International Multicenter Double-blind Placebo-Controlled Parallel-Group Randomized Clinical Trial of Efficacy and Safety of Ergoferon in the Treatment of Viral Intestinal Infections in Children

Phase IV

Sponsor	**OOO «NPF «MATERIA MEDICA HOLDING»**
Protocol number	**MMH-ER-008**
Version date:	**November 02, 2015**
ClinicalTrials.gov Id:	**NCT03039699**

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.

Title of Study

International multicenter double-blind placebo-controlled parallel-group randomized clinical trial of efficacy and safety of Ergoferon in the treatment of viral intestinal infections in children.

Phase: IV

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

Protocol No. MMH-ER-008

Objective of the study

- To obtain additional data on the efficacy and safety of Ergoferon in the treatment of viral intestinal infections in inpatient children.

Endpoints

Primary endpoint

1. Average diarrhea duration[1].

Secondary endpoints

1. Percentage of patients without diarrhea following 48, 72, and 96 hours of treatment.
2. Percentage of patients with recovery[2] following 48, 72, and 96 hours of treatment.
3. Average illness duration (from the enrollment to the recovery).
4. Total CDS score at 24, 48, and 72 hours after treatment initiation.
5. Average vomiting duration (if any).
6. Percentage of patients with negative PCR tests on Days 3, 4, 6, and 10 of observation versus baseline (no RNA detection of rotaviruses/ noroviruses/ astroviruses/ adenoviruses in patients who had positive tests at baseline).
7. Percentage of patients with worsening of illness[3] and/or hospital-acquired infection[4].

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1 Diarrhea duration is considered as the time between receiving the first dose of investigational medicine /placebo and the normal consistency of stool pattern (to the previous stool consistency before diarrhea), i.e.
1) time to the first loose stool which is followed by two normal consistency stools over 24 h (infants may have three episodes of loose stool over a 24-hour period), or
2) time to ≤3 episodes of stool occurring over 24 h, at least 2 of which are normal consistency stools, or
3) time to the absence of stools for ≥12 h which is not followed by new episodes of diarrhea (total stool frequency over 24 h – less than 3 times).

2 Recovery criteria: absence of diarrhea, vomiting, symptoms of dehydration, and increased body temperature (based on daily examinations by pediatrician).

3 Worsening of illness: an increase in dehydration scores and worsening of non-specific symptoms, as evidenced by a decline in general appearance, increasing fatigue and drowsiness, refusal to eat and drink, severe tachycardia/bradycardia, unstable hemodynamics, tachypnea, hypo- or hyperventilation, circulation disorders, peripheral cyanosis, sunken eyes, severe dryness of skin and mucous/tongue, poor tissue turgor, absent tears, persistent vomiting, anuria/acute kidney injury, seizure/convulsions, and meningismus.

4 **Hospital-acquired infection**: a viral or bacterial infection (intestinal, respiratory or urinary tract infection, etc.) occurring after at least 48 h of hospital stay and confirmed by laborator tests.

Safety assessment

- Adverse events (AE) during the treatment, AEs severity and relations to the study drug, and AEs outcomes.
- Changes in vital signs and laboratory parameters (complete blood count test, biochemistry blood test and urinalysis).
- Percentage of patients with abnormal biochemistry.

Study design

Study design: an international multicenter, double-blind, placebo-controlled, randomized clinical trial in parallel groups.

The study will enroll patients of either gender aged from 6 months to 6 years old who are admitted to hospital within 48 hours of the onset of acute intestinal infection (AII), presumably of viral etiology. The children with typical viral gastroenteritis/enteritis symptoms will be enrolled in the screening. The key symptom is acute watery diarrhea without visible pathological impurities (transparent mucus is possible) at least 3 times a day. Virus detection in stool specimens will be performed by polymerase chain reaction (PCR).After the parent/adopter signs a parents/adopters information sheet (Informed Consent form) for the child's participation in the clinical trial, the recording of medical history data, a medical examination including the evaluation of symptoms on the Clinical Dehydration Scale (CDS) by pediatrician, and laboratory examination[5] will be performed during Visit 1 (Day 1). If inclusion criteria are met and non-inclusion criteria are absent (day 1), the patient will be included in the trial and randomized to administer either Ergoferon or Placebo.

In addition to the standard/pathogenetic therapies, group 1 patients will take Ergoferon following a 5-day regimen, whereas group 2 patients will receive Placebo. The parents/adopters of patient will be provided with patient diary and instructed how to fill it.

Before treatment stool specimens will be collected from the patients for detection and differentiation of Rotavirus A, Norovirus 2 genotype, Astrovirus, Adenovirus F, Shigella spp., enterovasive E.coli (EIEC), Salmonella spp., and thermophilic Campylobacter spp. using a PCR assay[6] to diagnose the etiology of intestinal infection. In total the patients will be monitored for 10 days (screening, randomization, treatment initiation – Day 1; the treatment on Days 1 – 5; observation in hospital – Day 6, and follow-up period – Day 7 – 10). During the treatment and inpatient observation periods (Days 1-6, Visits 1-6), the patients will be examined daily by

[5] If an eligible patient (not meeting the non-inclusion criteria) is enrolled after the collection of blood and urine specimens for laboratory testing (specifically for the current hospitalization), these test results will be considered as the initial variables in the analysis of safety endpoints (i.e., no repeat specimen collection will be required provided the laboratory variables evaluated are those defined by this protocol).

[6] The data of a patient whose PCR test indicates a bacterial etiology of acute intestinal infection will not be included in the analysis of treatment efficacy. For the sake of sufficiency of data for the efficacy analysis, it is statistically assumed that 50% of patients will test negative for viral etiology of acute intestinal infection.

pediatrician, and the examination results, including the CDS scores, will be recorded in source documents. The patient's parent/adopter will fill patient diary on a daily basis, recording the presence/absence of diarrhea signs, vomiting, and body temperature. The pediatrician will check correctness of diary filling. After discharge on day 10 (±1) Visit 7 is scheduled (personal at the site/at home or distant/phone call) to interview the parents/adopters about the patient's health, presence of any complications, and use of medications (the investigator will fill out a questionnaire).

Collection of stool specimens and repeat PCR for Rotaviruses/Noroviruses/Astroviruses/ Adenoviruses, Shigella spp., EIEC, Salmonella spp., and Campylobacter spp. will be performed on Days 3, 4, and 6 of inpatient observation and after discharge from the hospital (Day 10); collection of blood and urine specimens for safety tests will be carried out at baseline and before hospital discharge (day 6). The recording of the intake of study therapies and of concomitant medications as well as the assessment of compliance with and safety of the study therapies will be performed on Days 2-6 and 10.

Patients who recovered while in hospital and are discharged from the unit earlier than at 5 days will undergo the procedures of Visit 6, including the collection of biological specimens for PCR (efficacy evaluation) and biochemistry, blood test and urinalysis (safety assessment). The parents/adopters will be given the blister pack with the remaining study drug so that the patient can continue the treatment.

Inclusion and exclusion criteria

Inclusion criteria

1. Patients of either gender aged from 6 months to 6 years old hospitalized to infectious department.
2. Diarrhea (watery stool without visible abnormal foreign substances [transparent mucus is possible] ≥ 3 times a day).
3. Dehydration symptoms according to CDS scale ≥1.
4. The first 48 hours from the onset of the first diarrhea episode.
5. Start of study treatment (Ergoferon/Placebo) within 12 hours after the start of the standard hospital therapy.
6. Availability of a patient information sheet (Informed Consent form) signed by the patient's parents/adopters to confirm the child's participation in the clinical trial signed by one parent/adopter of patient.

Exclusion criteria

1. Suspected bacterial intestinal infection.

2. Suspected infectious diseases of another localization including pneumonia, meningitis, sepsis, otitis media, urinary tract infection, etc.
3. Severe intestinal infection[7].
4. Severe dehydration (CDS score ≥7).
5. Anuria (acute kidney injury).
6. Medical history or prior diagnosis of serious diseases, including primary/secondary immunodeficieny, oncological disease, diabetes mellitus, infantile cerebral palsy, mucoviscidosis/cystic fibrosis etc.
7. Exacerbation or decompensation of a chronic disease, including diseases of the digestive system that would affect the patient's ability to participate in the clinical trial.
8. Malabsorption syndrome, including congenital or acquired lactose intolerance/lactase deficiency or any other disaccharidase deficiency and galactosemia.
9. Allergy/ intolerance to any of the components of study drugs.
10. Course administration of any medicines listed in the section "Prohibited concomitant treatment" for 2 weeks prior to the enrollment in the trial.
11. Participation in other clinical trials within 3 months prior to the enrollment in this study.
12. Patients whose parents/adopters, from investigator's point of view, will fail to comply with the observation requirements of the trial or with the dosing regimen of the study drugs.
13. The patient's parent/adoptive parent are a study specialist of the centre and is directly involved in the study, or is an immediate family member of the Investigator. Spouses, parents, children, or siblings, regardless of whether they are siblings or adopted are considered immediate family members.
14. The patient's parent/adoptive parent works for OOO "NPF "Materia Medica Holding", i.e. they are employees of the Company, temporary employees on a contract basis or appointed officials responsible for conduction of the study or their immediate family members.

Criteria for Withdrawal or Termination

1. The patient`s inability or refusal of the patient or parents/adopters to follow the protocol requirements.
2. The necessity to use medications prohibited within this trial.
3. An adverse event requiring discontinuation of the study drug.
4. The patient's or his/her parent/adopter wish to complete the study ahead of schedule for any reason.

[7] Criteria for a severe intestinal infection: sudden patient deterioration, sudden fatigue or even adynamia, marked apathy and drowsiness/excessive sleepiness and lethargy, dry mucous membranes, sunken eyes, loss of tearing, pool tissue turgor, lack of eye contact in the child on examination, aversion to food and drink, severe tachycardia/bradycardia, unstable hemodynamics, tachypnea, hypo- or hyperventilation, impaired microcirculation, peripheral cyanosis, slow capillary nail refill, persistent vomiting, anuria/acute renal disease, convulsions, and meningism.

5. Cases not specified by the protocol when, according to the investigator's opinion, further participation in the study harms the patient.
6. Incorrect inclusion of ineligible patient.
7. Early discharge of patient from hospital with persisting acute intestinal infection symptoms on days 2-5 of hospitalization, before the end of taking the study therapy at the parent's/adopter's request.

Number of subjects

It is planned to enroll 572 patients, which is expected to allow completion of all protocol procedures by at least 286 PCR-positive (for viral acute intestinal infection) patients (143 patients in the Ergoferon and Placebo groups).

Interim analysis

An interim statistical analysis will be performed as part of this study.

The interim analysis will be based on the patient assessment data and treatment outcomes recorded for the protocol-defined number of patients who have completed participation in the study.

Number of patients to be evaluated in the interim analysis:

144 patients (72 in the Ergoferon group and 72 in the Placebo group).

Number of patients to be evaluated in the final analysis:

286 patients (143 in the Ergoferon group and 143 in the Placebo group).

Treatment

Group 1

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: Tablet for oral use. Dose per administration - 1 tablet per intake (outside a meal/feeding). Within the first 2 hours - 1 tablet every 30 minutes, followed by 3 more tablets at time intervals equally separated throughout the rest of the day; from day 2 to day 5 − 1 tablet 3 times daily. For oral administration to a child aged from 6 months to 3 years old the

tablet should be dissolved in 10 mL of boiled water of room temperature (or solution used for oral rehydration).

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 25^{o}C. 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 Ergoferon scheme.

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 25^{o}C. Keep out of the reach of children.

Treatment duration

Ergoferon/Placebo treatment duration is 5 days.

Observation period

In total, the patient is observed up for 10 days (screening, randomization, treatment initiation – day 1, study therapy – days 1-5, hospital follow-up – day 6, personal visit (study site/home)/phone call − day 10).

Symptomatic (Standard) treatment

Throughout the study the patients can receive pathogenetic therapy for acute intestinal infections which includes:

1. Nutritional Interventions

Breast-feeding should not be interrupted. The volume and composition of food depends on the child's age, the severity of diarrhea symptoms, and preceding diseases. The frequency of feeding and amount of food per meal is determined by the child's age and presence and frequency of vomiting/regurgitation.

2) Oral rehydration using hypoosmotic rehydration compound Hydrovit ®[8].

3) Intestinal adsorbent (diosmectite − Smecta®).

4) Probiotic (Linex®).

[8] In medical centers of Uzbekistan the oral rehydration formulations authorized in these countries will be used.

In case of special indications and/or complications, the pediatrician may prescribe syndrome-specific treatments, such as enteral (nasogastric) or pareteral (intravenous) rehydration salt formulations and detoxicants, antiemetics (Domperidone/Metoclopramide), antipyretics (Paracetamol/Ibuprofen, or Metamizole - for fever not relieved by paracetamol/ibuprofen).

Prohibited concomitant therapy

Two weeks prior to enrollment[9] and during the study (from the time of signing the information sheet (Informed Consent Form) and screening initiation), it is prohibited to administer the following medications:

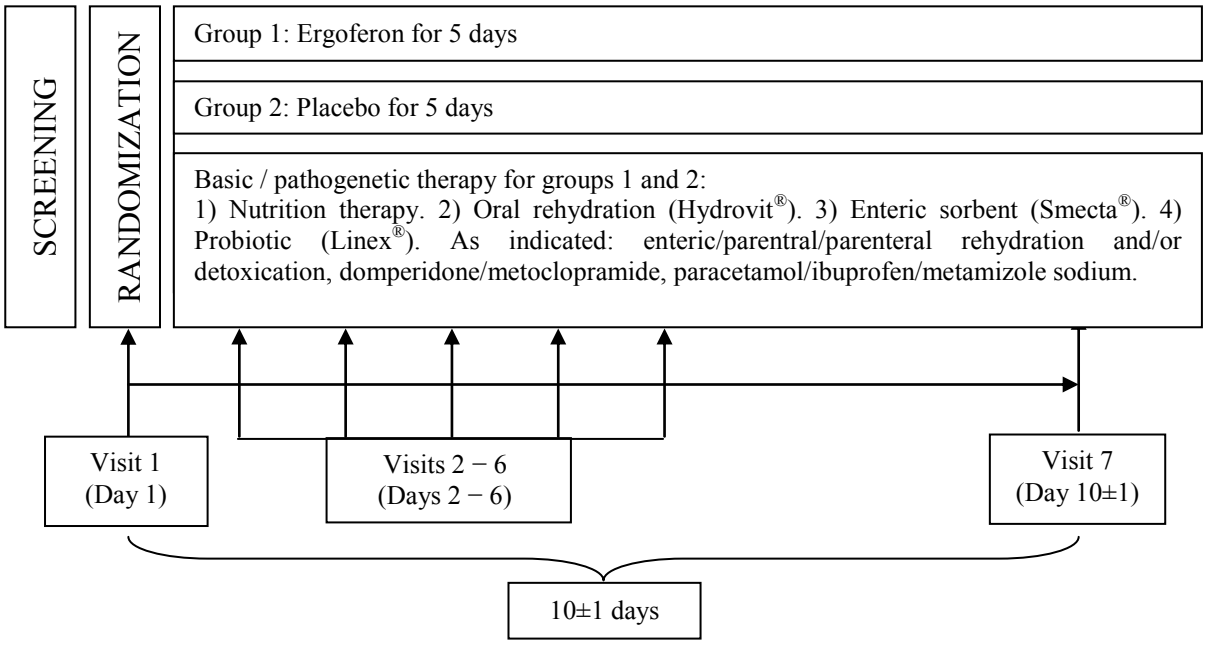
1. Antibacterials, including enteric antimicrobial agents (sulfonamide and trimethoprim preparations).
2. Antidiarrheal microorganisms (excluding Linex®).
3. Intestinal antiinflammatory agents.
4. Intestinal adsorbents (excluding diosmectite).
5. Antispasmodics and antipropulsives.
6. Antiemetics (excluding domperidone and metoclopramide).
7. Laxatives.
8. Digestives, including enzymes.
9. Prebiotics.
10. Nonsteroidal antiinflammatory drugs (excluding ibuprofen).
11. Analgesics and antipyretics (excluding paracetamol and metamizole).
12. Antiviral drugs except for Ergofern and Oseltamivir (Tamiflu®), which are prescribed within this study.
13. Immunostimulants, including interferon inducers (acridone acetic acid, meglumine acridone acetate, polyadenylic acid + polyuridylic acid, methylphenylthyomethyl-dimethylaminomethyl-hydroxybromindol carboxylic acid ethyl ether, sodium oxo-dihydro-acridinyl acetate, cagocel, tilorone, umifenovir); pidotimod, synthetic immunostimulants (levamizol or alfa-glutamyl-tryptophan); bacterial immunomodulators (including ribomunyl, ribonucleate sodium, deoxyribonucleate sodium, IRS 19, umudon etc.);
14. Immune sera and immunoglobulins (J06).
15. Vaccines.
16. Antineoplastic agents and antineoplastic endocrine therapy.
17. Immunosuppressants.
18. Corticosteroids for systemic use.

[9] A single use by a patient of any of the drugs on the 'non-permitted medications' list (sections 1-11) in the course of 48 hours prior to enrollment is not considered a non-inclusion criterion.

19. Homeopathic medicines.

20. Drugs known to previously cause allergic reactions in the patient.

Study design scheme



Schedule of study procedures

Procedure/Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 10±1
Informed consent	+						
Collection of complaints	+	+	+	+	+	+	
Medical history	+						
Physical examination	+	+	+	+	+	+	
Body weight measurement	+					+	
Body length/height measurement	+						
Evaluation of dehydration symptoms using CDS	+	+	+	+	+	+	
Diary supply	+						
Checking the correctness of filling the diary		+	+	+	+	+	
Parent/adopter inquiry (personal/by phone) and filling questionnaire “Parent’s/adopter’s inquiry data”							+
Return of patient diary						+	
Concomitant therapy	+	+	+	+	+	+	+
Eligibility assessment	+						
Obtaining stool sample for PCR diagnosis	+		+	+		+	+*
Safety laboratory tests (hematology, serum chemistry,	+					+	

urinalysis)							
Randomization and prescription of study drug	+						
Study drug supply	+						
Basic medication supply	+	+	+	+	+		
Study drug accountability, compliance assessment						+**	+**
Evaluation of treatment safety	+	+	+	+	+	+	+

** All the subjects will receive sterile containers for stool storage and transportation on day 10. In case of a phone visit on day 10 stool samples will be delivered to the local laboratory by a courier.*
*** Return of the study product is made after 5-day treatment course (on Day 6). If the subject is discharged sooner than on day 6, the parent/adopter will be given a blister with the remaining product to complete outpatient therapy; in this case the product return and determination of compliance will be made on Day 10±1.*

Statistical Analyses.

Samples

Total set: all patients included in the study whose parents/adoptive parents signed the Informed Consent Form for the patient's participation in the study. All AEs including those occurred prior to the study therapy will be considered throughout the study for this sample.

Safety population: all patients who received at least one dose of the study drug. This sample will be used to ***analyze the study treatment safety and tolerability***, since all the AEs identified after the study product administration will be recorded.

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

1) non-compliance with inclusion / exclusion criteria ;
2) the patient has not taken a single dose of the study drug;
3) lack of any data of the patient following randomization;
4) withdrawal of a patient due to early discharge (discharge of patient with persistent symptoms of acute intestinal infections on days 2-5 of hospitalization before the study treatment is completed at the parent's/adopter's request).

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

Per protocol set. This sample includes all patients who completed the therapy as per the study protocol without any missing visits or significant protocol deviations. This sample will be used for the ***Per Protocol analysis (PP- analysis) of the the study therapy efficacy***.

Mean value in Placebo group for the relevant day will be used to fill lacking/missing data.

Data treatment and all statistical calculations under the protocol will be made using SAS-9.4 statistical software[10].

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

Evaluation of sample size

The sample size has been 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 are 2-sided;

1.4 the calculation of the sample size is based on the assumptions about the expected effects, mainly declared in the primary efficacy criterion of the Protocol;

1.5 statistical null and alternative hypotheses are formulated as follows:

$$\mathbf{H_0: m_2-m_1 \leq 0}$$

$$\mathbf{H_1: m_2-m_1 > 0},$$

where $\mathbf{m_1}$ – mean disease duration in Ergoferon group,

$\mathbf{m_2}$ – mean disease duration in Placebo group;

1.6 to assure potential adjustment of sample size or terminate the study due to inadequate efficacy/high efficacy, interim analysis will be carried out in which:

a. calculations will be made using O'Brien-Fleming boundary;

b. proportions of the subjects completing the study and yielding the results for interim and final analyses, will be taken as 0.5 and 1.0 (i.e. interim analysis will be made after recruitment of half of the planned number of the clinical study subjects.

1.7 therefore, sample size will be calculated taking into account

a. interim analysis;

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

1.8 calculation of sample size of groups 1 and 2 for two-sided test for interim and final analysis will be made using the formula:

$$\mathbf{N_1=N_2=(\sigma_1^2 + \sigma_2^2)\, I},$$

where $\mathbf{N_1}$ and $\mathbf{N_2}$ are sample sizes in Ergoferon and Placebo groups;

$\mathbf{\sigma_1}$ and $\mathbf{\sigma_2}$ are expected standard deviations in groups 1 and 2;

I – Fisher's information determined using the formula:

$$\mathbf{I=(F^{-1}(1-\alpha)+F^{-1}(1-\beta))^2/\theta^2},$$

where $\mathbf{F^{-1}(1-\alpha)}$ and $\mathbf{F^{-1}(1-\beta)}$ are tabular values of z-test for $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$, a $\boldsymbol{\theta} = (\mathbf{m_1}-\mathbf{m_2})$.

1.9 final sample size will be determined using the formula:

$$\mathbf{N_F = N_{PP}/(1-C_w)},$$

where $\mathbf{N_F}$ – final sample size;

$\mathbf{N_{PP}}$ – result of calculation in cl. 1.8, i.e. scheduled number of subjects completing the study per protocol;

$\mathbf{C_W}$ – withdrawal coefficient.

2. Assumptions about the expected effects of the clinical study.

Given that the results of the previous studies, the difference between Ergoferon effect consisting in reduced mean diarrhea duration and Placebo effect is expected to be at least 12 hours in favour of Ergoferon with group standard deviation of at least 36 hours[11].

According to the statistical considerations and assumptions above, each group size will be:

a) at interim analysis - 72 subjects;
b) at final analysis - 143 subjects.

Hence, full PP analysis set will included 286 patients.

Given potential negative results of PCR diagnosis, screening failures and further withdrawals for various reasons it was decided to double the sample ($\mathbf{C_w}$=50%) and and enroll at least 572 subjects (286 per group).

Statistical criteria

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

- parametric – to evaluate continuous and interval random variables;
- non-parametric – for:
  - assessments of equality / inequality in the proportion of patients when compared for different visits,
  - analysis of frequencies of the compared features,
  - assessment of continuous and interval random variables in case of violation of the normality assumption.

The following SAS procedures are supposed to be used for interim analysis:

- SEQDESIGN, SEQTEST – design and performance of interim analysis.
- Conditions for early study termination will be established using O'Brien-Fleming stopping boundary.

Parametric criteria

[11] According to the report for multicenter double-blind placebo-controlled parallel-group randomized clinical study of therapeutic efficacy and safety of anti-IFN at rotavirus infection in children (phase III), mean diarrhea duration in active product group was 1.9±1.2 days, in Placebo group - 2.9±1.8 days.

The application of parametric criteria will be accompanied by a check for normality of the compared samples (Kolmogorov-Smirnov test).

The following parametric methods and approaches are supposed to be used:

1. To assess the differences of continuous variables obtained in two different (independent) groups –Student t-test for independent samples.
2. To assess the differences of continuous variables obtained in one group at two different visits – Student t-test for for paired samples.
3. To assess the temporal dynamics of the compared indicators – analysis of variance (ANOVA) or covariance (ANCOVA) in the modification with repeated measures.
4. In case of multiple comparisons between the groups will apply a variety of corrections for multiplicity Dunnett, Tukey, Scheffe, Holm adaptive test, etc.
5. In case of abnormal data distribution, approaches with the Generalized Linear Models and / or Mixed Linear Models will be used.
6. 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 assess the differences of continuous variables obtained in two different (independent) groups – Mann-Whitney U-test.
2. To assess the temporal dynamics of the compared indicators – Friedman test, non-parametric analogue of analysis of variance with repeated measures.
3. 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).

4. For the frequency analysis of cross tables with independent strata – Cochran–Mantel–Haenszel test (modification of the χ^2-test for multiple comparisons).
5. 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 – 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. Comparisons suggesting statistical conclusion 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.