CLINICAL STUDY REPORT

1. COVER PAGE

Name of the protocol: Multicenter open-label randomized trial with an active control group to evaluate the efficacy and safety of Polisorb® MP in the complex therapy of patients with atopic dermatitis.

Date of the report:	12/23/2024
Version:	1.0
Protocol No./Protocol code:	PRT-2690-Polisorb-SS
Date and version of the protocol:	2.0 dated 08/29/2023
Research phase:	III
The main researchers:	Gudkova I.N., Mitrofanov V.S., Givirovskii S.E., Evstafev S.E., Ziganshin O.R., Minchenko A. A., Sonin D.B., Khotko A.A
Start date of the study: (first-patient-in):	04/10/2024
End day of the study (database lock):	11/28/2024
Funder:	JSC “Polisorb”, Russia
Address:	Tomskaya str., 2, Kopeysk, Chelyabinsk region, 456652, Russia.
Name and contacts of CRO:	LLC «Ligand Research» Russia, 115419, Moscow, 2nd Verkhny Mikhailovsky passage, 9, building 2, office 501 Tel: +7 495 225 51 94 E-mail: info@ligand-research.com

This study was conducted in accordance with the protocol of the study, the Provisions of the International Council of Harmonization on Good Clinical Practice (ICH GCP), including compliance with the requirements for archiving primary documentation, and the decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 79 "On Approval of the Rules of Good Clinical Practice of the Eurasian Economic Union».

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SIGNATURE PAGE

Name of the study:
«Multicenter open-label randomized trial with an active control group to evaluate the efficacy and safety of Polisorb® MP in the complex therapy of patients with atopic dermatitis».

The clinical study report has been reviewed and approved:

Funder of the study:
JSC "Polisorb", Russia
Tomskaya str., 2, Kopeysk, Chelyabinsk region, 456652, Russia.
Project manager
Artamonov Sergei
Medical advisor JSC "Polisorb"

Signature _____Date _____

Contract research organization:
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Clinical Research Project Manager
Kipaikina Natalya Vladimirovna

Signature _____Date _____

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Version and date of the report 1.0 dated 12/23/2024 г.
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Research No. PRT-2690-Polisorb-SS

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I confirm that the Report reflects the goals and objectives of the clinical trial, complies with the approved Protocol, principles of good clinical and laboratory practice, applicable regulations of the Russian Federation, the EAEU, guidelines and orders of the state regulatory authority, applicable standard operating procedures (SOP) and policies.
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I confirm that all employees involved in conducting this study were properly qualified, strictly observed/monitored compliance with the procedures of the Study Protocol, authority in the research team, and the procedure for handling drugs and research materials.
All cases of adverse events have been documented and reported properly, in accordance with the Protocol.
I confirm that all documents of this study are kept properly in accordance with the requirements of Good Clinical Practice and local legislation.
Thus, I have read this report and, based on my knowledge of this study, I hereby confirm that it correctly outlines the procedures for conducting the study and its results.

Chief Researcher from the clinical center

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Gudkova Inna Nikolaevna

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Chief Researcher from the clinical center

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Dmitry Borisovich Sonin

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Chief Researcher from the clinical center

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Khotko Alkes Aslancherievich

2. SYNOPSIS

<table>
<tr><td>Name of the funder/company:
JSC “Polisorb”, Russia</td><td rowspan="3">A separate research table related to a part of the Dossier
Volume:
Page:</td><td rowspan="3">(This field is used by national authorized authorities only)</td></tr>
<tr><td>Name of the finished product:
Polisorb® MP</td></tr>
<tr><td>Name of the active ingredient:
Colloidal silicon dioxide</td></tr>
<tr><td colspan="3">Name of the study: Multicenter open-label randomized trial with an active control group to evaluate the efficacy and safety of Polisorb® MP in the complex therapy of patients with atopic dermatitis.</td></tr>
<tr><td colspan="3">Researchers: Gudkova Inna Nikolaevna, Mitrofanov Vladimir Sergeevich, Givirovskii Stanislav Evgenevich, Evstafev Sergei Vladimirovich, Ziganshin Oleg Raisovich, Minchenko Aleksandr Aleksandrovich, Sonin Dmitrii Borisovich, Khotko Alkes Aslancherievich.</td></tr>
<tr><td colspan="3">Research centers:
Detailed information on the centers, additional centers, researchers, and the number of patients enrolled in the centers is provided in Appendix 16.1.4.</td></tr>
<tr><td colspan="3">Publication (link): At the moment, there have been no publications regarding the study.</td></tr>
<tr><td colspan="2">Research period (years): 2023
First-patient-in – April 10, 2024
Date of last patient's last visit – September 9, 2024
Database lock: 11/28/2024</td><td>Drug development phase:
III</td></tr>
<tr><td colspan="3">Aims: evaluation of the efficacy and safety of the addition of the drug Polisorb® MP, powder for suspension for oral administration (JSC “Polisorb”, Russia) to the complex therapy of patients with mild and moderate atopic dermatitis receiving basic therapy.</td></tr>
<tr><td colspan="3">Study methodology:
The total duration of the study for the patient was no more than 30 days, taking into account the intervals for visits to the center.
All patient visits to the clinical center were carried out on an outpatient basis. The study included an introductory part - the screening period (up to 3 days, Visit 1). Main part of the study: Visit 2 – randomization and inclusion in one of the study groups: Group 1 – BT (basic therapy) + SD (study drug) and Group 2 – basic therapy (BT), treatment period (14 days), follow-up period (10 days). An unplanned visit could also have been scheduled (similar to the completion visit).
Visit 1 – (Days -3-0) screening – included the following:
• Informed consent signing
• Collection of medical history, including the duration of the underlying disease, previous and concomitant diseases, previous and concomitant therapy
• Electrocardiography in 12 standard leads
• Evaluation based on SCORAD, DLQI, BRS, IGA, EASI indexes and questionnaires
• Physical examination, including measurement of weight, height, assessment of the main indicators of body condition (BP, heart rate), body temperature
• Blood samples for general and biochemical analysis (glucose, ALT, AST, total protein, cholesterol, bilirubin, creatinine, uric acid)
• Blood samples for hepatitis/HIV in the absence of test results performed within 3 months prior to the screening visit
• Common urine analysis (pH, relative density, protein)
• Urine pregnancy test for women with childbearing potential
• Checking the inclusion/non-inclusion criteria
• Registration of adverse events
Visit 2 – (Day 1) randomization
• Assessment of exclusion criteria
• Assessment of the main body parameters (blood pressure, heart rate), body temperature</td></tr>
</table>

- Evaluation based on SCORAD, DLQI, BRS, IGA, EASI indexes and questionnaires
- Issue of the study drug
- Randomization
- Monitoring of hygiene procedures
- Assessment of concomitant therapy
- Registration of adverse events
- Issue of the patient's diary

Visit 3 – Intermediate treatment visit - Day 7±1

- Assessment of exclusion criteria
- Assessment of the main body parameters (blood pressure, heart rate), body temperature
- Assessment based on SCORAD and BRS indexes and questionnaires
- Monitoring of hygiene procedures
- Assessment of concomitant therapy
- Registration of adverse events
- Checking the patient's diary

Visit 4 – completion of the study - Day 14±1

- Assessment of exclusion criteria
- Assessment based on SCORAD, DLQI and BRS indexes and questionnaires
- Physical examination, including assessment of the main indicators of the body's condition (blood pressure, heart rate), body temperature
- Electrocardiography in 12 standard leads
- Taking blood samples for general and biochemical analysis (glucose, ALT, AST, total protein, cholesterol, bilirubin, creatinine, uric acid)
- General urinalysis (pH, relative density, protein)
- Urine pregnancy test for women with childbearing potential
- Return of the drug
- Mmonitoring of hygiene procedures
- Assessment of concomitant therapy
- Registration of adverse events
- Checking and returning the patient's diary

Visit 5 – delayed monitoring session-Day 24±2

- assessment of exclusion criteria
- assessment of the main body parameters (blood pressure, heart rate), body temperature.
- scores on SCORAD, DLQI, BRS, IGA, EASI indexes and questionnaires
- hygiene compliance
- assessment of concomitant therapy
- registration of adverse events

Unplanned visit

TheRRVto the clinic were performed in case of exclusion of the patient from the study based on the criteria of premature completion of the study and randomization. The session procedures were similar to the completion session.

Number of patients:
It was planned to:
Скринированные:Screened: 180
Randomized:162
Protocol population: 162
Analyzed:роанализировано:
Patients analyzed: Screened: 163
Randomized: 162
Protocol population: 161

Diagnoses and main inclusion criteria:

1. Age of patients from 18 to 65 years inclusive with a weight of more than 60 kg
2. Patient's written informed consent, as well as the desire and ability to comply with all aspects of the protocol

3. Clinical diagnosis of atopic dermatitis with the following characteristics:
   - presence of a verified diagnosis of Atopic dermatitis (ICD code 10: L20) according to the criteria of J. M. Hanifin and G. Rajka, no more than 3 years old
   -mild to moderate severity-SCORAD value from 20 to 40, inclusive
   - no signs of secondary infection
   - presence of pruritus (symptom intensity according to the BRS questionnaire ≥ 6)
   - the total score of the disease by the researcher on the IGA scale of 2 or 3 points
4. Non-smokers, current smokers and previous smokers patients with a history of smoking <10 pack-years (number of pack-years = [number of cigarettes per day/20] x number of years of smoking [i.e., smoking 20 cigarettes per day for 10 years years corresponds to 10 pack-years or 10 cigarettes per day for 20 years corresponds to 10 pack-years])
5. The patients must have tested negative for pregnancy at the screening visit, and they must have agreed to use suitable non-hormonal contraception during the study (i.e., women who are capable of childbearing should use highly effective contraceptives such as a condom and spermicide, a diaphragm or cervical cap and spermicide, a condom and diaphragm or cervical cap,etc.). non-hormonal IMU), or the women had to be unable to bear children, i.e. have undergone surgical sterilization (having a history of hysterectomy, or bilateral tubal ligation, or bilateral oophorectomy; partial hysterectomy or having a partner with vasectomy is not sufficient), be in a postmenopausal state (spontaneous amenorrhea for 12 months), or agree to abstain from sexual intercourse
6. . All male patients had to agree to abstain from sexual contact, or to use the highly effective methods of contraception described above
7. . The patient had to use the same products for washing and applying to the skin (soaps, lotions, creams, ointments, protective products, etc.) and hair (shampoo, balm, etc.) for at least two weeks. less than 2 weeks prior to the screening visit and must have agreed to continue using them for the entire study period
8. Ability to independently and correctly apply the investigational drugs
9. Patient's willingness to cooperate in performing research procedures.

Test preparation (T)

Trade name	Polisorb® MP
Chemical name	Colloidal Silicon dioxide
Grouping name	Enterosorbent agent [Adsorbents]
Dosage form	Powder d / suspension. for oral
administration Method of administration	orally
Packaging	Polymer cans
Manufacturer	JSC "Polisorb", Russia
Series/Shelf	life P26050423 / 04.2028

Duration of treatment: 14 days

Dose, method of administration of the study drug and the reference drug:

In the course of the study, two treatment groups were formed:

Group 1: Basic Therapy (BT) + Study drug (IP)

Group 2: Basic therapy (BT)

Basic therapy-taking up to 14 days:

- Permanent Use –
- On-demand Clients:
  - Pimecrolimus, cream for external use, is applied in a thin layer up to 2 times a day
  - Permanent use-cetirizine 10 mg, tablets, inside, 1 time a day

Single dose-1-2 tablespoons with a slide on half a glass of water, just before meals.

The daily dose is 15-20 gramsof the drug (6 tablespoons "with a slide") dividedx into 3-4 times a day, the course of therapy is 14 days. Ingestion only in the form of an aqueous suspension immediately before meals. The suspension is prepared by carefully stirring the required amount of the drug in ¼ or ½ cup of water. After stirring, an opaque suspension of white or almost white color is formed.

Evaluation criteria:

Efficiency:

- Mean change in the SCORAD index on day 14 of treatment (Visit 4) compared to the initial assessment (Visit 2)

- Average change in the total BRS score for Sessions 3, 4, and 5 compared to Session 2
- Average change in the total DLQI score for Sessions 4 and 5 compared to Session 2
- Average change in the SCORAD index for Sessions 3 and 5 compared to the original score (Session 2)
- Number of days of taking antihistamines from Visit 2 to Visit 4 based on the patient's diary
- Number of days of using a topical drug from Visit 2 to Visit 4 based on the patient's diary
- Average change in the EASI index by Visit 5 compared to Visit 1
- Average change on the IGA scale by Visit 5 compared to Session 1.

Security:

- Percentage of patients (%) with AE in the treatment groups at the end of follow-up.

Statistical methods:

Primary and secondary analyses

Statistical data processing was performed in the R software package (version 3.2.1). Continuous (quantitative) data are presented as the number of observations, arithmetic mean, 95% confidence interval (CI) for the mean, standard deviation, minimum and maximum. For data whose distribution is very different from the normal distribution, the median and interquartile range are additionally presented. Ordinal, categorical, and qualitative data are represented using absolute frequencies (quantities). observations) and relative frequencies (percentages). Theefficiency estimation was based on primary and secondary endpoints..

To evaluate the primary efficacy criterion-the average change in the SCORAD index on day 14 of treatment (Visit 4) compared with the initial assessment (Visit 2), we analyzed the ITT population using a mixed effects model for multiple measurements (MMRM), in which the treatment group was included as mixed effects factors, and the initial group was included as a mixed effect factor. score - as a covariate, with an unstructured covariance matrix among visits for each treatment group. Sensitivity analysis was performed on the PP population. For secondary qualitative performance variables, the comparison between groups 1 and 2 was performed using Pearson's $\chi 2$ criterion if the frequency in each cell is ≥ 5, otherwise-using the exact Fisher criterion.

For secondary quantitative performance variables, the comparison between groups 1 and 2 was carried out using the Student's t-test when the data distribution corresponds to the normal distribution law, otherwise using its nonparametric analog – the Mann-Whitney U-test. Verification of compliance with the normal distribution law was carried out using the Shapiro-Wilk criterion. The following characteristics were used for the quantitative efficiency variable: arithmetic mean, standard deviation, median, quartiles, minimum, maximum, and coefficient of variation. For high-quality ones, these are the frequencies (fractions and/or percentages). During the analysis, it was possible to expand the list of methods used, if this was necessary for high-quality data processing.

Summary-conclusions:

There were no differences between the ITT and PP populations in the study (one patient (declined to participate 06-025 immediately after randomization, did not take the drug). The results are presented on data from the ITT population, which made up the full data set (FAS-full analysis set). Data from 161 patienta were analyzed, the majority of the population was 61.5,% female, and the mean age (hereinafter: arithmetic mean ± standard deviation, median) of the population was 38.9 ±12.70, 39 years. There were no differences between the groups in terms of demographic and anthropometric parameters (height and weight). The groups незначительно differed slightlyin the calculation of BMI (u) 26.0±3.81, 25.0 vs. 24.9± 3.07, 24.6, p= 0.041.

In the study population, 19 (11.8%) patients had a bad habit (smoking) and smoked an average of 9.5±5.00 cigarettes per day. 39 (24.2%) patients consumed alcohol. No differences were found in the subgroups. The most common diseases (occurrence in more than 10% of patients) in the subgroups were (group data are presented in the sequence BT+IP vs BT): upper respiratory tract viral infection-8 (10.0%) vs. 8 (9.9%) patients, essential hypertension-9 (11.3%) vs. 9 (11.1%), chronic gastritis 11 (13.8%) vs. 4 (4.9%), there were no differences between the groups. Differences were registered in the frequency of registration of muscle, skeletal and connective tissue disorders, which were more often registered in the BT group 2 (2.5,%) versus 9 (11.1,%), p= 0.030,. The most common medications used to treat the underlying disease Prior to inclusion in the study, there were drugs from the corticosteroid group (topical use), which were used in 28 (35.0%) patients versus 31 (38.3%) and systemic antihistamines 25 (31.3%) versus 29 (35.8%). The drugs of choice were: betamethasone 15 (18.8%) vs. 15 (18.5%), methylprednisolone aceponate 11 (13.8%) vs. 11 (13.6%), cetirizine 11 (13.8%) vs. 10 (12.3%). In the course of the study, 29 (36.3%) vs. 29 (35.8%) cosmetic products were used mainly. There were no statistically significant differences in previous and concomitant therapy between the groups.

The group of patients who used only basic therapy consisted of 81 patients, in the study group Polisorb® MP was additionally prescribed in addition to ВТПолисорб® МП, the group consisted of 80 patients. Adherence to basic

therapy in both groups was 100%, compliance with Polisorb® MP in the BT+IP group (n=80) was 95.4 ±4.27%, 95.2%.

Performance evaluation results:

The primary parameter in this study was the mean change in the value andndex of SCORAD on day 14 of treatment (Visit 4) compared to the initial assessment (Visit 2).

The analysis showed a statistically significant decrease in the severity of atopic dermatitis manifestations according to the SCORAD index when Polisorb® MP was added to the basic therapy. The course of treatment was 14 days (from Visit 2 to Visit 4). Analysis of variance (ANOVA) of changesя индекса in the SCORAD index by day 14 of treatment showed positive dynamics in both groups. At visit 2, in the basic therapy group (BT) , the total score on the SCORAD index was 32.4,±5.33,, 33.6,, in the basic therapy group with the study drug (BT+IP), 32.6,±5.04,, 33.6,p=0.875,. After 14 days , the total score on the SCORAD index was 14.7,± 7.97,, 13.3,vs. 11.1,± 7.39,, 9.8,p=0.003,. Differences in dynamics were significant: -17.7,±7.80,, -17.8,vs -21.5,±7.48,, -22.1,p=0.002,. The dynamics of the primary parameter wasa analyzedby a mixed linear model with repeated measurements (MMRM). The analysis results are presented below.

Variable		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Differences
Session 2	LS-mean±CO	32.4446±0.5765	32.5735±0.5801	
Change to session 4	LS-mean±CO	-17.6974±0.8492	-21.5120±0.8545	3.6857±1.2123
	95% DI for LS-mean	16.0203 -19.3745	19.8244 -23.1996	1.2913- 6.0800
	6.0800 P-value	<.0001	<.0001	0.0028
	Note: Statistical method: (MRMM), LS-mean – caverage value according to the least squares method, CO – standard error of the mean.			

An exploratory analysis was performed to assess the effectof the os effect on the results of the primary parameter: therapeutic group (p = 0.0028,0028), visit (p<.0001) and combined effect group * visit (p=0.0190,0190), the results indicate in favor of adding Polisorb® MP to the basic therapy.

Secondary performance variables.

The average change in the total BRS score for Sessions 3, 4, and 5 compared to the initial assessment of Session 2.

Differences in the dynamics of the total BRS scoreS index score for sessions were significant between the groups, with a pronounced effect in the BT+IP group.

Visit	Basic therapy N=81	Basic therapy + Study drug N=80	p-value
	Mean ± CO (median)	Mean ± CO (median)	
Session 2*	6.1 ±0.58 (6.0)	6.1±0.37 (6.0)	0.734#
Session 3-3	**.0±-2.4 (-2.0)**	**-3.6±-2.9 (-2.03)**	**0.010#**
Session 4-4	**.3±1.55 (-4.0)**	**-4.8±1.48 (-5.0)**	**0.047#**
Session 5-4	**. 4 ± 1.94 (-5.0)**	**-5.1±1.46 (-6.0)**	**0.013#**
Note. CStatistical method: # - Comparison was performed by analysis of variance(ANOVA), mean – arithmetic mean, CO – standard deviation. * - initial data of the total index score.			

Mean change in the overall DLQI score by Visits 4 and 5 compared to the initial assessment of Visit 2.

Analysis of the dermatological Quality of life index (DLQI) revealed significant differences between the groups at the end of treatment (visit 4). The interpretation of the scale is inversely directed, the higher the score, the more negatively the disease affects the patient's quality of life. On session 2, no differences were found between the groups; on subsequent sessions, significant differences were noted. At visit 4, the total score in the BT + IT group was 3.6±3.81, 3.0 vs. 5.1±3.57, 4 in the BT group (p=0.015), and at visit 5 - 2.1± 3.12, 1.0 vs. 3.4± 3.60, 2.0 (p=0.010), respectively. Despite the improvement in quality of life indicators, there were no differences in dynamics between the groups: -5.6±4.02, -5.0 vs. -6.8± 4.72, -6.5 p= 0.089. This may be due to the high individual variability in the perception of symptoms.

Visit	Basic therapy N=81	Basic therapy + Study drug N=80	p-value
	Mean ± CO (median)	Mean ± CO (median)	
Session 2 (original index score)	10.6±4.79 (10.0)	10.4±4.59 (10.0)	0.731#
Session 4 (values)	5.1±3.57 (4.0)	3.6±3.81 (3.0)	0.015#
Session 4 (dynamics from the Session 2)	**-5.6±4.02 (-5.05.0)**	**-6.8±4.72 (-6.5)**	**0.089#**
Session 5 (values)	3.4± 3.60 (2,0)	2.1± 3.12 (1.0)	0,010#
Session 5 (dynamics from the Session 2)	**-7.2±4.70 (-6.0)**	**-8.3 ± 4.90 (-8.0)**	**0.134#**

Note: CStatistical method: # - Comparison was performed by analysis of variance (ANOVA), mean – arithmetic mean, CO – standard deviation.

The average change in the SCORAD index by Visit 3 and 5 compared to the initial assessment of Visit 2.
Differences in the dynamics of the SCORAD index between the groups by day 7 (visit 3) of treatment were significant, this was also observed during the delayed follow-up period (10-12 days) after the end of treatment (visit 5).

Visit	Basic therapy N=81	Basic therapy + Study drug N=80	p-value
	Mean ± CO (median)	Mean ± CO (median)	
Session 2 original index score	32.4±5.33 (33.6)	32.6 ± 5.04 (33.6)	0.875#
Session 3 dynamics	**-10.1±6.19 (-10.0)**	**-12.7 ± 6.23 (-13.3)**	**0.008#**
Session 5 dynamics	**-19.3 ± 9.78 (-19.0)**	**-24.3 ±8.92 (-24.9)**	**<0.001#**

Note: CStatistical method: # - Comparison was performed by analysis of variance (ANOVA), mean – arithmetic mean, CO – standard deviation.

Number of days of taking antihistamines and pimecrolimus from Visit 2 to Visit 4 based on the patient's diary.
Cetirizine and topical pimecrolimus were the Basic therapy, различий with no differences in the duration of treatment between the groups.

Variable	Basic therapy N=81	Basic therapy + Study drug N=80	p-value
	Mean ± CO (median)	Mean ± CO (median)	
Duration of cetirizine	administration 13.7±0.75 (14.0)	13.8±0.82 (14.0)	0.634#
Duration of pimecrolimus	administration 13.7±0.84 (14.0)	13.6±0.85 (14.0)	0.754#

Note: CStatistical method: # - Comparison was performed by analysis of variance (ANOVA), mean – arithmetic mean, CO – standard deviation.

Averagechangeндексain EASI idex a by Session 5 compared to Session 1.
According to the EASI index, there were no significant changes between the groups, which indicates that there are no changes in the area of atopic dermatitis damage to the skin of patients.

Variable	Basic therapy N=81	Basic therapy + Study drug N=80	p-value
	Mean ± CO (median)	Mean ± CO (median)	
EASI index on a session 1	3.6±3.41 (2.4)	3.5±3.32 (2.4)	0.840#
Dynamics of the overall EASI Index score per Session 5-2	**.1±2.76 (-1.4)**	**-2.3±2.70 (-1.5)**	**0.606#**
Note: cStatistical method: # - Comparison was performed by analysis of variance(ANOVA), mean – arithmetic mean, CO – standard deviation.			

Average change on the IGA scale by Visit 5 compared to Visit 1.
Despite the absence of the EASI lesion area in the dynamicsto the EASI index, the results of changes on the SCORAD index are supported by an IGA score (Investigators' Global Assessment), which is used to assess the severity of atopic dermatitis according to the doctor's opinion. Theevaluation was performed on a delayed follow-up visit, according to which a score of 0 points corresponds to clean skin, and a maximum score of 4 points corresponds to severe atopic dermatitis. By visit 5 (10-12 days after the end of treatment) in the BT+ IP group, the score decreased from 2.6±0.49, 3.0 to 0.9± 0.90, 1.0 and in the BT group from 2.6 ± 0.49, 3.0 to 1.4±0.89, 2.0, the differences at visit 5 between the groups were statistically significant (p<0.001). Differences in dynamics were significant -1.7±0.88, - 2.0 vs. -1.2± 0.79, - 1.0 (p<0.001).

Variable	Basic therapy N=81	Basic therapy + Study drug N=80	p-value
	Mean ± CO (median)	Mean ± CO (median)	
IGA scale on the session 1	2.6±0.49 (3.0)	2.6 ± 0.49 (3.0)	0.701#
Dynamics of the overall EASI Index score per Session 5-1	**.2±0.79 (-1.0)**	**-1.7 ± 0.88 (-2.0)**	**<0.001#**
Note: cStatistical method: # - Comparison was performed by analysis of variance (ANOVA), mean – arithmetic mean, CO – standard deviation.			

Safety assessment results:
Analysis of laboratory parameters and physical parameters revealed no statistically significant differences between the groups. Analysis of changes in laboratory parameters using shift tables did not reveal specific deviations characteristic of any group, and it is impossible to determine the trend towards a pathological effect of the studied therapy on specific parameters, both in terms of the sum of changes and in terms of values. Significant deviations in the assessment ofvital signs were registered as AES.
During the study, 34 AES were registered in 26 patients (16.1%), including 12 AES in 10 (12.3%) patients in the "BT" group, and 12 AES in the BI+group.IP - 22 AE in 16 patients (20.0%), without significant differences (p=0.187). The majority of AES were mild: 31 AES in 23 (14.3%) patients, by groups: in the BT+IT group-21 AES in 15 (18.8) patients and 10 AES in 8 (9.9%) patients in the BT group. ARhythmias (1 AE in the BT + IP group), increased transaminase levels (1 AE in the BT group), and exacerbation of atopic dermatitis (1 AE in the BT group) were considered to be of moderate severity. No serious AES were reported. Analysis of the structure of AES showed significant differences (p= 0.001), all gastrointestinal AES were observed in the study therapy group. There were 15 AES in 12 (15%) patients, including constipation - 9 AES in 7 patients (8.8%), of which 7 AES in 5 (6.3%) patients had a definite association and one AES with probable and possible links. 2 cases of dyschesia in 2 patients, one case oforo abdominal discomforta (1 AE) had a definite association with the therapy and one case was reported: bloating, dry mouth, nausea, a drug connection was considered "possible".
There were no significant differences in the remaining systems between the groups; the second most common after AES from the gastrointestinal tract were disorders of the nervous system.No drug-related association was established with AES such as headache (4 AES in 4 (4.9%) patients in the BT group and 1 AES in one patient (1.3%) in the BT+ IT group), one episode of dizziness in one patient (1.2%) in the BT group. In the BT+ IP group,

one case was registered: viral infection of the upper respiratory tract, dental pulpitis, repolarization disorders on the electrocardiogram, arrhythmia, and 2 AES - hypertension. In all cases, there was no association with the current therapy. In the BT group, the following AES were reported: increased transaminase levels (1 AES), grade 1 AV block (1 AES), essential hypertension (1 AES), back pain (1 AES), pain at the application site (2 AES, original description - tingling sensation in the area of applying the cream), There was no association between Basic therapy and events. In the BT group, 1 AE was registered - an exacerbation of atopicкого dermatitisa, the relationship was considered "possible".

All events resolved, the outcome is not known for the following AES: increased transaminases (1 AES in the BT group), arrhythmia (1 AES in the BT + IP group), and exacerbation of atopic dermatitis (1 AES) in the BT group.In relation to the actions taken in connection with AE: concomitant therapy was prescribed for back pain (1 AE in the BT group), pulpitis (1 AE in the BT + IP group), headache (2 AE in the BT group and 1 AE in the BT + IP group), dizziness (1 AE in the group BT), upper respiratory tract viral infection (1 AE in the BT group = IP), hypertension (2 AE in the BT + IP group). No action was taken in relation to the study therapy.

General conclusion based on the results obtained:

Based on the data obtained on the efficacy, safety and tolerability of Polisorb ® MP in the form of por. d / suspension. for oral administration, a research conclusion can be formulated – the drug can be recommended for addition to basic therapy for the treatment of patients with mild to moderate atopic dermatitis as part of complex therapy. Taking the drug can cause constipation and associated dyschesia, as well as dyspepsia in the form of abdominal discomfort, bloating, dry mouth, and nausea. These events with an assumed causal relationship can generally be classified as expected, and have already occurred. indicated in the OHLP of the drug Polisorb ® MP and are characteristic of the group of adsorbents. No symptoms of overdose were observed.

Conclusion: A multicenter open-label randomized trial with an active control group was conducted to evaluate the addition of the drug Polisorb® MP, por. d/suspension. for oral administration (Polisorb JSC, Russia) to the complex therapy of patients with mild to moderate atopic dermatitis receiving basic therapy. The study was conducted in accordance with the current regulatory norms of the Russian Federation, Good Clinical Practice of the EAEU and the Helsinki Declaration. The main objective of this study was to evaluate the efficacy and safety of Polisorb® MP, por. d/suspension. for oral administration (JSC Polisorb, Russia) as an additional drug in complex therapy. The effectiveness criterion was a change in the overall score on the SCORAD index, the study demonstrated clinical benefit when adding Polisorb ® MP, por. d/suspension. for oral administration (JSC Polisorb, Russia for basic therapy. There were no differences in the safety profile, but taking the drug is accompanied by side effects from the gastrointestinal tract such as constipation, dyspeptic phenomena.

Report Date:

23.12.2024

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

BP	Blood pressure
ATC	Anatomical-therapeutic-chemical classification
DBP	Diastolic blood pressure
CI	Confidence interval
Value	Value
UMU	Instructions for medical use
BMI	Body Mass index
IRC	Individual registration card
CIO	Contract Research organization
CS	Clinically significant
CIS	Clinically insignificant
Max.	Maximum value
MOH	Ministry of Health
Min.	The minimum value
NNR	Unexpected adverse reaction
AE	adverse events
CBC	Complete blood count
RU	Registration certificate
SBP	Systolic blood pressure
USAR	Unexpected serious adverse reaction
SAR	Serious adverse reaction
SD	Standard deviation
FZ	Federal law
RR	Respirationxcc rate
HR	heart rate
ECG	Electrocardiography
DF	the Number of degrees of freedom
Coefficient Contingency	Coefficient Contingency
Cramer's V	Cramer’s test
Covariance Structure	Covariance Structure
Dependent Variable	Dependent steamandthe m
Degrees of Freedom	Degree of freedom
Diff	Difference
Equality of Variances	Equality of variance
Estimation methods	Method estimates
Fixed Effects SE	Metod estimates of the standard errors from fixed effects
Folded F	Method fold f
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ITT	Intent-to-treat
N or n	Number
n/a	Not applicable
MedDRA	Medical dictionary of regulatory activities
Err.	probability of error when rejecting the null hypothesis (errors of the first kind)
Phi Coefficientp	Coefficient Phi
Coefficient Pr	Probability
Pooled	Pooled estimation variance
PP	Population of patients who completed the study according to the protocol [per protocol]
Residual Variance	Method for estimating the residual variance

5. ETHICAL ISSUES

5.1. Organization's Expert Council/Independent Ethics Committee (ESO/NEC)

Prior to the start of the study, all relevant documents, including the study protocol, patient information sheet, and формy the study informed consent form, were submitted to regulatory authorities and approved by them prior to the start of the study. This study was conducted after the appropriate ethical review of the Ethics Council and obtaining the approval of Independent Committees for the Ethical Review of research centers. All approved documents were obtained before patients completed any study procedures, including screening procedures to assess whether the patient could be included in the study.
Prior to the study, the Sponsor provided the NEC with up-to-date and complete copies of the following documentation:

- Protocol of the study, version 2.0 dated 08/29/2023
- Patient information sheet with an informed consent form, version 2.0 dated 02/02/2022;
- Researcher's brochure versionверсии 2.0 dated 08/29/2023г.;
- List of medical organizations where a clinical trial is expected to be conducted.

The main documents are presented in the Appendix 16.1.1.

Regulatory and ethical issues
As part of regulatory approvals, the study was approved by the Ethics Council (Minutes of Meeting No. 688 of November 29, 2023).
Before starting the study, the institution's management approved the research team.
Copies of the above-mentioned documents, as well as a list of all ESOs/NECs in which the study documentswere considered, are given in Appendix 16.1.3.

5.2. Application for conducting research in accordance with ethical principles

The study was conducted in accordance with the legal requirements and ethical principles set out in the Constitution of the Russian Federation (Article 21), Federal Law" On the Circulation of Medicinal Products " (No. 61-FZ of April 12, 2010 , as amended), the Helsinki Declaration of the World Medical Association (as amended in 2013, Fortaleza), and the rules of Good Clinical (practice. ICH GCP), the European Union Directive 2001/20 / EC, the EAEU Rules of Good Clinical Practice (approved by the Decision of the Council of the Eurasian Economic Commission No. 79 of November 3, 2016), the Order of the Ministry of Health of the Russian Federation No. 200n of April 1, 2016 "On Approval of the Rules of Good Clinical Practice".
The researchers involved in the clinical trial provided the Sponsor with signed and dated summaries containing a description of the Researcher's research activities, and also confirmed that they were informed about the principles of conducting clinical trials.
Qualified, trained and experienced personnel participated in the study.
Appendix 16.1.4 to the report provides a list of researchers and their organizations, their roles (responsibilities) in the study, and their qualifications.

5.3. Informed consent

The "Patient Information" and "Informed Consent" forms are provided in the study documentation. The Sponsor will receiveил a written approval or positive opinion from the EC/LEK regarding the informed consent form, as well as any other printed information intended to be provided to patients before starting CI. The process of obtaining informed consent of the patient should precede any procedure in this study in accordance with the ICH GCP principles.

The researcher explained to each patient the nature of the study, its purpose, the procedures used, the expected duration, possible risks and benefits, and any adverse events that it might cause. Each patient was informed that participation in the study is voluntary and that he / she can withdraw from the study at any time and that withdrawal of consent will not affect his / her subsequent treatment or relationship with the attending physician.
Compliance with ethical standards during the study was guaranteed by the approval of the study by the Ethics Council and Independent Ethical Committees and the signing of an Informed Consent Form by the patient.

A sample Informed Consent Form is included in Appendix 16.1.3.
Date when the last patient signed informed consent:

IP version and date	**Date of signing the version by the last patient**
Version 2.0 from 29.0.08.202.2023	16.0.08.2024.2024

6. RESEARCHERS AND ADMINISTRATIVE STRUCTURE OF THE STUDY

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Research Center (s):
The Appendix 16.1.4. to the report contains a list of researchers and their organizations, as well as a list of documents confirming their qualifications.

7. introduction

General information

According to the World Health Organization (WHO), the prevalence of allergic diseases has quadrupled over the past 25 years. Currently, more than 550 million people suffer from various forms of allergies, allergic diseases occupy the third place among various nosologies (in different countries from 10% to 40%). [18,21,21]

Allergic diseases that occur at an early age can last a lifetime: from infancy to extreme old age. Currently, due to the high prevalence of allergic diseases, starting from early childhood, the search for new methods of their prevention and treatment is very popular. Considering the pathogenetic mechanisms of these diseases, it is possible to identify common cause-dependent factors – both in food allergies and in chronic dermatoses [3]. The risk of allergopathology increases with hereditary predisposition, genetically determined insufficiency of the skin barrier function, pathology of the gastrointestinal tract (GIT), violation of the functional state of the central and autonomic nervous systems [4].

The mechanism of gradual development of allergies is as follows: ingestion of an antigen causes its sensitization. Sometimes sensitization is defined very broadly — as an increased reaction of the body to substances of an antigenic or haptic nature. In this case, the concept of sensitization merges with the concept of allergy [2]. Allergens have a different origin and nature and are classified by location: exogenous factors include a variety of allergens (food, household, tick-borne, pollen-bearing, fungal, epidermal, medicinal) and non-specific stimuli (climate, stress, smoking, cold). Endogenous factors are pathologic conditions associated with atopic dermatitis (AD). In 80-90% of children with atopic dermatitis, pathological changes in the gastrointestinal tract are observed, in 20-30% - in the respiratory system, and in 15-18% - in the kidneys. Violation of the barrier function of internal organs contributes to a faster intake of exo-allergens. With a long, continuously recurring course of the disease, the vast majority of patients have their elimination processes disrupted. There is an accumulation in tissues and biological fluids of products of impaired metabolism, the content of bile acids increases, the concentration of biologically active substances (histamine, serotonin, eicosanoids, cytokines, etc.) formed in the body during significant antigenic stimulation. The syndrome of endogenous intoxication develops. Clinically, the syndrome of endogenous intoxication is manifested in the form of marbling of the skin, acrocyanosis, grayish skin tone, dryness and peeling. Currently, a scientific point of view has been formed that allergic diseases develop under the influence of genetic and environmental factors Thus, the antigenic load on the body of factors of exogenous and endogenous origin plays one of the most important roles in the mechanisms of disease development.

For the purpose of detoxification, efferent therapy is used, aimed at removing allergens and toxins from the body. The most effective of them are sorption methods, which are widely used in pediatric practice [2].

Enterosorption is a treatment method based on the ability of an enterosorbent introduced into the gastrointestinal tract to bind and remove exogenous substances, pathogenic and opportunistic microorganisms and their toxins, endogenous intermediate and end products of metabolism (allergens, biologically active substances), viruses, gases that enter the gastrointestinal tract, diffuse into the intestinal lumen from the blood, they are secreted and can accumulate or enter the gastrointestinal tract. The enterosorbent does not enter into a chemical reaction with the sorbed substance and does not cause biochemical changes in the blood. Enterosorbents are drugs of various structures that bind exo-and endogenous substances in the gastrointestinal tract by adsorption. Intestinal villi are able to pass through all ingredients whose molecular weight is lower than that of albumin, and since toxic substances are based on the average molecular weight, the effectiveness of enterosorption in eliminating endotoxicosis becomes clear.

The therapeutic effect of enterosorbents is considered from the standpoint of direct and indirect effects. Direct action – the ability to bind poisons and xenobiotics directly from the lumen of the digestive system. Indirect action-suppression or weakening of toxic-allergic reactions, inflammatory processes, reducing the load on the detoxification and erection organs, eliminating flatulence and

improving the trophic structure of the intestinal wall. Advantages of enterosorption: a small number of contraindications, no complications, no changes in the biochemical composition of blood during a sustained course of treatment, non-invasiveness, does not require additional equipment and personnel, is much cheaper and simpler than hardware methods, although it is comparable in effects to them [3]. Enterosorbent drugs, which have long been successfully used for the treatment of intestinal infections, find their application points in the treatment of allergic diseases. This is due to the mechanism of action of this group of drugs: active sorption of toxins, infectious agents, allergens from the gastrointestinal tract lumen against the background of a decrease in the barrier function of the intestinal wall. Also, in addition to their effectiveness, drugs of this group have a significant therapeutic breadth, practically no side effects, which makes them practically irreplaceable in the treatment of many diseases [5, 6]. In food and drug allergies, AD, the use of sorbents in complex therapy leads to a more rapid regression of skin rashes and subjective sensations (reduction of hyperemia, dryness, itching of the skin, edema and dermatitis), normalization of gastrointestinal function. There is a positive dynamics of laboratory parameters, the number of patients decreases. eosinophils in the blood, the level of total IgE decreases [7].

The effectiveness of using Polisorb® MP sorbent (colloidal silicon dioxide) in the treatment and prevention of diseases based on allergic reactions is explained by the ability of the drug to bind and remove any allergens that enter the gastrointestinal tract with food or are formed during digestion. Polisorb® MP also binds and removes biologically active substances involved in the development of allergic reactions (circulating immune complexes, IgE), which are released into the intestinal lumen through blood and lymphatic capillaries. The effect of Polisorb® MP is that its smallest particles surround allergens, glue them together and remove them through the intestines. Allergen molecules are relatively large, and most sorbents are not able to effectively deal with them, while Polisorb® MP, due to its unique spatial structure, which it forms with water, is able to surround and remove allergens and undigested food particles from the body, which can cause painful reactions. For this reason, Polisorb® MP is indicated not only for food allergies, but also for diathesis, drug allergies, dermatitis, and other allergic diseases [3].

Previously conducted pilot studies of Polisorb® MP in adults and children in the complex therapy of atypical dermatitis showed that the inclusion of the drug in the initial therapy from the first day of hospitalization has a positive therapeutic effect on the manifestations of atopic dermatitis, and affects the reduction of IgE levels, which accordingly reduces the duration of the disease and the duration of hospitalization [8].

This study was initiated in order to obtain additional data on the effectiveness of Polisorb® MP therapy in the complex therapy of dermatoses. If positive results are obtained, a clarification will be made in the OHLP indicating the possibility of using the drug in the complex treatment of patients with an established diagnosis: atopic dermatitis (ICD code 10: L20).

8. PURPOSE AND OBJECTIVES OF THE STUDY

The aim of this study was to evaluate the efficacy and safety of adding the drug Polisorb® MP, por. d / suspension. for oral administration (Polisorb JSC, Russia) to the complex therapy of patients with mild to moderate atopic dermatitis receiving basic therapy.

Research objectives:

1) ПодтверConfirmation of the advantagesa of adding the drug Polisorb® MP, por. d / suspension. for oral administration (Polisorb JSC, Russia) to the basic complex therapy of patients with mild to moderate atopic dermatitis compared to the basic therapy;

2) ПроведениеConducting a comparativeoro analysisa of data on the safety and tolerability of the drug Polisorb® MP, por. d / suspension. for oral administration (Polisorb JSC, Russia) in patients with mild to moderate atopic dermatitis receiving basic therapy.

9. RESEARCH PLAN

9.1. General design and plan - description of the study

The study was a multicenter, randomized, phase III clinical trial.

The study was conducted on the territory of Russia on an outpatient basis.

The study population was to consist мof men and women aged 18 to6.5 years, with aconfirmedм diagnosis of atopic dermatitis with the following characteristics: the presence of a verified diagnosis of Atopic dermatitis (ICD code 10: L20) according to the criteria of J. M. Hanifin and G. Rajka, no more than 3 years old; mild and moderate severity – SCORAD value from 20 to 40, inclusive; no signs of secondary infection; presence of pruritus (symptom intensity according to the BRS questionnaire ≥ 6); overall assessment of the disease by the researcher on the IGA scale of 2 or 3 points. It was planned that 180 patients would be screened, of which 162 пациентов patients would be randomly assigned to 2 groups in a 1:1 ratio.

The total duration of the study for the patient was no more than 30 days, taking into account the intervals for visits to the center.

All patient visits to the clinical center were performed on an outpatient basis. The study consisted of several stages:

- Screening (up to 3 days, 1 Visit) - included informed consent, medical history collection, and assessment of the patient's condition.
- Randomization (Visit 2) - patients were divided into two groups: BT (basic therapy) and BT+IP (basic therapy + study drug).
- The main treatment period (14 days) included taking the study drug in accordance with the prescribed regimen.
- Follow-up (10 days) - evaluation of efficacy and safety.

An unscheduled session may also have been scheduled (similar to the completion session).

Session 1- (Day-3-0) screening - included:

- signing of informed consent
- collection of medical history, including the duration of the underlying disease, past and concomitant diseases, previous and concomitant therapy
- electrocardiography in 12 standard leads
- score based on SCORAD, DLQI, BRS, IGA, and EASI indexes and questionnaires.
- physical examination, including measurement of weight, height, assessment of the main indicators of the body's condition (blood pressure, heart rate), body temperature
- taking blood samples for general and biochemical analysis (glucose, ALT, AST, total protein, cholesterol, bilirubin, creatinine, uric acid)
- taking blood samples for hepatitis / HIV in the absence of test results performed within 3 months prior to the screening visit
- general urinalysis (pH, relative density, protein)
- urine pregnancy test for women with childbearing potential
- checking the inclusion/non-inclusion criteria
- registration of undesirable events

Session 2 – (Day 1) randomization

- evaluation of exclusion criteria
- assessment of the main indicators of the body (blood pressure, heart rate), body temperature.
- score based on SCORAD, DLQI, and BRS indexes and questionnaires

- issuing the study drug
- randomization
- monitoring compliance with hygiene procedures
- assessment of concomitant therapy
- registration of undesirable events
- issuing a patient's diary

Visit 3-Intermediate treatment visit-Day 7±1

- evaluation of exclusion criteria
- assessment of the main indicators of the body (blood pressure, heart rate), body temperature.
- score based on SCORAD, BRS indexes and questionnaires
- monitoring compliance with hygiene procedures
- assessment of concomitant therapy
- registration of undesirable events
- checking the patient's diary

Session 4 - completion of the study-Day 14±1

- evaluation of exclusion criteria
- score based on SCORAD, DLQI, and BRS indexes and questionnaires
- physical examination, including assessment of the main indicators of the body's condition (blood pressure, heart rate), body temperature
- electrocardiography in 12 standard leads
- taking blood samples for general and biochemical analysis (glucose, ALT, AST, total protein, cholesterol, bilirubin, creatinine, uric acid)
- general urinalysis (pH, relative density, protein)
- urine pregnancy test for women with childbearing potential
- drug refund
- monitoring compliance with hygiene procedures
- assessment of concomitant therapy
- registration of undesirable events
- checking and returning the patient's diary

Session 5-delayed follow-up session-Day 24±2

- evaluation of exclusion criteria
- assessment of the main indicators of the body (blood pressure, heart rate), body temperature.
- score based on SCORAD, DLQI, BRS, IGA, and EASI indexes and questionnaires
- monitoring compliance with hygiene procedures
- assessment of concomitant therapy
- registration of undesirable events

Unscheduled session

It was performed when a patient was excluded from the study based on the criteria of premature completion of the study and randomization. The session procedures were similar to the completion session.

The research design is shown in Figure 1 as a graphical diagram.

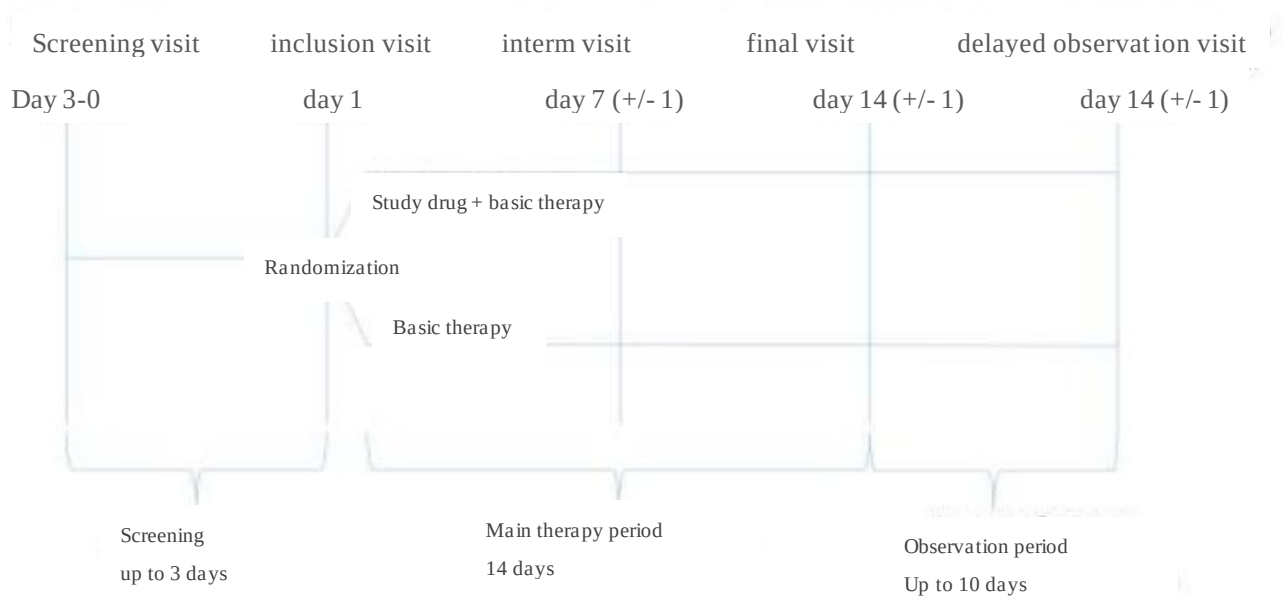


Figure Ошибка! Закладка не определена.**. Graphic diagram of the study**

9.2. Justification of the study design, including the choice of the control group

The study design was developed in accordance with the recommendations of the European Medical Agency guidelines (EMA, CPMP/EWP/252/03), as well as recommendations of the Board of the Eurasian Economic Commission No. 25 of September 2, 2019 "On Guidelines for Preclinical and clinical development of combined Medicines", Federal Clinical Guidelines for the Management of Patients with Atopic Dermatitis [9]. According to the requirements, a combination of 2 or more active substances that have an established effectiveness for the target indication for use is developed to increase the effectiveness of therapy (greater clinical response of the patient to taking the combined drug) compared to the primary therapy of any of the monocomponent drugs containing these active substances. The superior efficacy of such a combination and its acceptable safety profile should be confirmed by conducting a randomized controlled trial with an assessment of the clinical outcome at a specific time point. The duration of therapy and the dosage regimen of Polisorb® MP was chosen taking into account the approved MOH OHLP, according to which therapy can last up to 14 days for allergic diseases. The duration and mode of use of basic therapy is presented in accordance with the clinical recommendations "Atopic dermatitis" of the Ministry of Health of the Russian Federation 2021 [9]. After 14 days of the main treatment period, the doctor may decide whether to continue basic therapy.

The basic therapy in the study was unified on the basis of clinical recommendations for the treatment of patients with atopic dermatitis [9], according to which the following areas are provided for the treatment of mild and moderate severity: moisturizing and emollient agents, external therapy and systemic therapy of atopic dermatitis to reduce the intensity of itching. According to the clinical guidelines: "The choice of the drug and its form is carried out individually, taking into account the patient's preferences, individual skin characteristics, season, climatic conditions", due to ethical standards, the patient will not be limited to using individual products. External therapy provides, according to clinical recommendations, a number of drugs, for the purposes of the study, drugs with the highest degree of evidence were identified (Level of persuasiveness of recommendations A, level of reliability of evidence-1): drugs "Topical drugs containing calcineurin inhibitors" – Pime crolimus, cream for external use is indicated for both short-term and long-term use treatment of mild to moderate atopic dermatitis in adults, adolescents, and children. Cetirizine was chosen as a systemic therapy for pruritus, as it has the highest degree of evidence among all the listed ones - the level of persuasiveness

of recommendations B (level of reliability of evidence – 2). Treatment of patients with moderate blood pressure involves consideration and possible administration of systemic corticosteroids and immunosuppressive drugs. Patients requiring systemic therapy will not be part of the study population, as they require different therapeutic approaches to treatment. In accordance with the chosen design, it is planned to clarify the superiority of the use of basic therapy in combination with the drug "Polisorb®". MP" compared to the use of basic therapy after 14 days of treatment for exacerbation of moderate atopic dermatitis in adult patients.

In order to select the primary endpoint, we analyzed literature data on the selection and harmonization of methods for studying outcomes in eczema and atopic dermatitis, in particular, the HOME initiative [10]. According to this publication, the SCORAD index is the most frequently (used method (more than 30% of cases) for assessing the outcome of atopic dermatitis and eczema, and is an objective and validated assessment method. Moreover, (the minimal clinically important difference (MCID) of 8.7 points was determined for the SCORAD index [11], which is actively used in clinical trials of drugs for atopic dermatitis. Thus, the primary endpoint in the present study was the indicator "change in the SCORAD index by day 14 of basic therapy with Polisorb® MP compared to the initial score". Within the framework of secondary points, the impact on the intensity of pruritus (BRS index), quality of life (Dermatological Quality of Life Index DLQI) will be studied. былиChanges in the IGA and EASI scales were analyzed as additional assessments.

Safety was assessed based on reported adverse events in two treatment groups.

In this regard, this study is a multicenter, open-label, randomized trial with an active control group to evaluate the efficacy and safety of Polisorb MP in the complex therapy of patients with atopic dermatitis. The aim of the study was to demonstrate the superiority of adding Polisorb® MP, powder for suspension, to the basic therapy. for oral administration (Polisorb JSC, Russia) compared to the control group receiving only basic therapy in patients with atopic dermatitis.

9.3. Selection of the studied population

9.3.1. Inclusion criteria

The study included patients who met all the specified criteria:

1. Age of patients from 18 to 65 years inclusive with a weight of more than 60 kg;
2. Providing the patient with written informed consent, as well as the willingness and ability to comply with all aspects of the protocol;
3. Clinical diagnosis of atopic dermatitis with the following characteristics:
   - the presence of a verified diagnosis of Atopic dermatitis (ICD code 10: L20) according to the criteria of J. M. Hanifin and G. Rajka, no more than 3 years ago
   - mild to moderate severity-SCORAD value from 20 to 40, inclusive
   - no signs of secondary infection
   - the presence of pruritus (the intensity of the symptom according to the BRS questionnaire ≥ 6)
   - the overall assessment of the disease by the researcher on the IGA scale of 2 or 3 points
4. Non-smokers, current smokers and previous smokers patients with a history of smoking <10 pack-years (number of pack-years = [number of cigarettes per day/20] x number of years of smoking [i.e., smoking 20 cigarettes per day for 10 years corresponds to 10 pack-years or 10 cigarettes per day for 10 years). within 20 years corresponds to 10 pack-years]);
5. The patients must have tested negative for pregnancy at the screening visit, and they must have agreed to use suitable non-hormonal contraception during the study (i.e., women who are capable of childbearing should use highly effective contraceptives such as a condom and spermicide, a diaphragm or cervical cap and spermicide, a condom and diaphragm or cervical cap, etc.). non-hormonal IMU), or the women had to be unable to bear children, i.e. have undergone surgical sterilization (having a history of hysterectomy, or bilateral tubal ligation, or bilateral

oophorectomy; partial hysterectomy or having a partner with vasectomy is not sufficient), be in a postmenopausal state (spontaneous amenorrhea for 12 months), or agree to abstain from sexual intercourse. contacts

6. Male patients had to agree to abstain from sexual contact, or use the highly effective methods of contraception described above;
7. The patient must have used the same skin cleanser and application products (soaps, lotions, creams, ointments, protective products, etc.) and hair products (shampoo, balm, etc.) for at least 2 weeks prior to the screening visit and must have agreed to continue using them for the entire study period;
8. Ability to independently and correctly apply the studied drugs;
9. The patient's willingness to cooperate in performing research procedures.

9.3.2. Критерии Non-inclusion criteria

Patients could not be included in the study if at least one of the following non-inclusion criteria was met:

1. Data on the presence or presence in the anamnesis of allergies or hypersensitivity to colloidal silicon dioxide or any other substances that are part of the study preparations;
2. Patients with a history of allergic reactions and hypersensitivity to any topical or systemic medications containing tacrolimus and pimecrolimus;
3. Patients with a history of allergic reactions and hypersensitivity to antihistamines containing cetirizine;
4. Patients who require the use of systemic therapy (including corticosteroid therapy, immunosuppressive drugs, etc.) for the treatment of atopic dermatitis ;
5. Severity of atopic dermatitis according to the IGA researcher's general disease assessment scale of 1.4 points;
6. Patients with severe endocrine diseases (including insulin-dependent diabetes mellitus), which, in the opinion of the study, may affect the assessment of the effects of the study drugs;
7. Patients with cancer;
8. Patients who require the use of other topical medications (with the exception of basic therapy drugs), which may affect the evaluation of the effectiveness of the study drugs;
9. Topical application of corticosteroid, antibacterial and antifungal medications less than 2 weeks before the screening visit;
10. Use of inhaled corticosteroids less than 30 days before the screening visit;
11. Use of immunomodulators/ immunosuppressants, cyclosporine, methotrexate, phototherapy less than 30 days before the screening visit;
12. Vaccination less than 2 months before the screening visit, atypical rash morphology, rheumatoid arthritis, alopecia areata, psoriasis, molluscum contagiosum, including less than 2 weeks field of application, localization of foci in the scalp;
13. Use of prolonged forms of glucocorticosteroids less than 6 months prior to inclusion in the study;
14. Any changes in the skin that make it difficult to interpret the results of the study (for example, vitiligo, scars, hyperpigmentation, etc.);
15. Patients with immunodeficiency conditions / diseases;
16. A history of chronic renal failure;
17. History of liver dysfunction;
18. Any skin disease affecting the area of intended application of the drug – bacterial, viral, fungal infections of the skin, etc.;
19. Currently active herpes, chickenpox, shingles, tuberculosis, syphilis, other infectious skin diseases, any reactions to vaccines;
20. Acute infectious diseases less than 4 weeks before the screening visit or at the time of screening;

21. Regular alcohol consumption exceeding 5 units of alcohol per week (1 unit of alcohol corresponds to 30 ml of strong alcohol or 325 ml of beer) and/or information about alcoholism, drug addiction, and drug abuse in the anamnesis;
22. Hepatitis B, hepatitis C, HIV infection, or a history of syphilis.
23. Pregnancy or breastfeeding (for women);
24. Patients who participated in other clinical trials for 3 months. prior to the screening visit , or who took other investigational medications for 5 drug half-lives prior to the screening visit (whichever is longer);
25. Inability or inability to comply with protocol requirements, including for physical, mental, or social reasons, according to the researcher.

9.3.3. Criteria for termination of patients ' participation in the study

Unrelated to the study therapy:

- The occurrence of an exacerbation of the course of atopic dermatitis, leading to the use of additional therapy;
- The course of atopic dermatitis, which is complicated by a secondary infection
- Withdrawal of the patient's consent to participate in the study;
- The occurrence of serious or intolerable AES that, in the researcher's opinion, require the patient to be withdrawn from the study (please complete the AES section in the IRC; including serious AES[SES], death);
- The patient, according to the researcher, was not был able to use the investigated drugs properly;
- Continuing to participate in the study was notло in the best interests of the patient's health, based on the researcher's opinion.
- The patient, according to the researcher, does not meetthe requirements for conducting research procedures;
- The presence of deviations from the protocol that, in the opinion of the Sponsor and the researcher, requiredовали the patient's withdrawal from the study;
- The researcher canг withdraw the patient from the study if the patient hadелись significant comorbidities or underwentлась surgery during the study.
- A positive pregnancy test result at any time during the course of the study.

Related to the study therapy:

- Unavoidable adverse eventsthat requireddiscontinuation of the test drug;
- Deterioration of the condition due to the ineffectiveness of the studied pharmacotherapy,which requiresdiscontinuation of the studied therapy and the use of an alternative one.

9.4. Treatment

9.4.1. Prescribed treatment

In the course of the studyбыли, two treatment groups were formed:
Group 1: Basic therapy + Study drug
Group 2: Basic therapy

Basic therapy-taking up to 14 days:

- Permanent use-emollients
- On demand:
  - Pimecrolimus, a cream for external use, is applied in a thin layer up to 2 times a day
  - Permanent use-cetirizine 10 mg, tablets, inside, 1 time a day

Dosage regimen: A single dose-1-2 tablespoons with a slide (1 tablespoon contains 2.5-3 grams) in half a glass of water, just before meals.

The daily dose is 15-20 gramsof the drug (6 tablespoons "with a slide") dividedx into 3-4 times a day, the course of therapy is 14 days.

Method of administration: Oral administration only in the form of an aqueous suspension immediately before meals. The suspension is prepared by carefully stirring the required amount of the drug in ¼ or ½ cup of water. After stirring, an opaque suspension of white or almost white coloris formed.

According to the recommendations for the management of patients with atopic dermatitis, treatment of mild to moderate severity involves the use of basic therapy, external and antihistamine therapy (as indicated) [9, 12]:

Continuous use of basic therapy: Use of moisturizers and emollients (emollients) externally.

Commentson: Emollients couldbe used in the form of lotions, creams, ointments, detergents, bath products. The choice of the drug and its formis made individually, taking into account the patient's preferences, individual skin characteristics, season, climatic conditions and previous experience of use.

Recommendations for use: Patients with atopic dermatitis было needed to constantly, frequently and in large quantities use moisturizers and emollients (at least 3-4 times a day) both independently and after water treatments.

To achieve a clinical effect, it was necessary to use a sufficient amount of emollient drugs (an adult with a common skin lesion consumes up to 600 grams per week).

The most pronounced effect of moisturizing and emollient preparationsis observed when they are constantly used in the form of cream, ointment, bath oil and soap substitutes. The choice of the drug and its formis made individually, taking into account the patient's preferences, individual skin characteristics, season, season, and climate. They were supposed to be odorless, colorless, and contain preservatives. Ointment-based products (more oily ones) could be used in the cold season, and in the summer, creams and gels with a high water content could be used more frequently. Lotions were characterized by a higher content of water, which could evaporate, so they should not be used in patients with severe xerosis.

Systemic antihistamine therapy

It was prescribed to reduce itching. основного препарата были Cetirizine-containing drugs were selected as the main drug.

Cetirizine - 10 mg orally once a day, on request.

The frequency of cetirizine intake was recorded in the patient's diary.

External therapy

Drugs from the group "Calcineurin blockers for external use".

INN: Pimecrolimus, cream for external use

Comments: Pimecrolimus cream for external use is indicated for both short-term and long-term treatment of mild to moderate atopic dermatitis in adults. The ointment is applied in a thin layer to the affected areas of the skin, 2 times a day.

Recommendations for use: The drug is prescribedли 2 times a day for the affected areas of the skin of any part of the body, including the head, face, neck, diaper rash. It is not recommended to apply drugs to the mucous membranes and under occlusive dressings.

The amount of topical preparation for external use was measuredлось according to the rule of "fingertip length" (FTU, FingerTipUnit), while one 1 FTU corresponds to a column of ointment with a diameter of 5 mm and a length equal to the distal phalanx of the index finger, which corresponds to a mass of about 0.5 g. This dose of topical product was sufficient to apply to the skin of two palms of an adult humanbody, which accounted for about 2% of the total body surface area. During the use of pimecrolimus, itis recommended to avoid getting sunlight on the skin, visiting a tanning salon, and ultraviolet radiation of the skin with UV rays.

Emollients было can also be applied immediately after applying pimecrolimus. However, after water procedures, emollients should not следовалобе applied before applying calcineurin blockers.

Given the very low systemic absorption of calcineurin inhibitors, there are no restrictions on the total daily dose of the drug applied, the area of the treated skin surface and the duration of treatment.

9.4.2. Description of the test drug

Test preparation (T)	
Trade name	Polisorb® MP
Chemical name	Colloidal Silicon dioxide
Grouping name	Enterosorbent agent [Adsorbents]
Dosage form	Powder for suspension for oral administration
Method of administration	orally
Packaging	Polymer can
Manufacturer	JSC "Polisorb", Russia
Series/Expiration date	P26050423 / 04.2028

9.4.3. Methods for allocating patients to treatment groups

After signing the Informed Consent Form at the screening stage, the patient was assigned a screening number of the form XXYY, where XX is the number of the research center (for example, 01, 02, 03), YYY is the patient's serial number (starting from 001), according to the order of inclusion (3 digits). If, after performing all the procedures planned for the screening, the researcher has decided that this patient can participate in the study, the patient isла randomized.

Randomization (a method of distribution based on theory and probability) is necessary to minimize subjectivity in the distribution of patients into treatment groups.

The randomization number was presented in the RR format and былassigned to each patient who was screened and met the inclusion/non-inclusion criteria. The randomization number was also былapplied to the label of the study drug. The randomization number assigned to the patient corresponded to the number indicated on the label of the prescribed drug.

When drawing up the randomization plan for this studyбыл, the method of block randomization with a fixed block size in each research center was used. The distribution of patients into groups was made in a ratio of 1:1.

The randomization number was generated by a statistician using software with a random number generator function.

When assigning a randomization numberбыл, the method of online randomization was applied using the IWRS system. A randomized patient number is assigned to the subject of the study in the order of reference to the IWRS system. The number of randomization numbers was equal to the number of patients participating in the study.

The result of accessing the systemлось was a randomization confirmation containing:

– date and time of accessing the system.
– data on the researcher who performed the patient randomization procedure;
- patient identification data that does not contain personal information (patient's screening number);
– randomization number of the patient.
– the therapy group that the patient receivedл during the study.

The randomization confirmation was available for printing.

The randomization procedure, assigning a randomization number to the patient, was performed at Visit 1 immediately before prescribing the drug. The randomization number of each patient was necessarily былregistered in the primary documentation and the patient's IRC.

If the patient prematurely completed the study (excluded from the study for any reason), the randomization number was not reused.

The number of dispensed drugs was recorded for each patient and the randomization number of the patient who was prescribed the drug, the date of delivery of the drug to the patient, and its quantity were

recorded. In the process of dispensing drugs, the person responsible for recording and storing drugs filled out and signed the inventory log of the test drug.

The randomization list is attached to this report (Appendix 16.1.7).

9.4.4. Selection of doses to study

Polisorb MP for the phase III clinical trial was selected based on the approved instructions for medical use and OHLP of the registered drug and based on the experience of its post-marketing clinical use in the treatment of chronic dermatoses and atopic dermatitis, in particular. Thus, taking into account the consistency of scientific assessments based on the results of preclinical studies and many years of experience in the post-marketing use of Polisorb® In clinical practice, it was possible to consider an acceptable level of safety and effectiveness of colloidal silicon dioxide when it is used as an enterosorbent by a person in a daily dose of 0.15-0.20 g/kg of body weight.

9.4.5. Selection of dosage, time and interval of drug administration for each patient

In the course of the study, two treatment groups were formed:

Group 1: Basic therapy + Study drug

Group 2: Basic therapy

Basic therapy-taking up to 14 days:

- Permanent use – emolients
- On demand:
  - Pimecrolimus, a cream for external use, is applied in a thin layer up to 2 times a day
  - Permanent use-cetirizine 10 mg, tablets, inside, 1 time a day

Dosage regimen: A single dose-1-2 tablespoons with a slide (1 tablespoon contains 2.5-3 grams) in half a glass of water, just before meals.

The daily dose is 15-20 gramsof the drug (6 tablespoons "with a slide") dividedx into 3-4 times a day, the course of therapy is 14 days.

Method of administration: Oral administration only in the form of an aqueous suspension immediately before meals. The suspension is prepared by carefully stirring the required amount of the drug in ¼ or ½ cup of water. After stirring, an opaque suspension of white or almost white coloris formed.

9.4.6. Data masking (oblinding)

A double-blind study was conducted. Patients were randomly assigned to 2 groups in a 1:1 ratio. Randomization was performed using IWRS.

The randomization code of the patient was indicated in documents intended for use outside the research center (individual registration card [eIRC], reports of SNA, etc.). The assigned randomization code of the patient was entered in the eIRC and the corresponding forms. The randomization code of the patient does not change during the study.

The randomization plan is stored for control access. The randomization plan will be made known to the medical researcher, the principal investigator, the supervisor, and the regulatory authorities when SNA is detected.

9.4.7. Previous and concomitant therapy

Any medication (including over-the-counter medications) or therapy prescribed to the patient during the course of the study (starting from the date of informed consent) It was added to the IRC section "Previous and concomitant drug therapy" or "Non-drug procedures". The researcher entered all AES that

were associated with concomitant medication/therapy in the "Adverse event" section of the IRC. If a concomitant drug/therapy was used for a somatic disease present at the time of inclusion in the study, the researcher вreferredл this somatic condition to the section of the IRC "Anamnesis and current somatic conditions".

9.4.8. Treatment compliance measures

The research centers were supplied with a sufficient number of study drugs (the Study Drug) to conduct the study, taking into account the planned number of patients for randomization. The responsible employee of the research center kept a log of the study drugs, which noted the receipt of drugs to the center, the distribution of drugs to study participants, and the return of unused drugs. Storage conditions were also noted. Unused/remaining vials of the study/reference drug, as well as empty vials from the study/reference drug, were returned for accounting purposes.

The study also included monitoring of filling out the patient, 's diary and checking it. The study was conducted on an outpatient basis. To monitor compliance at Visit 4, patients returned patient diaries. Patients who took medications according to the schedule were considered to be compliant.

9.5. Performance and safety data

9.5.1. Estimated performance and safety indicators and flowchart

The procedures, performed during the study, and their frequency are presented below as a flowchart

Day	**Screening**	**Treatment Period**	**Visit**	**Unscheduled Visit ****
	HT			
Procedure/Visit	Visit 1/ Day -3-0	Visit 2/ Randomization Day 1	Visit 3 / Day 7 +/-1	Visit 4 / Day 14+/-1
Physical Examination	X	X	X	X
Measurement of Weight, Height	X			X
Electrocardiography (ECG) with 12 Standard Leads	X			X
Basic Vital Signs (Heart Rate, Blood Pressure, Body Temperature)	X	X	X	X
Collection of Blood and Urine Samples for Laboratory Safety Parameters (General and Biochemical Blood Analysis, Urine Analysis)	X	X		X
Urine test for beta-human chorionic gonadotropin (β-hCG)[1]	X	X		X
Blood test for Hepatitis/HIV*	X			X
Randomization		X		
IMP Dispensing		X		
IMP Return		X		
Baseline Therapy Initiation			X	
Assessment of Skin Manifestation Intensity by Indexes and Questionnaires SCORAD, BRS	X	X	X	X
Quality of Life Assessment with DLQI Questionnaire	X	X	X	X
Overall Disease Assessment by Investigator IGA	X			
Assessment by EASI Index	X			
Inquiry about Concomitant Medications	X	X	X	X
Patient Diary Distribution	X			
Patient Diary Review			X	X
Patient Diary Return			X	X
Adherence to Hygiene Procedures	X	X	X	X
Monitoring of Adverse Events	X	X	X	X

1 – for women with childbirth potential

* - in the absence of test results performed within 3 months prior to the screening visit

** - upon the appearance of exclusion criteria

9.5.1.1. Performance indicators

Evaluation parameters:

SCORAD index [13,14,15,14,15] - atopic dermatitis assessment scale (SCORAD) is a composite indicator (from 0 to 100 points), measured by a doctor according to three main clinical signs of the disease (separate scales), namely: lesion area, clinical severity, subjective symptoms.

The intensity of each trait is evaluated on a 4-level scale: 0-absent, 1-weak, 2-moderate, 3-strong. (see Appendix 1)

Pruritus Intensity Index BRS [16,17,17] - behavioral rating Scores (BRS) measure the severity of pruritus. It consists of two questions to analyze the severity of pruritus and the disruption of the patient's daily activities caused by it, both during the day and at night (the maximum possible value is 8 points). (see Appendix 3)

The dermatological quality of life index DLQI [18,13,13] is an indicator (from 0 to 30 points) that reflects the deterioration of the patient's quality of life associated with a skin disease (independent questionnaire). (see Appendix 2)

The doctor's Global Assessment Scale (IGA) [19] is a parameter that captures the clinical picture of the disease and its severity at a certain point in time, without taking into account the initial symptoms. It is used to assess the overall intensity of symptoms on a 5-point scale (0 — clear skin, 5 — very severe lesions). (see Appendix 4)

The Eczema Prevalence and Severity Index (EASI) [10,20,20] is used to assess the prevalence and severity of skin lesions. It is used to assess the main manifestations of the disease using a score assessment of the severity of symptoms on a scale from 0 to 3 (0-absent, 1-weak, 2-moderate, 3-pronounced, while half-estimates are allowed). (see Appendix 5)

Patient's diary.

The diary was issued to patients at the screening session to include information about:

- taking antihistamines – cetirizine
- the need to apply topical therapy-pimecrolimus
- taking the study drug-Polisorb® MP

9.5.1.2. Assessment ofsafety parametersов безопасности

List of security parameters:

- Percentage of patients (%) with AE in the treatment groups at the end of follow-up.

Adverse eventsлись were recorded based one patient complaints, physical examination results, including vitalsigns, and laboratory testing from the time the study drug was taken until the patient completed the study.

The safety assessment was carried out throughout the study.

The researcher was responsible for documenting all adverse events that occurred after the start of the study. Inclusion of the patient in the study was defined as the moment of signing informed consent. AE was evaluated based on the criteria presented in the study protocol.

At each visit, the AE was evaluated and documented. The AE assessment was carried out according to the following parameters:

- Description of the undesirable event.

- Severity of the manifestation.
- Duration.
- The presence of a connection with the test drug;
- Exodus.
- Severity assessment.

Cases that were already documented on a previous visit and were considered "ongoing" were to be checked on each visit. If the AE was completed, a corresponding note was made in the primary documentation. If the frequency or severity of AES changed, a new entry had to be made.

The researcher was required to monitor patients with AES until the symptoms disappeared, the condition was deemed medically stable, or the patient was no longer available for follow-up.

Adverse events were encoded in accordance with the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Methodology for evaluating the main safety parameters (including physical examination, laboratory and instrumental examinations):

Physical examination was carriedout according to the general rules of propaedeutics of internal diseases:ыл a general examination, examination of the mucous membranes and skin, including palpation of the lymph nodes, assessment of the musculoskeletal system, palpation, percussion and auscultation of the main organ systems (cardiovascular, respiratory, digestive, urinary systems) were sequentially performed.

The ECG includedло recording of the electrocardiogram in 3 standard and 3 enhanced leads from the extremities, as well as in 6 chest leads at rest in the supine position. ECG interpretation was performedby a cardiologist, general practitioner, or functional diagnostic doctor. If there are changes in the ECG, the Researcher evaluates their clinical significance.вал

Laboratory tests, in particular blood samples for analysis, are performedлin the morning on an empty stomach (at least 8 hours after the last meal) from the cubital vein with a disposable sterile syringe, subject to aseptic/antiseptic conditions. Approximately 40 ml of blood was required for the tests required in this study. For general urinalysis, the morning average portion was collected after adequate perineal hygiene, and the urine was delivered to the laboratory within two hours of collection. Sampling for laboratory testing is carried out in accordance with the study plan.

9.5.1.3. Other parameters

Ongoing therapy

The researchers recorded their therapy during the course of the study, including the follow-up period. Its effectiveness was evaluated.

9.5.2. Measurement compliance

Methods for evaluating primary and secondary indicators are well studied and previously validated in the literature.

9.5.3. Primary performance indicators

The main endpoints of effectiveness in the study were:

- Mean change in the SCORAD index on day 14 of treatment (Visit 4) compared to the initial assessment (Visit 2)

Secondary performance parameters:

- Average change in the total BRS score for Sessions 3, 4, and 5 compared to the original score (Session 2).
- Average change in the overall DLQI score for Sessions 4 and 5 compared to the original score (Session 2).
- Average change in the SCORAD index by Session 3 and 5 compared to the original score (Session 2).
- Number of days of taking antihistamines in the period from Visit 2 to Visit 4 based on the patient's diary;
- Number of days of using the topical drug in the period from Visit 2 to Visit 4 based on the patient's diary;
- Average change in the EASI Index by Session 5 compared to Session 1.
- Average change on the IGA scale by Session 5 compared to Session 1.

The evaluation parameters are described in section 9.5.1.1.

9.5.4. Measurement of drug concentration

Not applicable.

9.6. Data quality assurance

For the purpose of quality control, a Quality Control Plan was developed prior to the study. A copy is attached to the Report in the section **Ошибка! Источник ссылки не найден.**.

9.6.1. Quality control

The study sponsor has defined a quality control and assurance system, to ensure that the study is carried out in accordance with the protocol, GCP and current legal requirements. For this purpose, standard operating procedures describing all key processes were used to organize the study. The study sponsor was responsible for notifying regulators of the progress of the study.

9.6.2. Selection of research centers

The selection of study centers was approved by the Sponsor of the study prior to the start of the study to ensure the availability of the necessary research personnel and assess the feasibility of performing the study by these personnel in accordance with the requirements of Good Clinical Practice of the International Conference on Harmonization (ICG) and the requirements of regulatory authorities of the Russian Federation.

All selected centers are accredited by the Ministry of Health of the Russian Federation for the right to conduct clinical trials.

The researcher must have had the education, training, and experience necessary to assume responsibility for the proper conduct of the study. The researcher's qualification should meet regulatory requirements and be confirmed by his/her academic biography (curriculum vitae) and / or other documents.

The researcher should have known in detail how to use the investigational drug in accordance with the protocol, the current version of the researcher's brochure, and other sources provided by the Sponsor of the om and CIO.

The researcher was required to keep a list of qualified individuals who were assigned to perform certain activities within the framework of the study.

9.6.3. Monitoring

Monitoring was carried out by a clinical trial specialist (monitor), who monitored the activities of the study from its start to end in accordance with the organization's standard operating procedures (SOP), GCP, and relevant regulatory documents.

The monitoring plan was described in detail in the monitoring manual. The monitor monitored the conduct of the study, followed the completion of the IRC and primary documentation, the storage of documentation, and the proper accounting of study preparations. For this purpose, the monitor visited research centers at appropriate intervals, and also maintained constant communication, oral and written, with the staff of the centers. The monitor was given access to all documents (related to the study and individual participants) at any time and on demand. In turn, the monitor complied with all confidentiality requirements, as described in the informed consent form. The main researchers and their team members collaborated with the monitor, and were present for some time during the monitoring visits to answer questions and provide missing information.

9.6.4. Data identification

All data before being entered in the e-IRC was specified in the primary documentation. Primary documentation and data include printouts of laboratory parameters and instrumental techniques, as well as documents that are filled in during examinations (for example, medical history, adverse events, demographic data). For identification purposes, all data was marked with the patient's number (and the patient's date of birth, wherearequired).

Data verification was performed for all performance indicators, demographic data, inclusion and exclusion criteria, and adverse events.

9.6.5. Document storage

All documentation related to this study remains in the archive of research centers for 10 years after the completion of the CI. Destruction of any materials related to this study is possible only after approval from the relevant person.

9.6.6. Audit and inspection

Regulatory authorities, the organization's Expert Council/An independent ethics committee and organizations authorized by Спонсорthe Research Sponsor a could conduct inspections and audits.

9.6.7. Data disclosure and confidentiality

Participants ' personal data was stored and processed in accordance with the requirements of the Federal Law of the Russian Federation No. 152 "On Personal Data". Only the minimum personal data about the study participants that is most necessary for the implementation of the set goals (for example, demographic indicators) is provided. Names, addresses, and medical history/outpatient card numbers were not entered in the IRC. Not былоа single document that allows identifying the patient's

identity was disclosed. The names of the patients were not reported to Sponsors. If Patient's name is mentioned in any document, it should have been deleted before the copy or original document was provided to Sponsors. Results submitted electronically should have been stored in accordance with the Information Protection Act.

Before being included in the trial, the patient was familiar with the terms and conditions for maintaining the confidentiality of their personal data, including the need to provide access to these monitors and other persons, authorized фирмой-by the Sponsor company. The terms and conditions of confidentiality are set out in the Patient information. The patient could be included in the trial only after reading the above information and signing Informed Consent.

Researchers should keep a list of patient names in order to be able to provide primary patient documentation if necessary.

9.7. Protocol-defined statistical methods and sample size determination

9.7.1. Statisticalй plan and analysis plan

The statistical analysis was performed using R software version 3.2.1. The statistical plan was developed and finalized before the database was closed (provided in Appendix 16.1.9).

Continuous (quantitative) data are presented as the number of observations, arithmetic mean, 95% confidence interval (CI) for the mean (unless otherwise specified), standard deviation, median, interquartile range, minimum and maximum. When presenting pharmacokinetic parameters, a geometric mean was used. To assess the normality of the distribution of quantitative indicators, the Shapiro-Wilk criterion was used.

Qualitative data are presented as absolute frequencies (number of observations), relative frequencies (percent), and 95 % CI (unless otherwise specified).

Previous and concomitant diseases, operations, injuries, and other medical history data, as well as adverse events, were encoded using the MedDRA classifier. The drugs used for previous and concomitant therapy were encoded using the PBX classifier.

For more information on statistical analysis methodsa, see the Statistical Analysis Plan.

9.7.1.1. General plan of statistical analysis

Concomitant and previous diseases were encoded according to the MedDRA dictionary in the current version (version 25.1) and presented grouped by systems and organs (System Organ Class, SOC) and preferred medical terms (Preferred Term, PT).

All data obtained in the groups prior to the use of the studied drugs (demographic and anthropometric data, laboratory data, data from instrumental and physical examination methods, vital signs, etc.) сравниваwere compared between the groups in order to determine the comparability of the groups for analysis.

Population selected according to the principle of prescribed treatment ((intention-to-treat, ITT)

The ITT dataset, also known as the full analysis set (FAS), includes all randomized participants who were exposed to the study drug, regardless of the degree of protocol compliance during the study. This data set is generated using the conceptof" intent-to-treat " (ITT) in accordance with the principles set out in the ICH E9 manual. This set is the main one for analyzing primary and secondary performance parameters.

Aggregate " by protocol "(PP)

Primary and secondary performance indicators will additionally be analyzed using a data set selected according to the Protocol Compliance principle (PP). A participantis excluded from the PP dataset in the following cases:

- Meets the exclusion criteria
- Use of unauthorized concomitant therapy
- Any other significant violation of the protocol found to significantly violate the main performance assessment for this study participant

Population for security analysis

The population for safety analysis (safety) includes all patients, without exception, who have been exposed to at least a single exposure to the study drug or comparison drug. However, unlike the full analyzed population, which is formed depending on the prescribed treatment, patient data in the population for safety analysis are analyzed depending on the actual treatment (if it differs from the treatment that was prescribed by randomization). All types of security analysisются are based on the use of aggregate data for security analysis.

All decisions regarding the definition of the analyzed populationsыли were made before the database was closed.

9.7.1.2. Analysis of performance variables

The main population for performance analysis is FAS. As a supportive analysis, the primary endpoint analysis was repeated in the Per Protocol population. To assess the primary efficacy criterion , the average change in the SCORAD index on day 14 of treatment (Visit 4) compared to the initial assessment (Visit 2) прowas analyzedн in the ITT population using a mixed effects model for multiple measurements (MMRM), in which the treatment group was included as factors The initial estimate is used as a covariate, with an unstructured covariance matrix among visits for each treatment group.

Sensitivity analysis was performed in the PP population. As a sensitivity analysis, we also performed an analysis of the covariance analysis model (ANCOVA) with forward-looking data from the last observation (LOCF) using a PP population. Additionallyбыло, the effect of the "on-demand therapy" factor on the results of the primary endpoint was analyzed. For secondary qualitative performance variables, a comparison between groups 1 and 2едена is made using Pearson's $\chi 2$ criterion if the frequency of each cell was ≥ 5, otherwise-using the exact Fisher criterion. For secondary quantitative performance variables, the comparison between groups 1 and 2 was performed using the Student's t-test, if the data distribution corresponds to the normal distribution law, otherwise using its nonparametric counterpart, the Mann-Whitney U-test. Verification of compliance with the normal distribution law was carried out using the Shapiro-Wilk criterion. The following characteristics were used for quantitative performance variables: arithmetic mean, standard deviation, median, quartiles, minimum, maximum. For high-quality ones, these are the frequencies (fractions and/or percentages).

9.7.1.3. Analysis переменных of security variables

To compare the incidence of AE in the study groupsиспользовано, the use of the $\chi 2$ test and/or the exact Fisher test was used, and the use of the Mann-Whitney test is planned to compare the severity.

Laboratory parameters (general and biochemical blood analysis, general urinalysis), vital signs were evaluated separately for each group and compared using the paired Student t-test for related samples (for indicators with normal distribution) or using the nonparametric Wilcoxon test

for related samples (for indicators with ordinal distribution). by the scale type or if the distribution deviates significantly from the normal distribution).

Adverse events were encoded using the current version of the Medical Dictionary of Regulatory Activities (MedDRA). The number (percentage) of patients with AE registered while receiving (Treatment - emergent adverse events and the number of such AES were presented in tables by organ system class and preferred term (RR), as well as in relation to study therapy and severity, by therapeutic groups. At the same time, within the organ system class and the preferred term, each patient was counted once with the relation to the study therapy and the degree of severity of the maximum severity.

Laboratory parameters and their changes after the use of the study drug in comparison with the initial values and the "shift table" relative to normal values were tabulated by therapeutic groups and by assessment points.

The results of the physical examination of the patient are presented descriptively by therapeutic groups and assessment points.

All data on the safety are presented in patient lists.

9.7.1.4. Analysis of other data

Not applicable.

9.7.1.5. Interim analysis

In order to obtain reliable data on the effectiveness of the drug, an adaptive design was chosen for the calculation of the sample, since previously there was insufficient (lack of) data on studies of absorbents in placebo – controlled randomized trials in patients with atopic dermatitis. In this regard, after receiving data on the primary end point in (138 patients in each group were analyzed), an interim analysis was performed to assess the sufficiency of the calculated sample. Based on the results of which бы a decision would be made to continue the study, change the sample, or terminate the study. If the sample was changed, an amendment to the protocol would be drawn up and submitted to the MOH for approval. If the study is stopped -, a clinical report is prepared and submitted to the MOH for notification.

As part of the interim analysisбыл, only one parameter was calculated – the primary endpoint. The procedure for blinding once was not performed, as the study is open-ended. Secondary parameters and safety were not calculated correctly.

9.7.2. Determining размера the sample size

The calculation was performed using PASS 2022 validated software, version 22.0.4 (PASS 2022 Power Analysis and Sample Size Software (2022). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass. In accordance with the selected design it was planned to clarify the superiority of the use of basic therapy in combination with the drug Polisorb® MP compared with the use of basic therapy after 14 days of treatment for exacerbation of moderate atopic dermatitis in adult patients. In order to select the primary endpoint, we analyzed literature data on the selection and harmonization of methods for studying outcomes in eczema and atopic dermatitis, in particular, the HOME initiative. According to this publication, the SCORAD index is the most frequently (used method (more than 30% of cases) for assessing the outcome of atopic dermatitis and eczema, and is an objective and validated assessment method. Moreover, была определена минимальная клинически значимая разница (the minimal clinically important difference (MCID) of 8.7 points

was determined for the SCORAD index [9], which is actively used in clinical trials of drugs for atopic dermatitis.

Due to the fact that the drug "Polisorb® MP" has not previously been used in the treatment of patients with atopic dermatitis in placebo-controlled studies, the size of the effect when using this drugлось was the subject of study (with the condition that this effect exceededл the MCID value), the study былowas conducted using adaptive (group sequential) design with one intermediate analysis aimed at clarifying the actual size of the effect.

In order to justify the required sample size, we searched the literature for data on the dynamics of the SCORAD score and the variability of this indicator. Thus, according to the study [21], in which the dynamics of the SCORAD score was studied in patients with exacerbation of moderate and severe atopic dermatitis , the following data were obtained: 15 patients were analyzed, the results are presented as the average value and the standard error of the average, respectively, according to the table maximum standard deviation for the score for The SCORAD was just over 15 points (the standard deviation was calculated as the standard error of the mean multiplied by the square root of the sample size, i.e. 3.9 as the maximum value of the standard error of the mean multiplied by the square root of 15). We also analyzed data from studies evaluating the effect of drugs similar to Polisorb® MP on pathogenetic effects - the effect of adding probiotic therapy on the severity of symptoms in exacerbation of moderate atopic dermatitis, the following data were obtained [13]: Based on the 95% confidence intervals presented in the table for changes in the score on индексу the SCORAD index compared with the initial value the values of the standard error of the mean were calculated, and standard deviations were calculated from them using the same method presented earlier . The maximum value obtained is approximately 20 points.

Thus, in order to calculate the sample size, the following assumptions were made : 1) Statistical model of analysis – one-way comparison of two averages within the framework of the superiority hypothesis without establishing a margin of superiority (non-marginal superiority) based on the minimum clinically significant difference (MCID):

$$H0: \mu 1 - \mu 2 \leq 0$$
$$HA: \mu 1 - \mu 2 > 0$$

where

mk1 is the average change in the SCORAD score by day 14 of treatment compared to the initial score in group 1

mk2 is the average change in the SCORAD score by day 14 of treatment compared to the initial score in group 1

mk1 – mk2 – actually expected value of differences between groups equal to or greater than MCID

2) Adaptive approach to analysis:

a. Групповой последовательный дизайнGroup sequential design roup sequential design)

b. One interim analysis to achieve the share of information received (information proportion) of 50%

c. Establishment of one-sided boundaries of efficiency (efficiency) and futility(futility), the border of futility is not binding (non-binding) , that is, it is informational in nature for decision-making

d. The expenditure function for type I and II errors is based on the approach of Hwang, Shih & DeCani (6) with the value of the gamma distribution = 1

3) The level of type I error is 2.5% (one – sided), respectively, the total consumed type I error at the two stages of analysis (intermediate and final) will be 0.025. At each stage, if two-way confidence intervals are calculated for the difference in the average values with the boundaries corresponding to the threshold level of significance at this stage of analysis

4) The level of type II error is 0.2, respectively, the power of the study is 80%, provided that the initial assumptions are maintained

5) The groups are expected to have approximately the same variability of indicators with a maximum standard deviation of 20 points

6) The expected difference between the groups (m1 – m2) is slightly higher than the minimum clinically significant difference (MCID) and is 10 points or more (for calculation purposes, based on literature data, it is assumed that m1 – will be 5 points, and m2-15 points, with absolute values of m1 and m2 they do not affect the calculation of the sample size)

7) Withdrawal from the study after inclusion in the treatment period will not exceed 10% (according to the literature)

Power and Sample Size Summary

Solve For:	Sample Size
Maximum Number of Stages:	2
Alternative Hypothesis:	μ1 - μ2 > 0 (one-sided)
Alpha Spending Function :	Hwang-Shih-DeCani (γ = 1)
Beta Spending Function :	Hwang-Shih-DeCani (γ = 1)
Number of Simulations :	2000
Random Seed:	7157629 (Computer-Generated)

Target Power	Sim Power	N1	N2	N	μ1	μ2	σ1	σ2	Target Alpha	Sim Alpha
0,8	0,805	73	73	146	15	5	20	20	0,025	0,0215

Target Power	The desired power value (or values) entered in the procedure.
Sim Power	The proportion of simulation z-values that cross an efficacy boundary. Because "After Boundary Crossing" is set to "Hold out," it is the sum of the individual boundary crossing proportions.
N1 and N2	The anticipated number of individuals in each group if the final stage is reached.
N	The total sample size if the final stage is reached. N = N1 + N2.
μ1	The assumed mean of population 1 for power calculation simulations.
μ2	The assumed mean of population 2 for power calculation simulations. μ2 is also the assumed mean of populations 1 and 2 for alpha calculation simulations.
σ1 and σ2	The (assumed known) population standard deviations of groups 1 and 2. σ1 and σ2 are used for simulating values, the calculation of maximum information, and as the known standard deviations for the calculation of z-values.
Target Alpha	The alpha used in the computation of the boundaries. The desired overall probability of a Type 1 error.
Sim Alpha	The proportion of null simulation z-values that cross an efficacy boundary. Because "After Boundary Crossing" is set to "Hold out," it is the sum of the individual boundary crossing proportions.

Summary Statements

Final stage sample sizes of 73 and 73 achieve 80,5% power to detect a mean difference of 10 at a target alpha-level of 0,025. The assumed population means are 15 and 5, with known standard deviations of 20 and 20. These results are based on one-sided Z-test group sequential testing with 2 stages and boundary values calculated from spending functions.

References

Jennison, C. and Turnbull, B.W. 2000. Group Sequential Methods with Applications to Clinical Trials. Chapman and Hall/CRC. Boca Raton.

Lan, K.K.G. and DeMets, D.L. 1983. 'Discrete sequential boundaries for clinical trials.' Biometrika, 70, pages 659-663.

Reboussin, D.M., DeMets, D.L., Kim, K., and Lan, K.K.G. 1992. 'Programs for computing group sequential boundaries using the Lan-DeMets Method.' Technical Report 60, Department of Biostatistics, University of Wisconsin-Madison.

Thus, based on the calculations performed, we obtain that:

5) For intermediate analysis, it is necessary that at least 37 patients in each group complete the study, which corresponds to randomization in the group.

6) For the final analysis (if the intermediate analysis confirms the initial assumptions), it is necessary that the study as a whole (taking into account previously included patients) is completed by 73 patients per group, which corresponds to 81 randomization in the group.

7) In an interim analysisбыло бы, approximately 62.2% of type I and II errors would have been consumed 8) If an interim analysis былореveals a significant deviation from the initial

assumptions, it is possible to re-evaluate the sample size (sample size re-estimation), and adjust the error expenditure functions accordingly.

Taking into account the 10% dropout rate at screening, 180 patients were included in the study. Of these, 162 were randomized.

9.8. Changes in the course of the study or in the planned analysis

During the study, there were no changes in the planned analysis.

10. INFORMATION ABOUT RESEARCH SUBJECTS

10.1. Distribution of subjects by groups

The study included (screened) 163 patients in 6 research centers in Russia. The first patient was included in the study on 10.04.2024.04.2024. A total of 163 patients were included, one patient dropped out at the screening stage-08-014 (refusal to continue participation). All randomized patients had at least one use of the study drugs and were included in the ITT population, with the exception of patient 06-025. Who immediately after randomization reported that he did not want to continue participating but did not accept the drug. 161 patients completed the study without significant deviations from the protocol and were included in the PP population.

A list of patients who did not complete the study, indicating the reasons, is provided in sections 16.2.1 and 16.2.3.

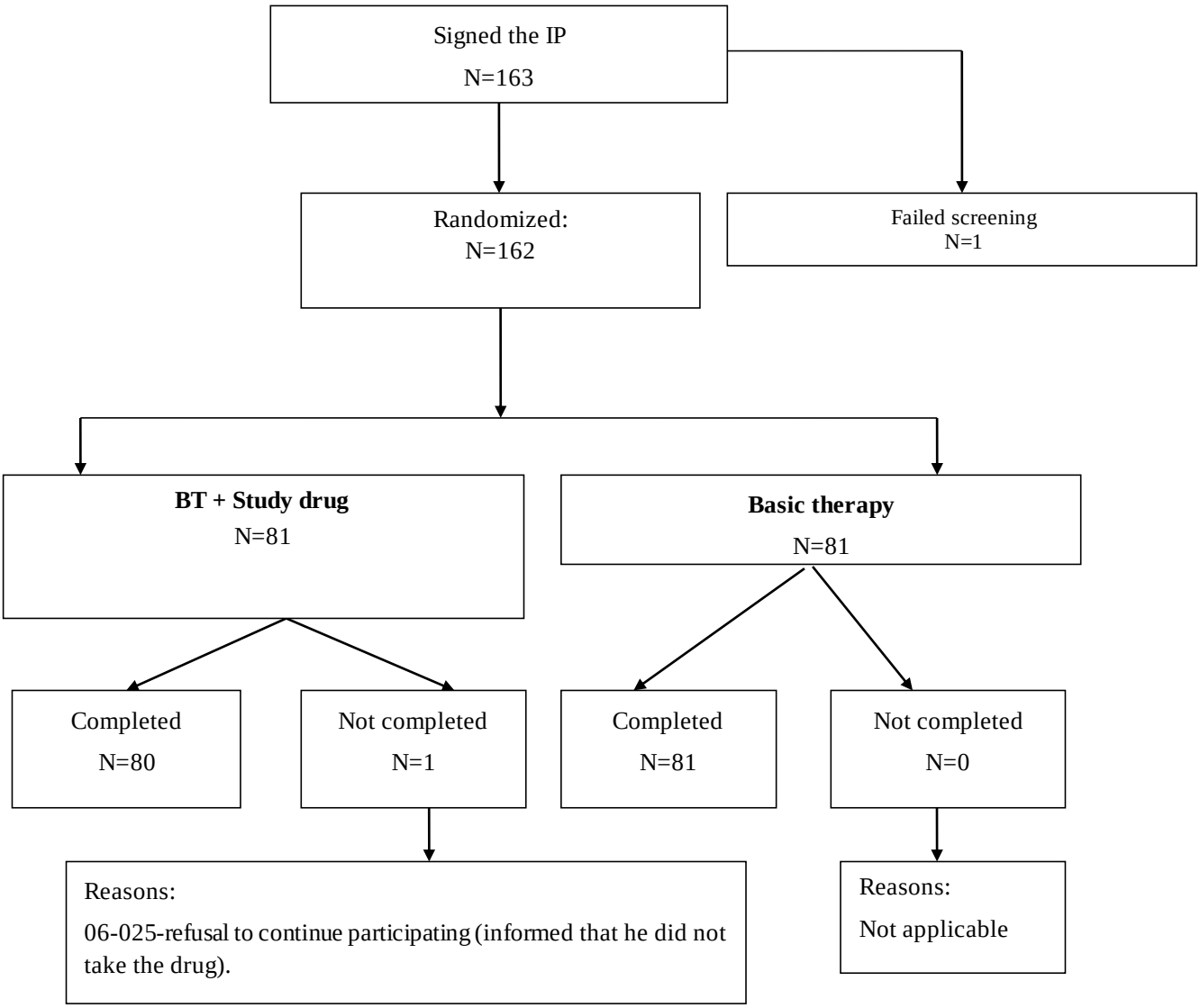


Figure *Ошибка! Закладка не определена.*. **Patient distribution**

10.2. Deviations from the protocol

The study included163 patient, and two patients dropped out before taking drug. 161 patients completed the study without significant clinical and protocol-specific abnormalities.

Project-specific deviations were noted – 10 patients (3 patients in the "basic therapy" group and 7 patients in the "Study drug" group) had deviations in patient diary management, which were formal in nature (marks went beyond the intended fields, crumpled diary), but did not affect the content and interpretation results. KNo CT abnormalities were registered.
No cases were registered in which the patient was treated, despite the presence of inclusion criteria or exclusion criteria;
No cases were reported in which patients received the wrong dose or unauthorized treatment.
Deviations registered in the study were submitted to local ethics committees in accordance with standard procedures.
Appendix 16.2.2 provides a list of deviations from the study procedures, indicating the center, patient number, description of the deviation, and assessment of this deviation.

11. EFFICACY EVALUATION

Data representation. The data in the report is presented in groups: the analysis of data from patients in the control group is presented with the designation "basic therapy" abbreviated version "BT", the analysis of data from patients who took the investigational drug is presented as "Basic therapy and investigational drug", abbreviated version "BT + SD". In the case of a description of the data, the data of the "Basic therapy and study drug" group are presented first, followed by the data of the "basic therapy" group, in another variant, the sequence is additionally indicated. When presenting the results of the analysis of quantitative parameters, the data is presented as an arithmetic mean ± standard deviation, median. When describing categorical parameters, the representation is in the form of % (percentage) of the total number of observations.

11.1. Data to be analyzed

163 patients were screened in the study, 163 of whom met all the criteria for inclusion/non-inclusion, and 162 patients were randomly assigned to the study in a 1:1 ratio in two groups (Table 1). All randomized patients used the investigational drug or the comparison drug at least once and were part of the ITT population. 161 patients completed the study (one patient dropped out ahead of schedule -06-025, did not take the drug) and were included in the PP population.

According to the protocol, the analysis and description of the data of patients who dropped out at the screening stage is not required. There were no significant differences in the collection of session data. The safety population was analyzed using the ITT population dataset (FAS), taking into account the absence of differences. The table, Table 2, shows data on patient visits and an assessment of exclusion criteria.

Table 1 – Distribution of research subjects.

Distribution of patients	**Number of patients (N)**
Screened	163 (100%)
Patients who meet the inclusion/non-inclusion criteria	163 (100%)
Randomized: • Group: **Basic therapy** • Group: **Basic therapy study drug**	 181 181
Population ITT / FAS	161 (98,8%)
Dropped out prematurely	2 (06-025, 08-014)
Completed the study according to the protocol	161 (98.8%)
Population according to the protocol (**PP-population**)	161 (98.8%)

Table 2 – Study subjects' visits and assessment of exclusion criteria (n= 161).

	Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total amount (N=161)**	**p-value.**
Visit 2				
Does the patient have no exclusion criteria?				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visit 3				
Does the patient have no exclusion criteria?				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visit 4				

	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Does the patient have no exclusion criteria?				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visit 5				
Does the patient have no exclusion criteria?				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Completion of the study				
Has the patient completed the study according to the protocol?				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	

Notes. Statistical method: #-The comparison was carried out by the analysis of variance (ANOVA), ~-The comparison was carried out by the Chi-square test, ^-The comparison was carried out by the Fisher exact test. The average is the arithmetic mean ± standard deviation (CO).

11.2. Demographic and other initial characteristics

The overall assessment was performed during Visit 0 (Screening). This assessment included the collection of demographic and anthropometric data (age, gender, race, height, weight). The Basic indicators and demographic characteristics of the patients were analyzed using descriptive statistics methods.

The results were summarized for all patients, as well as for various clinical subgroups. Two-way confidence intervals were used, and the results were considered statistically reliable with a two-way statistical significance level of $p < 0.05$, until other parameters were determined (if necessary, the values were rounded to the thousandth). In case of non-compliance with the assumptions underlying the planned logically derived analysis methods, they have been corrected accordingly for the analysis.

Of the 161 patients, 61.5% were women, the average age of the population was 38.9 ±12.70, 39 years, the average height was 171.4±8.3, 170.0 cm, weight was 74.9±11.55, 72.5 kg. There were 50 (62.5%) women in the BT+IP group, the average age of patients in the subgroup was 39.7±11.84, 41.0 years, height – 171.4±8.83, 168.0 and weight – 76.5± 12.25, 76.0. The BT group consisted of 49 (60.5%) women, the average age of patients in the subgroup was 38.0±13.51, 35 years old, height – 171.4± 7.86, 171.0 and weight - 73.3± 10.64, 71.0. There were no differences between the groups according to demographic and anthropometric parameters. The groups differed in BMI (units) of 26.0±3.81, 25.0 vs. 24.9± 3.07, 24.6, p= 0.041.

In the study population, 19 (11.8%) patients had a bad habit (smoking) and smoked an average of 9.5±5.00 cigarettes per day. 39 (24.2%) patients consumed alcohol. There were no differences in the subgroups.

Table 3 – Demographic characteristics

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Age					
	N	81	80	161	
	Average±CO	38.0 (13.51)	39.7 (11.84)	38.9 (12.70)	0.422#
	95% CI (average)	(35.1,41.0)	(37.0,42.3)	(36.9,40.8)	
	Median	35.0	41.0	39.0	
	[q1-q3]	[28.0-48.0]	[30.0-49.0]	[28.0-49.0]	
	Min-Max	18.0-65.0	18.0-63.0	18.0-65.0	
Gender					

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
	Female	49 (60.5%)	50 (62.5%)	99 (61.5%)	0.794~
	Male	32 (39.5%)	30 (37.5%)	62 (38.5%)	
Race					
	Caucasian	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Notes. Statistical method: #-The comparison was carried out by the analysis of variance (ANOVA), ~-The comparison was carried out by the Chi-square test. The average is the arithmetic mean± standard deviation (CO).					

Table 4 – Anthropometric characteristics

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Height (см)					
	N	81	80	161	
	Average±CO	171.4 (7.86)	171.4 (8.83)	171.4 (8.33)	0.973#
	95% CI (average)	(169.7,173.2)	(169.4,173.4)	(170.1,172.7)	
	Median	171.0	168.0	170.0	
	[q1-q3]	[166.0-176.0]	[164.0-177.5]	[165.0-177.0]	
	Min-Max	152.0-192.0	158.0-195.0	152.0-195.0	
Weight (kg)					
	N	81	80	161	
	Average±CO	73.3 (10.64)	76.5 (12.25)	74.9 (11.55)	0.079#
	95% CI (average)	(70.9,75.6)	(73.8,79.2)	(73.1,76.7)	
	Median	71.0	76.0	72.5	
	[q1-q3]	[64.0-81.7]	[65.9-83.7]	[65.0-83.0]	
	Min-Max	60.1-103.0	60.3-115.1	60.1-115.1	
BMI, units					
	N	81	80	161	
	Average±CO	24.9 (3.07)	26.0 (3.81)	25.5 (3.49)	0.041#
	95% CI (average)	(24.2,25.6)	(25.2,26.9)	(24.9,26.0)	
	Median	24.6	25.0	24.7	
	[q1-q3]	[22.8-26.7]	[23.4-28.4]	[23.0-27.6]	
	Min-Max	19.3-33.3	19.7-42.3	19.3-42.3	
Notes. Statistical method: #-The comparison was carried out by analysis of variance (ANOVA)					

Table 5 – Bad habits

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Does the patient smoke?					
	yes	9 (11.1%)	10 (12.5%)	19 (11.8%)	0.785~
	no	72 (88.9%)	70 (87.5%)	142 (88.2%)	
Does the patient drink alcohol?					
	no	60 (74.1%)	62 (77.5%)	122 (75.8%)	0.612~
	yes	21 (25.9%)	18 (22.5%)	39 (24.2%)	
Is the patient abusing narcotic substances and/or medications?					
	no	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Cigarettes per day					
	N	8	9	17	
	Average±CO	11.2 (6.64)	8.0 (2.45)	9.5 (5.00)	0.199#
	95% CI (average)	(5.6,16.7)	(6.1,9.9)	(6.9,12.1)	
	Median	10.0	10.0	10.0	
	[q1-q3]	[6.3-17.5]	[5.0-10.0]	[5.0-10.0]	
	Min-Max	2.0-20.0	5.0-10.0	2.0-20.0	

	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Notes. Statistical method: ~-Comparison was performed by Chi-square test, #-Comparison was performed by analysis of variance (ANOVA). The average is the arithmetic mean ± standard deviation (CO).				

Concomitant and previous illnesses are presented in Table 6. The most common diseases (occurrence in more than 10% of patients) in the subgroups were: upper respiratory tract viral infection - 8 (10.0%) versus 8 (9.9%) patients, essential hypertension - 9 (11.3%) versus 9 (11.1%), chronic gastritis 11 (13.8%) versus 4 (4.9%), there were no differences between the groups. Differences were recorded in the frequency of muscular, skeletal, and connective tissue disorders, which were more frequently reported in the BT group 2 (2.5%) versus 9 (11.1%), p= 0.030.

Table 6 – Concomitant diseases (MedDRA terminology coding, SOC class (system class) and PT (preferred term).

	Number of subjects (%) Number of diseases		
	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
infections and infestations			
Total amount	16 (19.8%) 21	12 (15.0%) 13	0.426~
viral infection of the upper respiratory tract	8 (9.9%) 8	8 (10.0%) 8	0.979~
chicken pox	7 (8.6%) 7	2 (2.5%) 2	0.167^
coronavirus	2 (2.5%) 2	1 (1.3%) 1	>0.999^
chronic pyelonephritis	1 (1.2%) 1	2 (2.5%) 2	0.620^
rubella	2 (2.5%) 2	0 (0.0%) 0	0.497^
respiratory tract infection	1 (1.2%) 1	0 (0.0%) 0	>0.999^
vascular disorders			
Total amount	11 (13.6%) 11	11 (13.8%) 11	0.975~
essential hypertension	9 (11.1%) 9	9 (11.3%) 9	0.978~
venous varices	2 (2.5%) 2	2 (2.5%) 2	>0.999^
gastrointestinal disorders			
Total amount	5 (6.2%) 5	13 (16.3%) 15	0.042~
chronic gastritis	4 (4.9%) 4	11 (13.8%) 11	0.054~
gastroesophageal reflux disease	0 (0.0%) 0	2 (2.5%) 2	0.245^
chronic pancreatitis	1 (1.2%) 1	0 (0.0%) 0	>0.999^
inguinal hernia	0 (0.0%) 0	1 (1.3%) 1	0.497^
stomach ulcer	0 (0.0%) 0	1 (1.3%) 1	0.497^
disorders of the muscular system. skeletal and connective tissue			
Total amount	9 (11.1%) 10	2 (2.5%) 2	0.030~
degeneration of intervertebral discs	5 (6.2%) 5	2 (2.5%) 2	0.443^
osteoarthritis	3 (3.7%) 3	0 (0.0%) 0	0.245^
bursitis	1 (1.2%) 1	0 (0.0%) 0	>0.999^
scoliosis	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart			
Total amount	7 (8.6%) 8	4 (5.0%) 4	0.360~
blockage of the right leg of the gis bundle	4 (4.9%) 4	4 (5.0%) 4	>0.999^
myocardial fibrosis	2 (2.5%) 2	0 (0.0%) 0	0.497^
congestive cardiomyopathy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
myocardial ischemia	1 (1.2%) 1	0 (0.0%) 0	>0.999^
metabolic and nutritional disorders			
Total amount	4 (4.9%) 4	6 (7.5%) 6	0.534^
obesity	3 (3.7%) 3	5 (6.3%) 5	0.495^
dyslipidemia	0 (0.0%) 0	1 (1.3%) 1	0.497^
diabetes mellitus	1 (1.2%) 1	0 (0.0%) 0	>0.999^

	Number of subjects (%) Number of diseases		
	Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**p-value.**
disorders of the immune system			
Total amount	4 (4.9%) 5	5 (6.3%) 8	0.746^
food allergy	4 (4.9%) 4	1 (1.3%) 2	0.367^
animal allergy	1 (1.2%) 1	2 (2.5%) 3	0.620^
allergic reaction to chemicals	0 (0.0%) 0	1 (1.3%) 1	0.497^
mite allergy	0 (0.0%) 0	1 (1.3%) 1	0.497^
seasonal allergy	0 (0.0%) 0	1 (1.3%) 1	0.497^
disorders of the liver and biliary tract			
Total amount	4 (4.9%) 4	3 (3.8%) 3	>0.999^
chronic cholecystitis	2 (2.5%) 2	1 (1.3%) 1	>0.999^
biliary dyskinesia	1 (1.2%) 1	1 (1.3%) 1	>0.999^
gallbladder polyp	1 (1.2%) 1	0 (0.0%) 0	>0.999^
cholelithiasis	0 (0.0%) 0	1 (1.3%) 1	0.497^
surgical and medical procedures			
Total amount	5 (6.2%) 6	2 (2.5%) 2	0.443^
appendectomy	3 (3.7%) 3	1 (1.3%) 1	0.620^
hip arthroplasty	0 (0.0%) 0	1 (1.3%) 1	0.497^
hysterectomy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
surgery on the nasal septum	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Salpingo-oophorectomy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
respiratory system disorders. thoracic and mediastinal organs			
Total amount	1 (1.2%) 1	5 (6.3%) 5	0.117^
chronic bronchitis	1 (1.2%) 1	4 (5.0%) 4	0.210^
allergic rhinitis	0 (0.0%) 0	1 (1.3%) 1	0.497^
visual disturbances			
Total amount	3 (3.7%) 3	1 (1.3%) 1	0.620^
myopia	3 (3.7%) 3	1 (1.3%) 1	0.620^
disorders of the blood and lymphatic system			
Total amount	1 (1.2%) 1	2 (2.5%) 2	0.620^
iron deficiency anemia	0 (0.0%) 0	2 (2.5%) 2	0.245^
anemia	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the reproductive system and mammary glands			
Total amount	1 (1.2%) 1	2 (2.5%) 2	0.620^
uterine polyp	0 (0.0%) 0	1 (1.3%) 1	0.497^
prostatitis	1 (1.2%) 1	0 (0.0%) 0	>0.999^
endometriosis	0 (0.0%) 0	1 (1.3%) 1	0.497^
benign, malignant and unspecified neoplasms including cysts and polyps			
Total amount	1 (1.2%) 1	1 (1.3%) 1	>0.999^
uterine leiomyoma	1 (1.2%) 1	0 (0.0%) 0	>0.999^
breast fibroadenoma	0 (0.0%) 0	1 (1.3%) 1	0.497^
injuries, intoxications and complications of procedures			
Total amount	0 (0.0%) 0	2 (2.5%) 2	0.245^
ankle fracture	0 (0.0%) 0	2 (2.5%) 2	0.245^
congenital, familial, and genetic disorders			
Total amount PT	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Gilbert's syndrome	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the nervous system			
Total amount	1 (1.2%) 1	0 (0.0%) 0	>0.999^
dysregulation of the autonomic nervous system	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the kidneys and urinary tract			
Total amount	1 (1.2%) 1	0 (0.0%) 0	>0.999^
nephrolithiasis	1 (1.2%) 1	0 (0.0%) 0	>0.999^
endocrine disorders			

	Number of subjects (%) Number of diseases		
	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
Total amount	1 (1.2%) 1	0 (0.0%) 0	>0.999^
goiter	1 (1.2%) 1	0 (0.0%) 0	>0.999^

Notes. Statistical method: ^-Comparison is carried out by the exact Fischer test, ~-Comparison is carried out by the Chi-square test. The average is the arithmetic mean ± standard deviation (CO).

The tables below show the drugs that were prescribed to patients for the treatment of the underlying disease and concomitant diseases during the project. There were no statistically significant differences in previous and concomitant therapy between the groups. The most common drugs for the treatment of the underlying disease were drugs from the group of corticosteroids (topical use), which were used in 28 (35.0%) patients versus 31 (38.3%) and systemic antihistamines in 25 (31.3%) versus 29 (35.8%). The drugs of choice were betamethasone 15 (18.8%) versus 15 (18.5%) and methylprednisolone aceponate 11 (13.8%) versus 11 (13.6%), cetirizine 11 (13.8%) versus 10 (12.3%). Cosmetics were mainly used in the study, 29 (36.3%) vs 29 (35.8%).

Table 7 – Previous therapy of the underlying disease, INN encoding by levels ATC 2 and ATC 5.

	Number of subjects (%) Number of drugs		
	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
corticosteroids used in dermatology			
All drugs	31 (38.3%) 31	28 (35.0%) 33	0.667~
betamethasone	15 (18.5%) 15	15 (18.8%) 15	0.970~
Methylprednisolone aceponate	11 (13.6%) 11	11 (13.8%) 11	0.975~
mometasone	1 (1.2%) 1	5 (6.3%) 5	0.117^
Hydrocortisone butyrate	1 (1.2%) 1	1 (1.3%) 1	>0.999^
clobetazole	2 (2.5%) 2	0 (0.0%) 0	0.497^
Alclomethasone	1 (1.2%) 1	0 (0.0%) 0	>0.999^
beclomethasone and antibiotics	0 (0.0%) 0	1 (1.3%) 1	0.497^
systemic antihistamines			
All drugs	29 (35.8%) 31	25 (31.3%) 29	0.541~
Cetirizine	10 (12.3%) 10	11 (13.8%) 11	0.791~
loratadine	7 (8.6%) 7	5 (6.3%) 5	0.563~
Levocetirizine	6 (7.4%) 6	5 (6.3%) 5	0.771~
Desloratadine	3 (3.7%) 3	3 (3.8%) 3	>0.999^
bilastin	3 (3.7%) 3	2 (2.5%) 2	>0.999^
Fexofenadine	1 (1.2%) 1	2 (2.5%) 2	0.620^
clemastine	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Chloropyramine	0 (0.0%) 0	1 (1.3%) 1	0.497^
other non-medical means			
All drugs	11 (13.6%) 12	7 (8.8%) 9	0.331~
cosmetics	11 (13.6%) 12	7 (8.8%) 9	0.331~
other drugs used in dermatology			
All drugs	7 (8.6%) 7	4 (5.0%) 4	0.360~
Tacrolimus	5 (6.2%) 5	2 (2.5%) 2	0.443^
pimecrolimus	2 (2.5%) 2	2 (2.5%) 2	>0.999^
antibacterial drugs of systemic action			
All drugs	1 (1.2%) 1	1 (1.3%) 1	>0.999^
Azithromycin	1 (1.2%) 1	1 (1.3%) 1	>0.999^
systemic corticosteroids			
All drugs	1 (1.2%) 1	1 (1.3%) 1	>0.999^

		Number of subjects (%) Number of drugs		
		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
	Methylprednisolone	1 (1.2%) 1	1 (1.3%) 1	>0.999^
antidiarrheal, intestinal anti-inflammatory and antimicrobial drugs				
	All drugs	1 (1.2%) 1	1 (1.3%) 1	>0.999^
	other intestinal adsorbents	1 (1.2%) 1	1 (1.3%) 1	>0.999^
antianemic drugs				
	All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
	iron sulfate	0 (0.0%) 0	1 (1.3%) 1	0.497^
antiseptics and disinfectants				
	All drugs	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	boric acid preparations	1 (1.2%) 1	0 (0.0%) 0	>0.999^
other medicinal products				
	All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
	sodium thiosulfate	0 (0.0%) 0	1 (1.3%) 1	0.497^
mineral supplements				
	All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
	calcium gluconate	0 (0.0%) 0	1 (1.3%) 1	0.497^
drugs for the treatment of wounds and ulcers				
	All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
	dexpanthenol	0 (0.0%) 0	1 (1.3%) 1	0.497^
drugs that promote digestion, including enzyme preparations				
	All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
	polyenzyme preparations lipase. protease, etc.	0 (0.0%) 0	1 (1.3%) 1	0.497^
Notes. Statistical method: ^-Comparison is carried out by an accurate Fischer test. ~-The comparison was performed by the Chi-square test				

Table 8 – Concomitant therapy (with the exception of the investigated one), INN encoding by levels ATC 2 and ATC 5.

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
other non-medical means				
	All drugs	29 (35.8%) 29	29 (36.3%) 29	0.953~
	cosmetics	29 (35.8%) 29	29 (36.3%) 29	0.953~
agents acting on the renin-angiotensin system				
	All drugs	7 (8.6%) 8	5 (6.3%) 5	0.563~
	valsartan	3 (3.7%) 3	1 (1.3%) 1	0.620^
	perindopril	3 (3.7%) 3	1 (1.3%) 1	0.620^
	amlodipine and perindopril	0 (0.0%) 0	1 (1.3%) 1	0.497^
	captopril	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	lisinopril	0 (0.0%) 0	1 (1.3%) 1	0.497^
	losartan	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	telmisartan	0 (0.0%) 0	1 (1.3%) 1	0.497^
calcium channel blockers				
	drugs All	3 (3.7%) 3	4 (5.0%) 4	0.720^
	Amlodipine	2 (2.5%) 2	3 (3.8%) 3	0.682^
	Lercanidipine	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	Nifedipine	0 (0.0%) 0	1 (1.3%) 1	0.497^
other drugs used in gynecology				
	All drugs	2 (2.5%) 2	4 (5.0%) 4	0.443^
	intravaginal contraceptives	2 (2.5%) 2	4 (5.0%) 4	0.443^
Analgesics				
	drugs All	3 (3.7%) 3	1 (1.3%) 1	0.620^
	acetylsalicylic acid	1 (1.2%) 1	0 (0.0%) 0	>0.999^

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**p-value.**
acetylsalicylic acid in combination with psycholeptics	1 (1.2%) 1	0 (0.0%) 0	>0.999^
metamizole sodium in combination with other drugs, excluding psycholeptics	1 (1.2%) 1	0 (0.0%) 0	>0.999^
paracetamol in combination with psycholeptics	0 (0.0%) 0	1 (1.3%) 1	0.497^
sex hormones and modulators of the genital function			
All drugs	0 (0.0%) 0	4 (5.0%) 4	0.059^
gestodene and ethinyl estradiol	0 (0.0%) 0	2 (2.5%) 2	0.245^
dienogest and ethinyl estradiol	0 (0.0%) 0	1 (1.3%) 1	0.497^
drospirenone and ethinyl estradiol	0 (0.0%) 0	1 (1.3%) 1	0.497^
beta-blockers			
All drugs	0 (0.0%) 0	3 (3.8%) 3	0.120^
bisoprolol	0 (0.0%) 0	3 (3.8%) 3	0.120^
hypolipidemic agents			
All drugs	2 (2.5%) 2	1 (1.3%) 1	>0.999^
Rosuvastatin	1 (1.2%) 1	1 (1.3%) 1	>0.999^
Atorvastatin	1 (1.2%) 1	0 (0.0%) 0	>0.999^
anti-inflammatory and Antirheumatic drugs			
All drugs	2 (2.5%) 2	1 (1.3%) 2	>0.999^
ibuprofen	1 (1.2%) 1	1 (1.3%) 1	>0.999^
diclofenac	1 (1.2%) 1	0 (0.0%) 0	>0.999^
nimesulide	0 (0.0%) 0	1 (1.3%) 1	0.497^
antithrombotic agent			
All drugs	2 (2.5%) 2	0 (0.0%) 0	0.497^
acetylsalicylic acid	2 (2.5%) 2	0 (0.0%) 0	0.497^
antihypertensives			
All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
moxonidin	0 (0.0%) 0	1 (1.3%) 1	0.497^
diuretics			
All drugs	1 (1.2%) 1	0 (0.0%) 0	>0.999^
indapamide	1 (1.2%) 1	0 (0.0%) 0	>0.999^
nasal preparations			
All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
other drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
preparations for the treatment of diseases associated with the violation of acidity			
All drugs	0 (0.0%) 0	1 (1.3%) 1	0.497^
pantoprazole	0 (0.0%) 0	1 (1.3%) 1	0.497^
preparations for the treatment of diabetes			
All drugs	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Metformin and sulfonylureas	1 (1.2%) 1	0 (0.0%) 0	>0.999^

11.3. Measuring treatment adherence

The study evaluated treatment adherence. The therapy included basic skin care (emollient use) in both study groups and topical pime crolimus on demand. In the study group, the study drug - Polisorb® MP was added to the basic therapy. There were no differences in basic care between the groupsвыявлено. The results of adherence to basic measures are presented in the table below (**Table** Ошибка! Закладка не определена.), compliance with Polisorb® MP intake is presented in the table - Table Ошибка! Закладка не определена.. The average compliance level of the study drug was 95.4,4 ±4.27,, 95.2,2%.

Table Ошибка! Закладка не определена. - **Analysis of adherence to basic therapy in the study groups (n=161).**

	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Visit 2				
The patient complies with restrictions during the study (compliance with hygiene procedures)				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visit 3				
The patient complies with the restrictions during the study (compliance with hygiene procedures)				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visit 4				
The patient complies with the restrictions during the study (compliance with hygiene procedures)				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visit 5				
The patient complies with the restrictions during the study (compliance with hygiene procedures)				
Yes	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a

Table Ошибка! Закладка не определена. **- Analysis of adherence to the study drug in the study groups (n= 80).**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total amount (N=161)	p-value.
Compliance					
	N	0	80	80	
	Average±CO		95.4 (4.27)	95.4 (4.27)	n / a#
	95% CI (average)		(94.4,96.3)	(94.4,96.3)	
	Median		95.2	95.2	
	[q1-q3]		[93.1-100.0]	[93.1-100.0]	
	Min-Max		78.6-100.0	78.6-100.0	
Notes: No cross-group comparison was performed. Mean – arithmeticmean± standard deviation (SD).					

11.4. Results of performance determination and summary tables of individual patient information

11.4.1. Performance analysis

11.4.1.1. Primaryendpoint

The primary parameter in this study wasthe c-axisearly change in the value and SCORAD index on day 14 of treatment (Visit 4) compared to the initial assessment (Visit 2).

The corresponding descriptive results of all patients who can be evaluated for efficacy in the ITT population are presented in the **Table** Ошибка! Закладка не определена.. The summary table shows the arithmetic mean, standard deviation, and median for the initial SCORAD score (Visit 2), the values 14 days after treatment (Visit 4), and the difference compared to the initial value.

Table Ошибка! Закладка не определена. **– Результаты aResultsof analysis of the primary parameter by descriptive statistics methods, depending on the treatment group (n= 161).**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value.
SESSION 2	N	81	80	161	
	Average±CO, median	32.4 ±5.33, 33.6	32.6 ±5.04, 33.6	32.5±5.17, 33.6	0.875#
	N	81	80	161	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value.
SESSION 4	Average±CO, median	14.7± 7.97, 13.3	11.1± 7.39, 9.8	12.9± 7.89, 11.0	0.003#
Change	In N	81	80	161	
	Average±CO, median	-17.7 ±7.80, -17.8	-21.5 ±7.48, -22.1	-19.6±7.86, -19.9	0.002#
Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).					

Changes in the mixedой linear model with repeated measurements (MMRM) were also analyzed. The least squares mean (L (east) and S (quares) for each treatment group and the difference between the LS mean values and the two-sided p-values from the MRMM model are shown in Table-**Table** Ошибка! Закладка не определена. and the figure below.

Table Ошибка! Закладка не определена. **- Анализ Primary endpoint analysis, visit 2 and visit 4, mixed linear model with repeated measurements.**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Differences
Session 2	LS-mean±CO	32.4446±0.5765	32.5735±0.5801	
Change to session 4	LS-mean±CO	-17.6974±0.8492	-21.5120±0.8545	3.6857±1.2123
	95% CI for chang			P- 6.0800
	value			**0.0028**

Primary endpoint

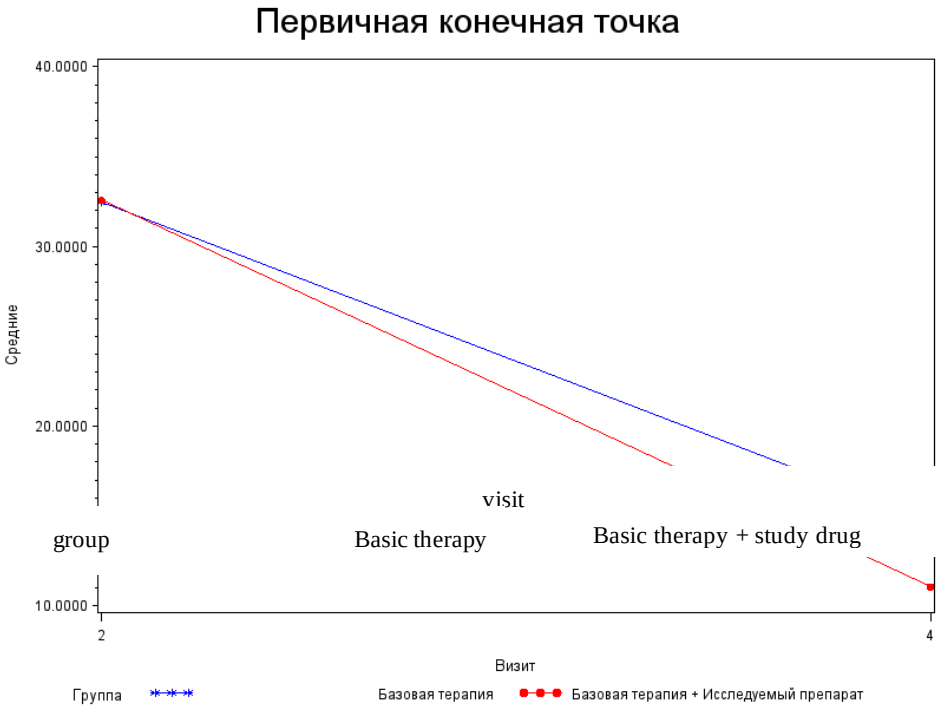


Figure Ошибка! Закладка не определена.**. Graphical representation of the dynamics of the total score on the SCORAD index.**

Exploratory analysis of the results using the ANCOVA model, which included the Basic SCORAD score as a covariate, showed a bilateral p-value <0.0001 in favor of adding Polisorb® MP to the Basic therapy when compared with the Basic drug therapy. The following table shows the results of the study using the ANCOVA model.

Table Ошибка! Закладка не определена. **- Analysis of differences in Session 4 значения индекса SCORAD index values, mixed linear model with repeated measurements.**

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Group	1	159	9.24	0.0028
Session	1	159	3921.43	<.0001
Group*Session	1	159	5.61	0.0190

Table Ошибка! Закладка не определена. **– . Primary endpoint population ITT, a general linear model with an initial level as covariates/**

Source	**DF**	**Type III SS**	**Mean Square**	**F Value**	**Pr > F**
Base Index Level SCORSE V2_INDX2_IN1	1	1016.928864	1016.928864	19.31	<.0001

11.4.1.2. Secondary endpoints

Average change in the overall BRS score for Sessions 3, 4, and 5 compared to the original score (Session 2)

The results of the analysis revealed statistically significant differences in the assessment of the BRS index. The tables: **Table** Ошибка! Закладка не определена., Table Ошибка! Закладка не определена., show an analysis of the BRS index. By session 4, relative to Session 2, there is a change of -4.8±1.48, -4.0 vs. -4.3 ±1.55, -5.0, p = 0.047.

Table Ошибка! Закладка не определена. **– Results of estimating the total BRS score by BRS descriptive statistics methods, depending on the treatment group (n= 161).**

			Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
BRS						
	VISIT 2	N	81	80	161	
		Average±CO	6.1 (0.58)	6.1 (0.37)	6.1 (0.49)	0.734#
		95% DI (average)	(6.0,6.2)	(6.0,6.2)	(6.0,6.2)	
		Median	6.0	6.0	6.0	
		[q1-q3]	[6.0-6.0]	[6.0-6.0]	[6.0-6.0]	
		Min-Max	4.0-8.0	6.0-8.0	4.0-8.0	
	SESSION 3	N	81	80	161	
		Average±CO	3.4 (1.30)	2.9 (1.60)	3.1 (1.48)	0.017#
		95% DI (average)	(3.1,3.7)	(2.5,3.2)	(2.9,3.4)	
		Median	4.0	3.0	3.0	
		[q1-q3]	[3.0-4.0]	[2.0-4.0]	[2.0-4.0]	
		Min-Max	0.0-6.0	0.0-7.0	0.0-7.0	
	SESSION 4	N	81	80	161	
		Average±CO	1.8 (1.47)	1.4 (1.51)	1.6 (1.50)	0.056#
		95% DI (average)	(1.5,2.1)	(1.0,1.7)	(1.3,1.8)	

			Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
		Median	2.0	1.0	1.0	
		[q1-q3]	[1.0-3.0]	[0.0-2.0]	[0.0-2.0]	
		Min-Max	0.0-6.0	0.0-6.0	0.0-6.0	
	SESSION 5	N	81	80	161	
		Average±CO	1.7 (1.88)	1.0 (1.49)	1.4 (1.72)	0.016#
		95% DI (average)	(1.3,2.1)	(0.7,1.4)	(1.1,1.6)	
		Median	1.0	0.0	1.0	
		[q1-q3]	[0.0-3.0]	[0.0-2.0]	[0.0-2.0]	
		Min-Max	0.0-8.0	0.0-6.0	0.0-8.0	
Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).						

Table Ошибка! Закладка не определена. **– Results of analysis of changes in the total BRS score by BRSdescriptive statistics methods depending on the treatment group (n= 161).**

			Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
BRS						
	VISIT 2	N	81	80	161	
		Average±WITH	6.1 (0.58)	6.1 (0.37)	6.1 (0.49)	0.734#
		95% CI (medium)	(6.0,6.2)	(6.0,6.2)	(6.0,6.2)	
		Median	6.0	6.0	6.0	
		[q1-q3]	[6.0-6.0]	[6.0-6.0]	[6.0-6.0]	
		Min-Max	4.0-8.0	6.0-8.0	4.0-8.0	
	a VISIT 3	N	81	80	161	
		Mean±WITH	-2.7 (1.28)	-3.3 (1.56)	-3.0 (1.45)	0.010#
		95% CI (medium)	(-3.0,-2.4)	(-3.6,-2.9)	(-3.2,-2.7)	
		The median	-2.0	-3.0	-3.0	
		[q1-q3]	[---4.0 2.0]	[2.0 -4.0--]	[---4.0 2.0]	
		Min-Max	-6.0-0.0	-6.0-1.0	-6.0-1.0	
	VISIT 4	N	81	80	161	
		Mean±FROM	-4.3 (1.55)	-4.8 (1.48)	-4.5 (1.53)	0.047#
		95% DI (medium)	(-4.6,-4.0)	(-5.1,-4.4)	(-4.8,-4.3)	
		Median	-4.0	-5.0	-5.0	
		[q1-q3]	[---5.0 4.0]	[4.0 -6.0--]	[---6.0 4.0]	
		Min-Max	--1.0 -8.0	-7.0--1.0	--1.0 -8.0	
	VISIT 5	N	81	80	161	
		Mean±FROM	-4.4 (1.94)	-5.1 (1.46)	-4.7 (1.74)	0.013#
		95% CI (medium)	(-4.8,-4.0)	(-5.4,-4.8)	(-5.0,-4.5)	
		Median	-5.0	-6.0	-5.0	
		[q1-q3]	[-6.0--4.0]	[4.0 -6.0--]	[---6.0 4.0]	
		Min-Max	-8.0-1.0	-7.0-0.0	-8.0-1.0	
Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).						

Average change in the overall DLQI score for Sessions 4 and 5 compared to the original score (Session 2).

Analysis of the dermatological quality of life index (DLQI) revealed significant differences at the end of treatment (visit 4). The interpretation of the scale is inversely directed – the higher the score, the more negatively the disease affects the patient's quality of life. On session 2, no differences were found between the groups; on subsequent sessions, significant differences were noted (**Table** Ошибка! Закладка не определена.). At visit 4, the total score in the BT + IT group was 3.6±3.81, 3.0 vs. 5.1±3.57, 4 (p=0.015), and at visit 5, it was 2.1± 3.12, 1.0 vs. 3.4± 3.60, 2.0 (p=0.010,). Despite the improvement in quality of life indicators, there were no differences in dynamics between the groups: -5.6±4.02, -5.0 vs. -6.8± 4.72, -6.5 p= 0.089 (**Table** Ошибка! Закладка не определена.). This may be due to the high individual variability in the perception of symptoms.

Table Ошибка! Закладка не определена. **– Results of estimating the total score on the DLQI index by descriptive statistics methods, depending on the treatment group (n= 161).**

_BASIC						
			therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
DLQI						
	VISIT 2	N	81	80	161	
		Mean±CO	10.6 (4.79)	10.4 (4.59)	10.5 (4.68)	0.731#
		95% DI (average)	(9.6,11.7)	(9.4,11.4)	(9.8,11.2)	
		Median	10.0	10.0	10.0	
		[q1-q3]	[7.0-14.0]	[7.0-12.5]	[7.0-13.0]	
		Min-Max	1.0-22.0	2.0-22.0	1.0-22.0	
	SESSION 4	N	81	80	161	
		Average±CO	5.1 (3.57)	3.6 (3.81)	4.3 (3.75)	0.015#
		95% DI (average)	(4.3,5.9)	(2.8,4.5)	(3.8,4.9)	
		Median	4.0	3.0	3.0	
		[q1-q3]	[3.0-7.0]	[1.0-4.0]	[2.0-6.0]	
		Min-Max	0.0-15.0	0.0-15.0	0.0-15.0	
	SESSION 5	N	81	80	161	
		Average±CO	3.4 (3.60)	2.1 (3.12)	2.8 (3.43)	0.010#
		95% DI (average)	(2.6,4.2)	(1.4,2.7)	(2.2,3.3)	
		Median	2.0	1.0	2.0	
		[q1-q3]	[0.0-6.0]	[0.0-2.5]	[0.0-4.0]	
		Min-Max	0.0-18.0	0.0-12.0	0.0-18.0	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Table Ошибка! Закладка не определена. **– Results of analysis of changes in the total score on the DLQI index by descriptive statistics methods depending on the treatment group (n= 161).**

			Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
DLQI						
	VISIT 2	N	81	80	161	
		Mean±CO	10.6 (4.79)	10.4 (4.59)	10.5 (4.68)	0.731#
		95% DI (average)	(9.6,11.7)	(9.4,11.4)	(9.8,11.2)	
		Median	10.0	10.0	10.0	
		[q1-q3]	[7.0-14.0]	[7.0-12.5]	[7.0-13.0]	
		Min-Max	1.0-22.0	2.0-22.0	1.0-22.0	
	SESSION 4	N	81	80	161	
		Mean±CO	-5.6 (4.02)	-6.8 (4.72)	-6.2 (4.41)	0.089#

			Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
		95% DI (average)	(-6.5,-4.7)	(-7.8,-5.7)	(-6.8,-5.5)	
		Median	-5.0	-6.5	-6.0	
		[q1-q3]	[-8.0--3.0]	[-10.0--3.0]	[-9.0--3.0]	
		Min-Max	-19.0-1.0	-22.0-2.0	-22.0-2.0	
	SESSION 5	N	81	80	161	
		Mean±CO	-7.2 (4.70)	-8.3 (4.90)	-7.8 (4.82)	0.134#
		95% DI (average)	(-8.2,-6.1)	(-9.4,-7.2)	(-8.5,-7.0)	
		Median	-6.0	-8.0	-7.0	
		[q1-q3]	[-10.0--4.0]	[-10.5--5.0]	[-10.0--4.0]	
		Min-Max	-22.0-0.0	-22.0-1.0	-22.0-1.0	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Mean change andndecca of the SCORAD ca for Sessions 3 and 5 compared to the original score (Session 2).

Analysis of changes in the SCORAD index showed significant differences between the groups both in the values of the overall score and in dynamics. The results are presented in the following tables: Table Ошибка! Закладка не определена., Table Ошибка! Закладка не определена..

Table Ошибка! Закладка не определена. **– Results of evaluating the total score on the SCORAD index using descriptive statistics methods, depending on the treatment group (n= 161).**

			Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	SESSION 2	N	81	80	161	
		Mean±CO	32.4 (5.33)	32.6 (5.04)	32.5 (5.17)	0.875#
		95% DI (average)	(31.3,33.6)	(31.5,33.7)	(31.7,33.3)	
		Median	33.6	33.6	33.6	
		[q1-q3]	[29.8-36.8]	[29.5-36.6]	[29.8-36.6]	
		Min-Max	20.4-39.6	20.9-39.6	20.4-39.6	
	SESSION 3	N	81	80	161	
		Mean±CO	22.4 (6.99)	19.9 (6.82)	21.1 (7.00)	0.022#
		95% DI (average)	(20.8,23.9)	(18.3,21.4)	(20.0, 22.2)	
		Median	21.6	19.6	21.2	
		[q1-q3]	[17.2-26.7]	[14.8-24.6]	[15.9-25.3]	
		Min-Max	7.7-39.7	3.5-37.4	3.5-39.7	
	SESSION 5	N	81	80	161	
		Mean±CO	13.1 (9.72)	8.2 (8.74)	10.7 (9.54)	<0.001#
		95% CI (mean)	(11.0,15.3)	(6.3,10.2)	(9.2,12.2)	
		Median	11.2	7.0	9.5	
		[q1-q3]	[7.0-20.8]	[0.0-11.9]	[3.5-17.5]	
		Min-Max	0.0-46.9	0.0-34.7	0.0-46.9	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Table Ошибка! Закладка не определена. **– Results of analysis of changes in the total score on the SCORAD index by descriptive statistics methods depending on the treatment group (n= 161).**

			Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
SCORAD						
	VISIT 2	N	81	80	161	
		Mean±CO	32.4 (5.33)	32.6 (5.04)	32.5 (5.17)	0.875#
		95% DI (average)	(31.3,33.6)	(31.5,33.7)	(31.7,33.3)	
		Median	33.6	33.6	33.6	
		[q1-q3]	[29.8-36.8]	[29.5-36.6]	[29.8-36.6]	
		Min-Max	20.4-39.6	20.9-39.6	20.4-39.6	
	SESSION 3	N	81	80	161	
		Mean±CO	-10.1 (6.19)	-12.7 (6.23)	-11.4 (6.33)	0.008#
		95% DI (average)	(-11.4,-8.7)	(-14.1,-11.3)	(-12.4,-10.4)	
		Median	-10.0	-13.3	-11.1	
		[q1-q3]	[-14.3--5.5]	[-17.0--7.3]	[-16.0--6.6]	
		Min-Max	-23.5-11.5	-33.1--0.5	-33.1-11.5	
	SESSION 5	N	81	80	161	
		Average±CO	-19.3 (9.78)	-24.3 (8.92)	-21.8 (9.67)	<0.001#
		95% DI (average)	(-21.5,-17.1)	(-26.3,-22.4)	(-23.3,-20.3)	
		Median	-19.0	-24.9	-22.5	
		[q1-q3]	[-26.4--13.7]	[-31.1--19.5]	[-29.2--16.2]	
		Min-Max	-39.4-18.7	-39.0-3.5	-39.4-18.7	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Number of days of taking antihistamines in the period from Visit 2 to Visit 4 based on the patient's diary;

The results of the analysis of the duration of use of antihistamines are presented in the table below (**Table** Ошибка! Закладка не определена.). There were no differences in the duration of treatment between the groups.

Table Ошибка! Закладка не определена. **– Results of the analysis of antihistamine medication intake based on the patient's diary using descriptive statistics methods, depending on the treatment group (n= 161).**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Days withcetirizine					
	N	81	80	161	
	Mean±CO	13.7 (0.75)	13.8 (0.82)	13.7 (0.78)	0.634#
	95% DI (average)	(13.5,13.9)	(13.6,13.9)	(13.6,13.9)	
	Median	14.0	14.0	14.0	
	[q1-q3]	[13.0-14.0]	[13.0-14.0]	[13.0-14.0]	
	Min-Max	12.0-15.0	12.0-15.0	12.0-15.0	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Number of days of topical drug administration in the period from Visit 2 to Visit 4 based on the patient's diary.

The results of the analysis of the duration of topical application of pime crolimus are presented in the table -**Table** Ошибка! Закладка не определена.. There were no differences in the duration of treatment between the groups.

Table Ошибка! Закладка не определена. **– Results of analysis of topical application of pimecrolimus based on the patient's diary by descriptive statistics methods, depending on the treatment group (n= 161).**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Days withpimecrolimus					
	N	81	80	161	
	Mean±CO	13.7 (0.84)	13.6 (0.85)	13.6 (0.84)	0.754#
	95% DI (average)	(13.5,13.8)	(13.4,13.8)	(13.5,13.8)	
	Median	14.0	14.0	14.0	
	[q1-q3]	[13.0-14.0]	[13.0-14.0]	[13.0-14.0]	
	Min-Max	11.0-15.0	10.0-15.0	10.0-15.0	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Average change in the EASI Index by Session 5 compared to Session 1.

EASI (Eczema Area and Severity Index) is designed to assess the severity of atopic dermatitis based on the prevalence and severity of skin lesions. The analysis did not show a statistically significant change in the area affected by atopic dermatitis. The results are shown in the table-**Table** Ошибка! Закладка не определена..

Table Ошибка! Закладка не определена. **– Results of analysis of changes in the total score индекса EASI index a by descriptive statistics methods depending on the treatment group (n= 161).**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
EASI index for session 1					
	N	81	80	161	
	Average±CO	3.6 (3.41)	3.5 (3.32)	3.5 (3.36)	0.840#
	95% DI (average)	(2.8,4.3)	(2.7,4.2)	(3.0,4.0)	
	Median	2.4	2.4	2.4	
	[q1-q3]	[1.2-4.2]	[1.2-4.4]	[1.2-4.3]	
	Min-Max	0.4-17.8	0.3-16.8	0.3-17.8	
EASI index for session 5					
	N	81	80	161	
	Average±CO	1.5 (2.07)	1.1 (1.82)	1.3 (1.95)	0.285#
	95% DI (average)	(1.0,1.9)	(0.7,1.5)	(1.0,1.6)	
	Median	0.6	0.4	0.6	
	[q1-q3]	[0.3-1.8]	[0.0-1.5]	[0.0-1.6]	
	Min-Max	0.0-11.5	0.0-9.0	0.0-11.5	
Dynamics of the overall score IndexaEASI by Session 5					
	N	81	80	161	
	Average±CO	-2.1 (2.76)	-2.3 (2.70)	-2.2 (2.72)	0.606#
	95% DI (average)	(-2.7,-1.5)	(-2.9,-1.7)	(-2.7,-1.8)	
	Median	-1.4	-1.5	-1.5	
	[q1-q3]	[-2.3--0.6]	[-2.4--0.9]	[-2.3--0.8]	
	Min-Max	-17.4-4.0	-13.8-2.9	-17.4-4.0	

Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).

Average change on the IGA scale by Session 5 compared to Session 1.

IGA Scale (Investigators' Global Assessment is used to assess the severity of atopic dermatitis according to the doctor's opinion, the results of the analysis show aoe significant change. A score of 0 points corresponds to clear skin, and a maximum score of 4 points corresponds to severe atopic dermatitis. By visit 5, the score in the BT+ IP group decreased from2.66±0.49,, 3.0 to 0.9,9± 0.90,, 1.0 and in the BT group from 2.6,6 ± 0.49,, 3.0 to 1.4,4±0.89,, 2.0, the differences at visit 5 were statistically significant (p<0.001). Differences in dynamics were also significant -1.7,7±0.88,, - 2.0 vs. -1.2,2± 0.79,, - 1.0 (p<0.001).

Table Ошибка! Закладка не определена. **– Results of analysis of changes in the IGA scale by descriptive statistics methods depending on the treatment group (n= 161).**

		Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
IGA scale at session 1					
	N	81	80	161	
	Average±CO	2.6 (0.49)	2.6 (0.49)	2.6 (0.49)	0.701#
	95% CI (mean)	(2.5,2.7)	(2.5,2.7)	(2.5,2.7)	
	Median	3.0	3.0	3.0	
	[q1-q3]	[2.0-3.0]	[2.0-3.0]	[2.0-3.0]	
	Min-Max	2.0-3.0	2.0-3.0	2.0-3.0	
Scale IGA on session 5					
	N	81	80	161	
	Average±CO	1.4 (0.89)	0.9 (0.90)	1.2 (0.93)	<0.001#
	95% DI (average)	(1.2,1.6)	(0.7,1.1)	(1.0,1.3)	
	Median	2.0	1.0	1.0	
	[q1-q3]	[1.0-2.0]	[0.0-2.0]	[0.0-2.0]	
	Min-Max	0.0-4.0	0.0-3.0	0.0-4.0	
Dynamics of the total score on wkaleIGAk Vizity5					
	N	81	80	161	
	Mean±CO	-1.2 (0.79)	-1.7 (0.88)	-1.4 (0.86)	<0.001#
	95% DI (average)	(-1.4,-1.0)	(-1.9,-1.5)	(-1.6,-1.3)	
	Median	-1.0	-2.0	-1.0	
	[q1-q3]	[-2.0--1.0]	[-2.0--1.0]	[-2.0--1.0]	
	Min-Max	-3.0-2.0	-3.0-0.0	-3.0-2.0	
Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).					

11.4.2. Statistical (analytical) results

Statistical analysis and generation of tables and lists were performed using software installed on the Microsoft Windows XP® operating system. Individual data for each patient was listed with an indication of the parameter and their assignment to the patient's number, center, visits, and therapy group.

Standard descriptive summary statistics were calculated for continuous variables (i.e. arithmetic mean, standard deviation, minimum value, lower quartile, median, upper quartile, maximum value, number of non-missing values). Lists of data about individual patients are presented by parameters and sorted by treatment group, center, patient number, and session.

11.4.2.1. Adjustments for covariates

In the section 11.4.1.1, an analysis is presented in which the initial level индекса of the SCORAD index is selected as a covariate.

11.4.2.2. Handling data from retired research subjects or missing data

Each case of a patient's premature termination of the study or withdrawal from the study was documented with the reason for the premature termination or withdrawal from the study. The missing data was not replaced. Patients who dropped out of the study were not replaced.

11.4.2.3. Intermediate data analysis and monitoring.

As part of the intermediate analysis, only one parameter was calculated – the primary endpoint - in order to assess the sufficiency of the calculated sample. In this regard, after receiving data on the primary endpoint (138 patients were analyzed). There was no decontamination procedure, as the study is open-ended. Secondary parameters and safety were not calculated. Based on the results of the analysis, a decision was made to continue the study, change the sample, or terminate the study. If the sample was changed, an amendment to the protocol would be drawn up and submitted to the MOH for approval. If the study is stopped, a clinical report is prepared and submitted to the MOH for notification. The results of the analysis showed a statistically significant effect of the study drug on the dynamics of the SCORAD index. It was decided to continue the study with the planned sample size.

ΠNo daily analysis or statistical monitoring of the data was provided.

11.4.2.4. Multicenter studies

B 6 161 patients were recruited in 6 research centers161. The set in the center was equal. An exploratory analysis was performed with repeated measurements and the effect of the center* visit*treatment group. The results of the analysis are presented below. There was no significant influence on the results of the primary variable (Group - group, visit-session, site_number-center number, Effect – effect).

.

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Group*visit_*site_number	5	149	2.15	0.0627

11.4.2.5. Multiple comparisons (multiplicity)

Multiplicity analysis was not performed.

11.4.2.6. Using a subgroup of patients who have been shown to be effective

There were no cases with patients excluded from the analysis due to low adherence, missed visits, or non-compliance with the study requirements. In the present study, all data were included in the efficacy analysis (PP and ITT populations were equal).

11.4.2.7. Equivalence studies with active control

Not applicable, the study did not include an equivalence assessment.

11.4.2.8. Subgroup research

Efficacy and safety studies have not been conducted in certain subgroups.

11.4.3. Summary tables of individual effects data

The individual data collected during the study are listed in the appendices in the section **Ошибка! Источник ссылки не найден. - Ошибка! Источник ссылки не найден.**.

11.4.4. Relationship between the dose of the drug, its concentration and effect

This study did not investigate the relationship between concentration and dose taken.

11.4.5. Drug interactions and the impact of comorbidities

The occurrence of comorbidities or risk factors during the study was documented as undesirable events. This study did not investigate specific interactions between drugs or diseases. The study drug was used as part of a complex therapy of acute bronchitis, all patients received antibiotic therapy, and therefore it is not possible to determine the effect of antibiotic use on the outcome of the response.

11.4.6. Presentation of data for each patient

Individual data collected during the study are listed in the appendices in 16.2.2.

11.4.7. Conclusion on effectiveness

The study found no differences between the ITT and PP populations. The results are presented on data from the ITT population, which made up the full data set (FAS-full analysis set). The primary parameter in this study was the average change in the SCORAD Index value on day 14 of treatment (Visit 4) compared to the initial assessment (Visit 2).

The analysis showed a statistically significant decrease in the severity of atopic dermatitis manifestations according to the SCORAD index when Polisorb® MP was added to the basic therapy, which consisted of cosmetic emollient care, cetirizine administration, and топического topicalя pime crolimus administration. The course of treatment was 14 days (from Visit 2 to Visit 4). Both groups show positive dynamics. In the basic therapy group, the total score on the SCORAD index changed from 32.4,±5.33, 33.6 to 14.7±7.97, 13.0 the difference was -17.7,±7.80,, -17.8,points. In the study therapy group (BT+ IT) at visit 2, the total score according to the SCORAD index was 32.6 ±5.04, 33.6 after 14 days-11.1± 7.39, 9.8, the difference was -21.5 ±7.48, -22.1, the differences between the groups were significant p= 0.002. Changes in the primary parameter were analyzed by a mixed group. using a linear model with repeated measurements (MMRM) with an assessment of the impact of the effect of : therapeutic group (p = 0.0028,), visit (p<.0001) and combined effect group * visit (p=0.0190,), the results indicate in favor of adding препарата Polisorb® MP to the basic therapy.

In the course of the study, other assessment scales were also used, in particular, the BRS index, the EAS Iindex, and the IGA scale. According to the EASI index, there were no significant changes between the groups, which indicates that there are no changes in the area of atopic dermatitis damage to the skin of patients. At the same time, the BRS index shows

significant dynamics: by visit 4, itching decreased by -4.8±1.48, -4.0 vs. -4.3 ±1.55, -5.0, p = 0.047. The results индекса of the SCORAD index dynamics are supported by an IGA score (Investigators' Global Assessment), which is used to assess the severity of atopic dermatitis according to the doctor's opinion the assessment was carried out at a delayed follow-up visit, according to which a score of 0 points corresponds to clean skin, and a maximum score of 4 points corresponds to severe atopic dermatitis. By visit 5 (10-12 days after the end of treatment) in the BT+ IP group, the score decreased from 2.6±0.49, 3.0 to 0.9± 0.90, 1.0 and in the BT group from 2.6 ± 0.49, 3.0 to 1.4±0.89, 2.0, the differences at visit 5 between the groups were statistically significant ($p<0.001$). Differences in dynamics were significant -1.7±0.88, - 2.0 vs. -1.2± 0.79, - 1.0 ($p<0.001$).

Taking into account that all patients were able to use the basic therapy throughout the study, the duration of cetirizine and pime crolimus administration in the groups was similar.

Analysis of the dermatological quality of life index (DLQI) revealed significant differences at the end of treatment (visit 4). The interpretation of the scale is inversely directed – the higher the score, the more negatively the disease affects the patient's quality of life. At session 2, there were no differences between the groups; in the BT + IT group, the total score was: 10.4±4.59, 10.0 to session 4-3. 6±3.81, 3.0 in the BT group at session 2-9.6±11.7, 10.0 and to session 4-5.1±3.57, 4. the difference between the groups was reliable ($p= 0.015$,). Despite the improvement in quality of life indicators, there were no differences in dynamics between the groups: in the BT group -5.6±4.02, -5.0 , in the BT+IT group -6.8± 4.72, -6.5 $p= 0.089$.

Thus, the data obtained indicate that the use of Polisorb ® MP in the framework of complex therapy affects the success of therapy in the main parameters: reduces the intensity of clinical проявлений manifestations (SCORAD, IGA scales), reduces the sensation of pruritusa(BRS index), improves the quality of life of patients (DLQI index).

12. SAFETY ASSESSMENT

12.1. Exposure value

In the x-phase of the study 161 patients were treated, of which 80 patients took the study drug. The table below shows the gender distribution.

Table Ошибка! Закладка не определена.**- Gender distribution of patients exposed to the study drug**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Gender					
	Female	49 (60.5%)	50 (62.5%)	99 (61.5%)	0.794~
	Male	32 (39.5%)	30 (37.5%)	62 (38.5%)	
Note. ~- The comparison was made using the Chi-square test.					

12.1.1. Duration

The study examined the dosage regimen – patients could take up to 20 mg per day. Data on the duration of patient follow-up are given below.

Table Ошибка! Закладка не определена.**-Duration of observation (ITT-population)**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	N	81	80	161	
	Mean±CO	13.7 (0.75)	13.8 (0.82)	13.7 (0.78)	0.634#
	95% DI (average)	(13.5,13.9)	(13.6,13.9)	(13.6,13.9)	
	Median	14.0	14.0	14.0	
	[q1-q3]	[13.0-14.0]	[13.0-14.0]	[13.0-14.0]	
	Min-Max	12.0-15.0	12.0-15.0	12.0-15.0	
Note: Statistical method: # - ANOVA analysis of variance.					

12.1.2. Dosage

The studied dosage regimen: A single dose-1-2 tablespoons with a slide (1 tablespoon contains 2.5-3 grams) for half a glass of water, immediately before meals.

The daily dose is 15-20 grams of the drug (6 tablespoons "with a slide") dividedx into 3-4 times a day, the course of therapy is 14 days.

Method of administration: Oral administration only in the form of an aqueous suspension immediately before meals. The suspension is prepared by carefully stirring the required amount of the drug in ¼ or ½ cup of water. After stirring, an opaque suspension of white or almost white color is formed.

12.1.3. Drug concentration

The analysis of concentration - undesirable phenomenon was not carried out because the drug does not have a systemic effect.

12.2. Undesirable effects

12.2.1. A brief summary of the NYA

During the study, 34 AES were registered in 26 patients (16,1%), из них в группе «БТ» - 1,6,1%), including 12 AES in 10 (1,2,3%) patients in the "BT" group, and 12 AES in the%) пациентов, в группе BI+group.IP - 22 AE in 16 patients (20,0%). There were no statistical differences between the groups (p= 0.1%). The majority of AES were mild: 31 AES in 23 (14.3%) patients, by groups: in the BT+IT group-21 AES in 15 (18.8) patients and 10 AES in 8 (9.9%) patients in the BT group. No serious AES were reported. Analysis of the structure of AES showed significant differences, all AES from the gastrointestinal tract were observed in the group of the studied therapy. There were 15 AES in 12 (15%) patients (p= 0.001), including constipation (p = 0.007) , 9 AES in 7 patients (8.8%) , of which 7 AES in 5 (6.3%) patients had a definite association and one AES with probable and possible connections. 2 cases of dyschesi and 2 patients had a definite association with the therapy performed and in oneому case: abdominal discomfort (definite association), bloating (possible association), dry mouth (possible association), nausea (possible connection).

There were no significant differences in the remaining systems различий between the groups; the second most common after AES from the gastrointestinal tract were disorders of the nervous system. The association was not established with AES such as headache (4 AES in 4 (4.9%) patients in the BT group and 1 AES in one patient (1.3%) in the BT+ IT group), one episode of vertigo in one головокруженияpatient (1.2%) in the BT group. In the BT+ IP group, one case was registered: upper respiratory tract viral infection, dental pulpitis, нECG repolarization failures, arrhythmia, and 2 AES - hypertension. In all cases, there was no association with the current therapy. In the BT group, the following AES were recorded : increased transaminase levels (1 AES), grade 1 AV block (1 AES), essential hypertension (1 AES), back pain со стороны спины(1 AES), pain at the application site (2 AES, original description - tingling sensation in the area of applying the cream), connections there was no difference between the phenomena. In the BT group, 1 AE was registered - an exacerbation of atopic dermatitis, the relationship was considered "possible".

All events resolved, the outcome is not known for the following AES: increased transaminases (1 AES), arrhythmia (1 AES in the BT + IP group), and exacerbation of atopic dermatitis (1 AES) in the BI group. In connection with the identified adverse events, the following actions were taken: the appointment of concomitant therapy in the case of back pain (1 AE in the BT group), pulpitis (1 AE in the BT + IP group), headache (2 AE in the BT group and 1 AE in the BT + IP group), dizziness (1 AE in the BT group), upper respiratory tract viral infection (1 AE in the BT group and BT + IP), hypertension (2 AE in the BT + IP group). No action was taken in relation to the study therapy.

All AES were mild, with the exception aof arrhythmia (1 AE in the BT + IP group), increased transaminase levels (1 AE in the BT group), and exacerbation of atopic dermatitis (1 AE in the BT group), which were considered moderate in severity.

No deaths or pregnancies were reported.

12.2.2. Presentation of data about a new instance

All AES are summarized below by organ system class (SOC) and preferred term (PT) according to the MedDRA dictionary, as well as by association with the study drug and severity.

The analysis for statistically significant differences between the groups was carried out using the exact Fisher test and χ^2 (chi square). There were no statistically significant differences.

The table below shows the frequency of AE registration depending on sessions. AES were registered evenly throughout the study after the start of therapy.

Table Ошибка! Закладка не определена.**-Adverse events, patient registration on visits. Safety population, n=161.**

	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Session 2				
Were there any adverse events?				
Not	yet 81 (100.0%)	80 (100.0%)	161 (100.0%)	n / a
Visit 3				
Were there any adverse events?				
Yes	4 (4.9%)	8 (10.0%)	12 (7.5%)	0.221~
Not	yet 77 (95.1%)	72 (90.0%)	149 (92.5%)	
Session 4				
Were there any adverse events?				
Yes	4 (4.9%)	9 (11.3%)	13 (8.1%)	0.142~
Not	yet 77 (95.1%)	71 (88.8%)	148 (91.9%)	
Session 5				
Were there any adverse events?				
Yes	2 (2.5%)	1 (1.3%)	3 (1.9%)	>0.999^
Not	yet 79 (97.5%)	79 (98.8%)	158 (98.1%)	

Note. Statistical method: ~ - Comparison is performed by the Chi-square test, ^ - Comparison is performed by the exact Fisher test.

The tables: **Table** Ошибка! Закладка не определена., Table Ошибка! Закладка не определена. show the distribution of patients depending on the class and nature of AES (preferred terms in the MedDRA reference book), version 25.1.

Table Ошибка! Закладка не определена.**-Adverse events registered during the analyzed period, by organ system class (SOC) and treatment group. Safety population, n=161.**

	Number of subjects (%) Number of events			
	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
All SoCs	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
GastrointestinalGastrointestinal disorders	0 (0.0%) 0	12 (15.0%) 15	12 (7.5%) 15	<0.001~
Nervous system disordersNervous system	disorders 4 (4.9%) 5	1 (1.3%) 1	5 (3.1%) 6	0.367^
infections and infestations	0 (0.0%) 0	2 (2.5%) 2	2 (1.2%) 2	0.245^
LAbortive and instrumental data	1 (1.2%) 1	1 (1.3%) 1	2 (1.2%) 2	>0.999^
Nheart	failure 1 (1.2%) 1	1 (1.3%) 1	2 (1.2%) 2	>0.999^
NVessel damage	1 (1.2%) 1	1 (1.3%) 2	2 (1.2%) 3	>0.999
^Skin disorders and subcutaneous tissue	1 (1.2%) 1	0 (0.0%) 0	1 (0.6%) 1	>0.999^
HMusculoskeletal disorders. skeletal and connective tissue	1 (1.2%) 1	0 (0.0%) 0	1 (0.6%) 1	>0.999^
OAcute disorders and reactions at the injection	site 1 (1.2%) 2	0 (0.0%) 0	1 (0.6%) 2	>0.999^

Note:Statisticalmethod: ~-Comparison is performed by the Chi-square test, ^-Comparison is performed by the exact Fisher test.

Table Ошибка! Закладка не определена.-**Adverse events, grouped by SOC and preferred terms (PT). Safety population, n=161**

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**p-value**
Wludochka-intestinal disorders				
	All PT	0 (0.0%) 0	12 (15.0%) 15	<0.001~
	constipation	0 (0.0%) 0	7 (8.8%) 9	0.007^
	dyschezia	0 (0.0%) 0	2 (2.5%) 2	0.245^
	abdominal discomfort,	0 (0.0%) 0	1 (1.3%) 1	0.497^
	bloating	0 (0.0%) 0	1 (1.3%) 1	0.497^
	dry mouth	0 (0.0%) 0	1 (1.3%) 1	0.497^
	nausea	0 (0.0%) 0	1 (1.3%) 1	0.497^
Nof arsenia from the nervous system				
	All PT	4 (4.9%) 5	1 (1.3%) 1	0.367^
	headache	4 (4.9%) 4	1 (1.3%) 1	0.367^
	dizziness	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Andof Peccei and invasion				
	All PT	0 (0.0%) 0	2 (2.5%) 2	0.245^
	a viral upper respiratory tract infection	0 (0.0%) 0	1 (1.3%) 1	0.497^
	pulpitis of the tooth	0 (0.0%) 0	1 (1.3%) 1	0.497^
Llaboratornye and instrumental data				
	All PT	1 (1.2%) 1	1 (1.3%) 1	>0.999^
	disorders of repolarization on the electrocardiogram	0 (0.0%) 0	1 (1.3%) 1	0.497^
	increase in transaminase levels	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Nof arsenia heart				
	All PT	1 (1.2%) 1	1 (1.3%) 1	>0.999^
	av blockade of the 1st degree	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	arrhythmia	0 (0.0%) 0	1 (1.3%) 1	0.497^
Nof arsenia from the vessels				
	All PT	1 (1.2%) 1	1 (1.3%) 2	>0.999^
	hypertension	0 (0.0%) 0	1 (1.3%) 2	0.497^
	essential hypertension	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Narsenia of the skin and subcutaneous tissue				
	All PT	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	dermatitis atopic	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Nof arsenia from the muscle. skeletal and connective tissue				
	All PT	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	back pain	1 (1.2%) 1	0 (0.0%) 0	>0.999^
OGeneral disorders and reactions at the injection				
	site All PT	1 (1.2%) 2	0 (0.0%) 0	>0.999^
	pain at the site of application	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.				

12.2.3. Analysis of adverse events

During the study, 34 AES were registered in 26 patients (16.1%), including 12 AES in 10 (12.3%) patients in the "BT" group, and 12 AES in the BI+group.IP - 22 AE in 16 patients (20.0%). There were no statistical differences between the groups (p= 0.187).

Analytical data is presented in the table – Table Ошибка! Закладка не определена.. For more detailed data, see в Section 14.3. (Table Ошибка! Закладка не определена.–Table Ошибка! Закладка не определена.).

Table Ошибка! Закладка не определена.**-Analysis of adverse events. Safety population, n=161**

	Number of subjects (%) Number of events			
	Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-Zn**
Total seriousness NYA _				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
no	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
General, the severity of AES _				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
easy	8 (9.9%) 10	15 (18.8%) 21	23 (14.3%) 31	0.108~
medium	2 (2.5%) 2	1 (1.3%) 1	3 (1.9%) 3	>0.999^
NYA Common bond with the drug				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
the link is missing	8 (9.9%) 10	3 (3.8%) 5	11 (6.8%) 15	0.123~
some	0 (0.0%) 0	8 (10.0%) 10	8 (5.0%) 10	0.003^
possible	1 (1.2%) 1	4 (5.0%) 5	5 (3.1%) 6	0.210^
a dubious connection	1 (1.2%) 1	1 (1.3%) 1	2 (1.2%) 2	>0.999^
probable	0 (0.0%) 0	1 (1.3%) 1	1 (0.6%) 1	0.497^
Common actions with the drug about IT _				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
no change	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
Common actions taken to treat IT _				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
no action was taken	6 (7.4%) 7	13 (16.3%) 17	19 (11.8%) 24	0.082~
the purpose of concomitant therapy	4 (4.9%) 5	3 (3.8%) 5	7 (4.3%) 10	>0.999^
Common outcome of IT				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
resolved	8 (9.9%) 10	15 (18.8%) 20	23 (14.3%) 30	0.108~
unknown	2 (2.5%) 2	1 (1.3%) 1	3 (1.9%) 3	>0.999^
not resolved	0 (0.0%) 0	1 (1.3%) 1	1 (0.6%) 1	0.497^
General continued IT				
All	10 (12.3%) 12	16 (20.0%) 22	26 (16.1%) 34	0.187~
no	8 (9.9%) 10	15 (18.8%) 20	23 (14.3%) 30	0.108~
Yes	2 (2.5%) 2	2 (2.5%) 2	4 (2.5%) 4	>0.999^
note. Statistical method:, ~ - Comparison was performed by the Chi-square test, ^ - Comparison was performed by the exact Fisher test.				

12.2.4. List of adverse events for each patient

Appendix 16.2.7 provides tables with an indication of the m NY for each subject.

12.3. Deaths, other serious adverse events, and other significant adverse events

12.3.1. List of deaths, other serious adverse events, and other significant adverse events

12.3.1.1. Fatal outcomes

It was not registered.

12.3.1.2. Other serious adverse events

B No SNA was recorded during the study. The table below (**Table** Ошибка! Закладка не определена.) provides an analysis of the severity assessment of AES.

Table Ошибка! Закладка не определена. **- Evaluation of AES according to severity criteria. Safety population, n=161.**

_count				
		of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
Intestinal disorders				
constipation				
	All	0 (0.0%) 0	7 (8.8%) 9	0.007^
	no	0 (0.0%) 0	7 (8.8%) 9	0.007^
Dischasia				
	All	0 (0.0%) 0	2 (2.5%) 2	0.245^
	no	0 (0.0%) 0	2 (2.5%) 2	0.245^
Andabdominally discomfort				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Inscootie belly				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Withuhost mouth				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
TOsnat				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Nof arsenia from the nervous system				
Gholovna pain				
	All	4 (4.9%) 4	1 (1.3%) 1	0.367^
	no	4 (4.9%) 4	1 (1.3%) 1	0.367^
Ggolovokruzhenie				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Andof Peccei and infestations				
viral infection of the upper respiratory tract				
	are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Pulet tooth				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Llaboratornye and instrumental data				
Narsenia of repolarization on the electrocardiogram				
	are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Nensuring the level of transaminases				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Nof arsenia of the heart				
AV-blockade of the 1st degree				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Andrytmie				

_count				
		of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	p-value.
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
Nof arsenia-side vessels				
Mr.hipertenzija				
	All	0 (0.0%) 0	1 (1.3%) 2	0.497^
	no	0 (0.0%) 0	1 (1.3%) 2	0.497^
esocialna hypertension				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Narsenia of the skin and subcutaneous tissue				
Darmatic atopic				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Nof arsenia from the muscle. skeletal and connective tissue				
Bol from the back				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	not yet	1 (1.2%) 1	0 (0.0%) 0	>0.999^
OGeneral disorders and reactions at the injection				
Bsite or at the application				
	site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^
	not	yet 1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.				

12.3.1.3. Other significant adverse events

It was not registered.

12.3.2. Description of deaths, other serious adverse events, and other significant adverse events

It was not registered.

12.3.3. Analysis and discussion of deaths, other serious adverse events, and other significant adverse events

It was not registered.

12.4. Evaluation of laboratory parameters

12.4.1. List ofindividual laboratory data for each patient and deviations of laboratory data from the norm

For more information, see the application and 16.2.8.

12.4.2. Evaluation of each laboratory parameter

Laboratory parameters were analyzed using descriptive statistics and differences between groups were also analyzed. All values were converted to common SI units of measurement.

12.4.2.1. Dynamics of laboratory parameters over time

The results of the analysis did not reveal any differences between the groups. The tables: **Table** Ошибка! Закладка не определена.-Table Ошибка! Закладка не определена. show the results of the analysis depending on the treatment group and visits. Analysis of the qualitative interpretation and laboratory parameters considered by the researchers as "clinically insignificant" deviations from the norms, also revealed no differences between the groups.

12.4.2.2. Individual changes

Changes in laboratory parameters are analyzed using shift tables. The table below (Table Ошибка! Закладка не определена.) shows the change at the end of treatment compared to the initial values. The number of tests with clinically significant abnormalities (CNS) or normal at the beginning of treatment, which changed by the end of treatment and were evaluated as CNS or norm, is presented.

The analysis showed that by the time of the end of treatment, the changes were equal for both groups.

Table Ошибка! Закладка не определена.**- Change of laboratory parameters (shift table).**

Laboratory parameters	**Basic therapy (N=81)**		**Basic therapy + Study drug (N=80)**	
	NCS deviations at the initial level with a change in the Norm	Norm of deviation at the initial level with a change in the NCS deviations	of the NCS deviations at the initial level with a change in the Norm	Norm of deviation at the initial level with a change in the NCS deviations
General clinical blood				
test Hemoglobin (g/l)	1 (1.2%)	6 (7.4%)	6 (7.5%)	7 (8.8%)
Hematocrit (units)	)7 (8.6%)	6 (7.4%)	4 (5.0%)	9 (11.3%)
Red blood cells (× 10x12/l)	6 (7.4%)	2 (2.5%)	3 (3.8%)	3 (3.8%)
White blood cells (× 10x9/l)	5 (6.2%)	5 (6.2%)	5 (6.3%)	5 (6.3%)
Neutrophils	5 (6.2%)	5 (6.2%)	8 (10.0%)	2 (2.5%)
Eosinophils	2 (2.5%)	6 (7.4%)	5 (6.3%)	7 (8.8%)
Basophils	***-2***	2 (2.5%)	-	
Monocytes (× 10x9/l)	--	-	-	1 (1.3%)
Lymphocytes (× 10x9/l)	8 (9.9%)	7 (8.6%)	8 (10.0%)	5 (6.3%)
Platelets (× 10x9/l)	4 (4.9%)	4 (4.9%)	2 (2.5%)	3 (3.8%)
Biochemical blood				
test ALT (units)	3 (3.7%)	2 (2.5%)	3 (3.8%)	-
AST (units)	1 (1.2%)	3 (3.7%)	1 (1.3%)	1 (1.3%)
Creatinine (mmol / l)	8 (9.9%)	7 (8.6%)	6 (7.5%)	2 (2.5%)
Glucose (mmol / l)	3 (3.7%)	9 (11.1%)	5 (6.3%)	11 (13.8%)
Alkaline phosphatase (units)	1 (1.2%)	2 (2.5%)	2 (2.5%)	-

Total bilirubin (mmol / l)	***-2***	2 (2.5%)	5 (6.3%)	5 (6.3%)
Cholesterol (mmol / l)	10 (12.3%)	12 (14.8%)	7 (8.8%)	9 (11.3%)
Total protein (g / l)	5 (6.2%)	2 (2.5%)	1 (1.3%)	5 (6.3%)
Uric acid (mmol / l)	7 (8.6%)	1 (1.2%)	3 (3.8%)	6 (7.5%)
Potassium (mmol / l)	4 (4.9%)	4 (4.9%)	4 (5.0%)	6 (7.5%)
Sodium (mmol / l)	6 (7.4%)	3 (3.7%)	1 (1.3%)	2 (2.5%)
General clinical analysis of urine				
pH (units)	3 (3.7%)	3 (3.7%)	8 (10.0%)	5 (6.3%)
Relative density (g / l)	5 (6.2%)	4 (4.9%)	9 (11.3%)	7 (8.8%)
Protein content (g / l)	4 (4.9%)	***-4***	4 (5.0%)	1 (1.3%)
Note. Data are presented by the number ofy tests (percentage of the total number of tests). of the total number in the subgroup).				

12.4.2.3. Clinically significant individual deviations

Medical-researchers evaluated the significance of the changes based on their professional opinion. The Protocol did not provide criteria for interpreting deviations. If clinically significant abnormalities were detected, the researchers evaluated the changes and recorded the abnormalities as AES. Individual abnormalities detected during clinical examination, considered as AES. The data is summarized in the following tables: Table Ошибка! Закладка не определена.,Table Ошибка! Закладка не определена., Table Ошибка! Закладка не определена..

12.5. Vital signs, objective research data, and other safety-related observations

An analysis of the results of physical examination of patients at various вsites of the study is presentedы in **Table** Ошибка! Закладка не определена., Table Ошибка! Закладка не определена.. The analysis did not reveal any differences between the groups.

Table Ошибка! Закладка не определена. **- Distribution of the researcher's estimates of physical examination indicators at screening. Safety population, n=161**

		_BASIC			
		therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
General condition					
	Normal	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Skin, hair and nails					
	Deviation	81 (100.0%)	80 (100.0%)	161 (100.0%)	n / a
Ears, nose and throat					
	Norm	80 (98.8%)	79 (98.8%)	159 (98.8%)	>0.999^
	Deviation	1 (1.2%)	1 (1.3%)	2 (1.2%)	
The endocrine system					
	is normal	75 (92.6%)	70 (87.5%)	145 (90.1%)	0.280~
	Rejection	rate 6 (7.4%)	10 (12.5%)	16 (9.9%)	
The cardiovascular system					
	is normal	74 (91.4%)	73 (91.3%)	147 (91.3%)	0.981~
	Rejection	rate 7 (8.6%)	7 (8.8%)	14 (8.7%)	
The respiratory system					
	is normal	79 (97.5%)	79 (98.8%)	158 (98.1%)	>0.999^
	Rejection	rate 2 (2.5%)	1 (1.3%)	3 (1.9%)	
The gastrointestinal tract					
	is normal	80 (98.8%)	80 (100.0%)	160 (99.4%)	>0.999^
	Rejection	rate 1 (1.2%)	0 (0.0%)	1 (0.6%)	
The kidneys and urinary system					

_BASIC					
		therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
	are normal	81 (100.0%)	80 (100.0%)	161 (100.0%)	n / a
The reproductive system					
	is normal	80 (98.8%)	80 (100.0%)	160 (99.4%)	>0.999^
	Rejection	rate 1 (1.2%)	0 (0.0%)	1 (0.6%)	
Musculoskeletal					
	system Norm	79 (97.5%)	79 (98.8%)	158 (98.1%)	>0.999^
	Rejection	rate 2 (2.5%)	1 (1.3%)	3 (1.9%)	
The nervous system					
	is normal	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visual system					
	Norm	80 (98.8%)	79 (98.8%)	159 (98.8%)	>0.999^
	Rejection	rate 1 (1.2%)	1 (1.3%)	2 (1.2%)	
The lymphatic system					
	The norm	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Note. Statistical method:, ~ - Comparison was performed by the Chi-square test, ^ - Comparison was performed by the exact Fisher test.					

Table Ошибка! Закладка не определена. **- Distribution of post-treatment physical examination scores by the researcher. Safety population, n=161.**

		Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
General condition					
	Normal	81 (100.0%)	80 (100.0%)	161 (100.0%)	n / a
Skin, hair and nails					
	Norm	1 (1.2%)	8 (10.0%)	9 (5.6%)	0.018^
	Rejection	rate 80 (98.8%)	72 (90.0%)	152 (94.4%)	
Ears, nose and throat					
	are normal	80 (98.8%)	79 (98.8%)	159 (98.8%)	>0.999^
	Rejection	rate 1 (1.2%)	1 (1.3%)	2 (1.2%)	
The endocrine system					
	is normal	75 (92.6%)	70 (87.5%)	145 (90.1%)	0.280~
	Rejection	rate 6 (7.4%)	10 (12.5%)	16 (9.9%)	
The cardiovascular system					
	is normal	74 (91.4%)	73 (91.3%)	147 (91.3%)	0.981~
	Rejection	rate 7 (8.6%)	7 (8.8%)	14 (8.7%)	
The respiratory system					
	is normal	79 (97.5%)	79 (98.8%)	158 (98.1%)	>0.999^
	Rejection	rate 2 (2.5%)	1 (1.3%)	3 (1.9%)	
The gastrointestinal tract					
	is normal	79 (97.5%)	79 (98.8%)	158 (98.1%)	>0.999^
	Rejection	rate 2 (2.5%)	1 (1.3%)	3 (1.9%)	
The kidneys and urinary system					
	are normal	81 (100.0%)	80 (100.0%)	161 (100.0%)	n / a
The reproductive system					
	is normal	80 (98.8%)	80 (100.0%)	160 (99.4%)	>0.999^
	Rejection	rate 1 (1.2%)	0 (0.0%)	1 (0.6%)	
Musculoskeletal					
	system Norm	79 (97.5%)	79 (98.8%)	158 (98.1%)	>0.999^
	Rejection	rate 2 (2.5%)	1 (1.3%)	3 (1.9%)	
The nervous system					
	is normal	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Visual system					

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	Norm	80 (98.8%)	79 (98.8%)	159 (98.8%)	>0.999^
	Rejection	rate 1 (1.2%)	1 (1.3%)	2 (1.2%)	
The lymphatic system					
	The norm	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Note. Statistical method: ~ - Comparison is performed by the Chi-square test, ^ - Comparison is performed by the exact Fisher test.					

Below is a listы of changes in vital signs (temperature, BMI, heart rate, SBP, DBP) during various Sessions. There were no statistically significant differences between the groups. Tablese- **Table** Ошибка! Закладка не определена.-show datacollected during observation sessions.

Table Ошибка! Закладка не определена. **– Vital dataon important indicators, the dynamics of indicators in relation to the initial values. Safety population, n=161.**

_BASIC					
		therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
SBP (mmHg)on session 2					
	N	81	80	161	
	Average (CO)	-0.5 (5.04)	-0.2 (5.70)	-0.4 (5.36)	0.752#
	95% DI (average)	(-1.6,0.6)	(-1.5,1.0)	(-1.2,0.5)	
	Median	-1.0	0.0	0.0	
	[q1-q3]	[-4.0-3.0]	[-5.0-4.5]	[-5.0-4.0]	
	Min-Max	-18.0-10.0	-20.0-12.0	-20.0-12.0	
DBP (mmHg)on session 2					
	N	81	80	161	
	Average (SB)	-0.7 (5.42)	-0.6 (6.27)	-0.6 (5.84)	0.910#
	95% DI (average)	(-1.9,0.5)	(-2.0,0.8)	(-1.5,0.3)	
	Median	-1.0	0.0	0.0	
	[q1-q3]	[-4.0-3.0]	[-4.0-3.0]	[-4.0-3.0]	
	Min-Max	-20.0-10.0	-19.0-15.0	-20.0-15.0	
Body temperature at session 2					
	N	81	80	161	
	Average (CO)	-0.0 (0.27)	-0.0 (0.20)	-0.0 (0.24)	0.866#
	95% DI (average)	(-0.1,0.1)	(-0.1,0.0)	(-0.0,0.0)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-0.2-0.1]	[-0.2-0.2]	[-0.2-0.1]	
	Min-Max	-0.7-0.8	-0.6-0.4	-0.7-0.8	
SBP (mmHg)on session 3					
	N	81	80	161	
	Average (CO)	-0.2 (6.56)	-0.3 (5.73)	-0.3 (6.14)	0.896#
	95% DI (average)	(-1.7,1.2)	(-1.6,0.9)	(-1.2,0.7)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-4.0-2.0]	[-4.0-2.0]	[-4.0-2.0]	
	Min-Max	-20.0-19.0	-15.0-16.0	-20.0-19.0	
DBP (mmHg)on session 3					
	N	81	80	161	
	Average (CO)	0.1 (5.86)	-0.8 (7.70)	-0.3 (6.83)	0.399#
	95% DI (average)	(-1.2,1.4)	(-2.5,0.9)	(-1.4,0.7)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-3.0-4.0]	[-5.0-4.5]	[-4.0-4.0]	
	Min-Max	-20.0-20.0	-27.0-20.0	-27.0-20.0	

_BASIC					
		therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
Body temperature at session 3					
	N	81	80	161	
	Average (CO)	-0.0 (0.23)	-0.0 (0.27)	-0.0 (0.25)	0.774#
	95% DI (average)	(-0.1,0.0)	(-0.1,0.0)	(-0.0,0.0)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-0.1-0.1]	[-0.2-0.1]	[-0.1-0.1]	
	Min-Max	-0.8-0.6	-0.7-0.6	-0.8-0.6	
SBP (mmHg)on session 4					
	N	81	80	161	
	Average (CO)	0.0 (6.45)	-0.8 (7.10)	-0.4 (6.77)	0.421#
	95% DI (average)	(-1.4,1.5)	(-2.4,0.8)	(-1.4,0.7)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-5.0-3.0]	[-5.0-3.5]	[-5.0-3.0]	
	Min-Max	-15.0-18.0	-31.0-21.0	-31.0-21.0	
DBP (mmHg)on session 4					
	N	81	80	161	
	Average (CO)	-0.1 (7.24)	-0.4 (6.68)	-0.2 (6.95)	0.811#
	95% DI (average)	(-1.7,1.5)	(-1.8,1.1)	(-1.3,0.9)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-5.0-5.0]	[-5.0-5.0]	[-5.0-5.0]	
	Min-Max	-20.0-15.0	-28.0-20.0	-28.0-20.0	
Body temperature at session 4					
	N	81	80	161	
	Mean (CO)	0.0 (0.24)	-0.0 (0.24)	0.0 (0.24)	0.379#
	95% DI (average)	(-0.0,0.1)	(-0.1,0.1)	(-0.0,0.1)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-0.1-0.2]	[-0.1-0.1]	[-0.1-0.2]	
	Min-Max	-0.6-0.9	-0.8-0.5	-0.8-0.9	
SBP (mmHg)on session 5					
	N	81	80	161	
	Average (CO)	0.4 (7.16)	0.5 (6.89)	0.4 (7.00)	0.996#
	95% DI (average)	(-1.1,2.0)	(-1.1,2.0)	(-0.6,1.5)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-5.0-5.0]	[-2.5-5.0]	[-4.0-5.0]	
	Min-Max	-19.0-17.0	-26.0-18.0	-26.0-18.0	
DBP (mmHg)on session 5					
	N	81	80	161	
	Average (CO)	0.5 (7.20)	-1.6 (7.26)	-0.5 (7.28)	0.071#
	95% DI (average)	(-1.1,2.1)	(-3.2,0.0)	(-1.7,0.6)	
	Median	0.0	-0.5	0.0	
	[q1-q3]	[-4.0-3.0]	[-5.5-3.0]	[-5.0-3.0]	
	Min-Max	-20.0-20.0	-30.0-15.0	-30.0-20.0	
Body temperature at session 5					
	N	81	80	161	
	Mean (CO)	0.0 (0.25)	-0.1 (0.23)	-0.0 (0.24)	0.155#
	95% DI (average)	(-0.1,0.1)	(-0.1,0.0)	(-0.1,0.0)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-0.1-0.1]	[-0.2-0.1]	[-0.1-0.1]	
	Min-Max	-0.8-0.7	-0.8-0.4	-0.8-0.7	
Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).					

The analysis of instrumental assessment of cardiac activity according to ECG data is presented in the tables: **Table** Ошибка! Закладка не определена.,Table 1. No significant changes were detected between the groups.

Table Ошибка! Закладка не определена. **-ECG data. Dynamics of ECG parameters in relation to the initial parameters. Safety population, n = 161.**

_BASIC					
		therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
HR (bpm)					
	N	81	80	161	
	Average (CO)	-2.0 (8.94)	0.6 (7.43)	-0.7 (8.29)	0.051#
	95% DI (average)	(-4.0,0.0)	(-1.1,2.2)	(-2.0,0.6)	
	Median	-2.0	0.0	-1.0	
	[q1-q3]	[-6.0-1.0]	[-3.0-5.0]	[-4.0-3.0]	
	Min-Max	-31.0-25.0	-17.0-21.0	-31.0-25.0	
PQ (ms)					
	N	81	80	161	
	Mean (CO)	4.1 (14.46)	3.6 (18.09)	3.9 (16.31)	0.839#
	95% DI (average)	(0.9,7.3)	(-0.4,7.6)	(1.3,6.4)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-2.0-10.0]	[-6.5-12.5]	[-3.0-11.0]	
	Min-Max	-42.0-50.0	-36.0-54.0	-42.0-54.0	
QRS (ms)					
	N	81	80	161	
	Mean (CO)	0.2 (11.02)	-1.1 (10.75)	-0.5 (10.87)	0.455#
	95% DI (average)	(-2.3,2.6)	(-3.5,1.3)	(-2.1,1.2)	
	Median	0.0	-1.0	0.0	
	[q1-q3]	[-3.0-4.0]	[-4.0-3.0]	[-4.0-4.0]	
	Min-Max	-37.0-30.0	-38.0-40.0	-38.0-40.0	
QT (ms)					
	N	81	80	161	
	Mean (CO)	1.9 (26.17)	0.9 (21.00)	1.4 (23.68)	0.784#
	95% DI (average)	(-3.9,7.7)	(-3.8,5.5)	(-2.3,5.1)	
	Median	2.0	-1.5	0.0	
	[q1-q3]	[-6.0-12.0]	[-11.0-7.0]	[-8.0-10.0]	
	Min-Max	-68.0-80.0	-67.0-70.0	-68.0-80.0	
Note: Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmeticmean± standard deviation (SD).					

12.6. Safety report

The results of the study concerning adverse events reflect the expected safety and tolerability of the drug in patients with atopicodermatitis and patients taking the study drug-Polisorb ® MP. During the study, 161 patients were treated, 81 of them received basic therapy and 80 patients received additional Polisorb ® MP. The duration of treatment was1-4 days. During the study, 34 AES were registered in 26 patients (16.1%), including 12 AES in 10 (12.3%) patients in the "BT" group, and 12 AES in the BI+group.IP - 22 AE in 16 patients (20.0%). There were no statistical differences between the groups (p= 0.187). The majority of AES were mild: 31 AES in 23 (14.3%) patients, by groups: in the BT+IT group-21 AES in 15 (18.8) patients and 10 AES in 8 (9.9%) patients in the BT group. Arrhythmia (1 AE in the BT + IP group), elevated transaminase levels (1 AE in the BT group) were considered moderate.

All events resolved, the outcome is not known for the following AES: increased transaminases (1 AES), arrhythmia (1 AES in the BT + IP group), and exacerbation of atopic dermatitis (1 AES) in the BI group. In connection with the identified adverse events, the following actions were taken: the appointment of concomitant therapy in the case of back pain (1 AE in the BT group), pulpitis (1 AE in the BT + IP group), headache (2 AE in the BT group and 1 AE in the BT + IP group), dizziness (1 AE in the BT group), upper respiratory tract viral infection (1 AE in the BT group and BT + IP), hypertension (2 AE in the BT + IP group). Действий No action was taken in relation to the study therapy.

Events related to the use of the study drugs (i.e., evaluated as definitely, probably, or possibly related) were associated with the group in which прием препарата Polisorb® MP was taken. 15AES were registered in 12 (15%) patients (p= 0.001) from the gastrointestinal tract, including constipation - 9 AES in 7 patients (8.8%), 2 cases of dyschesia in 2 patients and one case each: abdominal discomfort, bloating, dry mouth, nausea. These events with a presumed causal relationship can generally be classified as expected, and are indicated in the OHLP of Polisorb® MP.

Analysis of laboratory parameters and physical parameters revealed no statistically significant differences between the groups. Analysis of changes in laboratory parameters using shift tables did not reveal any specific deviations characteristic of any group. As for the laboratory results, it is impossible to determine the trend towards a pathological effect of the studied therapy on specific parameters, both in terms of the sum of changes and in relation to those values.

In conclusion, this clinical study did not reveal any potentially new or unexpected signs or symptoms specific to the drug under study, compared to the known spectrum of adverse reactions specific to Polisorb® MP. Adverse events such as severe constipation, dyschesia, abdominal discomfort, bloating, dry mouth, and nausea can be assessed as expected.

13. DISCUSSION AND GENERAL CONCLUSION

13.1. Discussion

The sponsor of the study, JSC POLISORB, initiated третьейа phase three study to evaluate the efficacy and safety of adding the drug Polisorb ® MP, por. d / suspension. for oral administration (Polisorb JSC, Russia) to the complex therapy of patients with mild to moderate atopic dermatitis receiving basic therapy. For the purposes of the study, the design was chosen: a muco center open randomized study with an active control group.

The study population consisted of adult male and female patients aged 18 to 65 years, with a confirmed diagnosis of atopic dermatitis with the following characteristics: the presence of a verified diagnosis of Atopic dermatitis (ICD code 10: L20) according to the criteria of J. M. Hanifin and G. Rajka, no more than 3 years ago; mild and moderate severity-the value of SCORAD from 20 to 40, inclusive; no signs of secondary infection; presence of pruritus (symptom intensity according to the BRS questionnaire ≥ 6); overall assessment of the disease by the researcher on the IGA scale of 2 or 3 points. The study population did not include high-risk patients, such as the elderly, children, pregnant or women of reproductive age, or patients whose physiological or pathological condition requires special attention. Patients had the option of alternative treatment.

163 patients were screened in the study, 162 of whom met all the inclusion/non-inclusion criteria and formed the ITT population, one patient immediately dropped out after randomization, before taking the drug, and therefore was excluded from the analysis (the ITT and PP populations were 161 patients). Of the 161 patients, 61.5% were women, the mean age of the population was 38.9 ±12.70, the median was 39 years. There were no differences between the groups in terms of demographic and anthropometric parameters. When calculating BMI (u), the groups differed slightly: 26.0±3.81, 25.0 vs. 24.9± 3.07, 24.6, p= 0.041.

Patients were randomly assigned to two groups: group 1 (or the "Basic therapy" group) (n=81) - patients received the basic therapy chosen according to clinical recommendations: continuous use-emolients, oral cetirizine 10 mg, tablets, orally, 1 time per day. On request: pime crolimus, cream for external use, applied in a thin layer up to 2 times a day. Group 2 received the above-mentioned basic therapy and additionally Polisorb® MP, por. d/suspension. for oral administration (JSC Polisorb, Russia) in the following dosage regimen: single dose – 1-2 tablespoons with a slide (1 tablespoon contains 2.5-3 grams) per half glass of water, immediately before meals. The daily dose is 15-20 grams of the drug (6 tablespoons "with a slide") dividedx into 3-4 times a day, the course of therapy is 14 days. The analysis of treatment compliance showed a high level (more than 80%): The average compliance level of the study drug was 95.4 ±4.27, 95.2%.

The main parameter of efficiency was the assessment of dynamics by the SCORAD index. The change was analyzed by various statistical methods.

In the basic therapy group, the total score on the SCORAD index (ANOVA) changed from 32.4,±5.33, 33.6 to 14.7±7.97, 13.0 the difference was -17.7,±7.80,, -17.8,points. In the study therapy group (BT+ IT) at visit 2, the total score on the SCORAD index was 32.6 ±5.04, 33.6 after 14 days-11.1,± 7.39,, 9.8,, the difference was -21.5,±7.48,, -22.1,, the differences between the groups were significant p= 0.002,.

Changes in the primary parameter were analyzed c using a mixed linear model with repeated measurements (MMRM), which evaluated the influence of the following factors: therapeutic group (p = 0.0028), visit (p<.0001). as well as the combined group * session effect (p=0.0190). The results suggest that Polisorb MP should be added to the Basic therapy.

As a sensitivity analysis, we also analyzed the covariance analysis model (ANCOVA), the average least squares value (L (east) and S (quares) means) for each treatment group, and the difference between the average LS values and bilateral p-values: in the BT group , the dynamics was -17.6974,±0.8492,8492 [95% CI: 16.0203,-19.3745,] in the study group,-21.5120±0.8545,[95% CI: 19.8244,-23.1996,], the differences were 3.6857,±1.2123,[95% CI: 1.2913,-6.0800,], p =0.0028.

H0: $\mu 1 - \mu 2 \leq 0$

HA: $\mu 1 - \mu 2 > 0$

The study showed, that the lower limit of 95% CI differences was 1.2913, which makes it possible to reject the null hypothesis.

The results are supported by an IGA score (Investigators' Global Assessment), which is used to assess the severity of atopic dermatitis according to the doctor's opinion, the assessment was carried out at a delayed follow-up visit. By visit 5 (10-12 days after the end of treatment) in the BT+ IP group, the score decreased from 2.6±0.49, 3.0 to 0.9± 0.90, 1.0 and in the BT group from 2.6 ± 0.49, 3.0 to 1.4±0.89, 2.0, the differences at visit 5 between the groups were statistically significant (p<0.001). Differences in dynamics were significant -1.7±0.88, - 2.0 vs. -1.2± 0.79, - 1.0 (p<0.001). At the same time, the BRS index shows significant dynamics: By visit 4, pruritus decreased by -4.8±1.48, -4.0 vs. -4.3 ±1.55, -5.0, p = 0.047. Analysis of the dermatological quality of life index (DLQI) revealed significant differences by the end of treatment (visit 4). The interpretation of the scale is inversely directed – the higher the score, the more negatively the disease affects the patient's quality of life. At session 2, there were no differences between the groups; in the BT + IT group, the total score was: 10.4±4.59, 10.0 to session 4-3.6±3.81, 3.0 in the BT group at session 2-9.6±11.7, 10.0 and to session 4-5.1±3.57, 4. the difference between the groups was reliable (p= 0.015). Despite the improvement in quality of life indicators, there were no differences in dynamics between the groups: in the BT group -5.6±4.02, -5.0 , in the BT+IT group -6.8± 4.72, -6.5 p= 0.089.

The analysis did not revealл any differences in the dynamics between the groups when evaluated using the EASI index, which is based on the assessment of the lesion area, despite significant differences at the time of assessment at visit 4. HIt should be noted that the results obtained are consistent, given, that the main population consisted of patients with atopic dermatitis with a history of more than 3 years and the changes may be organic in nature, as well as patients in both groups used a topical drug containing pime crolimus.

Taking into account that all patients were able to use the basic therapy throughout the study, the duration of cetirizine and pime crolimus use in the groups was similar.

Safety assessment was carried out based on the results of clinical, laboratory and instrumental examinations. 34 AES were registered in 26 patients (16.1%), including 12 AES in 10 (12.3%) patients in the BT group, and 12 AES in the BI+group.IP - 22 AE in 16 patients (20.0%). There were no statistical differences between the groups (p= 0.187). The majority of AES were mild: 31 AES in 23 (14.3%) patients, by groups: in the BT+IT group-21 AES in 15 (18.8) patients and 10 AES in 8 (9.9%) patients in the BT group. No serious AES were reported. It was reliably shown that the use of combination therapy with the addition препарата of Polisorb ® MP is associated with the development of gastrointestinal AES: constipation (9 AES), dyschesia(2 AES), abdominal discomfort (1 AES), bloating (1 AES), dry mouth (1 AES), nausea (1 AES). These events with an assumed causal relationship can generally be classified as expected and specific to adsorbents.

Analysis of laboratory parameters and physical parameters revealed no statistically significant differences between the groups. Analysis of changes in laboratory parameters using shift tables did not reveal any specific deviations characteristic of any group.

Thus, based on the data obtained on the efficacy, safety and tolerability of Polisorb® MP in the form of powder for preparing a suspension for oral administration, it can be concluded that the drug can be recommended for addition to basic therapy in the treatment of patients with mild to moderate atopic dermatitis as part of complex therapy. Taking the drug can cause constipation and associated dyschesia, dyspepsia in the form of abdominal discomfort, bloating, dry mouth, nausea. No symptoms of overdose were observed.

13.2. Заключение

A multicenter open-label randomized trial with an active control group was conducted to evaluate the addition of the drug Polisorb® MP, powder for suspension for oral administration (Polisorb JSC, Russia) to the complex therapy of patients with mild to moderate atopic dermatitis receiving basic therapy. The study was conducted in accordance with the current regulatory norms of the Russian Federation, Good Clinical Practice of the EAEU and the Helsinki Declaration. The main objective of this study was to evaluate the efficacy and safety of Polisorb® MP, por. d/suspension. for oral administration (Polisorb JSC, Russia). The effectiveness criterion was a change in the overall score on the SCORAD index, the study demonstrated clinical benefit when adding Polisorb ® MP, por. d/suspension. for oral administration (JSC Polisorb, Russia for basic therapy. There were no differences in the safety profile, but taking the drug is accompanied by side effects from the gastrointestinal tract such as constipation, dyspeptic phenomena.

14. TABLES, FIGURES, AND GRAPHS THAT ARE REFERENCED BUT NOT INCLUDED IN THE REPORT TEXT

14.1. Demographic data

Not applicable.

14.2. Performance data

Not applicable.

14.3. Safety Information

Table Ошибка! Закладка не определена. **- Assessment жизненно of vital signs depending on the visit and treatment group. Safety population, n= 161.**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
GARDEN (mm of mercury at visit 1					
	N	81	80	161	
	Secondary (CO)	120.9 (8.94)	121.9 (8.79)	121.4 (8.85)	0.487#
	95% CI (medium)	(118.9,122.9)	(119.9,123.8)	(120.0,122.7)	
	Median	121.0	121.0	121.0	
	[q1-q3]	[115.0-126.0]	[118.0-126.0]	[117.0-126.0]	
	Min-Max	90.0-140.0	95.0-147.0	90.0-147.0	
DBP (mm of mercury)at visit 1					
	N	81	80	161	
	Secondary (CO)	74.0 (6.81)	75.7 (8.25)	74.8 (7.58)	0.156#
	95% CI (medium)	(72.4,75.5)	(73.8,77.5)	(73.6,76.0)	
	Median	73.0	75.5	75.0	
	[q1-q3]	[70.0-80.0]	[70.0-80.0]	[70.0-80.0]	
	Min-Max	60.0-89.0	60.0-107.0	60.0-107.0	
body Temperature at visit 1					
	N	81	80	161	
	Secondary (CO)	36.5 (0.21)	36.5 (0.19)	36.5 (0.20)	0.157#
	95% CI (medium)	(36.4,36.5)	(36.5,36.5)	(36.4,36.5)	
	Median	36.5	36.5	36.5	
	[q1-q3]	[36.3-36.6]	[36.4-36.6]	[36.4-36.6]	
	Min-Max	35.9-36.8	36.0-36.8	35.9-36.8	
GARDEN (mm of mercury)at visit 2					
	N	81	80	161	
	Secondary (CO)	120.4 (8.00)	121.6 (9.92)	121.0 (9.00)	0.383#
	95% CI (medium)	(118.6,122.1)	(119.4,123.8)	(119.6,122.4)	
	Median	120.0	120.0	120.0	
	[q1-q3]	[116.0-125.0]	[118.0-127.0]	[117.0-125.0]	
	Min-Max	95.0-145.0	90.0-145.0	90.0-145.0	
DBP (mm of mercury)at visit 2					
	N	81	80	161	
	Secondary (CO)	73.3 (6.90)	75.1 (7.04)	74.2 (7.00)	0.103#
	95% CI (medium)	(71.8,74.8)	(73.5,76.7)	(73.1,75.3)	
	Median	72.0	75.0	74.0	
	[q1-q3]	[69.0-78.0]	[70.0-79.0]	[70.0-79.0]	
	Min-Max	60.0-90.0	60.0-94.0	60.0-94.0	

	Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
body Temperature at visit 2				
N	81	80	161	
Secondary (CO)	36.4 (0.22)	36.5 (0.19)	36.5 (0.20)	0.238#
95% CI (medium)	(36.4,36.5)	(36.4,36.5)	(36.4,36.5)	
The median	36.5	36.5	36.5	
[q1-q3]	[36.3-36.6]	[36.4-36.6]	[36.4-36.6]	
Min-Max	36.0-36.9	35.8-36.8	35.8-36.9	
GARDEN (mm of mercury)at visit 3				
N	81	80	161	
Secondary (CO)	120.7 (8.60)	121.5 (9.28)	121.1 (8.92)	0.549#
95% CI (medium)	(118.8,122.6)	(119.4,123.6)	(119.7,122.5)	
Median	120.0	120.0	120.0	
[q1-q3]	[115.0-126.0]	[118.0-127.0]	[117.0-126.0]	
Min-Max	95.0-141.0	90.0-140.0	90.0-141.0	
DBP (mm of mercury)at visit 3				
N	81	80	161	
Secondary (CO)	74.1 (6.31)	74.9 (7.05)	74.5 (6.68)	0.456#
95% CI (medium)	(72.7,75.5)	(73.3,76.4)	(73.4,75.5)	
Median	74.0	74.0	74.0	
[q1-q3]	[70.0-78.0]	[70.0-80.0]	[70.0-80.0]	
Min-Max	60.0-88.0	60.0-90.0	60.0-90.0	
body Temperature at visit 3				
N	81	80	161	
Secondary (CO)	36.5 (0.24)	36.5 (0.21)	36.5 (0.22)	0.350#
95% CI (medium)	(36.4,36.5)	(36.4,36.5)	(36.4,36.5)	
Median	36.5	36.5	36.5	
[q1-q3]	[36.3-36.6]	[36.4-36.6]	[36.3-36.6]	
Min-Max	35.8-36.9	36.0-36.8	35.8-36.9	
GARDEN (mm of mercury)at visit 4				
N	81	80	161	
Secondary (CO)	120.9 (8.49)	121.0 (9.46)	121.0 (8.96)	0.937#
95% CI (medium)	(119.0,122.8)	(118.9,123.1)	(119.6,122.4)	
Median	121.0	120.5	121.0	
[q1-q3]	[116.0-126.0]	[115.0-127.0]	[115.0-127.0]	
Min-Max	90.0-140.0	90.0-140.0	90.0-140.0	
DBP (mm of mercury)at visit 4				
N	81	80	161	
Secondary (CO)	73.9 (6.22)	75.3 (6.30)	74.6 (6.28)	0.148#
95% CI (medium)	(72.5,75.2)	(73.9,76.7)	(73.6,75.6)	
Median	74.0	75.0	75.0	
[q1-q3]	[70.0-80.0]	[70.0-80.0]	[70.0-80.0]	
Min-Max	60.0-89.0	60.0-90.0	60.0-90.0	
Body temperature at session 4				
N	81	80	161	
Average (CO)	36.5 (0.20)	36.5 (0.18)	36.5 (0.19)	0.714#
95% CI (mean)	(36.4,36.5)	(36.5,36.5)	(36.5,36.5)	
Median	36.5	36.5	36.5	
[q1-q3]	[36.4-36.6]	[36.4-36.6]	[36.4-36.6]	
Min-Max	36.1-36.9	36.0-36.8	36.0-	
36.9 GARDEN (mm of mercury)at visit 5				
N	81	80	161	
Secondary (CO)	121.3 (7.20)	122.3 (8.13)	121.8 (7.67)	0.419#
95% CI (medium)	(119.7,122.9)	(120.5,124.1)	(120.6,123.0)	
Median	120.0	122.0	121.0	
[q1-q3]	[118.0-127.0]	[120.0-128.0]	[119.0-127.0]	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	Min-Max	101.0-136.0	95.0-136.0	95.0-136.0	
DBP (mm of mercury)at visit 5					
	N	81	80	161	
	Secondary (CO)	74.4 (6.61)	74.1 (6.28)	74.3 (6.43)	0.717#
	95% CI (medium)	(73.0,75.9)	(72.7,75.5)	(73.3,75.3)	
	Median	74.0	74.0	74.0	
	[q1-q3]	[70.0-80.0]	[70.0-80.0]	[70.0-80.0]	
	Min-Max	60.0-90.0	60.0-85.0	60.0-90.0	
body Temperature at visit 5					
	N	81	80	161	
	Secondary (CO)	36.5 (0.22)	36.4 (0.21)	36.5 (0.21)	0.783#
	95% CI (medium)	(36.4,36.5)	(36.4,36.5)	(36.4,36.5)	
	Median	36.5	36.5	36.5	
	[q1-q3]	[36.4-36.6]	[36.3-36.6]	[36.3-36.6]	
	Min-Max	35.9-36.8	35.8-36.8	35.8-36.8	
note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA). Mean – arithmetic mean± standard deviation (SD).					

Table Ошибка! Закладка не определена.**- ECG score at visit 1. Safety population, n= 161.**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
HR (bpm)					
	N	81	80	161	
	Secondary (CO)	69.6 (10.50)	68.0 (8.70)	68.8 (9.65)	0.304#
	95% CI (medium)	(67.3,71.9)	(66.1,69.9)	(67.3,70.3)	
	Median	69.0	68.5	69.0	
	[q1-q3]	[63.0-74.0]	[62.0-74.0]	[62.0-74.0]	
	Min-Max	50.0-105.0	48.0-92.0	48.0-105.0	
PQ (MS.)					
	N	81	80	161	
	Secondary (CO)	151.0 (24.66)	149.4 (17.55)	150.2 (21.37)	0.652#
	95% CI (medium)	(145.5,156.4)	(145.5,153.3)	(146.9,153.5)	
	Median	148.0	152.5	150.0	
	[q1-q3]	[138.0-161.0]	[138.0-160.5]	[138.0-161.0]	
	Min-Max	96.0-281.0	100.0-188.0	96.0-281.0	
QRS (MS.)					
	N	81	80	161	
	Secondary (CO)	90.6 (12.72)	92.8 (8.97)	91.7 (11.04)	0.203#
	95% CI (medium)	(87.8,93.4)	(90.8,94.8)	(90.0,93.4)	
	Median	90.0	94.0	92.0	
	[q1-q3]	[82.0-100.0]	[87.5-99.0]	[84.0-99.0]	
	Min-Max	55.0-119.0	68.0-120.0	55.0-120.0	
QT (msec.)					
	N	81	80	161	
	Secondary (CO)	390.2 (30.84)	395.6 (29.76)	392.9 (30.33)	0.259#
	95% CI (medium)	(383.4,397.0)	(389.0,402.2)	(388.2,397.6)	
	Median	384.0	388.0	386.0	
	[q1-q3]	[368.0-411.0]	[375.0-418.5]	[371.0-416.0]	
	Min-Max	332.0-465.0	340.0-462.0	332.0-465.0	
evaluation of the results of electrocardiography					
	Norma	48 (59.3%)	52 (65.0%)	100 (62.1%)	0.453~
	With disabilities	33 (40.7%)	28 (35.0%)	61 (37.9%)	

Table 1. **Electrocardiography, session 4**

Table Ошибка! Закладка не определена.**- ECG score at visit 4. Safety population, n= 161.**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
HR (bpm)					
	N	81	80	161	
	Secondary (CO)	67.6 (8.37)	68.6 (9.15)	68.1 (8.75)	0.478#
	95% CI (medium)	(65.8,69.5)	(66.6,70.6)	(66.7,69.5)	
	Median	67.0	68.0	68.0	
	[q1-q3]	[62.0-73.0]	[62.5-75.0]	[62.0-74.0]	
	Min-Max	50.0-102.0	48.0-103.0	48.0-103.0	
PQ (MS.)					
	N	81	80	161	
	Secondary (CO)	155.1 (28.45)	153.0 (19.31)	154.1 (24.29)	0.594#
	95% CI (medium)	(148.8,161.4)	(148.7,157.3)	(150.3,157.8)	
	Median	151.0	156.0	154.0	
	[q1-q3]	[138.0-166.0]	[140.0-164.0]	[140.0-164.0]	
	Min-Max	120.0-322.0	110.0-216.0	110.0-322.0	
QRS (MS.)					
	N	81	80	161	
	Secondary (CO)	90.8 (12.77)	91.7 (11.84)	91.3 (12.28)	0.631#
	95% CI (medium)	(88.0,93.6)	(89.1,94.4)	(89.4,93.2)	
	Median	93.0	93.0	93.0	
	[q1-q3]	[85.0-100.0]	[86.0-98.0]	[86.0-99.0]	
	Min-Max	52.0-117.0	51.0-120.0	51.0-120.0	
QT (msec.)					
	N	81	80	161	
	Secondary (CO)	392.1 (28.28)	396.5 (29.30)	394.3 (28.78)	0.335#
	95% CI (medium)	(385.8,398.3)	(390.0,403.0)	(389.8,398.7)	
	Median	384.0	395.0	390.0	
	[q1-q3]	[375.0-412.0]	[375.5-420.0]	[375.0-418.0]	
	Min-Max	332.0-464.0	334.0-461.0	332.0-464.0	
evaluation of the results of electrocardiography					
	Norma	51 (63.0%)	53 (66.3%)	104 (64.6%)	0.663~
	With disabilities	30 (37.0%)	27 (33.8%)	57 (35.4%)	

Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test. Mean – arithmeticmean± standard deviation (SD).

Table Ошибка! Закладка не определена. **- Association of AES with the drug. Safety population, n= 161**

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
gastrointestinal disorders				
constipation				
	All	0 (0.0%) 0	7 (8.8%) 9	0.007^
	some	0 (0.0%) 0	5 (6.3%) 7	0.028^

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
probable	0 (0.0%) 0	1 (1.3%) 1	0.497^
possible	0 (0.0%) 0	1 (1.3%) 1	0.497^
dyschezia			
All	0 (0.0%) 0	2 (2.5%) 2	0.245^
some	0 (0.0%) 0	2 (2.5%) 2	0.245^
abdominal discomfort			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
some	0 (0.0%) 0	1 (1.3%) 1	0.497^
bloating			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
possible	0 (0.0%) 0	1 (1.3%) 1	0.497^
dry mouth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
possible	0 (0.0%) 0	1 (1.3%) 1	0.497^
nausea			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
possible	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the nervous system			
headache			
All	4 (4.9%) 4	1 (1.3%) 1	0.367^
no communication	4 (4.9%) 4	1 (1.3%) 1	0.367^
dizziness			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no communication	1 (1.2%) 1	0 (0.0%) 0	>0.999^
infections and infestations			
viral infection of the upper respiratory tract			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
the link is missing	0 (0.0%) 0	1 (1.3%) 1	0.497^
pulpitis of the tooth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
the link is missing	0 (0.0%) 0	1 (1.3%) 1	0.497^
laboratory and instrumental data			
of violation of repolarization on the electrocardiogram			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
possible	0 (0.0%) 0	1 (1.3%) 1	0.497^
increase in transaminase levels			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
a dubious connection	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart			
av blockade of the 1st degree			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no communication	1 (1.2%) 1	0 (0.0%) 0	>0.999^
arrhythmia			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
a dubious connection	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the vessels,			
hypertension			
All	0 (0.0%) 0	1 (1.3%) 2	0.497^
the link is missing	0 (0.0%) 0	1 (1.3%) 2	0.497^
essential hypertension			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no communication	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the skin and subcutaneous tissue			
dermatitis atopic			

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	possible	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the muscle. skeletal and connective tissue				
back pain				
	All over	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	there is no connection	1 (1.2%) 1	0 (0.0%) 0	>0.999^
general disorders and reactions at the injection				
site pain at the application				
	site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^
	no connection	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test. Average – arithmeticmean± standard deviation (SD).				

Table Ошибка! Закладка не определена.**-NYA exodus. Safety population, n= 161**

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
gastrointestinal disorders				
constipation				
	All	0 (0.0%) 0	7 (8.8%) 9	0.007^
	resolved	0 (0.0%) 0	7 (8.8%) 9	0.007^
dyschezia				
	All	0 (0.0%) 0	2 (2.5%) 2	0.245^
	resolved	0 (0.0%) 0	2 (2.5%) 2	0.245^
abdominal discomfort				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^
bloating				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^
dry mouth				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^
nausea				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the nervous system				
headache				
	All	4 (4.9%) 4	1 (1.3%) 1	0.367^
	resolved	4 (4.9%) 4	1 (1.3%) 1	0.367^
dizziness				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	resolved	1 (1.2%) 1	0 (0.0%) 0	>0.999^
infections and infestations				
viral infection of the upper respiratory tract				
	are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^
pulpitis of the tooth				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^
laboratory and instrumental data				
of violation of repolarization on the electrocardiogram				
	are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	not resolved	0 (0.0%) 0	1 (1.3%) 1	0.497^

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
increase in transaminase levels				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	unknown	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart				
av blockade of the 1st degree				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	resolved	1 (1.2%) 1	0 (0.0%) 0	>0.999^
arrhythmia				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	unknown	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the vessels,				
hypertension				
	All	0 (0.0%) 0	1 (1.3%) 2	0.497^
	resolved	0 (0.0%) 0	1 (1.3%) 2	0.497^
essential hypertension				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	resolved	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the skin and subcutaneous tissue				
dermatitis atopic				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	unknown	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the muscle. skeletal and connective tissue				
back pain				
	All over	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	resolved	1 (1.2%) 1	0 (0.0%) 0	>0.999^
general disorders and reactions at the injection				
site pain at the application				
	site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^
	resolved	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.				

Table Ошибка! Закладка не определена.**-Continues NYA. Safety population, n= 161**

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
gastrointestinal disorders				
constipation				
	All	0 (0.0%) 0	7 (8.8%) 9	0.007^
	no	0 (0.0%) 0	7 (8.8%) 9	0.007^
dyschezia				
	All	0 (0.0%) 0	2 (2.5%) 2	0.245^
	no	0 (0.0%) 0	2 (2.5%) 2	0.245^
abdominal discomfort				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
bloating				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
dry mouth				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^
nausea				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no	0 (0.0%) 0	1 (1.3%) 1	0.497^

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	**Basic therapy + study drug (N=80)**	**p-value**
violations of the nervous system			
headache			
All	4 (4.9%) 4	1 (1.3%) 1	0.367^
no	4 (4.9%) 4	1 (1.3%) 1	0.367^
dizziness			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
infections and infestations			
viral infection of the upper respiratory tract			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no	0 (0.0%) 0	1 (1.3%) 1	0.497^
pulpitis of the tooth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no	0 (0.0%) 0	1 (1.3%) 1	0.497^
laboratory and instrumental data			
of violation of repolarization on the electrocardiogram			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
Yes	0 (0.0%) 0	1 (1.3%) 1	0.497^
increase in transaminase levels			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Yes	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart			
av blockade of the 1st degree			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
arrhythmia			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
Yes	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the vessels,			
hypertension			
All	0 (0.0%) 0	1 (1.3%) 2	0.497^
no	0 (0.0%) 0	1 (1.3%) 2	0.497^
essential hypertension			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the skin and subcutaneous tissue			
dermatitis atopic			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
Yes	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the muscle. skeletal and connective tissue			
back pain			
All over	1 (1.2%) 1	0 (0.0%) 0	>0.999^
not	1 (1.2%) 1	0 (0.0%) 0	>0.999^
general disorders and reactions at the injection			
site pain at the application			
site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^
none	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.			

Table Ошибка! Закладка не определена. **– Actions taken to treat AES. Safety population, n= 161.**

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
gastrointestinal disorders			
constipation			
are All	0 (0.0%) 0	7 (8.8%) 9	0.007^
no action had been taken	0 (0.0%) 0	7 (8.8%) 9	0.007^
dyschezia			
All	0 (0.0%) 0	2 (2.5%) 2	0.245^
no action had been taken	0 (0.0%) 0	2 (2.5%) 2	0.245^
abdominal discomfort			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no action had been taken	0 (0.0%) 0	1 (1.3%) 1	0.497^
bloating			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no action had been taken	0 (0.0%) 0	1 (1.3%) 1	0.497^
dry mouth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no action had been taken	0 (0.0%) 0	1 (1.3%) 1	0.497^
nausea			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no action had been taken	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the nervous system			
headache			
All	4 (4.9%) 4	1 (1.3%) 1	0.367^
the appointment of concomitant therapy	2 (2.5%) 2	1 (1.3%) 1	>0.999^
no action was taken	2 (2.5%) 2	0 (0.0%) 0	0.497^
dizziness			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
the appointment of concomitant therapy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
infections and infestations			
viral infection of the upper respiratory tract			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
the appointment of concomitant therapy	0 (0.0%) 0	1 (1.3%) 1	0.497^
pulpitis of the tooth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
the appointment of concomitant therapy	0 (0.0%) 0	1 (1.3%) 1	0.497^
laboratory and instrumental data			
of violation of repolarization on the electrocardiogram			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no action had been taken	0 (0.0%) 0	1 (1.3%) 1	0.497^
increase in transaminase levels			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no action taken	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart			
av blockade of the 1st degree			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no action taken	1 (1.2%) 1	0 (0.0%) 0	>0.999^
arrhythmia			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no action had been taken	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the vessels,			
hypertension			
All	0 (0.0%) 0	1 (1.3%) 2	0.497^
the appointment of concomitant therapy	0 (0.0%) 0	1 (1.3%) 2	0.497^
essential hypertension			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
the appointment of concomitant therapy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the skin and subcutaneous tissue			
dermatitis atopic			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no action taken	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the muscle. skeletal and connective tissue			
back pain			
All over	1 (1.2%) 1	0 (0.0%) 0	>0.999^
appointment of concomitant therapy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
general disorders and reactions at the injection			
site pain at the application			
site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^
no action taken	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.			

Table Ошибка! Закладка не определена. **– Actions taken in relation to the study therapy. Safety population, n= 161.**

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
gastrointestinal disorders			
constipation			
are All	0 (0.0%) 0	7 (8.8%) 9	0.007^
no change	0 (0.0%) 0	7 (8.8%) 9	0.007^
dyschezia			
All	0 (0.0%) 0	2 (2.5%) 2	0.245^
no change	0 (0.0%) 0	2 (2.5%) 2	0.245^
abdominal discomfort			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
bloating			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
dry mouth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
nausea			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the nervous system			
headache			
All	4 (4.9%) 4	1 (1.3%) 1	0.367^
no change	4 (4.9%) 4	1 (1.3%) 1	0.367^
dizziness			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
no change	1 (1.2%) 1	0 (0.0%) 0	>0.999^
infections and infestations			
viral infection of the upper respiratory tract			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
no change	0 (0.0%) 0	1 (1.3%) 1	0.497^

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
pulpitis of the tooth				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
laboratory and instrumental data				
of violation of repolarization on the electrocardiogram				
	are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
increase in transaminase levels				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no change	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart				
av blockade of the 1st degree				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no change	1 (1.2%) 1	0 (0.0%) 0	>0.999^
arrhythmia				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	no change	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the vessels,				
hypertension				
	All	0 (0.0%) 0	1 (1.3%) 2	0.497^
	no change	0 (0.0%) 0	1 (1.3%) 2	0.497^
essential hypertension				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no change	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the skin and subcutaneous tissue				
dermatitis atopic				
	All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	no change	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the muscle. skeletal and connective tissue				
back pain				
	All over	1 (1.2%) 1	0 (0.0%) 0	>0.999^
	there are no changes	1 (1.2%) 1	0 (0.0%) 0	>0.999^
general disorders and reactions at the injection				
site pain at the application				
	site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^
	no changes	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.				

Table Ошибка! Закладка не определена. **– Severity of AES. Safety population, n= 161**

		Number of subjects (%) Number of events		
		Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
gastrointestinal disorders				
constipation				
	are All	0 (0.0%) 0	7 (8.8%) 9	0.007^
	easy	0 (0.0%) 0	7 (8.8%) 9	0.007^
dyschezia				
	All	0 (0.0%) 0	2 (2.5%) 2	0.245^
	easy	0 (0.0%) 0	2 (2.5%) 2	0.245^
abdominal discomfort				
	All	0 (0.0%) 0	1 (1.3%) 1	0.497^
	easy	0 (0.0%) 0	1 (1.3%) 1	0.497^

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
bloating			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
easy	0 (0.0%) 0	1 (1.3%) 1	0.497^
dry mouth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
easy	0 (0.0%) 0	1 (1.3%) 1	0.497^
nausea			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
easy	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the nervous system			
headache			
All	4 (4.9%) 4	1 (1.3%) 1	0.367^
easy	4 (4.9%) 4	1 (1.3%) 1	0.367^
dizziness			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
easy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
infections and infestations			
viral infection of the upper respiratory tract			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
easy	0 (0.0%) 0	1 (1.3%) 1	0.497^
pulpitis of the tooth			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
easy	0 (0.0%) 0	1 (1.3%) 1	0.497^
laboratory and instrumental data			
of violation of repolarization on the electrocardiogram			
are All	0 (0.0%) 0	1 (1.3%) 1	0.497^
easy	0 (0.0%) 0	1 (1.3%) 1	0.497^
increase in transaminase levels			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
average	1 (1.2%) 1	0 (0.0%) 0	>0.999^
disorders of the heart			
av blockade of the 1st degree			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
easy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
arrhythmia			
All	0 (0.0%) 0	1 (1.3%) 1	0.497^
average	0 (0.0%) 0	1 (1.3%) 1	0.497^
violations of the vessels,			
hypertension			
All	0 (0.0%) 0	1 (1.3%) 2	0.497^
easy	0 (0.0%) 0	1 (1.3%) 2	0.497^
essential hypertension			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
easy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the skin and subcutaneous tissue			
dermatitis atopic			
All	1 (1.2%) 1	0 (0.0%) 0	>0.999^
average	1 (1.2%) 1	0 (0.0%) 0	>0.999^
violations of the muscle. skeletal and connective tissue			
back pain			
All over	1 (1.2%) 1	0 (0.0%) 0	>0.999^
easy	1 (1.2%) 1	0 (0.0%) 0	>0.999^
general disorders and reactions at the injection			
site pain at the application			
site All	1 (1.2%) 2	0 (0.0%) 0	>0.999^

	Number of subjects (%) Number of events		
	Basic therapy (N=81)	Basic therapy + study drug (N=80)	p-value
easy	1 (1.2%) 2	0 (0.0%) 0	>0.999^
Note: Statistical method: ^ - Comparison was performed using the exact Fisher test.			

Table Ошибка! Закладка не определена. **– General blood test data. Session 1. Security population, n=161**

_BASIC				
	therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Hematocrit (%)				
N	81	80	161	
Mean±CO	40.4 (4.91)	40.3 (5.01)	40.3 (4.94)	0.938#
95% DI (average)	(39.3,41.4)	(39.2,41.4)	(39.6,41.1)	
Median	40.0	40.2	40.2	
[q1-q3]	[37.4-43.7]	[37.5-43.6]	[37.4-43.6]	
Min-Max	27.3-54.0	26.1-52.0	26.1-54.0	
Hematocrit (assessment)				
NCS	20 (24.7%)	16 (20.0%)	36 (22.4%)	0.475~
norm	61 (75.3%)	64 (80.0%)	125 (77.6%)	
Red blood cells				
N	81	80	161	
Mean±CO	4.6 (0.42)	4.5 (0.34)	4.5 (0.39)	0.378#
95% DI (average)	(4.5,4.7)	(4.4,4.6)	(4.5,4.6)	
Median	4.5	4.5	4.5	
[q1-q3]	[4.3-4.8]	[4.2-4.7]	[4.3-4.7]	
Min-Max	3.4-5.6	3.7-5.3	3.4-5.6	
Red blood cells (assessment)				
NCS	of cns 6 (7.4%)	4 (5.0%)	10 (6.2%)	0.746^
norm	75 (92.6%)	76 (95.0%)	151 (93.8%)	
Leukocytes				
N	81	80	161	
Mean±CO	6.2 (1.47)	6.0 (1.47)	6.1 (1.47)	0.422#
95% DI (average)	(5.9,6.5)	(5.7,6.3)	(5.9,6.3)	
Median	6.1	5.7	6.0	
[q1-q3]	[5.3-7.2]	[4.9-6.8]	[5.1-7.0]	
Min-Max	3.2-11.3	3.0-11.5	3.0-11.5	
White blood cells (assessment)				
NCS	9 (11.1%)	5 (6.3%)	14 (8.7%)	0.274~
the norm	72 (88.9%)	75 (93.8%)	147 (91.3%)	
Hemoglobin (g / l)				
N	81	80	161	
Average±CO	138.5 (11.91)	137.9 (15.72)	138.2 (13.89)	0.783#
95% DI (average)	(135.9,141.2)	(134.4,141.4)	(136.1,140.4)	
Median	138.0	138.5	138.0	
[q1-q3]	[131.0-146.0]	[127.5-149.5]	[129.0-148.0]	
Min-Max	101.0-162.0	75.0-169.0	75.0-169.0	
Hemoglobin (assessment)				
NCS	5 (6.2%)	9 (11.3%)	14 (8.7%)	0.253~
the norm	76 (93.8%)	71 (88.8%)	147 (91.3%)	
Platelets				
N	81	80	161	
Mean±CO	239.3 (50.74)	244.9 (59.35)	242.1 (55.08)	0.525#

_BASIC					
		therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	95% DI (average)	(228.1,250.5)	(231.7,258.1)	(233.5,250.6)	
	Median	244.0	233.0	234.0	
	[q1-q3]	[205.0-273.0]	[205.0-280.5]	[205.0-276.0]	
	Min-Max	108.0-334.0	133.0-438.0	108.0-438.0	
Platelets (assessment)					
		of 4 (4.9%)	4 (5.0%)	8 (5.0%)	>0.999^
	the norm	77 (95.1%)	76 (95.0%)	153 (95.0%)	
Neutrophils (%)					
	N	81	80	161	
	Mean±CO	59.3 (8.63)	59.3 (8.70)	59.3 (8.64)	0.969#
	95% DI (average)	(57.4,61.2)	(57.4,61.3)	(58.0,60.7)	
	Median	60.0	60.0	60.0	
	[q1-q3]	[55.6-64.0]	[55.2-63.9]	[55.4-64.0]	
	Min-Max	28.7-80.9	36.0-80.0	28.7-80.9	
Neutrophils (assessment)					
	NCS	8 (9.9%)	10 (12.5%)	18 (11.2%)	0.597~
	normal	73 (90.1%)	70 (87.5%)	143 (88.8%)	
Eosinophils (%)					
	N	81	80	161	
	Mean±CO	1.9 (1.56)	2.3 (2.15)	2.1 (1.88)	0.128#
	95% DI (average)	(1.5,2.2)	(1.8,2.8)	(1.8,2.4)	
	Median	1.3	2.0	1.7	
	[q1-q3]	[1.0-2.0]	[1.0-3.0]	[1.0-2.8]	
	Min-Max	0.0-7.2	0.0-10.0	0.0-10.0	
Eosinophils (assessment)					
	NCS	5 (6.2%)	8 (10.0%)	13 (8.1%)	0.373~
	the norm	76 (93.8%)	72 (90.0%)	148 (91.9%)	
Basophils (%)					
	N	81	80	161	
	Mean±FROM	0.3 (0.35)	0.3 (0.37)	0.3 (0.36)	0.730#
	95% DI (average)	(0.2,0.3)	(0.2,0.4)	(0.2,0.3)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[0.0-0.5]	[0.0-0.6]	[0.0-0.5]	
	Min-Max	0.0-1.0	0.0-1.2	0.0-1.2	
Basophils (score)					
	norm	81 (100.0%)	80 (100.0%)	161 (100.0%)	n/a
Monocytes (%)					
	N	80	80	160	
	Average±CO	5.8 (2.13)	5.7 (1.92)	5.7 (2.02)	0.750#
	95% DI (average)	(5.3,6.3)	(5.3,6.1)	(5.4, 6.0)	
	Median	6.0	5.5	5.9	
	[q1-q3]	[4.0-7.0]	[4.0-7.0]	[4.0-7.0]	
	Min-Max	0.5-10.0	1.6-10.0	0.5-10.0	
Monocytes (score)					
	norm	81 (100.0%)	80 (100.0%)	161 (100.0%	n / a
Lymphocytes (%)					
	N	81	80	161	
	Mean±CO	32.7 (7.73)	32.1 (7.59)	32.4 (7.64)	0.624#
	95% DI (average)	(31.0,34.4)	(30.4,33.8)	(31.2,33.6)	
	Median	32.0	32.0	32.0	
	[q1-q3]	[28.0-37.0]	[26.6-36.9]	[27.0-37.0]	
	Min-Max	12.3-60.4	12.0-48.0	12.0-60.4	

_BASIC				
	therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
Lymphocytes (assessment)				
NCS	of cns 17 (21.0%)	16 (20.0%)	33 (20.5%)	0.877~
the norm	64 (79.0%)	64 (80.0%)	128 (79.5%)	
Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).				

Table Ошибка! Закладка не определена. **– General blood test data. Session 4. Safety population, n=161**

	Basic therapy (N=81)	**Basic therapy + Study drug (N=80)**	**Total (N=161)**	**p-value**
Hematocrit (%)				
N	81	80	161	
Mean±CO	40.5 (5.24)	40.1 (5.13)	40.3 (5.17)	0.637#
95% DI (average)	(39.3,41.6)	(38.9,41.2)	(39.5,41.1)	
Median	40.3	39.3	40.0	
[q1-q3]	[36.7-45.3]	[36.5-44.2]	[36.6-45.0]	
Min-Max	26.7-49.8	26.3-49.0	26.3-49.8	
Hematocrit (assessment)				
NCS	19 (23.5%)	21 (26.3%)	40 (24.8%)	0.682~
norm	62 (76.5%)	59 (73.8%)	121 (75.2%)	
Red blood cells				
N	81	80	161	
Mean±CO	4.6 (0.43)	4.6 (0.42)	4.6 (0.43)	0.582#
95% DI (average)	(4.5,4.7)	(4.5,4.6)	(4.5,4.6)	
Median	4.6	4.5	4.6	
[q1-q3]	[4.3-4.8]	[4.2-4.9]	[4.3-4.9]	
Min-Max	3.3-5.8	3.5-5.6	3.3-5.8	
Red blood cells (score)				
NCS	2 (2.5%)	4 (5.0%)	6 (3.7%)	0.443^
the norm	79 (97.5%)	76 (95.0%)	155 (96.3%)	
Leukocytes				
N	81	80	161	
Mean±CO	6.1 (1.76)	6.1 (1.61)	6.1 (1.68)	0.965#
95% DI (average)	(5.7,6.5)	(5.7,6.4)	(5.8,6.3)	
Median	6.0	5.9	5.9	
[q1-q3]	[5.0-6.9]	[5.1-6.7]	[5.0-6.8]	
Min-Max	3.5-13.3	3.5-13.3	3.5-13.3	
White blood cells (assessment)				
NCS	9 (11.1%)	5 (6.3%)	14 (8.7%)	0.274~
the norm	72 (88.9%)	75 (93.8%)	147 (91.3%)	
Hemoglobin (g / l)				
N	81	80	161	
Mean±CO	139.3 (14.30)	136.5 (16.30)	137.9 (15.34)	0.245#
95% DI (average)	(136.1,142.4)	(132.8,140.1)	(135.5,140.3)	
Median	140.0	136.5	138.0	
[q1-q3]	[128.0-152.0]	[126.0-145.5]	[128.0-150.0]	
Min-Max	108.0-166.0	74.0-167.0	74.0-167.0	
Hemoglobin (assessment)				
NCS	10 (12.3%)	10 (12.5%)	20 (12.4%)	0.976~
the norm	71 (87.7%)	70 (87.5%)	141 (87.6%)	
Platelets				

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	N	81	80	161	
	Mean±CO	242.8 (56.47)	249.4 (63.50)	246.1 (59.97)	0.487#
	95% DI (average)	(230.3,255.3)	(235.3,263.5)	(236.7,255.4)	
	Median	240.0	244.0	240.0	
	[q1-q3]	[200.0-279.0]	[206.0-294.0]	[201.0-286.0]	
	Min-Max	115.0-448.0	114.0-460.0	114.0-460.0	
Platelets (assessment)					
	NCS	of cns 4 (4.9%)	5 (6.3%)	9 (5.6%)	0.746^
	the norm	77 (95.1%)	75 (93.8%)	152 (94.4%)	
Neutrophils (%)					
	N	81	80	161	
	Mean±CO	58.4 (8.08)	59.8 (6.65)	59.1 (7.41)	0.221#
	95% DI (average)	(56.6,60.2)	(58.3,61.3)	(57.9,60.2)	
	Median	59.7	59.6	59.6	
	[q1-q3]	[53.7-64.0]	[55.1-64.0]	[54.0-64.0]	
	Min-Max	37.4-72.0	45.0-77.5	37.4-77.5	
Neutrophils (assessment)					
	NCS	8 (9.9%)	4 (5.0%)	12 (7.5%)	0.239~
	norm	73 (90.1%)	76 (95.0%)	149 (92.5%)	
Eosinophils (%)					
	N	81	80	161	
	Mean±CO	2.4 (2.48)	2.3 (2.07)	2.4 (2.28)	0.841#
	95% DI (average)	(1.9,3.0)	(1.9,2.8)	(2.0,2.7)	
	Median	1.7	2.0	2.0	
	[q1-q3]	[1.0-3.0]	[1.0-3.0]	[1.0-3.0]	
	Min-Max	0.0-16.1	0.0-11.6	0.0-16.1	
Eosinophils (assessment)					
	NCS	9 (11.1%)	10 (12.5%)	19 (11.8%)	0.785~
	normal	72 (88.9%)	70 (87.5%)	142 (88.2%)	
Basophils (%)					
	N	81	80	161	
	Mean±FROM	0.3 (0.37)	0.3 (0.35)	0.3 (0.36)	0.871#
	95% DI (average)	(0.2,0.3)	(0.2,0.3)	(0.2,0.3)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[0.0-0.4]	[0.0-0.6]	[0.0-0.5]	
	Min-Max	0.0-1.3	0.0-1.0	0.0-1.3	
Basophils (estimated)					
	NCS	2 (2.5%)	0 (0.0%)	2 (1.2%)	0.497^
	the norm	79 (97.5%)	80 (100.0%)	159 (98.8%)	
Monocytes (%)					
	N	81	80	161	
	Mean±CO	6.0 (1.91)	6.0 (1.87)	6.0 (1.88)	0.996#
	95% DI (average)	(5.6,6.4)	(5.6,6.4)	(5.7,6.3)	
	Median	6.0	6.0	6.0	
	[q1-q3]	[5.0-7.4]	[5.0-7.0]	[5.0-7.2]	
	Min-Max	2.0-10.0	2.0-12.0	2.0-12.0	
Monocytes (assessment)					
	NCS	0 (0.0%)	1 (1.3%)	1 (0.6%)	0.497^
	norm	81 (100.0%)	79 (98.8%)	160 (99.4%)	
Lymphocytes (%)					
	N	81	80	161	
	Mean±CO	32.9 (7.90)	31.6 (6.60)	32.2 (7.29)	0.253#
	95% DI (average)	(31.1,34.6)	(30.1,33.0)	(31.1,33.4)	
	Median	31.9	32.0	31.9	
	[q1-q3]	[27.0-38.0]	[27.0-35.6]	[27.0-37.0]	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	Min-Max	18.0-54.0	14.6-47.0	14.6-54.0	
Lymphocytes (assessment)					
	NCS	of cns 16 (19.8%)	13 (16.3%)	29 (18.0%)	0.563~
	the norm	65 (80.2%)	67 (83.8%)	132 (82.0%)	
Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).					

Table Ошибка! Закладка не определена. **– General blood test data. Dynamics of Visit 1-Visit 4. Security population, n=161**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Hematocrit (%)					
	N	81	80	161	
	Mean±CO	0.1 (4.67)	-0.2 (4.32)	-0.1 (4.49)	0.646#
	95% DI (average)	(-0.9,1.1)	(-1.2,0.7)	(-0.7,0.6)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[-3.0-1.8]	[-2.5-1.6]	[-2.9-1.6]	
	Min-Max	-9.8-13.8	-11.6-12.9	-11.6-13.8	
Hematocrit (assessment)					
	NCS	19 (23.5%)	21 (26.3%)	40 (24.8%)	0.682~
	normal	62 (76.5%)	59 (73.8%)	121 (75.2%)	
Red blood cells					
	N	81	80	161	
	Mean±CO	0.0 (0.47)	0.0 (0.43)	0.0 (0.45)	0.817#
	95% DI (average)	(-0.1,0.1)	(-0.0,0.1)	(-0.0,0.1)	
	Median	0.1	0.0	0.0	
	[q1-q3]	[-0.3-0.3]	[-0.2-0.2]	[-0.2-0.3]	
	Min-Max	-1.0-1.5	-1.3-1.2	-1.3-1.5	
Red blood cells (score)					
	NCS	2 (2.5%)	4 (5.0%)	6 (3.7%)	0.443^
	the norm	79 (97.5%)	76 (95.0%)	155 (96.3%)	
Leukocytes					
	N	81	80	161	
	Mean±CO	-0.1 (1.71)	0.1 (1.93)	-0.0 (1.82)	0.543#
	95% DI (average)	(-0.5,0.3)	(-0.3,0.5)	(-0.3,0.3)	
	Median	-0.3	0.0	-0.1	
	[q1-q3]	[-1.2-0.5]	[-0.7-0.9]	[-1.1-0.8]	
	Min-Max	-4.7-6.2	-4.7-8.1	-4.7-8.1	
White blood cells (assessment)					
	NCS	9 (11.1%)	5 (6.3%)	14 (8.7%)	0.274~
	normal	72 (88.9%)	75 (93.8%)	147 (91.3%)	
Hemoglobin (g / l)					
	N	81	80	161	
	Average±FROM	0.8 (13.92)	-1.5 (14.28)	-0.3 (14.10)	0.320#
	95% DI (average)	(-2.3,3.8)	(-4.6,1.7)	(-2.5,1.8)	
	Median	-1.0	-1.5	-1.0	
	[q1-q3]	[-7.0-8.0]	[-9.0-4.5]	[-7.0-6.0]	
	Min-Max	-28.0-50.0	-40.0-42.0	-40.0-50.0	
Hemoglobin (assessment)					
	NCS	10 (12.3%)	10 (12.5%)	20 (12.4%)	0.976~
	normal	71 (87.7%)	70 (87.5%)	141 (87.6%)	
Platelets					

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	N	81	80	161	
	Mean±CO	3.5 (67.34)	4.5 (67.03)	4.0 (66.97)	0.921#
	95% DI (average)	(-11.4,18.4)	(-10.4,19.5)	(-6.4,14.4)	
	Median	-3.0	2.0	0.0	
	[q1-q3]	[-32.0-43.0]	[-27.0-37.5]	[-32.0-41.0]	
	Min-Max	-161-172.0	-153-247.0	-161-247.0	
Platelets (assessment)					
	NCS	of cns 4 (4.9%)	5 (6.3%)	9 (5.6%)	0.746^
	the norm	77 (95.1%)	75 (93.8%)	152 (94.4%)	
Neutrophils (%)					
	N	81	80	161	
	Mean±CO	-0.9 (9.09)	0.5 (8.63)	-0.2 (8.86)	0.325#
	95% DI (average)	(-2.9,1.1)	(-1.5,2.4)	(-1.6,1.1)	
	Median	-1.0	0.9	-0.6	
	[q1-q3]	[-5.7-3.8]	[-3.4-5.9]	[-5.0-4.6]	
	Min-Max	-19.6-36.3	-30.6-16.0	-30.6-36.3	
Neutrophils (assessment)					
	NCS	8 (9.9%)	4 (5.0%)	12 (7.5%)	0.239~
	normal	73 (90.1%)	76 (95.0%)	149 (92.5%)	
Eosinophils (%)					
	N	81	80	161	
	Mean±CO	0.5 (2.10)	0.0 (2.32)	0.3 (2.22)	0.135#
	95% DI (average)	(0.1,1.0)	(-0.5,0.5)	(-0.1,0.6)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[0.0-1.0]	[-1.0-1.0]	[-0.4-1.0]	
	Min-Max	-4.4-12.9	-8.0-6.0	-8.0-12.9	
Eosinophils (assessment)					
	NCS	9 (11.1%)	10 (12.5%)	19 (11.8%)	0.785~
	normal	72 (88.9%)	70 (87.5%)	142 (88.2%)	
Basophils (%)					
	N	81	80	161	
	Mean±CO	0.0 (0.43)	-0.0 (0.45)	-0.0 (0.44)	0.679#
	95% DI (average)	(-0.1,0.1)	(-0.1,0.1)	(-0.1,0.1)	
	Median	0.0	0.0	0.0	
	[q1-q3]	[0.0-0.0]	[-0.2-0.0]	[-0.1-0.0]	
	Min-Max	-1.0-1.3	-1.0-1.0	-1.0-1.3	
Basophils (estimated)					
	NCS	2 (2.5%)	0 (0.0%)	2 (1.2%)	0.497^
	the norm	79 (97.5%)	80 (100.0%)	159 (98.8%)	
Monocytes (%)					
	N	81	80	161	
	Mean±FROM	0.3 (2.21)	0.3 (2.09)	0.3 (2.14)	0.923#
	95% DI (average)	(-0.2,0.8)	(-0.1,0.8)	(-0.0,0.7)	
	Median	0.0	0.1	0.0	
	[q1-q3]	[-1.0-1.0]	[-0.8-1.0]	[-0.9-1.0]	
	Min-Max	-5.7-7.5	-7.0-7.0	-7.0-7.5	
Monocytes (assessment)					
	NCS	0 (0.0%)	1 (1.3%)	1 (0.6%)	0.497^
	norm	81 (100.0%)	79 (98.8%)	160 (99.4%)	
Lymphocytes (%)					
	N	81	80	161	
	Mean±FROM	0.2 (8.74)	-0.6 (7.44)	-0.2 (8.10)	0.573#
	95% CI (mean)	(-1.8,2.1)	(-2.2,1.1)	(-1.4,1.1)	
	Median	0.0	-1.0	-0.3	
	[q1-q3]	[-4.0-5.0]	[-6.0-3.7]	[-4.8-4.1]	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	Min-Max	-33.4-19.6	-15.2-25.7	-33.4-25.7	
Lymphocytes (assessment)					
	NCS	of cns 16 (19.8%)	13 (16.3%)	29 (18.0%)	0.563~
	normal	65 (80.2%)	67 (83.8%)	132 (82.0%)	

Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).

Table Ошибка! Закладка не определена. **– Blood chemistry data, visit 1. Safety population, n=161**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
AST (U/l)					
	N	81	80	161	
	Mean±CO	21.5 (6.89)	21.8 (6.65)	21.6 (6.75)	0.797#
	95% CI (mean)	(20.0,23.0)	(20.3,23.2)	(20.6,22.7)	
	Median	21.9	20.9	21.7	
	[q1-q3]	[17.0-26.0]	[17.0-24.6]	[17.0-25.0]	
	Min-Max	8.6-58.6	12.4-56.2	8.6-58.6	
AST (assessment)					
	of the NCS	1 (1.2%)	2 (2.5%)	3 (1.9%)	0.620^
	the norm	80 (98.8%)	78 (97.5%)	158 (98.1%)	
ALT (U/L)					
	N	81	80	161	
	Mean±CO	21.0 (8.52)	20.8 (11.81)	20.9 (10.25)	0.923#
	95% DI (average)	(19.1,22.9)	(18.2,23.4)	(19.3,22.5)	
	Median	20.8	18.9	20.0	
	[q1-q3]	[13.8-24.9]	[14.9-24.0]	[13.8-24.7]	
	Min-Max	5.5-51.8	7.8-97.4	5.5-97.4	
ALT (assessment)					
	of the NCS	3 (3.7%)	5 (6.3%)	8 (5.0%)	0.495^
	norm	78 (96.3%)	75 (93.8%)	153 (95.0%)	
Creatinine (mmol / l)					
	N	81	80	161	
	Mean±CO	78.1 (16.58)	75.5 (15.28)	76.8 (15.95)	0.293#
	95% DI (average)	(74.4,81.8)	(72.1,78.9)	(74.3,79.3)	
	Median	77.8	75.5	76.9	
	[q1-q3]	[68.3-87.9]	[63.9-83.8]	[65.0-85.3]	
	Min-Max	47.3-122.8	49.6-115.1	47.3-122.8	
Creatinine (assessment)					
	NCS	of cns 10 (12.3%)	10 (12.5%)	20 (12.4%)	0.976~
	the norm	71 (87.7%)	70 (87.5%)	141 (87.6%)	
Blood glucose (mmol / l)					
	N	81	80	161	
	Average±CO	5.0 (0.74)	5.0 (1.16)	5.0 (0.97)	0.656#
	95% DI (average)	(4.8,5.1)	(4.8,5.3)	(4.8,5.1)	
	Median	5.0	5.0	5.0	
	[q1-q3]	[4.4-5.4]	[4.4-5.6]	[4.4-5.5]	
	Min-Max	3.6-8.7	3.4-13.0	3.4-13.0	
Blood glucose (assessment)					
	NCS	of cns 4 (4.9%)	6 (7.5%)	10 (6.2%)	0.534^
	the norm	77 (95.1%)	74 (92.5%)	151 (93.8%)	
Alkaline phosphatase (U/L)					
	N	81	80	161	
	Average±CO	102.7 (52.43)	103.7 (55.15)	103.2 (53.63)	0.909#
	95% DI (average)	(91.1,114.3)	(91.4,116.0)	(94.9,111.6)	
	Median	86.7	85.0	86.0	
	[q1-q3]	[64.3-128.2]	[63.7-141.5]	[64.1-136.0]	
	Min-Max	37.7-252.0	36.9-260.0	36.9-260.0	
Alkaline phosphatase (assessment)					
	NCS	2 (2.5%)	3 (3.8%)	5 (3.1%)	0.682^
	the norm	79 (97.5%)	77 (96.3%)	156 (96.9%)	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Total bilirubin (mmol / l)					
	N	81	80	161	
	Mean±CO	11.4 (6.08)	11.0 (5.15)	11.2 (5.62)	0.638#
	95% DI (average)	(10.1,12.7)	(9.8,12.1)	(10.3,12.1)	
	Median	10.2	9.7	10.1	
	[q1-q3]	[8.2-13.1]	[7.5-13.5]	[7.8-13.3]	
	Min-Max	2.9-43.2	3.3-34.8	2.9-43.2	
Total bilirubin (assessment)					
	NCS	of cns 4 (4.9%)	6 (7.5%)	10 (6.2%)	0.534^
	the norm	77 (95.1%)	74 (92.5%)	151 (93.8%)	
Cholesterol (mmol / l)					
	N	81	80	161	
	Average±CO	4.8 (0.88)	5.0 (1.07)	4.9 (0.98)	0.191#
	95% DI (average)	(4.6,5.0)	(4.7,5.2)	(4.7,5.0)	
	Median	4.7	4.8	4.7	
	[q1-q3]	[4.3-5.2]	[4.3-5.3]	[4.3-5.2]	
	Min-Max	3.1-7.6	2.7-9.7	2.7-9.7	
Cholesterol (assessment)					
	NCS	of cns 19 (23.5%)	20 (25.0%)	39 (24.2%)	0.819~
	the norm	62 (76.5%)	60 (75.0%)	122 (75.8%)	
Uric acid (mmol / l)					
	N	81	80	161	
	Average±CO	278.7 (78.93)	273.1 (69.90)	275.9 (74.40)	0.634#
	95% DI (average)	(261.2,296.2)	(257.5,288.6)	(264.3,287.5)	
	Median	281.6	267.4	269.2	
	[q1-q3]	[210.0-344.1]	[218.9-309.4]	[216.0-322.0]	
	Min-Max	135.0-502.8	89.0-456.9	89.0-502.8	
Uric acid (assessment)					
	NCS	of cns 12 (14.8%)	8 (10.0%)	20 (12.4%)	0.354~
	the norm	69 (85.2%)	72 (90.0%)	141 (87.6%)	
Total protein (g / l)					
	N	81	80	161	
	Mean±CO	72.6 (4.68)	73.3 (4.80)	72.9 (4.74)	0.324#
	95% CI (mean)	(71.5,73.6)	(72.2,74.4)	(72.2,73.7)	
	Median	72.2	72.6	72.3	
	[q1-q3]	[69.8-76.0]	[70.3-76.0]	[69.8-76.0]	
	Min-Max	64.4-83.7	64.4-87.1	64.4-	
87.1 Total protein (score)					
	NCS	of the cns 5 (6.2%)	2 (2.5%)	7 (4.3%)	0.443^
	the norm	76 (93.8%)	78 (97.5%)	154 (95.7%)	
Potassium (mmol / l)					
	N	81	80	161	
	Average±CO	4.6 (0.64)	4.5 (0.63)	4.6 (0.64)	0.470#
	95% DI (average)	(4.5,4.8)	(4.4,4.7)	(4.5,4.7)	
	Median	4.6	4.5	4.6	
	[q1-q3]	[4.3-4.8]	[4.2-4.7]	[4.3-4.8]	
	Min-Max	3.6-9.1	3.6-8.7	3.6-9.1	
Potassium (assessment)					
	NCS	4 (4.9%)	5 (6.3%)	9 (5.6%)	0.746^

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	the norm	77 (95.1%)	75 (93.8%)	152 (94.4%)	
Sodium (mmol / l)					
	N	81	80	161	
	Mean±CO	140.3 (2.87)	140.7 (2.13)	140.5 (2.53)	0.432#
	95% DI (average)	(139.7,141.0)	(140.2,141.1)	(140.1,140.9)	
	Median	140.3	140.7	140.7	
	[q1-q3]	[139.0-142.0]	[139.5-142.0]	[139.2-142.0]	
	Min-Max	130.0-147.3	136.0-146.4	130.0-147.3	
Sodium (assessment)					
	NCS	7 (8.6%)	1 (1.3%)	8 (5.0%)	0.064^
	the norm	74 (91.4%)	79 (98.8%)	153 (95.0%)	
Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).					

Table Ошибка! Закладка не определена.**-Blood chemistry data, visit 4. Safety population, n=161**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
AST (U/l)					
	N	81	80	161	
	Mean±CO	20.9 (8.81)	21.5 (5.95)	21.2 (7.51)	0.635#
	95% DI (average)	(19.0,22.9)	(20.2,22.8)	(20.1,22.4)	
	Median	20.0	20.8	20.0	
	[q1-q3]	[17.3-22.8]	[18.1-24.1]	[17.8-24.0]	
	Min-Max	8.1-85.3	12.1-41.3	8.1-85.3	
AST (assessment)					
	of the NCS	3 (3.7%)	2 (2.5%)	5 (3.1%)	>0.999^
	the norm	78 (96.3%)	78 (97.5%)	156 (96.9%)	
ALT (Units/l)					
	N	81	80	161	
	Mean±CO	21.6 (16.75)	20.4 (10.75)	21.0 (14.06)	0.619#
	95% DI (average)	(17.9,25.3)	(18.1,22.8)	(18.8,23.2)	
	Median	19.1	19.6	19.4	
	[q1-q3]	[13.6-24.1]	[13.6-25.1]	[13.6-24.9]	
	Min-Max	5.6-152.0	5.0-85.7	5.0-152.0	
ALT (rating)					
	NCS	2 (2.5%)	2 (2.5%)	4 (2.5%)	>0.999^
	the norm	79 (97.5%)	78 (97.5%)	157 (97.5%)	
Creatinine (mmol / l)					
	N	81	80	161	
	Mean±CO	76.9 (14.49)	75.7 (13.34)	76.3 (13.90)	0.588#
	95% DI (average)	(73.7,80.1)	(72.7,78.7)	(74.1,78.5)	
	Median	75.5	74.5	75.0	
	[q1-q3]	[66.0-85.4]	[65.9-84.3]	[66.0-85.2]	
	Min-Max	49.0-128.9	45.7-120.6	45.7-128.9	
Creatinine (assessment)					
	NCS	of cns 9 (11.1%)	6 (7.5%)	15 (9.3%)	0.431~
	the norm	72 (88.9%)	74 (92.5%)	146 (90.7%)	
Blood glucose (mmol / l)					

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	N	81	80	161	
	Average±CO	4.8 (0.75)	4.8 (0.82)	4.8 (0.79)	0.519#
	95% CI (mean)	(4.6,4.9)	(4.7,5.0)	(4.7,4.9)	
	Median	4.8	4.9	4.8	
	[q1-q3]	[4.4-5.2]	[4.2-5.5]	[4.3-5.4]	
	Min-Max	2.8-7.2	3.0-6.9	2.8-7.2	
Blood glucose (assessment)					
	NCS	of cns 10 (12.3%)	12 (15.0%)	22 (13.7%)	0.624~
	the norm	71 (87.7%)	68 (85.0%)	139 (86.3%)	
Alkaline phosphatase (U/L)					
	N	81	80	161	
	Mean±CO	98.2 (53.66)	102.4 (54.09)	100.3 (53.75)	0.620#
	95% DI (average)	(86.3,110.1)	(90.4,114.4)	(91.9,108.7)	
	Median	76.7	83.2	79.0	
	[q1-q3]	[61.9-117.0]	[62.6-116.5]	[62.0-117.0]	
	Min-Max	37.0-244.0	35.5-245.0	35.5-245.0	
Alkaline phosphatase (assessment)					
	NCS	3 (3.7%)	1 (1.3%)	4 (2.5%)	0.620^
	the norm	78 (96.3%)	79 (98.8%)	157 (97.5%)	
Total bilirubin (mmol / l)					
	N	81	79	160	
	Mean±CO	10.9 (6.82)	11.4 (5.85)	11.2 (6.35)	0.577#
	95% DI (average)	(9.4,12.4)	(10.1,12.8)	(10.2,12.2)	
	Median	9.6	10.1	10.1	
	[q1-q3]	[7.6-11.9]	[8.2-13.4]	[7.9-12.4]	
	Min-Max	2.6-43.4	3.1-39.2	2.6-43.4	
Total bilirubin (assessment)					
	NCS	of cns 6 (7.4%)	6 (7.5%)	12 (7.5%)	0.982~
	the norm	75 (92.6%)	74 (92.5%)	149 (92.5%)	
Cholesterol (mmol / l)					
	N	81	80	161	
	Average±CO	4.7 (0.75)	4.9 (1.05)	4.8 (0.91)	0.157#
	95% DI (average)	(4.6,4.9)	(4.7,5.2)	(4.7,5.0)	
	Median	4.6	4.7	4.7	
	[q1-q3]	[4.3-5.2]	[4.3-5.4]	[4.3-5.2]	
	Min-Max	2.7-7.1	2.9-8.3	2.7-8.3	
Cholesterol (assessment)					
	NCS	of cns 21 (25.9%)	22 (27.5%)	43 (26.7%)	0.821~
	the norm	60 (74.1%)	58 (72.5%)	118 (73.3%)	
Uric acid (mmol / l)					
	N	81	80	161	
	Mean±CO	276.7 (74.08)	281.1 (75.35)	278.9 (74.51)	0.708#
	95% DI (average)	(260.3,293.0)	(264.3,297.8)	(267.3,290.5)	
	Median	271.5	266.1	269.0	
	[q1-q3]	[215.0-338.0]	[231.0-343.4]	[220.0-339.1]	
	Min-Max	143.7-474.4	109.4-445.3	109.4-474.4	
Uric acid (assessment)					
	NCS	of cns 6 (7.4%)	11 (13.8%)	17 (10.6%)	0.190~
	normal	75 (92.6%)	69 (86.3%)	144 (89.4%)	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
Total protein (g / l)					
	N	81	80	161	
	Mean±CO	72.1 (4.62)	72.7 (4.78)	72.4 (4.69)	0.434#
	95% CI (mean)	(71.1,73.2)	(71.7,73.8)	(71.7,73.2)	
	Median	71.5	72.6	71.9	
	[q1-q3]	[69.4-74.4]	[70.1-76.0]	[70.0-75.6]	
	Min-Max	61.6-90.9	61.5-86.1	61.5-	
90.9 Total Protein (estimated)					
	NCS	2 (2.5%)	6 (7.5%)	8 (5.0%)	0.167^
	the norm	79 (97.5%)	74 (92.5%)	153 (95.0%)	
Potassium (mmol / l)					
	N	81	80	161	
	Average±CO	4.5 (0.39)	4.4 (0.42)	4.5 (0.40)	0.559#
	95% CI (mean)	(4.4,4.6)	(4.3,4.5)	(4.4,4.5)	
	Median	4.5	4.4	4.4	
	[q1-q3]	[4.2-4.7]	[4.2-4.7]	[4.2-4.7]	
	Min-Max	3.8-6.0	3.4-5.8	3.4-6.0	
Potassium (score)					
	NCS	4 (4.9%)	7 (8.8%)	11 (6.8%)	0.338~
	the norm	77 (95.1%)	73 (91.3%)	150 (93.2%)	
Sodium (mmol / l)					
	N	81	80	161	
	Mean±CO	140.5 (2.59)	140.7 (2.51)	140.6 (2.54)	0.639#
	95% DI (average)	(139.9,141.1)	(140.1,141.2)	(140.2,141.0)	
	Median	140.2	141.0	140.8	
	[q1-q3]	[139.3-142.0]	[139.2-142.0]	[139.2-142.0]	
	Min-Max	132.0-147.5	130.0-148.0	130.0-148.0	
Sodium (assessment)					
	NCS	4 (4.9%)	2 (2.5%)	6 (3.7%)	0.682^
	norm	77 (95.1%)	78 (97.5%)	155 (96.3%)	

Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).

Table Ошибка! Закладка не определена. **– Blood chemistry data, changes Visit 1-Visit 4. Safety population, n=161**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
AST (U/l)					
	N	81	80	161	
	Mean±CO	-0.5 (9.55)	-0.3 (6.23)	-0.4 (8.05)	0.821#
	95% DI (average)	(-2.7,1.6)	(-1.6,1.1)	(-1.7,0.8)	
	Median	-1.0	0.0	-0.6	
	[q1-q3]	[-4.2-2.6]	[-3.1-2.1]	[-4.2-2.2]	
	Min-Max	-38.9-57.1	-15.4-21.5	-38.9-57.1	
AST (assessment)					
	of the NCS	3 (3.7%)	2 (2.5%)	5 (3.1%)	>0.999^
	norm	78 (96.3%)	78 (97.5%)	156 (96.9%)	
ALT (U/L)					
	N	81	80	161	
	Average±FROM	0.6 (15.35)	-0.4 (6.53)	0.1 (11.80)	0.610#

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	95% DI (average)	(-2.8,4.0)	(-1.8,1.1)	(-1.7,1.9)	
	Median	-0.1	0.0	0.0	
	[q1-q3]	[-5.6-2.7]	[-3.2-3.7]	[-3.5-3.4]	
	Min-Max	-21.7-115.4	-27.7-13.0	-27.7-115.4	
ALT (rating)					
	NCS	2 (2.5%)	2 (2.5%)	4 (2.5%)	>0.999^
	the norm	79 (97.5%)	78 (97.5%)	157 (97.5%)	
Creatinine (mmol / l)					
	N	81	80	161	
	Mean±CO	-1.2 (15.87)	0.3 (13.36)	-0.5 (14.65)	0.528#
	95% DI (average)	(-4.7,2.3)	(-2.7,3.2)	(-2.8,1.8)	
	Median	-1.1	0.4	-0.3	
	[q1-q3]	[-8.1-5.0]	[-4.9-6.2]	[-7.0-5.5]	
	Min-Max	-49.5-40.9	-42.1-43.9	-49.5-43.9	
Creatinine (assessment)					
	NCS	of cns 9 (11.1%)	6 (7.5%)	15 (9.3%)	0.431~
	normal	72 (88.9%)	74 (92.5%)	146 (90.7%)	
Blood glucose (mmol / l)					
	N	81	80	161	
	Mean±CO	-0.2 (0.88)	-0.2 (1.18)	-0.2 (1.04)	0.943#
	95% DI (average)	(-0.4,-0.0)	(-0.5,0.1)	(-0.4,-0.0)	
	Median	-0.1	-0.1	-0.1	
	[q1-q3]	[-0.6-0.2]	[-0.6-0.3]	[-0.6-0.2]	
	Min-Max	-4.6-1.9	-7.7-2.0	-7.7-2.0	
Blood glucose (assessment)					
	NCS	of cns 10 (12.3%)	12 (15.0%)	22 (13.7%)	0.624~
	the norm	71 (87.7%)	68 (85.0%)	139 (86.3%)	
Alkaline phosphatase (U / l)					
	N	81	80	161	
	Mean±CO	-4.5 (22.89)	-1.3 (34.80)	-2.9 (29.37)	0.486#
	95% DI (average)	(-9.6,0.5)	(-9.0,6.5)	(-7.5,1.7)	
	Median	-1.0	0.0	0.0	
	[q1-q3]	[-9.1-4.0]	[-7.0-6.3]	[-8.4-5.0]	
	Min-Max	-113-49.0	-124-153.0	-124-153.0	
Alkaline phosphatase (assessment)					
	NCS	3 (3.7%)	1 (1.3%)	4 (2.5%)	0.620 ^
	norm	78 (96.3%)	79 (98.8%)	157 (97.5%)	
Total bilirubin (mmol / l)					
	N	81	79	160	
	Mean±CO	-0.5 (4.54)	0.4 (6.62)	-0.1 (5.67)	0.296#
	95% DI (average)	(-1.5,0.5)	(-1.1,1.9)	(-0.9,0.8)	
	Median	0.0	0.3	0.2	
	[q1-q3]	[-2.9-1.7]	[-1.4-2.6]	[-2.2-2.0]	
	Min-Max	-11.4-17.3	-27.3-32.4	-27.3-32.4	
Total bilirubin (assessment)					
	NCS	of cns 6 (7.4%)	6 (7.5%)	12 (7.5%)	0.982~
	normal	75 (92.6%)	74 (92.5%)	149 (92.5%)	
Cholesterol (mmol / l)					
	N	81	80	161	
	Mean±CO	-0.0 (0.85)	-0.0 (1.05)	-0.0 (0.95)	0.988#
	95% DI (average)	(-0.2,0.2)	(-0.3,0.2)	(-0.2,0.1)	
	Median	0.0	0.1	0.0	

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-value
	[q1-q3]	[-0.4-0.3]	[-0.5-0.3]	[-0.4-0.3]	
	Min-Max	-2.8-2.5	-3.6-3.2	-3.6-3.2	
Cholesterol (assessment)					
	NCS	of cns 21 (25.9%)	22 (27.5%)	43 (26.7%)	0.821~
	normal	60 (74.1%)	58 (72.5%)	118 (73.3%)	
Uric acid (mmol / l)					
	N	81	80	161	
	Mean±CO	-2.0 (59.28)	8.0 (56.13)	2.9 (57.78)	0.273#
	95% DI (average)	(-15.1,11.1)	(-4.5,20.5)	(-6.0,11.9)	
	Median	3.0	3.2	3.0	
	[q1-q3]	[-21.0-23.0]	[-13.0-37.0]	[-17.8-27.4]	
	Min-Max	-216-184.3	-239-141.0	-239-184.3	
Uric acid (assessment)					
	NCS	of cns 6 (7.4%)	11 (13.8%)	17 (10.6%)	0.190~
	normal	75 (92.6%)	69 (86.3%)	144 (89.4%)	
Total protein (g / l)					
	N	81	80	161	
	Mean±CO	-0.4 (5.49)	-0.6 (6.54)	-0.5 (6.02)	0.868#
	95% CI (mean)	(-1.6,0.8)	(-2.0,0.9)	(-1.4,0.4)	
	Median	-0.1	0.5	0.1	
	[q1-q3]	[-3.3-2.0]	[-3.6-3.0]	[-3.3-2.1]	
	Min-Max	-18.3-18.2	-20.9-14.7	-20.9-18.2	
Total Protein (estimated)					
	NCS	2 (2.5%)	6 (7.5%)	8 (5.0%)	0.167^
	the norm	79 (97.5%)	74 (92.5%)	153 (95.0%)	
Potassium (mmol / l)					
	N	81	80	161	
	Mean±CO	-0.1 (0.76)	-0.1 (0.75)	-0.1 (0.76)	0.768#
	95% DI (average)	(-0.3,0.0)	(-0.3,0.1)	(-0.2,-0.0)	
	Median	-0.1	0.0	-0.0	
	[q1-q3]	[-0.4-0.2]	[-0.2-0.3]	[-0.4-0.2]	
	Min-Max	-5.3-1.3	-4.7-1.2	-5.3-1.3	
Potassium (assessment)					
	NCS	4 (4.9%)	7 (8.8%)	11 (6.8%)	0.338~
	the norm	77 (95.1%)	73 (91.3%)	150 (93.2%)	
Sodium (mmol / l)					
	N	81	80	161	
	Average±FROM	0.2 (2.65)	0.0 (3.01)	0.1 (2.82)	0.779#
	95% DI (average)	(-0.4,0.7)	(-0.6,0.7)	(-0.4,0.5)	
	Median	0.0	-0.1	0.0	
	[q1-q3]	[-1.1-1.8]	[-1.2-1.2]	[-1.2-1.6]	
	Min-Max	-7.1-6.0	-8.8-12.0	-8.8-12.0	
Sodium (assessment)					
	NCS	4 (4.9%)	2 (2.5%)	6 (3.7%)	0.682^
	the norm	77 (95.1%)	78 (97.5%)	155 (96.3%)	

Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).

Table Ошибка! Закладка не определена.**-General urinalysis data. Session 1. Security population, n=161**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-зн.
pH					
	N	81	80	161	
	Average±CO	5.710 (0.702)	5.863 (0.807)	5.786 (0.758)	0.202#
	95% DI (average)	(5.555,5.865)	(5.683,6.042)	(5.668,5.904)	
	Median	5.500	5.500	5.500	
	[q1-q3]	[5.000-6.000]	[5.500-6.000]	[5.000-6.000]	
	Min-Max	5.000-7.500	5.000-8.000	5.000-8.000	
pH (assessment)					
	NCS	6 (7.4%)	8 (10.0%)	14 (8.7%)	0.559~
	normal	75 (92.6%)	72 (90.0%)	147 (91.3%)	
Relative density					
	N	81	80	161	
	Average±CO	1.018 (0.007)	1.018 (0.007)	1.018 (0.007)	0.896#
	95% DI (average)	(1.017,1.020)	(1.017,1.020)	(1.017,1.019)	
	Median	1.020	1.020	1.020	
	[q1-q3]	[1.014-1.024]	[1.015-1.025]	[1.014-1.025]	
	Min-Max	1.005-1.034	1.004-1.030	1.004-1.034	
Relative density (estimate)					
	NCS	6 (7.4%)	12 (15.0%)	18 (11.2%)	0.126~
	the norm	75 (92.6%)	68 (85.0%)	143 (88.8%)	
Protein in the urine					
	No protein was detected in the urine	76 (93.8%)	72 (90.0%)	148 (91.9%)	0.373~
	detected	5 (6.2%)	8 (10.0%)	13 (8.1%)	
Protein in the urine (assessment)					
	NCS	4 (4.9%)	4 (5.0%)	8 (5.0%)	>0.999^
	the norm	77 (95.1%)	76 (95.0%)	153 (95.0%)	

Table Ошибка! Закладка не определена.**-General urinalysis data. Session 4. Safety population, n=161**

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-зн.
pH					
	N	81	80	161	
	Average±CO	5.685 (0.668)	5.808 (0.757)	5.746 (0.714)	0.279#
	95% DI (average)	(5.537,5.833)	(5.639,5.976)	(5.635,5.857)	
	Median	5.500	5.500	5.500	
	[q1-q3]	[5.000-6.000]	[5.250-6.000]	[5.000-6.000]	
	Min-Max	4.500-7.500	5.000-9.000	4.500-9.000	
pH (assessment)					
	NCS	6 (7.4%)	5 (6.3%)	11 (6.8%)	0.771~
	normal	75 (92.6%)	75 (93.8%)	150 (93.2%)	
Relative density					
	N	81	80	161	
	Average±CO	1.018 (0.007)	1.018 (0.008)	1.018 (0.007)	0.794#
	95% DI (average)	(1.017,1.020)	(1.016,1.020)	(1.017,1.019)	
	Median	1.020	1.020	1.020	
	[q1-q3]	[1.015-1.024]	[1.013-1.025]	[1.014-1.025]	
	Min-Max	1.005-1.030	1.002-1.030	1.002-1.030	
Relative density (estimate)					
	NCS	5 (6.2%)	10 (12.5%)	15 (9.3%)	0.167~
	the norm	76 (93.8%)	70 (87.5%)	146 (90.7%)	
Protein in the urine					

		Basic therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-зн.
	No protein was detected in the urine	80 (98.8%)	78 (97.5%)	158 (98.1%)	0.620^
	detected	1 (1.2%)	2 (2.5%)	3 (1.9%)	
Protein in the urine (assessment)					
	NCS	0 (0.0%)	1 (1.3%)	1 (0.6%)	0.497^
	norm	81 (100.0%)	79 (98.8%)	160 (99.4%)	
Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).					

Table Ошибка! Закладка не определена.**-General urinalysis data. Dynamics of Visit 1-Visit 4. Security population, n=161**

_BASIC					
		therapy (N=81)	Basic therapy + Study drug (N=80)	Total (N=161)	p-зн.
pH					
	N	81	80	161	
	Mean±CO	-0.025 (0.825)	-0.055 (1.020)	-0.040 (0.924)	0.836#
	95% DI (average)	(-0.207,0.158)	(-0.282,0.172)	(-0.184,0.104)	
	Median	0.000	0.000	0.000	
	[q1-q3]	[-0.500-0.500]	[-0.500-0.500]	[-0.500-0.500]	
	Min-Max	-2.500-2.500	-2.500-2.500	-2.500-2.500	
pH (assessment)					
	NCS	6 (7.4%)	5 (6.3%)	11 (6.8%)	0.771~
	normal	75 (92.6%)	75 (93.8%)	150 (93.2%)	
Relative density					
	N	81	80	161	
	Average±CO	0.000 (0.008)	-0.000 (0.008)	-0.000 (0.008)	0.729#
	95% DI (average)	(-0.002,0.002)	(-0.002,0.002)	(-0.001,0.001)	
	Median	0.000	0.000	0.000	
	[q1-q3]	[-0.005-0.005]	[-0.005-0.005]	[-0.005-0.005]	
	Min-Max	-0.029-0.020	-0.024-0.020	-0.029-0.020	
Relative density (estimate)					
	NCS	5 (6.2%)	10 (12.5%)	15 (9.3%)	0.167~
	normal	76 (93.8%)	70 (87.5%)	146 (90.7%)	
Protein in the urine					
	No protein was detected in the urine	80 (98.8%)	78 (97.5%)	158 (98.1%)	0.620^
	detected	1 (1.2%)	2 (2.5%)	3 (1.9%)	
Protein in the urine (assessment)					
	NCS	0 (0.0%)	1 (1.3%)	1 (0.6%)	0.497^
	norm	81 (100.0%)	79 (98.8%)	160 (99.4%)	
Note. Statistical method: # - Comparison was performed by analysis of variance (ANOVA), ~-Comparison was performed by Chi-square test, ^-Comparison was performed by Fisher's exact test. Mean – arithmeticmean± standard deviation (SD).					

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16. applications

16.1. Information about the study

16.1.1. Protocol and amendments to the protocol
16.1.2. AboutBrazets individual registration card
16.1.3. ESO/NEK bulletin, samples of written information for patients and informed consent forms
16.1.4. List and characteristics of the researchers and other persons responsible for the study, including a brief summary (1page) or equivalent description of training and work experience relevant to the conduct of the clinical trial
16.1.5. Signature ofthe Principal Investigator, Coordinator researcher, or responsible representative of Sponsora-depending on the requirements of the authorized body
16.1.6. B If more than one batch of the test drug is used in the study – lists of codes of patients who received drugs of different series
16.1.7. WithXEMA randomization and codes (patient identification and prescribed treatment)
16.1.8. Audit certificates (if any)
16.1.9. Documentation on statistical methods
16.1.10. Documentation oninternal laboratory standardization techniques and quality assurance procedures (if applicable)
16.1.11. Implicationsbased on this study
16.1.12. Asmany publications that are referenced in this report

16.2. List of data on research subjects

16.2.1. List of subjects who dropped out of the study ahead of schedule
16.2.2. Aboutdeviation from the protocol
16.2.3. Participants who were excluded from the performance analysis
16.2.4. Digital dataемографические данные
16.2.5. Compliance with the treatment regimen ("compliance") and /or) drug concentration data (if available))
16.2.6. Andindividual performance data
16.2.7. List ofadverse events (for each subject)
16.2.8. List ofindividual indicators of laboratory tests of patients, if required by the authorized body

16.3. Individual Registration Cards (IRCs)

16.3.1. IRC for deaths, other serious adverse events, and cases of withdrawal from the study due to the development of adverse events
16.3.2. OtherIRCs submitted for consideration

16.4. List of data for each subject of the study