a. assumption on expected effects declared in the main efficacy criterion of the protocol;

1.6 calculation of sample size of groups 1 and 2 for two-sided test for final analysis will be made using the formula[5]:

$$\mathbf{N_1=N_2=(p_a(1 - p_a) + p_b(1 - p_b))\ I,}$$

where $\mathbf{N_1}$ and $\mathbf{N_2}$ – samples sizes in Ergoferon and Oseltamivit groups

$\mathbf{p_a}$ and $\mathbf{p_b}$ – expected proportions of the patients with recovery/improvement in these groups

I – Fisher's information detected using the formula:

$$\mathbf{I=(z_\alpha + z_\beta)^2/(\theta - \delta)^2,}$$

where z_α and z_β – tabular values of z-test for **α** and **β, θ** – difference between proportions $(\mathbf{p_a - p_b})$, **δ** – clinically relevant difference;

1.7 final sample size will be determined using the formula:

$$\mathbf{N_F = N / (1 - K_B)},$$

[5] SAS/STAT(R) 9.2 User`s Guide, Second Edition.
http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_seqdesign_sect027.htm

1.8 where $\mathbf{N_F}$ – final sample size; **N** – result of calculation in cl. 1.6, i.e. scheduled number of patients completing the study per protocol; $\mathbf{C_w}$ – withdrawal coefficient.

2. Assumptions on expected clinical study effects:

2.1 The difference between proportions of the patients with recovery/improvement[6] on days 2-7 (according to the patient's diary) and on days 3 and 7 (according to objective medical examination) in Ergoferon group and Oseltamivir is expected to be ≥ 0%.

The minimum size of each group will be determined as follows:

Number of patients	Final analysis
Number of patients in both groups including - number of patients in Ergoferon groups - number of patients in Oseltamivir group	158 79 79

Taking into account that potential withdrawal of 20% patients during the screening and during the study, at least 198 patients (99 in Ergoferon and Oseltamivir group) should sign informed consent.

Statistical criteria

All statistical calculations will be made using two groups of statistical criteria:

- parametric - to evaluate continuous and interval random values;
- non-parametric – to obtain:
  - evaluations on equality/inequality of proportions of the patients upon their comparison for various visits,
  - analysis of frequencies of the features compared,

  and
  - to evaluate continuous and interval random values in case of non-compliance with normal random distribution.

Parametric criteria

Prior to analysis using parametric statistics, data samples under comparison will be tested for normality (the Kolmogorov-Smirnov test).

[6] **Recovery criteria:** body temperature <37.0^{0}C + no symptoms.
Improvement criteria: body temperature ≤37.2^{0}C + total symptom score (except for fever index) ≤2 scores.

The following parameters and approaches are to be used:

1. To evaluate the differences in continuous variables from two different (independent) groups – Student's test for independent samples.
2. To evaluate differences in continuous variables in one group at two different visits - Student's test for paired samples.
3. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or modified repeated measures covariance (ANCOVA).
4. In case of multiple comparisons of the groups various corrections for multiplicity will be used, e.g. Dunnett, Tukey, Scheffe, Holm adapted test, etc.
5. In case of abnormal data distribution generalized linear models and/or mixed linear models will be used.
6. Selection of the type of distribution, specification of factor and covariance structures of the model will be made using fit-statistics such as AIC (Akaike information criterion).

The following SAS software programs are supposed to be applied to the above listed tests and techniques:

- UNIVARIATE: normality verification of the distributions under comparison
- CORR, MEANS - calculation of descriptive statistics
- TTEST – Student's test with all modifications
- GLM – generalized linear models for analysis of time changes (ANOVA, ANCOVA)
- GENMOD – generalized linear models
- MIXED – mixed linear models.

Non-parametric tests:

Below are potential types of comparisons with relevant criteria:

1. To evaluate difference in continuous variables obtained in two different (independent) groups – Mann-Whitney test.
2. To evaluate time changes in the parameters compared – Friedman test, nonparametric analogue of repeated measures analysis of variance.
3. For frequency analysis of contingency tables 2×2 – χ^2 (if the frequency under comparison > 5) or exact Fisher's test (if one of the frequencies under comparison < 5).
4. Cochran-Mantel-Haenszel test (modified χ^2 test for multiple comparisons) – to perform frequency analysis based on independent strata.
5. For frequency analysis of data on presence/absence of an event or outcome during repeated measurements (contingency tables with dependent strata) – survival analysis.

To perform the above-mentioned nonparametric statistical analysis the following SAS procedures are to be used:

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

Safety parameters

The AEs recorded throughout the study will be pooled in the frequency tables for severity and relationship with the study drug.

Data presentation

Descriptive statistics will be given for each continuous/discrete variable tested. Numerical data will be presented as mean value, standard deviation, and maximum and minimum values. 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.