Official Title: A Multicenter, Prospective, Randomized, Placebo-controlled, Double-blind, Parallel-group Clinical Trial to Assess the Efficacy and Safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in Patients With Post-Polio Syndrome

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Clinical Study Protocol

Protocol Title:	A multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group clinical trial to assess the efficacy and safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in patients with Post-Polio Syndrome.
Study Drug:	Flebogamma® 5% DIF
Sponsor's Name and Address:	Instituto Grifols, S.A. Polígono Levante, C/ Can Guasch, 2 08150 - Parets del Vallès Barcelona (Spain)
EudraCT Number:	2013-004503-39
Development Phase:	Phase II/III
Sponsor Signatories:	[redacted] MD [redacted] Grifols Bioscience Industrial Group Email address: [redacted] Telephone number: [redacted] [redacted] Grifols Bioscience Industrial Group Email address [redacted] Telephone number: [redacted] See Sponsor Signatures on the cover page of the protocol

Protocol Version History

Protocol Version	Date of Approval/Effective Date
7.0 Amendment 6 + Integrated Protocol	See left margin
6.0 Amendment 5 + Integrated Protocol	11 Jan 2021
5.0 Amendment 4 + Integrated Protocol	09 Mar 2020
4.0 Amendment 3 + Integrated Protocol	27 Nov 2018
3.0 Amendment 2 + Integrated Protocol	12 Jun 2017
2.1 Amendment 1 + Integrated Protocol	02 Jul 2014
1.0 Original	15 Nov 2013

Amendment 6

The protocol for IG1104 (Version 6.0, dated 11 Jan 2021) has been amended and reissued as Protocol Amendment 6, Version 7.0. [redacted]

PRIMARY CONTACT INFORMATION

For the sponsor:

[redacted] PhD
[redacted]
Grifols Bioscience Industrial Group
Bioscience Clinical and Pharmacovigilance
Tel. [redacted]
Parc Empresarial Can Sant Joan
Avda. Generalitat, 152-158
08174 Sant Cugat del Vallès – Spain
Email: [redacted]

PROTOCOL SYNOPSIS

Protocol Title:	A multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group clinical trial to assess the efficacy and safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in patients with Post-Polio Syndrome.
Protocol Code:	IG1104
Protocol Version	Final Version 7.0
Sponsor:	Instituto Grifols, S.A. Polígono Levante, C/ Can Guasch, 2 08150 - Parets del Vallès Barcelona (Spain)
Coordinating Investigator:	Prof. Dr. Marinos Dalakas
Investigational (Test) Product:	Flebogamma® 5% DIF: liquid presentation of intravenous immune globulin (IVIG).
Therapeutic Indication:	Post-polio syndrome (PPS)
Trial Phase:	II/III
Trial Sites:	Trial sites will be located in Europe, Canada, and the United States of America.
Trial Design:	This is a phase II/III multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group clinical trial with an adaptive design (flexible group sequential design with adaptive dose selection) in subjects with PPS. This study will consist of 2 stages. The first stage (Stage 1) is for dose selection, and the second stage (Stage 2) is to establish the superiority (efficacy confirmation) of Flebogamma® 5% DIF in the change in physical performance (Two-Minute Walk Distance [2MWD]) as compared to placebo and for overall safety analysis in PPS subjects. Other clinically meaningful outcomes will also be evaluated such as pain, health-related quality of life (HRQoL), endurance, fatigue, muscle strength, and walking activity in daily life. Stage 1 will be a 3-arm evaluation of 2 dose levels of Flebogamma® 5% DIF (IVIG 1 g/kg and 2 g/kg of body weight) and placebo randomized in a 1:1:1 ratio. At the end of Stage 1 (when at least 80% of the randomized subjects have finished the treatment period of Stage 1), a formal unblinded interim analysis will be performed by an independent Data Monitoring

	Committee (DMC). Based on pre-defined criteria, 1 of the doses of Flebogamma® 5% DIF from the 2 active treatment groups in Stage 1 will be selected to continue to Stage 2 of the clinical trial. Subsequently, at Stage 2, a separate cohort of subjects will be randomized to receive the dose of Flebogamma® 5% DIF selected in Stage 1 or placebo in a 1:1 ratio for efficacy confirmation and overall safety analysis. During both stages of the study, randomization will be stratified by the main part of the body most significantly affected by PPS, that is, lower extremities or upper extremities. Both stages, Stage 1 and Stage 2, will consist of a screening period (up to 4 weeks), a treatment period (52 weeks), and a follow-up period (24 weeks).
Main Objective:	To test whether monthly infusions (every 4 weeks) of intravenous Flebogamma® 5% DIF in a 1-year treatment period in PPS subjects are superior to placebo by assessing physical performance, as measured by 2MWD. For Stage 1, to select the optimal dose of IVIG as compared to the placebo. For Stage 2, to establish superiority of the selected dose of IVIG as compared to placebo by combining both Stage 1 and Stage 2 data.
Primary Efficacy Endpoint:	• Physical performance (2MWD) from baseline (at Enrollment Visit) to the end of the treatment period (at End of Treatment Visit [EoTV] – Week 52).
Secondary Efficacy Endpoints:	• Pain (Visual Analogue Scale [VAS] of pain) from baseline to the end of the treatment period. • HRQoL (Medical Outcomes Study 36-Item Short Form Health Survey [SF-36] Physical Component Summary [PCS]) from baseline to the end of the treatment period. • Endurance (Six-Minute Walk Distance [6MWD]) from baseline to the end of the treatment period.
Exploratory Endpoints:	• Muscle strength of 2 newly weakened muscle groups (Manual Muscle Testing [MMT] using the Medical Research Council [MRC] scale) from baseline to the end of the treatment period. • Muscle strength of 2 newly weakened muscle groups (Quantitative Muscle Testing [QMT] using a dynamometer) from baseline to the end of the treatment period. • Walking activity in daily life (pedometer) from baseline to the end of the treatment period. • Subject's self-perceived exertion/fatigue level using the Borg scale before and after the 2MWD and 6MWD from baseline to the end of the treatment period. • Fatigue (Fatigue Severity Scale [FSS]) from baseline to the end of the treatment period.

	• HRQoL (SF-36 Mental Component Summary [MCS]) from baseline to the end of the treatment period. • Blood inflammatory cytokines (IL-1, IL-4, IL-6, IL-10, IL-13, IL-17, IL-23, TNF-alpha, and IFN-gamma) from baseline to the end of the treatment period. • Sustained effect of Flebogamma® 5% DIF compared to placebo as measured by: – Physical performance (2MWD) from baseline to Follow-up Visit (FU) 3 (Week 64) and to the Final Visit (FV; Week 76). – Pain (VAS of pain) from baseline to FU3 and to the FV. – HRQoL (SF-36 PCS) from baseline to FU3 and to the FV. – Endurance (6MWD) from baseline to FU3 and to the FV. – Muscle strength (MMT using the MRC scale) from baseline to the FV. – Muscle strength (QMT using a dynamometer) from baseline to the FV. – Walking activity in daily life (pedometer) from baseline to the FV. – Subject's self-perceived exertion/fatigue level using the Borg scale before and after the 2MWD and 6MWD from baseline to FU3 and to the FV. – Fatigue (FSS) from baseline to the FV. – HRQoL (SF-36 MCS) from baseline to FU3 and to the FV. – Blood inflammatory cytokines from baseline to the FV.
Safety Endpoints:	• Adverse events (AEs). AEs (includes suspected adverse drug reactions [ADRs]) occurring at any time between signature of the informed consent form (ICF) and the last day of the subject's participation in the clinical trial will be reported and recorded on the appropriate subject's electronic case report form (eCRF) entry. AEs will be elicited by spontaneous reporting by study subjects and by a non-leading inquiry/observation by study staff. • Vital signs during infusions. Clinically relevant changes (as determined by the Investigator) in vital signs (body temperature [T], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP] and diastolic blood pressure [DBP]) during infusions of Flebogamma® 5% DIF or Normal Saline Solution will be reported as AEs. • Physical assessments. Physical examinations will be recorded as normal or abnormal, according to the medical doctor's judgment

	criteria. Abnormal findings judged as clinically relevant will be considered AEs. • Blood biochemistry and cell counts. Blood testing will include: – Renal parameters: creatinine and blood urea nitrogen (BUN), and glomerular filtration rate (GFR). – Hepatic parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (TBL). – Haematological parameters: complete blood count (CBC), including differential leukocyte count. Laboratory results out of the normal range that are judged by the Investigator as clinically relevant will be considered AEs.
Treatment:	Subjects will receive intravenous infusions of investigational product (test or placebo) every 4 weeks during a treatment period of 52 weeks. A window period of ± 1 week is allowed for any infusion after Infusion 1. **Stage 1:** At Stage 1, subjects will be randomly assigned, at a 1:1:1 ratio, to 1 of the following 3 treatment arms: <u>IVIG 2 g/kg arm</u> A total dose of 2 g/kg of body weight of Flebogamma® 5% DIF will be administered over 2 consecutive days (IVIG 1g/kg on Day 1 and IVIG 1g/kg on Day 2). <u>IVIG 1 g/kg arm</u> A total dose of 1 g/kg of body weight of Flebogamma® 5% DIF will be administered on 1 day. To maintain the blind, a total dose of 20 mL/kg of body weight Normal Saline Solution (equivalent volume of 1 g/kg of body weight Flebogamma® 5% DIF infusions) will also be administered on a separate day, for a total dosing period of 2 consecutive days. The order of 1 g/kg of body weight of Flebogamma® 5% DIF or 20 mL/kg of body weight Normal Saline Solution infused on 2 consecutive days will be randomly determined for each subject by the Interactive Web Response System (IWRS), which will remain the same for the subject for all infusion visits during the treatment period. <u>Placebo arm</u> A total dose of 40 mL/kg of body weight Normal Saline Solution (equivalent volume of 2 g/kg of body weight Flebogamma® 5% DIF infusions) will be administered over 2 consecutive days. On Day 1, a dose of 20 mL/kg of body weight Normal Saline Solution (equivalent volume of 1 g/kg of body

	weight Flebogamma® 5% DIF infusions) will be administered and on Day 2, the second dose of 20 mL/kg of body weight Normal Saline Solution (equivalent volume of 1 g/kg of body weight Flebogamma® 5% DIF infusions) will be administered. **Stage 2:** At Stage 2, individuals will be randomly assigned, at a 1:1 ratio, to 1 of the following 2 treatment groups: IVIG arm - selected dose from Stage 1 Placebo arm - Normal Saline Solution During Stage 2, the selected dose of Flebogamma® 5% DIF and placebo (Normal Saline Solution) will be administered over 2 consecutive days in the same manner as in Stage 1, including administering the total dose for both treatment arms at a volume equivalent to that for the IVIG 2 g/kg arm, regardless of the selected dose.
Methodology (Stage 1 & Stage 2):	Blinding: For the entire clinical trial period, participating subjects, Investigators, study staff (subinvestigators, nurses, certified independent assessors, technicians, personnel involved in the administration of the investigational product, and other personnel), and testing laboratories will be blinded to the treatment group and the identity of solutions for infusion (test or placebo). Moreover, anyone from the sponsor or Contract Research Organization (CRO) who will be involved in site monitoring, analysis or interpretation of the data will also be blinded regarding each subject's treatment group. Unblinded personnel will be limited to people responsible for creation of the randomization list (independent of the study conduct), site pharmacists or designees responsible for preparing and blinding the investigational products, the unblinded clinical trial material personnel, the independent DMC for interim analysis, and the unblinded output will be reviewed by an independent [redacted] In order to address potential unblinding due to possible predictable side effects of the active product and product appearance, the following approaches will be employed: (1) pre-medication will be administered to all subjects for all treatment arms to reduce the side effects of IVIG; (2) all subjects will receive the same total dose volume (calculated to be equivalent to 2 g/kg Flebogamma® 5% DIF volume) for all treatments; (3) infusion bags will be covered with a non-transparent sleeve and translucent or coloured infusion tubing will be utilized; and (4) using an independent assessor

	(neurologist or qualified personnel who will only have access to the efficacy data) for the evaluation of the efficacy endpoints. The randomization code will not be broken until the clinical trial database is locked for final analyses or unless the Investigator considers it to be in the subject's best interest in the case of an emergency. <u>Clinical Trial Procedures</u>: After giving informed consent to participate in the clinical trial, study subjects will be examined for eligibility during the screening period, and the Investigator will determine whether or not a subject qualifies for inclusion in the clinical trial based on inclusion and exclusion criteria. Eligible individuals will be randomized to 1 of the treatment arms (test or placebo). Throughout the course of the clinical trial, clinical visits (or telephone contacts) will be scheduled at specified time points. A ± 1-week window is allowed for all study visits after the Enrollment Visit (EV)/Infusion Visit (IV) 1 (*i.e.*, EV/IV1). Study assessments will consist of physical assessments, infusion vital signs monitoring, blood analysis, physical exercise capacity evaluation, muscle strength measurements, assessments of HRQoL, pain and fatigue, and recording of AEs and concomitant medication(s). <u>Scheduling of assessments at clinical visits</u>: At the Screening Visit (SV), when 2MWD and MMT are scheduled, the tests will be performed in a specific order, as detailed in Section 5 of the protocol. At the EV/IV1, IV7, End of Treatment Visit (EoTV), and FV, when the SF-36, VAS for pain, 2MWD, MMT, QMT, and 6MWD are all scheduled, the tests will be performed in a specific order, as detailed in Section 5 of the protocol, over 2 days within the allowed visit window. At the EV/IV1 and IV7, when an infusion is also scheduled, the aforementioned tests must be performed prior to the infusion. Thus, infusions at EV/IV1 and IV7 will begin (administered over 2 consecutive days) on or after day 2 of the scheduled visit. At IV4, IV10 and FU3, when the SF-36, VAS for pain, 2MWD and 6MWD are all scheduled, the tests will be performed in specific order, as detailed in Section 5 of the protocol, over 1 day within the allowed visit window. At IV4 and IV10, when an infusion is also scheduled, the aforementioned tests must be performed prior to the infusion. Thus, infusions at IV4 and IV10 will begin (administered over 2 consecutive days) on or after the day of the scheduled visit. <u>Medical history</u>: A complete medical history will be performed on all individuals during the SV. Areas of questioning will include, but are not limited to, information regarding polio vaccination; past and present medical, surgical, and psychiatric history; identification

	of newly affected or weakened muscle groups; family history of neurological disorders, and history of employment. Physical assessments: A physical examination by body systems will be performed at the SV (Week -4 to -1), IV7 (Week 24), EoTV (Week 52), and FV (Week 76). A physical assessment will be carried out at the EV/IV1 (Week 0), IV4 (Week 12), IV10 (Week 36), and FU3 (Week 64). Subject's height and weight will be measured at the SV (Week -4 to -1) in order to calculate his/her body mass index (BMI). At EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24) and IV10 (Week 36), the subject's weight will be measured again. General health assessment: At the SV (Week -4 to -1), subjects will undergo: (1) a neurological examination; (2) 12 lead electrocardiogram (ECG); and (3) a depression assessment using the Center for Epidemiologic Studies (CESD) scale. Optionally, at the SV individuals may also have: (1) a new electro-diagnostic evaluation only if a previous one was unclear or had raised doubts about the diagnosis of PPS, or had revealed the emergence of another co-existent neuromuscular condition and it is needed according to the Investigator's judgment; and (2) a chest X-ray as medically indicated. Infusions and vital signs: During all treatment infusions, vital signs (T, RR, HR, SBP and DBP) will be monitored. Monitoring will be routinely performed within 20 minutes before the beginning of infusion as well as every 30 ± 10 minutes during the first hour of infusion. Thereafter, vital signs will be monitored and recorded at 30 ± 10 minutes post-completion of infusion. Thromboembolic events risk assessments: During all the infusion visits, thromboembolic events risk will be determined using: (1) the Wells prediction score for deep vein thrombosis (DVT) for pulmonary embolism (PE); (2) the measurement of blood D-dimer levels; and (3) evaluation of clinical signs and symptoms of thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities). Monitoring will be performed before the beginning and after the completion of every infusion from IV1 (Week 0) to IV13 (Week 48). Hemolysis detection: During all the infusion visits, hemolysis detection will be evaluated using: (1) blood assessments including whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), red blood count (RBC),

	hematocrit, total and indirect bilirubin, and blood smear; (2) urinalysis including urinary sediment; and (3) assessments of clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia). Monitoring of hemolysis will be performed before the infusion (Day 1), after the completion of the infusion (Day 2) and 10 days (±2 days) after initiation of the infusion (Day 1) from IV1 (Week 0) to IV13 (Week 48). Blood biochemistry and cell counts: Samples for blood biochemistry and cell counts testing will be collected at the SV (Week -4 to -1), within 8 hours prior to investigational product infusion at IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), and at EoTV (Week 52), FU3 (Week 64), and FV (Week 76). Blood immune globulin A class (IgA) level and anti-IgA antibodies: At the SV (Week -4 to -1), blood will be obtained for measurement of IgA levels (selective IgA deficiency). Anti-IgA antibodies will be determined only if IgA levels are below normal range. Blood assessment of general health: At the SV (Week -4 to -1), blood will be obtained for measurement of the following parameters: electrolyte panel (sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate and magnesium); albumin and glucose, thyroid panel (total thyroxine [T4]), free T4, free tri-iodothyronine (T3) and thyroid stimulating hormone (TSH); lactate dehydrogenase (LDH); creatine kinase (CK); aldolase; hemoglobin A1C; vitamin B12; folate; coagulogram (prothrombin time [PT], activated partial thromboplastin time [APTT], and international normalized ratio [INR]); erythrocyte sedimentation rate (ESR), D-dimer; lipid profile (total cholesterol, high density lipoprotein cholesterol [HDL-C], low density lipoprotein cholesterol [LDL-C] and triglycerides). Blood assessment of immunologic function: At the SV (Week -4 to -1), blood will be obtained for measurement of the following parameters: autoantibody panel (rheumatoid factor, anti-nuclear antibodies (ANA), and anti-thyroid antibodies); serum immunoglobulin and protein electrophoresis. Blood assessment of viral exposure: At the SV (Week -4 to -1), blood will be obtained for measurement of hepatitis C virus (HCV) antibodies and human immunodeficiency virus type 1 and 2 (HIV 1&2) antibodies. Viral monitoring will be performed by means of antibody testing and, if required, nucleic acid testing (NAT).

	In addition, retention blood samples for the possible measurement of viral status will be collected prior to the first infusion of investigational product at the EV/IV1 (Week 0) and after completion of the last infusion of investigational product at IV13 (Week 48). These retention samples will be tested only if the subject shows signs and symptoms of viral infection during the study. Blood assessment of inflammatory cytokines: Blood samples will be taken at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76). Possible future blood testing for biomarkers: Retention blood samples will be collected at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76) for possible future biomarker testing. Assessment of physical performance: A 2MWD will be carried out by certified independent assessors at the SV (Week -4 to -1), EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). Assessment of HRQoL: SF-36 questionnaire will be performed by study individuals at the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). Assessment of pain: VAS for pain will be performed by study individuals at the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). Assessment of endurance: Endurance will be measured with the 6MWD by certified independent assessors at the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64) and FV (Week 76). Assessment of muscle strength: At the SV (Week -4 to -1), a certified independent assessor will assess the pre-specified muscle groups by MMT. Muscle strength in 2 selected muscle groups (newly weakened due to PPS) will be measured by MMT and QMT at the EV/IV1 (Week 0), IV7 (Week 24), EoTV (Week 52), and FV (Week 76). Manual muscle testing (MMT) will be performed using the MRC scale. Quantitative muscle testing (QMT) will be carried out using a dynamometer to assess isometric muscle strength. Assessment of walking activity in daily life:

	Subjects will be instructed to attach a pedometer to their person for 7 consecutive days prior to the EV/IV1 (Week 0), EoTV (Week 52) and FV (Week 76), and the number of steps captured by the pedometer will be recorded/uploaded at the scheduled visits. Assessment of perceived exertion/fatigue: The Borg scale will be used to assess the subject's self-perceived exertion level/fatigue level immediately before and after each 2MWD and 6MWD. Assessment of fatigue: The FSS will be assessed when study individuals return the pedometer to the clinic at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76). Follow-up phone call: Follow-up phone calls with the study subjects will be performed at FU1 (Week 56), FU2 (Week 60), FU4 (Week 68) and FU5 (Week 72). Phone calls will include a semi-structured interview in which physical symptoms and general well-being of the subject, presence of AEs, and changes in concomitant medication will be discussed. Adverse events: AEs occurring any time between signature of the subject's ICF and the last day of subject's participation in the clinical trial will be reported on the appropriate subject's eCRF entry. When an AE is classified, assessing causal relationship by the Investigator, as "definite," "probable," "possible" or "doubtful/unlikely," the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definite" will be defined as an adverse reaction (AR). When the causal relationship is labeled "unrelated," then it will be considered that the AE is not imputable to the study treatment, and it is not a suspected ADR. For all subjects, all AEs that occur at any time, between the beginning of the first infusion of Flebogamma® 5% DIF or Normal Saline Solution and the final visit of the clinical trial, will be considered as treatment emergent AEs (TEAEs). AEs occurring during the 2-day infusion period and within 72 hours following the completion of the infusion of the total dose of investigational product, regardless of other factors that may impact a possible causal association with product administration, will be defined as infusional AEs (*i.e.*, an AE temporally associated with an infusion of the investigational product) and labeled TEAEs. For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE, and the time of AE change materially in intensity and/or to resolution will be captured.

Study Population and Sample Size:	The study population will be made up of individuals with PPS. The sample size of this clinical trial has been calculated based on the primary efficacy endpoint (2MWD) at the end of the treatment period (EoTV, Week 52). Baseline measure of 2MWD in patients with PPS has been estimated to be about 120 meters with standard deviations between 24 and 28 meters. The standard deviations for change from baseline to Week 3 and Week 17 in 2MWD are in the range of 8 to 11 meters. In order to show the superiority of Flebogamma® 5% DIF over placebo, an effect size of 5% (6 meters) in change from estimated baseline in 2MWD (120 meters) is assumed. A clinically relevant change in distance walked at the end of the treatment period (after 52 weeks of treatment) between groups (Flebogamma® 5% DIF versus placebo) has been stated to be 5% based on the intrinsic characteristics of the disease, that is, a chronic and slowly progressive condition with an average overall decline in 2MWD of 0.9%/year. The study will employ a flexible group sequential design with 2 stages and 1 interim analysis between stages for dose selection. [redacted] In order to show the treatment difference of 6 meters in 2MWD with a standard deviation of 11 meters, 99 subjects need to be randomized into 1 of 3 treatment groups in Stage 1 and 66 subjects need to be randomized into 1 of 2 treatment groups in Stage 2. Thus, to account for a 20% dropout rate, approximately 126 will be randomized into 1 of the 3 treatment arms (42 subjects/arm) in Stage 1, and approximately 84 subjects will be randomized into 1 of the 2 treatment arms (42 subjects/arm) in Stage 2.
Clinical Trial Duration:	The total duration of a subject's participation for subjects who complete the study will be approximately 80 weeks. Individuals will finish their clinical trial participation with the FV (Week 76). Each stage of the clinical trial will consist of the following periods: 1. Screening Period: up to 4 weeks. 2. Treatment Period: 52 weeks. 3. Follow-up Period: 24 weeks Clinical trial finalization will coincide with the last visit of the last subject included in the study.
Inclusion Criteria:	Clinical trial subject inclusion criteria:

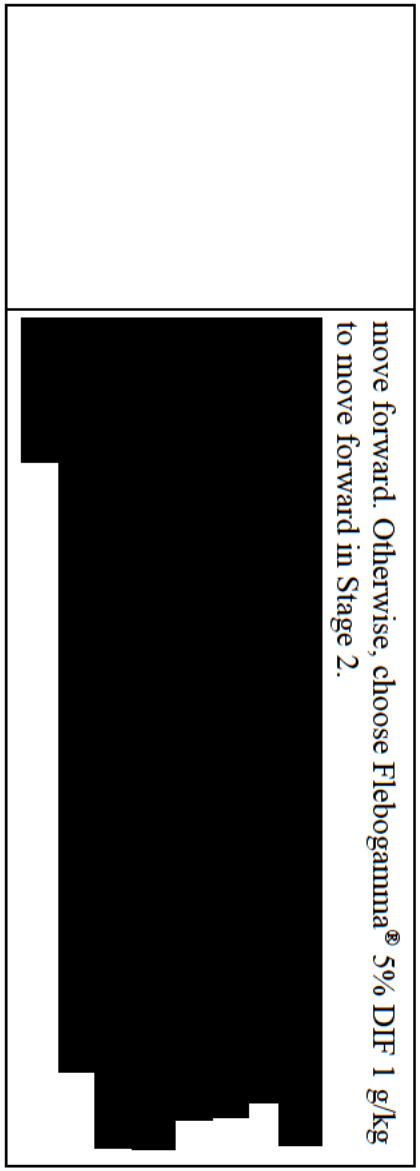
	1. Male or female aged 18 to 75 years. 2. Subjects who understand and voluntarily signed and dated the *Clinical Trial Written Informed Consent Form* for his/her clinical trial participation. 3. Subjects with a body mass index (BMI) less than 35 kg/m^2. 4. Subjects who meet the clinical criteria for diagnosis of PPS as set by the March of Dimes (ANNEX 17) 5. Subjects who are ambulatory or are able to walk with a cane or other aids or use a wheelchair (but they are not wheelchair-bound). 6. Subjects who have at least 2 newly weakened muscle groups due to PPS (as defined by medical history), with at least 1 of them in a lower extremity, and having an MRC scale score greater than 3 at the MMT performed by the independent assessor at the SV. 7. Female subjects of child-bearing potential must have a negative test for pregnancy (human chorionic gonadotropin [HCG]-based assay). 8. Female subjects of child-bearing potential and their sexual partners have agreed to practice contraception using a method of proven reliability (*i.e.*, hormonal methods; barrier methods; intrauterine devices methods) to prevent a pregnancy during the course of the clinical trial. 9. Subjects must be willing to comply with all aspects of the clinical trial protocol, including blood sampling and long-term storage of extra samples for the entire duration of the study. 10. Subjects who are able to walk a 2MWD of at least 50 meters at the SV and EV/IV1. 11. Subjects who are able to walk a consistent baseline 2MWD, that is, the difference in 2MWD between the SV and EV/IV1 is not more than 10%.
Exclusion Criteria:	Clinical trial subject exclusion criteria: 1. Subjects who have received human normal immune globulin treatment given by intravenous, subcutaneous or intramuscular route within the last 3 years. 2. Subjects who are not ambulatory (wheelchair-bound individuals). 3. Subjects with poor venous access. 4. Subjects with intractable pain requiring narcotics or other psychotropic drugs. 5. Subjects with a history of anaphylactic reactions or severe reactions to any blood-derived product. 6. Subjects with a history of intolerance to any component of the investigational products, such as sorbitol.

	7. Subjects who are receiving corticosteroids, except for those who are taking inhaled corticosteroids for asthma. 8. Subjects with a documented diagnosis of hyperviscosity or hypercoagulable state or thrombotic complications to polyclonal IVIG therapy in the past. 9. Subjects with a history of recent (within the last year) myocardial infarction, stroke, or uncontrolled hypertension. 10. Subjects who suffer from congestive heart failure, embolism, or ECG changes indicative of unstable angina or atrial fibrillation. 11. Subjects with a history of chronic alcoholism or illicit drug abuse (addiction) in the preceding 12 months prior to the SV. 12. Subjects with active psychiatric illness that interferes with compliance or communication with health care personnel. 13. Subjects with depression with scores >30 as assessed by the CESD validated scale. 14. Females who are pregnant or are nursing an infant child. 15. Subjects with any medical condition which makes clinical trial participation unadvisable or which is likely to interfere with the evaluation of the study treatment and/or the satisfactory conduct of the clinical trial according to the Investigator's judgment. 16. Subjects currently receiving, or have received within 3 months prior to the SV any investigational medicinal product or device. 17. Subjects who are unlikely to adhere to the protocol requirements, or are likely to be uncooperative, or unable to provide a storage serum/plasma sample prior to the first investigational drug infusion. 18. Subjects with a known selective IgA deficiency and serum antibodies anti-IgA. 19. Subjects with renal impairment (*i.e.*, serum creatinine exceeds more than 1.5 times the upper limit of normal [ULN] for the expected normal range for the testing laboratory). 20. Subjects with AST or ALT levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory. 21. Subjects with hemoglobin levels <10 g/dL, platelets levels <100,000/mm^3, white blood cells count <3.0 k/µL and ESR >50 mm/h or twice above normal. 22. Subjects with known seropositive to HCV, HIV-1 and/or HIV-2. 23. Subjects with a history of intolerance to fructose.

Analytical Plan/Statistical Method:	Demographic and baseline characteristics will be summarized using descriptive statistics. Efficacy analyses will be primarily run on the intent-to-treat (ITT) population. In addition, for sensitivity analysis, efficacy analyses will also be run on the per protocol (PP) population. The ITT population will include all randomized subjects. Subjects will be analyzed per the assigned randomized treatment. The PP population will include subjects in the ITT population who have received at least 8 infusions, without having 2 consecutive missed infusions, of any investigational product (test or placebo) during the treatment period, have baseline and at least 1 post-baseline measure of the 2MWD, and have no major protocol violations that might have impact on the primary efficacy endpoint (as determined at a data review meeting prior to database lock and unblinding). The primary efficacy endpoint is physical performance, evaluated by 2MWD, from baseline (at EV/IV1) to the end of the treatment period (at EoTV, Week 52) for Flebogamma® 5% DIF compared to placebo in the ITT population. Treatment difference between Flebogamma®5% DIF and placebo will be tested using the mixed-effect model with repeated measures (MMRM) method with change from baseline in 2MWD as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and main part of the body most significantly affected by PPS (lower/upper extremities) as the fixed effects; baseline 2MWD measure as covariate; and visit as a repeated measure. At Stage 1, the difference between treatment groups in the change in 2MWD, from baseline (at EV/IV1) to the end of the treatment period (at EoTV, Week 52), will be tested to determine the treatment effect of IVIG 2 g/kg versus placebo and IVIG 1 g/kg versus placebo. At Stage 2, the difference between treatment groups in the change in 2MWD, from baseline (at EV/IV1) to the end of the treatment period (at EoTV, Week 52), will be tested to determine the treatment effect of the selected dose of IVIG from Stage 1 and placebo. For the selected dose group of IVIG versus placebo, p-values will be obtained from Stage 1 and Stage 2 separately. The overall adjusted p-value will be calculated from the p-values from both Stage 1 and Stage 2 by the method proposed by Posch & Bauer (2005) (60) in order to control the overall type I error rate. For sensitivity analysis of combined data in 2MWD from Stage 1 and Stage 2 for the selected dose group of IVIG versus placebo, an analysis of covariance (ANCOVA) method with

	change from baseline in 2MWD as the dependent variable, treatment and main part of the body most significantly affected by PPS (lower/upper extremities) as the fixed effects and baseline 2MWD measure as covariate. Missing data will be imputed using last-observation carried forward approach for post-baseline 2MWD measurement. The primary analyses performed on the ITT population will be repeated for the PP population. For secondary efficacy endpoints and exploratory endpoints, the data from Stage 1 and Stage 2 for the selected dose will be combined and the same approaches (e.g., MMRM and ANCOVA) used in the primary efficacy analyses will be applied. A fixed-sequence testing method will be employed to address the multiplicity issue for multiple secondary efficacy variables. The safety analyses will be primarily focused on a descriptive analysis of suspected ADRs. Safety assessment will be based on the prevalence of suspected ADRs that occurred during the clinical trial. The safety analyses will be addressed by listing and tabulation of AEs (includes suspected ADRs), vital signs, physical assessments and clinical laboratory tests. Data will be described using descriptive analyses. For any subject, all AEs that occur at any time between the beginning of the first infusion of Flebogamma® 5% DIF or Normal Saline Solution and the final visit will be considered TEAEs for analyses. TEAEs will be summarized for the treatment period (from the first study drug infusion – IV1, Week 0 to 4 weeks after the last infusion – EoTV, Week 52) and for the follow-up period (from the EoTV, Week 52, to the FV, Week 76) collectively and separately. All AEs will be summarized by presenting subject incidences and percentages, and they will be individually listed by body system with subject identification codes. TEAEs, including suspected ADRs, will be summarized by treatment group, system organ class, preferred term, causal-relationship to the study product, intensity (severity) and seriousness (serious versus non-serious) using descriptive analysis. AEs, including suspected ADRs, of thromboembolic or hemolytic origin will be summarized separately. AEs temporally associated to the infusion of the investigational products (*i.e.*, infusional AEs, including infusional suspected ADRs,) defined as an AE that occurred during the 2-day infusion period (*i.e.*, from the initiation of the investigational product infusion on the first day to the completion of the total dose of investigational product on the last day) and within 72

	hours following the completion of the infusion of the total dose of investigational product on the last day, will be summarized and listed. In addition, AEs temporally associated to the infusion of the investigational products for which the incidence in the Flebogamma® 5% DIF exceeds the incidence in the placebo group will also be summarized separately. Subjects who have a serious adverse event (SAE) or who withdraw from the study because of an AE will also be individually listed and summarized. AEs for which the investigator causality assessment is missing or undetermined will be individually listed. Vital signs (T, RR, HR, SBP and DBP) will be listed for each subject. In case a subject presents with a clinically relevant abnormality of vital signs during an infusion, the event will be flagged and reported as an AE temporally associated to the infusion. For each subject and for each infusion, each of the 5 vital signs will be considered. Physical findings (normal and abnormal) will be listed for each clinical trial subject. Any clinically relevant abnormality developed by individual during the clinical trial and not already present at baseline will be reported as an AE. All clinical laboratory data for renal (creatinine, BUN and GFR), hepatic (ALT, AST, ALP and TBL) and haematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subject. The Investigator will be required to classify laboratory results out of the normal range reported by the laboratory as clinically relevant or not according to his/her judgment. Laboratory results out of the normal range judged by the Investigator as clinically relevant will be reported as AEs. A formal unblinded interim analysis will be performed to select 1 of the 2 doses for Stage 2 based on the primary efficacy endpoint of 2MWD. The interim analysis will be performed when at least 80% of randomized subjects have finished the treatment period of Stage 1. Based on the interim analysis results, the independent DMC will use the pre-specified dose selection rule to select 1 of the Flebogamma doses (2 g/kg or 1 g/kg) to continue the Stage 2 of the clinical trial. The following dose selection rules will be applied: At the interim analysis, conditional power (the power conditional on the partial information accumulated at the interim analysis) will be calculated for comparisons of 2 g/kg versus placebo and 1 g/kg versus placebo. Between the 2 active treatment arms, if conditional power based on the primary efficacy endpoint of 2MWD in Flebogamma® 5% DIF 2 g/kg group is at least 10% relatively higher than Flebogamma® 5% DIF 1 g/kg group, then choose Flebogamma® 5% DIF 2 g/kg to


move forward. Otherwise, choose Flebogamma® 5% DIF 1 g/kg
to move forward in Stage 2.

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APPENDICES

[redacted]

ANNEXES

ABBREVIATIONS AND DEFINITION OF TERMS

µL	Microliter
2MWD	Two-minute walk distance
6MWD	Six-minute walk distance
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AR	Adverse reaction
ARC	Absolute reticulocyte count
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
BLA	Biologics License Application
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CESD	Center for Epidemiologic Studies Depression
CFR	Code of Federal Regulations
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CK	Creatine kinase
CRO	Contract research organization
CSF	Cerebrospinal fluid
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
dL	Deciliter
DMC	Data monitoring committee
DSUR	Development Safety Update Report
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicines Agency
EoTV	End of Treatment Visit
ESR	Erythrocyte sedimentation rate
EV	Enrollment Visit

FDA	Food and Drug Administration
FSS	Fatigue severity scale
FU	Follow-up Visit
FV	Final Visit
g	Gram
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
H	Hour
HAV	Hepatitis A virus
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL-C	High density lipoprotein cholesterol
HIPAA	Health Insurance Portability Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
HRQoL	Health-related quality of life
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	Immune globulin A class
IGF-I	Insulin-like growth factor I
IgG	Immune globulin G class
INR	International normalized ratio
ITP	Idiopathic thrombocytopenia purpura
ITT	Intent-to-treat
IV	Infusion Visit
IVIG	Intravenous immune globulin
IWRS	Interactive Web Response System
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
MCS	Mental Component Summary
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MMRM	Mixed-effect model with repeated measures

MMT	Manual Muscle Testing
MRC	Medical Research Council scale
NAT	Nucleic acid testing
NSAIDS	Non-steroidal anti-inflammatory drugs
PASE	Physical Activity Scale for the Elderly
PCS	Physical Component Summary
PE	Pulmonary embolism
PID	Primary humoral immune deficiency
PiPEDA	Personal Information Protection and Electronics Documents Act
PP	Per protocol
PPS	Post-polio syndrome
PT	Prothrombin time
QMT	Quantitative muscle testing
RBC	Red blood cell
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SPC	Summary of Product Characteristics
SV	Screening Visit
T	Body temperature
T3	Tri-iodothyronine
T4	Thyroxine
TBL	Total bilirubin
TE	Thromboembolic
TEAE	Treatment emergent adverse event
TRALI	Transfusion related acute lung injury
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

1 GENERAL INFORMATION

1.1 Protocol title

"A multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group clinical trial to assess the efficacy and safety of Immune Globulin Intravenous (Human) Flebogamma® 5% DIF in patients with Post-Polio Syndrome."

1.2 Protocol identifying number, version, date and EudraCT number

Protocol Number: IG1104

EudraCT Number: 2013-004503-39

Version Number: 7

1.3 Name and address of sponsor

Sponsor:

Instituto Grifols, S.A.
Polígono Levante, C/ Can Guasch, 2
08150 - Parets del Vallès
Barcelona (Spain)
Phone: +34 935 710 700
Fax: +34 935 710 381

1.4 Name, title, address, and telephone number of sponsor's medical expert for the trial

[redacted], MD
[redacted]
Grifols Therapeutics, LLC.
4201 Research Commons
79 T.W. Alexander Drive
Research Triangle Park, NC 27709
Office phone: [redacted]
Cell phone: [redacted]

1.5 Name and title of Investigators who are responsible for conducting the trial, and address and telephone number of trial sites

Use of ANNEX 1 was discontinued with the issuance of IG1104 Protocol Amendment 2 (Version 3, June 12, 2017). For contact details of Investigators and study sites see the trial master file.

2 BACKGROUND INFORMATION

2.1 Name and description of the investigational products

The following investigational products will be used in this clinical trial (Table 1):

Table 1. Investigational products

INVESTIGATIONAL PRODUCTS	
Test: **Flebogamma® 5% DIF**	Vials containing liquid preparation of Intravenous Immune Globulin (human) 5% (50 g/L)
Control (placebo): **Normal Saline Solution**	Containers (per study site source) of sodium chloride solution (0.9 g per 100 mL) for infusion.

Flebogamma® 5% DIF will be the investigational product being tested, and Normal Saline Solution will be the investigational product used as control (placebo).

Flebogamma® DIF is a sterile and liquid preparation of human immune globulin G highly purified from human plasma intended for intravenous administration. Flebogamma® DIF is formulated at 5% and 10% concentrations. Production process is the same until the final concentration step; bulk product is adjusted to yield desired product strength. This clinical trial (Protocol code: IG1104) is to be performed with Flebogamma® DIF formulated at 5% (Flebogamma® 5% DIF).

[redacted]

[redacted]

Normal Saline Solution will be a sterile preparation of 0.9 % sodium chloride commercially available in the corresponding country.

2.2 Summary of findings from nonclinical studies and clinical trials that are relevant to the trial

Nonclinical and clinical data related to Flebogamma® 5% DIF are summarized in the Summary of Product Characteristics (SPC) (ANNEX 2).

Safety of the isotonic sodium chloride solutions is well-known in the fluid therapy field worldwide, thanks to the existing wide experience in the use of these solutions as hydroelectrolytic balance restorer.

2.3 Summary of the known and potential risks and benefits to human subjects

Intravenous Immune Globulin (IVIG) is a therapeutic preparation of pooled polyspecific immune globulin G (IgG) obtained from the plasma of a large number of healthy blood donors. These preparations were commercialized in the early 1980s to replace intramuscular preparations of polyspecific IgG, which were the only available substitutive therapy at that time for patients with primary or secondary immunodeficiencies [1]. IVIG has been widely available in several indications [2-4], has a well-documented safety profile [5,6] and, based on the accumulated experience, it has the potential to be of benefit in patients with post-polio syndrome (PPS) [7-12].

Possible risks associated to the administration of the investigational products (Flebogamma® 5% DIF and Normal Saline Solution) are detailed as follows.

Since Flebogamma® 5% DIF is prepared from human plasma, infectious diseases due to transmission of infective agents cannot be totally excluded. This also applies to pathogens of unknown nature. The risk of transmission of infective agents is however reduced by: (1) selection of donors by a medical interview and examination and screening of individual donations and plasma pools for hepatitis B virus (HBV) surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV) and hepatitis C virus (HCV); (2) testing of plasma pools for HCV genomic material; (3) inactivation/removal procedures included in the production process that have been validated using different relevant and/or model enveloped and non-enveloped viruses. The measures are considered effective for enveloped viruses such as HIV, HBV, HCV and for the non-enveloped viruses hepatitis A virus (HAV) and parvovirus B19. Viral safety of Flebogamma® 5% DIF has been monitored in 2 clinical trials (coded as IG201 and IG202). No viral safety concern has been raised. Taking into consideration the manufacturing process, the previous clinical data, and the positive post-marketing experience with Flebogamma® 5% DIF, specific monitoring of viral markers will not be performed in the current clinical trial. However, retention blood samples for the possible measurement of viral status will be collected; these retention samples will be tested only if the subject shows signs and symptoms of viral infection during the study.

In the final formulation, Flebogamma® 5% DIF contains 5 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection. Patients with very rare hereditary problems of fructose intolerance must not take this medicine. In case of inadvertent application and suspicion of hereditary fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.

As with all products containing human origin proteins, hypersensitivity reactions, or allergic reactions, cannot be rejected, including severe anaphylactic reactions (anaphylactic shock) with the IVIG administration.

Adverse reactions (ARs) associated with IVIG administration such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally. Rarely IVIG may cause a sudden fall in blood pressure, bronchitis, cough, wheezing, dyspnea, flushing, chest pain, diarrhea, hepatic enzymes increase, abdominal pain, decrease in blood cell counts, muscle pain, muscle cramp and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration. Cases of reversible aseptic meningitis, reversible haemolytic reactions, especially in those patients with blood groups A, B, and AB, and in isolated cases of reversible haemolytic anaemia/haemolysis, requiring transfusion and rare cases of transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown), have been observed with IVIG. Increase in serum creatinine level and/or occurrence of acute renal failure have also been observed. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism (PE), deep vein thrombosis (DVT), severe allergic cutaneous reactions and transfusion related acute lung injury (TRALI) have been reported [6].

All patients, but especially individuals receiving IVIG for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events.

Individuals with predisposition to acute renal failure (such as diabetes mellitus or age greater than 65 years) will be allowed to participate in the clinical trial provided that the investigational product will be infused as indicated in Section 4.4.4.3.

Flebogamma® 5% DIF must not be administered in subjects with selective immune globulin A (IgA) deficiency and who have antibodies against IgA, or in subjects with known marked hypersensitivity to the active substance or to any of the excipients contained in the product, described in its SPC, July, 2014 (ANNEX 2).

More detailed information about risks is exposed in the SPC of Flebogamma® DIF.

Regarding Normal Saline Solution, safety of the isotonic sodium chloride solution, in the fluid therapy field, is well known due to the worldwide experience in its use as hydroelectrolytic balance restorer. However, an inadequate or excessive administration of normal saline solution may lead to hyperhydration, hypernatremia, hyperchloremia and related symptoms, such as metabolic acidosis due to the decrease of bicarbonate ions concentration, and origination of oedema.

An inconvenience of participating in this research may be the time involved in multiple visits and assessments. This may cause a discomfort to the study subjects and because of that, they must be willing to comply with the visit schedule before accepting to take part in this clinical trial. Failure to comply with it may result in the individual's termination from the study.

Intravenous therapy may have several potential risks such as infection, phlebitis, dizziness, and fluid overload. Risks associated with blood drawing may be brief pain, slight bruising, hematoma, and very rarely infection where the needle went in. All intravenous infusions and blood drawn will be performed by trained personnel under medical supervision and every precaution will be taken to prevent any of these risks.

During the Two-Minute Walk Distance (2MWD) and the Six-Minute Walk Distance (6MWD), subjects may develop shortness of breath, heart rate acceleration and leg pain. There may also a risk of abnormal blood pressure, syncope, irregular heart rate, and, in very rare instances, heart attack. Individuals are allowed to stop at any time during the test if these symptoms discomfort them or are more than usually expected. Moreover, every effort will be made to minimize such changes through the preliminary examination and observations during testing. A technician will coach and supervise the performance of the walking test, and will take every precaution to prevent any event. If this occurs, treatment will be available.

Finally, time and attention involved in the act of completing self-administered questionnaires may imply a discomfort for the study subjects.

General benefits expected from participating in a clinical trial include helping others by contributing to medical research and helping advance the development of better treatments.

Particularly, knowledge will come from studying the data that are gathered over the course of the present study. The results and conclusions about what happened during this study might help make informed decisions about the effectiveness and safety of this drug in the future. This drug has already been tested and used in humans, and it has been found safe and effective for other indications such as PID or idiopathic thrombocytopenia purpura (ITP). The present trial might extend the understanding of the drug's potential clinical efficacy in the treatment of PPS.

A specific benefit expected from participating in this clinical trial includes the possibility to gain access to a promising treatment not available to the public. That is, subjects randomized to the active treatment arm will receive every 4 weeks intravenous infusions of IVIG over a period of 52 weeks. The use of IVIG therapy in subjects with PPS may theoretically reduce the inflammation and, as a consequence, may improve the physical performance of the PPS patients. If satisfactory clinical response occurs, participants receiving the active treatment would then experience a significant improvement in daily life activities as compared to individuals on other models of therapy or no therapy. It should be noted that no alternative effective treatment is currently available.

Another benefit is that subjects will receive protocol-specific care free of charge for the total period of the study. Close monitoring of participants during the study increases the likelihood of identifying potential adverse drug events or deterioration of their conditions thereby increasing the potential for early intervention and management.

Risk/Benefit Ratio: considering the lack of any therapies and the permanent disability caused by the disease, it is believed that the benefits outweigh the risks.

2.4 Description of and justification for the route administration, dosage, dosage regimen, and treatment period(s)

This study will consist of 2 stages. The first stage (Stage 1) is for dose selection, and the second stage (Stage 2) is to establish the superiority (efficacy confirmation) of Flebogamma® 5% DIF and for overall safety analysis.

At Stage 1, there will be 3 treatment arms: Flebogamma® 5% DIF 2 g/kg of body weight (IVIG 2 g/kg arm, IVIG 1 g/kg on Day 1 and IVIG 1g/kg on Day 2), the equivalent volume of Normal Saline Solution (placebo arm, 20 mL/kg of Normal Saline Solution on Day 1 and 20 mL/kg of Normal Saline Solution on Day 2), and Flebogamma® 5% DIF 1 g/kg of body weight plus the equivalent volume of Normal Saline Solution (20 mL/kg of body weight) (IVIG 1 g/kg arm; the order of 1 g/kg of body weight of Flebogamma® 5% DIF or 20 mL/kg of body weight Normal Saline Solution infused on 2 consecutive days will be randomly determined for each subject by the Interactive Web Response System [IWRS], which will remain the same for the subject for all infusion visits during the treatment period). Investigational product (test and placebo) will be administered every 4 weeks over 2 consecutive days during a 52-week treatment period.

At Stage 2, there will be 2 treatment arms: the selected dose of Flebogamma® 5% DIF from Stage 1 and Normal Saline Solution (40 mL/kg of body weight with 20 mL/kg infused on Day 1 and 20 mL/kg infused on Day 2), will be administered every 4 weeks over 2 consecutive days during a 52-week treatment period. During Stage 2, the selected dose of Flebogamma® 5% DIF and Normal Saline Solution will be administered in the same manner as in Stage 1, including administering the total dose for both treatment arms at a volume equivalent to that for the IVIG 2 g/kg arm, regardless of the selected dose.

Since optimal dose and IVIG cycle frequency has not been examined in PPS, the rationale for these doses, dosage regimen and treatment period is mainly based on experience in previous clinical trials of IVIG in PPS and in other inflammatory neuropathies, such as Guillain Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which, as PPS, is a slowly progressive disease.

Four of the 5 clinical trials that explored the effects of IVIG in PPS subjects used 1 single dose of 90 g or approximately 2 g/kg of body weight of IVIG administered over 3-5 days (approximately 0.4-0.7 g/kg of body weight/day) [8,10-12]. In the Gonzalez's trial, 2 doses of 90 g of IVIG were administered over 3-4 days (approximately 0.4-0.7 g/kg of body weight/day) at baseline and after 3 months [9]. This amount is equivalent to the recommended dose of IVIG for primary immunodeficiency, that is, approximately 0.4-0.8 g/kg of body weight. Regardless of the promising study results, the limited treatment effect was probably due testing of only a single dose in a chronic indication and secondly a dose that is lower than used in other neurological indications.

In case of GBS, a first-line treatment consisting of 0.4 g/kg of body weight over 5 days was recommended by the European Federation Neurological Society [13]. One trial compared 0.4 g/kg daily for 3 days with the same dose daily for 6 days. This was a high quality randomized double-blind trial involving 39 participants. Unfortunately, it was terminated prematurely because of a national directive not to use albumin as a placebo. Nevertheless, the results showed a trend in favour of the higher dose [14].

In case of CIDP, a first-line treatment consisting of 2 g/kg of body weight loading dose administered over 2-5 days followed by subsequent maintenance doses every 3 weeks were recommended by the European Federation Neurological Society [13]. In a randomized, placebo-controlled, double-blind, response-conditional crossover trial with IVIG (Gamunex), CIDP patients received a loading dose (2 g/kg of body weight) and maintenance doses (1 g/kg of body weight) every 3 weeks for up to 24 weeks (first period). Non-responder subjects were crossed over to receive the alternate treatment according to the same treatment schedule (second period) as was used in the first period. IVIG 10% showed a benefit with a significantly higher response rate in functional disability improvement versus placebo after 24 weeks of treatment (p=0.0002). Furthermore, long-term maintenance with IVIG also significantly had a reduced rate of relapse probability (13%) relative to IVIG responders who had therapy withdrawn (45%) [15].

In addition, Flebogamma® 5% DIF shows a suitable profile for this treatment schedule based on: 1) Flebogamma® 5% DIF pharmacokinetic studies in PID; 2) Flebogamma® 5% DIF administration with an immunomodulatory effect on other indications; 3) Flebogamma® 5% DIF safety profile. In a clinical study assessing safety and efficacy in PID, pharmacokinetics of Flebogamma® 5% DIF was assessed in 20 subjects after at least the 5th month of treatment. Pharmacokinetic analysis revealed that Flebogamma® 5% DIF infusions (at a dosage of 0.3 - 0.6 g/kg of body weight) had a mean estimated half-life for total IgG of approximately 31 days. Therefore, the reported half-life demonstrated that every 4 weeks infusions of Flebogamma® 5% DIF are suitable dosing intervals for maintenance doses.

Considering the similarities between the characteristics of PPS and CIDP, and the positive results of the above mentioned clinical trial in CIDP [15], 2 treatments consisting of IVIG 2 g/kg and 1 g/kg of body weight, administered every 4 weeks, will be tested in a first stage of this adaptive clinical trial in order to establish the best IVIG dose for the subsequent stage of the study. Because PPS is a chronic condition that progresses slowly, a longer therapy than that used in previous clinical trials may be required to show a significant benefit from the IVIG treatment. Therefore, a treatment period of 52 weeks has been considered appropriate for assessment of the magnitude of the treatment effect of IVIG in PPS. In addition, sustainability of effect over 24 weeks after the end of IVIG treatment will also be evaluated as an exploratory outcome. In order to determine the sustainability of effect of Flebogamma® 5% DIF over time, efficacy and exploratory endpoints will be assessed 12 and/or 24 weeks after the end of study drug treatment as exploratory outcomes.

In the case of Normal Saline Solution, a dosage of 40 mL/kg of body weight or 20 mL/kg of body weight is the necessary volume of Normal Saline Solution to obtain the same volume of Flebogamma® DIF 5%, IVIG 2 g/kg arm or IVIG 1 g/kg arm, respectively, for a subject with a fixed weight.

The usual route of administration of human immune globulin and normal saline solutions is the intravenous route because this is the best way to deliver the required large volumes of investigational product throughout the body. Both investigational products, Flebogamma® 5% DIF and Normal Saline Solution, will be administered intravenously as described in their SPC (see ANNEX 2 for the Flebogamma® 5% DIF SPC).

It should be noted that, in this clinical trial, approximately two fifths of the study population will be placed into the placebo-arm. Although subjects randomized to placebo may worsen during the study period, the disease progresses very slowly and it is not anticipated that a major change will

occur at the end of the study. Further, randomization to placebo does not deprive the study individuals from established therapies provided that they are permitted medications (see Section 7.2).

2.5 Compliance with the protocol, good clinical practice and the applicable regulatory requirements

This clinical trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki of the 18th World Medical Assembly, June 1964, in compliance with the approved protocol of the study (Protocol Identification Code IG1104, Final Version 2.1, July 2nd, 2014), with any approved amendment of the protocol, in compliance with Good Clinical Practice (GCP), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Topic E6 (R1) Guideline for Good Clinical Practice, CPMP/ICH/135/95, 1996 and E6 (R2) Guideline for Good Clinical Practice, EMA/CHMP/ICH/135/1995, 2016, and in compliance with the European Directive 2001/20/EC, the US FDA's 21 Code of Federal Regulation (CFR), Health Canada's Division 5 of the Food and Drug Regulations, and the applicable regulatory requirements.

2.6 Description of the population to be studied

Study population will be made up of individuals with PPS.

2.7 Reference to literature and data that are relevant to the trial, and that provide background for the trial

PPS refers to the new neuromuscular symptoms that occur after at least 15 years of stability in patients with prior acute paralytic poliomyelitis [16]. Since there are no specific diagnostic tests for PPS, diagnosis is based on exclusion of other possible causes for the new symptoms.

The cardinal feature of PPS is new onset of functional decline due to new muscle weakness and fatigue (both generalized and muscular), which is not otherwise explicable [17]. Fatigue is the major and likely most disabling symptom of PPS, and it is typically described as tiredness or lack of energy that increases with physical activity and decreases with rest [18]. Fatigue has a negative impact on activities of daily living and there is evidence that post-polio related fatigue is an important factor for the reduced quality of life in polio survivors [19].

PPS is regarded to be a slowly progressive condition. In a recent systematic review, researchers found that, among long-term studies, the deterioration in muscle strength varied from 7% in 4 years to 15% in 8 years [20]. The decline in muscle mass leads to a decline in physical functioning as the reduced muscle capacity falls short to meet the demands of daily physical activities [21].

The World Health Organization (WHO) estimates at 20 million polio survivors worldwide. The prevalence of PPS has been reported from 15% to 80% of all patients with previous paralytic polio depending on the criteria applied and the population [22]. The prevalence in 2 US polio populations was 28.5% and 64%, respectively [23, 24]. For European populations, 1 Dutch study reported a prevalence of late onset polio symptoms of 46%, 1 study from Edinburgh reported a prevalence of more than 60%, and a prevalence of 63% has been reported in Denmark [25-27].

The pathogenesis of PPS is still unclear and is probably multifactorial. The most widely accepted explanation attributes PPS to the premature attrition of motor neurons, especially those supporting large motor unit territories. After the acute polio attack, the surviving motor neurons over sprout to effectively reinnervate and recruit within their motor unit territory many muscle fibers left denervated from the loss of the neighboring motor neurons. Several years later, these over functioning neurons cannot keep up with the metabolic needs required to support large motor units, and several distal nerve terminals degenerate resulting in new muscle weakness and fatigue [28]. Whether some of the surviving motor neurons in PPS patients were marginally affected in the original infection but survived and their current dysfunction represents an immune or inflammatory reaction to possible viral remnants, remains unsettled.

The possibility that an inflammatory component may contribute to the manifestations of the new neuromuscular symptoms in PPS patients is however supported by the following observations: a) increased expression of mRNA for proinflammatory cytokines TNF-α, INF-γ, IL-10 and IL-4 in cerebrospinal fluid (CSF); b) perturbation of immunoregulatory T cells; c) oligoclonal bands in the CSF of PPS patients; d) perivascular and lymphocytic infiltrates and active gliosis in the spinal cord even after 30 years from the original polio attack; and e) spotty areas of inflammation in the muscles of post-polio patients with up-regulation of MHC-I or II class antigen [29].

The treatment options for PPS may be divided into non-pharmacological and pharmacological interventions. However, currently there is no proven curative treatment available for this neurological condition. Currently, rehabilitation management is considered the mainstay of treatment since no proven clinically effective approach exists. The aim is to reach a functional balance by increasing capacities and reducing demands. Rehabilitation schemes include individually tailored training programs, physiotherapy and lifestyle changes such as pacing of activities, taking rest intervals and reducing weigh [30]. Proper orthoses and assistive devices such as crutches, wheelchairs, motorized scooters and home adaptations may facilitate daily life activities [31].

Pharmacological treatments vary in terms of their respective points of action and targeted effects. Amantadine, bromocriptine and modafinil act on different regions of the brain and are intended to address generalized fatigue in PPS. Amantadine and modafinil provided no reduction in fatigue [32, 33], but bromocriptine [34] study suggested some benefit and may warrant further study. Lamotrigine, a glutamate release blocker, was studied to evaluate whether the neuroprotective effect of the drug reduces fatigue and pain in PPS. Preliminary results of a small clinical trial indicated that lamotrigine might relieve the symptoms and improve the life qualities of patients with PPS but further studies are needed [35]. Pyridostigmine is a cholinesterase inhibitor, thus prolonging the survival of acetylcholine in the neuromuscular synapse. It has been investigated in 2 randomized controlled trials but was found to be without benefits regarding fatigue, quality of life, and muscle strength [36, 37]. Insulin-like growth factor (IGF-I) and human growth hormone, which stimulates the secretion of IGF-I, may be suitable agents for the treatment of PPS. IGF-I is thought to enhance regeneration of peripheral nerves by axonal sprouting which in turn positively influences muscle strength. Unfortunately, 1 small study that scientists conducted showed that insulin-like growth factor (IGF-1), was not helpful [38]. Coenzyme Q10 was evaluated for their effects on muscle metabolism and muscle strength respectively, and the effect on PPS symptoms in general. A small double-blind pilot study did not find any additional positive effect on muscle resistance training for patients taking coenzyme Q10 daily [39].

Based on the findings of inflammatory markers in the serum and CSF from PPS patients [7], it raised the possibility that inflammation might be part of its pathophysiology. In this line, anti-inflammatory medications could have a benefit in PPS treatment. High-dose prednisone and IVIG were studied to determine whether their immunosuppressive or immunomodulating effects might have a beneficial effect on muscle strength, fatigue and pain [40]. Prednisone demonstrated a mild improvement in the PPS symptoms, but the results were not statistically significant. This, in addition to the drug's side effects, led researchers to recommend that prednisone was not used to treat PPS. The last Cochrane systematic literature review update published in 2015 concluded that results indicated that IVIG, lamotrigine, muscle strengthening exercises, and static magnetic fields may be beneficial but need further investigation to clarify whether any real and meaningful effect exists [41], [42]. The results from this systematic review are in line with the previous one published in 2011, where the authors concluded that due to insufficient good quality data and lack of randomised studies it was not possible to draw definite conclusions on the effectiveness of interventions for PPS.

With regard to IVIG, its clinical use has been expanded beyond its traditional place in the treatment of patients with PID. IVIG mechanisms of action are complex and include anti-infective, immunoregulatory, and anti-inflammatory properties. In primary and secondary immunodeficiency diseases, IVIG restores normal humoral immune function by increasing antibody levels and possibly enhancing other immune functions, such as removing immunosuppressive complexes [1]. Several mechanisms have been proposed for the immunomodulatory action of IVIG in autoimmune disorders. Short-term actions include neutralization of circulating autoantibodies or superantigens, blockade of Fc receptor-mediated events, and modulation of cytokines. Long-term IVIG therapy may promote down regulation of antibody production and regulate the production of helper or suppressor T-cell cytokines. The anti-inflammatory actions of IVIG may occur through several possible mechanisms, including the reduction of complement-mediated damage, neutralization of microbial toxins, and activation of leukocytes [2]. Due to its multiple anti-inflammatory and immunomodulatory properties, IVIG is used successfully in a wide range of autoimmune and inflammatory conditions. Recognized autoimmune indications include ITP, Kawasaki disease, GBS and other autoimmune neuropathies, myasthenia gravis, dermatomyositis and several rare diseases.

Gonzalez et al. were the first researchers to show that IVIG reduced CSF inflammatory cytokine levels in PPS patients and this observation provided the rationale for trying IVIG as a therapy in PPS [7].

To date, 9 prospective clinical studies have investigated the effects of IVIG in PPS, 3 of them with Xepol (Flebogamma 5%) [8-12,43,45-48].

An open pilot study done in 14 patients explored the effect of Flebogamma 5% 90 g (total dose given over 3 days) on muscle strength (dynamic dynamometry) in 2 muscle groups and physical performance (the Six-Minute Walk Distance [6MWD]) measured at 2 months after treatment, and quality of life (Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36] questionnaire) measured at 2 and 6 months after treatment. A statistically significant improvement was found for the SF-36 questionnaire, but not on muscle strength or physical ability. Although not statistically significant, there was a mean increase in the 6MWD from 321 meters (SD=175 meters) before treatment to 347 meters (SD=171 meters) after treatment (p=0.083). No safety data were published [8].

A randomized, placebo-controlled, double-blind clinical trial was performed including 142 patients treated with either Flebogamma 5% 90 g (dose given over 3 days) or a corresponding volume of placebo (5% glucose), and repeated after 3 months. The primary efficacy endpoints were muscle strength (dynamic dynamometry) in a pre-selected muscle group and quality of life (SF-36 questionnaire Physical Component Summary [PCS]). Secondary endpoints included physical performance (6MWD) and pain (visual analogue scale [VAS]). Outcome tests were done before first infusion and 3 months after the second infusion (at 6 months from baseline). Change in muscle strength showed a median difference of 8.3% in favor of the intervention group (p=0.029) but this did not reach the predetermined target of 15% for clinical significance. Change in SF-36 questionnaire PCS and VAS for pain did not differ significantly between groups. However, in the subgroup of patients with significant pain, those receiving IVIG had greater pain reduction than those in the placebo-group (p=0.037). Treatment with IVIG was well tolerated by most patients. Three serious adverse events (SAEs) were reported, 2 in the placebo and 1 in the intervention group, none of which was judged to be related to treatment [9]. One year after, 41 subjects were further evaluated before unblinding (21 placebo and 20 treated with IVIG) and were assessed for SF-36 questionnaire PCS, 6MWD and VAS for pain. Scores of SF-36 questionnaire PCS in IVIG-treated individuals were significantly higher at 1-year follow-up period when compared to baseline as well as control subjects. Walking ability and VAS for pain after 1 year showed a significant improvement in the IVIG group but not in the controls and there was no statistical difference after 1-year follow-up between IVIG and placebo group [43].

One smaller, randomized, controlled pilot study was carried out in 20 patients, treated with either Octagam 50 mg/mL (single dose of 2 g/kg of body weight administered over 2-4 days) or a corresponding volume of placebo (0.9% NaCl). The primary efficacy endpoints were muscle strength (dynamic dynamometry), pain (VAS for pain), and fatigue (fatigue severity scale [FSS]) after 3 months. Patients receiving IVIG reported significantly reduced levels of pain 3 months after treatment on the VAS for pain (p=0.001). No significant effect was found for muscle strength or fatigue. No safety data were published [10].

An uncontrolled clinical study done 45 patients explored the effect of Flebogamma 5% 90 g (single dose given over 3 days) on pain assessed by VAS before and 6 months after treatment. A statistically significant positive effect was found on pain after treatment (p=0.001). An improvement of more than 20 on the VAS scale was seen in 18 patients (40%). No safety data were published [11].

A randomized, placebo-controlled, double-blind clinical trial was performed including 50 patients treated with either Venital 50 mg/mL (single dose of 2 g/kg of body weight administered for 5 days) or a corresponding volume of placebo (0.9% NaCl). The primary efficacy endpoint was quality of life (SF-36 questionnaire PCS) after 2 months. Secondary endpoints included physical performance (6MWD) and pain (VAS) after 2 months. Change in SF-36 questionnaire PCS, the 6MWD and VAS for pain did not differ significantly between groups. However, statistically significant changes were found in SF-36 subscales (role physical and role emotional) between groups ($p<0.05$). In addition, data suggested that patients receiving IVIG reported a significant intragroup improvement in SF-36 questionnaire PCS ($p<0.05$). No safety data are available [12], [44].

A clinical, open-label, prospective study with randomization of 17 IVIG treated PPS patients to either muscular resistance training or to continue with "business as usual". The patients included had a clinically and a neurophysiological verified diagnosis of PPS, and were referred for IVIG

treatment. They were all able to walk for 6 minutes. The training programme was modified from a programme which earlier has shown a significant increase of muscle strength in PPS patients. Resistance training was performed with a physiotherapist 30-60 minutes per day, 3 days a week during 12 weeks. All patients were evaluated with the following instruments: muscle strength of the knee extensors and flexors measured with dynamic dynamometer and timed up & go test. Quality of life was evaluated with short-form SF-36 and EQ5D. Other measures used were The Physical Activity Scale for the elderly (PASE) and The Multidimensional Fatigue Inventory (MFI-20). The 6-minute walk test was also used with simultaneous registration of 3D movement analysis. The participants were evaluated before the treatment with IVIG and after the training session. Improved results were seen in the muscular resistance training group compared with the other group for General Health, SF-36 and General Fatigue, MFI-20 [45].

A study included 113 PPS patients who had received one IVIG treatment in a prospective open trial to evaluate the outcome of IVIG treatment in patients with PPS and to identify responders. Clinical examination was performed and clinical data were retrieved from medical records. The short form 36 (SF-36), PASE, and the VAS were used as measurements of quality of life, physical activity, and the intensity of pain. Data before treatment and at 6-month follow-up were collected. Analysis was performed in subgroups based on demographic and medical parameters. A statistically significant increase of the SF-36 sub domains bodily pain, vitality, social function, role emotional, and the mental compound score was found at the 6-month follow-up. A significant decrease of pain was found in patients who reported pain intensity over VAS of 20 mm, in patients younger than 65 years of age, and in patients who had paresis in the lower extremities. IVIG led to increase of quality of life at 6-month follow-up for SF-36 regarding sub domains of bodily pain, vitality, social function, and role emotional, as well as for pain. Age below 65 years, paresis in the lower extremities, and lack of concomitant disorders may be the main indicators for a future identification of responders [46].

A total of eleven patients, six men and five women, mean age 61 years (range 43-72 years), with established PPS diagnosis according to Halstead and Rossi, were included in an open-label study. All patients received IVIG Tegeline 0.4 mg/ kg per day, during five consecutive days every month for three to four months. Pain measured by VAS, muscle strength measured by manual testing and by quadriceps and hamstrings peak-torque using Con-Trex dynamometer, and walking performance analyzed by means of 6-minute-walk-test and 10-meters-walk speed, were noted before and after treatment. Eight patients (73%) improved significantly across all parameters, two patients (18%) felt an improvement without modification of clinical tests, and two (18%) had no change at all. The latter were the only patients who presented without any pain. One of them reported side effects with headaches, nausea, and transient cutaneous eruption [47].

With the objective to define and characterize responders and non-responders in a group of 124 patients with post-polio syndrome who received a single treatment with IVIG, a prospective open-label trial was conducted. Clinical examination and data from medical records was collected, SF-36, PASE and VAS measured quality of life, physical activity, and intensity of pain. Data were obtained before treatment and at 6-month follow-up. Two responder groups were identified with the outcome SF-36 Vitality and 3 with Bodily pain, respectively. Forty-five percent were positive-responders, identified before treatment by reduced physical function, muscle atrophy in the lower extremities, higher levels of fatigue and pain, and a VAS pain score above 20. Negative-responders were identified by good physical function and mental health, lesser muscle atrophy in the lower extremities, and low levels of fatigue and pain. The authors

concluded that IVIG is a biological intervention, and therefore it is important to be able to identify responders and non-responders. In order to maximise a positive outcome it was suggested that patients with a high level of fatigue and/or pain and reduced physical function are selected [48].

In addition, 3 case reports/case series articles that investigated the effects of IVIG in PPS have been published. One is a case series publication and two are single case report publications.

Thirteen PPS patients (5 male) were seen from June 2009 to March 2010. All underwent a complete physical examination including muscle testing and walking test (10 m test, 6 min test). Among these 13 patients, 10 also had isokinetic measurements of the lower limb. Two performed an exercise test. The isokinetic test was performed with a Con-Trex and concerned the quadriceps and hamstrings. The tests were in exocentric mode at 308/s and concentric mode at 30 and 1208/s, with passive continuous passive motion. The results were heterogeneous due to the wide range in force observed. Intra-patient reproducibility was less satisfactory at high speed. For eight patients, the isokinetic evaluation of the muscle force enabled an adjustment of the rehabilitation scheme. Three patients in this series were given immunoglobulin because of a severe post-polio syndrome. Improvement observed in clinical and instrumental tests was not significant [49].

A [redacted]-year-old [redacted] with a previous history of acute poliomyelitis developed progressive muscular weakness in [redacted] with muscular pain and fatigue. Clinical examination, magnetic resonance imaging (MRI), and electromyography gave no other explanation to [redacted] progressive muscular weakness and fatigue than PPS. [redacted] was treated with 400 mg/kg IVIG for five consecutive days. At follow-up two and three months later, [redacted] had a considerable increase in isokinetic muscle strength in knee extension and flexion on the [redacted] side, and experienced less fatigue [50].

Case report describing the case of a [redacted] years old, who contracted poliomyelitis in childhood with neurologic sequel (amyotrophy of legs). Subsequently, the patient developed a progressive erosive rheumatoid arthritis with rheumatoid factor positive and was treated with all the disease-modifying antirheumatic drugs and then, for ineffectiveness, with anti TNF-α (etanercept). After five years, the patient discontinued the use of etanercept, for ineffectiveness after initial benefit. The patient had worsening of neurological symptoms with the appearance of PPS which is characterized by new or progressive muscle weakness and disability occurring after the onset of acute poliomyelitis. The patient was treated with IVIG with an improvement of neurological symptoms and subsequently with abatacept for rheumatoid arthritis. In the active phase, Disease Activity Score (DAS) 28 = 5.4. After abatacept treatment, DAS 28 was reduced to 3.2 and obtained an improvement in the quality of life [51].

While these clinical trials provided some evidence of benefit from use of IVIG in PPS, they did not definitely demonstrate the clinical efficacy of IVIG in improving the disease symptoms. The existing studies should be interpreted according to their methodological limitations, in that they did not explore prolonged treatments or alternative efficacy endpoints. In addition, treatment efficacy in PPS is very difficult to establish due to the lack of suitable objective parameters to monitor the disease progression.

Limitation in walking activity, which is likely to affect level of independence and life satisfaction, is one of the most prominent problems of patients with PPS [52]. Walking capacity has been reported as an indicator of performance and activities of daily living in patients with

PPS [53]. Therefore, a therapeutic intervention should aim at increasing the walking ability (physical performance). In the present clinical trial, a walking test will be used as a surrogate marker for the evaluation of drug efficacy in the treatment of PPS subjects.

A wide range of walking tests has been used to measure walking capacity. The self-paced walking tests assess the submaximal level of functional capacity. Because most activities of daily living are performed at submaximal levels of exertion, self-paced walking tests may better reflect the functional exercise level for daily physical activities [54].

According to the previous experience of investigators directly involved in those trials where 6MWD was performed, it is anticipated that a number of PPS patients will not be able to complete a 6MWD, thereby introducing selection bias [55]. Consequently, the 2MWD, at self-preferred speed, has been selected as the appropriate walking test for this study. The 2MWD measures the distance that a patient can walk at self-preferred speed on an indoor 50-m track for 2 minutes [21]. The 2MWD has been validated in 2 different ways in this patient population: first, it is highly correlated with the SF-36 questionnaire PCS [21]; and, second, with walking activity in daily life (pedometer) [53]. It has excellent test-retest reliability and the smallest detectable change in walking performance at the individual level (15%) [56] which is better than that obtained by strength measurements using a fixed dynamometer (25%) [57] or a hand-held dynamometer (24%) [56]. Moreover, in a randomized placebo-controlled trial performed using pyridostigmine in PPS, a statistically significant ($p<0.01$) positive effect on the 2MWD (secondary efficacy endpoint) in favor of the pyridostigmine group was found. In this trial, there was no statistically significant change in quadriceps strength between groups [36], further reinforcing the selection of 2MWD.

Based on the results from published clinical trials on IVIG use in PPS [8-12], the VAS for pain and the SF-36 questionnaire PCS have been selected as secondary efficacy endpoints.

Pain is one of the most common complaints in patients with PPS; it affects quality of life and interferes with daily life. One of the most widely used pain rating scale is the VAS for pain.

Health-related quality of life is important when patients remain severely disabled, as it occurs to subjects suffering from PPS. Consequently, a self-reported improvement of the patient may demonstrate a benefit on disease progression. Currently there is no specific health-related quality of life questionnaire for PPS. The SF-36 questionnaire is one of the most widely used and evaluated generic health-related quality of life. Specifically, the SF-36 questionnaire PCS reflects limitations in self-care, physical, social and role activities as well as body pain, tiredness and general health. The reliability of SF-36 questionnaire PCS in PPS is good [55].

3 TRIAL OBJECTIVES AND PURPOSES

The purpose of this study is to test whether monthly infusions (every 4 weeks) of intravenous Flebogamma® 5% DIF in a 1-year treatment period in PPS subjects are superior to placebo by assessing physical performance, as measured by 2MWD.

Particularly, the Stage 1 primary efficacy objective is to select the optimal dose of IVIG. The Stage 2 primary efficacy objective is to establish superiority of the selected Stage 1 dose of IVIG as compared to placebo by combining both Stage 1 and Stage 2 data. Both primary efficacy objectives will be evaluated by assessing physical performance, as measured by 2MWD, compared to that of placebo.

Secondary efficacy objectives of Stage 1 and 2 are:

- To evaluate clinical effect of Flebogamma® 5% DIF in PPS subjects by assessing pain, as measured by VAS of pain, compared to that of placebo.
- To evaluate clinical effect of Flebogamma® 5% DIF in PPS subjects by evaluating health-related quality of life (HRQoL), as measured by SF-36 PCS, compared to that of placebo.
- To evaluate clinical effect of Flebogamma® 5% DIF in PPS subjects by assessing endurance, as measured by 6MWD, compared to that of placebo.

The safety objective is to assess safety of Flebogamma® 5% DIF, administered as every 4 weeks intravenous infusions, over a period of 52 weeks.

4 TRIAL DESIGN

4.1 Primary and secondary endpoints

Primary efficacy endpoint will be:

- Physical performance (2MWD) from baseline to the end of the treatment period (at End of Treatment Visit –Week 52).

Secondary efficacy endpoints will be:

- Pain (VAS of pain) from baseline to the end of the treatment period.
- HRQoL (SF-36 PCS) from baseline to the end of the treatment period.
- Endurance (6MWD) from baseline to the end of the treatment period.

Safety endpoints will include adverse events (AEs), vital signs during infusions, physical assessments and blood tests for clinical safety.

4.2 Description of the design of the trial to be conducted and a schematic diagram of trial design, procedures and stages

This is a phase II/III multi-centre, prospective, randomized, placebo-controlled, double-blind, parallel-group clinical trial with an adaptive design (flexible group sequential design with adaptive dose selection) in subjects with PPS.

This study will consist of 2 stages (Figure 1). The first stage (Stage 1) is for dose selection (Figure 2), and the second stage (Stage 2) is to establish the superiority (efficacy confirmation) of Flebogamma® 5% DIF (Figure 3) in the change in physical performance (2MWD) as compared to the placebo and for overall safety analysis, by combining the data from both stages, in PPS subjects.

Stage 1 will be a 3-arm evaluation of 2 active dose levels of Flebogamma® 5% DIF (IVIG 1 g/kg and 2 g/kg of body weight) and placebo randomized in a 1:1:1 ratio. At the end of Stage 1 (after at least 80% of the randomized subjects have finished the treatment period of Stage 1), a formal unblinded interim analysis will be performed by an independent Data Monitoring Committee (DMC). Based on a set of predefined criteria, 1 of the 2 active treatment groups will be selected

to continue to Stage 2 of the clinical trial. Subsequently, at Stage 2, a separate cohort of subjects will be randomized to receive either the selected dose from Stage 1 or placebo in a 1:1 ratio for efficacy confirmation and overall safety analysis. During both stages of the study, randomization will be stratified by the main part of the body most significantly affected by PPS, that is, lower extremities or upper extremities.

A difference in distance walked within 2 minutes has been considered a clinically meaningful endpoint directly relating to progression of PPS since walking capacity has been reported as an indicator of performance of daily living in these patients [43].

In this study, a clinically relevant difference in change from baseline in distance walked to the end of the treatment period (at End of Treatment Visit [EoTV] – Week 52) between groups (for Stage 1, Flebogamma® 5% DIF 1 g/kg and 2 g/kg of body weight versus placebo and, for Stage 2, the selected dose of Flebogamma® 5% DIF versus placebo) has been stated to be 5%, based on the intrinsic characteristics of the disease, that is, a chronic and slowly progressive condition with an average overall decline in 2MWD of 0.9%/year [53].

Secondary efficacy endpoints also considered clinically meaningful for assessment of progression of PPS symptoms will include the change from baseline in pain (by VAS for pain), in HRQoL (by SF-36 PCS), and in endurance (by 6MWD).

In addition, exploratory endpoints to study the treatment effect of Flebogamma® 5% compared to placebo include muscle strength (by manual muscle strength testing [MMT] using the Medical Research Council (MRC) scale and by quantitative muscle strength testing [QMT] using a dynamometer), walking activity in daily life (by pedometer), self-perceived exertion/fatigue (measured using the Borg scale), fatigue (FSS), HRQoL (by SF-36 Mental Component Summary [MCS]), and blood inflammatory cytokines. Moreover, the sustainability of treatment effect will be assessed 12 and/or 24 weeks after the end of study drug treatment as exploratory outcomes.

The present study has been designed as an adaptive clinical trial (flexible group sequential design with adaptive dose selection) in order to streamline clinical development from phase II to phase III. Both dose selection (Stage 1) and confirmation of treatment efficacy/overall safety analysis (Stage 2) are under a single protocol, and data from both stages are appropriately used in the final analysis [59-61]. An adaptive design combines into a single trial objective traditionally addressed in separate trials, and, therefore, reduces the lead time between phases. An adaptive design allows data from the learning phase (Stage 1) to be combined with data from the confirmation phase (Stage 2) suggesting that such a design could be able to draw stronger conclusions with the same or less number of exposed patients. To that effect, the inclusion of a control (placebo) is crucial to allow results from Stage 1 to be pooled with the data in the Stage 2. Alternatively, a smaller sample size may be required to provide the same strength of conclusions as in the standard paradigm.

Safety data will be added to the current safety data set already available for Flebogamma® 5% DIF, which comes from previous clinical trials and from post-licensure safety surveillance.

Study subjects will randomly be allocated to receive every 4 weeks infusions of either Flebogamma® 5% DIF (2 dose levels at Stage 1 and 1 dose level at Stage 2) or the equivalent volume of Normal Saline Solution (placebo), over a treatment period of 52 weeks. After the treatment period, a 24-week follow-up period is planned before subject's termination of his/her participation in the clinical trial (at the Final Visit [FV]).

The clinical trial will be performed at different sites in Europe, Canada, and the US. It is planned to randomize approximately 210 subjects in total (126 in Stage 1 and 84 in Stage 2) in the study.

After giving informed consent to participate in the clinical trial (*Clinical Trial Written Informed Consent Form*), subjects will be assigned a 7-digit subject number by the IWRS and will be examined during the screening period to assess their eligibility for inclusion in the clinical trial. The Investigator will determine whether or not a subject qualifies for inclusion in the clinical trial based on study inclusion and exclusion criteria (Sections 6.1 and 6.2). Eligible individuals will be randomized by the IWRS to one of the treatment arms according to the assigned 5-digit randomization number. The unblinded pharmacist or designee will be responsible for treatment assignment based upon the randomization number for each eligible individual from the IWRS.

Throughout the course of the clinical trial, clinical visits (or telephone contacts) will be scheduled. Study assessments will include physical assessments, infusion vital signs monitoring, blood analysis, walking activity in daily life evaluation, muscle strength measurements, assessments of HRQoL, pain and fatigue, and recording of AEs and concomitant medication.

Individuals are allowed to attend the study centre at any time during the study. If a subject is prematurely withdrawn from the study, he or she will be asked to attend the study centre as soon as possible thereafter so that end of study assessments can be conducted.

Figure 1. Schematic description of clinical trial design

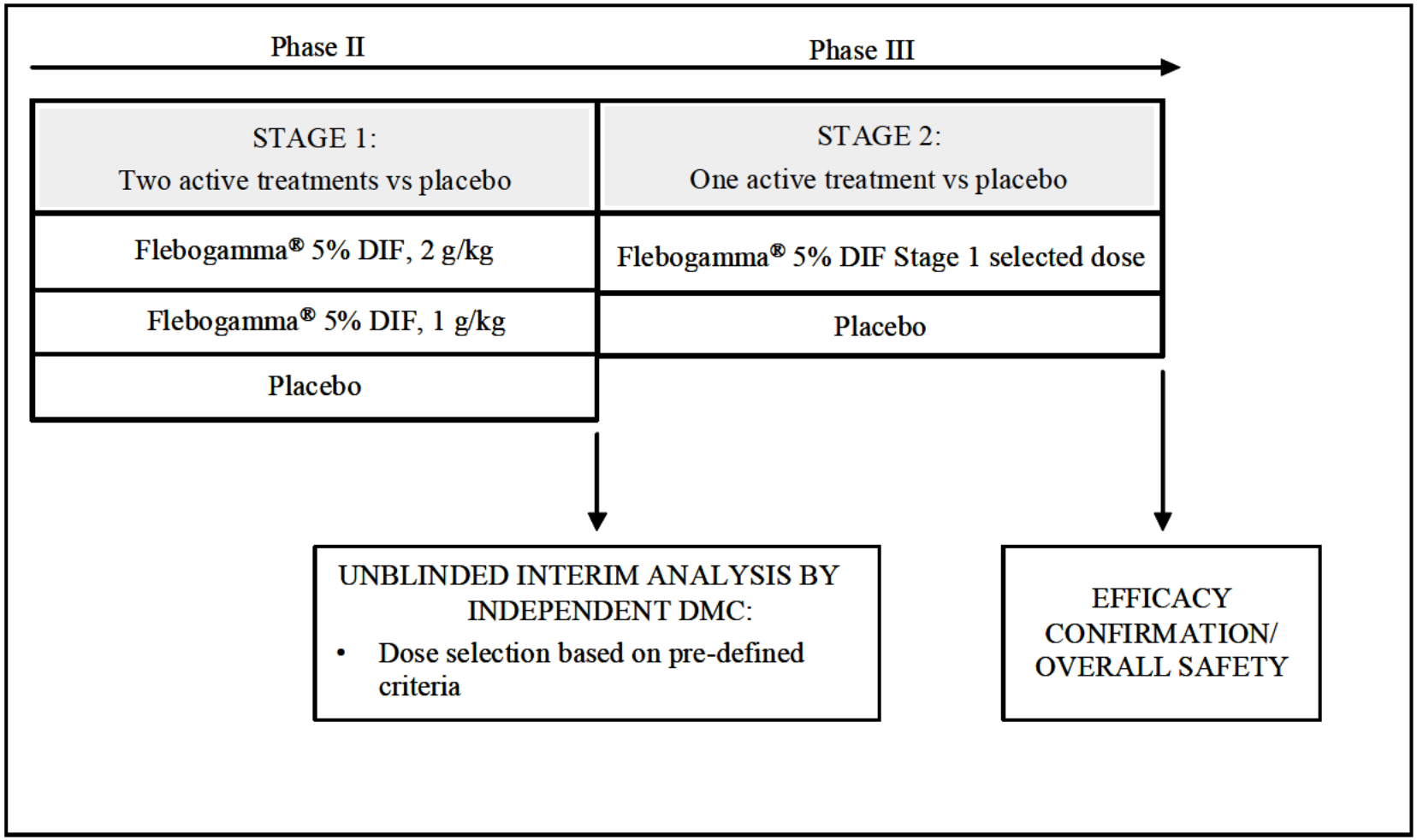
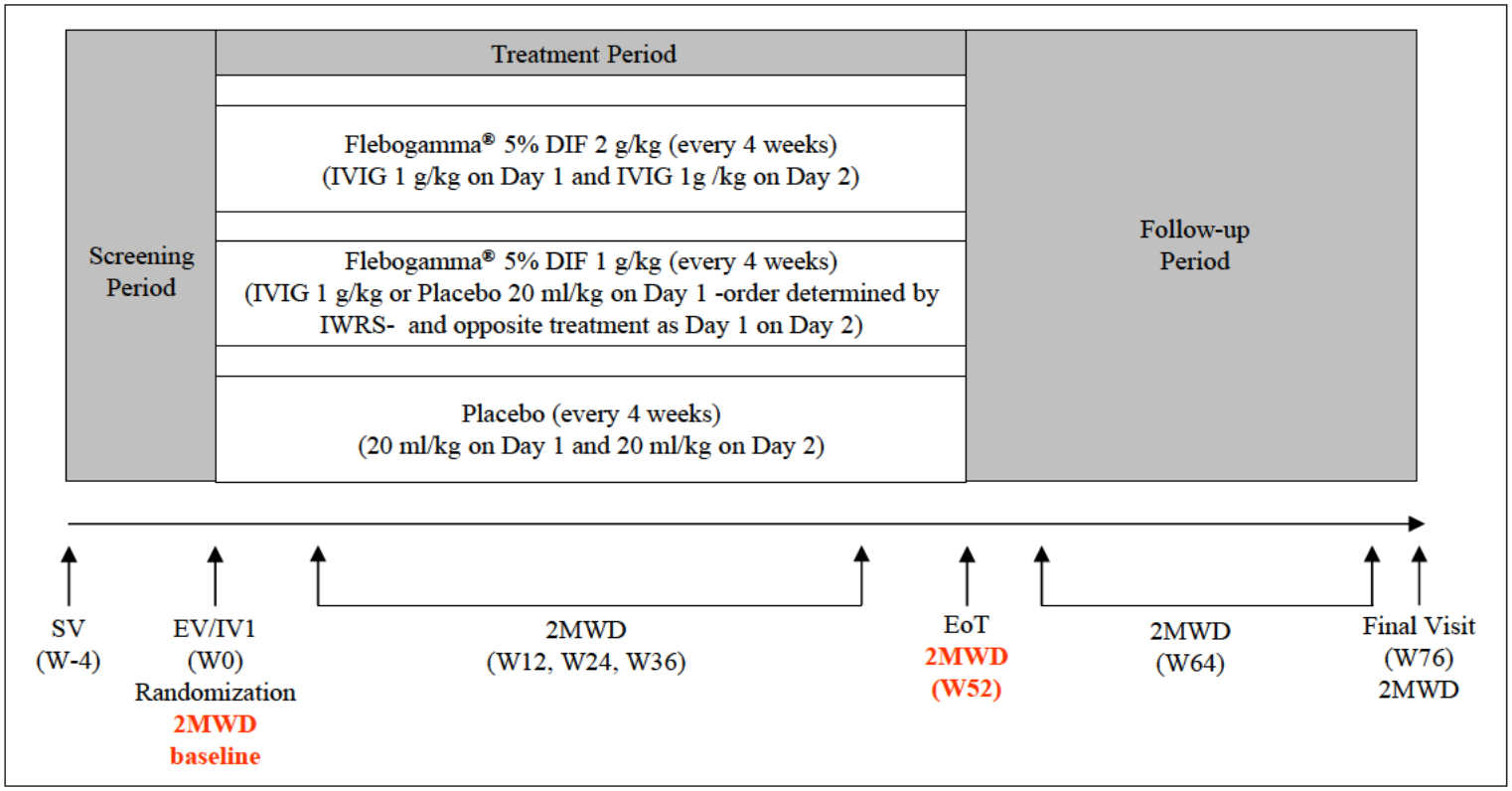
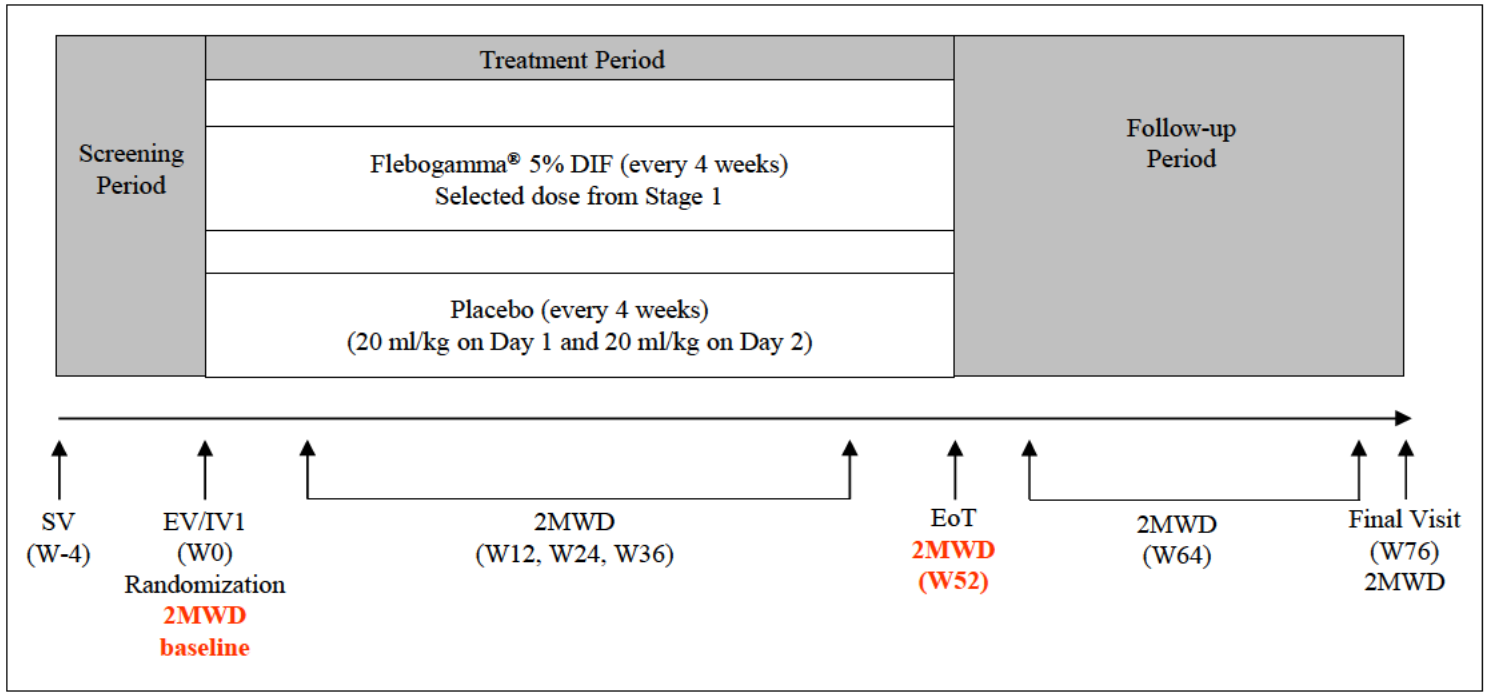


Figure 2. Schematic description of Stage 1 clinical trial design



Abbreviations: 2MWD: Two-Minute Walk Distance; EoTV: End of Treatment Visit; EV: Enrollment Visit; IV: Infusion Visit; SV: Screening Visit; W: Week.

Figure 3. Schematic description of Stage 2 clinical trial design



Abbreviations: 2MWD: Two-Minute Walk Distance; EoTV: End of Treatment Visit; EV: Enrollment Visit; IV: Infusion Visit; SV: Screening Visit; W: Week.

4.3 Measures to minimize/avoid bias

4.3.1 Randomization

It is planned to randomize approximately 210 subjects total (126 in Stage 1 and 84 in Stage 2) in the study.

At Stage 1, each study subject will randomly be allocated by the IWRS, at a ratio of 1:1:1, to receive every 4 weeks infusions of either IVIG 1 g/kg, IVIG 2 g/kg, or the equivalent volume of Normal Saline Solution (placebo) over a treatment period of 52 weeks. After the treatment period, a 24-week follow-up period is planned before the subject completes his/her participation in the clinical trial at the FV (Figure 2).

At Stage 2, each study subject will randomly be allocated by the IWRS, at a ratio of 1:1, to receive every 4 weeks infusions of either the selected dose of IVIG from Stage 1, or the equivalent volume of Normal Saline Solution (placebo), over a treatment period of 52 weeks. After the treatment period, a 24-week follow-up period is planned before the subject completes his/her participation in the clinical trial at the FV (Figure 3).

A 5-digit randomization number will be assigned to each subject in addition to the 7-digit subject number previously assigned by the IWRS. The randomization number will be assigned at the Enrollment Visit (EV)/Infusion Visit (IV) 1 (*i.e.* EV/IV1) at Week 0.

Additional details are located in the study file at each site and, if applicable, the local healthcare professional or agency designated pharmacy.

4.3.1.1 Stratification of randomization

Subject randomization will be stratified in 2 strata: upper extremities or lower extremities. Stratification will be based upon whether the lower extremities versus the upper extremities are considered by the principal investigator or designee subinvestigator to be the more significantly affected part of the body by PPS as assessed by physical examination at the SV (Section 4.5.2.2).

4.3.2 Blinding

This is a double-blind clinical trial. For the entire clinical trial period, participating subjects, Investigators, study staff (subinvestigators, nurses, technicians, personnel involved in the administration of the investigational product, and other personnel) and testing laboratories will be blinded to the treatment group and the identity of solutions for infusion (test or placebo). Moreover, anyone from the sponsor (with the exception of the unblinded sponsor's clinical trial materials and drug safety staff) or CRO who will be involved in site monitoring will also be blinded regarding each subject's treatment group.

Unblinded personnel will be limited to:

- People responsible for creation of the randomization list who are independent of the study conduct.
- Site pharmacists or designees responsible for preparing and blinding the investigational products.
- The independent DMC for interim analysis.
- Unblinded sponsor's clinical trial materials personnel responsible for drug supply logistics

[redacted]

In order to address potential unblinding due to possible predictable side effects of the active product and product appearance, the following approaches will be employed:

- Pre-medication will be administered for subjects in all treatment arms and on both days of infusion to reduce the side effects of IVIG (see Section 7.2),
- All subjects will receive the same total dose volume (calculated to be equivalent to 2 g/kg Flebogamma® 5% DIF volume) for all treatments,
- Intravenous solution bags containing the investigational product solutions (test or placebo) will be covered with non-transparent sleeves,
- Connection between intravenous bag and intravenous line will be performed by unblinded staff to maintain the blind,
- Translucent or coloured lines will be used to maintain blind of the infusion system during the administration of the investigational product, and
- An independent assessor (neurologist or qualified personnel who will only have access to the efficacy data) will perform the evaluation of the efficacy endpoints. The independent assessor will not have any access to safety or AE data.

Except in the circumstances detailed in Section 5.6, the randomization code will not be broken until data entry is completed, validity of data is checked, all queries are resolved, each subject's populations for statistical analysis is agreed, and the database is locked.

4.4 Description of the investigational products

4.4.1 Investigational products identification

4.4.1.1 Investigational product (test): Flebogamma® 5% DIF

Drug name:	Flebogamma® 5% DIF.
ATC code:	J06BA 02.
Active principle:	Human intravenous immune globulin.
Pharmaceutical form:	Vials containing a liquid presentation of Flebogamma® 5% DIF.
Manufacture and marketing authorization holder:	Instituto Grifols, S.A. Can Guasch, 2. 08150 Parets del Vallès. Barcelona (SPAIN).

4.4.1.2 Investigational product (placebo): Normal Saline Solution

Drug name:	Normal Saline Solution.
ATC code:	B05BB 01.
Active principle:	Sodium chloride 9 g/L.
Pharmaceutical form:	Vials containing Normal Saline Solution.
Manufacture and marketing authorization holder:	Sourced locally by study sites, thus will have marketing authorization in the country of use.

4.4.2 Dosage and dosage regimen of the investigational products

4.4.2.1 Dosage of investigational product (test): Flebogamma® 5% DIF

Dosage and regimen:	2 g/kg body weight administered over 2 consecutive days (1 g/kg infused on Day 1 and 1 g/kg infused on Day 2). 1 g/kg body weight administered on 1 day (Day 1 or Day 2) (if randomized to IVIG 1 g/kg arm)
Administration via:	Intravenously.
Administration form:	Investigational product will be prepared and administered per Pharmacy Manual.

4.4.2.2 Dosage of investigational product (placebo): Normal Saline Solution

Dosage and regimen:	40 mL/kg body weight administered over 2 consecutive days (20 mL/kg on Day 1 and 20 mL/kg on Day 2) 20 mL/kg body weight administered on 1 day (Day 1 or Day 2) (if randomized to IVIG 1 g/kg arm)
Administration via:	Intravenously.
Administration form:	Investigational product will be prepared and administered per Pharmacy Manual.

4.4.2.3 Dosage regimen of investigational product (test and placebo)

At Stage 1, Flebogamma® 5% DIF at a dosage of 2 g/kg body weight (IVIG 2 g/kg arm), Flebogamma® 5% DIF at a dosage of 1 g/kg body weight (IVIG 1g/kg arm), and Normal Saline Solution (placebo) will be administered every 4 weeks, with each dose being

administered over a dosing period of 2 consecutive days (Day 1 and Day 2) up to 13 infusions visits, that is, 26 intravenous infusions.

For the purpose of maintaining the treatment blind, the volume of each administration of investigational product in the IVIG 1 g/kg and placebo arms will be equivalent to that for the IVIG 2 g/kg arm so that all subjects receive the same total dose volume for all treatment arms. The total volume for each dose of investigational product will be administered over 2 consecutive days as follows:

- IVIG 2 g/kg arm - A total dose of 2 g/kg of body weight of Flebogamma® 5% DIF will be administered over 2 consecutive days.
- IVIG 1 g/kg arm - A total dose of 1 g/kg of body weight of Flebogamma® 5% DIF will be administered on 1 day, and a total dose of 20 mL/kg of body weight Normal Saline Solution (equivalent volume of 1 g/kg of body weight Flebogamma® 5% DIF infusions) will be administered on a separate day, for a total dosing period of 2 consecutive days. The order of 1 g/kg of body weight of Flebogamma® 5% DIF or 20 mL/kg of body weight Normal Saline Solution infused on 2 consecutive days will be randomly determined for each subject by the IWRS, which will remain the same for the subject for all infusion visits during the treatment period.
- Placebo arm - A total dose of 40 mL/kg of body weight Normal Saline Solution (equivalent volume of 2 g/kg of body weight Flebogamma® 5% DIF infusions) will be administered over 2 consecutive days.

Randomized Treatment Assignment	Day 1 (Day 1 Dose per IWRS Randomization list)	Day 2 (Day 2 Dose per IWRS Randomization list)
IVIG 2 g/kg	1g/kg Flebogamma® 5% DIF	1g/kg Flebogamma® 5% DIF
IVIG 1 g/kg	1g/kg Flebogamma® 5% DIF OR 20 mL/kg Normal Saline as determined by the IWRS (the opposite treatment as Day 2)	1g/kg Flebogamma® 5% DIF OR 20 mL/kg Normal Saline as determined by the IWRS (the opposite treatment as Day 1)
Placebo	20 mL/kg Normal Saline	20 mL/kg Normal Saline

At Stage 2, Flebogamma® 5% DIF at the selected dosage from Stage 1 and Normal Saline Solution (placebo) will be administered every 4 weeks, with each dose being administered over a 2-day dosing period. During Stage 2, the selected dose of Flebogamma® 5% DIF and Normal Saline Solution (placebo) will be administered over 2 days in the same manner as in Stage 1, including administering the total dose for both treatment arms at a volume equivalent to that for the IVIG 2 g/kg arm, regardless of the selected dose.

The unblinded pharmacist or designee will be responsible for preparing and blinding the investigational product (test or placebo) at each scheduled administration.

Only blinded study staff will administer the investigational product. Dosing, including infusion volumes, will be registered in the *electronic Case Report Form (eCRF)* by the study staff and will be available for monitors to verify compliance.

All doses after the first infusion will be administered every 4 weeks with a window period of ± 1 week.

4.4.3 Packaging and labeling of the investigational products

4.4.3.1 Investigational product (test): Flebogamma® 5% DIF

Instituto Grifols, S.A., will supply Flebogamma® 5% DIF free of charge. Flebogamma® 5% DIF will be supplied in type II glass vials containing a liquid presentation of human intravenous immune globulin for Flebogamma® 5% DIF.

Flebogamma® 5% DIF supplies will be appropriately packaged and labeled. A label sample is annexed to the clinical trial protocol (ANNEX 3). Labels will be translated into local languages.

4.4.3.2 Investigational product (placebo): Normal Saline Solution

Normal Saline Solution (9 g/L sodium chloride) is commercially available and will be sourced locally by the study sites and therefore will have marketing authorization in the country of use.

4.4.4 Storage, preparation, dispensation and administration of the investigational products

Details regarding the storage, preparation, dispensation, and administration of the investigational products are provide in the study Pharmacy Manual.

4.4.4.1 Storage and preparation of the investigational product (test): Flebogamma® 5% DIF

The unblinded pharmacist or designee will be responsible for storage, preparation and blinding of the investigational product (Flebogamma® 5% DIF).

Flebogamma® 5% DIF storage:

Unopened Flebogamma® 5% DIF vials must be stored at +2 to +25ºC (+35.6ºF to +77ºF) and must not be frozen. It must not be used after the expiry date stated on the label. Flebogamma® 5% DIF must be kept in a secure room with access restricted to necessary study site personnel. The pharmacist or designee must keep the investigational product accountability by means of *the IWRS Drug Accountability Log*. Reference the Pharmacy Manual for additional information on investigation product accountability.

Flebogamma® 5% DIF solution preparation:

Flebogamma® 5% DIF solution will be prepared according to detailed instructions included in the SPC (ANNEX 2) and the study Pharmacy Manual.

Maximum asepsis must be kept when preparing Flebogamma® 5% DIF solution. It is highly recommended that if large doses are to be administered, several vials from the same batch of Flebogamma® 5% DIF may be pooled into an empty transparent sterile intravenous solution container (infusion bag) by using aseptic technique, preferably in laminar-flow cabins. Unblinded pharmacist or designee should inspect the solution visually for particulate matter

and color prior to solution preparation. If particles are detected or it is turbid, the vial should not be used. Any vial that has been entered should be used promptly. Because the solution contains no preservative, **Flebogamma® 5% DIF should be infused as soon as possible**.

The infusion bag will be covered with a non-transparent bag to blind the content of the intravenous bag. This non-transparent bag will be labeled with the clinical trial code, the patient code, the volume of solution to be infused, and additional details per the Pharmacy Manual.

The unblinded pharmacist or designee must complete a preparation register for every preparation of Flebogamma® 5% DIF solution in the IWRS. This register must be kept confidential during the clinical trial.

In case of refrigerated solutions, they must be brought to room temperature before infusion.

IMPORTANT:

The removable part of the labels of investigational products, used to prepare the Flebogamma® 5% DIF solution, should be stuck on the appropriate form in the Pharmacy Manual for accountability reconciliation by the clinical monitor before being destroyed.

4.4.4.2 Storage and preparation of the investigational product (placebo): Normal Saline Solution

The unblinded pharmacist or designee will be responsible for storage, preparation and blinding of the investigational product (Normal Saline Solution).

Normal Saline Solution storage:

Normal Saline Solution does not need special storage conditions. Do not use after the expiry date stated on the label. It must be kept in a secure room with access restricted to necessary study site personnel. The unblinded pharmacist or designee must keep the investigational product accountability by means of the IWRS and the Pharmacy Manual.

Normal Saline Solution preparation:

Normal Saline Solution should be prepared according to detailed instructions included in the Pharmacy Manual.

Maximum asepsis must be kept when preparing Normal Saline Solution. Once the container has been opened, the product must be transferred immediately. Unused contents must be discarded. It is highly recommended that Normal Saline Solution will be transferred into a transparent and sterile intravenous solution container (intravenous bag) by using aseptic technique, preferably in laminar-flow cabins. The unblinded pharmacist or designee must ensure that the prepared Normal Saline Solution is clear and without precipitates. Otherwise, the solution must not be administered.

The infusion bag will be covered with a non-transparent bag to blind the content of the intravenous bag. This non-transparent bag will be labeled with the clinical trial code, the patient code and the volume of solution to infuse, and additional details per the Pharmacy Manual.

As a rule, Normal Saline Solution should be administered intravenously as soon as possible after the solution transfer.

The unblinded pharmacist or designee must complete a preparation register for every preparation of Normal Saline Solution in the IWRS. This register must be kept confidential during the clinical trial.

In case of refrigerated solutions, they must be brought to room temperature before infusion.

4.4.4.3 Dispensation and administration of the investigational product (test and placebo)

The unblinded pharmacist or designee will be responsible for dispensation of the investigational product (test and placebo).

Investigational product (test and placebo) dispensation:

The unblinded pharmacist or designee will serve, attending to Investigator requests, the investigational product (test or placebo). The unblinded pharmacist or designee responsible for serving the investigational product must log into the IWRS to obtain the randomized treatment assignment for each subject preparation and dispensing.

Investigational product (test and placebo) administration:

To attenuate infusion-related events and to maintain blinding, all subjects will be pre-medicated 30-60 minutes prior to each investigational product infusion with 975-1000 mg of acetaminophen and 20-25 mg of diphenhydramine (or the equivalent dose of the available antihistaminic drug) provided the subject has no known previous history of allergies to these medications. Use of the following drugs as pre-infusion medication for the investigational product administration is not allowed: acetyl salicylic acid (ASA; e.g., aspirin), non-steroidal anti-inflammatory drugs (NSAIDS), or corticosteroids (except for inhaled corticosteroids taken for asthma which will be allowed on-demand).

The investigational product must be at room temperature prior to intravenous administration. An in-line filter with a pore size of 15 to 20 microns is recommended for the infusion. Antibacterial filters (0.2 micron) may also be used; although, they may slow infusions. Blinded study staff will administer the investigational product (test or placebo), keeping maximum asepsis, at the investigational site facilities. Administration of investigational product outside of the investigational site facilities, e.g., at the subject's home or at an outpatient clinic, is not allowed. They must also complete an administration register in order to check treatment compliance in the eCRF.

Flebogamma® 5% DIF administered at a dosage of 2 g/kg body weight (IVIG 2 g/kg arm) will be infused over 2 consecutive days with a maximum of Flebogamma® 5% DIF 1 g/kg/day (Table 2).

Flebogamma® 5% DIF administered at a dosage of 1 g/kg body weight (IVIG 1 g/kg arm) will be infused on 1 day with a maximum of Flebogamma® 5% DIF 1 g/kg/day (Table 3). To maintain the blind, a total dose of 20 mL/kg of body weight Normal Saline Solution (equivalent volume of 1 g/kg of body weight Flebogamma® 5% DIF infusions) will also be administered on a separate day (Table 4), for a total dosing period of 2 consecutive days. The order of 1 g/kg of body weight of Flebogamma® 5% DIF or 20 mL/kg of body weight

Normal Saline Solution infused on 2 consecutive days will be randomly determined for each subject by the IWRS, which will remain the same for the subject for all infusion visits during the treatment period.

Normal Saline Solution administered at a dosage of 40 mL/kg body weight (placebo arm) will be infused over 2 consecutive days with a maximum of 20 mL/kg of body weight/day (Table 5).

Table 2. Summary of IVIG 2 g/kg arm's dose to be administered according to body weight

Body weight	Flebogamma® 5% DIF (2 g/kg body weight)		Maximum daily dose (mL) of Flebogamma® 5% DIF (20 mL/kg body weight/day)
	IVIG (g)	IVIG (mL)	
40 kg	80 g	1600 mL	800 mL
50 kg	100 g	2000 mL	1000 mL
60 kg	120 g	2400 mL	1200 mL
70 kg	140 g	2800 mL	1400 mL
80 kg	160 g	3200 mL	1600 mL
90 kg	180 g	3600 mL	1800 mL
100 kg	200 g	4000 mL	2000 mL
110 kg	220 g	4400 mL	2200 mL

Table 3. Summary of IVIG 1 g/kg arm's dose of Flebogamma® 5% DIF to be administered according to body weight

Body weight	Flebogamma® 5% DIF (1 g/kg body weight)		Maximum daily dose (mL) of Flebogamma® 5% DIF (20 mL/kg body weight/day)
	IVIG (g)	IVIG (mL)	
40 kg	40 g	800 mL	800 mL
50 kg	50 g	1000 mL	1000 mL
60 kg	60 g	1200 mL	1200 mL
70 kg	70 g	1400 mL	1400 mL
80 kg	80 g	1600 mL	1600 mL
90 kg	90 g	1800 mL	1800 mL
100 kg	100 g	2000 mL	2000 mL
110 kg	110 g	2200 mL	2200 mL

Table 4. Summary of IVIG 1 g/kg arm's dose of normal saline solution to be administered according to body weight

Body weight	Normal Saline Solution (20 mL/kg body weight)	Maximum daily dose (mL) of Normal Saline Solution (20 mL/kg body weight/day)
40 kg	800 mL	800 mL
50 kg	1000 mL	1000 mL
60 kg	1200 mL	1200 mL
70 kg	1400 mL	1400 mL
80 kg	1600 mL	1600 mL
90 kg	1800 mL	1800 mL
100 kg	2000 mL	2000 mL
110 kg	2200 mL	2200 mL

Table 5. Summary of placebo dose to be administered according to body weight

Body weight	Normal Saline Solution (40 mL/kg body weight)	Maximum daily dose (mL) of Normal Saline Solution (20 mL/kg body weight/day)
40 kg	1600 mL	800 mL
50 kg	2000 mL	1000 mL
60 kg	2400 mL	1200 mL
70 kg	2800 mL	1400 mL
80 kg	3200 mL	1600 mL
90 kg	3600 mL	1800 mL
100 kg	4000 mL	2000 mL
110 kg	4400 mL	2200 mL

During all treatment infusions, subject's vital signs, that is body temperature (T), respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), will be monitored and recorded as follows: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

Investigational products (test and placebo) will be administered intravenously at an initial rate of 0.01 mL/kg/min for the first thirty minutes. If tolerated, advance to 0.02 mL/kg/min for the second 30 minutes. Again, if tolerated, advance to 0.04 mL/kg/min for the third 30 minutes. If the patient tolerates the infusion well, additional increments of 0.02 mL/kg/min may be made at 30-minute intervals up to a maximum of 0.08 mL/kg/min.

Individuals with predisposition to acute renal failure (such as age greater than 65 years, pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products), their renal function will be assessed by means of the glomerular filtration rate (GFR) at scheduled visits (see Section 4.5.2.7). Subjects with predisposition to acute renal failure but normal GFR will be infused as indicated in the

previous paragraph. Subjects with predisposition to acute renal failure and abnormal GFR will be infused at the minimum practicable rate. Do not exceed the recommended dose and administer IGIV3I Grifols 5% at the minimum dose and infusion rate practicable and at less than 0.06 mL/kg/minute (3 mg/kg/minute).

The rate of infusion should be controlled by means of an infusion pump.

If an infusional AE (see Section 4.5.2.24) occurs during the first treatment course, the study staff will initiate 1 of the following actions which will be graded from 1 to 5 depending on the nature and/or severity of the event:

1. Does not modify the rate of the infusion upon evaluation; or
2. Staff reduces the current infusion rate to one-half the rate of the infusion at which the AE was observed; or
3. Staff progressively reduces the rate of the infusion more than one-half the rate at which the AE was observed, as necessary to subside symptoms; or
4. Staff reduces the rate of the infusion to one-half, or progressively reduces more than one-half the rate at which the AE was observed, and then stops the infusion, as necessary to subside symptoms; or
5. Staff directly stops the infusion to subside symptoms.

The study staff will evaluate the subject's AE and then:

- Will increase or resume the infusion at a rate tolerated by the subject once the symptoms have been subsided; or
- Will stop the infusion and not resume it.

To resume the infusion, the mandatory infusion rate titration schedule must be followed. To increase the infusion rate, the initial increment must be of 0.01 mL/kg/minute for 30 minutes. If well tolerated (no infusional AE occurs), additional increments of 0.02 mL/kg/minute must be made at 30-minute intervals up to a maximum rate of 0.08 mL/kg/minute.

If a subject has an infusional AE at the same infusion rate twice, then subsequent infusion escalations, if any, should be halted at the previously highest tolerated rate.

Infusional AEs (*i.e.*, AEs temporally associated with an infusion of the investigational product) may include, but are not limited to: headache, fever, chills, shaking, fatigue, malaise, muscle cramps, abdominal cramps, back pain, abdominal pain, blood pressure changes, tachycardia, palpitations, chest tightness, nausea, vomiting, diarrhea, cutaneous reactions, rash, edema, flushing, infusion site reaction, wheezing, arthralgia, anaphylactic reaction, non-cardiogenic pulmonary edema (transfusion-related acute lung injury), thrombo-embolic events, renal failure, hemolysis and blood hyperviscosity.

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured.

4.5 Expected duration of subject's participation and description of the sequence and duration of all trial periods

The total duration of a subject's participation for subjects who complete the study will be approximately 80 weeks. Individuals will finish their clinical trial participation with the FV (Week 76).

Each stage of the clinical trial will consist of the following periods:

1. Screening period (up to 4 weeks).
2. Treatment period (52 weeks).
3. Follow-up period (24 weeks).

Clinical trial finalization will coincide with the last visit of the last subject included in the study.

4.5.1 Clinical trial flow chart

Table 6 provides a summary of all proceedings and evaluations to be carried out during the clinical trial.

Table 6. Schedule of assessments, procedures and treatment

	Screening Period	Treatment Period [b]													Follow-Up Period [b]					
	SV	EV/ IV1[c]	IV2	IV3	IV4	IV5	IV6	IV7 [c]	IV8	IV9	IV10	IV11	IV12	IV13	EoTV [c]	FU1	FU2	FU3	FU4	FU5	FV/ EDV[c]
Event & Activity [a]	w-4 to -1	w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56	w60	w64	w68	w72	w76
Clinical Trial Written ICF	X																				
Incl/Excl Criteria	X	X																			
Medical History	X																				
Physical Assessment	X [d]	X			X			X [d]			X				X [d]			X			X [d]
Height	X																				
Weight	X	X			X			X			X										
General Health Assessment [e]	X																				
Blood or Urine Pregnancy Test	X																				
Blood Biochemistry and Cell Counts	X	X			X			X			X				X			X			X
Blood IgA level and IgA antibodies (only if IgA levels are below normal range)	X																				
Blood assessments (for general health, immunologic function, and viral exposure)	X																				
Retention blood sample for possible viral exposure testing		X												X							
Retention blood sample for possible future biomarker testing		X													X						X
Blood inflammatory cytokines		X													X						X
Walking Activity in Daily Life (Pedometer)		X													X						X
FSS		X													X						X
SF-36		X			X			X			X				X			X			X
VAS for Pain		X			X			X			X				X			X			X
Borg scale [f]	X	X			X			X			X				X			X			X

Event & Activity [a]	Screening Period	Treatment Period [b]													Follow-Up Period [b]					
	SV	EV/ IV1[c]	IV2	IV3	IV4	IV5	IV6	IV7 [c]	IV8	IV9	IV10	IV11	IV12	IV13	EoTV [c]	FU1	FU2	FU3	FU4	FU5	FV/ EDV[c]
	w-4 to -1	w0	w4	w8	w12	w16	w20	w24	w28	w32	w36	w40	w44	w48	w52	w56	w60	w64	w68	w72	w76
2MWD	X	X			X			X			X				X			X			X
6MWD		X			X			X			X				X			X			X
Randomization		X																			
MMT for Muscle Strength	X	X						X							X						X
QMT for Muscle Strength		X						X							X						X
Thromboembolic Events Risk Assessments [g]		X	X	X	X	X	X	X	X	X	X	X	X	X							
Hemolysis detection [h]		X	X	X	X	X	X	X	X	X	X	X	X	X							
Infusion & Vital Signs [i]		X	X	X	X	X	X	X	X	X	X	X	X	X							
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-Up Phone Calls																X	X		X	X	

Abbreviations: EoTV: End of Treatment Visit; EV: Enrollment Visit; FU: Follow-up Visit; ICF: Informed Consent Form; FV/EDV: Final Visit/Early Discontinuation Visit; IV: Infusion Visit; SV: Screening Visit; w: Week.

[a] Events/activities should be performed in the order specified in Section 5 for each visit.

[b] Time point for each visit is relative to EV/IV1. A ± 1-week window is allowed for all study visits after EV/IV1.

[c] Assessments will be performed over at least 2 days within the specified visit window in the order specified in Section 5.

[d] Physical examination by body systems.

[e] Includes neurological examination, 12-lead ECG, and depression assessment using the Center for Epidemiologic Studies scale.

[f] Borg scale is administered immediately before and immediately after the 2MWD and the 6MWD.

[g] Thromboembolic events risk monitoring will be performed before the beginning and after the completion of every infusion from IV1 (Week 0) to IV13 (Week 48).

[h] Hemolysis detection will be performed before the beginning and after the completion of every infusion from IV1 (Week 0) to IV13 (Week 48).

[i] Each IV infusion is administered over 2 consecutive days for a total of 26 IV infusions [per IWRS IV1 Day 1, IV1 Day 2 up to IV13 Day 1, IV13 Day 2]. A window period of ± 1 week is allowed for any infusion after Infusion 1.

4.5.2 Description of the clinical trial procedures

4.5.2.1 Medical history

A complete medical history will be carried out by the principal investigator or subinvestigator in all individuals during the Screening Visit (SV) to ensure that the diagnosis of PPS is confirmed, to identify newly affected or weakened muscle groups due to PPS (see Section 4.5.2.18), and to exclude any coexistent conditions which might be causing muscle weakness and global fatigue that could interfere with interpretation of the study. Areas of questioning will include, but not be limited to, information regarding polio vaccination, past and present medical, surgical, and psychiatric history.

4.5.2.2 Physical assessment

A physical examination by body systems will be performed by a medical doctor at the SV (Week -4 to -1), IV7 (Week 24), EoTV (Week 52), and FV (Week 76).

The physical examination performed at the SV will include identification of the main body part (*i.e.*, lower extremities versus upper extremities) that is most significantly affected by PPS for the purpose of stratifying randomization. Identification of the body part most significantly affected by PPS may also take into consideration findings obtained by neurological examination at the SV (Section 4.5.2.3). Selection of stratification must be documented in the medical notes.

Alternatively, the physical assessment will be carried out at the EV/IV1 (Week 0), IV4 (Week 12), IV10 (Week 36) and Follow-Up Visit 3 (FU3; Week 64).

Subject's height and weight will be measured at the SV (Week -4 to -1) in order to calculate his/her body mass index (BMI). At the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24) and IV10 (Week 36) the subject's weight will be measured again.

4.5.2.3 General health assessment

At the SV (Week -4 to -1), subjects will undergo: (1) a neurological examination; (2) 12 lead electrocardiogram (ECG); and (3) a depression assessment using the subject-reported Center for Epidemiologic Studies Depression (CESD) scale (ANNEX 4) performed by a medical doctor.

Optionally, at the SV individuals may also have: (1) a new electro-diagnostic evaluation only if a previous one was unclear or had raised doubts about the diagnosis of PPS, or had revealed the emergence of another co-existent neuromuscular condition and it is needed according to the Investigator's judgment; and (2) a chest X-ray as medically indicated.

4.5.2.4 Infusions and vital signs

Infusions will be administered according to the treatment schedule from Table 6. The scheduled date for infusion Day 1 is to be based on the randomization date. A ± 1-week window period is allowed for any infusion after Infusion 1.

During all infusions, vital signs (T, RR, HR, SBP and DBP) will be monitored. Temperature will be registered as body temperature. Heart rate will be measured by digital palpation to radial level. Respiratory rate will be determined by respiratory cycle count. SBP and DBP

will be registered to level of humerus. Body temperature and blood pressure measure instruments will be those instruments usually used at the investigational site. Heart rate, RR and blood pressure will be determined at rest.

Subject's vital signs (T, RR, HR, SBP, DBP) will be monitored and recorded as follows: (1) within 20 minutes before the beginning of infusion; (2) every 30 ± 10 minutes during the first hour of infusion; and (3) at 30 ± 10 minutes post-completion of infusion. Recorded values must be reviewed (with signature and date) by a medical doctor.

4.5.2.5 Thromboembolic events risk assessments

During all the infusion visits, thromboembolic events risk will be assessed using: (1) D-dimer blood levels (within 8 hours prior to the infusion [Day1] and 30 ± 10 minutes after the completion of the infusion [Day 2]); (2) the Wells prediction score for DVT and for PE (after the completion of the infusion [Day 2]); and (3) evaluation of clinical signs and symptoms of thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) after the completion of the infusion (Day 2).

After getting results from (1) to (3) and prior to the next study visit, a medical doctor will assess the risk of thromboembolic events considering algorithms provided in ANNEX 13 from IV1 (Week 0) to IV13 (Week 48).

4.5.2.6 Hemolysis detection

During all the infusion visits, hemolysis detection will be evaluated using: (1) blood assessments including whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, lactate dehydrogenase (LDH), direct antiglobulin test (DAT), absolute reticulocyte count (ARC), red blood count (RBC), hematocrit, total and indirect bilirubin, and blood smear within 8 hours prior to the infusion; (2) urinalysis including urinary sediment and hemoglobinuria within 8 hours prior to the infusion; and (3) clinical parameters including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor or tachycardia) evaluated at any time on the day of infusion before the infusion (Day 1), at any time on the day of infusion after the completion of the infusion (Day 2), and 10 days (±2 days) after the initiation of the infusion (Day 1) by a phone call.

After getting results from (1) to (3) and prior to the next study visit, a medical doctor will assess the hemolysis considering algorithm provided in ANNEX 14 from IV1 (Week 0) to IV13 (Week 48).

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.7 Blood biochemistry and cell counts

Laboratory test will include:

- Renal parameters: creatinine, blood urea nitrogen (BUN) and GFR.
- Hepatic parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TBL).
- Haematological parameters: complete blood count (CBC), including differential leukocyte count.

Samples for blood biochemistry and cell counts testing will be collected at the SV (Week -4 to -1), within 8 hours prior to investigational product infusion at the IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), and at EoTV (Week 52), FU3 (Week 64), and FV (Week 76).

Blood samples will be sent to a central laboratory for measurement of blood chemistry and cell count. Laboratory results must be reviewed by a medical doctor.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.8 Blood IgA level and anti-IgA antibodies

At the SV (Week -4 to -1), blood will be obtained for measurement of IgA levels (selective IgA deficiency). Anti-IgA antibodies will be determined only if IgA levels are below normal range.

Blood samples will be sent to a central laboratory for measurement of IgA levels and anti-IgA antibodies if appropriate. Laboratory results must be reviewed by a medical doctor.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.9 Blood testing of general health

At the SV (Week -4 to -1), blood will be obtained for measurement of the following parameters:

- Electrolyte panel: sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate and magnesium.
- Albumin and glucose.
- Thyroid panel: total thyroxine (T4), free T4, free tri-iodothyronine (T3) and thyroid stimulating hormone (TSH).
- Lactate dehydrogenase (LDH), creatine kinase (CK) and aldolase.
- Hemoglobin A1C, vitamin B12 and folate.
- Coagulation panel: prothrombin time (PT), activated partial thromboplastin time (APTT), and international normalized ratio (INR).
- Erythrocyte sedimentation rate (ESR).
- D-dimer.
- Lipid profile: total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides.

Blood samples will be sent to a central laboratory for measurement of blood parameters reflecting general health. Laboratory results must be reviewed by a medical doctor.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.10 Blood testing of immunologic function

At the SV (Week -4 to -1), blood will be obtained for measurement of the following parameters:

- Autoantibody panel: rheumatoid factor, anti-nuclear antibodies (ANA) and anti-thyroid antibodies.
- Serum immunoglobulin and protein electrophoresis.

Blood samples will be sent to a central laboratory for measurement of immunologic function. Laboratory results must be reviewed by a medical doctor.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.11 Blood testing of viral exposure

At the SV (Week -4 to -1), blood will be obtained for measurement of the following parameters:

- HCV antibodies.
- HIV type 1 and 2 antibodies.

Viral monitoring will be performed by means of antibody testing and, if required, nucleic acid testing (NAT).

Blood samples will be sent to a central laboratory for measurement of viral status. Laboratory results must be reviewed by a medical doctor.

In addition, retention blood samples for the possible measurement of viral status will be collected prior to the first infusion of investigational product at the EV/IV1 (Week 0) and after completion of the last infusion of investigational product at IV13 (Week 48). These retention samples will be tested only if the subject shows signs and symptoms of viral infection during the study. These samples will be stored and retained at a central laboratory for up to 5 years after the end of the study.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.12 Blood exploratory testing

Blood samples will be taken at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76) for testing of the following inflammatory cytokines: IL-1, IL-4, IL-6, IL-10, IL-13, IL-17, IL-23, TNF-alpha, IFN-gamma.

4.5.2.13 Possible future blood testing for biomarkers

Retention blood samples will be collected at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76) for possible future biomarker testing. These samples will be stored and retained at a central laboratory for up to 5 years after the end of the study.

4.5.2.14 Assessment of physical performance

The physical performance will be evaluated using the walking test 2MWD. The 2MWD measures the distance that a patient can quickly walk at a self-preferred, comfortable speed on an indoor, flat, hard surface 30 m (100-ft) hallway in a period of 2 minutes [20]. If a 30 m course is not possible, a course of at least 20 m can be used. Walking capacity has been reported as an indicator of performance and activities of daily living in patients with PPS [53]. Walking at comfortable speed in a clinical setting is assumed to represent walking daily life [62].

Assessment of perceived exertion/fatigue will be performed using the Borg scale immediately before and immediately after administering the 2MWD (see Section 4.5.2.21).

A 2MWD will be carried out by certified independent assessors (ANNEX 5) at the SV (Week -4 to-1), EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). This assessment preferably will be performed by the same certified independent assessors for all subjects at the same investigational site. The principal investigator or subinvestigator will review the results of the assessment.

At the SV (Week -4 to -1) and at EV/IV (Week 0), the 2MWD will be performed in order to check clinical trial inclusion criteria 10 and 11. Calculation to assess consistent baseline 2MWD (inclusion criteria 11) should be documented in the medical notes or in the 2MWD worksheet.

4.5.2.15 Assessment of health-related quality of life

PPS may impact subject's HRQoL. This impact will be assessed by the generic tool Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) [63]. Data will be recorded at each specified visit without reference to previous answers.

SF-36 is a short-form health survey with 36 items that will be self-reported by the subjects. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures. It is a generic measure that has proven useful in surveys of general and specific populations, and in differentiating health benefits produced by a wide range of different treatments. The 4-week recall form will be used (ANNEX 6). Scores calculation will be performed according to SF-36 user's manual and specified in the Statistical Analysis Plan (SAP).

SF-36 test will be administered by the principal investigator, subinvestigator, or designee study staff and reported by study individuals at the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.16 Assessment of pain

The VAS will be used to evaluate the pain level in a 24 hours period [64]. It consists of a 100 mm scale where 100 mm stands for the worst imaginable pain and zero stands for no pain (ANNEX 7).

VAS for pain will be administered by the principal investigator, subinvestigator, or other designee study staff and will be self-reported by study individuals at the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). The principal investigator or subinvestigator will review the results of the assessment.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.17 Assessment of endurance

The endurance will be evaluated using the walking test 6MWD. The 6MWD measures the distance that a patient can quickly walk at maximal speed on a flat, hard surface 30 m (100-ft) hallway in a period of 6 minutes [65]. If a 30 m course is not possible, a course of at least 20 m can be used.

Assessment of perceived exertion/fatigue will be performed using the Borg scale immediately before and immediately after administering the 6MWD (see Section 4.5.2.21).

A 6MWD will be carried out by certified independent assessors (ANNEX 8) at the EV/IV1 (Week 0), IV4 (Week 12), IV7 (Week 24), IV10 (Week 36), EoTV (Week 52), FU3 (Week 64), and FV (Week 76). This assessment preferably will be performed by the same certified independent assessor for all subjects at the same investigational site. The principal investigator or subinvestigator will review, sign, and date the results of the assessment.

4.5.2.18 Assessment of muscle strength by manual muscle testing

Muscle strength will be evaluated only in 2 newly weakened muscle groups by manual muscle testing (MMT) using the MRC scale [66]. This assessment will preferably be performed by the same certified independent assessor for all subjects at the same investigational site (ANNEX 9). Manual muscle testing is a procedure for the evaluation of the function and strength of individual muscles and muscle groups based on effective performance of limb movement in relation to the forces of gravity and manual resistance.

The process of selecting the 2 newly weakened muscle groups to be evaluated by MMT and QMT throughout the clinical trial includes: (1) assessment of muscle strength in the pre-specified muscle groups (ANNEX 9) by MMT performed by the certified independent assessor at the SV and (2) review of the subject's medical history (Section 4.5.2.1) to determine which muscle groups are newly weakened due to PPS.

The selection of 2 newly weakened muscle groups will be performed by the principal investigator or subinvestigator based on (1) and (2) (described above) information at the SV. The 2 selected muscle groups must comply with the following conditions:

- To have an MRC scale score (by MMT) at SV greater than 3, that is, 4-, 4, 4+ or 5.

- To be a newly weakened muscle group due to PPS.
- One of the selected muscles groups must be in a lower extremity.

This decision must be documented in the medical notes.

At EV/IV1 (Week 0), IV7 (Week 24), EoTV (Week 52), and FV (Week 76), MMT will only be performed on the 2 selected muscle groups by the certified independent assessor. The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

4.5.2.19 Assessment of muscle strength by quantitative muscle testing

Isometric muscle strength will be evaluated in the 2 selected (see Section 4.5.2.18) newly weakened muscle groups using a dynamometer (hand-held for upper extremities and chair-fixed for lower extremities). This assessment will preferably be performed by the same certified independent assessor at each investigational site and with the same brand name of dynamometer (ANNEX 10). QMT will be performed at the EV/IV1 (Week 0), IV7 (Week 24), EoTV (Week 52), and FV (Week 76). The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.20 Assessment of walking activity in daily life

To measure the amount of walking activity in daily life, subjects will be asked to wear an activity monitor (pedometer) which will record the number of steps the wearer walks daily during 7 consecutive days (ANNEX 11). The certified independent assessor should give instructions to the subject on how to properly use the pedometer. Subjects will be instructed to attach the pedometer to their person for 7 consecutive days prior to the scheduled study visit.

This number of steps taken during the previous 7 days will be recorded/uploaded at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76).

The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

4.5.2.21 Assessment of perceived exertion/fatigue

Assessment of perceived exertion/fatigue is evaluated using the Borg scale, which is a subject self-reported scale ranging from 0 (no exertion/fatigue at all) to 10 (very, very severe exertion/fatigue). The subject circles on the scale the level of exertion or fatigue they perceive at the time the scale is administered. Subjects will be administered the Borg scale immediately before and immediately after the 2MWD and 6MWD (see ANNEX 5 and ANNEX 8) by certified independent assessors. This assessment preferably will be administered by the same certified independent assessor for all subjects at the same investigational site.

The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

4.5.2.22 Assessment of fatigue

The FSS will be used to measure the level of fatigue during the walking activity in daily life (as measured by pedometer) monitoring period of 7 consecutive days. The scale is designed to measure the severity of mental, physical and total fatigue by scoring responses to scale items. It consists of 9 statements exploring the subject's perception of fatigue symptoms, with a self-reporting score ranging from 1 (no effect of fatigue on daily life) to 7 (severe disabling fatigue) depending on how well the statement described the subject's situation over the preceding week (ANNEX 12). Higher numerical values indicate an increasing level of agreement with the statement. The FSS has been demonstrated to be a reliable and valid measure with high internal consistency [67] and it has been used to quantify effects of fatigue in patients with chronic fatigue syndrome and PPS [68].

The FSS will be completed by the patient and will be administered by the principal investigator, subinvestigator, other designee study staff, or certified independent assessor. The FSS will be assessed when study individuals return the pedometer to the clinic after performing the daily physical assessment at the EV/IV1 (Week 0), EoTV (Week 52), and FV (Week 76). The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.23 Follow-up phone calls

The telephone follow-up will include a semi-structured interview in which symptoms and general well-being of the subject, presence of AEs and changes in concomitant medication will be discussed. Time scheduled for the telephone interview will be approximately 10-15 minutes.

Phone calls with the study subjects will be performed at FU1 (Week 56), FU2 (Week 60), FU4 (Week 68) and FU5 (Week 72) and will have a ± 1-week window period. The principal investigator or subinvestigator will review (sign and date) the results of the assessment.

4.5.2.24 Adverse events

AEs (includes suspected ADRs) occurring at any time between signature of the subject's informed consent form (ICF) and the last day of the subject's participation in the clinical trial will be reported and recorded on the appropriate subject's eCRF entry. Protocol Section 9.2.1 is specifically dedicated to AEs.

AEs occurring during the 2-day infusion period (*i.e.*, from the initiation of the investigational product infusion on the first day to the completion of the total dose of investigational product on the last day) and within 72 hours following the completion of the infusion of the total dose of investigational product on the last day, regardless of other factors that may impact a possible causal association with product administration, will be defined as infusional AEs (*i.e.*, an AE temporally associated with an infusion of the investigational product) and labeled treatment emergent adverse events (TEAEs).

AEs are to be assessed by the principal investigator or subinvestigator.

Clinically relevant changes in vital signs (T, RR, HR, SBP and DBP) during infusions of Flebogamma® 5% DIF or Normal Saline Solution will be reported as AEs. Clinical relevance will be based on the Investigator's judgment.

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.5.2.25 Concomitant medication

A registry of medications other than the investigational products administered to subjects will be maintained throughout the clinical trial. This registry is to be assessed by a medical doctor.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

4.6 Premature termination of study/closure of center

The sponsor, Ethics Committees (ECs), and/or regulatory authorities have the right to close this study or a study center, and the investigator/sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The ECs must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until by the sponsor for destruction.

The reasons a study center may be closed include, but are not limited to, the following:

- Lack of enrollment
- Non-compliance with the requirements of the study protocol
- Non-compliance with ICH GCP

5 CLINICAL TRIAL VISITS

5.1 Screening period

Screening Visit (SV)

Screening Visit will take place up to 4 weeks prior to the EV/IV1 (Week 0) to allow sufficient time for laboratory results to become available and to assess patient's consistency regarding the 2MWD.

Assessments and procedures planned to be done during this visit will be performed over different days and will include:

1. Information to be given to potential clinical trial individuals:

- Subjects will be informed of the nature, purpose and procedures of the study, with a description of the possible risks and benefits involved.
- Subjects will be informed of the voluntary nature of participation, and of the right to withdraw from the study at any time, without this implying any negative consequences for the patient.
- Subjects will receive the *Clinical Trial Subject Information Sheet* and they will be given enough time to think about their clinical trial participation.
- Investigator or study staff will make sure that potential individuals fully understand the elements of the *Clinical Trial Subject Information Sheet*.

2. Clinical Trial Written Informed Consent: before any study specific procedures will be performed, and after completely understanding the nature of the clinical trial, potential subjects must sign and date the *Clinical Trial Written Informed Consent Form*. The study staff involved in obtaining the informed consent will also sign and date it, thus reflecting that clinical trial informed consent has been obtained, and that the individual has had the opportunity to ask questions, and has received adequate answers. The subject will receive a copy of the *Clinical Trial Subject Information Sheet* and the signed and dated *Clinical Trial Written Informed Consent Form*, and the original one will be filed along with the study documentation.
3. Allocation of subject number: following the signature of the *Clinical Trial Written Informed Consent Form*, the Investigator will include the individual in the *IWRS Screening*.
4. Documentation of the subject's demographics: date of birth, gender, race, and ethnic origin.
5. Documentation of the subject's medical history: information regarding polio vaccination; past and present medical, surgical, and psychiatric history to ensure that the diagnosis of PPS is correct and to exclude any coexistent conditions which might be causing muscle weakness and global fatigue that could interfere with interpretation of the study; and identification of newly affected or weakened muscle groups due to PPS.
6. Documentation of medications that subject is taking or has been taking within the last 3 months, including transfusion of blood or any blood-derived product, except for immune globulin (intravenous [not for PPS therapy], intramuscular or subcutaneous) for which the administration within the last 3 years should be documented.
7. Physical examination by body systems will be performed, including assessment of the main body part (*i.e.*, lower extremities versus upper extremities) most significantly affected by PPS for the purpose of stratification of subject randomization.
8. Height and weight.
9. General health assessment: a neurological examination, a 12 lead ECG and a depression assessment, using the CESD scale, will be carried out.

   Optionally, individuals may also have: (1) a new electro-diagnostic evaluation only if a previous one was unclear or had raised doubts about the diagnosis of PPS, or had revealed the emergence of another co-existent neuromuscular condition and it is needed according to the Investigator's judgment; and (2) a chest X-ray as medically indicated.
10. Blood testing:

    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL and GFR.

- Blood IgA level and anti-IgA antibodies (anti-IgA antibodies will be determined only if IgA levels are below normal range).
- Blood assessment of general health: electrolyte panel, albumin and glucose, thyroid panel, LDH, CK, aldolase, hemoglobin A1C, vitamin B12, folate, coagulation panel, ESR, and lipid profile.
- Blood assessment of immunologic function: autoantibody panel, and serum immunoglobulin, and protein electrophoresis.
- Blood assessment of viral exposure: HCV and HIV (HIV 1 & 2) antibody testing and, if required, NAT.
- Pregnancy test: Human chorionic gonadotropin (HCG)-based assay (urine assay is also valid). This is only applicable for female subjects of childbearing potential.

***Procedures 11 through 13 must be performed in the following order on the same day:**

11. Physical performance: 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD. This 2MWD will be used to assess inclusion criteria 10 and 11.
12. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).
13. Muscle strength (must follow rest period):
    Muscle strength of the pre-specified muscle group will be assessed by MMT to select 2 muscle groups (from all muscle groups assessed) with an MRC scale score greater than 3, that is 4-, 4, 4+, or 5.

    Selection of the 2 newly weakened muscle groups for assessment by MMT and QMT throughout the clinical trial will be based on the MMT at SV and medical history of newly affected muscle groups due to PPS.
14. Review of clinical trial inclusion and exclusion criteria to confirm subject eligibility.

    Inclusion criteria (from criteria 1 to 10 of Section 6.1) and exclusion criteria (from criteria 1 to 19 of Section 6.2) will be reviewed to confirm each subject's eligibility for the clinical trial. If a subject is ineligible, the specific reason for ineligibility will be captured on the subject's eCRF, including medical history.

    Individuals who do not fulfill inclusion criteria (from criteria 1 to 10) and fulfill any of the exclusion criteria (from criteria 1 to 19) will be considered enrollment failures. If a subject is ineligible for the clinical trial, their demographic data and specific reason for ineligibility will be captured on the eCRF page. Only subjects who fulfill all inclusion criteria and do not fulfill any exclusion criteria will be considered eligible to continue with the EV/IV1.
15. Provide subject with pedometer for walking activity in daily life assessment.
16. Assessment of AEs: AEs occurring at any time between signature of *Clinical Trial Written Informed Consent Form* and the last day of the subject's participation in the clinical trial will be reported.

5.2 Treatment period

Those individuals who have been enrolled will attend to their investigational site for intravenous infusions every 4 weeks, counted from the date of randomization. Different study

assessments will be performed according to the infusion visit number. A ± 1-week window is allowed for all study visits in the treatment period after the EV/IV1.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

Enrollment Visit (EV)/Infusion Visit 1 (IV1)

This visit will include 2 visits: Enrollment Visit (EV) and Infusion Visit 1 (IVI 1). Assessments and procedures for the EV will take place prior to the planned first infusion (IV1) to assess patient's consistency regarding the 2MWD, to confirm the patient's eligibility for the study, and to obtain baseline values/assessments.

Assessments and procedures planned to be done during the EV will be performed over different days within a 1-week time window:

ENROLLMENT VISIT:

1. Physical assessment.
2. Weight.
3. Concomitant medication.
4. AEs.

***Procedures 5 through 10 must be performed *in the following order* on the same day:**

5. Subject questionnaires: Fatigue (Baseline FSS); HRQoL (Baseline SF-36); Pain (Baseline VAS for pain).
6. Record/upload number of steps from pedometer during 7 consecutive days prior to visit: Baseline Walking Activity in daily life.
7. Physical performance: Baseline 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD; this 2MWD will be used to assess inclusion criteria 10 and to calculate 2MWD consistency between SV and EV assessments (inclusion criterion 11).
8. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).
9. Endurance: Baseline 6MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 6MWD.
10. Review of the clinical trial inclusion criteria 10 and 11 and all exclusion criteria to confirm subject eligibility.

***Procedures 11 through 13 must be performed on the 2 muscle groups selected at the SV.**

***Procedures 11 through 15 must be performed prior to IV1 *in the following order* on the same day and on different day than earlier assessments:**

11. Muscle strength: Baseline MMT.

12. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the MMT).
13. Muscle strength: Baseline QMT.
14. Randomization.

    Individuals who fulfill all inclusion criteria and none of the exclusion criteria and have undergone all screening and enrollment assessments will be considered eligible to continue in the clinical trial. These subjects will be randomized to 1 of the treatment arms and will be included in the *IWRS Randomization*. Randomization is to be stratified based on the body part (lower extremities versus upper extremities) that was most significantly affected by PPS at the SV.

    Individuals who do not fulfill all of the inclusion criteria, fulfill any of the exclusion criteria, or have not undergone all enrollment assessments will be considered enrollment failures. If a subject is ineligible for the clinical trial, their demographic data and specific reason for ineligibility will be captured on the appropriate eCRF page and on the medical history eCRF.

INFUSION VISIT 1:

Investigational product will be infused at IV1 over 2 consecutive days (Day 1 and Day 2) which will start on the same day or after finishing the Enrollment Visit.

Infusion Day 1:

1. Blood testing (blood sample collected within 8 hours prior to the infusion):
    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL, and GFR.
    - D-dimer blood level for thromboembolic events risk assessment.
    - Hemolysis detection: whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, total and indirect bilirubin, and blood smear.
    - Inflammatory cytokines: IL-1, IL-4, IL-6, IL-10, IL-13, IL-17, IL-23, TNF-alpha, and IFN-gamma.
    - Retention blood sample for possible viral exposure testing (*sample will be tested only if subject shows signs and symptoms of viral infection during the study*).
    - Retention blood sample for possible future biomarker testing.
2. Urine testing (urine sample collected within 8 hours prior to the infusion):
    - Urine sediment and measuring of hemoglobinuria.
3. Infusion and vital signs:
    - Infusion of investigational product.
    - Subject vital signs (T, RR, HR, SBP and DBP) will be monitored: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

Infusion Day 2:

4. Infusion and vital signs:
    - Infusion of investigational product.
    - Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.
5. Blood testing (blood sample collected at 30 ± 10 minutes post-completion of infusion):
    - D-dimer blood level for thromboembolic events risk.
6. Wells score for thromboembolic events risk assessment (performed post-completion of infusion).
7. Evaluation of clinical signs and symptoms of arterial and venous thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) after completion of infusion.
8. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) after completion of infusion.

Day 10:

9. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) 10 days (±2 days) after the initiation of the infusion (Day 1) via telephone call.

Before Infusion Visit 2:

10. Monitoring thromboembolic risk assessment (Section 4.5.2.5, ANNEX 13).
11. Hemolysis detection (Section 4.5.2.6, ANNEX 14).

Infusion Visit 2 (IV2), Infusion Visit 3 (IV3), Infusion Visit 5 (IV5), Infusion Visit 6 (IV6), Infusion Visit 8 (IV8), Infusion Visit 9 (IV9), Infusion Visit 11 (IV11), and Infusion Visit 12 (IV12)

Investigational product will be infused over 2 consecutive days (Day 1 and Day 2). The following assessments and procedures will be performed at these visits except for those assessments and procedures specifically indicated.

1. Concomitant medication.
2. AEs.

Infusion Day 1:

3. Blood testing (blood sample collected within 8 hours prior to the infusion):
    - D-dimer.

- Hemolysis: whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, total and indirect bilirubin, and blood smear.

4. Urine testing (urine sample collected within 8 hours prior to the first day of the 2-day infusion period):
   - Urine sediment and measuring of hemoglobin.
5. Infusion and vital signs:
   - Infusion of investigational product.
   - Subject vital signs (T, RR, HR, SBP and DBP) will be monitored (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

Infusion Day 2:

6. Infusion and vital signs:
   - Infusion of investigational product.
   - Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.
7. Blood testing (blood sample collected at 30 ± 10 minutes post-completion of infusion).
   - D-dimer blood level for thromboembolic events risk assessment.
8. Wells score for thromboembolic events risk assessment (performed post-completion of infusion).
9. Evaluation of clinical signs and symptoms of arterial and venous thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) after completion of infusion.
10. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) after completion of infusion.

Day 10:

11. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) 10 days (±2 days) after the initiation of the infusion (Day 1) via telephone call.

Before next Infusion Visit:

12. Monitoring thromboembolic risk assessment (Section 4.5.2.5, ANNEX 13).
13. Hemolysis detection (Section 4.5.2.6, ANNEX 14).

Infusion Visit 4 (IV4) and Infusion Visit 10 (IV10)

Assessments and procedures planned to be done during the IV4 and IV10 will be performed over different days during a 1-week time window except for those assessments and procedures specifically indicated.

1. Physical assessment.
2. Weight.
3. Concomitant medication.
4. AEs.

***Procedures 5 through 8 must be performed on the same day and prior to the investigational product infusion *in the following order*:**

5. Subject questionnaires: HRQoL (SF-36); Pain (VAS for pain).
6. Physical performance: 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD.
7. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).
8. Endurance: 6MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 6MWD.

Infusion Day 1:

Investigational product will be infused only after procedure 8 has been performed (on the same day or after).

9. Blood testing (blood sample collected within 8 hours prior to infusion):
    - D-dimer.
    - Hemolysis: whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, total and indirect bilirubin, and blood smear.
    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL, and GFR.
10. Urine testing (urine sample collected within 8 hours prior to infusion):
    - Urine sediment and measuring of hemoglobinuria.
11. Infusion and vital signs:
    - Infusion of investigational product.
    - Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

Infusion Day 2:

12. Infusion and vital signs:

- Infusion of investigational product.
- Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

13. Blood testing (blood sample collected at 30 ± 10 minutes post-completion of infusion).
    - D-dimer.
14. Wells score for thromboembolic events risk assessment (performed post-completion of infusion).
15. Evaluation of clinical signs and symptoms of arterial and venous thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) after completion of infusion.
16. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) after completion of infusion.

Day 10:

17. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) 10 days (±2 days) after the initiation of the infusion (Day 1) via telephone call.

Before next Infusion Visit:

18. Monitoring thromboembolic risk assessment (Section 4.5.2.5, ANNEX 13).
19. Hemolysis detection (Section 4.5.2.6, ANNEX 14).

Infusion Visit 7 (IV7)

Assessments and procedures planned to be done during the IV7 will be performed over different days during a 1-week time window except for those assessments and procedures specifically indicated.

1. Physical examination by body systems performed.
2. Weight.
3. Concomitant medication.
4. AEs.

***Procedures 5 through 8 must be performed on the same day and prior to the investigational product infusion *in the following order*:**

5. Subject questionnaires: HRQoL (SF-36); Pain (VAS for pain).
6. Physical performance: 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD.
7. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).

8. Endurance: 6MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 6MWD.

***Procedures 9 through 11 must be performed on the same day (on a different day after procedure 8) and prior to the investigational product infusion *in the following order*:**

9. Muscle strength: MMT.
10. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the MMT).
11. Muscle strength: QMT.

Infusion Day 1:

12. Investigational product will be infused only after procedure 11 has been performed (on the same day or after).
13. Blood testing (blood sample collected within 8 hours prior to the first day of the 2-day infusion period):
    - D-dimer.
    - Hemolysis: whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, total and indirect bilirubin, and blood smear.
    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL, and GFR.
14. Urine testing (urine sample collected within 8 hours prior to the first day of the 2-day infusion period):
    - Urine sediment and measuring of hemoglobinuria.
15. Infusion and vital signs:
    - Begin infusion of investigational product over 2 consecutive days.
    - Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

Infusion Day 2:

16. Infusion and vital signs:
    - Infusion of investigational product.
    - Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.
17. Blood testing (blood sample collected at 30 ± 10 minutes post-completion of infusion):
    - D-dimer.
18. Wells score for thromboembolic events risk assessment (performed post-completion of infusion on the last day of the 2-day infusion period and before the next infusion visit).

19. Evaluation of clinical signs and symptoms of arterial and venous thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) after completion of infusion.
20. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) after completion of infusion.

Day 10:

21. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue, or tachycardia) 10 days (±2 days) after the initiation of the infusion (Day 1) via telephone call.

Before next Infusion Visit:

22. Monitoring thromboembolic risk assessment (Section 4.5.2.5, ANNEX 13).
23. Hemolysis detection (Section 4.5.2.6, ANNEX 14).

Infusion Visit 13 (IV13)

Investigational product will be infused over 2 consecutive days (Day 1 and Day 2). The following assessments and procedures will be performed over different days during a 1-week time window.

1. Concomitant medication.
2. AEs.

Infusion Day 1:

3. Blood testing (blood sample collected within 8 hours prior to the first day of the 2-day infusion period):
    - D-dimer.
    - Hemolysis: whole blood hemoglobin, serum or plasma free hemoglobin, haptoglobin, LDH, DAT, ARC, RBC, hematocrit, total and indirect bilirubin, and blood smear.
4. Urine testing (urine sample collected within 8 hours prior to the first day of the 2-day infusion period):
    - Urine sediment and measuring of hemoglobinuria.
5. Infusion and vital signs:
    - Infusion of investigational product.
    - Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

Infusion Day 2:

6. Infusion and vital signs:

- Infusion of investigational product.
- Subject vital signs (T, RR, HR, SBP, and DBP) will be monitored: (1) within 20 minutes before the beginning of each infusion; (2) every 30 ± 10 minutes during the first hour of each infusion; and (3) at 30 ± 10 minutes post-completion of each infusion.

7. Blood testing (blood sample collected at 30 ± 10 minutes post-completion of infusion on the last day of the 2-day infusion period:
    - D-dimer.
    - Retention blood sample for possible viral exposure testing (*sample will be tested only if subject shows signs and symptoms of viral infection during the study*).
8. Wells score for thromboembolic events risk assessment (performed post-completion of infusion).
9. Evaluation of clinical signs and symptoms of arterial and venous thromboembolic events (such as pain, dyspnea, discoloration—paleness or redness—in lower extremities) after completion of infusion.
10. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue or tachycardia) after completion of infusion.
11. Provide subject with pedometer for walking activity in daily life assessment.

Day 10

12. Evaluation of clinical parameters of hemolysis including red/dark urine, jaundice, as well as other signs and symptoms of anemia (such as pallor, fatigue or tachycardia) 10 days (±2 days) after the initiation of the infusion [Day 1] via telephone call.

Before End of Treatment Visit:

13. Monitoring thromboembolic risk assessment (Section 4.5.2.5, ANNEX 13).
14. Hemolysis detection (Section 4.5.2.6, ANNEX 14).

End of Treatment Visit (EoTV)

Assessments and procedures planned to be done during the EoTV will be performed over different days during a 1-week time window:

1. Physical examination by body systems performed.
2. Concomitant medication.
3. AEs.

Procedures 4 through 8 must be performed on the same day *in the following order:

4. Subject questionnaires: Fatigue (FSS); HRQoL (SF-36); Pain (VAS for pain).
5. Record/upload number of steps from pedometer during 7 consecutive days prior to visit: Walking Activity in daily life.

6. Physical performance: 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD.
7. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).
8. Endurance: 6MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 6MWD.

Procedures 9 through 11 must be performed on the same day (on a different day after procedure 8) *in the following order:

9. Muscle strength: MMT.
10. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the MMT).
11. Muscle strength: QMT.
12. Blood testing:
    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL, and GFR.
    - Inflammatory cytokines: IL-1, IL-4, IL-6, IL-10, IL-13, IL-17, IL-23, TNF alpha, and IFN-gamma.
    - Retention blood sample for possible future biomarker testing.

5.3 Follow-up period

Those individuals who have been enrolled will attend to their investigational site for follow-up visits after the treatment period. Different study assessments will be performed according to the follow-up visit number. A ± 1-week window is allowed for all study visits in the follow-up period.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

Follow-up Visit 1 (FU1), Follow-Up Visit 2 (FU2), Follow-Up Visit 4 (FU4) and Follow-Up 5 (FU5)

The following assessments will be carried out at these visits by a phone call during a 1-week time window:

1. Assessment of symptoms and general well-being of the subject.
2. Concomitant medication.
3. AEs.
4. At FU5 (phone call), give instructions to subject about how and when to wear the pedometer.

Follow-Up Visit 3 (FU3)

Assessments and procedures planned to be done during the FU3 will be performed over different days during a 1-week time window:

1. Physical assessment.
2. Concomitant medication.
3. AEs.
4. Provide subject with pedometer for walking activity in daily life assessment.

***Procedures 5 through 8 must be performed on the same day *in the following order*:**

5. Subject questionnaires: HRQoL (SF-36); Pain (VAS for pain).
6. Physical performance: 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD.
7. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).
8. Endurance: 6MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 6MWD.
9. Blood testing:
    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL and GFR.

Final or Early Discontinuation Visit (FV/EDV)

Assessments and procedures planned to be done during the FV/EDV will be performed over different days during a 1-week time window:

1. Physical examination by body systems performed.
2. Concomitant medication.
3. AEs.

***Procedures 4 through 8 must be performed on the same day *in the following order*:**

4. Subject questionnaires: Fatigue (FSS); HRQoL (SF-36); Pain (VAS for pain).
5. Record/upload number of steps from pedometer during 7 consecutive days prior to visit: Walking Activity in daily life.
6. Physical performance: 2MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 2MWD.
7. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the 2MWD).
8. Endurance: 6MWD with assessment of perceived exertion/fatigue by Borg scale immediately before and immediately after 6MWD.

***Procedures 9 through 11 must be performed on the same day (on a different day after procedure 8) *in the following order*:**

9. Muscle strength: MMT.
10. Rest period (sitting on a chair for at least 30 minutes and until the subject feels fully recovered after completion of the MMT).
11. Muscle strength: QMT.
12. Blood testing:
    - Blood biochemistry and cell counts: CBC, including differential leukocyte count, creatinine, BUN, ALT, AST, ALP, TBL, and GFR.
    - Inflammatory cytokines: IL-1, IL-4, IL-6, IL-10, IL-13, IL-17, IL-23, TNF alpha, and IFN-gamma.
    - Retention blood sample for possible future biomarker testing.

5.4 Premature discontinuation of participating subjects

Study participation is strictly voluntary. Individuals have the right to withdraw from the study at any time for any reason. Likewise, the Investigator can withdraw an individual from the clinical trial at any time if it is deemed in the subject's best interest. The Investigator must document the reason(s) for withdrawal of each subject in the eCRF.

In the case an individual expresses his/her intention to withdraw from the study, but informed consent is still not withdrawn, subject will be asked if he/she is willing to perform a final visit (Early Discontinuation Visit) as soon as possible so that all study-related information can be recorded. Sponsor will have access to all data gathered on subjects prior to termination.

Subject withdrawal criteria and procedures are described in Section 6.3.

5.5 Accountability procedures for the investigational products

The investigational site pharmacist must keep accurate drug accountability records in IWRS per the Pharmacy Manual. These will include: (1) dates of receipt for investigational product (test or placebo); (2) when and how much investigational product (test or placebo) was dispensed; and (3) destruction of unused/undispensed investigational medicinal product.

In addition, reasons for deviations from the expected dispensing regimen must also be recorded.

All study medication will be reconciled at the completion of the clinical trial.

5.6 Maintenance of trial treatment randomization codes and procedures for breaking codes

In case of emergency, and when knowledge of the actual treatment becomes medically necessary to affect treatment options, the Investigator will be able to obtain details of the treatment assigned to an individual subject through the IWRS. A Medical Monitor will be informed immediately that blind has been broken regardless of whether emergency was

related to the study medication or not, but will not be informed of the treatment assignment. Every attempt should be made to maintain the blind throughout the study.

5.7 Source data

All information contained in the medical history, nurse registrations, and complementary exploration reports, such as, but not limited to, laboratory test, physical assessments (2MWD, 6MWD, muscle strength, walking activity), subject self-reporting questionnaires (SF-36, VAS for pain and FSS), and specific study data sheets, will be considered as source data.

For every single individual enrolled, the Investigator will record the clinical trial title, EudraCT number and sponsor (Instituto Grifols, S.A.), as well as the inclusion date and the randomization number, into the subject's medical history.

The Investigator will be responsible for maintaining complete and adequate case histories in source records of each subject. Source data must be preserved, at least, for the maximum period requested by local regulations and made available by the Investigator in case of inspection or audit.

The intended location for source data should be clearly defined and documented. This document should be signed by the principal investigator and filed in the investigator's trial master file.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Clinical trial subject inclusion criteria

Subjects fulfilling the following criteria at the SV and the EV/IV1 are eligible for participation in the study:

1. Male or female aged 18 to 75 years.
2. Subjects who understand and voluntarily signed and dated the *Clinical Trial Written Informed Consent Form* for his/her clinical trial participation.
3. Subjects with a BMI less than 35 kg/m^2.
4. Subjects who meet the clinical criteria for diagnosis of PSS as set by the March of Dimes [69] (ANNEX 17).
5. Subjects who are ambulatory or are able to walk with a cane or other aids or use a wheelchair (but they are not wheelchair-bound).
6. Subjects who have at least 2 newly weakened muscle groups due to PPS (as defined by medical history), with at least one of them in a lower extremity, and having an MRC scale score greater than 3 at the MMT performed by the independent assessor at the SV.
7. Female subjects of child-bearing potential[†] must have a negative test for pregnancy (HCG-based assay).
8. Female subjects of child-bearing potential and their sexual partners have agreed to practice contraception using a method of proven reliability (*i.e.*, hormonal methods; barrier methods; intrauterine devices methods) to prevent a pregnancy during the course of the clinical trial.

9. Subjects must be willing to comply with all aspects of the clinical trial protocol, including blood sampling and long-term storage of extra samples for the entire duration of the study.
10. Subjects who are able to walk a 2MWD of at least 50 meters at the SV and EV/IV1.
11. Subjects who are able to walk a consistent baseline 2MWD, that is, the difference in 2MWD between the SV and EV/IV1 is not more than 10%.

[†]Women of child-bearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (postmenopausal is defined as amenorrhea for more than 12 consecutive months or women on hormone replacement therapy with documented serum follicle stimulating hormone level < 35 mIU/mL). Even in women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods to prevent pregnancy or practicing abstinence or where their sexual partner is sterile, e.g., vasectomy, should be considered to be of child-bearing potential.

6.2 Clinical trial subject exclusion criteria

Subjects who meet any of the following criteria at the SV and EV/IV1 are excluded from study participation:

1. Subjects who have received human normal immune globulin treatment given by intravenous, subcutaneous or intramuscular route within the last 3 years.
2. Subjects who are not ambulatory (wheelchair-bound individuals).
3. Subjects with poor venous access.
4. Subjects with intractable pain requiring narcotics or other psychotropic drugs.
5. Subjects with a history of anaphylactic reactions or severe reactions to any blood-derived product.
6. Subjects with a history of intolerance to any component of the investigational products, such as sorbitol.
7. Subjects who are receiving corticosteroids, except for those who are taking inhaled corticosteroids for asthma.
8. Subjects with a documented diagnosis of hyperviscosity or hypercoagulable state or thrombotic complications to polyclonal IVIG therapy in the past.
9. Subjects with a history of recent (within the last year) myocardial infarction, stroke, or uncontrolled hypertension.
10. Subjects who suffer from congestive heart failure, embolism, or ECG changes indicative of unstable angina or atrial fibrillation.
11. Subjects with a history of chronic alcoholism or illicit drug abuse (addiction) in the preceding 12 months prior to the SV.
12. Subjects with active psychiatric illness that interferes with compliance or communication with health care personnel.
13. Subjects with depression with scores >30 as assessed by the CESD validated scale.

14. Females who are pregnant or are nursing an infant child.
15. Subjects with any medical condition which makes the clinical trial participation unadvisable, or which is likely to interfere with the evaluation of the study treatment and/or the satisfactory conduct of the clinical trial according to the Investigator's judgment.
16. Subjects currently receiving, or have received within 3 months prior to the SV, any investigational medicinal product or device.
17. Subjects who are unlikely to adhere the protocol requirements, or are likely to be uncooperative, or unable to provide a storage serum/plasma sample prior to the first investigational drug infusion.
18. Subjects with a known selective IgA deficiency and serum antibodies anti-IgA.
19. Subjects with renal impairment (*i.e.*, serum creatinine exceeds more than 1.5 times the upper limit of normal [ULN] for the expected normal range for the testing laboratory).
20. Subjects with AST or ALT levels exceeding more than 2.5 times the ULN for the expected normal range for the testing laboratory.
21. Subjects with hemoglobin levels <10 g/dL, platelets levels <100,000 /mm^3, white blood cells count <3.0 k/µL and ESR >50 mm/h or twice above normal.
22. Subjects with known seropositive to HCV, HIV-1 and/or HIV-2.
23. Subjects with a history of intolerance to fructose.

6.3 Subject withdrawal criteria and procedures

A subject's participation in the study may be terminated early under the following circumstances:

1. Subject withdraws the informed consent to participate in the clinical trial.
2. Subject does not meet all inclusion criteria.
3. Subject meets any of the exclusion criteria.
4. Subject is not able to adhere to the main protocol requirements (major protocol violations). Major protocol violations might include, but are not limited to, repeated missed infusions (more than 1 consecutive missed every 4 weeks infusion or more than 4 missed infusions per treatment period).
5. The occurrence of an AE, which in the Investigator's opinion, requires the subject withdrawal from the clinical trial.
6. The occurrence of a confirmed thromboembolic event.
7. The occurrence of a confirmed clinically significant hemolysis event.
8. Undercurrent illness that could interfere in the study conduct or subject's safety might be threatened, at the Investigator's judgment.
9. Any event which in the Investigator's opinion impedes subject's participation in the study.
10. The subject is lost to follow-up (no attendance the scheduled study visits after randomization).

11. Subject's death.

If study participation is terminated due to an AE, the subject will be followed-up until the AE is resolved, or has been stabilized and no further change is expected, and the Investigator deems that further observations/examinations are no longer medically necessary.

If an individual is withdrawn from study due to pregnancy, the Medical Monitor must be informed by the site or by the Investigator. The pregnancy must be reported according to described procedures in Sections 9.3.8 and 9.4. If the subject had a spontaneous abortion then the event will be captured as a SAE.

Subjects who are discontinued early after randomization from the study will not be replaced.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

7 TREATMENT OF SUBJECTS

7.1 Treatments to be administered

During both stages of this clinical trial, each subject will receive intravenous infusions of investigational product (test or placebo) every 4 weeks during a treatment period of 52 weeks, with each dose being administered over a 2-consecutive-day dosing period (Day 1 and Day2) up to 13 infusions visits, that is, 26 intravenous infusions. A window period of ± 1 week is allowed for any infusion after Infusion 1.

Flebogamma® 5% DIF (test) and Normal Saline Solution (placebo) will be used as investigational products.

Subjects randomized to the IVIG 2 g/kg arm will receive a total dose of 2 g/kg of body weight of Flebogamma® 5% DIF over 2 consecutive days (1 g/kg Day 1 and 1 g/kg Day 2). Subjects randomized to the IVIG 1 g/kg arm will receive a total dose of 1 g/kg of body weight of Flebogamma® 5% DIF on 1 day and, to maintain the blind, a total dose of 20 mL/kg of body weight Normal Saline Solution (equivalent volume of 1 g/kg of body weight Flebogamma® 5% DIF infusions) on a separate day, for a total dosing period of 2 consecutive days. The order of 1 g/kg of body weight of Flebogamma® 5% DIF or 20 mL/kg of body weight Normal Saline Solution infused on 2 consecutive days will be randomly determined for each subject by the Interactive Web Response System (IWRS), which will remain the same for the subject for all infusion visits during the treatment period.

Individuals randomized to the placebo (Normal Saline Solution) arm will receive a total dose of 40 mL/kg of body weight of Normal Saline Solution over 2 consecutive days (20 mL/kg infused on Day 1 and 20 mL/kg infused on Day 2).

7.1.1 Missed infusions processing

It is not allowed to prolong the treatment period. Infusions will not be postponed beyond their window period (± 1-week window period will be allowed for any infusion after Infusion 1).

A missed infusion will occur when a subject will not be administered with any dose of the investigational product at the scheduled infusion visit. If subject receives the investigational product at Day 1 but does NOT receive at Day 2, this will NOT be considered a missed visit.

Missed infusions will not be replaced.

During the treatment period, study subjects will be allowed to miss up to 1 consecutive infusion. More than 1 consecutive missed infusion is defined as a major protocol violation and requires subject withdrawal (Section 6.3).

A maximum of 4 missed infusions will be allowed during the treatment period (52 weeks). More than 4 missed infusions during the treatment period are defined as a major protocol violation and require subject withdrawal (Section 6.3).

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

7.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial

Study individuals will receive their routine therapy to treat their symptoms of PPS provided that the dose remains stable, or modified according to the standard of care and previously approved by the Investigator.

Subjects will not be allowed to receive any of the following study-specific prohibited medications: other investigational drug and human normal immunoglobulin therapy out of this clinical trial. In addition, subjects will not be allowed to receive any of the following study-specific prohibited medications unless considered medically necessary for the subject's welfare which might be given at the discretion of the investigator: narcotics or corticosteroids (except for inhaled corticosteroids taken for asthma, which will be allowed on-demand).

In any case, administration of all concomitant medication must be recorded in the appropriate section of the subject's eCRF.

No drug-drug interactions have been reported with the use of IVIG therapy.

To attenuate infusion-related events and to maintain blinding, all subjects will be pre-medicated 30-60 minutes prior to each investigational product infusion with 975-1000 mg of acetaminophen and 20-25 mg of diphenhydramine (or the equivalent dose of the available antihistaminic drug) provided no previous history of allergies to these medications is known. The use of the following drugs is not allowed as pre-infusion medication for investigational product administration: ASA; e.g., aspirin), NSAIDS, or corticosteroids (except for inhaled corticosteroids taken for asthma which will be allowed on-demand).

7.2.1 Orthotic device and physical therapy

Usual care for PPS patients may also include usage of assistive and orthotic devices, and physical therapy.

Neither investigational or new assistive or orthotic device nor new physical therapy will be allowed during the clinical trial. A new orthotic device is defined as a newly prescribed intervention only. Trial subjects should perform the walking distance tests at similar

conditions throughout the clinical study, but variations from visit to visit in the use of different orthotic devices for the 2MWD and the 6MWD assessments which are not newly prescribed but rather reflect subject choice to use one of many different options the subject had previously used since before study start will not be considered a protocol deviation.

7.3 Procedures for monitoring subject compliance

Since all investigational product administrations will be performed only by study staff, compliance with the clinical trial treatment will be assessed by means of the infusions registration. Dosing information, including infusion volumes will be recorded in the *eCRF* by the study staff, which will be available for clinical trial monitors to check clinical trial compliance.

The sponsor will also instruct the study staff to document the full battery of orthotic devices the subject uses, at the point of study entry.

8 ASSESSMENT OF EFFICACY

8.1 Specification of clinical trial efficacy parameters

Primary efficacy endpoint will be:

- Physical performance (2MWD) from baseline to the end of the treatment period (at EoTV – Week 52).

Secondary efficacy endpoints will be:

- Pain (VAS of pain) from baseline to the end of the treatment period.
- HRQoL (SF-36 PCS) from baseline to the end of the treatment period.
- Endurance (6MWD) from baseline to the end of the treatment period.

Exploratory endpoints will be:

- Muscle strength of 2 newly weakened muscle groups (MMT using the MRC scale) from baseline to the end of the treatment period.
- Muscle strength of 2 newly weakened muscle groups (QMT using a dynamometer) from baseline to the end of the treatment period.
- Walking activity in daily life (pedometer) from baseline to the end of the treatment period.
- Subject's self-perceived exertion/fatigue level using the Borg scale before and after the 2MWD and the 6MWD from baseline to the end of the treatment period.
- Fatigue (FSS) from baseline to the end of the treatment period.
- HRQoL (SF-36 MCS) from baseline to the end of the treatment period.
- Blood inflammatory cytokines from baseline to the end of the treatment period.
- Sustained effect of Flebogamma® 5% DIF compared to placebo as measured by:
  - Physical performance (2MWD) from baseline to FU3 (Week 64) and to the FV (Week 76).
  - Pain (VAS of pain) from baseline to FU3 and to the FV.
  - HRQoL (SF-36 PCS) from baseline to FU3 and to the FV.
  - Endurance (6MWD) from baseline to FU3 and to the FV.
  - Muscle strength (MMT using the MRC scale) from baseline to the FV.
  - Muscle strength (QMT using a dynamometer) from baseline to the FV.

- Walking activity in daily life (pedometer) from baseline to the FV.
- Subject's self-perceived exertion/fatigue level using the Borg scale before and after the 2MWD and 6MWD from baseline to FU3 and to the FV.
- Fatigue (FSS) from baseline to the FV.
- HRQoL (SF-36 MCS) from baseline to FU3 and to the FV.
- Blood inflammatory cytokines from baseline to the FV.

8.2 Methods and timing for assessing, recording, and analyzing clinical trial efficacy parameters

8.2.1 Physical performance

Primary efficacy endpoint:

The treatment effect of Flebogamma® 5% DIF compared to placebo on physical performance will be calculated as the least squares means difference between treatment groups in the change in 2MWD from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

Exploratory endpoint:

The sustained effect of Flebogamma® 5% DIF compared to placebo on physical performance will be calculated as the least squares means difference between treatment groups in the change in 2MWD from baseline (at EV/IV1) to 12 and 24 weeks after the last investigational product infusion, that is, at FU3 and at the FV.

8.2.2 Pain

Secondary efficacy endpoint:

The treatment effect of Flebogamma® 5% DIF compared to placebo on pain will be calculated as the least squares means difference between treatment groups in the change in VAS for pain score from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

Exploratory endpoint:

The sustained effect of Flebogamma® 5% DIF compared to placebo on pain will be calculated as the least squares means difference between treatment groups in the change in VAS for pain from baseline (at EV/IV1) to 12 and 24 weeks after the last investigational product infusion, that is, at FU3 and at the FV.

8.2.3 Health-related quality of life physical component

Secondary efficacy endpoint:

The treatment effect of Flebogamma® 5% DIF compared to placebo on HRQoL will be calculated as the least squares means difference between treatment groups in the change in SF-36 PCS score from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

Exploratory endpoint:

The sustained effect of Flebogamma® 5% DIF compared to placebo on HRQoL will be calculated as the least squares means difference between treatment groups in the change in SF-36 PCS score from baseline (at EV/IV1) to 12 and 24 weeks after the last investigational product infusion, that is, at FU3 and at the FV.

8.2.4 Endurance

Secondary efficacy endpoint:

The treatment effect of Flebogamma® 5% DIF compared to placebo on endurance will be calculated as the least squares means difference between treatment groups in the change in 6MWD from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

Exploratory endpoint:

The sustained effect of Flebogamma® 5% DIF compared to placebo on endurance will be calculated as the least squares means difference between treatment groups in the change in 6MWD from baseline (at EV/IV1) to 12 and 24 weeks after the last investigational product infusion, that is, at FU3 and at the FV.

8.2.5 Muscle strength

Exploratory endpoints:

The treatment effect of Flebogamma® 5% DIF compared to placebo on muscle strength will be calculated as the least squares means difference between treatment groups in the change in MRC score and in QMT score from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

The sustained effect of Flebogamma® 5% DIF compared to placebo on muscle strength will be calculated as the least squares means difference between treatment groups in the change in MRC score and in QMT score from baseline (at EV/IV1) to 24 weeks after the last investigational product infusion, that is, at the FV.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

8.2.6 Walking activity in daily life

Exploratory endpoints:

The treatment effect of Flebogamma® 5% DIF compared to placebo on walking activity in daily life will be calculated as the least squares means difference between treatment groups in the change in number of steps performed during 7 consecutive days prior to the scheduled visit, from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

The sustained effect of Flebogamma® 5% DIF compared to placebo on walking activity in daily life will be calculated as the least squares means difference between treatment groups in the change in number of steps performed during 7 consecutive days prior to the scheduled

visit, from baseline (at EV/IV1) to 24 weeks after the last investigational product infusion, that is, at the FV.

8.2.7 Perceived exertion/fatigue

Exploratory endpoint:

The treatment effect of Flebogamma® 5% DIF compared to placebo on self-perceived exertion/fatigue using the Borg scale will be calculated as the least squares means difference between treatment groups in the change in Borg scale from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

The sustained effect of Flebogamma® 5% DIF compared to placebo on self-perceived exertion/fatigue using the Borg scale will be calculated as the least squares means difference between treatment groups in the change in Borg scale from baseline (at EV/IV1) to 12 weeks and 24 weeks after the last investigational product infusion, that is, at FU3 and at the FV.

8.2.8 Fatigue

Exploratory endpoints:

The treatment effect of Flebogamma® 5% DIF compared to placebo on fatigue will be calculated as the least squares means difference between treatment groups in the change in FSS from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

The sustained effect of Flebogamma® 5% DIF compared to placebo on fatigue will be calculated as the least squares means difference between treatment groups in the change in FSS from baseline (at IV1) to 24 weeks after the last investigational product infusion, that is, at the FV.

8.2.9 Health-related quality of life mental component

Exploratory endpoints:

The treatment effect of Flebogamma® 5% DIF compared to placebo on HRQoL will be calculated as the least squares means difference between treatment groups in the change in SF-36 MCS score from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

The sustained effect of Flebogamma® 5% DIF compared to placebo on HRQoL will be calculated as the least squares means difference between treatment groups in the change in SF-36 MCS score from baseline (at EV/IV1) to 12 and 24 weeks after the last investigational product infusion, that is, at FU3 and at the FV.

8.2.10 Inflammatory cytokines

Exploratory endpoints:

The treatment effect of Flebogamma® 5% DIF compared to placebo on inflammatory cytokines will be calculated as the least squares means difference between treatment groups in the change in blood inflammatory cytokine levels from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52).

The sustained effect of Flebogamma® 5% DIF compared to placebo on inflammatory cytokines will be calculated as the least squares means difference between treatment groups in the change in blood inflammatory cytokine levels from baseline (at EV/IV1) to 24 weeks after the last investigational product infusion, that is, at the FV.

9 ASSESSMENT OF SAFETY

9.1 Specification of safety parameters

Aspects of clinical safety will be evaluated in this clinical trial.

Safety endpoints will include:

- AEs and suspected ADRs.
- Vital signs during infusions.
- Physical assessments.
- Blood biochemistry and cell counts.

9.2 Methods and timing for assessing, recording, and analyzing safety parameters

Safety will be assessed throughout the clinical trial for all individuals who have received at least 1 infusion of the investigational product (test or placebo).

9.2.1 Adverse events

AEs (includes suspected ADRs) occurring at any time between signature of the subject's ICF and the last day of the subject's participation in the clinical trial will be reported and recorded on the appropriate subject's eCRF.

It is Investigator's responsibility to ensure that all AEs are appropriately recorded.

AEs will be elicited by spontaneous reporting by the study individual or by a non-leading inquiry or direct observation by the study staff.

9.2.2 Vital signs during infusions

During all treatment infusions, vital signs (T, RR, HR, SBP and DBP) will be monitored by the Investigator or study staff. Monitoring will be routinely performed within 20 minutes before the beginning of infusion as well as every 30 ± 10 minutes during the first hour of infusion. Thereafter, vital signs will be monitored and recorded at 30 ± 10 minutes post-completion of infusion. Recorded values must be reviewed (with signature and date) by a medical doctor.

Clinically relevant changes in vital signs during infusions of Flebogamma® 5% DIF or Normal Saline Solution will be reported as AEs. Clinical relevance will be based on the Investigator's judgment.

9.2.3 Physical assessment

Physical examinations will be registered as normal or abnormal, according to the medical doctor's judgment or study staff's judgment. Abnormal findings judged as clinically relevant by the Investigator will be considered AEs.

9.2.4 Blood biochemistry and cell counts

All clinical laboratory data for renal (creatinine, BUN and GFR), hepatic (ALT, AST, ALP and TBL) and haematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subjects.

The Investigator will be required to classify laboratory results out of the normal range reported by the laboratory as clinically relevant or not according to his/her judgment.

Laboratory results out of the normal range judged by the Investigator as clinically relevant will be considered AEs.

9.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses

9.3.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any AE that occurs at any time between signature of the ICF and last day of the subject's participation in the clinical trial must be reported and recorded on the AE eCRF.

9.3.2 Suspected adverse drug reaction/adverse reaction

All noxious and unintended responses to a medicinal product or device related to any dose should be considered suspected ADRs. The phrase "responses to a medicinal product or device" means that a causal relationship between a medicinal product or device and an AE is at least a reasonable possibility, that is, the relationship cannot be ruled out. In the framework of this study, a suspected ADR with a causal relationship of "definite" will be labeled as an AR; thus, ARs are a subset of suspected ADR.

9.3.3 Causality of adverse event

The investigator is required to provide a causality assessment for each AE reported to the sponsor. The sponsor will consider the investigator's causality assessment and also provide its own assessment. Assessment of the causal relationship to the study drug will be made according to the following classifications based on Karch FE, et al. [70]:

1. Definite: An event that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues; that follows a known response pattern to the suspected drug; and that is confirmed by

improvement on stopping the drug (dechallenge), and reappearance of the event on repeated exposure (rechallenge).

2. Probable: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern to the suspected drug; that is confirmed by dechallenge; and that could not be reasonably explained by the known characteristics of the patient's clinical state.
3. Possible: An event that follows a reasonable temporal sequence from administration of the drug; that follows a known response pattern to the suspected drug; but that could have been produced by the patient's clinical state or other modes of therapy administered to the patient.
4. Doubtful/Unlikely: An event that follows a reasonable temporal sequence from administration of the drug; that does not follow a known response pattern to the suspected drug; but that could not be reasonably explained by the known characteristics of the patient's clinical state.
5. Unrelated: Any event that does not meet the criteria above.

The operational tool to decide the AE causal relationship is based on algorithms by Karch-Lasagna and Naranjo (ANNEX 15) [71,72].

When an AE is classified, assessing causal relationship by the Investigator, as "definite", "probable," "possible" or "doubtful/unlikely," the event will be defined as a suspected ADR. A suspected ADR with a causal relationship of "definite" will be defined as an AR. When the causal relationship is labeled "unrelated," then it will be considered that the AE is not imputable to the study treatment, and it is not a suspected ADR.

In addition, when a causal relationship between the study treatment and the AE cannot be ruled out by the Investigator and/or sponsor, it means that the AE cannot be labeled "unrelated".

For any subject, all AEs that occur at any time, between the beginning of the first infusion of Flebogamma® 5% DIF or Normal Saline Solution and the final visit of the clinical trial, will be considered as TEAEs.

AEs occurring during the 2-day infusion period (*i.e.*, from the initiation of the investigational product infusion on the first day to the completion of the total dose of investigational product on the last day) and within 72 hours following the completion of the infusion of the total dose of investigational product on the last day, regardless of other factors that may impact a possible causal association with product administration, will be defined as infusional AEs (*i.e.*, an AE temporally associated with an infusion of the investigational product) and labeled TEAEs [73].

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured.

9.3.4 Intensity of adverse event or suspected adverse drug reaction

AEs and suspected ADRs will be classified depending on their intensity according to the following definitions:

1. Mild: an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.
2. Moderate: an AE that interferes with the subject's normal activities.
3. Severe: an AE that prevents the subject from performing their normal activities.

AE and suspected ADR intensity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate or severe but unusually is serious in all these cases.

The Investigator will be responsible for assessing the AE and suspected ADR intensity during the clinical trial, taking into account currently criteria included in this section.

9.3.5 Expectedness of adverse event or suspected adverse drug reaction

An AE or suspected ADR is considered "unexpected" if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness of an AR shall be determined by the sponsor according to the reference document (IB or SPC).

Events not listed for the particular drug under investigation in the IB (or SPC) are considered "unexpected" and those listed are considered "expected." When new AE information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for IND safety reporting purposes.

9.3.6 Seriousness of adverse event or adverse reaction; serious adverse event

An AE or suspected ADR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1. Death.
2. Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
3. In-patient hospitalization or prolongation of existing hospitalization.

   Note: hospitalization is to be considered only for hospital stays for $\geq$ 24 hours.

   The following hospitalizations should not be reported as SAEs:

   - Hospitalization or prolongation of hospitalization needed for procedures required by the clinical trial protocol.
   - Hospitalization or prolongation of hospitalization as part of a routine procedure followed by the center.
   - Hospitalization for a survey visit, annual physicals, or social reasons.
   - Elective (preplanned) hospitalizations for a pre-existing condition that had not worsened from Baseline (e.g., elective or scheduled surgery arranged prior to start of the study).

- Admissions not associated with an AE (e.g., social hospitalization for purposes of respite care).

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly/ birth defect.
6. An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above.

This definition permits either the sponsor or the Investigator to decide whether an event is "serious". If either the sponsor or the Investigators believes that the event is serious, the event must be considered "serious" and evaluated by the sponsor for expedited reporting.

A distinction should be drawn between serious and severe AEs. The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is defined on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) is a medical term while severity is a subjective term.

According to the medical criteria, an AE or a suspected ADR can be classified as serious, although it does not fulfill the conditions fixed in this section, if it is considered important from a medical point of view.

9.3.7 Adverse events of special interest

9.3.7.1 Thromboembolic events

Subjects will be monitored for signs and symptoms of arterial and venous thromboembolic (TE) events. In addition, the Grifols Medical Monitor (Clinical Assessment Monitor) will routinely review reported AEs for possible TE events. Arterial and venous TE events will be identified according to definitions in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Such events include, but are not limited to, DVT, PE, acute myocardial infarction, cerebral infarction, acute ischemic heart disease, embolism or thrombosis of arteries of lower extremities, sagittal sinus thrombosis, and portal vein thrombosis and injury of mesenteric artery. All TE events will be recorded as AEs and reported accordingly.

9.3.7.2 Hemolysis

Subjects will be monitored for signs and symptoms of hemolysis. In addition, the Grifols Medical Monitor (Clinical Assessment Monitor) will routinely review reported AEs for possible hemolysis. Hemolysis will be recorded as AEs and reported accordingly.

9.3.8 Procedures for eliciting reports of and for recording and reporting adverse events and adverse reactions

The occurrence and follow-up details of all AEs experienced by any of the subjects during the clinical trial, from signature of the *Clinical Trial Written Informed Consent Form* to the last follow-up visit, will be recorded on the AE eCRF entry and in the subject's hospital record. If no AE has occurred during the study period, this should also be indicated in the eCRF.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in way since the last visit?" Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures preferably should be grouped together and recorded as a single diagnosis or syndrome wherever possible. It is responsibility of the Investigator to ensure that AEs are appropriately recorded.

The following variables must be recorded on the AE eCRF entry:

1. the verbatim term (a diagnosis is preferred)
2. date/time of onset
3. date/time of resolution
4. intensity (mild, moderate, severe)
5. causality (unrelated, doubtful/unlikely, possible, probable, definite)*
6. seriousness (yes, no)
7. action taken (with regard to study drug)
8. other action (to treat the event)
9. outcome and sequel (follow-up on AE)

**Causality assessment will be only made when the AE occurs after the subject has received one or another study treatment. AE occurring before subject's exposure to study treatments will be always labeled as "unrelated".*

For AEs that occur during infusions, the infusion rate in effect at the time of onset of the AE, the time of onset of the AE and the time of AE change materially in intensity and/or resolve will be captured the eCRF entry.

In addition to the Investigator's own description of the AEs, each AE will be encoded by the sponsor (CRO) according to the Medical Dictionary for Regulatory Activities (MedDRA®).

The Development Safety Update Report (DSUR) for the investigational product Flebogamma® DIF is prepared by the sponsor of the clinical trial in compliance with the ICH Guideline "E2F Development Safety Update Report". The DSUR is annually submitted by the sponsor to the Competent Authorities on Medicines in the countries where the sponsor has been performing clinical trials with the investigational product Flebogamma® DIF.

A DSUR Executive Summary, supplemented with line listings of serious adverse reactions (SARs), is also annually submitted by the sponsor to ethics committees (ECs)/institutional

review boards (IRBs), where national or regional laws or regulations require submission of an annual safety report on an investigational product.

9.3.8.1 Reporting pregnancy

While pregnancy itself is not a true "AE," pregnancy occurring in a clinical study must be followed to collect information regarding the experiences of gestation and pregnancy with investigational product exposure. The Investigator must report any pregnancy that occurs in a female study subject or partner of a male study subject subsequent to informed consent until 28 days after the last dose of investigational product.

A pregnancy not verified before randomization but occurring during the course of the study will be not considered an AE, unless a relation to the study drug is suspected. In any case, a *Pregnancy Report Form must be completed* and sent as soon as possible to the sponsor, and the study treatment must be discontinued. A copy of the form should be filled at the study site for follow-up until the end of the pregnancy.

Any pregnancy occurring in a female study subject or partner of a male study subject must be followed by the Investigator until delivery or to the end of pregnancy. Any anomalies, complications, abnormal outcomes, or birth defect observed in the child must be reported as an SAE within 24 hours of the Investigator's or study personnel's first knowledge. Please use the email address or fax numbers (back up only) in Section 9.3.8.2 for reporting pregnancy.

9.3.8.2 Reporting of serious adverse events

Any SAE (see Section 9.3.6) that occurs after signing the ICF and last day of subject´s participation in the clinical trial must be expeditiously reported whether or not it is considered attributable to the study drug. Each SAE must be fully recorded in the subject's eCRF.

SAEs will be reported using the designated SAE Report Form. When the Investigator becomes aware of an SAE, she/he must submit it electronically through the electronic data capture (EDC) system **within 24 hours**. When the EDC system is not available, the SAE is to be reported to the sponsor **within 24 hours** by emailing or faxing a completed, signed and dated paper SAE Report Form (ANNEX 16, in English). The date of this SAE discovery by the site staff should be documented in the source documents (*i.e.*, medical records).

Each SAE must be followed up until its resolution or stabilization. After the initial report, all relevant follow-up information for SAE including the outcome, must also be supplied to the sponsor in a timely manner (within 3 days from its identification or within 24 hours for relevant new information) via EDC or by means of the SAE Report Form when EDC system is not available. In addition, the sponsor or the CRO may request additional information and/or reports.

All SAE Report Forms must be submitted to Grifols, electronically through the EDC system or with a paper SAE report form when the EDC system is not available, to:

Grifols Global Drug Safety

Email: [redacted]
FAX (back-up only): [redacted] (International)

When required by local law and regulations, SAEs must be reported to the IRB/EC and regulatory authorities.

SAEs will be assessed by the sponsor for expectedness assuming that all subjects have been treated with Flebogamma® 5% DIF. If the causality assessment was considered anything other than unrelated by the Investigator, the event will be considered serious, suspected, potentially related to the study drug and unexpected (SUSAR) and then the treatment allocation will be unblinded to unblinded sponsor staff included in Section 4.3.2 and to the sponsor global pharmacovigilance staff. Anyone involved in site monitoring and analysis or interpretation of data will be kept blinded. The following possibilities resulting from the unblinding will be considered:

1. If the study drug administered to the subject is Flebogamma® 5% DIF, the case will be reported in accordance to local regulations.

2. If the study drug administered to the subject is Normal Saline Solution, the suspected ADR will be reassessed for expectedness according to the reference safety information and:

    a. If the suspected ADR is still considered unexpected, it will be reported in accordance with applicable requirements and guidelines.

    b. If the suspected ADR is considered expected, it will not be reportable on an expedited basis, unless specifically requested by local regulations.

9.4 Type and duration of the follow-up of subjects after adverse events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected and the Investigator decides that no further follow-up is necessary.

10 STATISTICS

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

10.1 Statistical methods to be employed and timing of planned interim analysis

A SAP will describe study analyses in detail.

As a general rule, data will be summarized descriptively using count, mean and standard deviation (SD) of the mean for continuous variables, and count and percentage for categorical variables. Median, minimum and maximum for continuous variables could be also calculated. Estimations of confidence intervals of descriptive statistics could be done.

10.1.1 Statistical analysis of demographic data and baseline characteristics

Demographic data and other baseline characteristics will be presented in tables and summarized as descriptive statistics.

10.1.2 Statistical analysis of efficacy

Efficacy analysis will be primarily based on the intent-to-treat (ITT) population (see Section 10.6.1). In addition, for sensitivity analyses, efficacy analyses will also be run on the per protocol (PP) population (see Section 10.6.1).

10.1.2.1 Analysis of primary efficacy endpoint

The primary efficacy endpoint is physical performance, evaluated by 2MWD, from baseline (at EV/IV1) to the end of the treatment period (at the EoTV – Week 52) for Flebogamma® 5% DIF compared to placebo in the ITT population.

The treatment difference between Flebogamma® 5% DIF and placebo will be tested using the mixed-effect model with repeated measures (MMRM) method with change from baseline in 2MWD as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and main part of the body most significantly affected (lower/upper extremities) by PPS as the fixed effects; baseline 2MWD measure as covariate; and visit as a repeated measure.

At Stage 1, the difference between treatment groups in the change in 2MWD, from baseline (at EV/IV1) to the end of the treatment period (at EoTV – Week 52), will be tested to determine the treatment effect of IVIG 2 g/kg versus placebo and IVIG 1 g/kg versus placebo.

At Stage 2, the difference between treatment groups in the change in 2MWD, from baseline (at EV/IV1) to the end of the treatment period (at EoTV – Week 52), will be tested to determine the treatment effect of the selected dose of IVIG from Stage 1 and placebo.

For the selected dose group of IVIG versus placebo, p-values will be obtained from Stage 1 and Stage 2 separately. The overall adjusted p-value will be calculated from the p-values from both Stage 1 and Stage 2 by the method proposed by Posch & Bauer (2005) [60] in order to control the overall type I error rate for testing the equal means between the selected dose group and the placebo group:

$$H_0: \mu_{flebogamma} - \mu_{placebo} = 0 \ (or\ equivalently\ H_0: \mu_{flebogamma} = \mu_{placebo})$$

versus

$$H_A: \mu_{flebogamma} - \mu_{placebo} \neq 0 \ (\mu_{flebogamma} - \mu_{placebo} > 0 \ or \ \mu_{flebogamma} - \mu_{placebo} < 0)$$

where $\mu_{flebogamma}$ and $\mu_{placebo}$ are the means of 2MWD for the selected Flebogamma® 5% DIF dose group and placebo respectively. The superiority will be deemed to have been demonstrated if the 2-sided overall adjusted p-value is less than or equal to 0.05 and

$\mu_{flebogamma} - \mu_{placebo} > 0$.

For sensitivity analysis of combined data in 2MWD from Stage 1 and Stage 2 for the selected dose group of IVIG versus placebo, an analysis of covariance (ANCOVA) method with change from baseline in 2MWD as the dependent variable, treatment and main part of the body most significantly affected (lower/upper extremities) by PPS as the fixed effects, and baseline 2MWD measure as covariate. Missing data will be imputed using a last-observation carried forward approach for post-baseline 2MWD measurement.

The analyses performed on ITT will be repeated for the PP population.

10.1.2.2 Analysis of secondary efficacy endpoints

The data from Stage 1 and Stage 2 for the selected doses will be combined and the same approaches (e.g., MMRM or ANCOVA) used in the primary efficacy analyses will be applied to the analyses of the secondary efficacy endpoints. A fixed-sequence testing method will be employed to address the multiplicity issue for multiple secondary efficacy variables. The order in which the null hypotheses are tested is predetermined as below for all secondary efficacy variables:

- Pain by a VAS for pain:
  Treatment effect in change in VAS score, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).
- HRQoL by the SF-36 PCS:
  Treatment effect in change in SF-36 PCS score, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).
- Endurance by the 6MWD:
  Treatment effect in change in 6MWD, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

Each subsequent hypothesis is tested only if all previously tested null hypotheses have been rejected at a 2-sided significance level of 5%.

10.1.2.3 Analysis of exploratory endpoints

The data from Stage 1 and Stage 2 for the selected doses will be combined and the same approaches (e.g., MMRM or ANCOVA) used in the primary efficacy analyses will be applied to the analyses of the exploratory efficacy endpoints:

- Muscle strength by the MMT using the MRC scale in 2 newly weakened muscle groups:
  Treatment effect in change in MRC score, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- Muscle strength by the QMT using a dynamometer in 2 newly weakened muscle groups:
  Treatment effect in change in QMT score, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- Walking activity in daily life by a pedometer:
  Treatment effect in change in number of steps performed daily during 7 consecutive days prior to the scheduled study visit, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- Perceived exertion/fatigue by Borg scale:
  Treatment effect in change in Borg scale, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- Fatigue by FSS:
  Treatment effect in mean change in FSS score, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- HRQoL by the SF-36 MCS:
  Treatment effect in mean change in SF-36 MCS score, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- Blood inflammatory cytokines:
  Treatment effect in change in blood inflammatory cytokines, from baseline to the end of the treatment period, will be tested between the 2 treatment groups (test and placebo).

- Sustained physical performance by 2MWD:
  Treatment effect in change in 2MWD, from baseline to 12 and 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained HRQoL by SF-36 PCS:
  Treatment effect in change in SF-36 PCS score, from baseline to 12 and 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained pain by VAS for pain:
  Treatment effect in change in VAS score, from baseline to 12 and 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained endurance by 6MWD:
  Treatment effect in change in 6MWD, from baseline to 12 and 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained muscle strength by the MMT using the MRC scale in 2 newly weakened muscle groups:
  Treatment effect in change in MRC score, from baseline to 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained muscle strength by the QMT using a dynamometer in 2 newly weakened muscle groups:

Treatment effect in change in QMT score, from baseline to 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained walking activity in daily life by a pedometer:

  Treatment effect in change in the number of steps performed daily during 7 consecutive days prior to the scheduled study visit, from baseline to 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained perceived exertion/fatigue by Borg scale:
  Treatment effect in change in Borg scale, from baseline to 12 and 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained fatigue by FSS:

  Treatment effect in change in FSS score, from baseline to 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained HRQoL by SF-36 MCS:

  Treatment effect in change in SF-36 MCS score, from baseline to 12 and 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

- Sustained blood inflammatory cytokines:

  Treatment effect in change in blood inflammatory cytokines, from baseline to 24 weeks after the last investigational infusion, will be tested between the 2 treatment groups (test and placebo).

10.1.3 Statistical analysis of safety

The safety analyses will be addressed by listing and tabulation of AEs (includes suspected ADRs), vital signs, physical assessments and clinical laboratory tests. Data will be described using descriptive analyses.

- Adverse events:

  Safety analysis will be primarily focused on a descriptive analysis of suspected ADRs. Safety assessment will be based on the prevalence of suspected ADRs that occurred during the clinical trial.

  Adverse events will be coded and classified using MedDRA® terms (system organ class and preferred terms).

  Adverse events will be classified as treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment with the investigational product. A TEAE will be defined as an AE which occurs between the beginning of the first infusion of Flebogamma® 5% DIF or Normal Saline Solution and the final visit of the clinical trial. A non-TEAE will be defined as an AE which occurs prior to the start of study treatment. Non-TEAEs and TEAEs will be summarized separately. TEAEs that occurred during the Treatment period (from the first investigational product infusion at IV1, Week 0, to the

EoTV, Week 52) and Follow-up period (from EoTV, Week 52, to the FV, Week 76) will be collectively and separately summarized.

All AEs will be summarized by presenting subject incidences and percentages, and they will also be listed by body systems with subject identification codes.

In addition, TEAEs, including suspected ADRs, will be summarized by each treatment arm, system organ class, preferred term, causal-relationship, intensity (severity) and seriousness (serious versus non-serious) using descriptive statistics. At each level of summarization, a subject will only be counted once per system organ class or preferred term using the most severe or causal relationship AE.

AEs, including suspected ADRs, of thromboembolic and hemolytic origin will also be summarized separately.

AEs temporally associated to the infusion of the investigational products (*i.e.*, infusional AEs, including infusional suspected ADRs), will be summarized by presenting infusion/subject incidences and percentage and ordered by ordinal number of infusions, and listed. In addition, the infusion rate in effect at the time of onset of the AE, the time the AE is first reported, and the time the AE changes materially in intensity and/or resolves will be also reported and listed. In addition, AEs temporally associated to the infusion of the investigational products for which the incidence in the Flebogamma® 5% DIF exceeds the incidence in the placebo group will be summarized separately.

Subjects with a serious adverse event (SAE) or who withdraw from the study because of an AE will also be individually listed and summarized.

AEs for which the investigator causality assessment is missing or undetermined will be individually listed.

- Vital signs during infusions:

  Vital signs (T, RR, HR, SBP and DBP) will be listed for each clinical trial subject. In case a subject presents a clinically relevant abnormality of vital signs (based on the Investigator's judgment) during an infusion, the event will be flagged and reported as an AE temporally associated to the infusion. All vital signs will be evaluated for each subject and for each infusion.

- Physical assessment:

  Physical findings (normal and abnormal) will be listed for each clinical trial subject. Any clinically relevant abnormality (based on the Investigator's judgment) developed by individual during the clinical trial and not already present at baseline will be reported as AE.

- Blood biochemistry and cell counts:

  All clinical laboratory data for renal (creatinine, BUN and GFR), hepatic (ALT, AST, ALP and TBL) and haematological parameters (CBC including differential leukocyte count) will be listed for each clinical trial subjects. Laboratory results out of the normal range judged by the Investigator as clinically relevant will be considered AEs.

10.1.4 Timing of planned interim analysis [redacted]

A formal unblinded interim analysis will be performed by an independent DMC after at least 80% of randomized subjects have finished the treatment period of the Stage 1 in order to continue to Stage 2 of the clinical trial with 1 of the 2 active treatment groups selected from Stage 1. The following selection rules will be applied at interim analysis by the independent DMC. Further details will be specified in the DMC charter.

At the interim analysis, conditional power (the power conditional on the partial information accumulated at the interim analysis) will be calculated on the primary efficacy endpoint of 2MWD. Between the 2 active treatment arms (Flebogamma® 5% DIF 2 g/kg and 1 g/kg), if conditional power in Flebogamma® 5% DIF 2 g/kg group is at least 10% relatively higher than Flebogamma® 5% DIF 1 g/kg group, then choose Flebogamma® 5% DIF 2 g/kg to move forward. Otherwise, choose Flebogamma® 5% DIF 1 g/kg to move forward.

[redacted]

10.2 Sample size determination

The sample size of this clinical trial has been calculated based on the primary efficacy endpoint (2MWD) at the end of the treatment period (EoTV – Week 52).

Baseline measure of 2MWD in patients with PPS has been estimated in about 120 meters with standard deviations between 24 and 28 meters. The standard deviations for change from baseline to week 3 and week 17 in 2MWD are in the range of 8 to 11 meters [37,55,56]. In order to show the superiority of Flebogamma 5% DIF over placebo, an effect size of 5% (6 meters) in change from estimated baseline in 2MWD (120 meters) is assumed.

A clinically relevant change in distance walked at the end of the treatment period (after 52 weeks of treatment) between groups (Flebogamma® 5% DIF versus placebo) has been stated to be 5%.

The study will employ a flexible group sequential design with 2 stages and 1 interim analysis between stages for the purpose of adaptive dose selection. Sample sizes are estimated with group sequential design with O'Brien-Fleming Method [74] for alpha-level adjustment for interim analysis for dose selection.

In order to show the treatment difference of 6 meters with a standard deviation of 11 meters, 99 subjects need to be randomized into 1 of 3 treatment group in Stage 1 and 66 subjects need to be randomized into 1 of 2 treatment groups in Stage 2. Thus, to account for a 20% dropout rate, approximately 126 will be randomized into 1 of the 3 treatment arms (42 subjects/arm) in Stage 1, and approximately 84 subjects will be randomized into 1 of the 2 treatment arms (42 subject/arm) in Stage 2.

10.3 Level of significance

For 1-sided statistical tests, an alpha level of 0.025 will be considered to indicate statistical significance. For 2-sided statistical tests, an alpha level of 0.05 will be considered to indicate statistical significance.

10.4 Procedures for accounting for missing, unused, and spurious data

Procedures for the handling of missing, unused, and spurious data will be described in the SAP and clinical study report.

10.5 Procedures for reporting any deviation from the original statistical plan

Deviations from the original statistical plan are not anticipated. Nevertheless, major deviations from the original statistical plan will be documented in the SAP and clinical study report.

10.6 Selection of subjects to be included in the analyses

10.6.1 Population for statistical analysis of efficacy

Two study populations for statistical analysis of efficacy may be used: ITT population and PP population. All efficacy analysis will be primarily run on the ITT population and then they may be run on the PP population.

The **ITT population** will include all randomized subjects. Subjects will be analyzed per the randomized treatment.

The **PP population** will include subjects in the ITT population who have received at least 8 infusions, without having 2 consecutive missed infusions, of any investigational product (test or placebo) during the treatment period, have baseline and at least 1 post-baseline measures of the 2MWD, and have no major protocol violations that might have impact on the primary efficacy assessment (as determined at a data review meeting prior to database lock and unblinding).

The major protocol violations will include, but are not limited to, the following: entry inclusions/exclusions not met, more than 1 consecutive missed infusion or more than 4 missed infusions during the treatment period, randomization error (*i.e.*, wrong treatment received), and treatment unblinded during the study treatment period.

10.6.2 Population for analysis of safety

All patients who receive at least 1 infusion (at any dose) of the investigational product, test or placebo, (safety population) will be included in the safety analysis. The subjects will be analyzed per the treatment actually received.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The data will be recorded and kept current in CRF/eCRFs by the study site personnel directly responsible for the information and reviewed for completeness by the monitor. Grifols personnel or designee can review the records.

In accordance with ICH GCP guidelines, the monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the CRF/eCRFs for consistency and to verify adherence to the protocol, and the completeness, consistency, and accuracy of data entered. "Source documentation" includes individual subject files, separate from the CRF/eCRFs, which should be maintained and include visit dates, laboratory results, concomitant treatment, vital signs, medical history, examinations, AEs, investigational product dispensing logs, and other notes as appropriate. The investigator agrees to cooperate with the monitor to ensure that any problems noted during the course of these monitoring visits are resolved.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with ICH GCP guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, ICH GCP and legal aspects. The on-

site verification of the CRF/eCRF for completeness and clarity will include cross checking with source documents, and clarification of administrative matters.

Representatives of regulatory authorities or of Grifols may conduct audits or inspections or audits of the investigator study site. If the investigator is notified of an audit or inspection by a regulatory authority, the investigator agrees to notify the Grifols Representative (*e.g.*, Clinical Assessment Monitor, Program Manager, Program Leader) immediately. The investigator agrees to provide to representatives of a Regulatory Agency or Grifols access to records, facilities, and personnel for the effective conduct of an audit or inspection.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

13 ETHICS

13.1 Ethics Committee

Documented approval from appropriate ECs will be obtained for all participating centers/countries prior to study start, according to ICH GCP guidelines, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the ECs approval must be obtained and also forwarded to the sponsor. The ECs must supply to the sponsor, upon request, a list of the ECs members involved in the vote and a statement to confirm that the ECs is organized and operates according to ICH GCP guidelines and applicable laws and regulations.

13.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by ICH GCP guidelines. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an audit by the sponsor representatives and/or an inspection by regulatory authority representatives at any time. The investigator must agree to the audit or inspection of study-related records by the sponsor representatives and/or regulatory authority representatives and must allow direct access to source documents to the sponsor and/or regulatory authority representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the study subjects without prior EC/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate the proposed protocol amendment should be submitted to the EC/sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

No medical waivers for protocol inclusion/exclusion criteria will be allowed by the sponsor. If there is a need for changes to the protocol inclusion/exclusion criteria is identified, the protocol will be amended to include such changes. The protocol amendment will be submitted to the regulatory authority and/or EC as applicable per regulations, which allows implementation of the revised inclusion/exclusion criteria in the study.

13.3 Regulatory Authority Approvals/Authorizations

Regulatory authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start. Study information including contact information for investigator sites responsible for conducting the study will be posted on a publicly accessible clinical registry(ies) as required by local law.

13.4 Subject Information and Consent

Subject information and ICF will be provided to investigator sites. Prior to the beginning of the study, the investigator must have the EC written approval/favorable opinion of the written ICF and any other written information to be provided to subjects. The written approval of the EC together with the approved subject information/ICF must be filed in the study files and a copy of the documents must also be provided to sponsor by the investigator site.

Written ICF must be obtained before any study specific procedure takes place. Participation in the study and date of ICF given by the subject should be documented appropriately in the subject's files. A signed copy of the subject ICF will be provided to the subject or subject's authorized representative.

13.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject code number will be recorded in the CRF/eCRF, and if the subject's name appears on any other document (e.g., pathologist report), it must be redacted before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. Subjects will be informed in writing that representatives of the sponsor, EC, or regulatory authorities may inspect their medical records and personal health information to verify the information collected, and that all personal information made available for an audit or inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data collection and management

Data generated per protocol will be entered onto the eCRF in accordance with the parameters set forth in the point 5.5 of ICH Topic E6 (R1) Guideline for Good Clinical Practice, CPMP/ICH/135/95, 1996 and E6 (R2) Guideline for Good Clinical Practice, EMA/CHMP/ICH/135/1995, 2016 - Responsibilities of Sponsor, Clinical Study Monitor and Investigator.

The study data will be recorded and kept current in the CRF/eCRF by the site study personnel directly responsible for the information. The eCRF will be completed per

instructions, with reasons given for any missing data. Under no circumstances should entered data be permanently deleted. Since it is extremely important to have proper data collection in a timely manner, the investigator or study staff shall complete the eCRFs as soon as possible after each subject clinic visit. When the monitor requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily and in a timely manner.

Entries made in the CRF/eCRF must be verifiable against source documents. The data in the CRF/eCRF will be monitored at the site by Grifols representatives at regular intervals and reviewed for completeness and compared with the source documents. Examples of acceptable source documents include individual subject medical records, prospective information gathered on source documentation worksheets, lab reports, and other diagnostics pertinent to this study which are separate from the CRF/eCRFs. The listing of types of source documents which will be defined in the source data agreement will be filed in the TMF.

The eCRF data will be sent to the data management team for review. Subsequent electronic review of data may result in queries being generated that will be forwarded simultaneously to the appropriate investigator or study staff for prompt resolution. Resolutions will be sent back to the data management team in a timely fashion. All data modifications resulting from review or querying of the data will be electronically tracked.

Coding of AEs will be performed automatically by the data management team using the MedDRA® dictionary (current version or the immediately former version in force at the moment of the analysis). Similarly, coding of all medications will occur using the WHO Drug Dictionary. The clinical trial monitor team will perform a periodic medical review of the coding and of the AE profile.

Sites affected by the COVID-19 pandemic can refer to ANNEX 18 for extraordinary contingency measures to be implemented.

14.2 Record keeping

At study completion, all study data will be transferred to Grifols according to ICH GCP guidelines, local laws, regulations, and Grifols requirements. The study file and all source data should be retained until notification is given by the sponsor for destruction.

An investigator is required by ICH GCP guidelines to retain the study files. If an investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person (e.g., other investigator). Grifols must be notified in writing of the person responsible for record retention and the notification will be retained in the sponsor study file and the investigator site file.

Blood retention samples will be anonymously frozen and stored. These samples could be additionally tested for purpose of this clinical trial (e.g., requirement by Health Authorities) and for purposes related to the underling disease (PPS). Samples would be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. After storage period elapses, retention samples will be destroyed according to implemented procedures of the laboratory.

15 FINANCING AND INSURANCE

The study sponsor will pay for study related costs. A separate financial agreement will be made (as appropriate) with the Investigator and/or institution.

Where required, the sponsor will contract an insurance to cover possible damage to the subject resulting from their participation in the study, in accordance with applicable legislation; such coverage will be renewed periodically for the full duration of the study.

16 PUBLICATION POLICY

The sponsor will prepare a report summarizing the study results, based on statistical analysis of the results, and on any other relevant additional information. The study report will include a description of methods, materials and plans. The Investigator will express his/her approval by signing it.

After signing the final report, Investigators will be free to publish the results and conclusions in scientific journals or in conferences. Investigators will reflect as co-authors all persons who have significantly participated in the project. The sponsor will receive a copy of the manuscript at least 30 days prior to submission for publication or presentation of the abstract at some scientific meeting. All publications will record the ethic committees which give their clinical trial approval as well as their source of income. The name of Instituto Grifols, S.A. will appear as citation of the publication. Clinical trial subject's anonymity will be kept always.

During the clinical trial, interim analysis and other information related to the study will be considered confidential.

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