CLINICAL TRIAL PROTOCOL

Study title: Open-label, multicentre, tolerability, safety and pharmacokinetics study of the medicinal product BP-SCIG 20% (***Human normal immunoglobulin for subcutaneous administration)*** manufactured by BIOPHARMA PLASMA LLC, followed by an efficacy assessment of long-term use in patients with primary immunodeficiency (PID)

Study Code: 2024-SCIg-BP

Phase: III

Protocol Version: 1.1 dated 05/09/2025

Investigational medicinal product: BP-SCIG 20%

International Non-Proprietary Name: Human normal immunoglobulin for subcutaneous administration

Pharmaceutical form: solution for subcutaneous administration

Study Sponsor: BIOPHARMA PLASMA LLC, Ukraine

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2025

Study sponsor protocol approval page

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Sponsor Representative:

Viktoriia Yuriivna Kyrylenko

(full name of employee)

Head of Clinical Research and Medical Support Department

BIOPHARMA PLASMA LLC

(position)

Organisation Name:	BIOPHARMA PLASMA LLC
Address:	37-V Kyivska St., Bila Tserkva, Kyiv Region, 09100, Ukraine
Telephone number:	+38(044) 390-08-10
e-mail:	info@biopharma.ua

/signed/
Signature

05 09 2025
Date

Seal: UKRAINE, KYIV REGION, CITY OF BILA TSERKVA, Limited Liability Company BIOPHARMA PLASMA LLC, Identification code 39000694, FOR DOCUMENTS, No. 1.

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ABBREVIATIONS AND TERMS

AUC	area under the pharmacokinetic activity vs. time curve (where AUC 0-t is from zero to the last blood sampling point at which analyte activity is ≥LLOQ; and AUC 0- ∞ is from zero to infinity)
C max	maximum plasma concentration
Cl	serum clearance
CRO	Contract Research Organisation
CV	coefficient of variation
Vd	volume of distribution
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IR	incremental recovery of IgG immunoglobulin
IVIG	intravenous immunoglobulin (human normal immunoglobulin for intravenous administration)
K el	elimination constant of the analyte
M.g.	mean geometric value
Max	maximum value
Mean	mean value
Min	minimum value
r	correlation coefficient
R	response
ESID	European Society for Immunodeficiencies
RW	Wasserman reaction
SCIG	subcutaneous immunoglobulin (human normal immunoglobulin for subcutaneous administration)
GCLP	Good Clinical Laboratory Practice
SD	standard deviation
t ½	elimination half-life (a 2-fold reduction in concentration)
T max	time to reach the maximum concentration
t º	body temperature
HBV	hepatitis B virus
HCV	hepatitis C virus
ALT	alanine aminotransferase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
AST	aspartate aminotransferase
BP	blood pressure
HCG	chorionic gonadotropin
INR	international normalised ratio
aPTT	activated partial thromboplastin time
IVIG	intravenous immunoglobulin, BIOVEN
SCIG	subcutaneous immunoglobulin
ULN	upper limit of normal
HIV	human immunodeficiency virus
GCS	glucocorticosteroids
dBP	diastolic blood pressure

WHO	World Health Organisation
SEC of the MoH	Public Enterprise “The State Expert Centre” of the Ministry of Health of Ukraine
IMP	investigational medicinal product
CT	clinical trial
CS	clinical study
IEC	Independent Ethics Committee
CRO	contract research organisation
ECG	electrocardiogram
ORR	overall response rate
BMI	body mass index
eCRF	electronic case report form
CT	computed tomography
MP	medicinal product
TPI	treatment and prevention institution
CTS	clinical trial site
PD	patient diary
ALP	alkaline phosphatase
MRI	magnetic resonance imaging
AE/AR	adverse event/adverse reaction
PID	primary immunodeficiency
PCR	polymerase chain reaction
AR	adverse reaction
AR/AE	adverse reaction/adverse event
PI	prothrombin index
sBP	systolic blood pressure
AMS	aseptic meningitis syndrome
SD	stable disease
HF	heart failure
SND	standard normal distribution
SAR/SAE	serious adverse reaction/serious adverse event
TRALI	transfusion-related acute lung injury
Sex	is a biological characteristic of organisms that determines their belonging to the male or female sex, based on anatomical and physiological features, in particular, sex chromosomes, sex organs, and hormonal background
ANOVA	analysis of variance
ICF	informed consent form
PK	pharmacokinetics
RR	respiratory rate
HR	heart rate
ESR	erythrocyte sedimentation rate

1. GENERAL INFORMATION

Protocol name, protocol identification number and date:

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Version: 1.1

Date: 05/09/2025

Name and address of the Sponsor and Monitor (if different):
Study Sponsor:

Organisation name:	BIOPHARMA PLASMA LLC
Address:	37-V Kyivska St., Bila Tserkva, Kyiv Region, 09100, Ukraine
Telephone number:	+380 (44) 277-36-10
e-mail:	info@biopharma.ua

Contract Research Organisation:

Organisation name:	Limited Liability Company CLS UKRAINE
Address:	18/14 V. Khvoiky St., Building 2, Office 202, Kyiv, 04080, Ukraine
Telephone number:	+38 (050) 331-33-61
e-mail:	roman.byshovets@cls-ukraine.com

To perform CT monitoring services

Name and position of persons authorised on behalf of the Sponsor to sign the Protocol and amendments to the Protocol:

Full name:	Viktoriia Yuriivna Kyrylenko
Position:	Department Head
Organisation name:	BIOPHARMA PLASMA LLC
Address:	6 Academician Knyshov St., Building 5, 4th floor, Kyiv, Ukraine
Telephone number:	+38 (067) 249-68-69
e-mail:	v.kyrylenko@biopharma.ua

Names and positions of investigators responsible for conducting the study, addresses and telephone numbers of the clinical sites:

Full name of Investigator:	Valentyna Volodymyrivna Chopiak
Investigator's position:	Doctor of Medical Sciences, Professor, Head of the Regional Centre for Clinical Immunology and Allergology
Organisation name:	Municipal Non-Profit Enterprise of the Lviv Regional Council "Lviv Regional Teaching Diagnostic Centre"
Address:	69B Pekarska St., Lviv, 79010, Ukraine
Telephone number:	+38032 2756142
e-mail:	chopyakv@ukr.net

Full name of Investigator:	Marianna Ivanivna Derkach
Investigator's position:	Deputy Medical Director for Inpatient Care, Allergist-Immunologist at the Centre for Bronchopulmonary Diseases, Allergology and Immunology
Organisation name:	Municipal Non-Profit Enterprise "Ivano-Frankivsk Regional Teaching Hospital" of the Ivano-Frankivsk Regional Council
Address:	91 Fedkovycha St., Ivano-Frankivsk, 76008, Ukraine
Telephone number:	+380503732984
e-mail:	mariannaderkac@gmail.com

Full name of Investigator:	Nataliia Pavlivna Kozliuk
Investigator's position:	Clinical immunologist
Organisation Name:	Municipal Non-Profit Enterprise "Central Municipal Hospital" of Rivne City Council
Address:	25A Mykoly Karnaukhova St., Rivne, 33017, Ukraine
Telephone number:	+380666583618
e-mail:	kozlyukn@ukr.net

Full name of Investigator:	Olha Bronyslavivna Bondarchuk
Investigator's position:	Candidate of Medical Sciences, Associate Professor, Clinical Immunologist
Organisation Name:	Municipal Non-Profit Enterprise "Vinnytsia Regional Teaching Hospital named after M.I. Pyrohov" of the Vinnytsia Regional Council
Address:	46 Pyrohova St., Vinnytsia, 21018, Ukraine
Telephone number:	+380677843933
e-mail:	imunolga@ukr.net

Full name of Investigator:	Halyna Danylivna Koval
Investigator's position:	Professor of the Department of Clinical Immunology, Allergology and Endocrinology at Bukovinian State Medical University
Organisation Name:	Regional Municipal Non-Profit Enterprise "Chernivtsi Regional Teaching Hospital" Bukovinian State Medical University
Address:	137 Holovna St., Chernivtsi, 58001, Ukraine
Telephone number:	+380505138110
e-mail:	koval.halyna@bsmu.edu.ua

Full name of Investigator:	Oleh Kostiantynovych Yakovenko
Investigator's position:	Pulmonologist, Director of "Allergy and Cough Clinic" LLC
Organisation Name:	"Allergy and Cough Clinic" LLC
Address:	10 Zoriana St., Lutsk, Volyn Region, 43000, Ukraine
Telephone number:	+380505470790
e-mail:	Volyn_pulmo@gmail.com

Full name of Investigator:	Ihor Yaroslavovych Savchak
Investigator's position:	Paediatric Immunologist
Organisation Name:	Municipal Non-Profit Enterprise of the Lviv Regional Council "Clinical Centre of Children's Medicine", structural unit "West Ukrainian Specialised Centre"
Address:	27 Dnisterska St., Lviv, 79035, Ukraine
Telephone number:	+380679401426
e-mail:	doctorsavchak@gmail.com

Full name of Investigator:	Oksana Valeriivna Tykholaz
Investigator's position:	Paediatric Immunologist
Organisation Name:	Municipal Non-Profit Enterprise "Vinnytsia Regional Children's Teaching Hospital" of the Vinnytsia Regional Council
Address:	108 Khmelnytske Highway, Vinnytsia, Ukraine
Telephone number:	+38 063-318-60-35
e-mail:	tykholaz.ov@vnmu.edu.ua

Full name of Investigator:	Liliia Ivanivna Nazarenko
Investigator's position:	Paediatric Immunologist of the Paediatric Ward and the Outpatient Consultation Clinic
Organisation Name:	Municipal Non-Profit Enterprise "Cherkasy Regional Children's Hospital" of the Cherkasy Regional Council
Address:	16 Peremohy Avenue, Cherkasy, Ukraine
Telephone number:	+380672525970
e-mail:	liliya.nazarenko.65@i.ua

Full name of Investigator:	Iryna Mykhailivna Hrabovska-Mykytiuk
Investigator's position:	Paediatric Immunologist
Organisation Name:	Municipal Enterprise "Volyn Regional Territorial Medical Association for the Protection of Motherhood and Childhood" of the Volyn Regional Council
Address:	20 Zahorodnia St., Lutsk, Lutsk district, Volyn Region, Ukraine
Telephone number:	+380977910285
e-mail:	grabovska_i.m@ukr.net

Full name of Investigator:	Yurii Stepanovych Stepanovskyi
Investigator's position:	Paediatric Immunologist of the Infectious Disease Isolation Ward
Organisation Name:	Municipal Non-Profit Enterprise "Kyiv City Children's Teaching Hospital No. 1"
Address:	30 Bohatyrska St., Kyiv, 04209, Ukraine
Telephone number:	+380963730105
e-mail:	yuriy_stepanovskiy@hotmail.com

Full name of Investigator:	Vira Bohdanivna Semianchuk
Investigator's position:	Paediatric Immunologist
Organisation Name:	Municipal Non-Profit Enterprise "Ivano-Frankivsk Regional Children's Teaching Hospital" of the Ivano-Frankivsk Regional Council
Address:	132 Konovaltsia St., Ivano-Frankivsk, Ukraine
Telephone number:	+380996337907
e-mail:	virasem.if@gmail.com

Names and addresses of clinical laboratories and other medical and/or technical services and/or organisations involved in the study

Organisation Name:	ML DILA LLC
Address:	6A Pidvysotskoho St., Kyiv, Ukraine
Telephone number:	+38 (044) 201-59-80
e-mail:	info@dila.com.ua

2. BACKGROUND INFORMATION

2.1 Name and description of the investigational medicinal product

Human normal immunoglobulin for subcutaneous administration is used for replacement therapy in primary immunodeficiencies in adults and children in accordance with the EMA guidelines *"Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration" EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015, and "Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)" EMA/CHMP/BPWP/410415/2011 rev.1 23 July 2015*

The IMP BS-SCIG 20% belongs to the category of blood products. The raw material for the production of the medicinal product BS-SCIG 20% is human plasma for fractionation, which can be obtained from whole donor blood or through plasmapheresis. Each batch of the medicinal product is obtained from plasma, from no less than 1000 donors tested for the absence of hepatitis B surface antigen (HBsAg), antibodies against human immunodeficiency virus (HIV-1, HIV-2), and antibodies against hepatitis C virus.

The product is obtained from combined pools of human plasma using the method of cold ethanol fractionation followed by viral inactivation (by the solvent-detergent method and nanofiltration), and multi-stage purification.

During the manufacturing process, the natural (native) structure of immunoglobulin G, the subclass distribution, and the broad diversity of antibodies against various infectious agents are preserved.

The production of the medicinal product BS-SCIG 20%, starting with collection, testing and fractionation of plasma, and inactivation/elimination of potential viruses, is carried out in compliance with the requirements of the current legislation of Ukraine, the World Health Organisation, European Union Directives and EMA guidelines, including the "Guideline on plasma-derived medicinal products". A set of measures for viral safety of blood products is implemented, including the selection of donors, testing of individual donations and plasma pools for markers of blood-borne infections, and implementation of effective steps for inactivation/removal of potentially present viruses at various stages of the manufacturing process. The analysis and implementation of each stage ensures the proper level of safety of the medicinal product BS-SCIG 20%.

Investigational medicinal product

Name: BP-SCIG 20% Human normal immunoglobulin for subcutaneous administration

Active ingredient: Human normal immunoglobulin (including immunoglobulin G (IgG) ≥95 %) 1 mL of the product contains 0.2 g;

Distribution of immunoglobulin G (IgG) subclasses (approximate values):

IgG1 – 65.6 %;

IgG2 – 22.1 %;

IgG3 – 10.8 %;

IgG4 – 1.5 %

The maximum content of immunoglobulin A (IgA) is 100 µg/mL.

INN: Human normal immunoglobulin for subcutaneous administration;

Excipients: glycine, water for injection.

Pharmacotherapeutic group: Human normal immunoglobulin for subcutaneous administration.

ATC code: J06B A01

Pharmaceutical form: Solution for injection 20 % in vials: 5 mL (1 g) and 50 mL (10 g)

Basic physicochemical properties: clear or slightly opalescent, colourless or slightly yellowish liquid.

Pharmacodynamic properties

Human normal immunoglobulin for subcutaneous administration mainly contains immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin for subcutaneous administration contains the IgG antibodies present in a normal population, from pooled donor plasma obtained from no less than 1000 donations. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. The medicinal product restores abnormally low levels of immunoglobulin G to a normal range.

Shelf life and storage conditions: 3 years. Store in the original package to protect from light at a temperature of 2°C to 8°C. Transport at a temperature of 2°C to 8°C in compliance with the cold chain rules. When stored or transported at a temperature not exceeding 25°C, the shelf life is 1 month. Upon expiry of this time, the drug product must not be put into a refrigerator and must be disposed of. Do not freeze. Upon expiry of the shelf life, the drug product must be disposed of.

2.2 Summary of non-clinical findings of potential clinical significance, as well as the results of clinical studies related to the trial.

The investigational medicinal product BP-SCIG 20% is at the development stage.

The clinical trial programme has been compiled in accordance with the requirements of *Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) EMA/CHMP/BPWP/410415/2011 rev.1 23 July 2015*.

According to this guideline, a comprehensive pharmacokinetics, tolerability, safety, and efficacy clinical study of the SCIG is envisaged, provided that the dosing regimens recommended in the above-mentioned document are applied.

In this clinical study, one of the objectives is to confirm the adjustment factor for the dose of BP-SCIG 20% to ensure a steady-state area under the concentration-time curve (AUC) for the total IgG level, which is non-inferior to the values of BIOVEN, the drug of previous therapy. Since the bioavailability of SCIGs is 30 % lower than that of IVIGs, partly due to binding to the extracellular matrix and cleavage by tissue enzymes (Wang et al. 2008; Berger et al. 2013), a dose adjustment factor of 1.37 will be used to convert the IVIG dose to the SCIG dose. The dose adjustment factor is based on historical data for bioequivalence evaluation of the subcutaneous and intravenous administration routes (Wasserman et al. 2010, 2011; Berger et al. 2011) and meets the requirements of the US Food and Drug Administration (US FDA), according to which the SCIG doses must be adjusted to ensure an equivalent AUC for total IgG compared to previous IVIG therapy. The dose adjustment factor of 1.37 will be evaluated in an interim pharmacokinetic (PK) analysis and modified as needed.

For the IMP BP-SCIG 20%, a set of non-clinical studies was conducted in accordance with the guidelines ICH M3 (R2), ICH S7A, ICH S7B and ICH S6 (R1) (see the Investigator's Brochure).

In the pharmacodynamics study P-21-72-1, conducted at the D.K. Zabolotnyi Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine, specific pharmacological activity of the IMP was studied *in vitro* and *in vivo*.

The efficacy of the product was shown in a set of *in vitro* tests:

- *In vitro* study of the antimicrobial activity of the IMP against *S. pneumoniae* ATCC 49619
- A study of virus neutralising activity of the IMP on a model of clinical isolate of herpes zoster virus (Varicella-zoster virus, VZV).
- A study of virus neutralising activity of the IMP on a model of the vaccine strain of poliovirus type 1 (Poliovirus, Sebin strain type 1).
- Determination of the level of specific antibodies in the composition of the IMP

The efficacy of the product was also proven in an *in vivo* test on an experimental model of subcutaneous infection caused by *Staphylococcus aureus* in animals with haemoinimmunosuppression.

The results of each of the above tests indicated high antibacterial and antiviral activity of the investigational product, which was due to the presence of a wide range of antibodies to infectious agents.

The pharmacological safety study P-21-72-2 in Wistar rats, conducted at the D.K. Zabolotnyi Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine, did not reveal any negative changes in the condition of the cardiovascular and nervous systems after repeated administration of BP-SCIG 20%, manufactured by BIOPHARMA PLASMA LLC, confirming the good safety profile of the product.

The local tolerance study 853/SOP/LET/M226/1 conducted at the State Enterprise "Academician L.I. Medved Research Centre of Preventive Toxicology, Food and Chemical Safety" of the Ministry of Health of Ukraine has shown the product to exert no local irritant effect following subcutaneous administration.

Also, in the D.K. Zabolotnyi Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine, the non-clinical study P-21-72-3 was conducted to evaluate the pharmacokinetic properties of IMP BP-SCIG 20%. The results of the study indicate that the pharmacokinetic profile of the IMP in rabbit plasma following subcutaneous administration consists of two phases: the rise phase and the elimination phase. During the rise phase (absorption phase), the maximum concentration of hIgG is reached. The elimination phase, i.e. decrease in the plasma concentration of the investigational MP (IMP), is monoexponential in nature.

At present, there is a large body of publicly available scientific data on the main pharmacokinetic and pharmacodynamic parameters of human normal immunoglobulin, which are critical for selecting the dosing and administration route, as well as information on the efficacy and safety when used in a clinical setting.

Findings from clinical studies have confirmed the minimal level of IgG of 5.0 g/L as an appropriate initial minimal target for the prevention of infections in a PID setting [Hernandez-Trujillo H.S. et al., 2012]. However, further clinical findings were the rationale for the implementation of clinical recommendations regarding higher target IgG levels in the blood of patients, i.e. >8.0 g/L. It was also suggested to personalise treatment plans of PID patients according to their clinical status based on their incidence of infections [Ballow M., 2013, Li Z et al. 2024].

Overall, clinical studies have demonstrated a high efficacy of products of human normal immunoglobulin for subcutaneous administration in both adults [Kanegane H et al. 2014, Ochs

HD et al. 2006, Jolles S et al. 2011] and paediatric patients [Borte M et al. 2011, Sefer AP et al. 2025]. The use of SCIG products in patients with PID was shown to be effective in maintaining infection levels at a very low rate, including a low incidence of serious bacterial infections and overall infection episodes, a reduction in the number of days missed from school/kindergarten or unable to perform usual activities due to infections, the number of days of hospitalisation due to infections, and the use of antibiotics for prevention or treatment of infections [Shrestha P et al., 2019].

2.3 A short description of known and potential risks and benefits, if any, for humans.

A significant proportion of patients prefer subcutaneous administration of immunoglobulin products in the home and are more satisfied with it, primarily due to greater convenience compared with intravenous infusions in a hospital setting [Bril V et al., 2024].

The efficacy and safety of subcutaneous immunoglobulin administration as part of a home-based treatment regimen have been confirmed in numerous prospective, multicentre studies. Indeed, a randomised crossover study (Chapel et al., 2000) demonstrated subcutaneous and intravenous immunoglobulin therapy to be equivalent in terms of efficacy profile and frequency of adverse events. The works by Gardulf et al. (2006, 2008) that included both paediatric and adult patients have demonstrated maintaining sufficient serum IgG levels, low incidence of infections (0.04 severe infections/year) and high treatment compliance with weekly self-administered infusions in the home.

In a paediatric cohort (Borte et al., 2011), the safety of subcutaneous administration of 16 % IgG (Vivaglobin®) in a home-based setting has also been confirmed. No cases of serious bacterial infection were reported during the evaluation period, and the safety profile was similar to that in the adult population.

According to D. Ochs et al. (2006), self-administered subcutaneous treatment in a home-based setting not only is non-inferior in terms of efficacy, but also significantly improves patients' quality of life, especially when switching from intravenous therapy. The authors emphasise that even elderly patients and those with comorbidities are able to successfully master the self-administration technique (Stein et al., 2011), and the use of infusion pumps further enhances the controllability of the administration process and safety.

Multiple clinical studies described in the literature [Jolles S et al., 2018, Suez D et al., 2016, Fasshauer M et al. 2023] have shown that products of Human normal immunoglobulin for subcutaneous administration are generally well-tolerated by patients, and do not cause serious adverse reactions or adverse changes in the findings of objective examinations and laboratory tests.

A prospective multicentre study on the use of immunoglobulin products for subcutaneous administration showed that the incidence of general reactions was 1 %. These included fever, generalised weakness, chills, and cutaneous reactions. One patient experienced bronchial obstruction, which was relieved by a short-term discontinuation of infusion [Gardulf A et al., 2006].

The experience of using immunoglobulin for subcutaneous administration in medical practice suggests the existence of possible risks and adverse reactions in administration of human normal immunoglobulin products, especially in high-risk patients. For that reason, precautions and special recommendations have been developed that must be followed when using SCIG products,

as laid down in the *"Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration" EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015*.

Based on all the arguments presented, conducting a phase III clinical study of subcutaneous immunoglobulin BP-SCIG 20% is scientifically justified, ethically acceptable, and compliant with current regulatory requirements. The IMP has a proven pharmaceutical quality in accordance with the European Pharmacopoeia, and demonstrates expected biological activity and stability. The complete non-clinical programme has been performed taking into account modern guidelines. The primary assessment of immunogenic safety will not be conducted within the phase III study due to the immunocompromised status of patients with PID.

Given the absence of novelty in the administration route and concentration of the IMP, the presence of generally accepted and clearly defined administration schemes and dosing regimens described in the *Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015* compared with the already registered SCIG products, as well as the completed pharmaceutical and non-clinical development, a phase III study is sufficient to support the efficacy, safety and pharmacokinetic profile of BP-SCIG 20% in patients with primary immunodeficiency.

Based on the publicly available data described in the literature, it has been established that SCIG products are generally well tolerated by patients, do not cause serious adverse reactions, and do not lead to clinically significant hazardous changes in patients' health status.

The product must not be administered via the intravascular route. If BP-SCIG 20% is inadvertently administered into a blood vessel, the patient may develop shock. In the event of shock, standard treatment of shock must be instituted.

The recommended administration rate of the IMP must be strictly followed. During the initial 4 administrations of the IMP, the patients shall remain under the Investigator's supervision for the entire duration of the infusion period to detect hypersensitivity to the active ingredient or to any of the excipients. Observe for any adverse symptoms throughout the infusion period.

True allergic reactions are rare. They are especially more frequent in patients with antibodies against IgA. In rare cases, human normal immunoglobulin for subcutaneous administration may cause a drop in blood pressure with an anaphylactic reaction, even in patients who have tolerated previous treatment with human normal immunoglobulin well.

Certain adverse reactions may occur more frequently in patients who receive human normal immunoglobulin for the first time, or, in rare cases, when switching to a different human normal immunoglobulin product, or when a long time period has passed since the previous infusion.

There have been reports of the possible development of aseptic meningitis syndrome in connection with the treatment with subcutaneous immunoglobulin; symptoms usually begin within a few hours up to 2 days after IgG treatment. Discontinuation of treatment with immunoglobulin may lead to remission within a few days without any consequences. Patients will be informed about the initial symptoms which include severe headache, stiff neck, drowsiness, fever, photophobia, nausea and vomiting.

Arterial and venous thromboembolic events, including myocardial infarction, stroke, deep venous complications, pulmonary thrombosis and embolism, may be associated with the use of immunoglobulins. Prior to the use of immunoglobulins, the patients must receive a sufficient amount of fluid. Caution shall be exercised in patients with existing risk factors of thrombotic events (such as advanced age, hypertension, diabetes mellitus and vascular disease or history of thrombotic episodes, patients with acquired or hereditary thrombophilic disorders, patients with prolonged periods of immobilisation, severe hypovolaemia, and patients with diseases that increase blood viscosity).

Patients will be informed about the initial symptoms of thromboembolic events, including dyspnoea, pain and swelling of an extremity, focal neurological deficit and chest pain; they will also be recommended to seek medical attention immediately once these symptoms appear.

Monitoring of the blood clotting system is also envisaged as part of this clinical study.

Some potential complications can usually be avoided if the following conditions are met:

• slow start of IMP administration, from the infusion rate of 10 mL/h/line;

• careful monitoring of patients' well-being in relation to any symptoms throughout the infusion period. In particular, patients who have not previously received human normal immunoglobulin, patients who have switched from an alternative immunoglobulin product, or if a long period of time has passed since the previous administration must be monitored during the first infusion and throughout the first hour afterwards to identify any potential adverse manifestations.

In all other cases, the patient's well-being must be monitored for at least 20 minutes after the administration.

In case of an adverse reaction, either the infusion rate must be reduced, or administration must be stopped.

If an AE develops, the necessary treatment will depend on the nature and the severity of the AE.

Occasionally, adverse reactions may occur such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain.

In rare cases, human normal immunoglobulin may cause a sudden drop in blood pressure and, in isolated cases, an anaphylactic shock, even if the patient had no signs of hypersensitivity to the previous administration.

Local reactions at the injection sites may occur frequently, including: swelling, tenderness, redness, induration, local warmth, itching, bruising, and rash.

The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocytic antigens, such as A, B, or D, may affect some serological tests for determining alloantibodies against RBCs (for example, the Coombs test), and haptoglobin.

2.4 Description and justification of the administration route, dosing, dosing regimen, and treatment period(s).

When selecting the dosing, BIOPHARMA PLASMA LLC relied on the EMA guideline (*Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015*), namely Clause 4.2 of this Guideline. According to the Standards of Medical Care "Diagnosis and Treatment of Primary Immunodeficiencies" approved by the Order of the Ministry of Health of Ukraine No. 2952 dated 31.12.2021 and "Primary immunodeficiencies: an Evidence-Based Clinical Guideline" dated 2021, the diagnosis of primary immunodeficiency can be established in both infants up to 12 months of age and in adult patients. The mean age of onset of clinical manifestations occurs during the first years of life, often immediately after birth. Therefore, a diagnosis such as primary immunodeficiency with impaired antibody production shall be regarded as both a paediatric and an adult disease, with immunoglobulin products playing a leading role in treatment. Replacement therapy with immunoglobulin for subcutaneous administration has shown an improvement in health-related quality of life compared with intravenous immunoglobulin products. Based on Article 8 of the Law of Ukraine "On Medicinal Products", specifically the information stating that

"Clinical trials of medicinal products involving a minor or a child may be conducted only if the relevant medicinal product is intended for the treatment of paediatric diseases or if the purpose of the clinical trial is to optimise the dosing or regimen of the medicinal product accordingly for children or minors" and on other aforementioned data, a paediatric population **may** be included in this clinical study without prior full completion of clinical trials involving competent adult subjects.

As part of this clinical study, all patients will receive the investigational medicinal product BP-SCIG 20%, solution for subcutaneous administration, manufactured by BIOPHARMA PLASMA LLC subcutaneously.

The IMP BP-SCIG 20% will be administered at the frequency of once a week for 52 weeks, subcutaneously using a CRONO S-PID4 infusion pump, at the dose of 0.1–0.2 g/kg once a week (the dose over 4 weeks is 0.4–0.8 g/kg).

The dosing regimen shall be designed to achieve a minimum IgG level (at least 5–6 g/L), which will be measured monthly before each IMP infusion.

Efforts must be taken to maintain serum IgG within the reference range for the corresponding age group of patients.

Individual dose selection and adjustment may be required for each patient, depending on the pharmacokinetic response (IgG level) and clinical response. Threshold levels must be assessed in combination with the incidence of infectious episodes.

Dose adjustment of the IMP BP-SCIG 20% based on threshold IgG levels is performed by the Investigator based on the clinical presentation of each individual patient.

A loading dose of IMP may be required (at the Investigator's decision): at least 0.2–0.5 g/kg (1.0–2.5 mL/kg) of body weight per week. This dose is distributed across several days, with a maximum daily dose of 0.1 to 0.15 g/kg.

After achieving a steady-state (minimal) level of IgG, maintenance doses are administered at repeated intervals (approximately once a week) to achieve a cumulative monthly dose of 0.4–0.8 g/kg. Each single dose must be administered to different anatomical locations.

Since the bioavailability of SCIGs is 30 % lower than that of IVIGs, partly due to binding to the extracellular matrix and cleavage by tissue enzymes (Wang et al. 2008; Berger et al. 2013), a dose adjustment factor of 1.37 will be used to convert the IVIG dose to the SCIG dose. This is based on historical data for bioequivalence evaluation of these administration routes (Wasserman et al. 2010, 2011; Berger et al. 2011) and meets the requirements of the US Food and Drug Administration (US FDA), according to which the SCIG doses must be adjusted to ensure an equivalent AUC for total IgG compared to previous IVIG therapy. Dose calculation for patients who received IVIG prior to the start of their participation in the study (John W Sleasman et al. 2019):

The initial dose of SCIG

$$\text{IgG} = \frac{\text{Previous IVIG dose (in grams) x 1.37}}{\text{Number of weeks between IVIG administrations}}$$

The dose adjustment factor of 1.37 will be evaluated in an interim pharmacokinetic (PK) analysis and modified as needed.

The first four IMP administrations are for training purposes, during which the investigational medicinal product BP-SCIG 20% for subcutaneous administration will be administered by a responsible member of the study team in a hospital setting and by the patient/legally authorised representative or parents after an appropriate training and in compliance with aseptic/antiseptic precautions under the supervision of responsible and trained members of the study team.

The study doctor determines the dose and rate of subcutaneous administration of the IMP for home-based use. The patient/their legally authorised representative or parents must be instructed regarding the use of the CRONO S-PID4 infusion pump, the administration technique, filling out the patient's diary, recognition of adverse reactions and measures to be taken in the event of adverse reactions.

Prior to use, the solution must be at room temperature and remain outside the refrigerator for at least 30 minutes. Turbid solutions and/or solutions with sediment must not be used.

To administer the IMP, a CRONO S-PID4 infusion pump and a dedicated single-use infusion set are used.

The IMP BP-SCIG 20% can be administered in sites with ample subcutaneous fat, such as the abdomen, the shoulder, and lateral thigh.

The IMP BP-SCIG 20% is administered subcutaneously using a CRONO S-PID4 infusion pump. Multiple lines can be used for administration into several sites simultaneously.

It is recommended to use an initial infusion rate of 10 mL/h/line. If well tolerated, the infusion rate may be increased by 5 mL/h/line at each subsequent administration. The recommended maximum rate is 25 mL/h/line. [S. Jolles et al. 2014]. The amount of product infused into a certain site must not exceed 25 mL. In infants and children, the administration site can be rotated every 5–15 mL, as determined by the study doctor. For adults, doses above 30 mL can be divided into several doses, in accordance with the patient's preferences. There are no limitations regarding the number of injection sites.

In accordance with EMA guideline *"Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)" EMA/CHMP/BPWP/410415/2011 rev.1 23 July 2015:* the effectiveness of the investigational medicinal product BP-SCIG 20% (Human normal immunoglobulin for subcutaneous administration) must be evaluated over at least 1 year of treatment (52 weeks).

2.5 Declaration that the trial shall be conducted in accordance with the protocol, GCP and the applicable regulatory requirements.

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Olha Bronyslavivna Bondarchuk		
Position:	Candidate of Medical Sciences, Associate Professor, Clinical Immunologist		
Facility:	Municipal Non-Profit Enterprise "Vinnytsia Regional Teaching Hospital named after M.I. Pyrohov" of the Vinnytsia Regional Council		
Address:	46 Pyrohova St., Vinnytsia, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Iryna Mykhailivna Hrabovska-Mykytiuk		
Position:	Paediatric Immunologist		
Facility:	Municipal Enterprise "Volyn Regional Territorial Medical Association for the Protection of Motherhood and Childhood"		
Address:	20 Zahorodnia St., Lutsk, Lutsk district, Volyn Region, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025

Full name	Marianna Ivanivna Derkach
Position:	Deputy Medical Director for Inpatient Care, Allergist–Immunologist at the Centre for Bronchopulmonary Diseases, Allergology and Immunology
Facility:	Municipal Non-Profit Enterprise "Regional Teaching Hospital" of Ivano-Frankivsk Regional Council
Address:	91 Fedkovycha St., Ivano-Frankivsk, Ukraine

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Halyna Danylivna Koval		
Position:	Candidate of Medical Sciences, Associate Professor, Clinical Immunologist		
Facility:	Regional Municipal Non-Profit Enterprise "Chernivtsi Regional Teaching Hospital"		
Address:	137 Holovna St., Chernivtsi, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Nataliia Pavlivna Kozliuk		
Position:	Clinical immunologist		
Facility:	Municipal Non-Profit Enterprise "Central Municipal Hospital" of Rivne City Council		
Address:	25A Mykoly Karnaukhova St., Rivne, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Liliia Ivanivna Nazarenko		
Position:	Paediatric Immunologist of the Paediatric Ward and the Outpatient Consultation Clinic		
Facility:	Municipal Non-Profit Enterprise "Cherkasy Regional Children's Hospital" of the Cherkasy Regional Council		
Address:	16 Peremohy Avenue, Cherkasy, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Ihor Yaroslavovych Savchak		
Position:	Paediatric Immunologist		
Facility:	Municipal Non-Profit Enterprise of the Lviv Regional Council "Clinical Centre of Children's Medicine", structural unit "West Ukrainian Specialised Centre"		
Address:	27 Dnisterska St., Lviv, 79035, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Vira Bohdanivna Semianchuk		
Position:	Immunologist		
Facility:	Municipal Non-Profit Enterprise "Ivano-Frankivsk Regional Children's Teaching Hospital" of the Ivano-Frankivsk Regional Council		
Address:	132 Konovaltsia St., Ivano-Frankivsk, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Yurii Stepanovych Stepanovskyi		
Position:	Paediatric Immunologist of the Infectious Disease Isolation Ward		
Facility:	Municipal Non-Profit Enterprise "Kyiv City Children's Teaching Hospital No. 1"		
Address:	30 Bohatyrska St., Kyiv, 04209, Ukraine		

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I am ready to provide direct access to source documents and agree to be audited by representatives of the Sponsor and regulatory authorities. I guarantee that the investigational product(s) supplied by the Sponsor will only be used 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.
I am aware that all scientific information contained in this Protocol is confidential and that any disclosure of such information to any third parties (with the exception of persons taking part in approval, control or conduct of this study) is explicitly prohibited. I undertake to ensure all required precautions for the protection of such information from loss, inadvertent disclosure or access by third parties.
Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Oksana Valeriivna Tykholaz		
Position:	Paediatric Immunologist		
Facility:	Municipal Non-Profit Enterprise "Vinnytsia Regional Children's Teaching Hospital" of the Vinnytsia Regional Council		
Address:	108 Khmelnytske Highway, Vinnytsia, Ukraine		

PAGE OF THE RESPONSIBLE INVESTIGATOR CONSENT WITH THE PROTOCOL

I, the Responsible Investigator, confirm with my signature that I have carefully reviewed this 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 this Protocol, and to protect the rights, safety, and the health and well-being of the patients in accordance with the ethical requirements stated in the World Medical Association (WMA) Declaration of Helsinki, ICH E6 (R2) Guideline for Good Clinical Practice, and other regulatory requirements of Ukraine and of 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 the patients. I fully understand that any deviations from the procedures suggested by this Protocol made by the Investigator(s) without prior discussion with the Sponsor's representative will constitute a breach of the Protocol (other than the procedures required to maintain the subjects' health).
I agree to personally conduct or monitor the study described.
I agree to inform the subjects that the drugs are used for investigational purposes; I will ensure that Informed Consent requirements are met after approval by the Independent Ethics Committee (IEC) and in accordance with the principles of GCP (Good Clinical Practice).
In accordance with GCP principles, I agree to notify the Sponsor of adverse events that have developed during the study.
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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Valentyna Volodymyrivna Chopiak		
Position:	Doctor of Medical Sciences, Professor, Head of the Regional Centre for Clinical Immunology and Allergology		
Facility:	Municipal Non-Profit Enterprise of the Lviv Regional Council "Lviv Regional Teaching Diagnostic Centre"		
Address:	69B Pekarska St., Lviv, Ukraine		

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Investigator:

Signature:	/signed/	Date:	05/09/2025
Full name	Oleh Kostiantynovych Yakovenko		
Position:	Director, Pulmonologist		
Facility:	"Allergy and Cough Clinic" LLC		
Address:	10 Zoriana St., Lutsk, Volyn Region, Ukraine		

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I am aware that all scientific information contained in this Protocol is confidential and that any disclosure of such information to any third parties (with the exception of persons taking part in approval, control or conduct of this study) is explicitly prohibited. I undertake to ensure all required precautions for the protection of such information from loss, inadvertent disclosure or access by third parties.

Investigator:

Signature: _____ Date: _____

Full name _____

Position: _____

Facility: _____

Address: _____

2.6 Description of study population.

In accordance with the EMA guidelines *"Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration" EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015, and "Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)" EMA/CHMP/BPWP/410415/2011 rev.1 23 July 2015:* the investigational medicinal product BP-SCIG 20% (Human normal immunoglobulin for subcutaneous administration) is used ***for replacement therapy in primary immunodeficiencies with impaired antibody production*** in adults and children (0–18 years).

At present time, the list of indications for SCIG products and age-defined framework are defined in accordance with the *"Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration" EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015*.

Primary immunodeficiencies (PIDs) are congenital diseases of the immune system [26]. This is a group of heterogeneous rare diseases where the functioning of the immune system is impaired or individual links are not working. The International Union of Immunological Societies (IUIS) lists ten groups and 416 monogenetic primary immunodeficiencies (PIDs)/inborn errors of immunity. Predominant antibody deficiency represents the largest group; moreover, antibody deficiency is clinically relevant in many other PIDs [33].

Primary antibody deficiencies (PADs) are the most common types of primary immunodeficiencies, accounting for approximately 50–60 % of congenital immune system disorders. PADs comprise a heterogeneous group of immune defects characterised by insufficient antibody production in response to antigens. The PAD spectrum is diverse, ranging from selective IgA and IgG subclass deficiencies to severe agammaglobulinaemia with complete absence of B lymphocytes [34]. Congenital antibody production deficiencies have a similar clinical phenotype characterised by increased susceptibility to bacterial infections, while autoimmune diseases and malignant neoplasms are also characteristic of certain forms of antibody production deficiencies [35]. The importance of antibodies is clearly demonstrable by the high infection-associated morbidity and mortality in patients with primary immunodeficiency diseases (PIDs), which are typically associated with impaired antibody production. The onset of PAD can occur at a different age, depending on the immune defect. Early diagnosis and timely initiated adequate treatment are key factors in prolonging the life of patients with congenital antibody production deficiencies and improving its quality. Late diagnosis and/or inadequate treatment lead to irreversible organ and system damage due to severe recurrent infections, resulting in early death of the patients. Most patients with antibody production deficiencies can live normal lives while receiving regular replacement therapy with immunoglobulin products.

Antibodies are required for protection against infections not only because they specifically recognise a plethora of microorganisms, but also due to their effector capacity, which includes neutralisation, opsonisation, antibody-dependent cytotoxicity, and clearance of immune complexes.

Common variable immunodeficiency (CVID) is the most frequent form of significant antibody deficiency, affecting both children and adults. This is a genetically heterogeneous group of immune system defects characterised by hypogammaglobulinaemia with a deficiency of at least two immunoglobulin classes (predominantly IgG and IgA and/or IgM) in a setting of normal or

reduced counts of B lymphocytes, an increased risk of developing infectious diseases, and, in some patients, the development of autoimmune and granulomatous complications. The overall prevalence of CVID is estimated to range between 1:25,000 and 1:50,000 [36].

Among the most severe PIDs manifesting early in life are severe combined immunodeficiencies (SCIDs), which are characterised by pronounced T- and/or B-lymphopoenia. Patients with SCID are usually born without clinical signs of the disease, but the disorder manifests within the first year of life, most often during the first months, with severe infections. Without timely diagnosis and adequate treatment, the children do not survive. The use of replacement immunotherapy allows not only preserving their life but also ensuring its quality.

The prevalence of PID

The incidence rates and prevalences of primary immunodeficiencies vary significantly across regions with different populations. Thus, in the USA, newborn screening for SCID has revealed a SCID incidence of 1:58,000, demonstrating a substantially higher incidence of SCID than previously estimated. Based on data from the USA, the prevalence of clinically significant immunodeficiency is estimated to be between 1:1,200 and 1:2,000. Epidemiological calculations based on this data suggest the presence of primary immunodeficiency in Europe in approximately 600,000 people. At the same time, in 2014, only 19,355 patients were registered in the patient registry of the European Society for Primary Immunodeficiencies (ESID registry).

As of 2021, the number of registered individuals with PIDs in Ukraine is 1,220, of whom 1,040 are alive. However, based on global estimates, this figure apparently does not reflect the true situation due to insufficient detection of such patients, which in turn leads to their disability and premature death. According to an American study, the average delay from the onset of the first symptoms to diagnosis was approximately 4.7 years; moreover, the higher the age at diagnosis, the greater the associated mortality. In contrast to that, early diagnosis enables timely implementation of appropriate therapeutic measures and improves patients' quality of life in health-related aspects.

Manifestation of PID

The majority of severe forms of antibody production deficiencies manifest in the first years of life; at the same time, common variable immunodeficiency and selective antibody production deficiencies may have clinical manifestations in any age. Some primary immunodeficiencies, including severe hypogammaglobulinaemia (especially in cases of severe combined immunodeficiency or agammaglobulinaemia), may manifest as an infection during the neonatal period or infancy, posing a threat to life. Early diagnosis and treatment initiation in patients with primary immunodeficiency helps prevent disability and premature death.

Early detection of PID in paediatric patients

Prenatal and neonatal screening for primary immunodeficiencies allows early diagnosis and prevention of severe infectious complications.

In recent years, numerous immunology experts at the international level have emphasised the need for the development and implementation of neonatal screening for SCID, allowing detection of affected individuals before the appearance of clinical symptoms. In Ukraine, SCID in children is detected immediately after birth owing to neonatal screening [37]. According to the Order of the Ministry of Health of Ukraine No. 2142 dated 01 October 2021, severe combined immunodeficiency (SCID) has been included in the list of diseases covered by the programme of expanded mass screening of newborns. Neonatal screening enables timely detection of combined primary immunodeficiencies, especially severe ones, allowing timely implementation of

preventive measures against infections, adequate treatment, and the preservation of children's lives and the improvement of their quality of life. Thus, owing to the implementation of modern diagnostic methods, including prenatal diagnostics and neonatal screening for SCID, it is possible to diagnose this condition in a timely manner and initiate replacement therapy from the first months of life.

Neonatal screening also detects X-linked agammaglobulinaemia, which accounts for over 85 % of agammaglobulinaemia cases and is caused by a mutation in Bruton's tyrosine kinase (Btk), which is essential for the normal maturation of B lymphocytes. Mutations in the Btk gene lead to a developmental arrest of B lymphocytes in the bone marrow, with almost complete absence of the cells in the peripheral blood of patients, down to 1 %. Serum immunoglobulin levels are extremely low, and there is no humoral response to antigens. Clinical symptoms appear in 50 % of patients with agammaglobulinaemia at 6–12 months of age, when maternal IgGs are catabolised, and almost all patients manifest by 5 years of age. In the presence of characteristic clinical and laboratory features, molecular diagnosis of immunodeficiency is recommended to verify the diagnosis. Upon identification of a Btk gene mutation, it is important to determine all mutation carriers within the family, which allows, as needed, prenatal diagnosis and the prevention of the birth of a child with severe immunodeficiency.

Abnormal susceptibility to infectious diseases is often the leading symptom of primary immunodeficiencies [25]. Chronic or recurrent infections of upper and lower respiratory tract, sinusitis and otitis media are the most common types of infections. Severe bacterial infections (SBIs) may also occur, such as sepsis, meningitis, septic arthritis, and osteomyelitis.

To prevent infections, patients with primary antibody deficiency and hypogammaglobulinaemia (reduced IgG), with absent or reduced production of specific IgG antibodies, as well as an abnormal susceptibility to infection, must receive long-term (often lifelong) immunoglobulin replacement therapy. The main principles of immunoglobulin replacement therapy are outlined in the Standard of Medical Care "Diagnosis and Treatment of Primary Immunodeficiencies".

Expected outcomes of effective Ig therapy include: absence of severe infections; achieving remission of chronic diseases and eradication of chronic infectious foci; serum IgG levels not lower than 4.5 g/L before the next administration of Ig products (the optimum is the IgG level of 6 g/L or higher); absence of exacerbations of autoimmune, allergic, or immunoproliferative diseases; preservation of working capacity and improvement in quality of life.

2.7 References to the literature and data related to the trial and forming the basis for its conduct.

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38 Guidance for Industry. Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852- 1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

3. STUDY OBJECTIVE AND TASKS

Primary objective of the study:

1. To confirm that the PK indices of the IMP BP-SCIG 20% are comparable with those of the BIOVEN product.
2. To confirm the adjustment factor for the dose of BP-SCIG 20% to ensure a steady-state area under the concentration-time curve (AUC) for the total IgG level, which is non-inferior to the values of BIOVEN, the drug of previous therapy.
3. To confirm that the threshold IgG levels (in administration of the IMP BP-SCIG 20% to patients with PID in a monthly dose of 0.4–0.8 g/kg, under a once a week regimen) are non-inferior compared to threshold IgG levels on previous therapy (in patients previously receiving human normal immunoglobulin products intravenously or another product of human normal immunoglobulin for subcutaneous administration), or those reported in the literature (in treatment-naïve patients).
4. Assessment of the efficacy, tolerability, safety, and pharmacokinetic parameters of BP-SCIG 20% in long-term use in patients with primary immunodeficiency with impaired antibody production.

Additional pharmacokinetic assessment objectives:

- To confirm the adjustment factor for the dose of BP-SCIG 20% to ensure a steady-state area under the concentration-time curve (AUC) for the total IgG level, which is non-inferior to the values of BIOVEN, the drug of previous therapy.
- To assess the variability of trough IgG levels in children and adolescents compared with adult patients.
- To determine the pharmacokinetic parameters (Cmax, AUC0-t, AUC0-∞, Tmax, t1/2, Kel, IR, Cl, AUCextrapol, Vd) for the IMP BP-SCIG 20% in 20 adult patients with PID, and compare them with the available published literature.
- To compare the results of pharmacokinetic data for patients who have not previously received human normal immunoglobulin products with published literature (descriptively).
- To compare the results of pharmacokinetic parameter study (Cmax, AUC0-t, AUC0-∞, Tmax, t1/2, Kel, IR, Cl, AUCextrapol, Vd) between the cohorts.

Safety and tolerability assessment tasks

- Conduct an interim safety assessment for the first 10 patients enrolled in the study who must be adults and must have received at least 4 IMP administrations.
Based on the results of such assessment *(interim report)*, the possibility of enrolling patients younger than 18 years of age is determined;
- Assess the frequency of adverse events;
- Assess the incidence of adverse reactions to the IMP;
- Assess the frequency of serious adverse reactions;
- Assess the frequency of treatment-emergent adverse events;
- Assess the frequency of treatment-emergent adverse events related to infusion rate;
- Assess the incidence of administration site reactions;
- Assess the frequency of clinically significant deviations in vital signs (blood pressure, body temperature, pulse rate and respiratory rate);
- Assess the frequency of clinically significant deviations in laboratory findings (complete blood count, biochemical findings, markers of intravascular haemolysis, and viral safety parameters);
- Assess the safety data separately in children and adolescents, and compare them with the adult data**.**

Pharmacokinetic assessment tasks

- to assess the mean threshold concentration of total IgG in plasma before the next administration of the IMP after reaching steady state (after 4 months of treatment) within 6 months (efficacy criterion ≥5 g/L);
- to assess the pharmacokinetic parameters of BIOVEN in a subgroup of adult patients with PID who have previously received therapy with BIOVEN in the screening period;
- to assess the pharmacokinetic parameters of the IMP BP-SCIG 20% in a subgroup of 20 adult patients with PID after approximately 4 months of IMP treatment;
- assess the threshold levels of total IgG during the dose titration phase (the dose-effect dependence);
- plot the individual concentration-time curves;
- calculate the following pharmacokinetic parameters:

  AUC – area under the curve (AUC_{0-t}, $AUC_{0-\infty}$);

  T_{max} – the time when maximum concentration of the analyte is reached;

  C_{max} – the maximum serum concentration of the analyte;

  $T_{1/2}$ – elimination half-life of the analyte;

  K_{el} – elimination constant of the analyte;

  Cl – serum clearance;

  IR – incremental recovery;

  Vd – volume of distribution.

Efficacy assessment tasks in the study:

- to evaluate the efficacy of the investigational product in patients with certain humoral and combined primary immunodeficiencies according to the following parameters:
  - the number of cases of serious bacterial infections during the therapy period (**the primary variable,** the criterion of reaching efficacy: less than 1.0 cases of serious bacterial infections per 1 patient over 1 year of therapy);
  - to establish the incidence and the duration of non-serious infectious diseases throughout the course of treatment (a descriptive criterion);
  - to establish the incidence of any febrile conditions throughout the course of treatment (a descriptive criterion);
  - time from the onset of therapy to the first instance of any infectious disease/serious bacterial infection (a descriptive criterion);
  - the duration of antibiotic therapy throughout the course of treatment, expressed as days of dosing with the medication(s) (a descriptive criterion);
  - the duration of infection-related hospitalisation throughout the course of treatment, expressed in days of in-patient hospitalisation (a descriptive criterion);
  - the number of days of incapacity for work (sick leaves), or missing school/kindergarten due to an infection;
  - the quality of life level in the patients throughout the study period.

4. STUDY DESIGN

4.1. Endpoints

Safety and tolerability endpoints
- Frequency of adverse events
- Incidence of adverse reactions to IMP
- Frequency of serious adverse reactions
- Emergence of treatment-emergent adverse events
- The frequency of treatment-emergent adverse events related to infusion rate
- The incidence of administration site reactions
- The frequency of clinically significant deviations in vital signs (blood pressure, body temperature, pulse rate and respiratory rate)
- The frequency of clinically significant deviations in laboratory findings (complete blood count, biochemical findings, markers of intravascular haemolysis, and coagulation parameters)

Safety data are also assessed separately in children and adolescents (after an interim assessment in adults) and compared with the adult data.

Primary pharmacokinetic endpoint:
Mean threshold (trough) plasma concentration of total IgG prior to the next administration of the product, when reaching steady state (after 4 months of treatment), assessed over 6 months.

Primary pharmacokinetic variable:
The monthly trough IgG levels, measured after 4 months of treatment with the IMP, prior to the next infusion, once every 4 weeks, over 6 months, did not fall below the trough levels of the previous therapy with SCIG or IVIG (BIOVEN).

Secondary pharmacokinetic endpoints
These endpoints are tested in the subgroup of subjects aged over 18 years who received treatment with BIOVEN prior to their enrolment in the study and, respectively, throughout the screening period:
- To confirm or calculate the IMP dose adjustment factor when converting from previous IVIG therapy with BIOVEN;

Tested in a subgroup of at least 20 adult patients with PID after approximately 4 months of treatment with the IMP BP-SCIG 20%:
- Area under the concentration-time curve (AUC)
- Maximum concentration (Cmax)
- Time to reach maximum concentration (Tmax)
- The threshold levels of total IgG during the dose titration phase (the dose-effect dependence)
– the *in vivo* elimination half-life
– the elimination constant
– serum clearance
– volume of distribution
– incremental recovery
Secondary endpoints are transformed into corresponding variables.

Primary efficacy endpoint:

Primary efficacy endpoint: The number of serious bacterial infections per subject per year (in order to achieve less than 1.0 infections/subject/year)
Primary efficacy variable: Occurrence of less than 1.0 case of infection/patient/year of a ***serious bacterial infection*** [1] during one year of treatment.

[1] ***a serious bacterial infection*** *includes: sepsis; bacterial pneumonia; bacterial diseases of viscera (visceral abscess); bacterial meningitis; osteomyelitis/septic arthritis.*

This variable is categorical, dichotomous, with categories of "sufficient efficacy" (occurrence of a ***serious bacterial infection*** [1] during the year of treatment, less than 1 case per year) / "insufficient efficacy" (occurrence of a ***serious bacterial infection*** [1] during the year of treatment, 1 or more cases per year). It will be assessed after the end of 52 weeks of treatment.

Secondary efficacy endpoints:
1. The fraction of patients reaching the threshold serum IgG level ≥5 g/L before the scheduled administration of the product (according to the PK study plan).
This variable is categorical, dichotomous, with categories of "response achieved" / "response not achieved";
2. The incidence of any non-serious infectious diseases during the treatment course, per patient per 1 year of therapy
3. The duration of any non-serious infectious diseases during the treatment course, per patient per 1 year of therapy
4. The fraction (%) of patients who were prescribed treatment with antibiotics
5. The mean number of days of antibiotic therapy in a year (except for the cases where continuous antibiotic prophylaxis is performed)
6. Hospital admissions due to an infection (number of days and frequency in a year)
7. Fever episodes (number of events in a year)
8. The number of days of incapacity for work (sick leaves), or missing school/kindergarten due to an infection.
9. The quality of life level in the patients throughout the study period.

4.2. Description of the design

Study design: Open-label, multicentre, single-arm, cohort, uncontrolled, prospective clinical study of tolerability, safety and pharmacokinetics of the medicinal product BP-SCIG 20% for subcutaneous administration with further assessment of efficacy in long-term use.

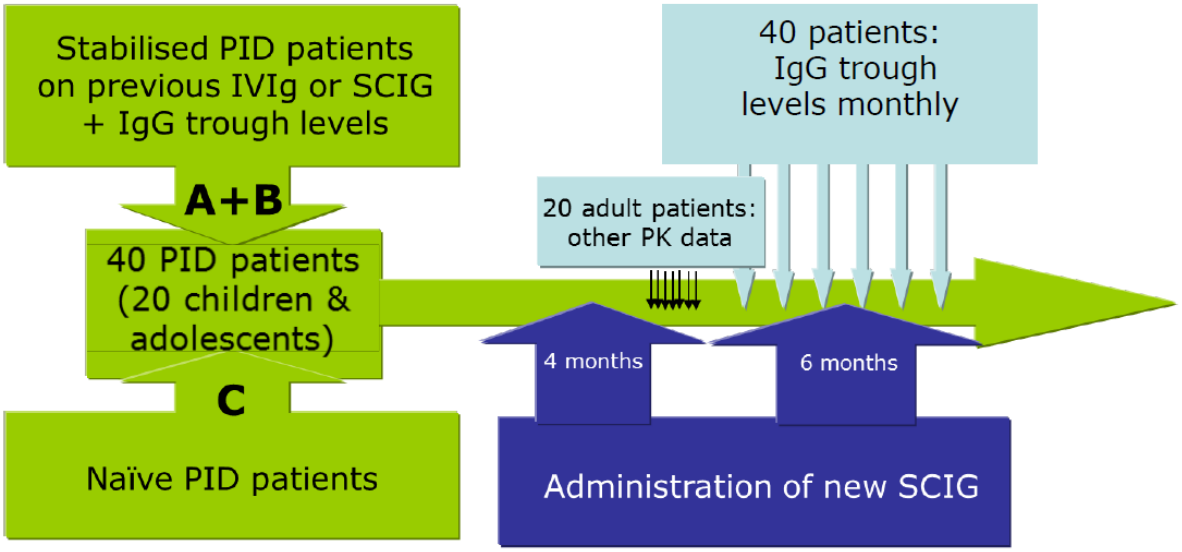

Fig. 1 Study diagram

Number of patients:
56 patients with PID – adults, adolescents, and children.
Patients older than 18 years – at least 20 patients
Patients younger than 18 years – at least 20 patients across different age groups:

- 0 to ≤2 years – at least 2;
- >2 to ≤6 years – at least 4;
- >6 to ≤12 years – at least 7;
- >12 to ≤18 years – at least 7.

The first 10 patients enrolled in the study must be adults, for an interim safety assessment in adult patients who received at least 4 infusions of the IMP BP-SCIG 20%.
Based on the results of such assessment, the possibility of enrolling patients younger than 18 years of age is determined. The interim report will be reviewed and assessed by the Independent Safety Committee.

In the pharmacokinetic assessment:
- the threshold IgG levels are determined in at least 40 patients, at least 20 of whom must be children and adolescents before the age of 18 years.
- pharmacokinetic parameters (AUC, Cmax, Tmax, $T_{½}$, K_{el}, Cl, IR, Vd) are determined in no less than 20 adult patients
- confirmation of the dose adjustment factor (adult patients of cohort B)

Groups:
This study does not involve the distribution of patients into groups. Of patients in all age categories who meet inclusion criteria and passed the screening, and who do not meet any of the non-inclusion (exclusion) criteria, one group is formed, which will receive the investigational product.

The following cohorts are formed from the general group to assess pharmacokinetics: **Cohort A**: the patients who have already received subcutaneous immunoglobulin (SCIG)*;* **Cohort B**: the patients who previously received intravenous IgG IVIG; **Cohort C**: newly identified patients who have not received treatment with IgG product yet.

Also, PK assessment subgroups are formed from the general group of patients to determine threshold IgG levels (in at least 40 patients, at least 20 of whom must be children and adolescents younger than 18 years), to determine pharmacokinetic parameters (at least 20 adults), and to confirm the dose adjustment factor (adult patients previously receiving BIOVEN)

Since patients were distributed across cohorts, the required number of patients in each cohort was established in accordance with the recommendations of the U.S. Department of Health and Human Services Food and Drug Administration (FDA) regarding the safety, pharmacokinetics and effectiveness studies of immunoglobulin in primary immunodeficient conditions. According to that guidance document, the optimal number of patients in subgroups for pharmacokinetic assessment (adult patients) ranges from 6 to 12, to obtain a reliable assessment of variability. Considering these recommendations, the number of patients in the cohorts for adult patients was determined to be between 8 and 10.

During the Data Analysis phase, it is envisaged to allow assessment of patients based on the identified covariates.

Study phases.

The patient/their legally authorised representative/the patient's parents should sign informed consent.

After signing the informed consent, the screening examinations are performed, and patient's eligibility is assessed against inclusion/non-inclusion criteria.

During the screening phase, verification of PID diagnosis is required (according to the ESID criteria) based on source documentation data (see Section 6.3.3 of the Protocol).

- **Screening period:**
  - Visit 1: Day 0 – signing the ICF, determination of IgG levels*
  - Visit 2: Day 21–28 (range: 21–28 days) – determination of IgG levels*
  - Visit 3: Day 42–56 (range: 21–28 days) – determination of IgG levels*. Determination of pharmacokinetic parameters of BIOVEN in patients aged over 18 years who have previously received therapy with BIOVEN (7 blood sampling points additionally)

*For the group of patients from Cohorts A and B who have already received SCIG or IVIG, an assessment of monthly threshold IgG levels is performed during prior treatment (the prior treatment continues).

The screening period is different across different cohorts:

- For Cohort A, patients who have previously received SCIG are required to undergo Visits 1 and 2 of the screening period. In the event of meeting the criterion "total serum IgG level ≥5 g/L – as confirmed by the results of at least two (2) measurements performed immediately prior to the subsequent administration of SCIG after signing the ICF", the patient proceeds to treatment with the IMP BP-SCIG 20%, starting from Cycle 1. If the criterion is not met, then Visit 3 is performed.
- For Cohort B, patients who have previously received IVIG:
  - Paediatric patients are required to undergo Visits 1 and 2 of the screening period. In the event of meeting the criterion "total serum IgG level ≥5 g/L – as confirmed by the results of at least two (2) measurements performed immediately prior to the subsequent administration of IVIG after signing the ICF", the patient proceeds to treatment with the IMP BP-SCIG 20%, starting from Cycle 1. If the criterion is not met, then Visit 3 is performed.

  - Adult patients are required to undergo Visits 1 and 2 of the screening period to determine whether they meet inclusion/non-inclusion criteria, and Visit 3 of the screening period to conduct a mandatory pharmacokinetic assessment of BIOVEN.
- For Cohort C, newly diagnosed (treatment-naïve) patients are required to undergo Visit 1 of the screening period; if meeting inclusion/non-inclusion criteria, the patient proceeds to treatment with the IMP BP-SCIG 20%, starting from Cycle 1.

Study phases. Treatment period.

The phase begins after the end of the screening period.
Cycles 1–13: These include on-site visits to the CTS: 4 visits in Cycle 1; all subsequent cycles: each first visit of the cycle (every 28 days ±3 days) and interim self-administrations of the product by patients in the home (every 7 days ±1 day) for 52 weeks. A total of 13 cycles that include 13 main on-site visits (1 visit to the CTS in each cycle), and 3 on-site visits for interim administration of the IMP. The period lasts 52 weeks.
Individualised dose titration is performed.
A loading dose of IMP may be required (at the Investigator's decision): at least 0.2–0.5 g/kg (1.0–2.5 mL/kg) of body weight. This dose is distributed across several days, with a maximum daily dose of 0.1 to 0.15 g/kg.
After achieving a steady-state level of IgG, maintenance doses are administered at repeated intervals (approximately once a week) to achieve a cumulative monthly dose of 0.4–0.8 g/kg. Each single dose must be administered to different anatomical locations. (see Section 6.1 of this Protocol).
Pharmacokinetic parameters of the IMP are assessed at Week 21 (see Table 4.2.2)

Cycle 1:
- Visit 4 (C1W1): **On-site visit** Week 1 – the first administration of the IMP BP-SCIG 20%;
- Interim administration 1(C1W2) on-site – Week 2, administration of the IMP;
- Interim administration 2(C1W3) on-site – Week 3, administration of the IMP;
- Interim administration 3(C1W4) on-site – Week 4, administration of the IMP.

Cycle 2:
- Visit 5 (C2W5): **On-site visit –** Week 5 of IMP administration;
- Interim administration 1(C2W6) – Week 6, IMP administration in the home;
- Interim administration 2(C2W7) – Week 7, IMP administration in the home;
- Interim administration 3(C2W8) – Week 8, IMP administration in the home.

Cycle 3:
- Visit 6 (C3W9): **On-site visit –** Week 9 of IMP administration;
- Interim administration 1 (C3W10) – Week 10, IMP administration in the home;
- Interim administration 2(C3W11) – Week 11, IMP administration in the home;
- Interim administration 3(C3W12) – Week 12, IMP administration in the home.

Cycle 4:
- Visit 7 (C4W13): **On-site visit –** Week 13 of IMP administration;
- Interim administration 1(C4W14) – Week 14, IMP administration in the home;
- Interim administration 2(C4W15) – Week 15, IMP administration in the home;
- Interim administration 3(C4W16) – Week 16, IMP administration in the home.

Cycle 5:

- Visit 8 (C5W17): **On-site visit** – Week 17 of IMP administration;
- Interim administration 1(C5W18) – Week 18, IMP administration in the home;
- Interim administration 2(C5W19) – Week 19, IMP administration in the home;
- Interim administration 3(C5W20) – Week 20, IMP administration in the home.

Cycle 6:

- Visit 9 (C6W21): **On-site visit –** Week 21 of IMP administration; Start of additional visits for the assessment of pharmacokinetic parameters in adult patients. Assessment of PK parameters may require elective hospitalisation, which is not viewed as a SAR;
- Interim administration 1(C6W22) – Week 22, IMP administration in the home;
- Interim administration 2(C6W23) – Week 23, IMP administration in the home;
- Interim administration 3(C6W24) – Week 24, IMP administration in the home.

Cycle 7:

- Visit 10 (C7W25): **On-site visit –** Week 25 of IMP administration;
- Interim administration 1(C7W26) – Week 26, IMP administration in the home;
- Interim administration 2(C7W27) – Week 27, IMP administration in the home;
- Interim administration 3(C7W28) – Week 28, IMP administration in the home.

Cycle 8:

- Visit 11 (C8W29): **On-site visit –** Week 29 of IMP administration;
- Interim administration 1(C8W30) – Week 30, IMP administration in the home;
- Interim administration 2(C8W31) – Week 31, IMP administration in the home;
- Interim administration 3(C8W32) – Week 32, IMP administration in the home.

Cycle 9:

- Visit 12 (C9W33): **On-site visit**– Week 33 of IMP administration;
- Interim administration 1(C9W34) – Week 34, IMP administration in the home;
- Interim administration 2(C9W35) – Week 35, IMP administration in the home;
- Interim administration 3(C9W36) – Week 36, IMP administration in the home.

Cycle 10:

- Visit 13 (C10W37): **On-site visit**– Week 37 of IMP administration;
- Interim administration 1(C10W38) – Week 38, IMP administration in the home;
- Interim administration 2(C10W39) – Week 39, IMP administration in the home;
- Interim administration 3(C10W40) – Week 40, IMP administration in the home.

Cycle 11:

- Visit 14 (C11W41): **On-site visit –** Week 41 of IMP administration;
- Interim administration 1(C11W42) – Week 42, IMP administration in the home;
- Interim administration 2(C11W43) – Week 43, IMP administration in the home;
- Interim administration 3(C11W44) – Week 44, IMP administration in the home.

Cycle 12:

- Visit 15 (C12W45): **On-site visit** – Week 45 of IMP administration;
- Interim administration 1(C12W46) – Week 46, IMP administration in the home;
- Interim administration 2(C12W47) – Week 47, IMP administration in the home;
- Interim administration 3(C12W48) – Week 48, IMP administration in the home.

Cycle 13:

- Visit 16 (C13W49): **On-site visit** – Week 49 of IMP administration;
- Interim administration 1(C13W50) – Week 50, IMP administration in the home;
- Interim administration 2(C13W51) – Week 51, IMP administration in the home;
- Interim administration 3(C13W52) – Week 52, the last IMP administration in the home.

Data are entered into the eCRF in accordance with the Schedule of Study Procedures (see Table 4.2.1).

The patient/parents of the patient/legally authorised representative fill(s) in the patient's diary after each interim administration of the cycle starting with Visit C2W6.

The Investigator shall contact the patient/parents/legally authorised representative by telephone at least once per interim IMP administration period of each Cycle, in order to monitor/remind them about IMP administration in the home, filling in the patient diary, and tracking of any potential adverse reactions. The fact of the telephone contact shall be recorded in the "Telephone Contact Form" provided by the Sponsor.

Pharmacokinetic assessment phase

Determination of threshold (trough) IgG levels

Prior to the start of the phase, each patient who has completed 4 months of treatment must have a monthly assessment of threshold IgG level (immediately before the administration).

The assessment of threshold (trough) IgG levels is to be performed in at least 40 patients enrolled in the CT; of these, 20 subjects must be children or adolescents with an appropriate age distribution for this patient group. The trough levels of the IgG from the investigational medicinal product must be assessed after 4 months of treatment with the IMP, prior to the next infusion, once every 4 weeks (once per month/treatment cycle) over 6 months.

The obtained monthly trough IgG levels shall be compared with the trough levels for at least two prior infusions of the previous SCIG or IVIG product. Alternatively, for treatment-naïve patients, a descriptive comparison with published literature (if available) is performed.

Phase of IVIG pharmacokinetic assessment

This phase includes patients older than 18 years who had been receiving previous therapy with the medicinal product BIOVEN prior to their study entry and, accordingly, throughout the screening period.

PK will be assessed through an additional sampling of 3.5 mL of venous blood (per one sampling, a total of 8–9 sampling time points) for subsequent determination of patient's levels of plasma immunoglobulin in the samples over 21–28 days after the infusion of BIOVEN. The total volume of venous blood for the entire IVIG PK assessment per one patient is 28–31.5 mL.

The data obtained during the phase of BIOVEN pharmacokinetics will be used to confirm or recalculate the dose adjustment factor for switching from IVIG to the IMP.

The assessment begins at Visit 3 of the screening period (see Table 4.2.3 Pharmacokinetic assessment of IVIG – BIOVEN). The time of blood sampling is documented.

Phase of IMP BP-SCIG 20% pharmacokinetic assessment

This phase includes at least 20 patients older than 18 years who had been receiving the investigational medicinal product for at least 4 months, and did not have any severe bacterial complications during the trial.

PK will be assessed through an additional sampling of 3.5 mL of venous blood (per one sampling, a total of 8 sampling time points) for subsequent determination of patient's levels of plasma immunoglobulin in the samples over 7 days after the infusion of the IMP BP-SCIG 20%. The total volume of venous blood for PK assessment for one patient is 28 mL.

The assessment is performed at Week 21 (see Table 4.2.2 – Pharmacokinetic assessment of the IMP). The time of blood sampling is documented.

Study phases. Follow-up and completion of the study

The phase begins after the last administration of the IMP. It lasts 1 week after the last administration of the IMP.

- Visit 17: 1 week after the last administration of the IMP, the end of study.

At this phase, a set of laboratory tests is assessed and vital signs are measured. Registration of AEs/ARs is also performed.

The results of the study are entered into the eCRF, according to the Schedule of Study Procedures (see Table 4.2.1).

The procedures and phases are listed in Tables 4.2.1–4.2.3

Tabular schedule of study procedures

Table 4.2.1. Schedule of study procedures.

Visits	Visit 1	Visit 2	Visit 3	Cycle 1 Weeks 1–4		Cycle 2 Weeks 5–8		Cycle 3 Weeks 9–12		Cycle 4 Weeks 13–16		Cycle 5 Weeks 17–20		Cycle 6 Weeks 21–24		Cycle 7 Weeks 25–28	
Study phase	**Screening period ∞**			**Treatment period**													
Procedures / Time point	**Day 0**	**Day 21–28**	**Day 42–56**	**Week 1 (C1W1)**	**Weeks 2–4 (C1W2-C1W4)**	**Week 5 (C2W5)**	**Weeks 6–8 (C2W5-C2W8)**	**Week 9 (C3W9)**	**Weeks 10–12 (C3W10 - C3W12)**	**Week 13 (C4W13)**	**Weeks 14–16 (C4W14-C4W16)**	**Week 17 (C5W17)**	**Weeks 18–20 (C5W18-C5W20)**	**Week 21 (C6W21)**	**Weeks 22–24 (C6W22-C6W24)**	**Week 25 (C7W25)**	**Weeks 26–28 (C7W26-C7W28)**
Informed Consent signing	●																
Collection of demographics	●																
Collection of anthropometrics [1]	●	X	X	X	X	X		X		X		X		X		X	
Collection of medical history[2]	●																
Data on antibiotic therapy and concomitant therapy	●	●	●	●	●	●	#	●	#	●	#	●	#	●	#	●	#
Presence of infections	●	●	●	●	●	●	#	●	#	●	#	●	#	●	#	●	#
Physical examination[3]	●	●	●	●		●		●		X		X		●		X	
Vital signs[4]	●	●	●	●		●		●		●		●		●		●	
Chest X-ray/CT/MRI[5]	X													●			
12-lead ECG;	●																
Complete blood count[6]	●			●		●						●					
Serum chemistry[7]	●			●		●						●					
Direct Coombs' test (antiglobulin test)[8]	●	X	X	●		●		X		X		X		X		X	

[1] Height, body weight, BMI. x – Starting from Visit 2, only body weight is measured
[2] Confirmation of underlying disease, information on administration of prior therapy ([type of therapy, dose/schedule, duration, time interval since the last administration], transfusion history, allergy history, infectious history, comorbidities, information on therapy for comorbidities, presence/absence of harmful habits).
[3] auscultation and percussion of the heart and lungs; palpation and percussion of abdominal organs; examination of the skin and mucous membranes; x – at visits where not mandatory, performed in a suspected infection
[4] BP, HR, RR, Body t°;
[5] The screening chest X-ray/CT/MRI is only performed if there has been no such assessment during the last 6 months prior to enrolment.
[6] Haemoglobin, haematocrit, red blood cells, white blood cells and white blood cell differential, and platelets;
[7] ALT, AST, total bilirubin, creatinine, urea, glucose;
[8] x – if haemolysis is detected based on laboratory results, the Coombs' test may be performed at any visit at the Responsible Investigator's discretion;

Haptoglobin level[9]	●	x	x	●		●		x		x		x		x		x		
Threshold level of total serum IgG (pre-administration) [10]	●	●	●	●		●		●		●		●		●		●		
Total serum IgG level (PK assessment)[11]			●											●				
Urinalysis[12]	●			●		●						●						
HIV test (express test), RW, HBs-Ag, anti-HCV	●																	
Pregnancy test (for women of childbearing potential)[13]	●	x	x	x		x		x		x		x		x		x		
Coagulation panel (INR, Prothrombin percentage by Quick, Prothrombin time, aPTT, fibrinogen)	●	x	x	x		●		x		x		●		x		x		
Glycated haemoglobin	●																	
Assessment of inclusion and non-inclusion criteria during the screening	●	●	●															
Assessment of exclusion criteria	●	●	●	●		●		●		●		●		●		●		
Assigning the date of the next visit	●	●	●	●		●		●		●		●		●		●		
Issuance of IMP for interim administrations						●		●		●		●		●		●		
Administration of the study drug				●	●	●	#	●	#	●	#	●	#	●	#	●	#	
Checking the used IMP vials						●		●		●		●		●		●		
Registration of AEs/ARs	●	●	●	●	●	●	#	●	#	●	#	●	#	●	#	●	#	
Filling in the patient's questionnaire				●		●						●						
Checking the completion of patient's diary								●		●		●		●		●		
Telephone contact with the patient							●		●		●		●		●		●	

[9] x – if haemolysis is detected based on laboratory results, testing for haptoglobin levels may be performed at any visit at the Responsible Investigator's discretion;
[10] Total IgG is determined using the nephelometry method for PK assessment, i.e. the threshold level on Day 7 post-infusion of the IMP BP-SCIG 20% in at least 40 patients, of whom no less than 20 subjects are children and adolescents younger than 18 years;
[11] PK parameters are determined using the nephelometry method at Visit 3 (7 blood sampling points additionally) in adult patients receiving previous therapy with BIOVEN, and at Visit C6W21 (7 blood sampling points additionally), in at least 20 adult patients treated with the IMP BP-SCIG 20% for at least 4 months with no severe bacterial complications and who have signed Informed Consent to participate in the pharmacokinetic assessment;
[12] Specific gravity; pH, glucose, microscopic sediment examination (red blood cells, white blood cells, casts, crystals, bacteria, fungi);
[13] The test (HCG) can be performed at any visit during the study if a female patient reports a potential pregnancy;

Table 4.2.1. Schedule of Study Procedures (Continued)

Visits	Cycle 8 Weeks 29–32		Cycle 9 Weeks 33–36		Cycle 10 Weeks 37–40		Cycle 11 Weeks 41–44		Cycle 12 Weeks 45–48		Cycle 13 Weeks 49–52		Visit 17	Unscheduled
Study phase	**Treatment period**												**Follow-up**	-
Procedures / Time point	**Week 29 (C8W29)**	**Weeks 30–32 (C8W30-C8W32)**	**Week 33 (C9W33)**	**Weeks 34–36 (C9W34-C9W36)**	**Week 37 (C10W37)**	**Weeks 38–40 (C10W38-C10W40)**	**Week 41 (C11W41)**	**Weeks 42–44 (C11W42-C11W44)**	**Week 45 (C12W45)**	**Weeks 46–48 (C12W46-C12W48)**	**Week 49 (C13W49)**	**Weeks 50–52 (C13W50-C13W52)**	**Week 53**	**Actual Date**
Informed Consent signing														
Collection of demographics														
Collection of anthropometrics [14]	X		X		X		X		X		X			X
Collection of medical history[15]														X
Data on antibiotic therapy and concomitant therapy	●	#	●	#	●	#	●	#	●	#	●	#	●	X
Presence of infections	●	#	●	#	●	#	●	#	●	#	●	#	●	X
Physical examination[16]	X		●		X		X		●		X		●	X
Vital signs[17]	●		●		●		●		●		●		●	X
Chest X-ray/CT/MRI											●			
12-lead ECG;														
Complete blood count[18]	●						●						●	X
Serum chemistry[19]	●						●						●	X
Direct Coombs' test (antiglobulin test) [20]	X		X		X		X		X		X		X	X
Haptoglobin level[21]	X		X		X		X		X		X		X	X

[14] Height, body weight, BMI. x – Starting from Visit 2, only body weight is measured
[15] Confirmation of having PID, information on administration of prior therapy ([type of therapy, dose/schedule, duration, time interval since the last administration], transfusion history, allergy history, infectious history, comorbidities)
[16] auscultation and percussion of the heart and lungs; palpation and percussion of abdominal organs; examination of the skin and mucous membranes; x – at visits where not mandatory, performed in a suspected infection
[17] BP, HR, RR, Body t°;
[18] Haemoglobin, haematocrit, red blood cells, white blood cells and white blood cell differential, and platelets;
[19] ALT, AST, total bilirubin, creatinine, urea, glucose;
[20] x – if haemolysis is detected based on laboratory results, the Coombs' test may be performed at any visit at the Responsible Investigator's discretion;
[21] x – if haemolysis is detected based on laboratory results, testing for haptoglobin levels may be performed at any visit at the Responsible Investigator's discretion;

Threshold level of total serum IgG (pre-administration) [22]	●		●		●		●		●		●		●	X
Total serum IgG level (PK assessment) [23]														
Urinalysis[24]	●						●						●	X
HIV test (express test), RW, HBs-Ag, anti-HCV													●	
Pregnancy test (for women of childbearing potential) [25]	X		X		X		X		X		X		X	X
Coagulation panel (INR, Prothrombin percentage by Quick, Prothrombin time, aPTT, fibrinogen)	●		X		X		●		X		X		●	X
Glycated haemoglobin														
Assessment of inclusion and non-inclusion criteria during the screening														
Assessment of exclusion criteria	●		●		●		●		●		●			X
Assigning the date of the next visit	●		●		●		●		●		●			
Issuance of IMP for interim administrations	●		●		●		●		●		●			
Administration of the study drug	●	#	●	#	●	#	●	#	●	#	●	#		
Checking the used IMP vials	●		●		●		●		●		●		●	
Registration of AEs/ARs	●	#	●	#	●	#	●	#	●	#	●	#	●	X
Filling in the patient's questionnaire	●						●						●	
Checking the completion of patient's diary	●		●		●		●		●		●		●	X
Telephone contact with the patient		●		●		●		●		●		●		

– Self-administered by the patient on the day of each interim administration of the cycle. The data are recorded in the patient's diary.

● – Performed by the study doctor as a mandatory part of on-site visits.

[22] Total IgG is determined using the nephelometry method for PK assessment, i.e. the threshold level on Day 7 post-infusion of the IMP BP-SCIG 20% in at least 40 patients, of whom no less than 20 subjects are children and adolescents younger than 18 years;
[23] PK parameters are determined using the nephelometry method at Visit 3 (7 blood sampling points additionally) in adult patients receiving previous therapy with BIOVEN, and at Visit C6W21 (7 blood sampling points additionally), in at least 20 adult patients treated with the IMP BP-SCIG 20% for at least 4 months with no severe bacterial complications and who have signed Informed Consent to participate in the pharmacokinetic assessment;
[24] Specific gravity; pH, glucose, microscopic sediment examination (red blood cells, white blood cells, casts, crystals, bacteria, fungi);
[25] The test (HCG) can be performed at any visit during the study if a female patient reports a potential pregnancy;

x – Is optional or there are differences depending on the specific procedure. The procedures of an unscheduled visit are performed as needed depending on the reason and the clinical condition of the study subject.

∞The screening period is different across different cohorts:

For Cohort A, patients who have previously received SCIG are required to undergo Visits 1 and 2 of the screening period. In the event of meeting the criterion "total serum IgG level ≥5 g/L – as confirmed by the results of at least two (2) measurements performed immediately prior to the subsequent administration of SCIG after signing the ICF", the patient proceeds to treatment with the IMP BP-SCIG 20%, starting from Cycle 1. If the criterion is not met, then Visit 3 is performed.

For Cohort B, patients who have previously received IVIG:

Paediatric patients are required to undergo Visits 1 and 2 of the screening period. In the event of meeting the criterion "total serum IgG level ≥5 g/L – as confirmed by the results of at least two (2) measurements performed immediately prior to the subsequent administration of IVIG after signing the ICF", the patient proceeds to treatment with the IMP BP-SCIG 20%, starting from Cycle 1. If the criterion is not met, then Visit 3 is performed.

Adult patients are required to undergo Visits 1 and 2 of the screening period to determine whether they meet inclusion/non-inclusion criteria, and Visit 3 of the screening period to conduct a mandatory pharmacokinetic assessment of BIOVEN.

For Cohort C, newly diagnosed (treatment-naïve) patients are required to undergo Visit 1 of the screening period; if meeting inclusion/non-inclusion criteria, the patient proceeds to treatment with the IMP BP-SCIG 20%, starting from Cycle 1.

Table 4.2.2 Schedule of Procedures at Week 21 – Pharmacokinetic assessment of the IMP

Structure of PK assessment*		
No.	**PK point**	**Description**
1	PK0 (pre-administration)	Before IMP administration (10–30 min prior)
2	PK1 (30 min)	30 minutes after IMP administration (±10 min)
3	PK2 (3 hours)	3 hours after IMP administration (±30 min)
4	PK3 (1 day)	24 hours after IMP administration (±5 h)
5	PK4 (2 days)	48 hours after IMP administration (±5 h)
6	PK5 (3 days)	72 hours after IMP administration (±5 h)
7	PK6 (4 days)	96 hours after IMP administration (±5 h)
8	PK7 (7 days, threshold)	After 7 days (±5 h), before the next administration of the IMP

* – The points for pharmacokinetic assessment of BP-SCIG 20% were selected in accordance with the available data on achieving Cmax following subcutaneous administration of the MPs belonging to the subcutaneous immunoglobulin category, and for the purpose of clear demonstration of differences in concentration-time curves for IVIG and SCIG.

Table 4.2.3. Schedule of procedures at Visit 3 – Pharmacokinetic assessment of IVIG

Structure of PK assessment**		
No.	**PK point**	**Description**
1	PK0 (pre-administration)	Before administration of BIOVEN (10–30 min prior)
2	PK1 (15 min)	15 minutes after administration of BIOVEN (±10 min)
3	PK2 (1 hour)	1 hour after administration of BIOVEN (±15 min)
4	PK3 (1 day)	24 hours after administration of BIOVEN (±5 h)
5	PK4 (3 days)	72 hours after administration of BIOVEN (±5 h)
6	PK5 (7 days)	7 days after administration of BIOVEN (±5 h)
7	PK6 (14 days)	14 days after administration of BIOVEN (±5 h)
8	PK7 (21 days)	21 days after administration of BIOVEN (±5 h)
9	PK8 (28 days)	28 days after administration of BIOVEN (±5 h) (where applicable***)

**The points for pharmacokinetic assessment of BIOVEN were selected based on previous PK studies of BIOVEN.

***Interval between the administrations (every 21–28 days) of BIOVEN, used as a prior therapy, is determined individually for each patient in accordance with the approved instructions for medical use.

4.3. Randomisation and blinding.

No randomisation or blinding is used in this clinical trial.

4.4. IMP description and labelling

Name: BP-SCIG 20% (Human normal immunoglobulin for subcutaneous administration)

Active ingredient:

Human normal immunoglobulin (including immunoglobulin G (IgG) ≥95 %) 1 mL of the product contains 0.2 g;

The following batches of the investigational medicinal product will be used as part of this clinical study:

- 24S5001R, 50 mL;
- 24S5002R, 50 mL;
- 24S5003R, 50 mL;
- 24S05001R, 5 mL;
- 24S05002R, 5 mL;
- 24S05003R, 5 mL.

Labelling of the investigational product

The necessary information shall be provided in the official language.
The investigational medicinal product must be labelled with the following symbols and fields:
Secondary packaging:
a) name of the legal entity acting as the clinical trial sponsor, location and phone number of the clinical trial sponsor;
b) pharmaceutical form, route of administration, number of dosage units, name/identifier and strength/activity;
c) batch number;
d) clinical trial code allowing identification of the trial, clinical trial site, clinical trial sponsor;
e) identification number of the study subject;
f) surname and first name of the Responsible Investigator/Investigator;
g) “For clinical trial use only” labelling;
h) storage conditions;
i) period of use (“use before”, expiry date, etc.), specified in the Month/Year format and in a manner that excludes ambiguity of interpretation;
j) “Keep out of reach of children” labelling.

Instructions for Use are specified in the “Guidance on home-based administration of BP-SCIG 20% for adults and children”.

Immediate packaging:
a) name of the legal entity acting as the clinical trial sponsor;
b) pharmaceutical form, route of administration, number of dosage units, name/identifier, and strength/activity;
c) batch of the investigational medicinal product;
d) clinical trial code allowing identification of the trial, clinical trial site, clinical trial sponsor;
e) identification number of the study subject.

LABELLING TO APPEAR ON THE OUTER PACKAGING OF THE MEDICINAL PRODUCT

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection 5 mL in vials No. 1

SECONDARY PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection

2. STATEMENT OF ACTIVE INGREDIENT(S)

Composition: 1 mL of the product contains:

Active ingredient: Human normal immunoglobulin 200 mg/mL (including immunoglobulin G (IgG) no less than 95 %)

Distribution of immunoglobulin G subclasses in the product:

IgG_1: 65.6 %, IgG_2: 22.1 %, IgG_3:10.8 %, IgG_4:1.5 %

The maximum content of immunoglobulin A is 100 µg/mL.

3. LIST OF EXCIPIENTS

Excipients: glycine; water for injection

4. PHARMACEUTICAL FORM AND NUMBER OF DOSAGE UNITS PER PACKAGE

Solution for injection 20 %

1 vial 5 mL

Protein concentration: 200 mg/mL

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach of children.

7. OTHER SPECIAL WARNING(S)

Sterile. Do not administer intravenously!

8. EXPIRY DATE

Available

9. STORAGE CONDITIONS

Store in the original package to protect from light at a temperature of 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MANUFACTURER AND/OR APPLICANT

BIOPHARMA PLASMA LLC

Legal address and place of business:
37-V Kyivska Street, Bila Tserkva, Kyiv Region, 09100, Ukraine

Tel: (044) 390-08-10

12. MARKETING AUTHORISATION NUMBER

-

13. BATCH NUMBER

Available

14. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only medicine

15. IF THE MEDICINAL PRODUCT IS INDICATED FOR SELF-TREATMENT, INFORMATION FOR ITS USE

Specified in the "Guidance on home-based administration of BP-SCIG 20% for adults and children"

16. INFORMATION IN BRAILLE

-

17. OTHER INFORMATION

BIOPHARMA PLASMA, LLC Logo

Bar-code

FOR CLINICAL STUDY USE
Study Code: 2024-SCIg-BP
Study subject No.: _____
Investigator:_____

LABELLING TO APPEAR ON THE OUTER PACKAGING OF THE MEDICINAL PRODUCT

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection 50 mL in vials No. 1

SECONDARY PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection

2. STATEMENT OF ACTIVE INGREDIENT(S)

Composition: 1 mL of the product contains:

Active ingredient: Human normal immunoglobulin 200 mg/mL (including immunoglobulin G (IgG) no less than 95 %)

Distribution of immunoglobulin G subclasses in the product:

IgG_1: 65.6 %, IgG_2: 22.1 %, IgG_3:10.8 %, IgG_4:1.5 %

The maximum content of immunoglobulin A is 100 µg/mL.

3. LIST OF EXCIPIENTS

Excipients: glycine; water for injection

4. PHARMACEUTICAL FORM AND NUMBER OF DOSAGE UNITS PER PACKAGE

Solution for injection 20 %

1 vial 50 mL

Protein concentration: 200 mg/mL

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach of children.

7. OTHER SPECIAL WARNING(S)

Sterile. Do not administer intravenously!

8. EXPIRY DATE

Expires on

9. STORAGE CONDITIONS

Store in the original package to protect from light at a temperature of 2°C to 8°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MANUFACTURER AND/OR APPLICANT

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Legal address and place of business:
37-V Kyivska Street, Bila Tserkva, Kyiv Region, 09100, Ukraine

Tel: (044) 390-08-10

12. MARKETING AUTHORISATION NUMBER

-

13. BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only medicine

15. IF THE MEDICINAL PRODUCT IS INDICATED FOR SELF-TREATMENT, INFORMATION FOR ITS USE

Specified in the "Guidance on home-based administration of BP-SCIG 20% for adults and children"

16. INFORMATION IN BRAILLE

-

17. OTHER INFORMATION

BIOPHARMA PLASMA, LLC Logo

Bar-code

FOR CLINICAL STUDY USE
Study Code: 2024-SCIg-BP
Study subject No.: _____
Investigator:_____

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection 5 mL in vials No. 1

IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection

2. STATEMENT OF ACTIVE INGREDIENT(S)

Protein concentration: 200 mg/mL

5 mL

3. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach of children.

4. BATCH NUMBER

Batch No.

5. EXPIRY DATE

Expires on

6. STORAGE CONDITIONS

Store at a temperature of 2°C to 8°C.

7. NAME OF THE MANUFACTURER AND APPLICANT, IF APPROPRIATE

BIOPHARMA PLASMA LLC

8. OTHER INFORMATION

Sterile

FOR CLINICAL STUDY USE
Study Code: 2024-SCIg-BP
Study subject No.: _____
Investigator:_____

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection 50 mL in vials No. 1

IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

BP-SCIG 20%, Human normal immunoglobulin for subcutaneous administration, solution for injection

2. STATEMENT OF ACTIVE INGREDIENT(S)

Protein concentration: 200 mg/mL

50 mL

3. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach of children.

4. BATCH NUMBER

Batch No.

5. EXPIRY DATE

Expires on

6. STORAGE CONDITIONS

Store at a temperature of 2°C to 8°C.

5. NAME OF THE MANUFACTURER AND APPLICANT, IF APPROPRIATE

BIOPHARMA PLASMA LLC

6. OTHER INFORMATION

Sterile

BIOPHARMA PLASMA, LLC Logo

FOR CLINICAL STUDY USE
Study Code: 2024-SCIg-BP
Study subject No.: _____
Investigator:_____

BIOVEN used as a prior therapy. Marketing authorisation No. UA/14526/01/02. To be used in accordance with the approved Instructions for medical use.

4.5. Duration

The clinical trial will consist of three periods, namely:

- screening period: lasting up to 2 months, and involving three screening visits;
- treatment period (from Cycle 1 visit [the first 4 administrations of the IMP are to be performed in a hospital setting] during the 52 weeks to the last visit of Cycle 13).
- follow-up period after completion of the last cycle of the treatment period, with a duration of 1 week.

A visit window of ± 3 days is allowed for scheduled visit days due to objective reasons beyond one's control.

A visit window of ± 1 day is allowed for scheduled days of administration of the IMP BP-SCIG 20% (every 7 days) due to objective reasons beyond one's control.

The actual dates and times of interim administrations are recorded by the patient/parents/legally authorised representative in the patient's diary.

The duration of individual patient's participation in the study is approximately up to 62 weeks.

Total study duration is 28 months.
Estimated start date of the study: October 2025
Estimated end date of the study: January 2028

4.6. Rules for termination of a part of the clinical study and/or the clinical study as a whole

The Investigator and the Sponsor reserve the right to terminate the study at any time. If required, the procedures will be agreed upon after consultation with both parties. If the study is terminated or suspended prematurely, the Sponsor shall immediately inform the Investigators/organisations and the authorised bodies about the termination or suspension, and

indicate the reasons for the termination or suspension. Independent Ethics Committees must also be immediately informed by the Sponsor or the Investigator/organisation (as required by regulatory requirements), including about the reasons for terminating or suspending the study. The Investigator, in their turn, shall immediately inform the enrolled patients, including about the reasons for terminating or suspending the study. Upon termination of the study, the Sponsor and the Investigator shall ensure compliance with the provisions for the best protection of the patients' interests.

The study may be stopped for the following reasons:

1. At the Sponsor's initiative:
   a. obtaining new toxicological or pharmacological data, or SAE data associated with the investigational product, which necessitate a review of the previous benefit/risk assessment regarding participation in the study;
   b. the frequency and/or severity of AEs associated with the investigational product do not allow continuation of the study;
   c. other reasons, including administrative ones.
2. At the Investigator's initiative: the frequency of AEs associated with the product and/or their severity unacceptably increases the risk resulting from the patients' participation in the study;
3. Upon decision of regulatory authorities.

In case of early termination of the study, the Sponsor is obliged to notify the staff of study sites and regulatory authorities with an indication of the reason for such early termination of the study.

Termination of individual subjects' participation in the study shall be carried out by study doctors in accordance with the exclusion criteria.

4.7. Management of the IMP and related materials

Circulation of the investigational product

Manufacturing, packaging and labelling of the investigational medicinal product is carried out by the Sponsor, i.e. manufacturer of the product, BIOPHARMA PLASMA LLC.

The investigational medicinal product is provided in a CTS by the Sponsor in the amount required for conducting the study in question. The transfer of the product shall be confirmed by a delivery and acceptance certificate, which shall indicate the following: name and quantity of the drug product, batch numbers, and date of transfer. The Certificate is signed by the Sponsor and the person responsible for IMP accounting at the CTS.

At the CTS, the investigational product must be placed into a separate place dedicated for the CT in question, labelled with an identifier with the study code. The product shall be stored in a dry, dark place at a temperature of 2 to 8°C. The product shall be stored indoors, accessible only to investigator or study team members to whom the responsible investigator has delegated the relevant authority.

The IMP shall be transported at 2 to 8°C according to the cold chain rules. When stored or transported at a temperature not exceeding 25°C, the shelf life is 1 month.

A person authorised by the Responsible Investigator keeps a form for accounting of the investigational medicinal product. With each release of the product to a patient, the following shall be recorded in the form: name, date of issue, quantity, and the patient's screening number in this clinical study, and the signature of the investigator who carried out the issuance. Information about the issued IMP is also documented in eCRF.

The IMP is issued by the person authorised by the Responsible Investigator to the patient in accordance with the Schedule of Study Procedures. At each subsequent on-site visit, the patient shall return to the Investigator all used vials and secondary packaging of the IMP. The Investigator signs off the returned used IMP vials and packages and records them in the form for returned used

vials and packages. The Investigator may dispose of the used packages and vials only with the Sponsor's approval, in accordance with the procedure provided for by TPI, after verification by the monitor.

The packaging of the used product shall be retained for the period specified by the Sponsor.

Unused products are returned to the Sponsor, which is confirmed by a Certificate of Transfer.

To ensure optimisation of transportation, the IMP may be transferred from one CTS to another, which shall be confirmed by a certificate of delivery and acceptance between the CTSs.

To allow for re-testing if required by the competent authorities, the Study Sponsor shall keep a sufficient number of samples of the investigational product for one year after the expiration date or for two years after the study completion (whichever is longer).

Related materials

Throughout the patients' participation in the clinical study, the following related materials shall be used:

1. Outpatient infusion pump – CRONO S-PID4 100
2. Outpatient infusion pump – CRONO S-PID4 50
3. 100 mL reservoir for use with an outpatient infusion pump – CRN® CRONO® 100
4. 50 mL reservoir for use with an outpatient infusion pump – CRN® CRONO® 50
5. MiniSpike-CRN spike for withdrawal and aspiration of solutions and drugs for use with syringe reservoirs CRN CRONO ® 100 and CRN® CRONO® 50
6. CRONO JET 50 accessory for filling CRN CRONO® 50 reservoirs
7. CRONO JET 100 accessory for filling CRN CRONO® 100 reservoirs
8. CRN Connector
9. Multicomponent infusion sets OPTFlow SUB-Q with needles and tubes of various lengths.
10. Three-component sterile injection syringe for single use "ALEXPHARM" 5 mL Luer Lock, with a 22G needle
11. Thermal bag to transport the IMP home between study visits;
12. 1 L sharps container for storage of used infusion materials.

The company that imports related materials: BIOPHARMA PLASMA LLC

Provision (supply) of materials and study documents

The Sponsor shall provide the Investigator with the investigational medicinal products, the Clinical Study Protocol, the Investigator's Brochure, ICF, and other documents, materials and equipment (where applicable) required for the conduct of the study.

The Investigator shall provide the Sponsor with a signed clinical study agreement, a signed confidentiality and non-disclosure agreement, a copy of IEC approval, a list of IEC members, the current-date signed curricula vitae of the Responsible Investigator and the study team, etc.

All deliveries to the site and recovery of critically important study materials from the CTS shall be documented using the forms for transfer/return of study materials.

BIOVEN, which is used as a prior therapy and is not used in Cohort B (adult patients) for the purpose of a pharmacokinetic assessment: a site-procured medicinal product can be used. Appropriate tracking of used batches is the responsibility of the Sponsor.

4.8. Randomisation and unblinding codes

No randomisation or blinding is used in this clinical trial.

4.9. The list of information entered into the CRF

Information will be entered into the eCRF in accordance with the examination methods that will be used during the study:

- Signing of Informed Consent (date);
- Collection and registration of demographics;
- Collection and registration of medical history;
- Verification of PID diagnosis;
- Registration of information about the use of prior therapy for PID (type of therapy, dose/schedule, duration, response (if any) and time interval since the last administration);
- Registration of information about symptomatic therapy and taking medicinal products for the treatment of comorbidities;
- Transfusion history;
- Allergy history;
- Presence of infections
- Data on antibiotic therapy and additional therapy of PID;
- Collection of anthropometrics (measurement of body weight, height, and BMI);
- Objective physical examination (auscultation and percussion of the heart and lungs; palpation and percussion of abdominal organs; examination of the skin and mucous membranes);
- Measurement of vital signs (BP, HR, RR, body temperature);
- 12-lead electrocardiogram;
- Chest X-ray/CT/MRI (it is permitted to use data of assessments performed within the past 6 months);
- Collection of biomaterials for laboratory investigations (performed at the CTS, at a collection point or by a mobile team of a Sponsor-designated Central Laboratory):
    - Blood test for HIV (express test), RW, HBs-Ag, anti-HCV;
    - Complete blood count (haemoglobin, haematocrit, red blood cells, white blood cells and white blood cell differential, platelets);
    - Serum chemistry (ALT, AST, creatinine, urea, glucose, total bilirubin);
    - Coombs' test (antiglobulin test);
    - Haptoglobin level
    - Threshold level of total serum IgG (pre-administration);
    - Pharmacokinetic measurements of serum IgG;
    - Urinalysis (specific gravity, pH, protein, glucose; microscopic sediment examination – white blood cells, red blood cells, casts, salts, bacteria, fungi);
    - Pregnancy test (HCG) (for women of childbearing potential);
    - Coagulation panel (INR, Prothrombin percentage by Quick, Prothrombin time, aPTT, fibrinogen);
- Assessment of the incidence, severity and duration of infectious diseases;
- Registration of AEs/ARs
- Transferring data from the patient's diary regarding interim administrations of the cycle (date and time of start and end of administration, dose, infusion rate, administration points, volume of administration into each point, the amount of drug, the presence of adverse events, data on antibiotic therapy and concomitant therapy, the presence of infections)
- Obtaining data of the quality of life questionnaire

The detailed plan, phased breakdown, and content of each of the Study Visits are set out in 4.2.1 Tabular Schedule of Procedures.

Upon completion of subject participation in the study, a completion date and subject health condition at completion time shall be recorded.

The data entered shall be checked carefully.

5. SELECTION AND EXCLUSION OF STUDY SUBJECTS

The first 10 patients enrolled in the study must be adults, for an interim safety assessment in adult patients who received at least 4 infusions of the IMP BP-SCIG 20%.
Based on the results of such assessment, the possibility of enrolling patients younger than 18 years of age is determined. The interim report will be reviewed and assessed by the Independent Safety Committee.

5.1. Inclusion Criteria

Table 5.1.1 – Inclusion criteria for CT subjects

No.	Inclusion criterion
1.	a signed informed written consent of the patient/patient's parents or legally authorised representative to take part in the study;
2.	children from 0 to 18 years of age, of both sexes; or adult patients: males and females older than 18 years;
3.	a diagnosis of primary immunodeficiency with impaired antibody production document-supported according to the ESID criteria, requiring replacement therapy with immunoglobulins;
4.	patients with a body weight of no less than 9.1 kg;
5.	patients who received replacement therapy with intravenous immunoglobulin (IVIG) products at intervals from 21 to 28 days at the dose of 0.4–0.8 g/kg, for at least 4 months prior to the start of the study and have total serum IgG levels ≥5 g/L*, which is confirmed by the results of no less than 2 measurements performed immediately before the scheduled IVIG administration after signing the ICF, or patients who received replacement therapy with subcutaneous immunoglobulin (SCIG) products at the dose of 0.4–0.8 g/kg per month, for at least 4 months prior to the start of the study, and have total serum IgG levels ≥5 g/L*, based on the results of no less than 2 measurements performed immediately before the scheduled SCIG administration after signing the ICF; or patients with a newly established diagnosis of PID who have not yet received replacement therapy with IgG products (treatment-naïve patients) and have a serum IgG level ≤ 4 g/L;
6.	absence of episodes of serious bacterial infections (bacteraemia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, visceral abscess) while taking the previous medicinal product and absence of episodes of hospitalisation for at least 3 months prior to inclusion in the study and during the screening period (prior to the first administration of the IMP BP-SCIG 20%);
7.	a negative pregnancy test (in female patients with childbearing potential); readiness to use reliable methods of contraception throughout the study period;
8.	patient's ability, in the Investigator's judgement, to comply with all the requirements of the study protocol.

Note: **If patients with PID who have already received IVIG or SCIG did not have serum IgG levels* ≥5 g/L *during the screening (*based on the results of no less than 2 measurements performed immediately before the scheduled administration of IVIG or SCIG over 2–3 months*), the patient may undergo repeated screening for participation in this study, after correction of the dosage regimen by the doctor and achievement of target IgG level* ≥5 g/L.

5.2 Subject non-inclusion criteria

Table 5.2.1. Non-inclusion criteria for CT subjects

No.	Non-inclusion criterion
1.	known intolerance, drug allergy or hypersensitivity to immunoglobulin products;
2.	any contraindications to the use of immunoglobulin products;
3.	patients with secondary immunodeficiencies;
4.	patients with autoimmune diseases;
5.	absolute neutrophil count in peripheral blood <1 g/L;
6.	pregnancy or breastfeeding;
7.	liver cirrhosis, any clinically significant hepatic function impairment (elevated serum transaminases (AST, ALT) more than 2.5 times the upper limit of normal);
8.	serum creatinine level > 2 times the age- and sex-specific upper limit of normal;
9.	history of clinically significant renal impairment (acute or chronic renal failure) or hepatic impairment (acute liver failure);
10.	history of cancer (active or cancer in remission for less than 5 years);
11.	receiving any blood products (with the exception of IVIG or SCIG products, which are allowed in the screening period) during the last 3 months prior to screening;
12.	therapy with antibiotics, antiviral, or antifungal drugs for the treatment of infection and/or for infection prophylaxis within the 30 days prior to screening (with the exception of topical agents);
13.	acute infections within 2 weeks prior to inclusion, or at the time of inclusion in the study;
14.	episodes of serious bacterial infections while receiving the previous IVIG or SCIG product and episodes of hospitalisation: within 3 months prior to inclusion in the study, or detected during the screening phase (prior to the first administration of the IMP BP-SCIG 20%);
15.	history of immunopathological systemic disease (rheumatic diseases, nephritis, etc.)
16.	vaccination with live vaccines, including vaccination against measles and mumps performed less than 3 months prior to screening;
17.	known alcohol or substance abuse;
18.	the need to prescribe medicinal products not allowed as part of this study;
19.	the need for therapy with anticoagulants;
20.	history of thrombosis and venous embolism episodes within the last year;
21.	severe thrombocytopenia (platelets less than 30 G/L) and other coagulation disorders;
22.	history of myocardial infarction, angina pectoris (Stage 2–3) or stroke within the last year;
23.	diabetes mellitus;
24	hypertension (Stage 2–3);
25.	any other comorbidities or acute conditions that, in the Investigator's judgement, may affect the patient's ability to take part in the clinical trial;

26.	taking part in any other interventional clinical trial (currently or during the last 30 days prior to the screening visit).

5.3 Subject exclusion criteria (discontinuation of treatment with the investigational product)

Table 5.3.1 – Exclusion criteria for CT subjects

No.	Exclusion criterion
1.	at the request of the patient/patient's parents/patient's legally authorised representative at any time and for any reason;
2.	patient developing serious and/or unexpected AEs/ARs during the study, which require discontinuation of the product;
3.	blood transfusions or transfusions of blood components and products, with the exception of the IMP;
4.	the need to use medicinal products disallowed as part of this study;
5.	systematic lack of patient compliance with the treatment regimen prescribed by the Investigator;
6.	systematic lack of patient compliance with the procedures specified in this protocol;
7.	exclusion based on screening results, including emergence of episodes of serious bacterial infections while receiving a previous IV immunoglobulin product and episodes of hospitalisation during the screening period (before the first administration of the IMP BP-SCIG 20%).

For all subjects withdrawn from the study due to AEs requiring discontinuation of treatment with the investigational medicinal product, it is required to conduct the final visit procedures as soon as possible after AE development. After discontinuation of treatment, the subject shall remain under observation until the reaction or its clinically significant signs disappear.

The reasons for leaving the study early must be documented in the eCRF.

Table 5.3.2. Criteria for exclusion of CT subjects from the investigation of PK parameters at the time of starting PK assessment

No.	Exclusion criterion
1.	Receiving the IMP BP-SCIG 20% for less than 4 months;
2.	Presence of episodes of serious bacterial infections (bacteraemia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, visceral abscess) at the time of investigation of PK parameters.

6. TREATMENT OF SUBJECTS

6.1. Treatment regimen

The IMP shall be administered subcutaneously.

All patients will receive the investigational medicinal product BP-SCIG 20%, solution for subcutaneous administration manufactured by BIOPHARMA PLASMA LLC.

The IMP BP-SCIG 20% shall be administered at the frequency of once a week for 52 weeks, subcutaneously using a CRONO S-PID4 infusion pump.

The dosing regimen shall be designed to achieve a trough IgG level (at least 5–6 g/L), which will be measured before the next infusion.

Efforts must be taken to maintain serum IgG within the reference range for the corresponding age group of patients.

Individual dose selection and adjustment may be required for each patient, depending on the pharmacokinetic response (IgG level) and clinical response. Threshold levels must be assessed in combination with the incidence of infectious episodes. To reduce the risk of infection, it may be necessary to increase the dose and aim to achieve higher trough IgG levels.

A loading dose of IMP may be required (at the Investigator's decision): at least 0.2–0.5 g/kg (1.0–2.5 mL/kg) of body weight. This dose is distributed across several days, with a maximum daily dose of 0.1 to 0.15 g/kg.

After achieving a steady-state (minimal) level of IgG, maintenance doses are administered at repeated intervals (approximately once a week) to achieve a cumulative monthly dose of 0.4–0.8 g/kg. Each single dose must be administered to different anatomical locations.

Since the bioavailability of SCIGs is 30 % lower than that of IVIGs, partly due to binding to the extracellular matrix and cleavage by tissue enzymes (Wang et al. 2008; Berger et al. 2013), a dose adjustment factor of 1.37 will be used to convert the IVIG dose to the SCIG dose. This is based on historical data for bioequivalence evaluation of these administration routes (Wasserman et al. 2010, 2011; Berger et al. 2011) and meets the requirements of the US Food and Drug Administration (US FDA), according to which the SCIG doses must be adjusted to ensure an equivalent AUC for total IgG compared to previous IVIG therapy. Dose calculation for patients who received IVIG prior to the start of their participation in the study (John W Sleasman et al. 2019):

The initial dose of SCIG

$$\mathbf{IgG} = \frac{\text{Previous IVIG dose (in grams)} \times 1.37}{\text{Number of weeks between IVIG administrations}}$$

The dose adjustment factor of 1.37 will be evaluated in an interim pharmacokinetic (PK) analysis and modified as needed.

The first four IMP administrations are for training purposes, during which the investigational medicinal product BP-SCIG 20% for subcutaneous administration will be administered by a responsible member of the study team in a hospital setting and by the patient/legally authorised representative or parents after an appropriate training and in compliance with aseptic/antiseptic precautions under the supervision of responsible and trained members of the study team.

The study doctor prescribes the dose and rate of subcutaneous administration of the IMP for home-based use. The patient/their legally authorised representative or parents will be instructed by the Investigator regarding the use of the CRONO S-PID4 infusion pump, the administration technique, filling out the patient's diary, recognition of adverse reactions and measures to be taken in the event of adverse reactions.

Prior to use, the solution must be at room temperature and remain outside the refrigerator for at least 30 minutes. Turbid solutions and/or solutions with sediment must not be used.

To administer the IMP, a CRONO S-PID4 infusion pump and a dedicated single-use infusion set are used.

The IMP BP-SCIG 20% can be administered in sites with ample subcutaneous fat, such as the abdomen, the shoulder, and lateral thigh.

The IMP BP-SCIG 20% is administered subcutaneously using a CRONO S-PID4 infusion pump. Multiple lines can be used for administration into several sites simultaneously.
It is recommended to use an initial infusion rate of 10 mL/h/line. If well tolerated, the infusion rate may be increased by 5 mL/h/line at each subsequent administration. The recommended maximum rate is 25 mL/h/line. The amount of product infused into a certain site must not exceed 25 mL. In infants and children, the administration site can be rotated every 5–15 mL. For adults, doses above 30 mL can be divided into several doses, in accordance with the patient's preferences. There are no limitations regarding the number of injection sites.

Hypersensitivity to active ingredient or any of the excipients is a contraindication.

The product must not be administered via the intravascular route. If BP-SCIG 20% is inadvertently administered into a blood vessel, the patient may develop shock. In the event of shock, standard treatment of shock must be instituted.

The recommended infusion rate must be followed strictly. During the initial administration, the patients shall remain under supervision for the entire duration of the infusion period to detect hypersensitivity to the active ingredient or to any of the excipients. Monitoring for any adverse symptoms shall be in place. It is forbidden to administer the IMP BP-SCIG 20% in pronounced thrombocytopenia or other disorders of haemostasis.

Potential complications described in this Protocol (see Section 2, item 3) can usually be avoided in adherence to:
• slow start of administration, from the infusion rate of 10 mL/kg/line;
• careful monitoring of patients' well-being in relation to any symptoms throughout the infusion period. In particular, patients who have not previously received human normal immunoglobulin, patients who have switched from an alternative immunoglobulin product, or if a long period of time has passed since the previous administration shall be monitored by health care workers during the first infusion and throughout the first hour afterwards to identify any potential adverse manifestations.

In all other cases, the patient's well-being must be monitored for at least 20 minutes after the administration.

In case of an adverse reaction, either the infusion rate must be reduced, or administration must be stopped. If an AE develops, the necessary treatment will depend on the nature and the severity of the AE.

The route of administration and dosing shall not exceed the maximum single and course doses that can be used in patient treatment, within the limits specified in *"Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration" EMA/CHMP/BPWP/143744/2011 rev.1 26 February 2015, and "Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)" EMA/CHMP/BPWP/410415/2011 rev.1 23 July 2015.*

6.2. Allowed and disallowed therapy

Allowed concomitant therapy

During the study, if a patient develops infectious complications of underlying disease, the administration of broad-spectrum antibiotics is permitted, in accordance with accepted medical practice, local and national protocols, and in compliance with the legislation of Ukraine.

The patients participating in this trial may receive the concomitant therapy continuously used to manage their comorbidities and life-threatening conditions (such as antibiotic therapy as needed).

It is allowed to continue replacement therapy with previous IVIG or SCIG products during the screening period.

If vaccination is required, in accordance with legal requirements, the use of inactivated vaccines, vaccines against meningococcal infection and vaccines against influenza is permitted (as decided by the Responsible Investigator, taking into account the patient's clinical condition).

The use of contraceptives is allowed in women of childbearing potential.

Disallowed concomitant therapy.

During patients' participation in the clinical study, the use of the following medicinal products is disallowed:
- any agents with potential immunostimulatory or immunosuppressive effects;
- anticoagulants;
- all live vaccines;
- other human immunoglobulin products (with the exception of those allowed during the screening period) blood products;
- any agents, which, in the Investigator's judgement, could confound study results.

6.3 Procedures

6.3.1 Informed Consent signing

A written informed consent to participation in the study shall be obtained from all patients enrolled in the study, or from the patient's legally authorised representative, or from both parents of minors prior to start of any study procedures.

Prior to enrolment in the study, the patient shall have his/her rights and responsibilities related to participation in the study explained to him/her. The patient or his/her legally authorised representative should know that he/she may refuse to take part in the study at any time with no negative impact on his/her further treatment. He/she shall also be informed that the fact of his/her participation in the study is strictly confidential and that any clinical trial documents will only use his/her initials and subject identification number.

The Investigator/study personnel shall explain to the patient that his/her personal data obtained during the study will be used for statistical processing of the study results and for reporting purposes; this data may also be discussed by the persons conducting the study and may be disclosed to representatives of state regulatory authorities during clinical audits.

The patient or his/her legally authorised representative shall have sufficient time to consider his/her participation in the study and to ask the Investigator any questions he/she might have. The Investigator is obliged to explain in detail the sections of Informed Consent where the patient has questions, and provide clear instructions regarding the safeguards and patient's actions in the event of risks for the patient in the course of the CT. The Investigator shall not attempt to coerce the patient with an intent to influence his/her decision.

If the patient or his/her legally authorised representative decides to take part in the study, he/she shall personally complete and sign 2 copies of Informed Consent Form (ICF). One original copy of Informed Consent is issued to the patient to keep for his/her records, and the other remains in the Investigator's file.

The fact of informed consent discussion shall be documented in the patient's medical record and the CRF with an indication of the signature date.

The screening and inclusion of the patient into the clinical study are performed only after signing the Informed Consent Form.

In the event changes are made to the ICF during the clinical study, and if such changes are not related to the safety or well-being of the study subject, a repeated signing of the form by already included patients is not required.

For patients younger than 18 years, ICF signing is envisaged under a procedure identical to the one above, with mandatory signing of the ICF by both parents of the patient.

6.3.2 Entering information into the Patient's Diary

- The use of Patient's Diary (PD) is envisaged as part of the study. The diary is intended for entering information regarding self-administration of the IMP by the patient.
- Investigators conduct a training for each patient on how to work with the Patient's Diary.
- Filling the PD begins with the C2W6 Visit after administration of the IMP and ends after the last administration of the IMP;
- The patient receives a printed brochure (Patient Diary) signed off by the Responsible Investigator.
- The data into the diary are entered by the patient, patient's legally authorised representative, both patient's parents or one of their parents (for children from 0 to 12 years of age inclusive).
- The patient/legally authorised representative/parents of the patient enter the following data after each home-based administration of the IMP: **date and time of start and end of administration, dose, infusion rate, administration points, volume of administration into each point, the batch and the number of vials of each batch, the presence of adverse events, data on antibiotic therapy and concomitant therapy, the presence of infections). The data entered shall be carefully checked by the patient.**
- The Investigator is obliged to check the completion of the diary at the nearest on-site visit, make a copy of checked PD pages, and enter the data into the eCRF.
- The correctness of transferring data into the eCRF is checked by the Monitor.

6.3.3 Procedure to verify the diagnosis of PID (primary immunodeficiency)

Patients must have a well-documented PID (primary immunodeficiency) with impaired antibody production.

Data of examinations from primary medical records are taken into account. The scope of the conducted investigations and their sufficiency for differential diagnosis from other variants of immunodeficiencies is assessed.

The patient's history of treatment with immunoglobulin replacement therapy products is assessed (for previously treated patients).

Impaired antibody production in a patient can be demonstrated by the presence of diagnosis of primary immunodeficiency with obligate indications for replacement therapy (hereditary agammaglobulinaemia, hyper IgM syndrome, common variable immunodeficiency, severe combined immunodeficiency established according to ESID or WHO criteria, if such exist for them), low IgG levels (lower than 5 g/L) or impaired response to vaccines in other diagnoses of primary immunodeficiency.

In case of any doubts regarding the validity of the diagnosis, additional investigations are prescribed from a list previously agreed with the Sponsor.

6.3.4 Medical history, demographics, complaints and body weight measurement

During collection of medical history, the Investigator shall pay special attention to any direct and indirect findings that may suggest impossibility of including the patient into study. Any available medical records on comorbidities the patient might have and pharmacological and non-pharmacological treatments he/she is receiving must be analysed. Complete patient's history shall be reflected in source documents and in CRF. When taking a history, attention shall be paid to previous diseases, chronic comorbidities, heredity, habitual intoxications (smoking status, alcohol, drug use), allergy history, previous surgeries and injuries, clarification of occupational history,

permanent or periodic drug therapy. The patient's sex and age, as well as their race and ethnicity, are indicated in the source documentation. Body weight shall be measured using medical balances.

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

Patients shall be weighed in the morning under fasting conditions, after urination and bowel movement, in their underwear (followed by deducting the average weight of clothing). The balances shall be positioned on a rigid base, horizontally. Measurement error shall not exceed 0.2 kg according to the standards. It is not allowed to write down body weight based on the patient's words, even in cases where body weight measurement is not possible.

Height measurement shall be performed in all patients (causes preventing height measurement include inability of the patient to stand, exceeding the scale of the stadiometer). Stadiometer – a vertically positioned board with centimetre markings and a sliding ruler – is used to determine height. The scale error shall not exceed 2 millimetres according to the standard. The patient is asked to remove their shoes, dense clothing, hairpins, and hairdo accessories. The patient must touch the vertical board with the back of their head, back, buttocks, calves, and heels, with the toes together. The upper edge of the external auditory canal opening must be at the same horizontal level as the lower edge of the orbit (zygomatic bone). The patient is asked to look straight ahead. The stadiometer ruler is lowered onto the head, and the markings are counted. Height is noted while the patient remains under the measuring visor. The error must not exceed half a centimetre.

The respective measurements for the paediatric population are performed according to the norms of the appropriate age-related category using the calibrated and metrologically verified measuring instruments.

Body mass index (BMI) will be calculated from the following formula:

$$BMI = body\ weight\ (kg) / (height\ in\ m)^2$$

The eCRF shall capture information on disease onset, date of diagnosis, and review the source documentation regarding objective assessments on the basis of which the diagnosis was confirmed.

Information on comorbidities shall be recorded. Any drug products the patient was receiving within 3 months prior to onset of the study shall be documented in the CRF as a prior/concomitant treatment with reference to relevant indications, start date(s) and end date(s) of therapy.

6.3.5 Physical examination and vital sign measurements

Objective examination shall include auscultation of the heart and lungs, inspection of the skin and mucous membranes, abdominal palpation, measurement of HR, RR, BP and body temperature as well as other methods of physical examination according to current clinical situation. The data on the changes found during the examination shall be documented in the source documentation and in the eCRF.

Measurement of HR, RR, BP, and body temperature shall be conducted at rest (after 15 minutes of rest, not earlier than an hour after smoking cigarettes and 2 hours after eating). Heart rate (HR) shall be measured by auscultation of the heart in parallel with the determination of radial artery pulse rate (or carotid artery pulse rate if radial artery pulse is weak) per minute in the sitting position, both parameters shall be recorded in case of pulse deficit: HR and pulse rate. Respiratory rate (RR) shall be measured per minute at rest in the supine position with recording the respiratory movements of the chest or abdominal wall, without attracting the patient's attention.

Measurement of blood pressure (BP) will be performed in the brachial artery in the supine position by Korotkoff method using a certified sphygmomanometer or blood pressure monitor with cuff length and width suitable for patient's upper arm length and circumference. BP cuff size shall match the upper arm size: the rubber part of the cuff shall cover at least 80 % of the upper arm circumference; BP cuff of 12–13 cm wide and 30–35 cm long (average size) shall be used for adults; but availability of large- and small-size cuffs shall be required for large and small arms, respectively. The sphygmomanometer pointer must be at the zero mark before the start of measurement. To assess blood pressure levels in each arm, at least two measurements with intervals of at least 1 minute shall be performed; if BP difference is ≥ 5 mm Hg, one more additional measurement shall be performed on each arm; the minimum value of three measurements on the hand where the BP is higher shall be taken as the final (recorded) value.

Measurement method:

- Quickly inflate the air into the cuff to a pressure 20 mm Hg greater than systolic blood pressure (SBP) (estimated from the disappearance of the pulse);
- Measure BP with an accuracy of 2 mm Hg;
- Deflate the pressure in the cuff at a rate of approximately 2 mm Hg per 1 second;
- The pressure level at which the 1st sound appears corresponds to SBP (phase 1 of Korotkoff sounds);
- The pressure level at which the sounds disappear (Korotkoff phase 5) corresponds to dBP; when it is impossible to measure phase 5 in children, adolescents and young people immediately after exercise, and in adults in some pathological conditions, one shall attempt to identify Korotkoff phase 4, which is characterised by a significant weakening of the sounds;
- If the sounds are very weak, the patient shall be asked to raise the arm and perform several fist-clenching movements. After that, the measurement must be repeated; in doing so, the artery must not be strongly compressed with the diaphragm of the stethoscope;
- In initial examination of the patient, blood pressure shall be measured on both arms; subsequently, the measurements are performed on the arm where the BP is higher.

Temperature measurement is performed in the armpit using a medical thermometer (mercury thermometer), with the end of the thermometer, after shaking down, pressed firmly against the armpit by the upper arm; the skin in the armpit must be dry, because the thermometer shows a lower temperature if the skin is wet. The thermometer is kept in the armpit for 10–15 minutes. During the measurement, the patient must remain completely still.

Auscultation of the lungs and heart, palpation of the abdomen and examination of the skin and mucous membranes shall be carried out according to the standard procedure accepted in clinical practice for the screening phase, considering the general serious condition of patients. The objective of these procedures shall be to detect abnormal changes, including clinically significant ones. During the follow-up period, a less physically burdensome set of procedures shall be performed according to the standard procedure accepted in clinical practice, which allows assessment of the patient's condition.

The respective measurements for the paediatric population are performed according to the norms of the appropriate age-related category using the calibrated and metrologically verified measuring instruments (where applicable).

6.3.6 Chest X-ray/CT/MRI

Chest X-ray/CT/MRI is performed under a generally accepted procedure by a referral from the Investigator or the doctor who treated the patient prior to start of their participation in the clinical study. During the screening, this assessment is performed if not carried out during the last 6 months.

It is permitted to use of examination data obtained within the last 6 months prior to inclusion in the study.

6.3.7 Obtaining the results of quality of life questionnaires

According to the Schedule of Study Procedures, the Responsible Investigator/co-investigator provides the patient with a quality of life questionnaire to complete.
Adult patients will use the "Adult subject quality of life questionnaire" developed based on Isabella Quinti, MD, PhD et al. Development and Initial Validation of a Questionnaire to Measure Health-Related Quality of Life of Adults with Common Variable Immune Deficiency: The CVID_QoL Questionnaire.
The procedure for filling in the "Adult subject quality of life questionnaire":

1. The physician provides the questionnaire to the patient during the visit, to fill in Part I.
2. The patient completes the questionnaire by circling the scores corresponding to their condition.
3. The physician calculates the total score for each domain separately (psychological domain: 0–56 points; social domain: 0–36 points; clinical domain: 0–36 points).
4. A domain is not included in the assessment if more than 3 questions in it are left unanswered.
5. Calculation of Score for each domain is performed using the following formula:

$$x = \frac{\text{Sum of the scores for the domain} \times 100\%}{\text{Maximum sum of the scores for all items of the domain included in the analysis}}$$

$$\text{Sum of the scores for the domain} = \text{the sum of all numbers in the domain circled by the patient..}$$

$$\text{Maximum sum of the scores for all items of the domain included in the analysis} = \text{the number of questions answered by the patient x 4}$$

6. After the calculation, the physician records the result into the field for the respective domain (Part II).
7. The total score is calculated in a manner similar to assessment of each individual domain

$$x = \frac{\text{Sum of the scores for all domains} \times 100\%}{\text{Maximum sum of the scores for all items included in the analysis}}$$

8. After the calculation, the physician records the result into the Total Score field (Part II).

For paediatric patients (6–17 years), the "Quality of Life Questionnaire for Children and Adolescents" will be used, which was developed based on SCALING AND SCORING for the Acute and Standard versions OF THE Pediatric Quality of Life Inventory™ PedsQLTM.
Procedure of assessment on the "Quality of Life Questionnaire for Children and Adolescents":
Step 1: Conversion of scores
Tasks are scored in reverse order and linearly transformed to a scale from 0 to 100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0

Step 2: Scoring
Assessment by domains:
- If more than 50 % of the items in the scale are missing, the score for the scale in question is not calculated.
- Mean score = Sum of the scores for each item of the scale divided by the number of items answered by the respondent.
Summary score for psychosocial health = Sum of the scores for the emotional, social, and school functioning scales.
Summary score for physical health = score for the physical functioning scale.
Total score: Sum of the scores for all scales according to the number of responses to all items.

6.3.8 Bioanalytical procedures and laboratory investigations

The procedure is described in detail in the Laboratory Manual.

The following shall be collected as biological material: blood, urine.

The procedure for collection of biological material for laboratory tests is carried out at the clinical trial site or in a collection point (if, in the Investigator's judgement, the patient is mobile), or by a mobile team of a Sponsor-designated Central Laboratory.

Blood samples for analysis will be collected under fasting conditions (8–10 hours after the last meal) from a vein using a disposable sterile syringe, through a catheter or with a vacutainer, with adherence to aseptic/antiseptic precautions. Amount of blood taken shall be determined by the list of laboratory tests that need to be performed at the Visit (see Table 4.2.1)

For urinalysis, the middle portion of morning urine shall be collected after adequate perineal hygiene; the urine shall be delivered to the laboratory within two hours after collection.

Blood and urine samples for clinical analysis are collected under a standard procedure in accordance with the Laboratory Manual, according to the Schedule of Study Procedures (Table 4.2.1).

The procedures of preparation for analysis, collection, storage, transportation of biological material, and completion of accompanying documentation are carried out in accordance with the regulations described in the Laboratory Manual.

The list of Protocol-specified laboratory investigations:

- Complete blood count (haemoglobin, haematocrit, red blood cells, white blood cells and white blood cell differential, platelets);
- Serum chemistry (ALT, AST, creatinine, urea, glucose, total bilirubin);
- Blood test for HIV, RW, HBs-Ag, anti-HCV;
- Coombs' test (antiglobulin test);
- Haptoglobin level;
- Total serum IgG level;
- Urinalysis (specific gravity, pH, glucose; microscopic sediment examination – red blood cells, white blood cells, casts, crystals, bacteria, fungi);
- Pregnancy test (for women of childbearing potential);
- HIV test (express test), RW, HBs-Ag, anti-HCV;
- Glycated haemoglobin;
- Coagulation panel (INR, Prothrombin percentage by Quick, Prothrombin time, aPTT, fibrinogen);

6.3.9 Collection of samples for pharmacokinetic assessment

Testing for total serum IgG levels is carried out using the nephelometric method.

Blood samples for the tests will be taken according to a scheme that allows obtaining an adequate pharmacokinetic profile after a single administration of the investigational product for further calculation of pharmacokinetic parameters.

The investigation of PK parameters of the IMP will include at least 20 patients older than 18 years who had been receiving the investigational medicinal product for at least 4 months, and did not have any severe bacterial complications during the study.

PK will be assessed through an additional sampling of 3.5 mL of venous blood (for one sampling) for subsequent determination of patient's levels of immunoglobulin in the samples over 7 days after the infusion of the IMP BP-SCIG 20%. The total volume of venous blood for PK assessment for one patient is 28 mL.

The procedure is performed at Week 21 (Table 4.2.2 – Pharmacokinetic assessment of the IMP). The time of blood sampling is documented.

Structure of PK assessment of the IMP

1	PK0 (pre-administration) Before IMP administration (10–30 min prior)
2	PK1 (30 minutes) 30 minutes after IMP administration (±10 min)
3	PK2 (3 hours) 3 hours after IMP administration (±30 min)
4	PK3 (1 day) 24 hours after IMP administration (±5 h)
5	PK4 (2 days) 48 hours after IMP administration (±5 h)
6	PK5 (3 days) 72 hours after IMP administration (±5 h)
7	PK6 (4 days) 96 hours after IMP administration (±5 h)
8	PK7 (7 days, threshold level) at 7 days (±5 h), prior to the next administration of the IMP

The points for pharmacokinetic assessment of BP-SCIG 20% were selected in accordance with the available data on achieving Cmax following subcutaneous administration of the MPs belonging to the subcutaneous immunoglobulin category, and for the purpose of clear demonstration of differences in concentration-time curves for BIOVEN and SCIG.

The investigation of PK parameters of BIOVEN will include subjects aged over 18 years who received treatment with BIOVEN prior to their enrolment in the study and, respectively, throughout the screening period.

PK will be assessed through an additional sampling of 3.5 mL of venous blood (for one sampling) for subsequent determination of patient's levels of immunoglobulin in the samples over 21–28 days after the infusion of BIOVEN. The total volume of venous blood for the PK assessment per one patient is 28–31.5 mL.

The procedures are performed at Visit 3 of the screening period (Table 4.2.3. Pharmacokinetic assessment of IVIG). The time of blood sampling is documented.

Structure of PK assessment of IVIG

1	PK0 (pre-administration) Before administration of BIOVEN (10–30 min prior)
2	PK1 (15 min) 15 minutes after administration of BIOVEN (±10 min)
3	PK2 (1 hour) 1 hour after administration of BIOVEN (±15 min)
4	PK3 (1 day) 24 hours after administration of BIOVEN (±5 h)
5	PK4 (3 days) 72 hours after administration of BIOVEN (±5 h)
6	PK5 (7 days) 7 days after administration of BIOVEN (±5 h)
7	PK6 (14 days) 14 days after administration of BIOVEN (±5 h)
8	PK7 (21 days) 21 days after administration of BIOVEN (±5 h)
9	PK8 (28 days) 28 days after administration of BIOVEN (±5 h) (where applicable)

The points for pharmacokinetic assessment of BIOVEN were selected based on previous PK studies of BIOVEN.

The data obtained during the phase of BIOVEN pharmacokinetics will be used to confirm or recalculate the dose adjustment factor for switching from BIOVEN to the IMP.

The procedures of preparation for analysis, collection, storage, transportation of biological material, and completion of accompanying documentation are carried out in accordance with the regulations described in the Laboratory Manual.

Blood collection can be performed, at the study doctor's discretion, in a hospital, on an outpatient basis or by a Sponsor-designated Central Laboratory, in a collection point (if the study subject is mobile in the Investigator's judgement), or by a mobile team.

In the event of deterioration of the patient's well-being or the patient's desire to withdraw from the study, blood sample collection is discontinued. Information about these cases shall be entered in the eCRF, source documentation, and reported to the Sponsor.

In the event a sample was not collected according to the protocol-scheduled time (missed), the information explaining that event shall be entered in the eCRF and source documentation, and sample collection shall be resumed at the next time scheduled according to the Schedule.

6.3.10 Bioanalytical testing plan

Bioanalytical study procedures will be carried out at a certified central laboratory, DILA (represented in Ukraine as the legal entity ML DILA LLC), whose activities are organised in accordance with the requirements of Good Clinical Laboratory Practice (GCLP).

All plasma, serum, and urine samples are subject to bioanalytical investigation, including samples obtained from patients who did not complete the study in full (those who were prematurely discontinued from the study).

6.3.11 Validation of bioanalytical procedures

The bioanalytical method used must be properly validated/verified and documented in accordance with GCLP standards and regulatory requirements valid within the study period.

The main objective of validation/verification of the method is to prove the reliability of this method for quantification of serum analyte concentrations.

Validation/verification shall be carried out taking into account the main acceptance criteria of the bioanalytical method established in the guidelines.

The following characteristics of the bioanalytical method shall be evaluated during the validation/verification process:

1) within-run precision;
2) between-run precision;
3) accuracy;
4) clinical sensitivity;
5) specificity;
6) measurement uncertainty.

The results and the course of validation/verification of the bioanalytical method must be listed in the Validation/Verification Protocol.

6.3.12 Test tube labelling procedure

All consumables (vacutainers, test tubes, and other materials included in laboratory kits), together with the requisitions, are prepared, labelled, and delivered to the CTS or the collection point of the Central Laboratory directly by the Central Laboratory at the request of the Sponsor or the Principal Investigator. The composition of laboratory kits and the procedure for ordering the consumables is described in detail in the Laboratory Manual.

6.3.13 Blood sampling procedure

Blood samples for analysis will be collected under fasting conditions (8–10 hours after the last meal) with a vacutainer, with adherence to aseptic/antiseptic precautions. Further processing of the biological sample is carried out in accordance with the specific sample requirements, according to the instructions provided in the Laboratory Manual.

Volume of venous blood:

- serum chemistry (ALT, AST, creatinine, urea, total bilirubin), pregnancy test (HCG), hepatitis B (HBsAg), hepatitis C, syphilis, immunoglobulin G – 5.5 mL;
- haptoglobin – 3.5 mL;
- direct Coombs' test – 2 mL;
- complete blood count (red blood cells, haemoglobin, white blood cells and white blood cell differential, platelets) – 2 mL;
- glucose – 2 mL;

- coagulation panel – 3 mL;
- glycated haemoglobin – 4 mL.

Blood volume by time points:

- Visit 1: 22 mL
- Visit 2: 11 mL
- Visit 3: 11 mL
- Pharmacokinetic assessment of BIOVEN (at Visit 3):
  PK0 (as part of determination of threshold IgG levels at Visit 3)
  PK1, PK2 – 7 mL per day (on the day of Visit 3);
  PK3 – 3.5 mL per day,
  PK4 – 3.5 mL per day,
  PK5 – 3.5 mL per day,
  PK6 – 3.5 mL per day,
  PK7 – 3.5 mL per day,
  PK8 – 3.5 mL per day.
- Visit 4: 15 mL
- Visit 5: 18 mL
- Visit 6: 11 mL
- Visit 7: 11 mL
- Visit 8: 18 mL
- Visit 9: 11 mL
- Pharmacokinetic assessment of IMP (at Week 21):
  PK0 (as part of determination of threshold IgG levels at Visit 9)
  PK1, PK2 – 7 mL per day (on the day of Visit 9);
  PK3 – 3.5 mL per day,
  PK4 – 3.5 mL per day,
  PK5 – 3.5 mL per day,
  PK6 – 3.5 mL per day,
  PK7 – 3.5 mL per day.
- Visit 10: 11 mL
- Visit 11: 18 mL
- Visit 12: 11 mL
- Visit 13: 11 mL
- Visit 14: 18 mL
- Visit 15: 11 mL
- Visit 16: 11 mL
- Visit 17: 18 mL

No pharmacokinetic studies are performed in the paediatric population.

An additional blood collection at the visits is permitted provided a repeated measurement of parameters is required, which shall not exceed a total of 18 mL per visit.

The patients may also have additional assessments at **unscheduled visits**.

Blood volumes required for these tests shall be determined by the patient's condition, and will be determined considering the actual conditions, taking into account the need not to harm the patient.

The total single volume of blood collected for analysis from a child/adult shall not exceed 22 mL. Blood collection is performed once every 4-week period; therefore, the blood volume of a child weighing from 9.1 kg for analyses shall not exceed 3 % of the total blood volume per collection.

In the event a sample for a pharmacokinetic time point was not collected according to the protocol-scheduled time (missed), the information explaining that event shall be entered in the eCRF and source documentation, and sample collection shall be performed at the next time scheduled according to the Schedule.

6.3.14 The procedure for venous blood collection and the specific features of its preparation before transportation

The process is regulated in detail by the Laboratory Manual provided by the Sponsor-selected Central Laboratory.

1. During venipuncture, fill the test tube with the patient's blood to the mark on the test tube (until the blood flow stops due to exhaustion of the vacuum).
2. When collecting blood, follow a certain sequence of filling the test tubes:
   - test tubes for serum (vacutainers with and without separating gel) 3.5 and/or 5.5 mL
   - EDTA test tubes 2 mL for CBC and Coombs' test
   - a sodium fluoride test tube for glucose
   - a sodium citrate test tube

3. Immediately after venipuncture, gently invert the test tube 8–10 times through 180 degrees with smooth rocking motions to mix the blood with the anticoagulant. Avoid shaking the test tubes vigorously.

4. Centrifuge the test tubes for serum separation 30–40 minutes after collection at 2000 g for 10 (15)* minutes.

5. Centrifuge the test tubes for plasma separation immediately or 30–40 minutes after collection at 2000 g for 10 (15)* minutes. Transfer the plasma into a secondary test tube.

After centrifugation, visually assess the sample to make sure that the serum/plasma and cells have separated.

The samples obtained shall be sent to the Sponsor-designated Central Laboratory (temperature conditions shall be in accordance with the Laboratory Manual provided by the Central Laboratory) and accompanied by completion of the relevant documentation provided by the Central Laboratory.

6.3.15 Procedure for storage and transportation of biological samples

The process is regulated in detail by the Laboratory Manual provided by the Sponsor-selected Central Laboratory.

Storage of aliquots of serum samples from the time of obtaining them and to the start of bioanalytical procedures shall be carried out at the temperature regulated by the Central Laboratory procedures and reflected in the Laboratory Manual. The main samples, prior to transfer to a courier, shall be stored in a packaged, ready-to-transfer form at a temperature of 2 to 8°C. The shipment of such samples to the Central Laboratory is carried out in accordance with the Laboratory Manual.

The main samples, after they have been obtained and before they are transferred to the Central Laboratory, must be stored in a packaged form.

The transfer of biological samples from the CTS to the Central Laboratory is accompanied by a Referral (the referral form is regulated by the Laboratory Manual).

The referral shall be signed by the Responsible Investigator, a co-investigator or a person authorised by him/her. The original shall be transferred to the Central Laboratory, and its copy shall remain at the CTS.

If necessary, and if provided for in the Laboratory Manual, the transportation of biosamples to the laboratory shall be carried out by a specialised courier service. The transportation period shall not exceed the period specified in the Laboratory Manual, under conditions stipulated for the

specific type of biological sample. After 30 days of archival storage, biological samples are disposed of in the Central Laboratory in accordance with the in-house procedures of the laboratory. The referrals are stored for no less than 25 years in the TPI archive, together with other CT documents.

6.3.16 Analysis of deviations from bioanalytical testing plan

All deviations from the initial statistical analysis plan will be described and justified in the relevant sections of the Final Clinical Trial Report.

Withdrawal of subjects from the study will be analysed according to the criteria in accordance with the CT Protocol. The quantitative and qualitative (in accordance with the procedures set out in the protocol) determination will be carried out for all biosamples received for analysis and not rejected for quality attributes, including the biosamples of subjects who were discontinued from the study.

A repeated analysis with the use of archival biosamples (provided such a sample is stable and meets the required quality attributes at the time of repeated analysis) must be conducted as needed in all cases of confirmed inability to obtain a reliable result:

- when confirming the fact of mixing of biosamples;
- when confirming the error of an operator/person responsible during sample preparation, carrying out the analytical procedure and during the post-analytical period;
- when lacking sufficient amount of biomaterial;
- in the event of technical problems with equipment or reagents, the conditions of transport and/or storage of biosamples.

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

6.3.17 Unscheduled visit.

An unscheduled visit may be conducted at any time throughout the clinical study at the patient's request or at the discretion of the Responsible Investigator and/or co-investigator.

The date of and reason for the unscheduled visit, and the data obtained during the visit will be recorded in the source medical documentation and the eCRF.

The following can be the reasons for an unscheduled visit:

- An emergent AE/AR or observation of the course of an AE/AR;
- Assessment of changes in patient's condition over time;
- Assessment of changes in instrumental findings over time;
- Assessment of changes in laboratory findings over time;
- Substantial changes in concomitant therapy, which may affect the patient's safety;
- Another important reason (must be specified).

During an unscheduled visit, depending on the reason for conducting the visit, the following clinical study procedures may be performed:

- Anthropometric data (body weight);
- Collection of medical history (history of the underlying disease); data on previous therapy of the underlying disease; history of allergy, transfusion history, history of comorbidities, data on the therapy for comorbidities, presence/absence of harmful habits (smoking, alcohol abuse, etc.);
- Data on antibiotic therapy and concomitant therapy;
- Presence of infections;
- Physical examination (auscultation and percussion of the heart and lungs; palpation and percussion of abdominal organs; examination of the skin and mucous membranes);

- Measurement of vital signs (body temperature, HR, BP, RR);
- Complete blood count: haemoglobin, haematocrit, red blood cells, white blood cells, white blood cell differential, platelets;
- Serum chemistry: ALT, AST, total bilirubin, creatinine, urea, glucose;
- Direct Coombs' test (antiglobulin test).
- Determination of haptoglobin levels
- Determination of total serum IgG level;
- Urinalysis (specific gravity; pH, glucose; microscopic sediment examination (red blood cells, white blood cells, casts, crystals, bacteria, fungi);
- Pregnancy test (HCG) (for women of childbearing potential);
- Coagulation panel (INR, Prothrombin percentage by Quick, Prothrombin time, aPTT, fibrinogen);
- Assessment of eligibility according to the exclusion criteria;
- Registration of AEs/ARs;
- Checking the completion of the patient's diary.

Additional procedures of the clinical study during an unscheduled visit may include any of the clinical study procedures, which will be decided case-by-case by the Investigator after coordinating with the Sponsor.

6.3.18 Dietary and fluid intake regimen.

Throughout the study period, the patients must maintain their usual diet, fluid intake and physical activity regimen.

The patients are advised to abstain from foods and beverages, which may lead to impairment of renal and hepatic function (such as alcoholic beverages, high-fat foods, and large amounts of fried foods).

Blood samples must be obtained under fasting conditions, i.e. the last food intake shall be no less than 8–10 hours before the sampling.

6.3.19 Physical activity regimen.

Throughout the study period, the patients must follow a physiologically normal regimen of sleep and activity, free from increased motor activity and physical strain. These parameters are evaluated by the Investigator as needed using the method of direct supervision and by collecting history during each visit.

6.3.20 Immunogenicity

Immunogenicity is the ability of a therapeutic protein product (including biological medicinal products) to induce an immune response in the recipient, including the formation of antibodies to the active ingredient (ADA, anti-drug antibodies). These antibodies can be neutralising (Nab, neutralising antibodies) or non-neutralising (non-Nab, non-neutralising antibodies), and, depending on the type and intensity of the immune response, may affect the safety, effectiveness or pharmacokinetics of the medicinal product containing therapeutic protein (U.S. FDA, Guidance for Industry. Immunogenicity Assessment for Therapeutic Protein Products. 2014; EMA Immunogenicity assessment of biotechnology-derived therapeutic proteins 2017).

Immunogenicity assessment of the therapeutic protein must take into account the characteristics of both the medicinal product, and the immune status of patients.

According to the FDA recommendations laid out in "Immunogenicity Assessment for Therapeutic Protein Products: Guidance for Industry" (FDA, 2014), immunogenicity assessment

of a therapeutic protein product must take into account the immune system status of the target population. The document states the following: “Patients who are immune suppressed may be at lower risk of mounting immune responses to therapeutic protein products compared to healthy volunteers with intact immune responses.” [FDA, 2014, Section 4.1, p. 9]

The target population of this clinical study, i.e., patients with primary immunodeficiencies (PID), is an immunocompromised group characterised by impaired or absent ability to synthesise antibodies (hypogammaglobulinaemia, agammaglobulinaemia). In this connection, the use of routine immunogenicity assessment, in particular the detection of anti-drug antibodies (ADA) or neutralising antibodies (NAb), is not informative in this study.

In addition, the analysis of the available scientific literature demonstrates that immunogenicity assessment in clinical studies of subcutaneous presentations of immunoglobulin was conducted only in limited cases, in particular when recombinant human hyaluronidase (rHuPH20) was added to the composition of the medicinal product. The immune response in such cases was caused specifically by the presence of hyaluronidase, and not by human normal immunoglobulin. In particular, in the clinical study of HyQvia (subcutaneous presentation of immunoglobulin with recombinant hyaluronidase [rHuPH20]) development of antibodies to hyaluronidase was reported in approximately 18 % of the patients (15 out of 83 patients who participated in the pivotal study with HyQvia developed antibodies binding to rHuPH20, which accounts for approximately 18 %). However, the clinical significance of this reaction was evaluated as minimal or absent.

Unlike such combination products, the investigational product does not contain hyaluronidase or other recombinant protein components that may cause an additional immune response (immunogenicity).

Human immunoglobulins are natural proteins, the safety and tolerability of which are well studied. Human normal immunoglobulin for SC administration 20 % contains native human IgG, which is a natural component of human plasma.

Given the above stated, immunogenicity is not viewed by the Sponsor as an important risk when using the IMP BP-SCIG 20%. The fact that the SCIG products derived from the plasma of healthy donors do not possess the expected immunogenic properties is reflected in the following EMA guidelines:

- *“Guideline on Immunogenicity assessment of therapeutic proteins. 18 May 2017 EMEA/CHMP/BMWP/14327/2006 Rev 1. Committee for Medicinal Products for Human Use (CHMP)”* regulates the requirements for biosimilars and does not apply to products derived from the plasma of healthy donors, which includes the IMP BP-SCIG 20%.
- *“Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)” EMA/CHMP/BPWP/410415/2011 rev.1 23 July 2015* does not contain requirements on immunogenicity assessment.

Thus, performing an immunogenicity assessment as part of this clinical study is not justified, and the absence of such an assessment meets current scientific and regulatory approaches to therapeutic protein products for immunocompromised populations.

6.3.21 Safety of IMP use and Independent Safety Committee

Based on the publicly available data described in the literature, it has been established that SCIG products are generally well tolerated by patients, do not cause serious adverse reactions, and do not lead to clinically significant hazardous changes in the parameters of objective and laboratory examinations.

According to the available information on adverse reactions that may occur with the use of the IMP, the ICF for patients and parents in the CT protocol provides information about the use of the IMP (instruction on self-administration of the IMP) and a cautionary statement describing dangerous changes in the patient's health and the required actions by the patient/legally authorised representative or parents when such changes occur.

In addition, for the confirmation of such control, the patients (CT subjects) shall independently (through parents or a legally authorised representative) fill in the Patient's Diary, which is an important source document for the complete collection of data about any changes in the patient's health status and will allow independently analysing and appending information about adverse effects associated with the use of the IMP.

As for the physician's assessment of the subject's health status and making an appropriate decision regarding continuing/discontinuing the patient's participation in the CT, physicians will receive the Investigator's Brochure with the description of potential ARs and warnings, and, respectively, the algorithm of actions in the occurrence of an AE.

In addition, the Independent Safety Committee will conduct a safety assessment of the IMP after the first 10 adult patients receive at least 4 administrations of the IMP BP-SCIG 20%, or earlier, in the event of serious AEs, which may be potentially related to administration of the IMP and be defined as an AR.

After such an interim safety assessment in adult patients, the feasibility of including patients younger than 18 years is determined based on its results.

In addition, the Independent Safety Committee will conduct a safety analysis of the IMP for each age group of subjects after the patients receive their first 4 administrations of the IMP, prior to inclusion of a new age group of patients.

6.3.22 Contraception and pregnancy

Before the onset of participation in the study, male and female subjects of reproductive potential will be informed about the importance of using contraception throughout the study period and for 30 days after its completion. Study subjects with intact reproductive potential must use effective methods of barrier contraception. The objective of using barrier contraception is to prevent the occurrence of sexually transmitted diseases, including HIV, HBV, and HCV.

According to the "Recommendations related to contraception and pregnancy testing in clinical trials", Version 1.2, highly effective birth control methods are defined as methods that, when used consistently and correctly, can achieve a failure rate of less than 1 % per year. Such methods include:

- combined (oestrogen–progestogen) contraception associated with inhibition of ovulation;
- oral, intravaginal, or transdermal hormonal contraception;
- progestogen-only hormonal contraception associated with inhibition of ovulation;
- oral/injectable/implanted contraception;
- intrauterine device (IUD);
- intrauterine hormone-releasing system (IUS);
- bilateral tubal occlusion;
- partner's vasectomy;
- sexual abstinence.

The acceptable birth control methods, with an annual failure rate over 1 %, include the following:

- progestogen-only oral hormonal contraception where inhibition of ovulation is not the principal mode of action;
- a male or female condom with or without spermicide;
- a cervical cap, diaphragm, or spermicide sponge.

The combinations of a male condom with a cervical cap, diaphragm, or spermicide sponge (double-barrier methods) are also considered acceptable, but not highly effective birth control methods.

Participation in the study is also available for women who are not using acceptable methods of contraception if they are recognised to have no childbearing potential, i.e.:

- female subjects who have undergone a hysterectomy (removal of the uterus) or tubal ligation;
- female subjects with a clinical diagnosis of infertility;
- female subjects who are in the postmenopausal period for more than 1 year (absence of menstruation for at least 12 months);
- female subjects who have not had a menarche.

6.3.23 Mandatory pregnancy information collection period

Information on the occurrence of pregnancy must be collected throughout the clinical study, from the administration of the first dose of the investigational medicinal product until the completion of the CT.

6.3.24 The actions to be performed in case of pregnancy

The Investigator will collect information about the pregnancy of any female patient who became pregnant while taking part in this study. The Investigator will register pregnancy information and submit that information to the Sponsor. The procedure for pregnancy reporting is identical to the procedure for reporting a serious adverse event.

Pregnancy is not considered an AE; however, any complications of pregnancy or elective termination of pregnancy for medical indications will be documented as an AE. A spontaneous abortion is always considered an AE and shall also be reported to the Sponsor. Any patients who become pregnant will be withdrawn from the study. In addition to that, the Sponsor shall be notified of any AE resulting from a pregnancy that occurred after the end of study, if that AE is regarded by the Investigator as reasonably related to the IMP. Although the Investigator is not under an obligation to actively collect this information from former female study subjects, the Investigator may learn of the AE from spontaneous patient-reported outcomes.

7 EFFICACY ASSESSMENT

7.1 Efficacy parameters

Primary efficacy variable:

Occurrence of less than 1.0 case of infection/patient/year of a ***serious bacterial infection*** [1] during one year of treatment.

[1] ***a serious bacterial infection*** *includes: sepsis; bacterial pneumonia; bacterial diseases of viscera (visceral abscess); bacterial meningitis; osteomyelitis/septic arthritis.*

This variable is categorical, dichotomous, with categories of "sufficient efficacy" (occurrence of a ***serious bacterial infection*** [1] during the year of treatment, less than 1 case per year) / "insufficient efficacy" (occurrence of a ***serious bacterial infection*** [1] during the year of treatment, 1 or more cases per year). It will be assessed after the end of 52 weeks of treatment.

Secondary efficacy variables:

1. The threshold serum IgG level ≥5 g/L before the scheduled administration of the product (according to the PK study plan).
This variable is categorical, dichotomous, with categories of "response achieved" / "response not achieved";
2. Cases of any non-serious infectious diseases during the treatment course, per patient per 1 year of therapy.
3. The duration of any non-serious infectious diseases during the treatment course, per patient per 1 year of therapy.
4. The fraction (%) of patients who were prescribed treatment with antibiotics.
5. The number of days of antibiotic therapy in a year (except for the cases where continuous antibiotic prophylaxis is performed).
6. Hospital admissions due to an infection (number of days and frequency in a year).
7. Fever episodes (number of events in a year).
8. The number of days of incapacity for work (sick leaves), or missing school/kindergarten due to an infection.
9. The quality of life level in the patients throughout the study period (data from questionnaires).

7.2 Assessment methods:

Subjects who withdrew during the screening phase are not counted in the efficacy and safety analysis since they have not received any administration of the investigational medicinal product (IMP).

The efficacy analysis counts only patients who have fully completed their participation in the study.

A detailed description of methods that are used for the efficacy assessment is given in Section 9.

8 SAFETY ASSESSMENT

8.1 Definitions for safety assessment

Adverse event

Adverse event (AE) is any untoward medical occurrence in a study subject, which is not necessarily related to the use of the medicinal product. An adverse event may be any undesirable and unexpected manifestation (including changes in laboratory findings), a symptom or a disease that occurs in temporal association with the administration of the medicinal product (to the study

subject), regardless of whether it is related to the administration of the medicinal product (to the study subject) or not;

Any medical condition that is present at the time of patient's screening, but does not worsen during the study, must not be registered as an AE. However, in case of deterioration of this medical condition at any time during the study, it shall be registered as an AE.

Medical interventions, such as surgeries, diagnostic and therapeutic procedures, are not AEs; however, they are measures undertaken to treat the respective medical condition, and may therefore be registered as AE treatment, unless they are elective.

Deviation of laboratory findings from normal

Any deviation of a laboratory finding from normal, which has appeared for the first time or the severity or frequency of which has increased compared to baseline, and which meets at least one of the following criteria, shall be recorded as an AE:

- Requires a therapeutic intervention or a diagnostic procedure;
- Leads to discontinuation of the IMP;
- Is accompanied by complaints or symptoms, or causes them;
- Is assessed by the investigator as "clinically significant".

In any doubt as to whether the observed clinical event is an AE, the same shall be registered as an AE.

Adverse reaction

Adverse reaction (AR) within a clinical trial of a medicinal product (original/generic) or its evaluation for new use, especially if the therapeutic doses of the medicinal product have not been established, adverse reactions to a medicinal product must encompass all adverse and unpredictable responses to administration of any dose of the medicinal product. The term "response to administration of the medicinal product" implies that there is at least an assumed probability of a causal relationship between the administration of the medicinal product and the adverse reaction, i.e. the correlation cannot be ruled out.

During the study period, the Investigator or study personnel shall survey and document information on cases of adverse events/reactions according to definitions given in this Section of the Protocol.

Unexpected adverse reaction

Unexpected adverse reaction means an adverse reaction the nature or severity of which is not consistent with the available information on the medicinal product (for instance, with the Investigator's Brochure for a non-marketed medicinal product or with the Instruction for Medical Use/Summary of Product Characteristics for a marketed medicinal product);

Serious adverse reaction/Serious adverse event

Serious adverse reaction (SAR) or Serious adverse event (SAE) means any untoward medical occurrence while using the medicinal product (regardless of dosing) leading to death; being life-threatening; requiring hospitalisation or extension of an existing hospitalisation; leading to prolonged or significant incapacitation or disability, congenital abnormalities or birth defects.

Death is usually a result of underlying clinical phenomenon that causes it. Therefore, the cause of death shall be considered as serious AE. The only exception is a "sudden death" when its causes have not been established. In this case, "sudden death" shall be viewed as an AE; the cause of its "seriousness" is its "lethality".

Life threatening: the term "life threatening" (event) is defined as an AE, during the existence of which there was a threat to a patient's life. This does not mean any AE that could hypothetically lead to death if it were more severe.

Hospitalisation: any adverse event leading to hospitalisation or extended hospitalisation will automatically be considered serious if it does not meet any of the non-inclusion criteria listed below:
the hospitalisation lasts less than 12 hours
or
the hospitalisation is planned in advance (i.e. it is an optional or elective surgery, 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, e.g. a congenital anomaly/developmental defect.

8.2 AE detection and documentation

The identification and registration of AEs begins from the time of signing the informed consent and continues until the end of the given patient's participation in the study.

AE identification and registration starts from the moment of drug administration and continues until the end of the patient's participation in the study.

The AEs that occur between the screening and drug administration and that are not SAEs must be recorded as medical history.

All AEs occurring from the moment of drug administration, which are reported by the patient or identified during the follow-up, physical examination and other diagnostic procedures, shall be registered in the AE Report Form, which is a structural constituent of the eCRF.

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

Information on any AEs observed during the study period, starting with the first administration of the investigational product and up to the end of investigational product use is documented in medical records/outpatient card of the patient and under the AE section in the eCRF. All AEs must be documented, regardless of their severity or causality with the investigational medicinal product.

The following events **must** be classified as AEs:

- exacerbations/flares of pre-existing conditions;
- increase in incidence or severity (intensity) of diseases or previously observed episodic events;
- any disease(s) detected or diagnosed after the onset of treatment with the investigational medicinal product, even if it was possible for the disease(s) to be present before the start of patient's participation in the study;
- any prolonged and/or persistent illnesses or symptoms present at baseline, the severity of which increased after the patient joined the study;
- new signs or any increase in severity of signs and symptoms of diabetes that required immediate treatment, hospitalisation, surgery and/or any other intervention;
- any clinically significant abnormalities of laboratory results or findings of other tests occurring after the onset of treatment with the investigational product, or any such baseline abnormalities, the severity of which increased in a setting of treatment with the investigational medicinal product.

The following events **shall NOT** be classified as AEs:

1. any diseases or abnormalities, which were detected or diagnosed before the start of treatment with the investigational medicinal product, the severity of which does not increase;
2. situations where no adverse medical occurrence is present (e.g. hospitalisation for an elective surgery);

3. overdose of any investigational medicinal product(s) or concomitant medicinal product(s) without any adverse signs or symptoms;
4. any clinically significant laboratory abnormality detected before first dose of the investigational product;
5. signs and symptoms observed during the study that are associated with lack of adequate response to treatment.
6. Death occurring under force majeure circumstances (as defined by Ukrainian law)

The emergence of any adverse events (AEs) will be tracked during the study. Table 8.2.1 presents the treatment tolerability scale.

Table 8.2.1. Treatment tolerability scale

Category	Category description
Good	An objective overview over time shows no abnormal changes or clinically significant deviations, data of the laboratory examination do not change significantly and remain within the normal; the patient does not report any manifestations of adverse reactions
Satisfactory	An objective overview over time shows minor transitory changes that require no modifications in the treatment schedule or additional medical interventions and/or laboratory examination data are insignificantly outside normal limits and/or insignificant adverse reactions are observed that do not cause serious problems for the patient and do not require discontinuation of the product
Unsatisfactory	An objective review over time shows abnormal changes that require discontinuation of the drug and additional medical interventions and/or laboratory findings are subject to clinically significant adverse changes, entailing the need for additional examinations and interpretation of data and/or there is an adverse side reaction that has a significant negative effect on the patient's condition and requires the discontinuation of the product and additional medical interventions

Signs and symptoms underlain by general disease shall, if possible, be indicated as a single complex event. If the diagnosis is known, it must be registered as the name of the AE. If the diagnosis is not known, each complaint and symptom must be registered as a separate AE.
Information to be recorded includes the event type, AE onset date, investigator's assessment of AE severity and AE association with the IMP, AE cessation (resolution) date, AE seriousness, measures taken, and AE outcome.
All AEs shall be monitored until they are adequately resolved.
During and after the subject's participation in the study, the investigator (medical institution) must ensure that the subject is provided with necessary medical care in case of any study-related adverse events, including clinically significant changes in laboratory findings. The Investigator (medical institution) must inform the study subject about any concurrent diseases requiring medical attention, which have become known to the Investigator.
Assessment of AE severity

AE severity (intensity) indicates the extent to which the AE affects the patient's daily activity. AE severity degree will be determined according to NCI CTCAE criteria developed by the US National Cancer Institute (version 5.0) (in each item, a semicolon means "or") Table 8.2.2.

Table 8.2.2. AE severity degree according to NCI CTCAE (version 5.0)

Severity degree 1	Mild; no symptoms or minor symptoms; only clinical or diagnostic observations; no intervention is required
Severity degree 2	Moderate; requires minimal, local or non-invasive intervention (e.g., tamponade, cauterisation); restriction corresponds to Instrumental Activities of Daily Living (ADL*)
Severity degree 3	Severe or clinically significant but not life-threatening; hospitalisation or continuation of hospitalisation is required; restriction in Self Care Activities of Daily Living (ADL**)
Severity degree 4	Life-threatening condition; immediate intervention is required
Severity degree 5	Death associated with AE

Activities of Daily Living (ADL):
*Instrumental Activities of Daily Living include cooking, buying food or clothing, using the phone, handling money, etc.
**Self Care Activities of Daily Living include taking a bath, dressing and undressing, eating independently, using the toilet, taking medication and not being bedridden.

The terms "serious" and "severe" are not synonymous. A severe AE (3rd or 4th severity degree) must not always be considered serious. For example, a white blood cell count of 1000 to 2000 / mm^3 shall be considered a degree 3 (severe) AE, but such an AE may not be recognised as serious. A benchmark for submitting information to regulatory authorities is the seriousness (but not severity) of an AE.

Assessment of causal relationship between the AE and the investigational product

During the assessment of causal relationship, the Investigator must take into account the possible aetiology of the observed AE/AR, which may be related to the administration of the investigational medicinal product, concomitant medications, the course of the underlying disease, comorbidities, procedures performed during the study, and other causes. Of all the possible causes, the Investigator must identify the single cause with the likeliest causality to the event in question. During assessment of causality in case of a serious AE, the report shall provide the rationale for the Investigator's judgement. This rationale has to include all of the available facts supporting the judgement, including laboratory results and other diagnostic findings.

- **Verified causality.** The clinical event and/or changes in laboratory results have temporal connection with the use of the medicinal product and cannot be attributed to a comorbidity or to other medicinal products or chemical substances. The response to product discontinuation must be clinically significant. If necessary, the event has been confirmed by a rechallenge.
- **Probable causality.** The clinical event and/or changes in laboratory results have temporal connection with the use of the medicinal product and are unlikely to be attributed to a comorbidity or to other medicinal products or chemical substances and a clinically distinctive response to discontinuation of the product has been observed.
- **Possible causality.** The clinical event and/or changes in laboratory results have temporal connection with the use of the medicinal product, but they are also attributable to existing comorbidities or to other medicinal products or chemical substances. The results of rechallenge may be negative or ambiguous.
- **Dubious causality.** The clinical event and/or changes in laboratory results may have temporal connection with the use of the medicinal product, but other medicinal products, chemical substances or comorbidities are a more likely explanation for the event.

- **No causality.** The clinical event and/or changes in laboratory results are *beyond any reasonable doubt* unrelated to the use of the product in question due to lack of substantiated temporal connection between the drug and the AE and/or implausibility of such a connection.

Categories of AE outcomes and their definitions

The event ended without sequelae: the symptoms are absent and the patient does not require treatment to reverse the AE in question.
Stabilised condition: the outcome of an AE has been evaluated as stable condition, per Investigator's judgement.
The event ended with sequelae: the event was managed successfully, but with sequelae; as a result of the AE, the patient became temporarily or permanently disabled/unable to work; any AE that ended with sequelae is classified as a serious AE.
The event is ongoing: the associated symptoms remain.
Death of the patient.
Result is unknown.

For each AE, actions that were undertaken to improve the patient's general condition must be recorded, namely:

- No treatment;
- Discontinuation of suspected medicinal product;
- Dose reduction of suspected medicinal product;
- Discontinuation of concomitant treatment;
- Use of pharmacological therapy;
- Non-pharmacological therapy (including surgery).

8.3 Reporting of SAE/SAR cases

Any SAE shall be reported to the Study Sponsor within 24 hours after the Investigator first became aware of this SAE. When an SAE develops, the Investigator fills in the SAE registration form and determines whether the SAE is related to the investigational product and sends the completed form to the Sponsor by email. The original SAE form and the letter with confirmation of form receipt by the Sponsor must be stored. The fact of the SAE must be recorded in the eCRF. Sponsor has the right to urgently request additional information about the SAE from the Investigator for reporting to the health authorities.

After the initial urgent notification, a detailed written notification shall be submitted as soon as possible. The initial and subsequent reports must identify study subjects by the unique code assigned to them, and not by the subjects' names, personal identification numbers and/or addresses.

In case of hospitalisation of the patient in connection with an SAE development, a copy of hospital discharge summary must be sent to the Study Sponsor by email as soon as possible.

The Study Sponsor or his/her authorised representative shall be responsible for telephone or fax notifications of unexpected or life-threatening SAEs related to the use of the investigational product (in the form of urgent reports) to the relevant bodies and competent authorities within 7 calendar days of receipt of information about the SAE. The Study Sponsor or his/her authorised representative shall report any other significant SAEs associated with the use of the investigational product to the relevant competent authorities, investigators and the Independent Ethics Committee by providing a written safety report within 15 calendar days of receipt of information about the SAE.

In Ukraine, within 7 calendar days from the time of awareness of any suspected unexpected serious adverse reactions related to the investigational medicinal product, which led to death of or were life-threatening to a study subject, the Sponsor shall immediately record and report such

occurrence(s) to SEC MoH of Ukraine and the Ethics Committee. Additional information in this connection shall be provided to SEC MoH of Ukraine and the Ethics Committee within the next 8 calendar days. The notification of a suspected unexpected serious adverse reaction shall be compiled in accordance with Order of the Ministry of Health of Ukraine No. 690 of 23/09/2009, as amended.

In addition to the notification of deaths, the investigator shall provide any additional information at the request of the regulatory competent authority (e.g. autopsy report and final medical reports after they have been duly completed in accordance with the legislation of the country where the study is conducted – Ukraine).

8.4 Reporting requirements after the end of treatment with the investigational product.

In case the Investigator receives information about any AE that has occurred at any time after the patient has completed treatment with the investigational medicinal product, and if there is sufficient evidence to suggest a relationship between this event and use of the investigational product, the Investigator must notify the Sponsor.

9. STATISTICS

9.1. Contents of statistical analysis

Subjects who withdrew during the screening phase are not counted in the efficacy and safety analysis since they have not received any administration of the investigational medicinal product (IMP).

Subjects who have not received a full IMP course are included in the safety analysis, but are not included in the efficacy analysis.

Subjects who discontinued from the study after completing IMP administration during the follow-up period are included in the efficacy and safety analysis. The data of such subjects are evaluated by parameters that may be analysed at a certain time point. The dropped data are not analysed.
Subjects who received at least one dose of the IMP but withdrew from the study prematurely are included by the Investigator in the tolerability analysis of the investigational product.

Statistical analysis:
Populations for statistical analysis:
ITT (Intention-to-treat population) includes all study subjects who received the investigational product at least once. The data obtained from this sample will be used for the safety analysis.
PP (Per Protocol) includes all patients who complied with the protocol requirements. This population includes all patients who received full protocol therapy, who underwent all scheduled visits, and did not have significant protocol deviations. The data obtained from this sample will be used for analysis by efficacy criteria.
The main efficacy analysis is performed on the PP population, and the additional, confirmatory analysis is performed on the ITT population (all subjects who received ≥1 dose and who meet the inclusion criteria, and for whom efficacy can be established).

Plan of statistical analysis of CS results

Statistical analysis is performed by a qualified biostatistician, a third party contracted by the Sponsor. Statistical analysis includes the following:

- description of patients enrolled in the study;
- the number of drop-out subjects;
- the number of adverse events;
- efficacy analysis in the group;
- tolerability assessment in the group;
- safety assessment in the group;
- analysis of pharmacokinetic data;
- statistical inferences.

9.2 Sample size assessment

According to European guidelines (Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration [SCIg/IMIg]), the number of patients must be greater than 40, with previously verified humoral and combined primary immunodeficiencies, to ensure a minimum of 80 % statistical power for rejecting the null hypothesis when using a one-tailed test and a significance level of p = 0.01. For the primary

efficacy variable, the null hypothesis H0 is that the frequency of serious bacterial infection cases is 1.0 or greater per year. The alternative hypothesis H1 is that the frequency of serious bacterial infection cases is less than 1.0 per year. The null hypothesis is rejected if the upper limit of the 99 % confidence interval is less than 1.0 case of serious bacterial infection per patient per year.

The study must provide at least an 80 % probability of rejecting the null hypothesis regarding the number of serious bacterial infection cases ≤ 1.0 per 1 patient over the treatment period using a one-tailed test and a type I error according to the chosen significance level of $p \leq 0.01$.

Taking into account possible subject withdrawals at different phases, 56 subjects are enrolled in the study to achieve a required sample size.

Since patients were distributed across cohorts, the required number of patients in each cohort was established in accordance with the recommendations of the U.S. Department of Health and Human Services Food and Drug Administration (FDA) regarding the safety, pharmacokinetics and effectiveness studies of immunoglobulin in primary immunodeficient conditions. According to that guidance document, the optimal number of patients in subgroups for pharmacokinetic assessment (adult patients) ranges from 6 to 12, to obtain a reliable assessment of variability. Considering these recommendations, the number of patients in the cohorts for adult patients was determined as 8–10.

9.3 General plan of statistical analysis

General principles of statistical analysis

All continuous variables will be summarised using descriptive statistics and represented as absolute numbers, sample size, arithmetic mean, standard deviation, median and percentiles, minimum and maximum values (depending on the type of distribution). The data on ЗОТ and on AR frequency will be presented as percentages of the entire population of patients enrolled in the study.

No inferential statistical analysis is planned as part of this uncontrolled study, since the design does not provide for comparison groups. The statistical analysis of the endpoints will be descriptive with testing of the null hypothesis, except for the statistical analysis of PK parameters, which will be compared with the pre-dose and post-dose values in several time intervals.

The source data are presented as tables, with individual study subjects listed in the rows and the values of the characteristic under investigation listed in the columns.

If the measured value of the characteristic under analysis in an individual study subject equals zero, the corresponding cell of the table shall contain the digit “0”.

All statistical calculations will be performed using the software package for statistical analysis R ver. 4.5.0 (2025-04-11 ucrt) and RStudio ver. 2025.05.1 “Mariposa Orchid”.

After study completion (after the last subject completes the study), a final statistical analysis of the results obtained is performed.

Analysis of baseline plan of the group

Perform analysis of the group by clinical and demographic parameters at the time of inclusion in the study. Use the methods of descriptive statistics to describe the baseline state in groups (for

quantitative parameters – n, arithmetic mean, median, standard deviation, minimum and maximum value; for categorical parameters – number and percentage).

9.4 Efficacy analysis

According to European guidelines (Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration [SCIg/IMIg]), the number of patients greater than 40 has to ensure a minimum of 80 % statistical power for rejecting the null hypothesis when using a one-tailed test and a significance level of p = 0.01. For the primary efficacy variable, the null hypothesis H0 is that the frequency of serious bacterial infection cases is 1.0 or greater per patient per year. The alternative hypothesis H1 is that the frequency of serious bacterial infection cases is less than 1.0 per patient per year. The null hypothesis is rejected if the upper limit of the 99 % confidence interval is less than 1.0 case of serious bacterial infection per patient per year.

Secondary efficacy variables include the following parameters:

1. The threshold serum IgG level ≥5 g/L before the scheduled administration of the product (according to the PK study plan).
This variable is categorical, dichotomous, with categories of “response achieved” / “response not achieved”;
2. Cases of any non-serious infectious diseases during the treatment course, per patient per 1 year of therapy.
3. The duration of any non-serious infectious diseases during the treatment course, per patient per 1 year of therapy.
4. The fraction (%) of patients who were prescribed treatment with antibiotics.
5. The number of days of antibiotic therapy in a year (except for the cases where continuous antibiotic prophylaxis is performed).
6. Hospital admissions due to an infection (number of days and frequency in a year).
7. Fever episodes (number of events in a year).
8. The number of days of incapacity for work (sick leaves), or missing school/kindergarten due to an infection.
9. The quality of life level in the patients throughout the study period.

For quantitative variables, provide descriptive statistics in each group (n, arithmetic mean, standard deviation, median and percentiles, minimum and maximum values – depending on the type of distribution) for each visit according to the schedule of patient assessments. For the primary efficacy variable, the 95 % confidence interval, the absolute number, and the percentage of patients who achieved the efficacy endpoint are indicated.

Determine the relative changes in quantitative variables based on their mean values from the following formula:

$$X(\%) = \frac{Ti - Tbaseline}{Tbaseline} x100,$$

where T-baseline is the arithmetic mean of the variable at baseline, and Ti is the arithmetic mean of the analysed variable at subsequent visits. Represent these changes over time as a plot.

For variables measured only twice according to the schedule of patient assessments (at baseline and after completion of the course of treatment), evaluate the significance of their changes in each group using either a t-test for paired data or a Wilcoxon signed rank test, depending on the normality of the distribution, the latter checked with Shapiro–Wilk's test.

For the variables measured according to the schedule of patient assessments more often than twice, evaluate the changes in quantitative variables over time using a one-way analysis of variance (ANOVA) or rank analysis depending on the normality of the distribution, checked using the Shapiro–Wilk test. In this setting, the dependent variable is the parameter being analysed, and the "visit" factor is the fixed parameter. Evaluate the value and significance for the reliability of the difference between the visits using a contrast analysis (simple contrasts) or post hoc analysis with Tukey's test (for ANOVA) or the Wilcoxon signed rank test with Holm's adjustment (for the rank test). To verify the preconditions for the use of analysis of variance, the normality of distribution of the residuals will be tested using the Shapiro–Wilk test. If the residuals are not distributed normally, a corresponding rank analysis will be performed.

Statistical inferences shall be made. For categorical variables, provide descriptive statistics (frequency and percentage [%]) and represent the distribution of categories in each group as a plot.

9.5 Analysis of safety and tolerability parameters

a) Laboratory results (the indicators of complete blood count, serum chemistry and urinalysis).
Compare the results of indicators at screening and at the last visit.
Provide descriptive statistics for each laboratory indicator at time points T before treatment and T after treatment.

Determine the relative changes in quantitative variables based on their mean values from the following formula:

$$X(\%) = \frac{Ti - Tbaseline}{Tbaseline} x100,$$

where T-baseline is the arithmetic mean of the variable at baseline, and Ti is the arithmetic mean of the analysed variable at subsequent visits. Represent these changes over time as a plot.
For variables measured only twice according to the schedule of patient assessments (at baseline and after completion of the course of treatment), evaluate the significance of their changes in each group using either a t-test for paired data or a Wilcoxon signed rank test, depending on the normality of the distribution, the latter checked with Shapiro–Wilk's test.
For the variables measured according to the schedule of patient assessments more often than twice, evaluate the changes in quantitative variables over time using a one-way analysis of variance (ANOVA) or rank analysis depending on the normality of the distribution, checked using the Shapiro–Wilk test. In this setting, the dependent variable is the parameter being analysed, and the "visit" factor is the fixed parameter. Evaluate the value and significance for the reliability of the difference between the visits using a contrast analysis (simple contrasts) or post hoc analysis with Tukey's test (for ANOVA) or the Wilcoxon signed rank test with Holm's adjustment (for the rank test). To verify the preconditions for the use of analysis of variance, the normality of distribution of the residuals will be tested using the Shapiro–Wilk test. If the residuals are not distributed normally, a corresponding rank analysis will be performed.
For each variable, plot the changes of mean values (when the distribution is normal) or median values (when the distribution is not normal) over time, for each group.

Convert the variables measured on a continuous scale into categorical variables with the following two categories: “within normal” and “outside normal”. Perform an analysis of the converted variables using the methods of descriptive statistics (the frequency and percentage [%] in each group have been provided) and represent the distribution of categories as plots.
Statistical inferences shall be made.

b) The results of HR, BP, RR and body temperature measurements.
Calculate descriptive statistics (n, arithmetic mean, standard deviation, the median and the percentiles, the minimum and maximum values – depending on the type of distribution) for each visit according to patient assessment schedule.

c) AE data.
Provide descriptive statistics (frequency and percentage for the group).

9.6 Assessment of pharmacokinetic data

Analysis of pharmacokinetic parameters.
The main pharmacokinetic parameters include:

1. AUC-t value. Steady-state area under the concentration-time curve (AUC) for the total IgG level shall be compared with the values for the prior therapy (BIOVEN) for the relevant patient cohorts.
2. Trough IgG levels. The monthly trough IgG levels obtained, measured after 4 months of treatment with the IMP, prior to the next infusion, once every 4 weeks, over 6 months, shall be compared with the trough levels for at least two prior infusions of the previous SCIG or IVIG product. For treatment-naïve patients, a descriptive comparison with the data in published literature (if available) is required.

Methods of descriptive statistics: n, arithmetic mean, standard deviation, the median and the percentiles, the minimum and maximum values (depending on the type of distribution), including the plotting of graphs and charts and methods of interval estimation.

To evaluate the significance of changes over time in the event of assessing the parameter at two visits (before and after) in the case of quantitative variables, the analysis will use Student’s t-test for paired data or Wilcoxon signed rank test–depending on the results of checking the normality of the distribution of difference [after - before] using the Shapiro–Wilk test. In order to assess changes over time in the event of measuring variables at more than two visits, methods of one-way analysis of variance (ANOVA) with subsequent application of post hoc analysis using Tukey’s test will be used. In order to compare by those variables, by which the data were heterogeneous at baseline, covariance analysis (ANCOVA) will be used. In order to check the preconditions for the use of analyses of variance and covariance, the normality of distribution of the data and their residuals will be tested using the Shapiro–Wilk test. If the residuals are not distributed normally, or if the data do not pass the normality check, a corresponding rank analysis will be performed.
For the Shapiro–Wilk test, the significance level will be set at 0.01, and for other tests it will be set at 0.05. If a multiple comparisons effect occurs, significance level adjustments will be applied using the Holm method or Benjamini–Hochberg method.

9.7 Analysis of pharmacokinetic parameters

Analysis of pharmacokinetic parameters in the respective group (n = 20) shall be performed by the variable of quantitative change of serum immunoglobulin IgG concentrations in patients (in grams per litre of blood) at protocol-specified time points.

For the aforementioned quantitative variable, provide descriptive statistics (n, arithmetic mean, standard deviation, the median and the percentiles, the minimum and maximum values– depending on the type of distribution) for each visit according to patient assessment schedule, and for the (Ti – T-baseline) differences.

Determine the relative change in the quantitative variable based on its mean values from the following formula:

$$X(\%) = (Ti\text{-}Tbaseline)/Tbaseline*100,$$

where T-baseline is the arithmetic mean of the variable at baseline (screening visit) and Ti is the arithmetic mean of the analysed variable at subsequent visits.

Plot graphs of changes of mean values over time (for normally distributed data) or changes of median values over time (for non-normally distributed data) for the variable.

Assess the significances of changes in these values in each group using Student's t-test for paired data or a Wilcoxon signed rank test depending on the normality of distribution of individual (Ti – Tbaseline) differences, the latter tested using the Shapiro–Wilk's test.

For the variables measured according to the schedule of patient assessments more often than twice, evaluate the changes in quantitative variables over time using a one-way analysis of variance (ANOVA) or rank analysis depending on the normality of the distribution, checked using the Shapiro–Wilk test. In this setting, the dependent variable is the parameter being analysed, and the "visit" factor is the fixed parameter. Evaluate the value and significance for the reliability of the difference between the visits using post hoc analysis with Tukey's test (for ANOVA) or the Wilcoxon signed rank test with Holm's adjustment (for the rank test). To verify the preconditions for the use of analysis of variance, the normal distribution of residuals will be tested using the Shapiro–Wilk test. If the residuals are not distributed normally, a corresponding rank analysis will be performed. Assessment of pharmacokinetic parameters will be informed by fundamental principles of descriptive statistics for the main pharmacokinetic parameters, preliminary assessment of statistical homogeneity of study patient population, as well as by the obtained values for the parameters and the homogeneity of their distribution.

For each patient, individual pharmacokinetic parameters will be calculated:

Cmax, the maximum serum concentration of the analyte;

AUC0-t, the area under the concentration-time PK curve (from zero to last blood sampling, where the concentration of the analyte is higher than or equal to the lower limit of quantification [LLOQ]);

AUC0-∞, the area under the concentration-time PK curve (from zero to infinity).

Tmax, the time to maximum concentration of the analyte;

t1/2, the elimination half-life of the analyte;

Kel, the elimination rate constant of the analyte;

IR, the incremental recovery of class G immunoglobulin;

Vd, volume of distribution;

Cl, serum clearance;

($AUC_{0-\infty}$ - AUC_{0-t})/$AUC_{0-\infty}$), the residual (extrapolated) area (AUCextrapol).

The values of Cmax and Tmax were calculated using a model-independent method, as the largest of the measured concentrations in each patient and as a corresponding time of observed maximum, respectively.

AUC0-t was calculated using trapezoidal method.

All other parameters were calculated using a model-independent method.

9.8 Levels of significance

The significance level for the Shapiro–Wilk test and for the primary efficacy variable shall be set at 0.01; for other statistical tests, it shall be set at 0.05.

9.9 Working with missing or incomplete data

Missing or incomplete data shall be replaced using the Last-Observation-Carried-Forward (LOCF) method. Or by rank aggregation technique for rows where the last observation carried forward is not applicable.

9.10 Conclusion regarding non-inferiority

Conclusion on non-inferiority shall be made by the primary efficacy variable using a confidence interval-based approach.
For the primary efficacy variable, the null hypothesis H0 is that the frequency of serious bacterial infection cases is 1.0 or greater per patient per year. The alternative hypothesis H1 is that the frequency of serious bacterial infection cases is less than 1.0 per patient per year. The null hypothesis is rejected if the upper limit of the 99 % confidence interval is less than 1.0 case of serious bacterial infection per patient per year. Then it will be considered that the investigational route of administration of the drug (SCIG manufactured by BIOPHARMA PLASMA LLC) is non-inferior in terms of efficacy compared to the literature data on the level of efficacy of existing SCIG products and compared to the efficacy of BIOVEN use.

9.11 Analysis dataset

ITT (Intention-to-treat population) includes all study subjects who received the investigational product at least once. The data obtained from this sample will be used for the safety analysis.
PP (Per Protocol) includes all patients who complied with the protocol requirements. This population includes all patients who received full protocol therapy, who underwent all scheduled visits, and did not have significant protocol deviations. The data obtained from this sample will be used for analysis by efficacy criteria.

9.12 Final presentation of results

The results of statistical analysis of the obtained findings shall be presented in the form of tables, which, if necessary, are illustrated by graphs and diagrams. Data presentation shall be structured in accordance with the purpose and objectives of the CS. It is necessary to clearly indicate the methods used, to characterise the data set.

10.DIRECT ACCESS TO SOURCE DOCUMENTS

Source data include all information contained in the original records and/or 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 ensures the possibility of conducting study monitoring and audit(s), expert assessment by IEC and regulatory authorities, and provides direct access to source data/records to the representatives of the aforementioned bodies.

Source data shall be stored for a maximum period of time permitted by local regulations, but for no less than 25 years after CT completion and archiving. For each enrolled subject, the Investigator shall indicate the fact of participation in this study in the source records, and shall record at least the following information: individual screening number, patients' personal data (full name, address), dates of drug administration, vital signs, any AEs, study completion dates and main reasons for treatment discontinuation (if any), etc.

It is the Investigator's responsibility to ensure direct access to source data and documents for the clinical study specialist of the Sponsor and/or its authorised representatives (CRO), the auditor of competent authorities, the representatives of the insurance company, independent ethics committees or other organisations according to the current legislation.

11.QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Study monitoring

Regular visits by the Study Monitor, as requested by the Sponsor and according to standard operating procedures (SOPs), before the onset of the study, during the study and after the end of the study contribute to successful completion of the trial, and serve as a guarantee of accurate data collection, timely identification of potential errors, documenting the process of the clinical trial and ensuring the protection of rights of study subjects, as well as the compliance of the study conduct with the requirements of Ukrainian legislation.

Routine monitoring of the study includes the following:

- confirmation of proper conduct and documenting of the informed consent process as well as screening and subject enrolment;
- verification of data in the eCRF and their compliance with source medical records of study subjects;
- verification of completion of patient's diary (PD) and source medical records of study subjects;
- confirming adherence of clinical site personnel to the protocol-specified requirements for diagnostic tests and therapeutic interventions;
- confirmation of documented supplies, storage, distribution and disposal of the investigational medicinal product and study materials;
- confirming the competencies of personnel of the clinical site and the external laboratory, which are essential for study conduct;
- confirming the compliance of diagnostic and laboratory equipment to the requirements of safe and appropriate use during the study;
- confirming the interactions of the Investigator with the Independent Ethics Committee concerning study safety and making Sponsor-approved amendments to the Study Protocol. Quality control assurance of study results is carried out by the employees of the Sponsor/employees of Sponsor's authorised representative (e.g., the CRO) who maintain the database of the study and detect inconsistencies, erroneous data entries and missing data. In the event of questions or a need for clarification, an inquiry is sent to the Investigator by e-mail, to which a written response must be provided within 7 days of receipt.

As required by law, the Sponsor or authorised public authorities have the right to conduct an inspection (audit) of material and technical support and documentation of the study. The Investigator must provide the persons authorised to perform audits or inspections with access to documentation and to all required information.

11.2. Amendments to the protocol, deviations from and violations of the protocol

The signatures of investigators on the signature page of the Protocol constitute a written confirmation of their agreement to conduct the study according to this Protocol and the regulatory and legal requirements to CT conduct. During conduct of the clinical study, changes and additions can be made to study materials. Such changes and additions shall be viewed as amendments.

Amendments to the clinical study materials are considered substantial if they may affect the goals, forms of organisation, methodology, and statistical methods for processing the clinical study results. Amendments to the protocol shall be stored with the initial version of the protocol.

Any changes shall be agreed upon between the Investigator and the Sponsor prior to their coming into force. Any changes to the study conduct that occurred after the protocol was approved must be documented as alterations to the protocol and/or as an updated version of the protocol. Depending on the nature of the amendment, an approval by or notification of the IEC and regulatory authorities will be required, except when there is an immediate threat to the life or health of patients participating in the clinical study, or when changes to the protocol concern only administrative aspects or supply issues.

All deviations from the protocol occurring during the study must be documented and checked during monitoring of the clinical study and reported to the Sponsor.
The investigator shall 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 deviation from the protocol-defined procedures, the Investigator must seek consultation with the Sponsor or its representative (and IEC if required) to determine an appropriate procedure.

The study site shall document all deviations from the protocol in patients' source documentation. In the event of a substantial deviation, the Investigator must notify the Sponsor or its representative (and IEC if required). To do this, the Investigator shall complete the "Protocol Deviations" form, which is sent by email to the Sponsor. During the monitoring of the CTS, the Monitor may identify deviations from the Study Protocol. In this case, he/she is responsible for notifying the investigators about the identified deviations and for preparing the "Protocol Deviations" form.

Deviations from the Protocol can be divided into substantial and non-substantial.

Substantial deviations include, but are not limited to, those deviations that include document forgery or improper conduct of the study, increase the risk to the patient's health, or confound the analysis of the main study results.

Examples of such deviations are given below.

Substantial deviations from the protocol:

1) unsigned/incorrectly signed Patient Informed Consent to participate in the clinical study;
2) deviation from patient inclusion/non-inclusion criteria;
3) significant deviation from the Schedule of Study Procedures (deviation from the list of protocol-specified procedures);
4) significant deviation from the schedule of therapy of patients (inconsistency with the Protocol-specified therapy);
5) unreasonable disclosure of a patient's personal data and failure to notify the Sponsor of such disclosure;
6) failure to report (concealment of information) about a serious adverse event that occurred in a patient during the study;

7) failure to comply with the IMP storage conditions.
8) untimely (with delay) notification of an SAE;

Non-substantial deviations from the protocol:
1) violation of the Schedule of Study Procedures on the visit days, which slightly exceeds the time-frames provided by the Protocol;
2) untimely entering of data in the eCRF;
3) other unexpected deviations that do not pose a threat to patient safety.

All deviations from the Protocol occurring during the study must be documented during the monitoring of the clinical study and reported to Sponsor.

11.3. Audits by quality control bodies and regulatory authorities.

During any phase of CT conduct, the Sponsor can conduct a CT audit at the clinical trial site to verify and ensure the quality of CT conduct. In the first case, a Sponsor-appointed auditor will contact the Investigator in advance to arrange a visit for the purpose of conducting an audit. The auditor has the right to inspect the place where laboratory samples are collected, where the medicinal product is stored, and any other place used during the study, including verification of source medical documentation.

In the event of knowledge about a scheduled conduct of a clinical audit/inspection by representatives of regulatory authorities of Ukraine or other countries, the Investigator must immediately inform the Sponsor about it.

12. ETHICAL AND LEGAL ASPECTS OF THE STUDY

12.1. General requirements

The study must be approved by the official regulatory authorities of the host country.

The study shall be conducted in accordance with the principles stated in the WMA Declaration of Helsinki (approved at the 18th WMA Assembly in Helsinki in June 1964, the latest version was approved at the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

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

12.2. Ethical conduct of the study

The study approvals by Independent Ethics Committee shall guarantee compliance with ethical standards in the study.

Patient participation in the study is voluntary. The patient has the right to refuse to participate in the study at any phase; enrolment of the patient without the patient's signing informed consent is not possible.

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

12.3. Independent Ethics Committee (IEC)

Ethics review of clinical trials of medicinal products is conducted by the Independent Ethics Committee. The IEC is intended to protect the rights, safety, and well-being of all patients in the study. The IEC must evaluate the suitability of qualifications of the Investigator in the proposed study based on his/her scientific biography (curriculum vitae). Prior to study initiation, the approval of the protocol, written informed consent form and any other document provided to

a subject shall be obtained from the IEC(s) of the institution(s) where the clinical study will be conducted. The IEC opinion shall be dated, signed and issued in writing. A clinical study may only be initiated after obtaining the approval of the appropriate IEC.

The Investigator or a different responsible person must submit the necessary documentation for review to the Independent Ethics Committee in a timely manner. The documents submitted to the IEC may differ across institutions but must necessarily include the final version of the Clinical Study Protocol, the Patient Information and Informed Consent Form, the Investigator's Brochure containing information about the investigational medicinal product, and other documents in accordance with the current legislation.

12.4. Approval of the Protocol

The study Sponsor shall provide a copy of this Protocol, as well as other required study documentation, for review to the regulatory authority and the Ethics Committee at the TPI for the purpose of obtaining opinions.

13. DATA PROCESSING AND RECORD KEEPING

13.1. Clinical study documents

The Sponsoring Company provides the CTS with the following core documents and materials:

- Study Protocol (and amendments to it, if any);
- Investigator's Brochure;
- Guide to eCRF Completion;
- Patient Information with the Informed Consent Form;
- Scales, survey forms, questionnaires (if any);
- Investigator's File;
- Investigational medicinal product;
- Copy of insurance contract;
- Contract;
- Copy of Approval by the regulatory authorities of the country where the clinical study is conducted and approval by the Independent Ethics Committee;
- Documents required for submission to the IEC.

The Investigator provides the Sponsor with the following core documents prior to the start of the study:

- Signed confidentiality agreement;
- Contract with the TPI/Investigator regarding the conduct of CT;
- List of IEC members;
- Current Curriculum Vitae documents of all investigators and co-investigators (signed and dated);
- Certificates for medical/laboratory equipment (documentation regarding metrological calibration).

The documentation must comply with legislative requirements regarding the CT conduct.

The Investigator must retain documentation related to the conduct of the study (source documentation and Investigator's File) for no less than 25 years after the completion of the study.

13.2. Source Documentation

The presence of source medical documentation at the study site is required to confirm the fact of existence of patients and to confirm the information collected. Source medical

documentation includes the originals of documents related to the study, treatment, history, and description of the patient's condition. For example, such documents include inpatient/outpatient medical records, extracts (printouts) of laboratory test results, medical consultation opinions, etc.

Source medical records shall reflect the following information:

- Demographic data;
- Date and time of signing the ICF;
- Information related to inclusion and non-inclusion criteria;
- The fact of participation in the study, indicating the study number and patient number;
- Dates and times of all visits;
- History data and physical examination data;
- Adverse events;
- Previous therapy and concomitant treatment;
- Results of instrumental examinations;
- Results of laboratory tests;
- Information about administration of the investigational medicinal product;
- The reason for early termination of study participation (if applicable);
- Other information.

13.3. Data collection: Case Report Forms (eCRFs)

All data obtained for each patient, including examination results, must be entered in the eCRF. For patients who withdrew early from the study for any reason, all the necessary documentation is filled in completely, indicating the reason for the early termination of the study.

The eCRF is designed for registration of all required information on each study patient, which must be presented to the Sponsor.

The eCRF serves for:

- Provision of data collection in accordance with the Protocol;
- Compliance with the requirements of the regulatory-authority system for information collection;
- Contribution to the efficient and complete processing of data, their analysis and reporting based on the results; facilitating the exchange of safety data among the project team and other units of the organisation.

The data collected during conduct of the study at the CTS must be complete and fully reflect what has occurred to each patient.

The Monitor shall check the information entered in the eCRF for compliance with the source medical documentation, which will confirm the absence of discrepancies in the various documents during data registration. If the Monitor detects any inconsistencies, the necessary changes shall be entered in the eCRF. If any discrepancies are identified, the Monitor must discuss this with the Investigator to ensure that relevant changes are entered in the eCRF in a timely manner.

The Monitor must supervise the completeness and correctness of filling in the eCRF. The Monitor does not have the right to make corrections in the eCRF personally.

The Investigator or another person authorised to complete the eCRF must enter data into the eCRF during or as soon as possible after each visit, according to the source medical documentation.

13.4. Data processing and introduction of changes to the eCRF

Data processing shall be coordinated by the Sponsor or the CRO. All information about each patient is registered according to the Protocol-defined procedures, and must be entered in the eCRF in a timely manner.

In order to ensure the most efficient data collection process, information must be entered into the eCRF as soon as possible, immediately after the patient visit.

Any changes or corrections are entered into the eCRF after verification of the source documentation and will be reflected in the change tracking log directly within the eCRF itself.

13.5. Data collection: Patient's Diary (PD)

The Patient's Diary is kept personally by the patient in paper form to record all necessary information regarding the self-administration of the IMP as part of the study.

- The diary is intended for entering information regarding self-administration of the IMP by the patient.
- Investigators conduct a training for each patient on how to work with the PD.
- Completion of the PD begins after the first interim administration of the IMP in the home and ends after the last interim administration of the IMP during 2 days;
- The data are entered into the diary by the patient/legally authorised representative/parents.
- The following shall be recorded in the diary: **the date and time of the start and end of administration, the dose, infusion rate, administration points, volume of the IMP administered at each site in mL, the number of IMP vials used, the presence of adverse events). The data entered shall be carefully checked by the patient/legally authorised representative/parents.**
- The Investigator is obliged to check the completion of the diary at the Visit and transfer the data to the eCRF.

The Diary is required for:

- Provision of data collection in accordance with the Protocol;
- Ensuring the quality collection of data on the safety of the IMP
- Reflection of the patient's treatment compliance
- Facilitating the effective and complete processing of data, their analysis, and reporting based on CT results.

The Monitor shall also check the information entered into the PD for its consistency with the eCRF. If any discrepancies are identified, the Monitor must discuss this with the Investigator and ensure that the training for the patient on how to use the diary was conducted properly.

13.6. Confidentiality of patient data

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

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

Complete identification information about each patient will be stored only by the investigator, who must provide it upon request by the auditor, insurance company or other official bodies in accordance with the current legislation. This information must be stored taking into account its confidential nature. For this purpose, the CTS will fill in and keep a Patient Identification Logbook, which contains information about the patient (full name, date of birth, number of source medical documentation in the institution, etc.), and the number assigned to the patient. The Identification Logbook or its copy are not transferred to the Sponsor/CRO and must be stored in the TPI archive after the end of the study in accordance with the requirements of current legislation.

All persons involved in the process of conducting clinical studies must ensure the confidentiality of patients' personal data, not allowing unauthorised use of any information that may identify the patient (such as last name or address).

13.7. Investigator's File

The Investigator is obliged to keep all records to ensure complete documentation of the study process in accordance with the standards of Good Clinical Practice and requirements of current legislation. The Investigator must take measures to prevent inadvertent or premature destruction of CT documents.

It is unacceptable to destroy study documents without the prior written approval of the Sponsor.

The Investigator's File includes the following documents (mandatory for detailed review):

- Investigator's Brochure;
- Clinical Trial Protocol;
- Patient Information and Informed Consent Form;
- Reports on the progress of the clinical study;
- Guide to eCRF Completion;
- Delegation of Duties Form;
- Forms for IMP accounting/IMP dispensing;
- Patient identification forms;
- Other documentation according to current legislation.

13.8. Archival data storage

Study documentation must be stored in the TPI archive for at least 25 years in accordance with the current legislation and the contractual agreements between the TPI and the Sponsor. The TPI must store all the necessary study documentation for at least 25 years or longer if such Sponsor requirements exist.

If a need arises to transfer the documentation to a third party for storage (archiving) in the event of impossibility for the TPI to store the documentation, the TPI is obliged to notify the Sponsor and coordinate it with them. The description of the data stored will be kept with the Investigator at the TPI, and a copy will be provided to the Sponsor.

The Clinical Study Protocol and protocol amendments, all versions of the Investigator's Brochure, copies of regulatory approvals, all correspondence and reports, the Study Master File, and other documents related to the study will be kept by the Sponsor or its authorised representative for at least 25 years.

14. FINANCING AND INSURANCE

This study will be organised and conducted at the expense of the Sponsor.

The financial aspects of the study will be documented in the form of a contract between the Sponsor and the TPI.

Before the start of the study, liability insurance shall be arranged for the clinical trial Sponsor against third parties in the event of harm to the life or health of study subjects (healthy volunteers) during their participation in the clinical trial. In the event of harm to the patient's health related to the clinical study, the Insurance Company with which the Sponsor has concluded the insurance contract shall undertake to reimburse all costs for the necessary medical examination and treatment, the need for which arises from the direct effect of the investigational medicinal product and/or procedures conducted in accordance with the Study Protocol according to the insurance agreement.

No payments to the patient from the Sponsor are envisaged, except for possible reimbursement of the patient's transportation costs (if necessary).

All discussions (if any arise) shall be governed by the terms of the insurance contract signed by the Sponsor and the Insurance Company.

15. THE ISSUES OF PUBLICATIONS AND USE OF STUDY RESULTS

Information regarding the investigational medicinal product and/or the conditions of conduct of this study or study results, as well as unpublished scientific data on the IMP, shall be treated as confidential and owned by the Sponsor. This information may only be disclosed to the authorities that authorise the conduct of the study or to the individuals who take part in conducting the study on the basis of confidentiality. The Investigator must use this information only for the purpose of conducting this study, unless other use is provided for by a separate written authorisation/agreement by the Sponsor.

The Investigator shall agree that the Sponsor may use the information obtained during the clinical study for publication and, thus, may make it available to other investigators or regulatory authorities, taking into account the confidentiality of the study subjects' personal data.

The results of this study may be published or presented at scientific conferences. Publication or presentation of study results by the Investigator shall only be permitted after coordination with the Sponsor. In this case, the Investigator shall provide all manuscripts and abstracts of the planned publication to the Sponsor for approval prior to submission to the editorial board or scientific expert council. This will allow the Sponsor to protect information that is its property and to supplement the communication with comments based on information that may not yet be available to the Investigator.

In accordance with the standards of publishing practice, the Sponsor usually supports the publication of the results of multicentre studies in their entirety, and not in the form of data from individual study sites. Any publication of results of the study where the Sponsor's specialist participated beyond the performance of standard monitoring shall be considered a joint publication of the Investigator and that person.

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

16. FINAL REPORT

The final study report is prepared after database lock and statistical data analysis in the event of study completion in accordance with the CT protocol.

Regardless of whether the study was completed per protocol or terminated early, the Sponsor shall ensure the preparation and submission of the CT report to regulatory authorities and the IEC in accordance with the standards of the guideline ICH E3 STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS. In some cases, abbreviated reports may be acceptable.

The final report constitutes confidential information, which cannot be disclosed by the Investigator without an appropriate authorisation of the Sponsor.

17. CONFIDENTIALITY

The information contained in this document is the property of the Sponsor and its disclosure to third parties is permitted only with the written consent of the Sponsor. The right to review this information is granted only to the Investigator(s) and CTS employees who take part in the study, IEC members and employees of health authorities authorised to oversee the CT. Information about the study, to the extent necessary to make a decision to consent to participate, is provided to patients whom the Investigator plans to include in the study.