International observational non-interventional retrospective program for studying the efficiency and safety of Ergoferon in patients with influenza and acute respiratory viral infections

(HERMITAGE)

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
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Protocol Summary

This document represents the program 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.

Title of Study

International observational non-interventional retrospective program for studying the efficiency and safety of Ergoferon in patients with influenza and acute respiratory viral infections (HERMITAGE).

Phase: post-registration

Sponsor: OOO "NPF "Materia Medica Holding", Moscow, Russia

Protocol No. HERMITAGE

Objective of the study

- To study the practice of Ergoferon using in outpatients (adults and children) with influenza / acute respiratory viral infections (ARVI).
- To obtain additional data on the efficacy and safety of Ergoferon in the treatment of influenza/ ARVI in outpatients (adults and children).
- To obtain additional data on the efficacy and safety of Ergoferon for influenza/ARVI in case of late initiation of treatment.
- To obtain additional data on the efficacy and safety of the drug Ergoferon in the treatment of influenza/ARVI in patients with an allergic history.

Endpoints

Primary endpoint

1. Duration[1] of Influenza/ARVI Symptoms.

Secondary endpoints

1. Duration of increased body temperature(>37 °C).
2. Duration of systemic symptoms (chills, headache, muscle pain, weakness, loss of appetite).
3. Duration of nose symptoms (nasal congestion, discharge from the nose), other symptoms.
4. Duration of throat symptoms (sore throat, etc).
5. Percentage of patients with complications of influenza/ARVI).

[1] The time from the onset of treatment with Ergoferon to the resolution of the symptoms, i.e. a body temperature ≤37.0 °C remaining at this level for 24 h (with no further increases throughout the rest of the observation period) in the absence of catarrhal signs and systemic symptoms.

Safety assessment

- Adverse events (AE) during the treatment, AEs severity and relations to the study drug, and AEs outcomes.

Study design

This observational study is aimed to provide additional safety and effectiveness data for Ergoferon in the treatment of influenza/ARVI in adult and pediatric outpatients, including cases with delayed treatment initiation (after 48 or 72 h of the onset of illness), and in allergy patients. Routine clinical practice in the management of outpatients with ARVI is to be studied in Azerbaijan, Armenia, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan and Uzbekistan: the demographic characteristics of patients, duration and time points of treatment with the use of Ergoferon, its safety, and the frequency of additional medication.

Scope of the study: 519 general practitioners; 8411 patients.

Physical examinations and tests are performed according to local outpatient clinical practice, and to local and international medical care standards.

Data to be collected and analyzed after the completion of treatment:

- demographics (age, gender, and city/town of residence)
- severity of illness (mild, moderate, or severe)
- comorbidities (chronic ENT conditions, chronic obstructive pulmonary disease (COPD), chronic cardiovascular disease, allergic rhinitis/sinusitis, atopic dermatitis/eczema, asthma, or other)
- the time of resolution of infection symptoms (absence of fever – a body temperature below 37.0°C), systemic symptoms (chills, headaches, myalgias, weakness, and loss of appetite), nasal symptoms (nasal congestion/ discharge), laryngeal symptoms (a sore throat, or other), and other symptoms
- illness time points: onset of illness, first visit to the doctor's office, and start of treatment.
- symptomatic therapy (drug name, date prescribed, and date discontinued)
- therapy for bacterial complications (date the antimicrobial drug is prescribed, drug name, diagnosis, hospitalization or no hospitalization required, date of hospitalization)
- adverse events (description of the event, causality (related/ not related to Ergoferon), severity, date of the onset, and actions taken)
- efficacy assessment of the Ergoferon treatment (high efficacy: recovery / satisfactory: improvement/ insufficient: no effect)

- observational study model: cohort

Cohort study is an observation of outcomes in a group of individuals linked by shared characteristics (an acute respiratory viral infections and use of Ergoferon).

Inclusion and exclusion criteria

Inclusion criteria

1. Data of children from 6 months to 18 years old and adults over 18 years old.
2. Diagnosis: Flu/ARVI.
3. Axillary temperature above 37.4 °C.
4. At least one systemic and/or catarrhal symptom lasting 12 hours to 3 days by the time the doctor is consulted, for which treatment with Ergoferon is prescribed.
5. A specific decision of the doctor to prescribe Ergoferon in strict accordance with the indications, regardless of the factor of including patient data in the program.
6. CRF, filled by a doctor on the basis of medical documentation, at the end of patient observation.

Exclusion criteria

1. Use for the treatment Flu/ARVI antiviral and immunomodulatory therapy except for Ergoferon.

Criteria for Withdrawal or Termination

Not applicable.

Number of subjects

It is planned to enroll 8411 patients.

Interim analysis

An interim statistical analysis is not scheduled within the study.

Treatment

Name of the medicinal product: Ergoferon

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

** Mixture of water-ethanol dilutions 100^{12}, 100^{30}, 100^{50} of active substance used for saturation of lactose monohydrate.*

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

Method of administration: Oral administration in the therapeutic dosage specified in the instructions for medical use.

Dosage form: Tablets.

Description: White to off-white, round, flat, scored on one side and beveled tablets.

Storage conditions: Store in a place protected from light, at the temperature not exceeding 25ºC. Keep out of the reach of children.

Treatment duration

The duration of the treatment course will be determined by the physician based on the registered indications, general clinical experience and treatment tolerance.

Observation period

The total duration of the program will be approximately 6 months from October 2016 to April 2017.

Symptomatic (Standard) treatment

Not applicable.

Prohibited concomitant therapy

Not applicable.

Study design scheme

Ergoferon® therapy will be carried out in accordance with the registered indications in a therapeutic dosage (treatment regimen) in accordance with the instructions for medical use.

Inside, oral use. 1 tablet per intake (outside a meal). The tablet should be kept in the mouth without swallowing until it is completely dissolved. Children from 6 months. For young children (from 6 months to 3 years), it is recommended to dissolve the tablet in a small amount (1 tablespoon) of boiled water at room temperature.

Treatment should be started as early as possible when the first signs of an acute infection appear according to the following scheme: in the first 2 hours – 1 tablet every 30 minutes, then 3 more intakes are taken at regular intervals during the first day. From the second day onwards, take 1 tablet three times a day until complete recovery.

Schedule of study procedures

This program does not provide for additional instrumental or laboratory examination of the patient, all necessary, from the point of view of the doctor, examinations will be carried out within the framework of the existing practice of managing patients with this pathology, regardless of participation in it.

Statistical Analyses

Samples

Total set includes all the subjects who have signed ICF. This sample will consider all adverse events throughout the study, including those occurred prior to the study therapy.

The sample including all subjects who received at least one dose of the study product to be used for ***analysis of the study treatment safety and tolerability*** (*Safety population*), as all adverse events identified after the study product administration will be recorded.

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

1) failure to meet inclusion/non-inclusion criteria;
2) subject failing to take any dose of the study drug;
3) absence of any data on the subject after the study drug administration.

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.***

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software.[2]

Evaluation of sample size

The sample size was prespecified.

Statistical criteria

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

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

  and
  - evaluation of 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). Data normalizing transformations (e.g. Box-Cox, Yeo-Johnson etc.) would be applied if necessary.

The following parameters and approaches are to be used:

[2] Holder of license: OOO "NPF "Materia Medica Holding", No. 70100045.

1. To evaluate the differences in continuous variables obtained in one group at two different visits – Student's test for matched samples.
2. To evaluate time changes in parameters compared - analysis of variance (ANOVA) or modified repeated measures covariance (ANCOVA).
3. In case of multiple comparisons of the groups various corrections for multiplicity will be used, e.g. Dunnett, Tukey, Scheffe, Holm adapted test, etc.
4. Generalized Linear Models and/or Mixed Linear Models will be used in case of abnormal data distribution.
5. 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 criteria

Below are potential types of comparisons with relevant criteria:

1. To evaluate time changes in the parameters compared – Friedman test, nonparametric analogue of repeated measures analysis of variance.
2. For frequency analysis of contingency tables 2×2 – $\chi 2$ (if the frequency under comparison > 5) or exact Fisher's test (if one of the frequencies under comparison < 5).
3. Cochran-Mantel-Haenszel test (modified $\chi 2$ test for multiple comparisons) – to perform frequency analysis based on independent strata.
4. 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, $\chi 2$ test and/or exact Fisher's test; Cochran-Mantel-Haenszel test.
- LIFETEST – survival analysis.
- NPAR1WAY - Mann-Whitney 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. Comparisons suggesting statistical inference will have the relevant confidence intervals. Outliers will be analyzed individually. The data will be grouped by visits. The categorical variables will be presented as frequency tables by visits.