CLINICAL STUDY PROTOCOL

Title: Open, multicenter, international study to evaluate the efficacy, safety, and tolerability of Bioven, manufactured by Biopharma Plasma LLC, in adult patients with chronic primary immune thrombocytopenia (ITP)

Trial Code: 2021-BV-ITP-BP

Version: Version 1.4 from July 03, 2023

Investigational Drug: Bioven

International non-proprietary name: Human normal immunoglobulin for intravenous administration

Pharmaceutical form: solution for infusion

Sponsor: Biopharma Plasma, LLC

Protocol approval page (Sponsor)

Title: Open, multicenter, international study to evaluate the efficacy, safety and tolerability of Bioven, manufactured by Biopharma Plasma LLC, in adult patients with chronic primary immune thrombocytopenia (ITP)

Trial Code: 2021-BV-ITP-BP

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Sponsor Representative:

Sofiia Matsybokh
(employee name)
Clinical trial lead
Biopharma Plasma, LLC
(position)

Organization name:	Biopharma Plasma, LLC
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_____ «____»_____ 20__.
Signature Date

Page of consent of the Principal Investigator with the study protocol *(sample)*

I, the Principal Investigator, hereby certify that I have carefully read this study protocol, the investigator's brochure, including potential risks and adverse reactions of the drug, and other information about the drug and the study provided by the Sponsor.

I agree to conduct this study in accordance with the requirements of the protocol and to protect the rights, confidentiality, safety and health of patients in accordance with the ethical requirements of the World Medical Association (WMA) Declaration of Helsinki, ICH E6 (R2) Guideline for Good Clinical Practice and other regulatory requirements of Ukraine and the European Union.

I agree to make changes to the protocol only after informing the Sponsor, except when necessary to protect the safety, rights and health of patients. I fully understand that any changes made by the Investigator(s) without prior approval from Sponsor representatives will constitute a protocol violation (other than those procedures necessary to preserve patient health).

I agree to personally conduct or supervise the research described.

I agree to inform patients that the drugs are used for research purposes; I will ensure compliance with the requirements related to obtaining informed consent, after the approval of the Local Ethics Committee (LEC) and in accordance with the principles of GCP.

In accordance with GCP principles, I agree to report adverse events that develop during the study to the Sponsor.

I agree to ensure that all employees, colleagues and persons involved in the conduct of the study are informed of their obligations to comply with the arrangements described above. I agree to keep adequate and accurate records and to provide those records for analysis in accordance with GCP principles.

I will ensure that the LEC, acting in accordance with the requirements of the GCP, is responsible for carrying out the ethical review as well as for the approval of the study. I also agree to promptly report to the LEC all changes in research activities and all unexpected problems, including patient risk and other aspects. In addition, I will not make any changes to the study without the approval of the LEC, except for the necessary cases of eliminating a clear unexpected threat to the life and health of patients.

I am ready to provide direct access to primary documents and agree to audit by auditors from the Sponsor's representatives and regulatory authorities. I warrant that the investigational product(s) supplied by Sponsor will be used only as described in this protocol.

I agree to comply with all other requirements regarding the responsibilities of clinical investigators, as well as all other important requirements of Good Clinical Practice.

Investigator:

Signature: _____ Date: _____

Full name _____

Position: _____

Institution: _____

Address: _____

CONFIDENTIALITY

CONTENT

LIST OF ABBREVIATIONS

AHA	- Antinuclear antibodies
CMV	- Cytomegalovirus
CR	- Complete response
CV	- Coefficient of variation
EBV	- Epstein-Barr virus
eCRF	- Electronic Case Report Form (ІРФ)
GCP	- Good Clinical Practice (Належна клінічна практика)
IVIG	- Intravenous immunoglobulin
M.g.	- Geometric mean phenomenon
Max	- Maximum value
Mean	- Average value
Min	- Minimum value
NR	- No response
r	- Correlation coefficient
R	- Response
RW	- Wasserman's reaction
SD	- Standard deviation
ALT	- Alanine transaminase
AST	- Aspartate transaminase
BUN	- Blood urea nitrogen
BP	- Blood pressure
APTT	- Activated partial thromboplastin time
IVIG	- Intravenous immunoglobulin
SID	- Secondary immunodeficiency
HIV	- Human immunodeficiency virus
R	- Response to therapy
GCS	- Glucocorticosteroids
SEC MOH	- State Enterprise "State Expert Center" of the Ministry of Health of Ukraine
SD	- Study drug
ECG	- Electrocardiography
ORT	- Overall response to therapy
BMI	- Body mass index
IRF	- Individual patient registration form
ITP	- Immune thrombocytopenia
AE/AR	- Adverse event/adverse reaction
CR	- Complete response to therapy
PID	- Primary immunodeficiency
PI	- Prothrombin index
SAM	- Syndrome of aseptic meningitis
HF	- Heart failure
SAE	- Serious adverse events
TRALI	- Transfusion-related acute lung injury
ICF	- Informed consent form
RR	- Respiratory rate
HR	- Heart rate

GENERAL INFORMATION (SYNOPSIS)

Name of Sponsor/Company: BIOPHARMA PLASMA LLC, Ukraine	
Name of Study Drug: Bioven	**Study code:** 2021-BV-ITP-BP
Name of Active Ingredient: Human normal immunoglobulin for intravenous administration	**Date and version of the protocol:** Version 1.4 from 03.07.2023
Title of Study: Open, multicenter, international study to evaluate the efficacy, safety, and tolerability of Bioven, manufactured by Biopharma Plasma LLC, in adult patients with chronic primary immune thrombocytopenia (ITP).	
Indication: Primary immune thrombocytopenia (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count. *According to the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), EMA / CHMP / BPWP / 94033/2007 rev. 4, 16 December 2021; Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94038/2007 Rev. 6, 16 December 2021*	
Number of Study Centers: It is planned to involve 5-15 centers in Ukraine and 3-5 centers in the Republic of Turkey.	
Duration of Study: This study is expected to start in 2022 and be completed in 2024.	**Phase of Clinical Trial:** **III**
Objectives of Study: To evaluate the efficacy, safety, and tolerability of Bioven in patients with chronic primary immune thrombocytopenia, with evidence of non-inferiority efficacy, compared with the literature data	
Study design: Open-label, multicenter, international, uncontrolled, single-group	
Number of patients: The number of patients to be studied in Ukraine and worldwide is 40. No more than 36 patients will be enrolled in Ukraine.	
Patient selection criteria: ***Inclusion criteria:*** - Signed Patient Informed Consent Form for participation in the study; - Men and women aged 18-65; - Confirmed primary chronic ITP (lasting > 12 months since diagnosis); - A full blood count should be normal except for the isolated thrombocytopenia. Patients with low hemoglobin levels (but above 90 g/L) may be included if there are symptoms of bleeding; - If bleeding symptoms are diagnosed, the reticulocyte count should be measured; - Platelet count <30 x 10^9 /L; - If the patient is taking corticosteroids, the treatment regimen/dose should be stable (at least 2 weeks prior to screening); - Negative pregnancy test (for women of child-bearing potential);	

- Willingness to use effective and reliable methods of contraception throughout the entire study period;
- The results of physical, instrumental and laboratory examination of patients should be within the normal range or deviations should be regarded by the researcher as clinically insignificant.
- Ability, according to the researcher, to follow all the requirements of the study protocol;

Non-inclusion criteria:

Patients cannot participate in this study if they meet one of the following criteria:

- Known intolerance to plasma and immunoglobulin preparations;
- Drug allergy or hypersensitivity to immunoglobulin preparations;
- Confirmed deficiency of Ig A and antibodies to IgA.
- Contraindications to immunoglobulin administration according to the instructions for medical use;
- Pregnancy and lactation;
- Any clinically significant hepatic impairment (increase of serum transaminase levels by more than 3 times the upper limit of normal);
- Serum creatinine levels are more than two times higher than the upper limit of normal for a given age and sex;
- Severe cardiovascular insufficiency (HF III);
- History of thrombosis or presence of significant risk factors for thrombosis.
- Patients with preventive splenectomy;
- Hemostatic disorders other than chronic thrombocytopenia;
- Persons with acute or exacerbation of chronic diseases of the gastrointestinal tract associated with the risk of bleeding, acute infectious diseases, pathologies of the respiratory system;
- Proven case of primary immunodeficiency;
- Secondary immune thrombocytopenia;
- Virus infections (Epstein-Barr, Cytomegalovirus, Parvovirus, Hepatitis B and C);
- Documented HIV infection
- Positive RW test result;
- Systemic immunopathological diseases (rheumatic diseases, nephritis, etc.);
- Oncological diseases;
- Diabetes mellitus;
- Thyroid diseases;
- History of mental illness;
- Known drug addiction;
- Any other concomitant decompensated diseases or acute conditions, the presence of which, according to the researcher, may significantly affect the results of the study;
- The need to prescribe drugs that are incompatible with the administration of the drug in this study: other immunoglobulin preparations in addition to the study drug, cytostatic drugs, monoclonal antibodies, avatrombopag);
- Experimental treatment (e.g. Rituximab therapy) for 3 months prior to screening);
- Blood transfusions or transfusions of blood products in the last 6 months prior to inclusion in the study;
- Administration of IVIG 30 days prior to screening;
- Participation in any other study currently or within the last 30 days;

Criteria for exclusion of subjects (discontinuation of treatment with the study drug):

Any patient can leave the study at any time and under any conditions.

Patients may be excluded by the researcher from taking the study drug and from the study in the following circumstances:

- The desire of the patient
- Occurrence of severe and/or unexpected AE/AR in patient during the study, that require discontinuation of the drug;
- The need to prescribe drugs prohibited in this study.
- Significant deterioration of the patient's condition during the study period;
- Failure of the patient to adhere to the treatment regimen;
- Failure of the patient to follow the procedures established under the protocol;

Groups of patients

One single group that will receive the study drug, will be formed from patients who have been screened and meet the inclusion criteria, and do not fall under the non-inclusion (exclusion) criteria.

At the data analysis stage, it is possible to evaluate patients based on the detected covariates.

Duration of treatment

Each patient will receive the study drug at a dose of 0.8-1.0 g / kg intravenously once a day for 2 consecutive days, the course dose is 1.6-2.0 g / kg.

Test Product, Dose, Mode of Administration:

Name: Bioven

Active ingredient: Human normal immunoglobulin for intravenous administration;

1 ml of the drug contains immunologically active protein fraction of immunoglobulin G - 0.1 g;

Excipients: glycine (aminoacetic acid); water for injection.

Pharmacotherapeutic group. Human normal immunoglobulin for intravenous administration

Dosage form: solution for infusion

Dose schedule:

Patients included in the study will receive the drug Bioven, 10% solution for infusion according to the protocol for the use of IVIG in ITP treatment – at a dose of 0.8-1.0 g / kg once a day for 2 consecutive days, the course dose is 1.6-2.0 g / kg. Allowed repeat course at same dosage in period 14-28 days from first infusion, if required.

Bioven should be administered intravenously dropwise at the initial rate of 0.5-1.0 ml/kg of body weight/hour for 30 minutes. If no adverse reactions occur, the rate of administration may be gradually increased (it is recommended to increase by 0.5-1.5 ml/kg of body weight/hour every 10 min). According to the data from clinical studies the maximum rate of administration is 8.5 ml/kg of body weight/hour.

The study drug is administered only in hospital environment while observing the rules of aseptic. The solution should be of room temperature before use. Cloudy solutions and those containing sediment are not used. For the administration of the drug, it is necessary to use a separate infusion system.

When administering the drug, it is necessary to consider the information specified in the relevant sections of the instructions for medical use: administration details, special safety measures, contraindications, interaction with other medicinal products, etc.

Patients participating in this study may receive concomitant therapy, which is used for the treatment of comorbidities and life-threatening conditions.

It is allowed to use glucocorticoids in a stable dose for at least 2 weeks before starting treatment with the test drug. The need to increase the dose of corticosteroids during the study is considered as ineffective use of the study drug.

Duration of treatment:

The duration of treatment with the study drug for each patient is no less 2 days. The total period of stay in the study is 4 weeks.

Efficacy and safety endpoints:

Efficacy:

Primary efficacy endpoint:

Part (percent) of patients with response (R).
R is determined according to the following criteria:
- Patients with R: platelets count > $30x10^9$/L and at least a two-fold increase from the baseline count. This must be confirmed by at least 2 blood tests at least 7 days apart, and the absence of bleeding;

The primary efficacy variable is achievement of R during the study (yes/no).

Secondary efficacy endpoints:
Part (percent) of patients with a complete response (CR).
CR is determined according to the following criteria:
- Patients with CR: platelets count > 100 x 10^9/L, which is confirmed by 2 blood tests performed at least 7 days apart and the absence of bleeding;

Part (percent) of patients with no response (NR).
NR is determined according to the following criteria:
- Patients with NR: platelet count < 30 x 10^9/L or less than two-fold increase of baseline platelet count. This must be confirmed by at least 2 blood tests performed approximately 1 day apart, or the presence of bleeding;

Part (percent) of patients with loss of response (loss of R).
Loss R is determined according to the following criteria:
- Patients with loss R: a decrease platelet count < 30 x 10^9/L or less than two-fold increase of baseline platelet count, or the occurrence of bleeding. Platelet counts confirmed at least 2 blood tests performed approximately 1 day apart.

Part (percent) of patients with loss of complete response (loss of CR).
CR loss is determined according to the following criteria:
- Patients with loss of CR: decrease platelet count < 100 x 10^9/L, or the occurrence of bleeding. Platelet counts confirmed at least 2 blood tests performed approximately 1 day apart.

Time (in days) from treatment start to onset of a response (R);
Time (in days) from treatment start to onset of a complete response (CR);
Duration (in days) of response (R);
Duration (in days) of complete response (CR);

Secondary efficacy endpoints are transformed into corresponding efficacy variables.

Safety
- Frequency (percent) of adverse events
- Frequency (percent) of serious adverse events

Summary data on study design, procedures, and statistical analysis plan:
Study design:
Screening phase
The patient or their legal representative must sign an informed consent form.

After the informed consent form is signed, the screening tests are performed and the compliance with the inclusion / non-inclusion criteria is evaluated. The patient who passed the screening tests is enrolled in the study.[1]

Clinical phase
Patients enrolled in the study receive Bioven at a dose of:

- 0.8-1.0 g / kg intravenously once a day for 2 consecutive days, the course dose is 1.6-2.0 g / kg. Allowed repeat course at same dosage in period 14-28 days from first infusion, if required.

The CRF records the time of administration of the study drug, the occurrence of possible adverse events.
Prescribed therapy and diagnostic results are recorded in the CRF based on the primary documentation.
Data are entered into the CRF according to the patient management plan.

Follow-up phase and completion of the study
This stage lasts for 4 weeks after the last administration of the drug (possible repeat course is not considered).
In all patients, the platelet count will be determined 48 hours after the start of the first administration of the study drug, on the 7th (± 1 day), 14th (± 2 days), 21st (± 3 days), 28th (+ 1- 3 days) days after the start of therapy.
The results of the study are evaluated by endpoints.
Phase-by-phase breakdown and breakdown of visits are detailed in Section 6.4 “Tabulated schedule of events”. Information is entered into the CRF after each visit, according to the “Schedule of study events”.

The decision on any examinations and diagnostic procedures in routine clinical practice is made and controlled by professionals.
Blood sampling for platelet count is performed 6 times:

- at the screening phase;
- 48 (± 3) hours after the start of study drug administration;
- on the 7th (± 1) day from the start of study drug administration;
- on the 14th (± 2) day from the start of study drug administration;
- on the 21st (± 3) day from the start of study drug administration;
- on the 28th (+ 1-3) day from the start of study drug administration.

The time of each blood draw and the start time of drug administration should be recorded; during each administration of the drug, it is necessary to evaluate the physical data, such as heart rate, blood pressure, body temperature, respiratory rate, and the severity of hemorrhagic syndrome.
Patients' serum samples should be stored frozen at the temperature of -65 - -85 ° C (second aliquot) to ensure the possibility of performing repeat laboratory tests if necessary, in the future.
The study involves scheduled visits of patients to the doctor:
1st visit (Day -14 – Day -1) – the patients are screened, checked for compliance with the criteria of inclusion / non-inclusion (exclusion), enrolled in the study;
2nd visit (Day 0 - Day +1 – Day +2) – hospitalization, administration of the study drug for 2 days, physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine platelet count, manual platelet counts, Coombs test, Total IgG levels (g/l);

[1] Due to the variability in PLT levels in patients with chronic immune thrombocytopenia (wave-like), it is possible to re-screen or extend the duration of the screening stage, but only if the study subject meets all other specified inclusion criteria, does not have non-inclusion and exclusion criteria.

3rd visit (Day +7 ± 1 day) – physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine platelet count, manual platelet counts, Coombs test in case hemolysis was detected during the previous visit (according to the laboratory data);
4th visit (Day +14 ± 2 days) – physical examination, assessment of the status of the hemorrhagic syndrome, blood sampling to determine platelet count, manual platelet counts, Coombs test in case hemolysis was detected during the previous visit (according to the laboratory data).
If a decrease of platelets count < 30 x 10^9/L was recorded, then approximately a day after the visit, an additional blood test is performed with a platelet count.
This visit can be performed by telephone / video, provided that the patient's status can be adequately assessed and biomaterials for laboratory tests can be sampled in Local Laboratory or at the collection point of the or Central Laboratory designated by the Sponsor;
5th visit (Day +21 ± 3 days) – physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine platelet count, manual platelet counts, biochemical blood test, Coombs test in case hemolysis was detected during the previous visit (according to the laboratory data).
If a decrease of platelets count < 30 x 10^9/L was recorded, then approximately a day after the visit, an additional blood test is performed with a platelet count.
This visit can be performed by telephone / video, provided that the patient's status can be adequately assessed and biomaterials for laboratory tests can be sampled in Local Laboratory or at the collection point of the Central Laboratory designated by the Sponsor;
6th visit (Day +28 + 1-3 days) – physical examination, assessment of the status of the hemorrhagic syndrome, blood sampling to determine platelet count, manual platelet counts, biochemical blood test, Coombs test, Total IgG levels (g/l).
If a decrease of platelets count < 30 x 10^9/L was recorded, then approximately a day after the visit, an additional blood test is performed with a platelet count.
This is a face-to-face visit. Completion of the study.

Statistical analysis:

Populations for statistical analysis:
ITT (Intention-to-treat population) – all participants of the study who have taken the study drug at least once. The data obtained from this sample will be used for safety analysis.
PP (Per Protocol) – all patients who have met the requirements of the protocol. This population includes all patients who received the protocol-prescribed therapy in full, who completed all the prescribed visits and did not have significant deviations from the protocol. The data obtained from this sample will be used for analysis based on efficacy criteria.
Sample size calculation.
Statistical analysis of endpoints will be descriptive with testing of the null hypothesis (non-inferiority study).
In accordance with the EU recommendations on the clinical investigation of human normal immunoglobulin for intravenous administration *(Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94033/2007 rev. 4, 16 Dec 2021)* the obtained results will be compared with literature data.
Null hypothesis H0: $p–p0 \leq \delta$, where clinical efficacy p- is the part of patients who responded to therapy with BIOVEN 10%; p_0 – part of patients responding to therapy according to literature data; δ is the limit of the difference of parts without clinical significance. Alternative hypothesis H1: $p-p0 > \delta$
The non-inferiority assessment is performed according to the EMA guideline "Points to consider on switching between superiority and non-inferiority" CPMP/EWP/482/99, London, July 27, 2000, and the EMA guideline "ICH Topic E 9 Statistical Principles for Clinical Trials" CPMP/ICH/363/96.

To test the null hypothesis, a two-tailed test will be used, based on the principles of estimating a 95% confidence interval for the difference in proportions and comparing it with the lower limit of equivalence (at a significance level of α 5%). For non-inferiority research, the null hypothesis is rejected if the following conditions are met:

$$\sqrt{n}(p-p_0-\delta) / \hat{p}(1-\hat{p}) > z_{\alpha/2}$$

or

$$(p-p_0-\delta) / \sqrt{\left(\frac{p(1-p)}{n}+\frac{p0(1-p0)}{n0}\right)} > z_{\alpha/2}$$

The sample size n in a group when comparing proportions for a study with no less efficiency is calculated by the formula (Chow, S. C., Wang, H., & Shao, J. (2007). Sample size calculations in clinical research. Chapman and Hall/CRC .):

$$n=(Z_{a/2}+Z_{b/2})^2\times(p\times(1-p))/ (p-p_0-\delta)^2$$

According to the literature, the effectiveness of IVIG when used in patients with ITP ranges from 60-80% *[Anurag Singh, Günalp Uzun, Tamam Bakchoul / Primary Immune Thrombocytopenia: Novel Insights into Pathophysiology and Disease Management // J. Clin. Med. 2021, 10, 789. https://doi.org/10.3390/jcm10040789]. [Godeau B., Caulier M-T. Decuypere L. et al. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0´5 and 1 g/kg b.w. // British Journal of Hematology, 1999, 107, 716-719; Ruqayyah J. Almizraq, Donald R. Branch Efficacy and mechanism of intravenous immunoglobulin treatment for immune thrombocytopenia in adults // Ann Blood 2021;6:2 | http://dx.doi.org/10.21037/aob-20-87; Drew Provan, Roberto Stasi, Adrian C. Newland et al. International consensus report on the investigation and management of primary immune thrombocytopenia // Blood, 14. - Jan 2010, Vol. 115, Number 2]).* However, the most similar in performance evaluation standards and study design is the 2020 publication *[Parodi E, Russo G, Farruggia P, Notarangelo LD, Giraudo MT, Nardi M, et al. Management strategies for newly diagnosed immune thrombocytopenia in Italian AIEOP Centers: do we overtreat? Data from a multicenter, prospective cohort study. Blood transfusion. 2020;18(5):396.]*, which indicates the effectiveness of IVIG in the treatment of ITP – 78% (the drug administration scheme recommended by the EMA and this Protocol, the total number of patients in the group is 82). According to our data and data from the literature, immunoglobulin belongs to drugs with a highly variable efficacy of 20-25%. Therefore, we consider it expedient to set the limit of the difference in efficacy δ between the obtained and expected results for non-inferiority research at -25%.

Thus, for a significance level of 5% and a statistical power of 80%, the effectiveness of the comparison drug reaches 78%, the limit of the difference in fractions (difference in effectiveness) without clinical significance δ is -0.25. Then the calculation of the minimum sample size will look like this:

$$n = (1,96+1,28)2\times(0,78\times(1-0,78) / (0,78 - 0,78+0,25)^2 = 29$$

Taking into account the risk (20%) of dropping out of patients for various reasons, 36 patients will be included in the study.

Methods of statistical analysis that will be used:

Methods of descriptive statistics (for categorical variables – number and share in %, for quantitative variables – n, arithmetic mean, median, standard deviation, minimum and maximum), including plotting graphs and diagrams, interval estimation methods (plotting 95% confidence intervals for fractions and differences of fractions).

To assess the significance of the dynamics in the case of evaluating a parameter at two visits (before and after) in the case of quantitative variables, the Student's t test for paired data or Wilcoxon signed rank test will be applied depending on the results of checking the normality of the distribution of differences [after - before] using the Shapiro-Wilk test. To assess the dynamics of categorical variables, we will use the McNimar test or the test of homogeneity of

marginal frequencies depending on the number of categories. To evaluate the statistical significance of differences in categorical variables in unrelated groups, we will use Pearson's chi-squared test or Fisher's exact test (depending on the frequency distribution in Table 2 * 2).

To assess the dynamics in the case of measuring variables at more than two visits, methods of univariate variance analysis (Anova) will be used, followed by contrast analysis (simple contrasts) or a posteriori analysis using the Tukey's test. Covariance analysis (ANCOVA) will be used to compare the variables for which the data were inhomogeneous in the initial state. To check the prerequisites for applying variance and covariance analysis, the normality of the distribution of data and their balances will be checked using the Shapiro-Wilk test. If the balances are not distributed normally, or if the data does not pass the normality check, the corresponding rank analysis will be performed. For the Shapiro-Wilk test, the significance level will be 0.01, and for other criteria – 0.05. If the effect of multiple comparisons occurs, the significance level adjustment will be applied using the Holm method or the Benjamini–Hochberg procedure.

Working with missing or incomplete data

Missed or incomplete data will be replaced using the Last-Observation-Carried-Forward (LOCF) method, or the method of enlarging intervals for series where the transfer of the last measurement is not applicable.

Conclusion on efficacy

In accordance with the EMA recommendations on the clinical investigation of human normal immunoglobulin for intravenous administration (*Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94033/2007 rev. 4, 16 Dec 2021*) the obtained results will be compared with literature data The conclusion of non-inferiority of the drug Bioven, solution for infusions 10%, in the treatment of chronic immune thrombocytopenia, will be made according to the main efficacy variable using an approach based on confidence intervals.

To do this, the calculated limits of the 95% confidence interval (CI) for the difference in the percentage of positive results according to the main variable ("the drug is effective") for the studied group must be compared with the limit of the non-inferiority zone - effectiveness that is not inferior (-25%) to the calculated based on data for comparison. If the lower limit of the CI is greater than the lower limit of the non-inferiority zone (non-inferiority), then it will be considered that the study drug is not inferior in effectiveness compared to literature data. A detailed description of statistical analysis is provided in the corresponding section of this Protocol.

Examination methods:

Examination methods are performed according to the schedule of events provided in the relevant section of the Protocol of this clinical trial.

- Collection and recording of demographic data;
- Collection and recording of medical history;
- Verification of ITP diagnosis (according to primary documentation);
- Recording information about previous ITP therapy (dose/schedule, duration, response (if any), and time interval since the last administration);
- Recording information about symptomatic therapy and medication intake for the treatment of concomitant diseases;
- Transfusion history;
- History of allergies;
- Determination of body weight;
- Objective physical examination with mandatory assessment of the severity of hemorrhagic syndrome;

- Measurement of vital signs (blood pressure, heart rate, respiratory rate, body temperature); - Biomaterials sampling for laboratory tests is carried out at collection points or by mobile team of the Central Laboratory designated by the Sponsor: - Blood test for HIV and RW, PCR EBV, CMV; - Pregnancy test (for women of reproductive age) - Complete blood count (erythrocytes, reticulocytes, hemoglobin, hematocrit, white blood cells + expanded leukogram, platelets with manual counting; - Biochemical blood test (ALT, AST, creatinine, urea, glucose, total bilirubin); - Coombs test (antiglobulin test) - Determination of total IgG g / l in blood serum; - Urinalysis (specific gravity, pH, protein, glucose; sediment microscopy – white blood cells, red blood cells, cylinders, salts); - Coagulogram (PTI, APTT, fibrinogen) - Hepatitis B and C markers (Hbs-Ag, HCV); - Antinuclear antibodies (ANA); - 12-lead ECG;
Blinding, randomization: The study will be open, non-blinded

1. GENERAL INFORMATION

Protocol name, protocol identification number and date:

Name: Open, multicenter, international study to evaluate the efficacy, safety, and tolerability of Bioven, manufactured by Biopharma Plasma LLC, in adult patients with chronic primary immune thrombocytopenia (ITP).

Protocol identification number: 2021-BV-ITP-BP

Version: 1.4

Date: from July 03, 2023

Name and address of the sponsor and monitor (if different):
Sponsor of the study:

Name of organization:	LLC “BIOPHARMA PLASMA”
Address:	37-V, Kyivska St, Bila Tserkva, Kyiv region 09100,Ukraine
Phone:	+380 (44) 277-36-10
e-mail:	info@biopharma.ua

Contract Research Organization:

Name of organization:	MonitorCRO Monitor Medical Research and Consulting Trade LLC
Address:	Kumhuriyet Mahallesi, 2 Yeniol St., Beaumonti Plaza, 7th Floor, Office 58, 34380 Shishli/Istanbul
Phone:	+90 212 234 12 60
e-mail:	info@monitorcro.com

Name and position of persons authorized on behalf of the sponsor to sign the protocol and amendments to the protocol:

Name:	Matsybokh Sofiia
Position:	Clinical trial lead
Name of organization:	LLC “BIOPHARMA PLASMA”
Address:	Kyiv, Amurska street, 6
Phone:	+38(067) 249 68 69
e-mail:	s.matsybokh@biopharma.ua

Name, position, address, and telephone number of the sponsor-designated medical expert for this study:

Expert's name:	Svitlana Donska
Expert position:	Medical advisor
Name of organization:	LLC “BIOPHARMA PLASMA”
Address:	Kyiv, Amurska street, 6
Phone:	+38(050) 545 98 51
e-mail:	s.donska@biopharma.ua

Name and position of researchers responsible for the study, as well as addresses and telephone numbers of clinical centers:

Researcher's name:	Yermolytska Iryna Pavlivna
Researcher position:	Head of the hematology department
Name of organization:	Municipal Non-Profit Enterprise "Kirovohrad Regional Hospital of the Kirovohrad Regional Council"
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Researcher's name:	Masliak Zvenyslava Volodymyrivna
Researcher position:	Head of the hematology department
Name of organization:	State Institution "Institute of Blood Pathology and Transfusion Medicine of the National Academy of Medical Sciences of Ukraine"
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2. JUSTIFICATION OF THE STUDY

2.1 Introduction

Primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 10^9 /L, and the absence of any underlying cause. Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but due to the current knowledge of the immune mediated mechanism of the disease, and the absence or minimal signs of bleeding in most cases have led to a revision of the terminology.

In Europe, adult ITP has an incidence of 1.6 to 3.9 cases per 100,000 per year with increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes. [1]

ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (≥ 12 months' duration). Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months. [1]

Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, whereas others experience serious bleeding, which may include gastrointestinal hemorrhage (GI), extensive skin and mucosal hemorrhage, or intracranial hemorrhage (ICH). The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk. Additional factors (eg, age, lifestyle factors, concomitant medications, congenital or acquired coagulation disorders) affect the risk and should be evaluated before the appropriate management is determined.Although death from bleeding is a serious problem, it has been reported that the estimated incidence of fatal bleeding ranges from 0.02 to 0.04 cases per adult patient-year risk.

The diagnosis of ITP is an exclusion diagnosis when the history, physical examination, complete blood count, and examination of the peripheral blood smear do not suggest other etiologies for the thrombocytopenia [2]. Physical examination should be normal aside from bleeding manifestations. The isolated thrombocytopenia with normal indicators of red blood cells and white blood cells are defined in the complete blood count. Anemia caused by significant blood loss may be present but it should be proportional to the amount of bleeding and may result in iron deficiency. The normal or big size of platelets may indicate in a peripheral blood smear, in the same time there should be no deviations in morphology of red blood cells and white blood cells. Currently, bone marrow examination is usually not performed in patients with typical manifestations of ITP, but it can be conducted only in some cases, such as atypical manifestations.

The main goal of ITP treatment is to provide a platelet count that can prevent massive bleeding, rather than adjusting the platelet count to normal. Treatment of ITP should be selected individually for each patient and it is rarely indicated in patients with platelet counts above 50 × 10^9/L in the absence of bleeding, trauma, surgery or high-risk factors (persons who receive anticoagulation therapy). The threshold value of the number of platelets required for the diagnosis of ITP is 100 x 10^9/L [2]. In some patients the disease may be asymptomatic, in others - manifested by hemorrhagic syndrome with different severity. It is known that at the level of platelets 30-50 x 10^9/L due to minor trauma excessive ecchymoses occur and at the level of platelets 10-30x10^9/L - spontaneous ecchymoses occur. Severe hemorrhagic syndrome occurs at a platelet count ≤ 10 x 10^9/L. [3].

The management of ITP varies widely and current international guidelines recommend several first- and second-line options, including some medicinal products that have not been approved in the EU for this particular condition.

First line treatment options include corticosteroids, intravenous immunoglobulin (IV Ig) and intravenous anti-D immunoglobulin (the latter only for non-splenectomised Rhesus-D positive patients). Patients who fail to respond or who relapse face the options of treatment with second line drug therapy or splenectomy but there is no clear evidence to support the best approach. Splenectomy can provide long term efficacy in around 60% of cases. Second line drug therapies include high dose corticosteroids, high dose IV Ig or anti-D Ig, vinca alkaloids and danazol, the immunosuppressants cyclophosphamide, azathioprine and cyclosporine or mycophenolate mofetil, and the anti-CD-20 monoclonal antibody [4].

IVIg have been used in the treatment of ITP since 1981, after the publication of P. Imbach et al., Which proved the high effectiveness of IV Ig in the treatment of ITP in children. [5].

The therapeutic effects of IV Ig in ITP include:

- blockade of neonatal Fc receptors on the surface of endothelial cells and acceleration of catabolism of the whole pool of plasma immunoglobulins, including antiplatelet antibodies;
- inhibition of FcγRIIIa- receptors and phagocytosis mediated by them;
- suppression of the expansion of autoreactive lymphocytes by signal transduction through FcγRIIIa;
- idiotype-mediated inhibition of B-cell receptors and neutralization of cytokines-survival factors: B-cell activation factor (BAFF) and proliferation-promoting ligand (APRIL) [6,7,8]. The binding of anti-idiotypic antibodies (BP) to membrane-bound Ig G or Ig M B-lymphocytes can transmit inhibitory signals and reduce the production of pathogenic auto-BP [9];
- utilization of active components of complement [10].

In addition, IV Ig drugs cause immune tolerance by modulating subpopulations of T-lymphocytes, namely T-reg- increasing their number and changing the quality of the composition [11].

It is likely that the effect of Ig G therapy in time exceeds the half-life of IV Ig [12].

Immunoglobulin drugs for intravenous administration are not generic drugs and cannot not be interchangeable [15,16].

Clinical studies on the efficacy of intravenous immunoglobulin Bioven 10% solution for infusion in immune thrombocytopenia have not been performed.

2.2 Name and description of the investigational drug.

Composition:
active substance: Human normal immunoglobulin for intravenous administration;
1 ml of the drug contains 0.1 g of normal human immunoglobulin;
excipients: glycine (aminoacetic acid), water for injections.
Pharmaceutical form. Solution for infusion.
General physical and chemical properties: transparent or slightly opalescent, colorless liquid or liquid with slightly yellowish color.
Pharmacotherapeutic group. Human normal immunoglobulin for intravenous administration. Code ATC J06B A02.
Pharmacological properties.
Pharmacodynamics properties.
The product is an immunologically active protein fraction (ratio of immunoglobulin G subclasses in the drug product: IgG1: 65.6 %, IgG2: 22.1 %, IgG3: 10.8 %, IgG4: 1.5 %) max. content of immunoglobulin A in the drug product is 50 μg/ml.

Active components of the product are antibodies that have a specific activity against different pathogenic agents such as viruses and bacteria including hepatitis A and B, cytomegalovirus, human herpes virus type 1, type 2 and type 6, Epstein-Barr virus, chicken pox, influenza, measles, parotitis, poliomyelitis, German measles, whooping cough, staphylococcus, Escherichia coli, pneumococcus, tetanus and diphtheria toxins. It also has a non-specific activity to increase organism resistance.
The drug product has a low spontaneous anticomplementary activity.
The drug product is a native immunoglobulin G and retains all biological properties: complement activation; effector and opsonocytophagic function.
The product is an immunologically active protein fraction extracted from human blood serum or plasma and screened negative for antibodies to HIV-1, HIV-2, hepatitis C virus and surface antigen of hepatitis B virus, purified and concentrated by use of the fractionation method with water-alcohol precipitating agent that passed the phase of virus inactivation by use of solvent-detergent method and nanofiltration method.
Clinical studies
In an open-label international multicenter phase III study, according to the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) 28 June 2018 EMA/CHMP/BPWP/94033/2007 rev.3 Committee for Medicinal Products for Human Use (CHMP) the efficacy, safety and some parameters of the pharmacokinetics of Bioven were studied in patients with primary immunodeficiency (PID). Patients received Bioven for 1 year once during every 4 weeks at an average dose of 0.5 g / kg body weight. Patients were evaluated for immunoglobulin levels, the number of cases of infections, clinical and biochemical blood tests. The most important indicators of heart function, respiration, body temperature were determined, and all cases of possible adverse reactions were recorded.
During 1 year of treatment, one case of serious infectious diseases was recorded (2.3%, or 0.023 cases per 1 patient per year). The median minimum concentration of immunoglobulin in blood plasma was significantly higher than the minimum target level of 5 g/l and after 6 months of treatment was 8.6 g/l, and after 1 year - 8.8 g/l.
In the group of 49 patients receiving Bioven, 20 cases of mild (2%) and moderate (0.5%) adverse events were reported, representing a total of 2.5% of episodes of administration. There were no cases of clinically significant abnormalities in laboratory tests that were associated with drug administration or required discontinuation of treatment. In 18 patients (adults and children), Bioven was administered at increasing infusion rates. At the first stage of the study, the rate of administration was increased to 5.0 ml/kg/h (0.08 ml/kg/min); in the second stage - up to 7.0 ml/kg/h (0.11 ml/kg/min). The maximum rate of administration in the third stage was 8.5 ml/kg/h (0.14 ml/kg/min). The incidence of adverse events was low (2 cases per 35 separate injections), they were mild in nature and did not correlate with the infusion rate. Based on the prevalence of side effects and assessment of the dynamics of the main vital signs, the tolerability of Bioven at a maximum rate of 8.5 ml/kg/h (0.14 ml / kg / min) in 94.0% of patients was assessed as good, in 6.0% - as satisfactory.
The clinical efficacy of Bioven in the complex therapy of patients with severe pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2 is provided by its ability to have an immunomodulatory effect. As a result, the severity of acute respiratory distress syndrome is reduced and, consequently, the degree of respiratory failure is reduced.
The clinical efficacy was confirmed in the clinical study "Open multicenter randomized study of the effectiveness of Bioven, manufactured by Biopharma Plasma, evaluation in the treatment of patients with pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2" (code research - 2020-BV-BP).

The study involved 76 patients with a confirmed diagnosis by all criteria. 66 patients who were screened and did not have exclusion criteria were randomized into 2 groups (study group - Bioven + basic therapy and control group - only basic therapy).
Patients were determined by the indicators of the respiratory system, general condition, duration of the need for intensive care, the need for artificial lung ventilation (ALV), the total duration of treatment. Survival during the 28-day follow-up period, laboratory blood counts (general analysis and biochemical), as well as cytokine levels, inflammatory factors and other indicators of the immune system were also assessed.
The results of the study proved the predominant efficiency of the main variable.
Improvement occured significantly faster: in the study group - on day 5 (interquartile range - 3.50-7.25 days), in the control group - on day 9 (interquartile interval - 6.00-14.75 days), p = 0, 0073.
The probability of achieving stabilization in patients of the study group was significantly higher by 2.27 times (95% confidence interval (CI) - 1.26-4.11, p = 0.006) than in patients from the control group.
The predominant efficiency is also confirmed by secondary variables. The mortality from COVID-19 was significantly lower, when Bioven was used: 6.25% in the study group (2 cases out of 32 participants), and 23.63% in the control group (8 cases out of 34 participants), p = 0.039.
The duration of lymphopenia was also significantly reduced. The median time to achieve the level of lymphocytes 1000 cells/mm3 and above in the study group was 4 days (interquartile range - 3.00-5.00 days), in the control group - 7 days (interquartile range - 3.00-7.50 days), p = 0.0097.
Pharmacokinetics properties.
The high level of efficacy of the Bioven product is provided by a fast and 100% entrance of antibodies into bloodstream as well as by normal elimination half-life.

After intravenous administration the bioavailability of the normal human immunoglobulin in the circulating blood is immediate and complete. It is rapidly distributed between the plasma and extravascular liquid, and the balance between intra- and extravascular compartments is reached in approximately 3-5 days.

For normal human immunoglobulin the half-life is approximately 40 days. This half-life period can differ from patient to patient, especially in case of primary immunodeficiency. IgG and IgG-complexes degrade in reticuloendothelial system cells.

A clinical study of individual pharmacokinetic parameters of Bioven was performed and involved 22 patients. Cmax was 19.94 ± 4.73 g/l, Tmax – 0,63 hours, AUC(0-t) – 8309.60 ± 2631.49 g/year /l. The content of immunoglobulin in blood plasma was consistently kept above the minimum target level of 5 g/l for at least 28 days after a single administration of Bioven.

Clinical particulars.
Therapeutic indications.
The product should be used for adults, children and adolescents for replacement immunotherapy in the treatment of primary and secondary immunodeficiency and related diseases:
- primary immunodeficiency syndromes: congenital agammaglobulinemia, hypogammaglobulinemia, severe combined immunodeficiency, unclassified variable immunodeficiency, Wiskott — Aldrich syndrome;- secondary antibody deficiency syndrome: cytopenia of different genesis (acute and chronic leukemia, aplastic anemia, situation after cytostatic therapy), severe bacterial and toxic and viral infections (including surgical complications accompanying by bacteremia and septicopyemic conditions and for preparation of surgical patients for operation);

- autoimmune diseases: idiopathic thrombocytopenic purpura with a high risk of bleeding or prior to surgical intervention to correct platelet level, Guillain— Barre syndrome, chronic inflammatory neuropathy (demyelinating), inflammatory myopathy, Wegener's granulomatosis, dermatomyositis, systemic diseases of connective tissue (rheumatoid arthritis etc.), Kawasaki disease;
- bone marrow transplantation.

Replacement therapy in adults, children, and adolescents (0 - 18 years) in:
- syndromes of primary immunodeficiency (PID) deficiency of antibodies' production;
- secondary immunodeficiency (SID) in patients who suffers from severe or recurrent infections, ineffective antimicrobial treatments and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g / L.

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Use as part of the complex therapy of adult patients with severe pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2

2.3 Summary of clinical trial results

Table 1

1	2
Study name	Clinical study report «Open multicenter randomized study to evaluate the effectiveness of Bioven, manufactured by LLC "Biopharma Plasma", in the complex therapy of patients with pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2»
Year	2020
Clinical center	Communal non-commercial enterprise "Kyiv City Clinical Hospital No.17". Department of Anesthesiology and Intensive Care. Communal non-commercial enterprise of Bila Tserkva City Council "Bila Tserkva City Hospital No.3", III Infectious Diseases Department. Communal non-commercial enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital for Infectious Diseases", Department of Resuscitation and Intensive Care Communal non-commercial enterprise "City Clinical Hospital for Infectious Diseases" of Odessa City Council, infectious boxing department No.10. Communal non-commercial enterprise "Kyiv City Clinical Hospital No.4" of the executive body of the Kyiv City Council (Kyiv City State Administration), Department of Anesthesiology and Intensive Care of Infectious Patients. Vinnytsia National Pirogov Memorial Medical University, Department of Infectious Diseases with a course in epidemiology, Vinnytsia National Pirogov Memorial Medical University on the basis of the infectious department of the communal non-commercial enterprise "Vinnytsia City Clinical Hospital No.1". Communal non-commercial enterprise "Ternopil City Municipal Ambulance Hospital", Infectious Diseases Department. Communal non-commercial enterprise "Central City Clinical Hospital of Ivano-Frankivsk City Council", therapeutic department No.1. Communal enterprise "Volyn Regional Clinical Hospital" of the Volyn Regional Council, Department of Pulmonology.
Type	Efficacy and safety
Identifier	2020-BV-BP
Design and type of control	Open, multicenter, randomized, controlled, in parallel groups
Investigated drug: -dose; -regime; -way of administration	 0.8-1.0 g/kg 1 time per day; for 2 days i.v. drip, 1 ml / min
Number of subjects	76
Healthy / diagnoses of the patients	Severe pneumonia, according to the criteria (Appendix 10 to the "Standards of medical care "CORONAVIRUS DISEASE (COVID-19)", approved by the Order of the Ministry of Health of Ukraine from 28.03.2020 № 722 "Organization of medical care for patients with coronavirus disease (COVID-19)")
Duration of treatment	Shortterm (2 days)
Study status and report type	Finished. Full.
Results	General Conclusion: 1) The predominant efficacy by the main variable in the inclusion of BIOVEN in the complex scheme of treatment of patients with pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2 has been proven. The median of achievement of

	normalization in the study group – 5 days (interquartile range – 3.50-7.25 days), in the control group – 9 days (interquartile range – 6.00-14.75 days), (p = 0.0073). The probability of achieving stabilization in patients of the study group is significantly 2.27 times higher (95% CI – 1.26-4.11), (p = 0.006) than in patients from the control group. 2) The predominant efficacy is also confirmed by secondary variables. When using Bioven treatment regimen, mortality from COVID-19 is significantly lower: in the study group – 6.25% (2 cases out of 32 participants) in the control group – 23.63% (8 cases out of 34 participants), (p = 0.039). The duration of lymphopenia is also significantly reduced. The median of achievement of the level of lymphocytes 1000 cells/mm3 and above in the study group – 4 days (interquartile range – 3.00-5.00 days), in the control group – 7 days (interquartile range – 3.00-7.50 days), (p = 0.0097). 3) For all safety variables the drug BIOVEN has shown a high safety profile when used in the complex therapy of patients with pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2. Bioven was well tolerated by patients, adverse effects and significant deviations of laboratory parameters associated with administration in the study were not recorded. There were no serious adverse effects associated with the drug. Thus, the superior efficacy and high safety of the drug BIOVEN in the complex therapy of patients with pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2 was confirmed. The drug can be used for the treatment and prevention of complications in patients with COVID-19 / SARS-CoV-2 (course dose – 1.6-2.0 g/kg body weight).

Table 2

1	2
Study name	Open, international, multicenter study to evaluate the efficacy, safety, tolerability and some parameters of the pharmacokinetics of the drug Bioven, solution for infusion 10% manufactured by LLC “Biopharma Plasma”, in patients with primary immunodeficiency.
Year	2017-2020
Clinical center	Department of Clinical Immunology, Danylo Halytsky Medical University, Regional Clinical Hospital, Lviv, Ukraine. Western Ukrainian Center for Pediatric Immunology, Lviv, Ukraine Department of Pediatric Infectious Diseases and Pediatric Immunology Shupyk National Healthcare University of Ukraine, Kyiv city children clinical hospital № 1, Kyiv, Ukraine. State Institution "Republican Scientific and Practical Center for Radiation Medicine and Human Ecology", Gomel, Republic of Belarus.
Type	Efficacy Safety Pharmacokinetics
Identifier	1601-BV-BF
Design and type of control	Open, multicenter, non-comparative, uncontrolled, prospective
Investigated drug: -dose; -regime; -way of administration	 0.2–0.8 (average 0.5) g / kg of body weight 1 time per 3-4 weeks for 52 weeks (14 infusions in total) i.v. drip, up to 8.5 ml / min
Number of subjects	54
Healthy / diagnoses of the patients	Humoral and combined primary immunodeficiencies
Duration of treatment	52 weeks (14 infusions in total)
Study status and report type	Finished. Full.
Results	Patients were evaluated for immunoglobulin levels, the number of cases of infections, clinical and biochemical blood tests. The most important indicators of heart function, respiration, body temperature were determined, and all cases of possible adverse reactions were recorded.

	During 1 year of treatment, one case of serious infectious diseases was recorded (2.3%, or 0.023 cases per 1 patient per year). The median minimum concentration of immunoglobulin in blood plasma was significantly higher than the minimum target level of 5 g/l and after 6 months of treatment was 8.6 g/l, and after 1 year - 8.8 g/l. In the group of 53 patients receiving Bioven, 20 cases of mild (2%) and moderate (0.5%) adverse events were reported, representing a total of 2.5% of episodes of administration. There were no cases of clinically significant abnormalities in laboratory tests that were associated with drug administration or required discontinuation of treatment. In 18 patients (adults and children), Bioven was administered at increasing infusion rates. At the first stage of the study, the rate of administration increased to 5.0 ml/kg/h (0.08 ml/kg/min); in the second stage - up to 7.0 ml/kg/h (0.11 ml/kg/min). The maximum rate of administration in the third stage was 8.5 ml/kg/h (0.14 ml/kg/min). The incidence of adverse events was low (2 cases per 35 separate injections), they were mild in nature, did not correlate with the infusion rate. Based on the prevalence of side effects and assessment of the dynamics of the main vital signs, the tolerability of Bioven at a maximum rate of 8.5 ml/kg/h (0.14 ml/kg/min) in 94.0% of patients was assessed as good, in 6.0% - as satisfactory. The study of individual pharmacokinetic parameters of the drug Bioven was performed in a group of 23 patients. Cmax was 19.94 ± 4.73 g/l, Tmax was 0.63 hours, AUC (0-t) was 8309.60 ± 2631.49 g/h/l. The content of immunoglobulin in blood plasma was consistently kept above the minimum target level of 5 g/l for at least 28 days after a single injection of Bioven.

Table 3

1	2
Study name	Clinical study report "Evaluation of the effectiveness and tolerability of Bioven, 10% solution for infusion manufactured by PJSC" Biopharma "in comparison with Octagam®, solution for infusion manufactured by" Octafarma Pharmaxeuticaka Produktins "in patients with severe influenza complicated by pneumonia ».
Year	2011
Clinical center	Department of Infectious Diseases, Dnipropetrovsk National Medical Academy
Type	Effectiveness and tolerability
Identifier	1009 BF/BV/sol/DSMA
Design and type of control	Parallel, randomized, active control
Investigated drug: -dose; -regime; -way of administration	 0.4 g / kg / day; once; i.v. drip, 1 ml / min
Number of subjects	60
Healthy / diagnoses of the patients	Influenza: severe, complicated by pneumonia (J11.0)
Duration of treatment	Short term (4 days)
Study status and report type	Finished. Full.
Results	In the process of the clinical study, the dynamics of clinical indicators of pneumonia and data from bacteriological examination of sputum was studied to assess the effectiveness of the investigated and reference drugs. In parallel, the tolerability of drugs was assessed taking into account the frequency of occurrence and the nature of adverse reactions. The following results were obtained: 1. The Bioven, has shown high efficacy during prescribing in combination with antimicrobial agents in the treatment of patients with severe influenza complicated by pneumonia. The effectiveness of the treatment was 96.67%, which did not significantly differ from corresponding value in the control group.

	2. The use of the Bioven contributed to the rapid reduction of clinical manifestations of pneumonia, normalization of laboratory blood parameters, normalization of basic immunological parameters that characterise the state of cellular immunity. There were no significant differences in the rate and degree of reduction of the main symptoms of the disease with the control group receiving the comparison drug Octagam ®, a solution for infusion manufactured by Octapharma Pharmazeutika Produktions. 3. The occurrence of adverse reactions and side effects, adverse changes in laboratory parameters of blood and urine, objective observation data was not observed during the use of the investigated product. The investigated product Bioven showed good tolerability in 100% of subjects. 4. The data of the conducted study allow us to conclude that the studied drug Bioven, 10% solution for infusions manufactured by PJSC "Biopharma" is therapeutically equivalent to the comparison drug Octagam®, solution for infusions manufactured by Octapharma Pharmazeutika Produktions in terms of overall effectiveness.

2.4 A brief description of the known and anticipated risks and benefits (if any) for the subjects

Contraindications.

Hypersensitivity to any component of the drug. Hypersensitivity to homological immunoglobulins, especially in very rare cases of IgA deficiency when patient develops antibodies to IgA. Immunoglobulin administration is contraindicated for persons who have in their history any severe allergic reactions caused by human blood protein products administration. Patients with allergic diseases or predisposed to allergic reactions are recommended to use antihistamines during immunoglobulin administration and for the next 8 days. For persons with immunopathological systemic diseases (blood immune diseases, collagenosis, nephritis etc) the product should be prescribed after consultation with a specialist. During periods of allergic processes exacerbation, administration of the product should take place only after medical assessment by an allergist in accordance with life-saving indications.

Special warnings and precautions for use.

Some serious adverse reactions may be caused to the rate of product administration. Patients who receive immunoglobin for the first time usually experience a slight adverse reaction more frequently than those who receive immunoglobulin therapy regularly. The parameters of administration rate mentioned below should be followed and patients should be closely monitored both during infusion and for 1 hour after completion of the first infusion. In case of any adverse reactions infusion rate should be reduced or infusion itself should be stopped until undesirable symptoms disappear. If after administration stopping symptoms persist then symptomatic therapy is reasonable. In case of shock, appropriate anti-shock therapy should be initiated. The level of creatinine should be measured in patients with diabetes mellitus and with a risk of renal failure as well as in patients with systemic lupus erythematosus with kidney involvement for 3 days after administration of the product. During following infusions patients should be thoroughly monitored for 20 minutes from the moment of product administration completion.

BIOVEN should only be used in a clinical setting of hospital and in compliance with aseptic requirements. Before administration vials should be kept at a temperature of (20±2) °C for at least 2 hours. Solution must be transparent or slightly opalescent, colorless or of slightly yellowish color. Do not use if solution is cloudy or contains precipitate. A separate infusion system should be used for administration of the product. Special warnings and precautions for use.

Відформатовано: Відступ: Перший рядок: 0,5 см

Interference with serological testing

After immunoglobulin injection a temporary increase of different antibodies blood level that are passively transferred can result in false positive results of serologic analyses.

Passive transfer of antibodies to red blood cells antigens, for example, A, B or D can have an impact on some serologic tests for determination of alloantibodies to red blood cells (for example, Coombs test), reticulocyte count and haptoglobin.

Particular of use.

Precautions for product administration

Some severe adverse reactions may relate to product infusion rate. The recommendations on infusion rate should be followed strictly. A patient condition should be monitored closely and special attention to occurrence of any symptoms during the whole period of infusion should be paid.

Some adverse reactions can occur more often:

-in the case of a high infusion rate;

-in patients who receive normal human immunoglobulin for the first time or in rare cases of change to normal human immunoglobulin or when a long period of time has passed from the moment of the previous infusion.

Any potential complications can be prevented if it is ensured that:

-a patient is not sensitive to human normal immunoglobulin during the first slow infusion of the product;

-a patient is closely monitored for occurrence of any symptoms during the whole period of infusion. To identify signs of a potential negative impact during the first infusion and during the first hour after infusion it is essential to monitor condition of a patient who have not previously received immunoglobulin products, who received therapy using alternative products or after a long period of time has elapsed since the last immunoglobulin administration. Such patients require monitoring during the whole period of the first infusion as well as for 1 hour after administration is completed. All other patients should be monitored for the first 20 minutes after administration.

In case of any adverse reaction in is necessary to either decrease infusion rate or stop infusion. Treatment required depends on the nature and severity of adverse reaction. In case of a shock measures should be taken in accordance with approved recommendations on anti-shock therapy.

For all patients in case of IgG administration it is necessary to:

-perform an adequate hydration before starting IgG infusion;

-monitor diuresis;

-monitor blood serum creatinine level;

-avoid a concomitant use of loop diuretics.

Hypersensitivity

Some serious allergic reactions can occur. Because of this, persons who have received the product must be monitored for 30 minutes. In case of occurrence of such reactions administration of Bioven product through infusion should be immediately stopped and appropriate therapy should be assigned. In patients with deficiency of immunoglobulin A and antibodies to immunoglobulin A there is a significant risk of development of some serious allergic and anaphylactic reactions that can occur in connection with BIOVEN product administration.

In rare cases human normal immunoglobulin can cause a decrease in arterial pressure with an anaphylactic reaction even in the patients who have previously received human normal immunoglobulin.

Renal failure

Some cases of renal failure were reported in patients who received IgG therapy. They include acute renal failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis. In most cases such risk factors were identified as preliminary existing renal failure, diabetes mellitus, hypovolemia, excess body weight, concomitant use of nephrotoxic drug products, age 65 years or older, sepsis or paraproteinemia.

The reports about renal dysfunction and acute renal failure were associated with use of many licensed IgG products containing different excipients, such as sucrose, glucose and maltose Particularly large number of the total number of such reports were connected to medicines that were containing sucrose as stabilizer. In patients with increased risk IgG products that do not contain excipients mentioned above may be considered.

Before start of BIOVEN product infusion it should be ensured that a patient does not have signs of dehydration.

For the patients with a potential risk of acute renal failure a regular monitoring of renal function and diuresis should be performed. Renal function parameters including blood urea nitrogen

(BUN)/ blood serum creatinine should be assessed before starting the first administration of the BIOVEN product and with regular intervals thereafter. In case of the renal function deterioration administration of the product should be stopped.

For patients with a potential risk of renal function impairment and/or thrombotic complications development amount of BIOVEN administered per unit time should be carefully reduced.

Hyperproteinemia.

Hyperproteinemia, increased blood serum viscosity and hyponatremia can occur in patients who receive therapy with immunoglobulin. Hyponatremia may appear to be a pseudohyponatremia that can manifest itself as a decreased calculated osmolarity of plasma and as an increase of osmolarity interval. It is clinically important to distinguish actual hyponatremia from pseudohyponatremia as in case of decrease of free water in blood serum target treatment of patients with pseudo hyponatremia can cause dehydration, and because of this blood serum viscosity may increase and thromboembolic complications can occur.

Thromboembolic complications

Thrombosis can occur as a result of therapy with immunoglobulin products. Risk factors: obesity, history of atherosclerosis, cardiac output impairment, arterial hypertension, diabetes mellitus with history of vessel diseases and cases of thrombosis, patients with acquired and hereditary thrombophilia, patients with severe hypovolemia, patients with diseases that increase blood viscosity, old age, long-time immobilization, hypercoagulation states, history of venous or arterial thrombosis, use of estrogens, central indwelling catheters, increased blood viscosity and risk of cardiovascular diseases. Thrombosis can occur even in cases where the known risk factors are absent.

An overall assessment of blood viscosity should be performed for patients with risk of increased viscosity, which is connected with cryoglobulins, starvation chylomicronemia/evidently high level of triglycerides or monoclonal gammopathy. For patients with risk of thrombosis minimal doses of immunoglobulin products are used along with a minimal rate of infusion. Before using the product, it should be ensured that a patient has an adequate level of hydration. Monitoring of thrombosis symptoms and assessment of blood viscosity should be performed for patients with a risk of increased viscosity.

Aseptic meningitis syndrome

As reported aseptic meningitis syndrome (AMS) can rarely occur in connection with administration of immunoglobulin products. Discontinuation of therapy with these products leads to remission of AMS without complications in few days. This syndrome usually occurs during the period from several hours to two days after using immunoglobulin products and their rapid administration. It is characterized by symptoms that include severe headache, rigidity of occipital muscles, somnolence, fever, photophobia, sensation of pain with eye movement, vomiting and nausea. Results of cerebrospinal fluid (CSF) analysis often reveal pleocytosis with few thousands of cells per mm3 predominantly of granulocytic lineage, and an increase of protein level up to few hundred mg/dl. Patients with such symptoms should undergo neurological examination including a CSF analysis to exclude other causes of meningitis. Patients who have a history of migraine are more disposed to it. Meningitis aseptic syndrome can occur more often in case of treatment with high doses IgG.

Hemolysis

Immunoglobulin products can contain blood group antibodies that can act as hemolysins and assist in vivo in covering of red blood cells with a coating of immunoglobulin leading to a direct positive immunoglobulin reaction and in rare cases to hemolysis. Hemolytic anemia can occur in connection with immunoglobulin therapy due to increase of red blood cell sequestration. Patients receiving immunoglobulin therapy should be monitored for clinical symptoms of hemolysis. A

laboratory analysis should be carried out for confirmation of hemolysis in cases of occurrence of such symptoms after immunoglobulin administration through infusion.

Transfusion related acute lung injury

Non-cardiogenic pulmonary edema was reported (transfusion related acute lung injury (TRALI) in patients whom immunoglobulin was administered. TRALI is characterized by severe respiratory impairment, pulmonary edema, hypoxemia, normal function of left ventricle and fever, and it usually occurs during 1-6 hours after transfusion. Oxygen therapy with adequate additional artificial ventilation should be used for patients with TRALI.

Patients receiving immunoglobulin should be monitored for respiratory system adverse reactions. If TRALI is suspected an analysis for the presence of anti-neutrophil antibodies both in product and in patient's blood should be carried out.

Laboratory testing

Appropriate laboratory tests should be carried out in case of occurrence of symptoms of hemolysis after administration of immunoglobulin through infusion.

If there is a suspicion of TRALI then an analysis for the presence of anti-neutrophil antibodies both in product and in patient's blood serum should be performed.

In connection with a potential increased risk of thrombosis an assessment of blood viscosity should be performed in the patients with the risk of increased viscosity including cryoglobulins, starvation chylomicronemia/evidently high level of triglycerides or monoclonal gammopathy.

General information

The product is manufactured from human plasma. Donor selection, screening of donor blood samples and plasma pools for specific markers of infection as well as inclusion of effective manufacture stages for inactivation/elimination of viruses are standard measures for infection prevention occurring as a result of use of drug product manufactured from human blood or plasma. Nevertheless, risk of infection transmission in case of administration of drug product manufactured from human blood and plasma cannot be completely eliminated. The same applied to unknown and new viruses and other pathogens.

The taken measures are considered effective for enveloped viruses such as HIV, hepatitis B virus and hepatitis C virus. In respect of viruses without envelop such as hepatitis A virus and parvovirus B19, these measures can have a limited effectiveness. Clinical experience evidently demonstrates the absence of cases of hepatitis A and parvovirus B19 transmission in case of administration of human immunoglobulin products. In addition, it is assumed that antibody content is important for increase of viral safety.

The product does not contain preservative or antibiotics.

Elderly patients

Patients over the age of 65 may be at risk for some adverse reactions, such as thromboembolic complications and acute renal failure.

Pregnancy and lactation.

Safety of the product for pregnant women has not been established by controlled clinical studies, and therefore, it should be prescribed with caution to pregnant and breastfeeding women. The study of IgG product use in pregnant women has shown it crosses placenta, especially during a III trimester. The clinical experience of immunoglobulin use demonstrates that the product has no adverse effect on pregnancy course, fetus or baby.

Immunoglobulins penetrate into breast milk and can facilitate transmission of protective antibodies to a newborn.

The clinical experience of immunoglobulin use has shown the product does not have any effect on fertility.

Effects on ability to drive and use machines.

No effect on the ability to drive a vehicle or operate other mechanisms has been reported.

Special safety measures.

Some serious adverse reactions may be caused to the rate of product administration. Patients who receive immunoglobin for the first time usually experience a slight adverse reaction more frequently than those who receive immunoglobulin therapy regularly. The parameters of administration rate mentioned below should be followed and patients should be closely monitored both during infusion and for 1 hour after completion of the first infusion. In case of any adverse reactions infusion rate should be reduced or infusion itself should be stopped until undesirable symptoms disappear. If after administration stopping symptoms persist then symptomatic therapy is reasonable. In case of shock, should be followed appropriate anti-shock therapy. The level of creatinine should be measured in patients with diabetes mellitus and a risk of renal failure as well as in patients with systemic lupus erythematosus with kidney involvement for 3 days after administration of the product. During following infusions patients should be thoroughly monitored for 20 minutes from the moment of product administration completion.

BIOVEN should only be used in a clinical setting of hospital and in compliance with aseptic requirements. Before administration vials should be kept at a temperature of (20±2) °C for at least 2 hours.

Solution must be transparent or slightly opalescent, colorless or of slightly yellowish color.

Do not use if solution is cloudy or contains precipitate.

A separate infusion system should be used for administration of the product.

Drug-drug interactions and other kinds of interactions.

Administration of this product can be combined with administration of other drug products.

Live attenuated viral vaccines

Immunoglobulin administration can decrease effectiveness of live attenuated viral vaccines against measles, rubella, epidemic parotitis and chicken pox during a period of 6 weeks to 3 months. A period of 3 months is required after administration of this product before vaccination with live attenuated viral vaccines. In case of vaccination against measles this attenuation of vaccine effectiveness can last up to 1 year. Therefore, in patients administering vaccine against measles antibody status should be checked.

After vaccination against these infections the product should be administered not earlier than after two weeks; if it is needed to use Bioven earlier, vaccination against measles or epidemic parotitis should be repeated. Vaccination against any other infection can be performed at any time before or after administration of this product.

Impact on results of serologic tests

After immunoglobulin injection a temporary increase of different antibodies blood level that are passively transferred can result in false positive results of serologic analyses.

Passive transfer of antibodies to red blood cells antigens, for example, A, B or D can have an impact on some serologic tests for determination of alloantibodies to red blood cells (for example, Coombs test), reticulocyte count and haptoglobin.

Administration details.

Warnings on product administration

Some severe adverse reactions may be connected with product infusion rate. The recommendations on infusion rate should be followed strictly. A patient condition should be monitored closely and special attention for occurrence of any symptoms during the whole period of infusion should be paid.

Some adverse reactions can occur more often:

- in the case of a high infusion rate;

- in patients who receive normal human immunoglobulin for the first time or in rare cases of change to normal human immunoglobulin or when a long period of time has passed from the moment of the previous infusion.

Any potential complications can be prevented if it is ensured that:

- a patient is not sensitive to human normal immunoglobulin during the first slow infusion of the product;
- a patient is closely monitored for occurrence of any symptoms during the whole period of infusion. In particular, to identify signs of a potential negative impact during the first infusion and during the first hour after infusion it is essential to monitor condition of a patient who have not previously received immunoglobulin products, who received therapy using alternative products or after a long period of time has elapsed since the last immunoglobulin administration. Such patients require monitoring during the whole period of the first infusion as well as for 1 hour after administration is completed. All other patients should be monitored for the first 20 minutes after administration.

In case of any adverse reaction in is necessary to either decrease infusion rate or stop infusion. Treatment required depends on the nature and severity of adverse reaction. In case of a shock measures should be taken in accordance with approved recommendations on anti-shock therapy.

For all patients in case of IgG administration it is necessary to:

- perform an adequate hydration before starting IgG infusion;
- monitor diuresis;
- monitor blood serum creatinine level;
- avoid a concomitant use of loop diuretics.

Overdose.

Overdose can cause hypervolemia and increase of blood viscosity especially in patients with such risks including older patients or patients with renal impairment.

Adverse reactions.

Blood and lymphatic system disorders: anemia, lymphadenopathy, hemolysis, leukopenia, hemolytic anemia.

Immune system disorders: hypersensibility, anaphylactic shock, anaphylactic reactions, anaphylactoid reactions, angioneurotic edema, facial edema.

Endocrine system disorders: abnormality of thyroid function.

Nervous system disorders: headache, disorder of cerebral circulation, aseptic meningitis, migraine, dizziness, paresthesia, hyposthesia, amnesia, burning sensation, dysarthria, dysgeusia, balance disorders, transient ischemic attack, tremor.

Psychiatric disorders: excitation, anxiety, insomnia.

Cardiac disorders: myocardial infarction, tachycardia, palpilation, cyanosis.

Vascular disorders: peripheral vascular failure, arterial hypotension, arterial hypertension, peripheral coldness, phlebitis, deep venous thrombosis.

Respiratory, thoracic and mediastinal disorders: respiratory failure, pulmonary embolism, pulmonary edema, bronchial spasm, dyspnea, cough, increased respiratory rate, rhinorrhea, asthma, nasal blockage, oropharyngeal edema, pharyngolaryngeal pain.

Gastrointestinal disorders: nausea, vomiting, diarrhea, abdominal pain.

Skin and subcutaneous tissue disorders: eczema, urticaria, rash, erythematous rash, dermatitis, pruritus, alopecia, cold sweat, photosensitivity reactions, night sweating.

Musculoskeletal and connective tissue disorders: back pain, pain in extremities, arthralgia, muscle spasm, clonus, myalgia.

Renal and urinary disorders: acute renal failure, proteinuria.

Eye disorders: conjunctivitis, eye pain, eye edema.

Ear and labyrinth disorders: vertigo, liquid in internal ear.

General disorders and administration site conditions: fever, influenza-like symptoms, weakness, chest discomfort, pain, chest congestion, asthenia, malaise, peripheral edemas, fever sensation, fatigue, rigor, hot flushes, hyperemia, hyperhidrosis; administration site reactions, including pain, increased sensibility, hyperemia, edema, phlebitis, pruritus.

Laboratory tests: increase of hepatic enzymes, false positive level of blood glucose, increase of blood creatinine, increased level of blood cholesterol, increased level of urea, decreased level of hematocrit, decreased level of red blood cells, positive direct Coombs test, decreased level of saturation with oxygen.

Infections and infestations: bronchitis, nasopharyngitis, chronic sinusitis, mycosis, infection, renal infection, sinusitis, infections of upper airways, urinary tract infections, bacterial infections of urinary tract.

Injuries, poisoning and general procedural complications: contusion, transfusion related acute lung injury.

Children: During clinical trials of BIOVEN, most adverse reactions in children were assessed as mild, resolved rapidly on their own or in response to simple measures (decreasing of the speed of infusion, or stop of the infusion).

2.5 Description and justification of the method of administration, dosage, scheme and duration of treatment

As part of this clinical study, patients will receive the drug Bioven, a 10% solution for infusion produced by "Biopharma Plasma" LLC in a dose 0.8-1.0 g/kg 1 time per day for 2 consecutive days (course dose 1.6-2.0 g/kg).

Bioven should be administered intravenously, at an initial rate of 0.5 - 1.0 ml/kg of body weight /h for 30 minutes. If no unwanted adverse reactions are occurred, the rate of administration can be gradually increased (recommended increase by 0.5 - 1.5 ml/kg of body weight/h every 10 minutes). According to clinical studies, the maximum rate of administration is 8.5 ml/kg of body weight/h.

The investigational drug is administered only in a hospital setting in accordance with the rules of asepsis. The solution should be at room temperature before use. Turbid solutions and solutions with precipitate are not used. A separate infusion system should be used for drug administration.

The information specified in the instructions for medical use in the relevant sections: Administration details, Special safety measures, Contraindications, Drug-drug interactions and other kinds of interactions, etc. should be taken into account during the drug administration. Including, but not limited to, measures to control the state of the coagulation system, hydration levels, kidney function and others.

According to the section "Administration details" of the Package leaflet for medical use of the drug, and as described in section 2.4. of this protocol, the administration of immunoglobulins in minimal doses and with a minimum infusion rate is practiced for patients with risk of thrombosis. It is necessary to make sure the patient's hydration level is adequate before using the drug. Patients with a risk of high blood viscosity should be monitored for thrombosis symptoms and blood viscosity assessed.

Patients who are participating in this study may receive concomitant therapy, which is used to treat comorbidities and for vital signs.

The route of administration and dosage does not exceed the maximum single and course doses that can be used in the treatment of patients, according to the approved Package leaflet for medical use of the drug Bioven. They fully meet the requirements for the medicinal product, which are strictly regulated by the European Pharmacopoeia (monograph Eur. Ph.0918), the State Pharmacopoeia of Ukraine, and are laying within the limits set out in the Guideline on Core SmPC for human normal immunoglobulin for intravenous administration (IVIg) EMA / CHMP / BPWP

/ 94038/2007 Rev. 5 June 28, 2018.

Route of administration and dosage in accordance with the approved Package leaflet for medical use of the drug Bioven.

Bioven should be administered intravenously, at an initial rate of 0.5 - 1.0 ml/kg of body weight /h for 30 minutes. If no unwanted adverse reactions are occurred, the rate of administration can be gradually increased (recommended increase by 0.5 - 1.5 ml/kg of body weight/h every 10 minutes). According to clinical studies, the maximum rate of administration is 8.5 ml/kg of body weight/h.

In cases of congenital agammaglobulinemia or hypogammaglobulimenia, severe combined immunodeficiency, unclassified variable immunodeficiency, Wiscott-Aldrich syndrome: 4-5 ml (0.4-0.5g)/kg (minimal dose is 2 ml (0.2 g)/kg, maximal dose is 8 ml (0,8 g)/kg every 3-4 weeks, and adjustment of the dose should be decided individually depending on intensity of infective syndrome (achievement of a serum level of IgG 5 g/l but not less than 3-4 g/l is considered to be optimal).

In case of replacement therapy and secondary immunodeficiency (in general): 2-4 ml (0.2-0.4 g)/kg every 3-4 weeks.

In case of cytopenia of different genesis (acute and chronic leukemia, aplastic anemia, status post cytostatic therapy): 2-4 ml (0.2-0.4 g)/kg/day for 4-5 days or 10 ml (1 g)/kg/day for 2 days.

In case of severe bacterial and toxic and viral infections (including surgical complications accompanied by bacteremia and septicopyemic conditions and for preparation of surgical patients for operation): 4 ml (0.4 g)/kg/day for 1-4 days.

In case of idiopathic thrombocytopenic purpura: 2-4 ml (0.2-0.4 g)/kg/day for 2-5 days or 8-10 ml (0.8-1 g)/kg/day on the first day and if required on the third day.

In case of Guillain-Barre syndrome, chronic inflammatory neuropathy (demyelinating), inflammatory myopathy, Wegener's granulomatosis: 2-4 ml (0.2-0.4 g)/kg/day for 3-7 days, and if required a 5-day course of treatment should be repeated at intervals of 4 weeks.

In case of dermatomyositis: 10 ml (1 g)/kg/day for 3-5 days.

In case of systemic diseases of connective tissues (rheumatoid arthritis etc.): 2-5 ml (0.2-0.5 g)/kg/day for 5 days.

In case of Kawasaki disease: 10-20 ml (1-2 g)/kg in equal doses for 2-5 days or 20 ml (2 g)/kg as single dose (addition to treatment with acetylsalicylic acid).

In case of bone marrow transplantation: 5 ml (0.5 g)/kg as a single dose 7 days prior to transplantation, thereafter once weekly for 3 months after transplantation.

For use in the complex therapy of adult patients with severe pneumonia caused by coronavirus infection COVID-19 / SARS-CoV-2 (see section "Indications"), the recommended dose of 0.8-1.0 g/kg body weight per day for 2 days (course dose 1.6-2.0 g/kg body weight).

The physician depending on the patient’s condition determines the frequency of infusions and the rate of administration. The daily dose may be adjusted for reasons of not exceeding the maximum allowable daily volume of infusion therapy. Monitoring of the coagulation system and diuresis is mandatory, especially for overweight patients.

Pediatric patients. For children (aged 0 to 18 years) might be use same dosage as per body weight as for adults, however the dosage should be corrected for body weight and adjusted accordingly to the clinical tests.

Children. The product might be use in pediatric practice. (see section "Indications").

3. PURPOSE AND OBJECTIVES OF RESEARCH

Objective: To evaluate the efficacy, safety and tolerability of Bioven in patients with chronic primary immune thrombocytopenia, with evidence of non-inferiority compared to the literature data regarding the level of effectiveness of existing IVIG products..

Tasks of study:

- To evaluate the proportion (%) of patients who achieved the response (R) during the study, platelet count> $30x10^9$ / l and at least double their initial number, as confirmed by at least 2 blood tests performed every 7 days; absence of bleeding) during therapy with the studied drug Bioven.
- To evaluate the effeciency of the studied drug Bioven in comparison with the literature data
- To evaluate the presence and severity of hemorrhagic syndrome as a result, which is included within 4 weeks after starting therapy;
- To evaluate the proportion (%) of patients who achieved a complete response (CR) during the study (platelet count> 100 x 10^9 / l, confirmed by at least 2 blood tests performed every 7 days; no bleeding) during treatment with the study drug Bioven.
- To evaluate the proportion (%) of patients who did not respond (NR) during the study with a platelet count <30 x 10^9 / L or less than a 2-fold increase in platelet count from baseline. This must be confirmed by at least 2 blood tests with a difference of one day, or the presence of bleeding during therapy with the study drug Bioven.
- To evaluate the proportion (%) of patients who lost the response (R) during the study (a decrease in platelet count (<30 x 10^9 / L, or less than twice the initial or bleeding. Platelet counts should be confirmed at least twice with an interval of 1 day).
- To evaluate the proportion (%) of patients who lost a complete response (CR) during the study, a decrease in platelet count, <100 x 10^9 / l, or the occurrence of bleeding. Platelet counts should be confirmed at least twice with an interval of 1 day).
- To determine the time from the start of treatment with the study drug Bioven to the onset of the response (R);
- To determine the time from the start of treatment with the studied drug Bioven to the onset of a complete response (CR);
- To set the duration of the response (R);
- To set the duration of the complete response (CR);
- To evaluate the frequency and severity of possible adverse events/adverse reactions (AE/AR).
- To evaluate the frequency of clinically significant changes in laboratory parameters after infusion of the study drug using the study drug Bioven.
- To evaluate the frequency of clinically significant changes in vital signs after infusion of the study drug using the study drug Bioven.

4. STUDY DESIGN

4.1. Model description, number of patients, groups

Study design: open-label, multicenter, international, non-randomized, non-controlled, single-group study evaluating the efficacy, safety and tolerability of Bioven, 10% solution for infusion.

Number of patients: The number of subjects in Ukraine and worldwide is 40 patients: men and women aged 18-65 years with a confirmed diagnosis of chronic primary immune thrombocytopenia (at least 12 months from the date of diagnosis). In Ukraine, no more than 36 patients will be enrolled.
Groups: This study does not provide for the division of patients into groups. Patients who have been screened and meet the inclusion criteria, who do not have non-inclusion (exclusion) criteria and those who have signed the Informed Consent Form (ICF), are included in the study, and receive the study drug (SD).

4.2 Stages of the study. Screening
The patient or his or her legal representative must sign an informed consent form.
After signing the informed consent form, the screening surveys are performed and the compliance with the inclusion / non-inclusion criteria is assessed.
At the screening stage, verification of the diagnosis of chronic primary ITP is required (based on primary documentation data) (Section 6.5.3 of the Protocol).

4.3 Stages of the study. Clinical stage
The stage starts after the screening is completed.
Patients receive the study drug Bioven, solution for infusion of 10%, at a dose of 0.8-1.0 g / kg 1 time per day for 2 consecutive days (course dose 1.6 - 2.0 g / kg).
The time of administration of the studied drug, the occurrence of adverse events is recorded in the CRF.
Prescribed therapy and examination results are recorded in the CRF based on primary documentation.
The CRF data are entered according to the patient's management plan (Section 6 of the Protocol).
Patients participating in this study may receive corticosteroid therapy if the patient is taking long-term and stable doses (at least 2 weeks before screening). Increasing the dose of corticosteroids less than 2 weeks before, during, and after SD administration is considered an ineffectiveness of SD.
If the patient has been treated with cyclophosphamide, azathioprine or attenuated androgens, the treatment regimen and dose should be stable for at least 2 months before day 0 (immunosuppressant dose should remain unchanged until day 30).

4.4 Stages of the study. Follow-up and completion of the study

The stage starts after the last administration of the drug and lasts for 4 weeks. At this stage a set of laboratory tests, measurement of vital signs is carried out. AE/AR registration is also performed.
The results of the study are entered into the CRF according to the "Schedule of research procedures" (Section 6.4 Table 1 of the Protocol).

5. SELECTION AND EXCLUSION OF RESEARCH SUBJECTS

5.1. Inclusion criteria

- Signed Informed consent form to participate in the study;
- Men and women aged 18-65 years;
- Significantly confirmed chronic primary ITP (at last 12 months after diagnosis);
- The general analysis of blood should be normal except for the isolated thrombocytopenia. Patients with low hemoglobin (but above 90 g / l) may be included if there are symptoms of bleeding;
- In case of diagnosis of bleeding symptoms, reticulocyte counts should be monitored;
- Platelet count < 30 x 109/L;
- If the patient is taking corticosteroids, the treatment regimen / dose should be stable (at least 2 weeks before screening);
- Negative pregnancy test (in women of reproductive age), willingness to use reliable methods of contraception throughout the study;
- The results of physical, instrumental and laboratory examination of patients - within the norm and deviations are considered by the investigator as clinically insignificant;
- The ability, according to the investigator, to follow all the requirements of the study protocol.

5.2 Non-inclusion criteria

A patient cannot participate in this study if he or she meets one of the following criteria:

- Known intolerance to plasma and immunoglobulin drugs;
- Drug allergy or hypersensitivity to immunoglobulin drugs;
- Confirmed deficiency of IgA and antibodies to IgA;
- Contraindications to immunoglobulin according to the instructions for medical use;
- Pregnancy and lactation;
- Any clinically significant hepatic impairment (increase serum transaminases levels by more than 3 times the upper limit of normal);
- Serum creatinine level is more than 2 times higher than the upper limit of normal for a given age and sex;
- Severe heart failure (NYHA III);
- History of thrombosis or presence of significant risk factors for thrombosis;
- Patients with preventive splenectomy;
- Hemostasis disorders other than chronic thrombocytopenia;
- Persons with acute or exacerbation of chronic diseases of the gastrointestinal tract associated with the risk of bleeding, acute infectious diseases, pathologies of the respiratory system;
- Proven case of primary immunodeficiency;
- Secondary immune thrombocytopenia;
- Refractory thrombocytopenia;
- Viral infections (Epstein-Barr (EBV), cytomegalovirus (CMV), hepatitis B and C);
- Presence of documented HIV infection;
- Positive RW test result;
- Systemic immunopathological diseases (rheumatic diseases, nephritis, etc.);
- Oncological diseases;

- Diabetes mellitus;
- Thyroid diseases;
- History of mental illness;
- Known drug addiction;
- Any other concomitant decompensated diseases or acute conditions, the presence of which, according to the investigator, may significantly affect the results of the study;
- The need to prescribe drugs that are incompatible with the administration of the drug in this study: other immunoglobulin drugs in addition to the study drug, cytostatics, monoclonal antibodies, Avatrombopag);
- Experimental treatment (e.g. Rituximab therapy) for 3 months before screening);
- Blood transfusions or transfusions of blood products in the last 6 months before inclusion in the study;
- Administration of IVIG 30 days before screening;
- Participate in any other study now or in the previous 30 days.

5.3 Criteria for exclusion of subjects (discontinuation of treatment with the study drug):

Any patient can leave the study at any time and under any conditions.

Patients may be excluded by the investigator from taking the study drug and from the study in the following circumstances:

- Patient's wish
- Occurrence of severe and/or unexpected AE/AR in patient during the study, that require discontinuation of the drug;
- The need to prescribe drugs prohibited in this study.
- Significant deterioration of the patient's condition during the study period;
- Failure of the patient to adhere to the treatment regimen;
- Failure of the patient to follow the procedures established under the protocol;

Due to the variability of PLT levels in patients with chronic immune thrombocytopenia (wave), it is possible to re-screen or extend the duration of the screening phase, but only if the subject meets all other specified inclusion criteria and has no inclusion or exclusion criteria.

Patients who drop out at the screening stage are not included in the efficacy and safety analysis, as they do not receive any doses of the investigational drug (ID).

Patients who do not receive a full course of study drug are included in the safety analysis but not in the efficacy analysis.

Patients who dropped out of the study after completion of SD administration during the follow-up period are considered in the efficacy and safety analysis. The data of such patients are evaluated by parameters that can be analyzed at a certain point in time. The dropped data are not analyzed.

For all patients who complete the study due to AE, requiring discontinuation of treatment with the studied drugs, it is necessary to conduct the procedures of the final visit in the near future after the development of AE. After stopping treatment, the patient should be monitored until the reaction disappears or its clinically significant signs. Patients who received at least 1 dose of SD but prematurely dropped out of the study are included by the investigator in the analysis of tolerability of the study drug.

The reasons for premature withdrawal from the study are indicated in the Individual registration form.

6. PATIENT EXAMINATION AND TREATMENT PLAN

A breakdown into visits is provided for this Clinical Study.

The study is conducted in stages.

A detailed plan and content of the Stages and visits of the study are given in section 6 "Plan of examination and treatment" (subclauses 6.1, 6.2, 6.3), a step-by-step breakdown is also set out in section 6.4 "Schedule of procedures in tabular form".

The information is entered into the CRF in accordance with the "Schedule of study procedures".

6.1. Screening stage

After signing the Informed Consent, at the screening stage, the procedures provided for by the Protocol are performed to assess the eligibility criteria (inclusion/exclusion) of the patient for participation in the study.

Due to the variability of PLT levels in patients with chronic immune thrombocytopenia (wave-like), it is possible to re-screen or extend the duration of the screening stage, but only if the subject meets all other specified inclusion criteria and has no inclusion and exclusion criteria.

Procedures are performed according to the schedule of procedures (Section 6.4, Table 1).

- Signing the Informed Consent Form;
- Collection and registration of demographic data;
- Collection and registration of medical history;
- Verification of the diagnosis of ITP;
- Registration of information on the reception of previous ITP therapy (dose / schedule, duration, response (if any) and time interval since the last administration);
- Registration of information on symptomatic therapy and administration of drugs for the treatment of comorbidities;
- Transfusion history;
- Allergic history;
- Determination of body weight;
- Objective physical examination with obligatory assessment of the severity of the hemorrhagic syndrome;
- Measurement of vital signs (blood pressure, heart rate, frequency of respiratory movements, body temperature);
- Collection of biomaterials for laboratory research (performed at the collection point or by the visiting team of the Central Laboratory designated by the Sponsor):
- Blood test for HIV and RW, PCR EBV, CMV;
- Blood test for blood group and Rh factor;
- General blood test (erythrocytes, reticulocytes) (with low hemoglobin, but not less than 90 g / l), hemoglobin, hematocrit, leukocytes and expanded leukocyte formula, platelet counting by the Fonio method;
- Biochemical blood test (ALT, AST, creatinine, urea, glucose, total bilirubin);
- Coombs' test (antiglobulin test);
- Determination of total serum IgG in grams per liter;
- General analysis of urine (specific gravity, pH, protein, glucose; sediment microscopy - leukocytes, erythrocytes, cylinders, salts); pregnancy test (for women of reproductive age);
- Coagulogram (PTI, APTT, fibrinogen);

- Hepatitis B and C markers (Hbs-Ag, anti-HCV);
- Antinuclear antibodies (AHA);
- Electrocardiogram in 12 leads.

6.2. Clinical stage

Visiting plan

The study involves scheduled visits of patients to the doctor:

1st visit (Day -14 – Day -1) - Screening, verification of compliance with the inclusion/exclusion criteria, enrollment in the study; due to the variability of PLT levels in patients with chronic immune thrombocytopenia (wave), it is possible to re-screen or extend the duration of the screening phase, but only if the subject meets all other specified inclusion criteria and has no inclusion or exclusion criteria;

2nd visit (Day 0 - Day +1 – Day +2) - hospitalization, administration of the study drug for 2 days, physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine the platelet count by Fonio, Coombs test, determination of Ig G level (g/l);

3rd visit (Day +7 ± 1 day) - physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine platelet counting by the Fonio method, Coombs test in case hemolysis was detected during the previous visit (according to the laboratory data);

4th visit (Day +14 ±2 day) -physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine the level of platelets by Fonio; Coombs tests, in case of detection of hemolysis according to the laboratory examination at the previous visit, determination of the level of Ig G (g/l). If a decrease in platelet count < 30 x 109/L is detected, an additional blood test with Fonio platelet count is performed one day after the visit.

This visit can be performed by telephone/video, if it is possible to adequately assess the patient's status and take biomaterials for laboratory tests at the collection point of the Central Laboratory designated by the Sponsor;

5th visit (Day +21 ±3 day) – physical examination, assessment of the status of hemorrhagic syndrome, blood sampling to determine platelet counting by the Fonio method, biochemical blood test, Coombs test in case hemolysis was detected during the previous visit (according to the laboratory data).

This visit can be performed by telephone / video, provided that the patient's status can be adequately assessed and biomaterials for laboratory tests can be sampled at the collection point of the Central Laboratory designated by the Sponsor;

6th visit (Day +30 ± 3 days) **-** physical examination, assessment of the status of the hemorrhagic syndrome, blood sampling to determine platelet counting by the Fonio method, biochemical blood test, Coombs test, determination of Ig G levels (g / l). This is a face-to-face visit. Completion of the study.

Patients' serum samples should be stored frozen at the temperature of -65 - -85 ° C (second aliquot) to ensure the possibility of performing repeat laboratory tests, if necessary, in the future.

Patients receive Biven 10% solution for infusion, produced by LLC "Biopharma Plasma" at a dose of 0.8-1.0 g / kg 1 time per day for 2 consecutive days, the course dose of 1.6-2.0 g / kg. Allowed repeat course at same dosage in period 14-28 days from first infusion, if required.

Bioven should be administered intravenously dropwise at the initial rate of 0.5-1.0 ml/kg of body weight/hour for 30 minutes. If no adverse reactions occur, the rate of administration may be gradually increased (it is recommended to increase by 0.5-1.5 ml/kg of body weight/hour every 10

min). According to the data from clinical studies the maximum rate of administration is 8.5 ml/kg of body weight/hour.

The study drug is administered only in hospital environment while observing the rules of aseptics. The solution should be of room temperature before use. Cloudy solutions and those containing sediment are not used. For the administration of the drug, it is necessary to use a separate infusion system.

When administering the drug, it is necessary to consider the information specified in the relevant sections of the instructions for medical use: administration details, special safety measures, contraindications, interaction with other medicinal products, etc. Including, but not limited to, measures to control the condition of the coagulation system, hydration levels, renal function, etc.

According to the section of the instructions for the drug " Administration details ", and as described in section 3.4. and 3.5 of this protocol for patients at risk of thrombosis practice the introduction of immunoglobulin drugs in minimal doses and with a minimum infusion rate. Before using the drug, make sure the patient's level of hydration is adequate. Patients at risk of high viscosity should be monitored for thrombosis symptoms and blood viscosity assessed.

The CRF records the time of administration of the study drug, the occurrence of possible side effects.

Prescribed therapy and examination results are recorded in the CRF based on primary documentation.

CRF data are entered according to the patient's management plan.

6.3 Stage of follow-up and completion

The stage lasts from the last administration of the study drug and for 4 weeks.
The procedures are performed according to the schedule of procedures (Section 6.4, Table 1).
If a decrease in platelet count < 30 x 109/L is detected, an additional blood test with platelet count by Fonio is performed one day after the visit.
Face-to-face or telephone/video visits are made to assess the patient's condition. The patient visits the blood collection point for laboratory testing. The investigator fills in all information about the patient's condition and examination results in the IRF.

6.4 Schedule of study procedures in tabular form Table 1. Schedule of study procedures.

Visits	Visits 1	Visits 2 (госпіталізація)			Visits 3	PLT control	Visits 4	PLT control	Visits 5	PLT control	Visits 6	PLT control
Study stage	**Screening**[2]	**IMP admin.**	**IMP admin**	**Follow-up**	**Follow-up**	**every other day***	**Follow-up**	**every other day***	**Follow-up**	**every other day***	**Follow-up**	**every other day***
Day relative to the first administration of the drug/Injection	**Day (-14 -1)**	**Day 0**	**Day +1**	**Day +2**	**Day +7**		**Day +14**		**Day +21**		**Day +28**	
Signing the Informed Consent Form	●											
Collection of demographics data	●											
Collection of anthropometric data, body weight[3]	●	●	●									
Collection of medical history [4]	●											
Objective physical examination [5]	●	●	●	●	●		●		●		●	
Measurement of vital signs [6]	●	●	●	●	●		●		●		●	
ECG in 12 leads;	●											
Coombs Direct Test (Antiglobulin Test) *	●			●	*		*		*		●	
Determination of the level of total Ig G in the blood (g/l)	●			●	●		●		●		●	
General blood test [7]	●			●	●	*	●	*	●	*	●	*
Biochemical blood test [8]	●										●	
Blood test for blood group and Rh factor	●											
Coagulogram (PTI, APTT, fibrinogen)	●											
General urine analysis [9]	●											
Antinuclear antibodies (AHA)	●											
Blood test for HIV, RW, HBs-Ag, anti-HCV, EBV, CMV[10]	●											
Pregnancy test (for women of reproductive age)	●											
Assessment of patients' compliance with the inclusion/non-inclusion criteria based on the results of screening	●											
Evaluation of exclusion criteria	●	●	●	●	●		●		●		●	
Setting a date for your next visit	●			●	●		●		●			
Administration of the study drug		●	●									
Registration AE/AR		●	●	●	●		●		●		●	

2 The stage may be extended or re-screened by the decision of the PI and/or agreement with the Sponsor.
3 Body weight before the introduction of the IMP
4 ITP disease, data on previous ITP therapy (dose/schedule, duration, response (if applicable) and time interval since the last administration), data on therapy of comorbidities; transfusion anamnesis, allergic anamnesis;
5 Визначення вираженості геморагічного синдрому (огляд шкіри і слизових оболонок, наявність кровотечі); аускультація і перкусія серця і легень; пальпація та перкусія органів черевної порожнини;
6 Blood pressure, heart rate, respiratory rate, body temperature;
7 Hemoglobin, hematocrit, erythrocytes, reticulocytes (in case of diagnosis of bleeding symptoms), leukocytes and leukocyte formula, Fonio platelet count;
8 ALT, AST, total bilirubin, creatinine, urea, glucose;
9 Color, transparency, specific gravity; pH, glucose, protein, ketone bodies, sediment microscopy (erythrocytes, leukocytes, cylinders, crystals, bacteria/fungi); pregnancy test for women of reproductive age;
10 PCR EBV, CMV, or data from primary documentation;
* The Coombs test at the 3rd, 4th, and 5th visits is carried out in case of detection of hemolysis according to laboratory examination at the previous visit.
* If a decrease in the level of platelets < 30 x 109/l was recorded, then a day after the visit, an additional blood test is performed with a platelet count, according to Fonio.

6.5 Study procedures.

6.5.1 Signing the Informed Consent Form

All patients enrolled in the study, or the patient's legal representative, must obtain written informed consent to participate in the study.

Before enrolling in a study, the patient must be explained his or her rights and responsibilities associated with participating in the study. The patient, or legal representative, should be aware that he may at any time refuse to participate in the study without prejudice to his further treatment, that his participation in the study is strictly confidential, that only his initials will be used in clinical trial documents and ID number.

The patient should be explained that his personal data obtained during the study will be used for statistical processing of study results and reporting and can be discussed with the persons conducting the study and may be provided to government officials during the clinical audit.

The patient, or legal representative, should have sufficient time to consider the possibility of participating in the study and to ask the investigator questions of interest. The investigator is required to explain in detail the sections of the Informed Consent that the patient has questions about. The investigator should not put pressure on the patient to influence his decision.

If the patient, or legal representative, has decided to participate in the study, he must personally fill in 2 copies and sign the Informed Consent Form. One copy of the Informed Consent is handed over to the patient, the other remains in the investigator's file.

The fact of discussing the informed consent should be recorded in the medical history and CRF with the date of signing.

The screening and inclusion of the patient in the clinical trial provided for in this protocol is carried out only after signing the Informed Consent Form.

6.5.2 Entering information into the CRF

- The study provides for the use of electronic CRF (eCRF, electronic Case report Form). Investigators receive separate training on eCRF.
- Entering the CRF / eCRF begins after signing the Informed Consent
- The date of signing the Informed Consent must be indicated;
- The two-digit center number (for example 01) is indicated;
- The information identifying the patient in the study is filled in;
- A four-digit screening number is assigned immediately (for example 0101 - consists of a two-digit number of the Center + a two-digit serial number according to the sequence of patient recruitment at the Center);
- Demographic data of the patient, date of diagnosis are entered;
- The breakdown of this Clinical Study into Visits is provided.

The detailed plan and content of each of the Study Visits is specified in Section 6 “Examination and Treatment Plan” (sub-items 6.1, 6.2, 6.3), the step-by-step breakdown is also set out in the section “Schedule of procedures in tabular form”.

Upon completion of the patient's participation in the study, the completion date and the patient's condition at the time of completion are recorded.

The data entered must be carefully verified.

6.5.3 Diagnosis verification procedure - chronic primary immune thrombocytopenia

Patients should have a confirmed chronic primary ITP (lasting at least 12 months from diagnosis).

Examination data from primary medical records are considered. The volume of the conducted research and their sufficiency for differential diagnosis with other variants of thrombocytopenia is estimated.

In case of doubt about the reliability of the diagnosis of chronic primary immune thrombocytopenia, additional studies are scheduled according to a list previously agreed with the Sponsor.

You should also pay attention to the fact that:

- general blood test should be normal, except for isolated thrombocytopenia. If patients with symptoms of bleeding are included in the Clinical Study, low hemoglobin levels are acceptable. But the hemoglobin level should be at least 90 g/l;
- bone marrow examination (aspirate and biopsy) is performed as part of routine clinical practice and is not provided for in this protocol.

6.5.4 Collection of anamneses, demographic data, complaints, determination of body weight

When collecting a medical history, the investigator should pay special attention to the presence of direct and indirect data in the patient, which may indicate the impossibility of including the patient in the study. Available medical records of comorbidities of the patient, medical and non-medical treatment received by the patient should be reviewed. The patient's life history and illness should be reflected in the primary documentation and CRF. When collecting anamnesis, attention is paid to previously transferred diseases, concomitant chronic diseases, heredity, habitual intoxications (smoking status, alcohol, drug use), allergy history, operations and injuries, professional anamnesis, permanent or periodic drug therapy.

The primary documentation records the patient's gender and age, as well as race and ethnicity. Medical scales are used to measure body weight.

Anthropometric studies will be conducted in accordance with the recommendations Health Risk Monitoring (EHRM) Recommendation for indicators, international collaboration, protocol and manual of operations for chronic disease risk factor surveys, 2002 (European Health Risk Monitoring (EHRM), 2002).

Patients should be weighed in the morning on an empty stomach, after urination and stool, in underwear (followed by a discharge of medium weight clothing). The scales must stand on a rigid base, horizontally. The measurement error according to the standards should not exceed 0.2 kg. It is not possible to record weight from the patient's words, even in cases where weight measurement is not possible.

Growth should be measured for all patients (reasons that make it impossible to measure height include features of the hair (eg mohawk), refusal of the patient to remove the headdress for any reason (eg turban), inability of the patient to stand, exceeding the height scale). To determine the height is a height meter - a vertically placed board with divisions in centimeters and a sliding ruler. The standard scale error should not exceed 2 millimeters. The patient is asked to remove shoes, tight clothing, hairpins, and hair accessories. The patient should touch the vertical board with the back of the head, back, buttocks, calves and heels, socks together. The upper limit of the opening of the external auditory canal should be at the same horizontal level with the lower border of the

edge of the orbit (chin bone). The patient is asked to look directly. If the patient's height is higher than the investigator's height, the latter gets on the platform. The ruler of the height meter is lowered on the head and the divisions are counted. The growth is observed until the patient came out from under the measuring visor. The error should not exceed half a centimeter.

The CRF registers information on the onset of the disease, the date of diagnosis, studies the primary documentation for objective studies based on which the diagnosis was confirmed.

Information about comorbidities is recorded. Any medication that the patient has taken for 3 months prior to the start of the study should be registered with the CRF as prior / concomitant therapy, indicating the appropriate indications for use, start and end dates.

6.5.5 Objective physical examination and measurement of vital signs

Objective examination includes auscultation of the heart and lungs, examination of the skin and mucous membranes, palpation of the abdomen, measurement of heart rate, blood pressure and body temperature, as well as other methods of physical examination according to the current clinical situation. Data on changes recorded during the survey are entered in the primary documentation and CRF.

Measurements of heart rate, respiratory rate, blood pressure, body temperature are made at rest (after 15 minutes of rest, not earlier than one hour after smoking cigarettes and 2 hours after eating). Heart rate (HR) is measured by auscultation of the heart in parallel with the determination of pulse rate in the radial artery (or carotid artery with weak pulsation in the radial artery) for one minute in a sitting position, in case of pulse deficit both parameters are recorded: heart rate and pulse rate. Respiratory rate (RR) is measured for a minute at rest in a supine position, noting the respiratory movements of the chest or abdominal wall, without attracting the attention of the patient.

Blood pressure will be measured on the brachial artery in the supine position according to the Korotkov method using a certified sphygmomanometer or tonometer using a cuff length and width selected by the length and circumference of the patient's shoulder. The size of the cuff should correspond to the size of the hand: the rubber part of the cuff should cover at least 80% of the circumference of the shoulder; for adults a cuff 12-13 cm wide and 30-35 cm long (medium size) is used; but it is necessary to have a large and a small cuff for full and thin arms, respectively. The mercury column or tonometer needle must be at the zero mark before the start of the measurement. To assess the level of blood pressure on each arm should perform at least two measurements with an interval of at least 1 min; with a blood pressure difference ≥ 5 mmHg perform one additional measurement; the minimum of three dimensions is taken as the final (registered) value.

Measurement technique:

- Quickly pump air into the cuff to a pressure level 20 mmHg higher than systolic pressure (after the pulse disappears);
- Blood pressure is measured with an accuracy of 2 mmHg;
- Reduce the cuff pressure at a rate of approximately 2 mm Hg in 1 second;
- The level of pressure at which the 1st tone appears corresponds to systolic pressure (1 phase of Korotkov tones);
- The level of pressure at which the disappearance of tones (phase 5 Korotkov tones) corresponds to diastolic pressure; in children, adolescents and young people immediately after exercise, in some pathological conditions in adults, when it is impossible to determine the 5th phase, you should try to determine the 4th phase of Korotkov tones, which is characterized by a significant weakening of tones;

- If the tones are very weak, you should raise your hand and perform a few compressive movements with a brush, then repeat the measurement, without squeezing the artery with the membrane of the phonendoscope;
- At the initial examination of the patient, the pressure on both arms should be measured; further measurements are performed on the hand on which the blood pressure is higher.

Temperature measurements are performed in the axilla using a medical thermometer (thermometer), and the end of the thermometer after shaking should be tightly pressed to her shoulder; the skin of the axilla should be dry, because with wet skin the thermometer shows a lower temperature. The thermometer is kept for 10-15 minutes (the lower the temperature, the longer the column of mercury reaches a peak). The patient should remain completely calm.

Auscultation of the lungs and heart, palpation of the abdomen and examination of the skin and mucous membranes are carried out according to standard procedures adopted in clinical practice at the screening stage, considering the general serious condition of patients. The task of these procedures is to detect pathological changes, including clinically significant. During the observation period, a physically less burdensome set of procedures is performed according to the standard procedure adopted in clinical practice, which allows to assess the patient's condition.

An examination for hemorrhagic syndrome is required. The scale of assessment of severity according to Table 1.

Table.1 Assessment of the severity of hemorrhagic syndrome

No signs of bleeding	No
Several petechiae (<100 in total) and / or <5 small ecchymoses (<3 cm in diameter, without mucosal bleeding)	Mild
Multiple petechiae (100 and more) and / or 5 large ecchymoses, 3 cm in diameter, no bleeding of mucous membranes	Moderate
Multiple bleeding of mucous membranes, bleeding gums, menorrhagia, gastrointestinal bleeding	Severe

6.5.6 Bioanalytical procedures and laboratory tests

Blood and urine are taken as biomaterial.

The procedure for taking biomaterial for laboratory analysis is carried out at the study site or at the collection point (if the investigator thinks the patient is mobile), or by the visiting team of the Central Laboratory designated by the Sponsor.

Blood samples for analysis will be taken on an empty stomach (8-10 hours after the last meal) from a vein with a disposable sterile syringe, catheter, or vacutainer under aseptic / antiseptic conditions.

The amount of blood taken is determined by the list of laboratory tests that need to be performed.

For the general analysis of urine, the morning average portion after adequate hygiene of a perineum is collected, urine must be delivered to laboratory within two hours after collecting.

Blood tests for HIV, blood samples for clinical blood tests, biochemical blood tests, urine samples for general analysis, inflammatory markers are selected according to standard procedures according to laboratory guidelines, according to the "Schedule of study procedures" (Table 1, Section 6.4).

List of laboratory tests:

- blood test for HIV, RW, HBs-Ag, anti-HCV (virological screening), PCR CMV, EBV or primary documentation data;
- general blood test (erythrocytes, hemoglobin, platelet counting by the Fonio method, leukocytes and leukocyte formula, reticulocytes with low hemoglobin, but not less than 90 g / l);
- biochemical blood test (ALT, AST, creatinine, urea, glucose, total bilirubin);
- Coombs' test (antiglobulin test);
- determination of the level of total IgG g / l in serum;
- antinuclear antibodies (AHA);
- general analysis of urine (color, transparency, specific gravity, pH, glucose, protein, ketone bodies, sediment microscopy (erythrocytes, leukocytes, cylinders, crystals, bacteria / fungi);
- pregnancy test for women of reproductive age.

6.5.7 Bioanalytical study plan

Bioanalytical research procedures will be conducted in a certified laboratory designated by the Sponsor of the study, whose activities are organized in accordance with the requirements of Good Clinical Practice - GSP.

All plasma and serum samples, as well as the blood itself, including samples obtained from patients who did not pass the study in full (prematurely dropped out of the study) are subject to bioanalytical tests.

Examination of samples that have not been subjected to freezing is carried out according to standard methods by routine methods of biochemical and hematological analysis.

Defrosting of plasma samples should be performed at room temperature.

6.5.8 Validation of bioanalytical methods

The bioanalytical method used must be properly validated and documented in accordance with GSP standards and regulatory requirements during the study period.

The main purpose of validation is to prove the reliability of this method for quantifying the concentration of the analyte in serum.

Validation is carried out considering the main criteria for the acceptability of the bioanalytical method set out in the guidelines.

The following characteristics of the bioanalytical method should be evaluated during the validation process:

1) selectivity;
2) transfer of the sample;
3) lower limit of quantification;
4) the range of concentrations to be determined and the shape of the calibration curve;
5) correctness;
6) precision;
7) extraction degree;
8) stability of the basic and working solutions of the analyte, stability of the analyte in the biomaterial (blood serum) under processing conditions and throughout the storage period (post-preparation stability; short-term temperature stability, stability after freezing / thawing; long-term stability).

Validation of each bioanalytical method should consist of two separate phases:

1) phase preceding the study, during which the compliance of the method of quantification of the above characteristics is checked;
2) phase of the study itself, during which the validated bioanalytical method is checked for compliance with the obtained results to the criteria of acceptability - to decide on the acceptance of the results of analytical runs in the routine analysis of biosamples.

The results and progress of the validation should be presented in the validation report (for the first phase of validation) and in the Analytical report (for the second phase of validation), prepared by the laboratory involved in the study.

6.5.9 Test tube labeling procedure.

The procedure for taking biomaterial for laboratory analysis is carried out at the collection point (if the investigator thinks the patient is mobile) or by the visiting team of the Central Laboratory designated by the Sponsor.

In case of taking biomaterial not at the point of collection, blood sampling tubes, plasma vacutainers are pre-labeled. Markings are applied by the printer on labels and protected with an adhesive tape.

The label should contain the following information:

- study code;
- site code (01, 02, 03 …);
- patient number (01001, 01002 …);
- date and time (or time point) of biomaterial capture.

6.5.10 Blood sampling procedure

Blood samples for analysis will be taken on an empty stomach (8-10 hours after the last meal) from a vein with a disposable sterile syringe, catheter or vacutainer with asepsis/antiseptics. The blood is mixed with the anticoagulant (if required by the procedure for preparing the sample to obtain plasma) and in vitro on the day of blood collection is sent at room temperature to the central laboratory.

Blood volume:

- general blood test (erythrocytes, reticulocytes, hemoglobin, leukocytes and expanded leukocyte formula, platelet counting by the Fonio method- 4 ml;
- biochemical analysis of blood (ALT, AST, creatinine, urea, glucose, total bilirubin and its fractions) and determination of IgG levels in serum - 10 ml;
- virological screening and antinuclear antibodies - 5 ml;
- blood type and Rh factor - up to 5 ml;
- Coombs test - 4 ml;
- coagulogram - 4 ml.

Blood volume by visits:

- at the screening stage - 32 ml,
- on the 2nd visit - 13 ml,
- on the 3rd visit - 9 ml,
- on the 4th visit - 9 ml,
- on the 5th visit - 9 ml,
- on the 6th visit - 23 ml.

1 additional blood sample (20 ml in total) is allowed.

On other days of visits, blood sampling is provided to perform a general blood test. Each test requires 4 ml of blood. Additional blood sampling for a general blood test is performed one day after the visit, which showed a decrease in platelet count below 30 x 10^9 /l.

Patients may also have periodic general blood tests and / or biochemical blood tests. The amount of blood required for these tests is determined by the patient's condition and duration of treatment, and will be determined in fact, taking into account the non-harm to the patient.

If the sample was not taken according to the time scheduled by the protocol (missed), the labeled tube remains empty. Information explaining this event is entered into the CRF and primary documentation, and sampling continues at the scheduled time.

6.5.11 Plasma production procedure

In detail, the process is regulated by the Manual of Laboratory Procedures provided by the Central Laboratory selected by the Sponsor.

After sampling, the closed tubes are inverted several times to ensure mixing with the anticoagulant recommended for the study (citrate / EDTA). The presence of visible clots indicates that the study is impossible. In this case, the Sponsor is informed immediately.

The tubes are centrifuged at a temperature of 21 ° C at 2000g for 20 minutes The presence of visible hemolysis indicates the unsuitability of the material. In this case, the Sponsor is informed immediately.

Plasma over the precipitate of blood cells is collected in a plastic tube (0.4-0.5 ml of plasma over the precipitate is not taken!) And re-centrifuged for 20 min at 2000 g (the last 0.2 ml of plasma after re-centrifugation is not taken). The total plasma yield should be at least 3.8 - 4 ml.

The obtained plasma sample is sent to the central laboratory determined by the Sponsor (temperature regime - in accordance with the manual of laboratory procedures provided by the contracting laboratory).

6.5.12 Procedure for storage and transportation of biological samples

In detail, the process is regulated by the Manual of Laboratory Procedures provided by the Central Laboratory selected by the Sponsor.

Storage of aliquots of blood plasma samples from the moment of their receipt to the beginning of bioanalytical procedures is carried out at a temperature regulated by the manual of laboratory procedures provided by the contracting laboratory. The main samples that do not require freezing after receipt until the moment of transfer to the courier should be stored in a packaged, ready for transfer form at a temperature of 2-8 ° C. Sending such samples to the Bioanalytical Laboratory is carried out in accordance with laboratory guidelines.

Re-thawing / freezing of aliquots of plasma samples is not allowed for samples requiring freezing.

All plasma samples (basic and archival aliquots) are subject to transfer to the Bioanalytical Laboratory).

The main samples must be stored in packaged form after receipt and until transfer to the Bioanalytical Laboratory.

Time of storage of archival aliquots of plasma on a clinical basis before transfer to the Bioanalytical laboratory - no more than the term provided by the laboratory manual.

The transfer of serum samples from the clinical base to the Bioanalytical Laboratory is accompanied by the Direction and the Act of acceptance and transfer of samples of the courier company, determined by the Sponsor. The forms of the above documents are provided by the Sponsor.

The referral is signed by the Responsible Investigator of the clinical base, or a person authorized by him. The original is transferred to the Bioanalytical Laboratory, a copy remains at the clinical base. The act of acceptance and transfer of samples (in 2 copies) is signed by the Responsible investigator of the clinical base (or his authorized person) and a representative of the courier company, and upon delivery to the Bioanalytical Laboratory - a representative of the courier company and responsible executor of the bioanalytical laboratory.

If necessary, if provided by the laboratory manual, the transport of biosamples to the laboratory is carried out by a specialized courier service. Period of transportation - no more than 8 hours or the term provided by the laboratory manual, in the frozen kind in the cryocontainers filled with "dry ice" (solid carbon dioxide).

Upon full completion of the study and after the period of storage of archival samples agreed with the Sponsor and obtaining the written permission of the Sponsor for their disposal, the remaining unclaimed archival samples of blood plasma are subject to destruction in the Bioanalytical Laboratory. An appropriate act on the destruction of archival samples of blood plasma, which is stored in the archives of the bioanalytical laboratory for at least 15 years.

Serum samples for serological and biochemical tests, as well as whole blood for hematological tests are delivered to the Bioanalytical Laboratory on the day of their receipt by a special courier service at room temperature. The design of the accompanying documentation is similar to that for plasma samples.

Invoices are stored together with the directions and acts of acceptance of the transfer for 15 years in the archives of the research center.

6.5.13 Analysis of deviations from the plan of bioanalytical study

All deviations from the initial statistical processing plan will be described and justified in the relevant sections of the Final Clinical Trials Report. The method of analysis of deviations from the research plan is based on the principles set out in the current instructions.

The withdrawal of subjects from the study will be analyzed against the criteria under this Protocol. Quantitative determination will be performed for all biosamples received for analysis, including biosamples of subjects that dropped out of the study. The results obtained will be included in the Analytical Report.

Re-analysis using archival biosamples, if necessary, should be carried out in all cases of confirmed inability to obtain a reliable result:

- in case of confirming the fact of mixing biosamples;
- in case of confirming the error of the operator/performer during the sample preparation, analytical procedure, and post-analytical period;
- in the absence of sufficient amount of biomateur;
- in case of technical problems with equipment or reagents, conditions of transportation and/or storage of biosamples.

The statistical analysis will not include the results of those subjects for whom the data obtained will not be suitable for analysis. Such data should be excluded from the calculations.

6.5.14 Rules for stopping parts of a clinical trial and (or) a clinical trial in general.

The study may be stopped for the following reasons:

1. Initiated by the Sponsor:

a. obtaining new toxicological or pharmacological data, or data on SAE related to the study drug, forcing a review of a previous evaluation of the benefits / risks of participating in the study;
b. the frequency of AEs associated with the study drug and / or their severity do not allow to continue the study;
c. other reasons, including administrative.

2. At the initiative of the investigator: the frequency of AEs associated with the drug and / or their severity unacceptably increases the risk of participation of patients in the study;
3. According to the decision of regulatory authorities.

In case of premature termination of the study, the sponsor should inform the staff of the research centers, as well as regulatory authorities, indicating the reason for the premature termination of the study.

6.6 Content of visits

Visit 1 (days -14 … -1) Screening. Assessment of compliance with inclusion / exclusion (exclusion) criteria based on screening results.

The procedure for taking biomaterial for laboratory analysis is carried out at the collection point (if the researcher thinks the patient is mobile) or the visiting team of the Central Laboratory designated by the Sponsor.

The following procedures will be performed:

- Signing an Informed Consent Form to participate in the study; forms for processing the results of routine examination in a clinical trial;
- Collection and registration of demographic data (sex, age, race);
- Collection of anthropometric data (height, body weight, BMI calculation);
- Collection of medical anamneses (anamnesis of ITP, data on the reception of previous therapy ITP, allergy anamnesis, transfusion anamnesis, comorbidity analysis, data on the treatment of comorbidities, bad habits)
- Physical exploring (necessarily be sure to assess the severity of the hemorrhagic syndrome (exploring of the skin and mucous membranes, the presence of bleeding); palpation and percussion of the abdominal organs; auscultation and percussion of the heart and lungs.
- Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
- Electrocardiography in 12 deviations;
- General blood test: hemoglobin, hematocrit, erythrocytes, reticulocytes (at the lowered level of hemoglobin, but not below 90 g/L), leukocytes + expanded leukocyte formula, platelet count according to Fonio;
- Biochemical blood test: ALT, AST, bilirubin, creatinine, urea, glucose;
- Analysis for HIV, RW, HBsAg, anti-HCV, CMV, EBV or data from primary documentation;
- Determination of the level of total IgG in blood serum in grams per liter;
- Blood test for blood type and rhesus factor;
- Coagulogram (PTI, fibrinogen, APTT);
- Blood test for antinuclear antibodies (ANA);
- Straight Coombs' test (antiglobulin test);
- General urine analysis: color, transparency, question. weight; pH, glucose, protein, ketone bodies; sediment microscopy (erythrocytes, leukocytes, cylinders, crystals, bacteria / fungi);
- Pregnancy test for women of reproductive age;

- Assessment of the patient's compliance with the inclusion / non-inclusion criteria based on the screening results;
- Rating according to the exclusion criteria;
- Appointment of the date of hospitalization.

All screening data are entered into the primary documentation and IRF of patients. The researcher checks the patient's compliance with the inclusion/exclusion (exclusion) criteria and decides on possible participation in the clinical trial. Due to the variability in PLT levels in patients with chronic immune thrombocytopenia (wave-like), it is possible to re-screen or extend the duration of the screening stage, but only if the study subject meets all other specified inclusion criteria, does not have non-inclusion and exclusion criteria.

Visit 2. (Day 0, Day +1, Day +2): Study Drug administration within 2 days. Observation.

Content of the visit:
The patient is hospitalized for 3 days for the introduction of the Study Drug (SD).
- 15 minutes before the start of each SD administration and after drug administration, a physical exploring is performed: determination of the dynamics of the hemorrhagic syndrome (exploring of the skin and mucous membranes, the presence / absence of bleeding); palpation and percussion of the abdominal organs; auscultation and percussion of the heart and lungs; Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
- Administration of SD for 2 consecutive days at a dose of 0.8-1.0 g/kg per day (course dose 1.6-2.0 g/kg);
- After 48 hours (+/- 2 hours) from the beginning of the first SD administration, a blood sample is taken for general blood test, biochemical blood test, Coombs' test and Ig G level according to the "Schedule of Procedures";
- AE/AR registration;
- Discharge of the patient and appointment of the date of the next visit.

Visit 3 (Day +7 ± 1 day): Observations.
The patient is:
- Physical exploring is performed: determination of the dynamics of the hemorrhagic syndrome (exploring of the skin and mucous membranes, the presence / absence of bleeding); palpation and percussion of the abdominal organs; auscultation and percussion of the heart and lungs;
- Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
- General blood test: hemoglobin, hematocrit, erythrocytes, leukocytes, platelet count according to Fonio;
- Coombs' test is performed in case of hemolysis according to the laboratory test at the previous visit;
- Determination of total IgG in serum (g/l);
- Rating according to the exclusion criteria;
- AE/AR registration;
- Discharge of the patient and appointment of the date of the next visit.

Visit 4 (Day 14 ± 2 days): Observations.

The visit may be conducted by telephone / video, provided that an adequate assessment of the patient's condition is possible and that a laboratory examination is mandatory at the collection point of the Central Laboratory designated by the Sponsor.

At visit 4, the following procedures are performed:

- Physical exploring is performed: determination of the dynamics of the hemorrhagic syndrome (exploring of the skin and mucous membranes, the presence / absence of bleeding); palpation and percussion of the abdominal organs; auscultation and percussion of the heart and lungs;
- Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
- General blood test: hemoglobin, hematocrit, erythrocytes, leukocytes, platelet count according to Fonio;
- Coombs' test is performed in case of hemolysis according to the laboratory test at the previous visit;
- Determination of total IgG in serum (g/l);
- Rating according to the exclusion criteria;
- AE/AR registration;
- Discharge of the patient and appointment of the date of the next visit.

Visit 5 (Day 21 ± 3 days): Observations.

The visit may be conducted by telephone / video, provided that an adequate assessment of the patient's condition is possible and that a laboratory examination is mandatory at the collection point of the Central Laboratory designated by the Sponsor.

At visit 4, the following procedures are performed:

- Physical exploring is performed: determination of the dynamics of the hemorrhagic syndrome (exploring of the skin and mucous membranes, the presence / absence of bleeding); palpation and percussion of the abdominal organs; auscultation and percussion of the heart and lungs;
- Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
- General blood test: hemoglobin, hematocrit, erythrocytes, leukocytes, platelet count according to Fonio;
- Coombs' test is performed in case of hemolysis according to the laboratory test at the previous visit;
- Determination of total IgG in serum (g/l);
- Rating according to the exclusion criteria;
- AE/AR registration;
- Discharge of the patient and appointment of the date of the next visit.

Visit 6 (Day 28 ± 1- 3 days): Observations.

Face-to-face visit.

At visit 6, the following procedures are performed:

- Physical exploring is performed: determination of the dynamics of the hemorrhagic syndrome (exploring of the skin and mucous membranes, the presence / absence of bleeding); palpation and percussion of the abdominal organs; auscultation and percussion of the heart and lungs;
- Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
- General blood test: hemoglobin, hematocrit, erythrocytes, leukocytes, platelet count according to Fonio;
- Biochemical blood test: ALT, AST, bilirubin, creatinine, urea, glucose, Coombs' test;
- Determination of total IgG in serum (g/l);

• Rating according to the exclusion criteria;
• AE/AR registration;
• Final visit.

6.6.1 Unscheduled visit

An unscheduled visit may be made at any time throughout the clinical trial at the request of the patient or at the discretion of the principal investigator and/or the investigating physician.

The date and reason for the unscheduled visit will be recorded in the primary medical record and individual registration form. The data of the unscheduled visit will be registered in the primary medical documentation and the individual registration form of the patient.

The reasons for an unscheduled visit may be:
• Occurrence of AE/AR or observation of the course of AE/AR;
• Assessment of the dynamics of the patient's condition;
• Assessment of the dynamics of instrumental survey indicators;
• Changes in concomitant therapy;
• Another significant reason (must be specified).

The following clinical trial procedures will be performed during the unscheduled visit:
• Physical exploring;
• Measurement of vital signs (body temperature, heart rate, blood pressure, respiratory rate);
• Assessment of the presence and severity of AE/AR.

Additional clinical trial procedures during an unscheduled visit may include any of the clinical trial procedures that will be decided on a case-by-case basis by the investigating physician in consultation with the Sponsor.

6.7 Diet and fluid intake

Patients should follow a regular diet, fluid intake and physical activity throughout the study period.

Patients are advised to refrain from food and drink that may impair kidney and liver function (eg., alcoholic beverages, high-fat foods, fried foods in large quantities). When receiving blood samples - the last meal the day before at least 12 hours. Blood sampling is also performed on an empty stomach.

6.8 Mode of physical activity

Throughout the study period, patients should adhere to physiologically normal sleep and activity, without increased physical activity and exercise.

7 INFORMATION ON MEDICINAL PRODUCTS USED IN CLINICAL TRIAL

7.1 Study drug

Name of the medicinal product: BIOVEN
Composition:
active substance: Human normal immunoglobulin for intravenous administration;
1 ml of the drug contains normal human immunoglobulin 0.1 g (including immunoglobulin G (IgG) at least 95%);
Excipients: glycine (amino acetic acid); water for injections.
Pharmacotherapeutic group: Human normal immunoglobulin for intravenous administration.
ATC code J06B A02
Dosage form: solution for infusion.

The product is an immunologically active protein fraction (ratio of immunoglobulin G subclasses in the drug product: IgG1: 65.6 %, IgG2: 22.1 %, IgG3: 10.8 %, IgG4: 1.5 %) max. content of immunoglobulin A in the drug product is 50 μg/ml.

Active components of the product are antibodies that have a specific activity against different pathogenic agents such as viruses and bacteria including hepatitis A and B, herpes, chicken pox, influenza, measles, parotitis, poliomyelitis, German measles, whooping cough, staphylococcus, Escherichia coli and pneumococcus. It also has a non-specific activity to increase organism resistance.

The drug product is a native immunoglobulin G and retains all biological properties: complement activation; effector and opsonocytophagic function.

The product is an immunologically active protein fraction extracted from human blood serum or plasma and screened negative for antibodies to HIV-1, HIV-2, hepatitis C virus and surface antigen of hepatitis B virus, purified and concentrated by use of the fractionation method with water-alcohol precipitating agent that passed the phase of virus inactivation by use of solvent-detergent method and nanofiltration method.

7.2 Circulation of the study drug

Manufacturing, packaging and labeling of the investigated drug is carried out by the Sponsor - the manufacturer of the drug LLC "BIOPHARMA PLASMA".

The study drug is provided to the clinical base by the Sponsor in the amount required for this study. Transfer of the drug is confirmed by the act of transfer, which indicates: the number of drugs, batch numbers, expiration date, date of transfer. The act is signed by the Sponsor and the Responsible Researcher of the clinical base.

On a clinical basis, the study drug should be placed in an individual clearly marked package for each patient. The drug should be stored in a dry, protected from light at a temperature of 2- 8 degrees Celsius. The drug should be stored indoors, accessible only to the investigating physician or members of the research team to whom the responsible researcher has delegated the appropriate authority.

The person authorized by the Responsible Researcher keeps a journal of the study drug.

The journal, at each delivery of the drug to the patient, indicates: the name of the drug, date of issue, quantity, as well as the patient's number in this clinical trial and the patient's initials, the researcher's signature.

The packaging of the used drug is stored for a period determined by the Sponsor. Unused drugs are returned to the Sponsor, which is confirmed by the act of transfer.

To allow for re-testing if required by the Authority, the Study Sponsor must maintain a sufficient number of specimens of investigational medicinal products for one year after the expiration date or for two years after completion of the study (whichever is longer).

7.3 Labeling of the study drug

The study drug should be marked with the following symbols and fields:
• mark "Only for clinical trials";
• drug name;
• composition, including the content of active substances in the vial;
• method of administration;
• manufacturer's name, location, telephone number;
• serial number;
• expiration date;
• storage conditions;
• clinical trial code;
• center code;
• patient code.

The serial number indicated on the label must correspond to the batch number indicated in the quality certificate of BIOPHARMA PLASMA LLC.

7.4 The order of administration of the study drug

The introduction of SD will be carried out in a hospital or day hospital under the supervision of a investigator. The primary documentation and IRF record the time of drug administration, the occurrence of possible side effects.
As part of this clinical study, patients will receive the drug Bioven, 10% infusion solution, manufactured by "Biopharma Plasma" LLC at a dose of 0.8-1.0 g / kg 1 time per day for 2 consecutive days (course dose 1.6-2.0 g / kg). Allowed repeat course at same dosage in period 14-28 days from first infusion, if required.

Bioven should be administered intravenously at an initial rate of 0.5 - 1.0 ml / kg body weight / h for 30 minutes. In the absence of any undesirable side effects, the rate of administration can be gradually increased (recommended increase by 0.5 - 1.5 ml / kg body weight / h every 10 minutes). According to clinical studies, the maximum rate of administration is 8.5 ml / kg body weight/ hour.

The study drug is administered only in a hospital setting in accordance with the rules of asepsis.

The solution should be at room temperature before use. Turbid and sedimentary solutions are not used. A separate infusion system should be used for drug administration. When administering the drug should take into account the information provided in the instructions for medical use in the relevant sections: *Features of application, Special safety measures, Contraindications, Interaction with other drugs*, etc. Including but not limited to, measures to control the state of the coagulation system, hydration levels, kidney function and more.

According to the section "Special features of use", and as described in section 2.5 "Specifics of use" of this protocol for patients at risk of thrombosis, the introduction of immunoglobulin drugs in minimal doses and with a minimum infusion rate.

Before using the drug, make sure the patient's level of hydration is adequate. Patients at risk of high viscosity should be monitored for thrombosis symptoms and blood viscosity assessed. Patients in this study may receive concomitant therapy, which is used to treat comorbidities and vital signs.

The route of administration and dosage doesn't exceed the maximum single and course doses that can be used in the treatment of patients, according to the approved Instructions for medical use of the drug Bioven. They fully meet the requirements for the finished medicinal product, which are strictly regulated by the European Pharmacopoeia (monograph Eur. Ph.0918), the State Pharmacopoeia of Ukraine, and are within the limits set out in the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) EMA / CHMP / BPWP / 94038/2007 Rev. 5 June 28, 2018.

7.5 Concomitant therapy is allowed.

The use of any drugs other than those listed in section 7.4 is permitted. Patients should refrain from unprotected sexual intercourse throughout the study. Within 30 days of completion, study participants with preserved reproductive potential should use effective barrier contraception. The purpose of barrier contraception is to prevent sexually transmitted diseases, including HIV, HBV, HCV.

Effective methods of contraception include:

- Full maintenance;
- Condom or double barrier method.

7.6 Concomitant therapy is prohibited.

The following drugs are prohibited during the participation of patients in a clinical trial:

1. Corticosteroids are allowed only if the patient is taking long-term stable doses at least 2 weeks before screening;
2. The dose of corticosteroids or other immunosuppressant should remain unchanged for up to 31 days;
3. If patients have been treated with cyclophosphamide, azathioprine or attenuated androgens, the treatment regimen should be stable for at least 2 months before Day 0;
4. Monoclonal antibodies;
5. Avatrombopag;
6. Antiplatelet agents;
7. Anticoagulants.

8 EVALUATION OF EFFICIENCY

8.1 Primary efficacy endpoint:

Part (percent) of patients with response (R).

R is determined according to the following criteria:

- Patients with R: platelets count > $30x10^9$/L and at least a two-fold increase from the baseline count. This must be confirmed by at least 2 blood tests at least 7 days apart, and the absence of bleeding;

The primary efficacy variable is achievement of R during the study (yes/no).

8.2 Secondary efficiency endpoints

Part (percent) of patients with a complete response (CR).
CR is determined according to the following criteria:

- Patients with CR: platelets count > 100 x 10^9/L, which is confirmed by 2 blood tests performed at least 7 days apart and the absence of bleeding;

Part (percent) of patients with no response (NR).
NR is determined according to the following criteria:

- Patients with NR: platelet count < 30 x 10^9/L or less than two-fold increase of baseline platelet count. This must be confirmed by at least 2 blood tests performed approximately 1 day apart, or the presence of bleeding;

Part (percent) of patients with loss of response (loss of R).
Loss R is determined according to the following criteria:

- Patients with loss R: a decrease platelet count < 30 x 10^9/L or less than two-fold increase of baseline platelet count, or the occurrence of bleeding. Platelet counts confirmed at least 2 blood tests performed approximately 1 day apart.

Part (percent) of patients with loss of complete response (loss of CR).
CR loss is determined according to the following criteria:

- Patients with loss of CR: decrease platelet count < 100 x 10^9/L, or the occurrence of bleeding. Platelet counts confirmed at least 2 blood tests performed approximately 1 day apart.

Time (in days) from treatment start to onset of a response (R);
Time (in days) from treatment start to onset of a complete response (CR);
Duration (in days) of response (R);
Duration (in days) of complete response (CR);

Secondary efficacy endpoints are transformed into corresponding efficacy variables

Safety
- Frequency (percent) of adverse events
- Frequency (percent) of serious adverse events

9 SECURITY ASSESSMENT

9.1 Security endpoints

- Frequency of side effects;
- Frequency of serious side effects;
- Frequency of clinically significant changes in laboratory parameters and vital signs after infusion of the study drug;
- Dynamics of laboratory parameters.

9.2 Definitions concerning safety assessment.

Adverse event

Adverse event (AE) is any adverse change in the health of a patient or subject who has been administered a drug, regardless of the causal relationship with its use.

AE can be any adverse and unintentional change, symptom or disease, the time of occurrence of which does not exclude a causal relationship with the use of the drug, regardless of the presence or absence of a relationship with the use of the drug.

AEs may be abnormal laboratory parameters, first-time symptoms, or diseases that are related to the use of the drug, or if they existed before treatment of a condition whose severity or frequency increased after administration of the study drug.

Any medical condition present at the time of the patient's screening, but not deteriorating during the study, should not be recorded as an AE. However, if this medical condition worsens at any time during the study, it should be recorded as an AE.

Medical interventions, such as surgeries, diagnostic and treatment procedures, are not AEs, but they are interventions to treat the relevant medical condition and should be registered as a treatment for ANs.

Deviations from the norm of laboratory parameters

Any deviation from the norm of the laboratory indicator, which appeared for the first time, or the degree of severity, the frequency of which has increased compared to baseline, and meets at least one of the following criteria, must be recorded as AE:

- Requires medical intervention or diagnostic procedure;
- Leads to the cancellation of the study drug;
- Accompanied by complaints or symptoms, or causes them;
- Considered by the researcher as "clinically significant".

If there is any doubt as to whether a clinical event is an AE, it should be recorded as an AE.

Adverse reaction

Adverse reaction (AR) is an adverse reaction of the body associated with the use of a medicinal product (study drug), which implies the presence of at least a possible relationship with the use of a suspected drug (study drug).

During the study period, the investigator or study staff should conduct surveys and record information on adverse events / reactions as defined in this section of the protocol.

Unforeseen adverse reaction

Unforeseen AR - adverse reaction, nature, severity or outcome of which does not correspond to the information contained in the general characteristics of the medicinal product (instructions for medical use) or in the researcher's brochure (for unregistered medicinal product).

Serious adverse event

Serious adverse event (SAE)- Adverse medical event that leads to death, threatens life, requires hospitalization or continuation of hospitalization, leads to permanent or severe disability or incapacity, congenital anomalies or malformations, requires medical intervention to prevent the development of these conditions.

Death- is usually the result of the underlying clinical phenomenon that causes it. Therefore, the cause of death should not be considered serious. The only exception is "sudden death", when its causes have been established. In this case, "sudden death" should be considered AE, the reason for its "seriousness" - its "lethality".

Threat to life- the term "threat to life" is defined as an AE during which there was a threat to the patient's life. This does not mean any AE that can hypothetically lead to death in the case of its increased complexity.

Hospitalization- any adverse event leading to hospitalization or continuation of hospitalization will automatically be considered serious if it does not meet any of the non-inclusion criteria listed below:

hospitalization lasts less than 12 hours or hospitalization is planned in advance (it is an optional or planned operation, which was agreed upon before the start of this study).

Disability is defined as a significant impairment of a person's ability to perform daily functions, such as a congenital anomaly / malformation.

9.3 Detection and registration of AE

Detection and registration of SAE begins from the moment of signing the informed consent and lasts until the end of the patient's participation in the study.

Detection and registration of AE begins with the introduction of the drug and lasts until the end of the patient's participation in the study.

AE that occur between screening and administration of a drug, but does not considered as a SAE should be recorded as a medical history.

All AEs arising from the administration of the drug reported by the patient or detected during observation, physical examination and other diagnostic procedures must be registered in the AE Reporting Form attached to the Individual Registration Card.

Laboratory parameters will be evaluated during screening and throughout the study.

Information on any AE observed during the study period, from the first use of the study drug to the end of its use, is recorded in the patient's medical history / outpatient card and in the IRF registration section. All AEs are subject to registration, regardless of the severity or the presence of a causal relationship with the investigational medicinal product.

As AE should be classified:

- exacerbation of previous diseases;
- increase in the frequency or intensity of diseases or episodic phenomena observed earlier;
- diseases detected or diagnosed after the start of the study drug, even if it is possible before the patient's participation in the study;
- long-term, persistent disease or symptoms that were in the initial stage, the severity of which increased after the start of the patient's participation in the study;

- the appearance of new signs or an increase in the severity of the signs and symptoms of diabetes mellitus, which require urgent therapy, hospitalization, surgery and / or other intervention;
- clinically significant abnormalities detected by laboratory diagnostics or other examinations after the start of the study drug or available at baseline, the severity of which increased on the background of the study drug.

AS a AE should not be classified:

1. diseases or pathologies detected or diagnosed before the use of the investigational medicinal product, the severity of which does not increase;
2. situations in which there is no medically unfavorable event (for example, hospitalization for the planned surgery);
3. overdose of any of the studied drugs or concomitant drugs without unwanted signs or symptoms;
4. any clinically significant deviation of the laboratory indicator from the norm, detected before the first use of the study drug;
5. signs and symptoms observed during the study, which are associated with insufficient effectiveness of treatment.

The study will monitor the occurrence of any adverse events (AE). Table 1 presents the tolerance assessment scale.

9.4. Table 1. Tolerance assessment scale

Category	Category description
Good	At objective inspection in dynamics any pathological changes or clinically significant deviations does not find, data of laboratory inspection do not change reliably and do not go out of norm, the patient does not feel the side reactions.
Satisfactory	At objective inspection in dynamics insignificant changes which have temporary character and do not demand change of the scheme of treatment and carrying out additional medical actions come to light. and / or laboratory test data deviate slightly from normal. and / or there are minor side effects that do not cause serious problems to the patient and do not require discontinuation of the drug
Unsatisfactory	At objective inspection in dynamics the pathological changes demanding drug cancellation and carrying out additional medical actions come to light. and / or laboratory test data undergo clinically significant negative changes, which entails the need for additional examination and interpretation of data and / or there is an undesirable side effect that has a significant negative impact on the patient's condition, requiring discontinuation of the drug and the use of additional medical measures

Signs and symptoms, which are based on general pathology, if possible, should be noted as one complex phenomenon. If the diagnosis is known, it should be registered as the name of the AE. If the diagnosis is unknown, each complaint and symptom should be recorded as a separate AE.

The information to be recorded includes the type of phenomenon, the date of development of the AE, the researcher's assessment of the severity and relationship of the AE with the study drug, the date of termination (decision) of the AE, the severity of the AE, the measures taken and the outcome of the AE.

All the AEs should be monitored until they are adequately addressed.

During and after the subject's participation in the study, the researcher (medical institution) must ensure that the subject is provided with the necessary medical care in the event of any study-related adverse events, including clinically significant changes in laboratory parameters. The researcher (medical institution) is obliged to inform the research subject about intercurrent diseases that require medical care, which became known to the researcher.

9.5. Assessment of the severity of AE

The severity (expressiveness) of AEs indicates the extent to which AEs affect the patient's daily activities. The severity of the AE will be determined according to the NCI CTCAE criteria developed by the US National Cancer Institute (version 5.0) (in each paragraph a semicolon means "or") Table 2.

9.6. Table 2. The severity of NOT according to NCI CTCAE (version 5.0)

Severity 1	Easy; no symptoms or minor symptoms; only clinical or diagnostic observations; no intervention is required
Severity 2	Moderate; requires minimal, local or non-invasive intervention (eg, tamponade, cauterization); the restriction corresponds to the Social Daily Activities (SDA), Instrumental Activities of Daily Living (ADL *)
Severity 3	Severe or clinically significant but not life-threatening; hospitalization or continuation of hospitalization is required; restriction of vital activity; Self Care Activities of Daily Living (ADL **)
Severity 4	Life-threatening condition; immediate intervention is required
Severity 5	Death associated with AE

Daily activity (ADL):
* Social daily activities (SDA) include cooking, buying food or clothing, using the phone, handling money, etc.
** Self-care (SC) includes taking a bath, dressing and undressing, eating alone, using the toilet, taking medication and not being bedridden.

The terms "serious" and "severe" are not synonymous. Severe AE (Grade 3 or 4) should not always be considered serious. For example, leukocyte counts between 1000 and 2000 / mm3 should be considered grade 3 (severe), but such may not be considered severe. The benchmark for submitting information to regulators is the severity (not the expressiveness) of the AE.

9.7. Assessment of the causal relationship of AE with the study drug

In assessing the cause-and-effect relationship, the investigator should consider the possible etiology of the observed AE / AR phenomenon, which may be due to the study drug, concomitant

medications, underlying disease, comorbidities, study procedures, and other reasons. For all possible reasons, the researcher must determine the one that has the most likely causal relationship with the phenomenon. When assessing the causal relationship in the case of a serious AR, the report must provide a justification for this assessment. The justification should include all available evidence confirming the assessment, including the results of laboratory tests and other diagnostic procedures.

- **The causal relationship is determined.**The clinical phenomenon and / or changes in laboratory parameters are time-related to the drug and cannot be explained by comorbidities, other drugs or chemicals. The response to drug withdrawal should be clinically accurate. The phenomenon was confirmed by conducting, if necessary, a provocative test procedure.
- **Probable causation.**Clinical events and / or changes in laboratory parameters related to the time of administration of the drug, which can hardly be explained by concomitant disease or the use of other drugs or chemical compounds, in the presence of a clinically pronounced response to drug withdrawal.
- **A causal relationship is possible.** Clinical phenomenon and / or changes in laboratory parameters related to the time associated with the drug, but which can be explained by the presence of comorbidities or other drugs and chemicals. Information on drug response may be missing or unclear.
- **Unlikely causation.**Clinical events and / or changes in laboratory parameters may be related in time to the administration of the drug, but other drugs, chemicals or comorbidities provide a more plausible explanation for the phenomenon.
- **No connection.**The clinical phenomenon and / or changes in laboratory parameters are certainly not related to the use of the drug due to the unreasonable temporal relationship between the drug and AR and / or the improbability of such a relationship.

9.8. Categories of consequences of AE and their definitions

Measures taken:

- *Without treatment;*
- *Cancellation of the suspected drug;*
- *Reducing the dose of the suspected drug;*
- *Cancellation of concomitant treatment;*
- *Use of drug therapy;*
- *Non-drug therapy (including surgery).*

The phenomenon passed without consequences -there are no symptoms, and the patient is not treated to eliminate this AR.

Stabilization of the state -the result of AR is classified as stabilization of the state according to the researcher.

The phenomenon passed with consequences -the phenomenon was curtailed, but its consequences remained; as a result of AR the patient has a temporary or permanent disability / incapacity; any AR that have passed with consequences are classified as serious AR.

The phenomenon has not yet passed -symptoms persist.

Death of the patient.

The result is unknown.

9.9. Reports of SAE

In the case of any SAE, the Study Sponsor must be notified within 24 hours of the researcher first learning about the SAE. During the development of SAE, the researcher fills in the SAE registration form and determines whether it is associated with the study drug and sends by fax or e-mail the completed form to the Sponsor of the study. The original SAE form and the fax confirmation letter must be kept. The fact of SAE should be recorded in the IRF. The sponsor has the right to urgently request from the researcher additional information about SAE for reporting to health authorities.

After the initial urgent notification, a detailed written notification must be submitted as soon as possible. Primary and subsequent reports should identify the subjects of the study by the unique code assigned to them, and not by the names of the subjects, personal identification numbers and (or) addresses.

In case of hospitalization of the patient in connection with the development of SAE, it is necessary to send as soon as possibleby fax or e-mail to the Sponsor of the study a copy of the hospital discharge.

The sponsor of the study or his authorized representative is responsible for notifying by telephone or fax of unforeseen or life-threatening SAEs related to the use of the study drug (in the form of urgent reports) to the relevant authorities and competent authorities within 7 calendar days obtaining information about SAE. The sponsor of the study or his authorized representative will report other significant SAEs related to the use of the study drug to the appropriate authorities, researchers and the local ethics committee by providing a written safety report within 15 calendar days of receiving the information about SAE.

In Ukraine, the sponsor shall immediately register and within 7 calendar days from the moment he became aware of it, inform the SEC of the Ministry of Health of Ukraine and the Ethics Commission of all suspected unforeseen serious adverse reactions to the investigational medicinal product that resulted in death or threat for the life of the subject. Additional information on this subject is provided by the SEC of the Ministry of Health of Ukraine and the Ethics Commission within the next 8 calendar days. The notification of a suspected unforeseen serious adverse reaction must be made in accordance with the order of the Ministry of Health of Ukraine № 690 of 23.09.2009, as amended.

In addition to the death notification, the researcher shall provide any additional information at the request of the regulatory authority (autopsy report and final medical reports after their proper preparation in accordance with the legislation of the country where the study is conducted - Ukraine).

9.10. Requirements for reporting after completion of the study drug

If the Researcher receives information about any AR that has occurred at any time after the patient has taken the study drug, and there are sufficient grounds to suggest a connection between this phenomenon and the study drug, the Researcher must notify Sponsor.

9.11. Contraception and pregnancy

Prior to the start of the study, men and women of childbearing potential will be informed of the importance of contraception during the study and within 3 weeks of completion. Reliable methods of contraception include: surgical sterilization, double barrier method of contraception, local contraception. The study will also be open to women who do not use acceptable methods of

contraception if they are declared unfit for childbirth: women who have undergone a hysterectomy (removal of the uterus) or tubal ligation, women with a clinical diagnosis of infertility, and women who are in the menopausal period more than 1 year (absence of menstruation for at least 12 months).

9.12. The period of time during which the collection of information about pregnancy is required.

It is necessary to collect information on the course of any pregnancy throughout the clinical trial, starting with the first dose of the study drug.

9.13. Actions to be taken in case of pregnancy.

The researcher will collect information about the pregnancy of any patient who became pregnant during the study. The researcher will record information about the onset of pregnancy and pass the information to the Sponsor of the study. The procedure for reporting a pregnancy is similar to the procedure for reporting a serious adverse event.

Pregnancy is not considered as a AE, but any complication of pregnancy or planned termination of pregnancy on medical grounds will be registered as AE, and such a patient will be monitored. Spontaneous abortion is always considered a AE and should also be reported to the Sponsor. In addition, the Sponsor must be notified of any AE that has occurred as a result of a post-study pregnancy that is considered by the investigator to be reasonably related to the study drug being studied. Although the researcher is not required to actively seek this information from former study participants, he / she may learn about AE spontaneously from the participants' own reports. Patients who become pregnant will be excluded from the study.

10 STATISTICS

10.1 Content of statistical analysis

The null hypothesis for the primary efficacy endpoint H0: $p-p_0 \leq \delta$, where clinical effectiveness p is the proportion of patients who responded to therapy with the study drug BIOVEN; p_0- proportion of patients responding to therapy according to literature data: δ- the limit of the difference of proportions without clinical significance. An alternative hypothesis H1: $p-p_0 > \delta$ («non-inferiority study» according to the guideline EMA «Points to consider on switching between superiority and non-inferiority» CPMP/EWP/482/99, London, 27 July 2000 та EMA "ICH Topic E 9 Statistical Principles for Clinical Trials" CPMP/ICH/363/96).

According to the EU recommendations on clinical studies of immunoglobulin normal for intravenous administration *(Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94033/2007 rev. 3, 28 June 2018)* the obtained results will be compared with literature data.

To test the null hypothesis, a two-tailed test will be used, based on the principles of estimating a 95% confidence interval for the difference in proportions and comparing it with the lower limit of equivalence (at a significance level of α 5%). For non-inferiority research, the null hypothesis is rejected if the conditions are met:

$$\sqrt{n}(p-p_0-\delta) / \hat{p}(1-\hat{p}) > z_{\alpha/2}$$

or

$$(p-p_0-\delta) / \sqrt{\left(\frac{p(1-p)}{n} + \frac{p0(1-p0)}{n0}\right)} > z_{\alpha/2}$$

Confidence intervals of the difference will be calculated according to the generally accepted Wald method:

$$(p_1-p_2) \pm z_{\alpha/2} * \sqrt{\left(\frac{p1(1-p1)}{n1} + \frac{p2(1-p2)}{n2}\right)}$$

The number of patients for the portion taken from literature sources is taken from the 2020 publication and will be 82 [Parodi E, Russo G, Farruggia P, Notarangelo LD, Giraudo MT, Nardi M, et al. Management strategies for newly diagnosed immune thrombocytopenia in Italian AIEOP Centres: do we overtreat? Data from a multicentre, prospective cohort study. Blood Transfus. 2020;18(5):396.]

Methods of descriptive statistics (for categorical variables - number and part in %, for quantitative variables - n, arithmetic mean, median, standard deviation, minimum and maximum), including construction of graphs and charts, methods of interval estimation (calculate of 95% confidence intervals for proportions and differences of fractions).
For variables that are "time to event" survival curves will be constructed in each group using the Kaplan-Meier method, median survival will be estimated, and group comparisons will be made using the log-rank test. If the survival curves intersect, then Cox regression will be used to compare the groups according to these variables.

To evaluate the significance in the dynamics in the case of evaluating the parameter on two visits (before and after):
- To assess the dynamics of quantitative variables, the Student's test for paired data or the Wilcoxon signed rank test will be applied, depending on the results of testing the normality of the distribution of differences [after - before] using the Shapiro-Wilk test.
- To assess the dynamics of categorical variables in groups, the McNemar criterion or the criterion of homogeneity of marginal frequencies will be applied, depending on the number of categories.
- To assess the statistical significance of differences in categorical variables in unrelated groups, Pearson's chi-square or Fisher's exact test will be applied (depending on the frequency distribution in table 2*2).
To evaluate the dynamics in the case of measuring variables on more than two visits, methods of univariate analysis of variance (ANOVA) will be used followed by contrast analysis (simple contrasts) or a posteriori analysis using Tukey's test. Analysis of covariance (ANCOVA) will be used to compare those variables for which the data were heterogeneous at baseline.
To verify the prerequisites for the application of variance and covariance analyses, a check of the normality of the data distribution and their residuals will be performed using the Shapiro-Wilk test. If the residuals are not normally distributed, or if the data fail the normality test, an appropriate rank analysis will be performed.
For the Shapiro-Wilk test, the significance level will be 0.01, and for other criteria - 0.05. In the event of the effect of multiple comparisons, an adjustment of the level of significance will be applied using the Holm method or the Benjamini-Hochberg method.

10.2 Sample size assesment

The sample size is determined in accordance with S.C. Chow, J. Shao, H.Wang. Sample Size Calculations in Clinical Research. London: Taylor&Francis, 2003. – 358 p.
Since the main variable will be expressed as the proportion of patients who responded to therapy with BIOVEN 10%, the sample size was determined based on the possibility of using non-inferior efficacy assessment criteria with a two-sided test at a significance level of α 5%.
Null hypothesis H0: $p–p_0 \leq \delta$, where the clinical effectiveness *p-* the proportion of patients who responded to therapy with the drug BIOVEN 10%; p_0- proportion of patients responding to therapy according to literature data. δ- the limit of the difference of proportions without clinical significance. An alternative hypothesis H1: $p-p_0 > \delta$.
The sample size in a group when comparing proportions for a study with non-inferiority efficiency is calculated by the formula (Chow, S. C., Wang, H., & Shao, J. (2007). Sample size calculations in clinical research. Chapman and Hall/CRC.):

$$n=(Z_{a/2}+Z_{b/2})^2\times(p\times(1–p))/ (p – p_0 – \delta)^2$$

According to the literature, the effectiveness of IVIG when used in patients with ITP varies between 60-80% [*Anurag Singh, Günalp Uzun, Tamam Bakchoul / Primary Immune Thrombocytopenia: Novel Insights into Pathophysiology and Disease Management // J. Clin. Med. 2021, 10, 789. https://doi.org/10.3390/jcm10040789*], [*Godeau B., Caulier M-T. Decuypere L. et al. Intravenous immunoglobulin for adults with autoimmune thrombocytopenic purpura: results of a randomized trial comparing 0′5 and 1 g/kg b.w. // British Journal of Haematology, 1999, 107, 716-719; Ruqayyah J. Almizraq, Donald R. Branch Efficacy and mechanism of intravenous immunoglobulin treatment for immune thrombocytopenia in adults // Ann Blood 2021;6:2 | http://dx.doi.org/10.21037/aob-20-87; Drew Provan, Roberto Stasi, Adrian C. Newland et al. International consensus report on the investigation and management of primary immune thrombocytopenia // Blood, 14. - Jan 2010, Vol. 115, Number 2*]). However, the most similar to this study (in terms of performance evaluation standards and study design) is the 2020 publication. In this publication, the drug administration

scheme is recommended by the EMA and this Protocol, the total number of patients in the group is 82, the effectiveness of the use of IVIG in the treatment of ITP is indicated - 78% [Parodi E, Russo G, Farruggia P, Notarangelo LD, Giraudo MT, Nardi M, et al. Management strategies for newly diagnosed immune thrombocytopenia in Italian AIEOP Centres: do we overtreat? Data from a multicentre, prospective cohort study. Blood Transfus. 2020;18(5):396.]. According to our data and data from the literature, immunoglobulin belongs to drugs with a highly variable efficiency of 20-25%. Therefore, for a non-inferiority study, we consider it appropriate to set δ (the limit of the difference in efficiency between the obtained and expected results) at the level of -25%.

Thus, for a significance level of 5% and a statistical power of 80%, the effectiveness of the drug in the comparison model reaches 78%, the limit of the difference in specific weights (difference in effectiveness) without clinical significance δ is - 0.25. Then the calculation of the minimum sample size will look like this:

$$n = (1{,}96+1{,}28)2\times (0{,}78\times(1-0{,}78) / (0{,}78 - 0{,}78+0{,}25)^2 = 29$$

Considering the risk of dropping out of patients for various reasons (20%), 36 patients will be included in the study.

10.3 General plan of statistical analysis

10.3.1. General principles of statistical analysis

Statistical analysis is performed by a qualified biostatistician. It includes:
— description of patients included in the study;
— the number of patients dropped out of the study;
— the number of AE/AR, SAE;
— analysis of initial homogeneity;
— efficiency analysis;
— tolerability and safety analysis;
— statistical conclusions.

10.3.2. Analysis of the initial state/base-line state of the group

Analyze the group according to clinical and demographic parameters at the time of inclusion in the study. Use methods of descriptive statistics to describe the initial state/base-line state in groups (for quantitative parameters - n, arithmetic mean, median, standard deviation, minimum and maximum value; for categorical parameters - number and share in %).

10.3.3. Analysis of effectiveness

Additional information about the statistical model for evaluating the effectiveness of the drug by the main variable is given in Section 10.1. "The content of statistical analysis".

A) The primary outcome of efficiency – Proportion (%) of patients with response (R).

Primary efficiency variable – achievement of R during the study.
*R is defined according to criteria *:*

- Patients with R: the number of platelets > $30x10^9$/l and at least a two-fold increase from the baseline count. This must be confirmed by at least 2 blood tests performed once every 7 days and the absence of bleeding;

The categories of the variable will be defined as "Yes" or "No" respectively.

** The criteria are defined according to the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94033/2007 rev. 4, 16 December 2021 as well as according to the criteria of the international working group on ITP in 2009. (Rodeghiero, F., Stasi, R., Gernsheimer, T., Michel, M., Provan, D., Arnold, D. M., ... & George, J. N. (2009). Standardization of terminology, definitions, and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood, The Journal of the American Society of Hematology, 113(11), 2386-2393.);*

B) Secondary effectiveness variables.

For variables assessed once at the final visit, descriptive statistics methods will be used to describe these variables (for quantitative parameters - n, arithmetic mean, median, standard deviation, minimum and maximum value; for categorical parameters - number and share in %) . 95% confidence intervals will be calculated. In the case of measuring variables at more than two visits, one-way analysis of variance (ANOVA) methods will be used.

Censored data will be analyzed using the Kaplan-Meier method or the log-rank test.

Secondary efficacy endpoints are transformed into corresponding efficacy variables:

Achieving a complete response (CR) during the study.

*CR is determined according to the criteria *:*

- Patients with CR: platelets count > 100 x 10^9/L, which is confirmed by 2 blood tests performed at least 7 days apart and the absence of bleeding;

The categories of the variable will be defined as "Yes" or "No" respectively.

The variable is analyzed for patients who achieved a response (R) during the study.

Non-response (NR) during the study.

*NR is determined according to the criteria *:*

- Patients with NR: platelet count < 30 x 10^9/L or less than two-fold increase of baseline platelet count. This must be confirmed by at least 2 blood tests performed approximately 1 day apart, or the presence of bleeding;

The categories of the variable will be defined as "Yes" or "No" respectively.

The variable is analyzed relative to the total number of patients included in the analysis.

Loss of response (loss of R).

*R loss is determined according to the criteria *:*

- Patients with loss R: a decrease platelet count < 30 x 10^9/L or less than two-fold increase of baseline platelet count, or the occurrence of bleeding. Platelet counts confirmed at least 2 blood tests performed approximately 1 day apart.

The categories of the variable will be defined as "Yes" or "No" respectively.

The variable is analyzed for patients who achieved a response (R) during the study.

Loss of complete response (loss of CR).

*CR loss is determined according to the criteria *:*

- Patients with loss of CR: decrease platelet count < 100 x 10^9/L, or the occurrence of bleeding. Platelet counts confirmed at least 2 blood tests performed approximately 1 day apart.

The categories of the variable will be defined as "Yes" or "No" respectively.
The variable is analyzed for patients who achieved a complete response (CR) during the study.

Time (in days) from treatment start to onset of a response (R);
A Kaplan Meier curve will be constructed and the median time to event will be estimated. The variable is analyzed for patients who achieved a response (R) during the study.

Time (in days) from treatment start to onset of a complete response (CR);
A Kaplan Meier curve will be constructed and the median time to event will be estimated. The variable is analyzed for patients who achieved a complete response (CR) during the study.

Duration (in days) of response (R);
A Kaplan Meier curve will be constructed and the median time to event will be estimated. The variable is analyzed for patients who achieved a response (R) during the study.

Duration (in days) of complete response (CR);
A Kaplan Meier curve will be constructed and the median time to event will be estimated. The variable is analyzed for patients who achieved a complete response (CR) during the study.

C) Quantitative variables of efficiency, which are measured at study entry (T_{start}) and at the final visit ($T_{endpoint}$).
Provide indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for time points T_{start} and $T_{endpoint}$, and also for differences [$T_{endpoint} - T_{start}$].
Represent this dynamic graphically.
Calculate for these parameters their relative change in comparison with the initial state/base-line according to the formula:

$$X\,(\%) = \frac{T\,endpoint - T\,start}{T\,start} * 100,$$

Evaluate the dynamics using the Student's paired test or the Wilcoxon signed rank test, depending on the results of testing the normality of the distribution of differences [$T_{endpoint} - T_{start}$] using the Shapiro-Wilk test.

D) Evaluation of quantitative variables measured at more than two measurement points.
Specify the indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for each measurement point, as well as for the differences [$T_i - T_{start}$], where *i* are subsequent visits. Build a dynamics graph.
Calculate for these parameters their relative change at each subsequent visit in comparison with the initial state according to the formula:

$$X\,(\%) = \frac{T\,i - T\,start}{T\,start} * 100,$$

where *i* is subsequent visits according to the patient examination scheme.
Evaluate the dynamics of changes in quantitative variables using univariate analysis of variance (ANOVA) or rank analysis depending on the normality of the distribution, which is tested using the Shapiro-Wilk test. At the same time, the dependent variable is the analyzed parameter, the "visit" factor is a fixed parameter. To assess the magnitude and significance of the difference between visits using contrast analysis (simple contrasts) or post hoc analysis using Tukey's test (for ANOVA) or Wilcoxon signed rank test with Holm's correction (for rank test). To verify the prerequisites for the application of variance analysis, a check of the normality of the distribution of residuals will be

performed using the Shapiro-Wilk test. In the event that the balances are not normally distributed, an appropriate rank analysis will be performed.
Make statistical conclusions.

10.3.4. Analysis of safety and tolerability parameters

A) *Data on AE/AR,* Indicators of descriptive statistics (frequency and part in percent) and a list of adverse reactions according to the MeDRA classification
B) Data on SAE. Indicators of descriptive statistics (frequency and part in percent) and a list of adverse reactions according to the MeDRA classification.
Clinically significant deviations in indicators characterizing the safety and tolerability of the drug: *Laboratory results of general blood analysis, biochemical blood analysis and general urinalysis; the result of determining the Coombs test and signs of hemolysis.*
Provide descriptive statistics for these indicators (n, arithmetic mean, median, standard deviation, minimum and maximum value) for all visits.
To evaluate the dynamics of laboratory indicators, we used the Student's test for paired data or the Wilcoxon signed rank test, depending on the normality of the distribution of paired differences ["after" - "before"]. Create dichotomous variables with the categories "normal" and "abnormal", calculate the indicators of descriptive statistics (frequency and part in %) for these variables.
Measurement results of heart rate, blood pressure, respiratory rate, body temperature. Indicators of descriptive statistics (n, arithmetic mean, median, standard deviation, minimum and maximum value) for each visit in accordance with the patient examination scheme. Evaluate the trend of changing these parameters.

10.3.5. Significance level

The level of significance for the Shapiro-Wilk test is set at 0.01, and for other statistical tests at 0.05. In the case of the effect of multiple comparisons, the adjustment of the level of significance will be applied using the Holm method or the Benjamini-Hochberg method.

10.3.6. Work with missing or incomplete data.

Missing or incomplete data will be replaced using the Last-Observation-Carried-Forward (LOCF) method. Or by the method of enlarging the intervals for series where the transfer of the last measurement is not applicable.

10.3.7. Conclusion on non-inferiority effectiveness

In accordance with EMA recommendations for clinical studies of immunoglobulin normal for intravenous administration *(Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94033/2007 rev. 4, 16 December 2021)* the obtained results will be compared with literature data The conclusion of non-inferiority of the drug Bioven, solution for infusions 10%, in the treatment of chronic immune thrombocytopenia, will be made according to the main efficacy variable using an approach based on confidence intervals.
To do this, the calculated limits of the 95% confidence interval (CI) for the difference in the percentage of positive results according to the main variable ("the drug is effective") for the studied group must be compared with the limit of the non-inferiority zone - effectiveness that is not inferior (-25%) to the calculated based on data for comparison. If the lower limit of the CI is greater than the

lower limit of the non-inferiority zone (non-inferiority), then it will be considered that the study drug is not inferior in effectiveness compared to literature data.

10.4. Data set for analysis

ITT (Intention-to-treat population) - all study participants who took the study drug at least once. Data from this sample will be used for safety analysis.
PP (Per Protocol) - all patients who met the requirements of the protocol. This population includes all patients who received protocol therapy in full, completed all scheduled visits, and had no significant protocol deviations. The data obtained on this sample will be used for analysis according to the criteria of drug effectiveness.

10.5. Representation of summary results

The results of the statistical analysis of the obtained results should be presented in the form of tables, which, if necessary, are illustrated with graphs and diagrams. Presentation of data should be structured, in accordance with the purpose and tasks of Study. It is necessary to clearly indicate the methods used, to characterize the array of data.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Clinical trial monitoring

Regular visits of the study monitor on behalf of the sponsor and in accordance with standard operating procedures (SOPs), before, during and after the study contribute to the success of the study, and guarantee accurate data collection, timely detection of possible errors, documentation of clinical trials and ensuring the protection of the rights of clinical trial participants, compliance of the trial with the requirements of the legislation of Ukraine and Republic of Turkey.

Routine monitoring of the study includes:

- confirmation of the proper conduct and documentation of the process of obtaining informed consent, as well as screening and inclusion of participants in the study;
- verification of data in the IRF (eCRF) and primary medical records of study participants;
- confirmation of compliance with the requirements of the clinical center staff to perform diagnostic and therapeutic procedures of the study protocol;
- confirmation of documented deliveries, storage, distribution and disposal of the investigational medicinal product and clinical trial materials;
- confirmation of the competence of the staff of the clinical center, external laboratory, necessary for the study;
- confirmation of compliance of diagnostic and laboratory equipment with the requirements of safe and adequate use during the study;
- confirmation of the investigator's interaction with the local ethics committee on clinical trial safety and making amendments to the clinical trial protocol agreed with the sponsor.

Quality control of trial results is carried out by the Sponsor's staff / Sponsor's authorized representative (eg., CRO) who maintains an electronic survey database that identifies inconsistencies, erroneously entered data and omitted data.

If you have any questions or need clarification, the investigator is sent a special form by e-mail / fax, the request for which must be satisfied in writing within 7 days after delivery. In accordance with the requirements of the legislation, the sponsor or authorized state bodies have the right to inspect (audit) the logistics of the study and clinical trial documentation. The investigator must provide access to the documentation and all necessary information to the persons authorized to conduct the audit or inspection.

11.2. Amendments to the protocol, rejections, and violations of the protocol

The signatures of the investigators on the page of the protocol mean a written confirmation of consent to conduct study in accordance with this protocol. During the clinical study, changes and additions may be made to the study materials. Such changes and additions should be considered as amendments.

Amendments to clinical trial materials are considered significant if they may affect the objectives, forms of organization, methodology, statistical methods of processing the results of clinical trials. Amendments to the protocol should be kept together with the original version of the protocol. The number of the amendment and the date of its entry into force must be written on the title page of the protocol.

All deviations from the protocol during the study should be recorded during the monitoring of the clinical trial and reported to the Sponsor.

The investigator should not deviate from the protocol, except where it is necessary to exclude a serious risk to the health of patients in the study. If there are other unexpected circumstances that

require deviations from the protocol procedures, the investigator should consult the developer of the medicinal product or its representative (and the Ethics Committee, if necessary) to determine the appropriate procedure.

The study center must document all deviations from the protocol in the patient's original documentation. In the event of a significant deviation, the center should notify the developer of the medicinal product or its representative (and the Ethics Committee, if required). To do this, the investigator must fill out the form "Violation / deviation from the protocol" which is sent by fax to the clinical trial department of the company developing the drug. During the monitoring of the study center, the monitor of the clinical trial department may detect violations / deviations from the clinical trial protocol. In this case, he is responsible for notifying the investigators of the identified violations and for compiling the form "Violation / deviation from the protocol."

Violations/deviations from the protocol can be divided into gross (significant) and non-gross (minor). Examples of such deviations are given below.

Significant deviations from the protocol:

1) unsigned/incorrectly signed informed consent of the patient to participate in a clinical trial;
2) violation/deviation from the criterion of patient selection;
3) significant violation of the schedule of study procedures (deviation from the list of procedures provided by the protocol);
4) significant violation/deviation from the schedule of treatment of patients (inconsistency of the therapy provided by the protocol, replacement of packaging of the study drug);
5) unreasonable disclosure of the patient's code and failure to notify the company conducting the study;
6) failure to report (concealment of information) about a serious adverse event that occurred to the patient during the study;
7) non-compliance with the conditions of storage of the study drug.

Minor violations/deviations from the protocol:

1) violation of the schedule of study procedures on the days of the visit, slightly exceeding the time frame provided by the protocol;
2) untimely (late) notification of SAE;
3) other unforeseen deviations.

Significant deviations include, but are not limited to, deviations that include forgery or improper study, increase the risk to the patient's health or distort the analysis of the main results of the study. All deviations from the protocol during the study should be recorded during the monitoring of the clinical trial and notification to the Sponsor.

11.3. Audits of quality control bodies and regulatory bodies

The study center may also be subject to quality assurance audits by the medicinal product developer or its authorized representatives. In these circumstances, the auditor appointed by the Sponsor will contact the Center in advance to arrange an audit visit. The auditor may want to visit the place where laboratory samples are collected, where the drug is stored, and any other place used during the study.

In addition, if it is possible that this study will be audited by regulatory authorities, the clinical trials of the study drug developer should be reported immediately.

12. ETHICAL AND LEGAL ASPECTS OF CLINICAL TRIAL

12.1. General requirements

The trial must be approved by the official regulatory authorities of the host countries.

The study is conducted in accordance with the principles set out in the Helsinki Declaration of the WMA (adopted at the 18th WMA Assembly in Helsinki in June 1964, the last edition was adopted at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

Investigators involved in a clinical trial shall, prior to its initiation, provide the Sponsor with signed and dated resumes containing a description of the clinical trial experience, data on professional and scientific activities.

12.2. Ethical clinical trial

The approval of the trial by the Local Ethics Committee (Medical Ethics Commission) guarantees the observance of ethical norms during the study.

Patient participation in the study is voluntary. The patient has the right to refuse to participate in the study at any stage, it is not possible to involve the patient without signing the patient's informed consent.

Each patient will be informed that his / her personal data, including those related to the study, may be examined by the study monitor, the quality assurance auditor or the health inspector, in accordance with applicable regulations.

12.3. Local Ethics Committee (LEC)

Ethical examination of clinical trials of medicines is conducted by the Local Ethics Committee. The Local Ethics Committee (LEC) is committed to protecting the rights, safety and well-being of all study patients. The LEC must assess the suitability of the investigators qualifications of the proposed study on the basis of his scientific biography (curriculum vitae). Prior to the start of the study, the approval of the protocol, the Written Informed Consent Form and any other document provided to the patient should be obtained from the LEC of the facilities where the clinical trial will be conducted. The LEC opinion must be dated, signed and issued in writing. A clinical trial can only be initiated after approval of the appropriate LEC. The investigator, the head of the medical institution or another responsible person must timely submit the necessary documentation for consideration to the local ethics committee. The documents submitted to the LEC may differ from institution to institution, but must include the final version of the clinical trial protocol, the Patient's Informed Consent and the Written Informed Consent Form, the Investigator's Brochure with information on the investigational medicinal product.

A list of all those advising the LEC, as well as the head (s) of the committee, will be included in the study report.

12.4. Approval of the protocol by regulatory authorities

The sponsor of the study provides a copy of this protocol, as well as other necessary documentation related to the study, for consideration by the regulatory authority and the commission on ethics at the LPZ.

12.5. Obtaining the written informed consent of the patient

The investigator will inform each potential study participant about the study drugs, the purpose and nature of the study, the expected benefits, the degree of risk and the requirements that the patient will have to comply with during the study.

Each patient / legal representative is also provided with written information about the investigational drugs and studies contained in the Patient Information. Oral and written information is provided to the patient in Turkish.

The patient / legal representative should have sufficient time to consider their participation in the study and to ask the investigator questions of interest. The investigator is required to explain in detail the sections of the Informed Consent that the patient has questions about. The investigator should not put pressure on the patient / legal representative to influence his / her decision.

If the patient / legal representative has decided to participate in the study, he / she must fill in and sign the Informed Consent Form in 2 copies. One copy of the Informed Consent is handed over to the patient / legal representative, the other remains in the investigator's file.

The consent must be signed before the patient undergoes any procedures related to the study. Only patients who have signed the Informed Consent Form will be included in the study.

13. DATA WORKING AND RECORD KEEPING

13.1. Clinical trial documents

The Sponsor Company provides the following key documents and materials to the study center:
- Study protocol (and amendments to it if available);
- Investigator's brochure;
- IRF;
- Information for the patient with the Informed Consent Form;
- Scales, questionnaires, questionnaires (if any);
- Investigator file;
- Study drugs;
- A copy of the insurance contract;
- Contract;
- A copy of the Approval of the regulatory authorities of the country in which the clinical study is conducted by the local ethics committee (in the presence of LEK);
- Documents required for submission to the local ethics committee.

The investigator provides the Sponsor with the following basic documents before the start of the study:
- Cover letter to the local ethics committee (if there is a LEK);
- Signed agreement on confidentiality;
- Signed "Agreement with the principal investigator" - agreement with the terms of the protocol;
- Contract;
- Approval of the study and clinical trial documents by the local ethics committee (in the presence of LEK);
- List of members of the local ethics committee (if available by the LEK);
- Recently compiled scientific summaries (Curriculum Vitae) of all investigators and co-investigators (signed and dated);
- Laboratory standards with the date and signature of the responsible employee of the laboratory (when using a local laboratory), scientific resume of the head of the laboratory;
- Certificates for medical / laboratory equipment (at the request of the Sponsor).

The investigator must keep the documentation related to the study (primary documentation, copies of the IRF and the investigator's file) for 15 years after the completion of the study.

13.2. Provision (supply) of study materials and documents.

The Sponsor shall provide the Investigator with the study medicinal product, the Clinical Trials Protocol, the Investigator's Brochure, and other documents, materials and equipment (where possible) necessary for the investigation.

The investigator must provide the Sponsor with a signed clinical trial agreement, a signed confidentiality and non-disclosure agreement, a copy of the LEC's approval, a list of LEK members, a current resume of the principal investigator and investigator team, unused IRF and other documents (where possible).

All deliveries to the center and collection of clinical trial materials from the center will be documented using transfer / return forms of clinical trial materials.

13.3. Primary documentation

The availability of primary documentation in the study center is necessary to confirm the existence of patients and confirm the veracity of the information collected. Primary documentation includes original documents that are relevant to the study, treatment, history, and description of the patient's condition. For example, such documents include medical history and discharge (printouts) with the results of laboratory tests.

The following information must be reflected in the primary medical records:
• Demographic data;
• Information regarding inclusion and non-inclusion criteria;
• The fact of participation in the study, indicating the study number and patient number;
• Date and time of all visits;
• Anamnesis and physical examination data;
• Adverse events;
• Preliminary therapy and concomitant treatment;
• Results of instrumental research;
• Results of laboratory tests;
• Information on the intake of the investigational medicinal product;
• Reason for premature termination of participation in the study (if any).

13.4. Data collection: individual registration forms (IRF, eCRF)

All data obtained, including test results, for each patient should be recorded in the IRF. For patients who dropped out of the study for any reason early, all the necessary documentation is completed, indicating the reason for the early termination of the study.

The IRF can be in paper or electronic form, designed to record all the necessary protocol information for each patient of the study, which must be provided to the Sponsor.

Individual registration cards are used for:
- Ensuring data collection in accordance with the Protocol;
- Satisfaction of the requirements of the control and permitting system for the collection of information;
- Contribute to the efficient and complete processing of data, their analysis and reporting on the results, promote the exchange of security data among the project team and other departments of the organization.

The data collected during the test at the study center must be complete and accurately reflect what happened to each test.

The monitor should check the information entered in the IRF for compliance with the primary documentation, which will confirm the absence of discrepancies in the various documents when registering data. If the monitor detects inconsistencies, the necessary changes will be made to the IRF.

The monitor should monitor the completeness and correctness of the IRF. The monitor doesn’t have the right to make corrections to the IRF itself.

The investigator or other person authorized to complete the IRF must enter the data into the IRF during or immediately after each visit, but no later than 5 working days after the visit, according to the primary documentation.

13.5. Data processing and changes in the IRF

Data processing will be coordinated by the Sponsor or CRO. All information about each patient is recorded in accordance with the protocol, must be entered in a timely manner in the IRF, which was developed in accordance with the protocol.

To ensure the most efficient process of data collection and transmission to the investigator or the authorized employee of the study center, it is necessary to enter information into the IRF as soon as possible, immediately after the patient's visit. IRF and other documents (such as primary documentation) should be available for verification by the monitor.

Any changes or corrections are made to the IRF after the verification of the primary documentation and will reflect:

- The value to be corrected - crossed out, but with the ability to read;
- Correct value;
- Date and data of the person who made changes to the IRF data.

After verification of the data and changes in the IRF, requests for clarification will be addressed. The investigator is obliged to respond to requests for clarification of data within 5 working days after their generation / sending to the center. In rare cases, permission is allowed for requests for clarification of data before the next scheduled monitoring visit.

13.6. Confidentiality of patient data

The patient's personal medical information obtained during the study is considered confidential and may not be disclosed to third parties. This information may be communicated to the patient's physician or other health care professional responsible for the patient's health (with the patient's consent only).

Each patient will be assigned an identification number, which will be used instead of the patient's last name to maintain the confidentiality of personal data when transmitting information about AEs or other data related to the study.

Complete identification information about each patient will be kept only by the investigator, who must provide it at the request of the auditor, insurance company or other official bodies. This information should be kept confidential. To this end, the study center will fill in and keep a Patient Identification Journal, which contains information about the patient (name, date of birth, outpatient card number in the institution, etc.) and the code assigned to him. The identification journal or its copy is not transferred to the Sponsor / CRO and must be kept in the archives of the study center after the end of the study. This journal provides the identification of coded information about the study participant with his personal data and ambulatory card.

All those involved in clinical trials should ensure the confidentiality of patients, not allowing the use of any information that could identify the patient (eg name or address).

13.7. Investigator file

The investigator is required to keep all records to ensure complete documentation of the study process in accordance with the standards of Good Clinical Practice. The investigator must keep all

necessary clinical trial documentation for 15 years, unless otherwise required by the Sponsor; The investigator must take steps to prevent accidental or premature destruction of this document.

The investigator is required to maintain a confidential journal of patient identification codes, which provides a unique link between the original records containing the name and anonymous IRF data intended for the Sponsor. The investigator must organize the storage of this confidential code for 15 years (at least) after the completion or termination of the study.

It isn't allowed to destroy clinical trial documents without the prior written permission of the Sponsor and the Investigator. If the Investigator wishes to transfer the documentation to a third party or move it to another location, the Investigators is obliged to notify the Sponsor.

The Investigator file includes (required for detailed reference):

- Investigator's brochure;
- Clinical trial protocol;
- Patient Information and Written Informed Consent Form;
- Reports on the progress of the clinical trial;
- Printout of individual registration form (IRF);
- Form of division of responsibilities;
- Patient identification journal;
- Forms of accounting for SD / issuance of SD;
- Forms of accounting screening.

13.8. Archive data storage.

Copies of the eCRF and primary documentation relevant to the study, the patient identification list and the Written Informed Consent Form must be kept by the investigator for 15 years. In the event of relocation, retirement or other changes related to the retention of the archive for a specified period (at least 15 years), the Sponsor must be notified of who will be responsible for maintaining the eCRF and other information of the study. A description of the data stored will be kept by the Investigator, a copy will be provided to the Sponsor. The clinical trial protocol and amendments to the Protocol, all editions of the Investigator's Brochure, eCRF, copies of regulatory approvals, all correspondence and reports and other documents relevant to the study will be kept by the Sponsor or his authorized representative for 15 years.

13.9. Direct access to primary documentation

Primary data is all the information contained in the original records and certified copies of clinical data, observations, and other activities within the study, and which is necessary for the reconstruction and evaluation of the study. The investigator provides the opportunity to monitor trial, audit (s), expertise by the Ethics Council and regulatory authorities, provides direct access to primary data / records.

Primary data should be stored for the maximum period allowed by local rules. For each participant included, the investigator shall indicate in the primary records the fact of participation in this study, as well as record at least the following information: individual identification code, personal data of patients (name, address), dates of medication, indicators of vital signs, any AR, dates of completion of the study and the main reasons for stopping treatment (if any).

It is the investigator's responsibility to provide direct access to the primary data and documentation to the sponsor's clinical trial specialist and / or his / her authorized representatives (CRO), the competent authority auditor, the insurance company's representatives, and the ethics committees.

14. FINANCING AND INSURANCE

This clinical trial will be organized and conducted at the expense of the Sponsor. The financial aspects of the trial will be documented in the form of an agreement between the Sponsor and the study center.

If the patient follows the investigator's instructions and he/she is harmed by the medication or procedures performed in accordance with the study plan, the Sponsor shall pay all medical expenses for the treatment. No other compensation from the Sponsor is provided, except for compensation for the transport costs of patients (if possible).

Prior to the start of the study, there is a procedure for ensuring the health of patients and civil liability of persons conducting clinical trials. In the event of harm to the health of a patient related to a clinical trial, the Insurance Company through which the Sponsor has concluded an insurance contract undertakes to reimburse all costs for necessary medical examination and treatment required because of direct exposure to the study drug and / or procedures carried out in accordance with the Clinical Trial Protocol.

The sponsor of the clinical study is the company LLC "BIOPHARMA PLASMA", UKRAINE.

The Sponsor assumes responsibility for the insurance of each subject, in accordance with the requirements for clinical trials. The company-representative of the Sponsor will conclude an agreement on life and health insurance of patients participating in the study of drugs for medical use, in accordance with current legislation of Ukraine.

All discussions (if any) will be governed by the terms of the local insurance policy signed by the Sponsor and the Insurance Company.

15. ISSUES OF PUBLICATION AND USE OF RESEARCH RESULTS

Information regarding the study drug and / or the conditions of the study or the results of the study, as well as unpublished scientific data on the study drug is considered confidential and owned by the Sponsor of the study. This information may be disclosed only to the authorities that authorize the study or to those who participate in the study in confidence. The researcher should use this information only for the purpose of conducting this study, unless otherwise provided by separate written permission of the Sponsor.

The researcher agrees that the Sponsor may use the information obtained during the clinical trial for publication and thus may make it available to other researchers or regulators.

The results of this study can be published or presented at scientific conferences. Publication or presentation of research results by the Researcher is possible only after consultation with the Sponsor. In this case, the Researcher must provide all manuscripts and abstracts of the planned publication to the Sponsor for approval for submission to the editorial board or scientific expert council. This will allow the Sponsor to protect information that is his property and to supplement the message with comments based on information that may not yet be available to the Researcher.

In accordance with the standards of publishing practice, the Sponsor is usually in favor of publishing the results of multicenter research in its entirety, rather than in the form of data from individual research centers. Any publication of the results of a study in which the Sponsor's specialist was more involved than the performance of standard monitoring should be considered as a joint publication of the Researcher and this person.

Before presenting the results (written or oral), the material of the clinical study must be submitted for consideration and approval by LLC "BIOPHARMA PLASMA". The authorship of materials for an oral report or article is determined by agreement between the Sponsor and the Researcher.

16. FINAL REPORT

The final report on the study is written after the closure of databases and statistical data processing in case of completion of the study in accordance with the protocol.

Whether the study was completed on a protocol or early basis, the Sponsor ensures that the clinical trial report is prepared and submitted to the regulatory authorities and the LEC in accordance with the ICH guidelines "Structure and content of effects in a clinical trial". Abbreviated reports may be acceptable in some cases.

The final report must be prepared in accordance with the requirements of the clinical trial report set out in ICH E3 STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS.

The final report and its annexes should provide information on the dates of all stages of the study to ensure that the work can be traced.

The report should clearly state the efficacy, safety, and tolerability of the investigational medicinal product. Conclusions and recommendations should be consistent with the results obtained. In addition to the report, the Sponsor must be provided with the original IRF and, at the request of the Sponsor, copies of primary data with the results of research that are not included in the report prepared in accordance with the established procedure.

The final report is submitted to the Research Sponsor for approval. The final report, as well as other research documents, is confidential information that cannot be disclosed by researchers without the appropriate permission of the Sponsor.

17. CONFIDENTIALITY

The information contained in this document is the property of the Sponsor and its transfer to third parties is permitted only with the written permission of the Sponsor. The right to access this information is granted only to the Researcher (s) and the staff of the research center (s) participating in the study, the members of the independent ethics committee (s) and the staff of the authorized health authorities. to exercise control over the conducted research. Information about the study, to the extent necessary to decide on the consent to participate, is provided to patients whom the Researcher plans to include in the study.

18. AMENDMENTS TO THE PROTOCOL AND / OR UPDATED VERSION OF THE PROTOCOL

Any changes will be agreed between the Researcher and the Sponsor prior to its entry into force. Any changes to the study that occurred after the puncture was approved should be documented as appendices or changes to the protocol and / or an updated version of the protocol. Depending on the nature of the amendment, approval or notification from the Ethics Committee and regulators will be required, except when there is an imminent threat to the life or health of patients participating in a clinical trial, or when changes to the protocol concern only administrative aspects or issues. supply.

19. TERMS OF THE STUDY

Estimated start date of the study: 2022.
Estimated completion date: 2024.

The Researcher and the Sponsor reserve the right to terminate the study at any time. If necessary, the procedures will be agreed after consultation with both parties. If the study is prematurely stopped or suspended, the Sponsor must immediately notify the Researchers / Organizations and the Authorized Bodies of the stop or suspension, as well as the reasons for the stop or suspension. The Local Ethics Committee should also be immediately informed by the Sponsor or the Researcher / organization (as required by regulatory requirements), including the reasons for terminating or suspending the study. At the end of the study, the Sponsor and the Researcher will ensure compliance with the provisions to best protect the interests of patients.

20. LIST OF REFERENCES

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