CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor / Company: Instituto Grifols, S.A.

Name of Finished Product: Flebogamma 5% DIF

Name of Active Ingredient: Immune Globulin Intravenous (Human)

Title of Study: 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

Investigators: Full list of investigators is provided in **Appendix 16.1.4** of the clinical study report.

Study Center(s): The study was conducted at 22 sites in the following countries: Canada (1), Czech Republic (1), Denmark (2), Germany (5), Italy (1), Netherlands (1), Poland (4), Spain (2), and United States (5).

Publication (reference): Not applicable

Studied Period (years):	**Phase of Development**: 2/3
(date of first subject enrolled): 23 September 2014 (date of last subject completed): 24 November 2022	

Objectives:

Primary Efficacy Objective:

The purpose of this study was to evaluate whether intravenous Flebogamma® 5% DIF with monthly infusions (every four weeks) in a 1-year treatment period is superior to placebo in Post-Polio Syndrome (PPS) participants by assessing physical performance, as measured by change in 2MWD from baseline to the end of the treatment period (Week 52). Particularly:

- At Stage 1, the primary efficacy objective was to select the optimal dose of Flebogamma® 5% DIF.
- At Stage 2, the primary efficacy objective was to establish superiority of the selected dose of Flebogamma® 5% DIF as compared to placebo by using the data from both Stage 1 and Stage 2.

Secondary Efficacy Objectives:

Secondary objectives were the following:

- To evaluate the clinical effect of Flebogamma 5% DIF in PPS participants by assessing pain, as measured by Visual Analog Scale (VAS) of pain from baseline to the end of the treatment period (Week 52), compared to placebo.
- To evaluate the clinical effect of Flebogamma 5% DIF in PPS participants by evaluating the health-related quality of life (HRQoL), as measured by change in 36

item Short Form (SF-36) Physical Component Summary (PCS) from baseline to the end of the treatment period (Week 52), compared to placebo.

- To evaluate clinical effect of Flebogamma 5% DIF in PPS participants by assessing endurance, as measured by change in Six Minute Walk Distance (6MWD) from baseline to the end of the treatment period (Week 52), compared to placebo.

Safety Objectives:

- The safety objective was to assess the safety of Flebogamma 5% DIF, as every 4 weeks intravenous infusions, over a period of 52 weeks, compared to placebo.

Methodology:

This study was a Phase 2/3 multicenter, prospective, randomized, placebo-controlled, double-blind, parallel-group clinical study with an adaptive design (flexible group sequential design with adaptive dose selection) to evaluate the efficacy and safety of Flebogamma® 5% DIF in participants with PPS.

This study consisted of two stages. The first stage (Stage 1) was for dose selection by the Data Monitoring Committee (DMC). The second stage (Stage 2) was to establish the superiority (efficacy confirmation) of the selected dose of Flebogamma 5% DIF in the change in physical performance (two-minute walk distance [2MWD] at Week 52) as compared to placebo. For overall safety analysis combining the data from both stages provided a tolerability profile for PPS participants.

Stage 1 was a 3-arm evaluation of 2 active dose levels of Flebogamma 5% DIF (intravenous immunoglobulin [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 participants had finished the treatment period of Stage 1), a formal unblinded interim analysis was performed by an independent DMC to select the dose of Flebogamma 5% DIF for Stage 2. The interim analysis was performed based on 124 randomized participants (of a total of 126 randomized participants) with some participants (10 to 12% per treatment arm) ongoing in the Treatment Period. The independent DMC used the prespecified dose selection rule to select one of the Flebogamma 5% DIF doses (2 g/kg or 1 g/kg) to continue in Stage 2. Conditional power (the power conditional on the partial information accumulated at the interim analysis) was calculated for comparisons of Flebogamma 5% DIF 2 g/kg versus Placebo and Flebogamma 5% DIF 1 g/kg versus Placebo. Between the two active treatment arms, if conditional power based on primary efficacy endpoint of 2MWD in the Flebogamma 5% DIF 2 g/kg arm was at least 10% relatively higher than the Flebogamma 5% DIF 1 g/kg arm, then Flebogamma 5% DIF 2 g/kg was to be chosen for Stage 2. Otherwise, Flebogamma 5% DIF 1 g/kg was to be chosen for Stage 2.

The DMC decided that the dose for Stage 2 would be 1 g/kg. The study team remained blinded to the DMC decision. Subsequently, in Stage 2, a separate cohort of participants was randomized to receive either the selected dose from Stage 1 (1 g/kg/ per the DMC) or placebo in a 1:1 ratio for efficacy confirmation and overall safety analysis.

During both stages of the study, randomization was 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, were planned to have a screening period (up to 4 weeks), a treatment period (52 weeks), and a follow-up period (24 weeks). However, the follow-up

period was truncated in Stage 2 due to an upper management business decision to close the study before full enrollment was complete and truncate the timeline so that the full followup period was not completed for ongoing participants at the time of that decision (12 participants terminated the study early due the Sponsor's business decision). However, all participants were allowed to complete the year-long double-blind Treatment Period.

Study participants were randomly 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 was planned before participant's termination of his/her participation in the clinical trial (at the Final Visit [FV]). However, as noted this was truncated for Stage 2 participants who were on-study at the time of the business decision to prematurely discontinue the trial for business reasons.

Number of participants (planned and analyzed): To show the treatment difference of 6 meters in 2MWD with a standard deviation of 11 meters, 99 participants needed to be randomized into 1 of 3 treatment arms in Stage 1 and 66 participants needed to be randomized into 1 of 2 treatment arms in Stage 2. To account for a 20% dropout rate, approximately 126 needed to be randomized into 1 of the 3 treatment arms (42 participant/arm) in Stage 1, and approximately 84 participants into 1 of 2 treatment arms (42 participant/arm) in Stage 2.

A total of 161 participants were screened in Stage 1, of which 126 were randomized. Seventy-seven participants were screened in Stage 2, of which 65 were randomized.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

A treatment-experienced participants met all the following inclusion criteria to be eligible for participation in this study:

1. Male or female aged 18 to 75 years.
2. Participants who understand and voluntarily signed and dated the Clinical Trial Written ICF for his/her clinical trial participation.
3. Participants with a body mass index (BMI) less than 35 kg/m^2.
4. Participants who met the clinical criteria for diagnosis of PPS as set by the March of Dimes.
5. Participants who were ambulatory or able to walk with a cane or other aids or use a wheelchair (but were not wheelchair-bound).
6. Participants who had 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 a Medical Research Council (MRC) scale score greater than 3 at the Manual Muscle Testing (MMT) performed by the independent assessor at the Screening Visit (SV).
7. Female participants of child-bearing potential required a negative test for pregnancy (human chorionic gonadotropin [HCG]-based assay).
8. Female participants of child-bearing potential and their sexual partners 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. Participants must have been 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. Participants must have been able to walk a 2MWD of at least 50 meters at the SV and EV/IV1.
11. Participants must have been 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 (all participants)

1. Participants who had received human normal IG treatment given by IV, subcutaneous, or intramuscular route within the last 3 years.
2. Participants who were not ambulatory (wheelchair-bound individuals).
3. Participants with poor venous access.
4. Participants with intractable pain requiring narcotics or other psychotropic drugs.
5. Participants with a history of anaphylactic reactions or severe reactions to any blood-derived product.
6. Participants with a history of intolerance to any component of the investigational products, such as sorbitol.
7. Participants who were receiving corticosteroids, except for those who were taking inhaled corticosteroids for asthma.
8. Participants with a documented diagnosis of hyperviscosity or hypercoagulable state or thrombotic complications to polyclonal IVIG therapy in the past.
9. Participants with a history of recent (within the last year) myocardial infarction, stroke, or uncontrolled hypertension.
10. Participants with congestive heart failure, embolism, or electrocardiogram (ECG) changes indicative of unstable angina or atrial fibrillation.
11. Participants with a history of chronic alcoholism or illicit drug abuse (addiction) in the preceding 12 months prior to the SV.
12. Participants with active psychiatric illness that interferes with compliance or communication with health care personnel.
13. Participants with depression with scores >30 as assessed by the Center for Epidemiological Studies Depression (CESD) validated scale.
14. Females who were pregnant or are nursing an infant child.
15. Participants with any medical condition which made clinical trial participation unadvisable, or which was 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. Participants currently receiving, or had received within 3 months prior to the SV, any investigational medicinal product or device.

17. Participants who were unlikely to adhere the protocol requirements, or were likely to be uncooperative, or unable to provide a storage serum/plasma sample prior to the first investigational drug infusion.
18. Participants with a known selective immune globulin A (IgA) deficiency and serum antibodies anti-IgA.
19. Participants 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. Participants with aspartate transferase (AST) or alanine transaminase (ALT) levels >2.5 times the ULN for the expected normal range for the testing laboratory.
21. Participants with hemoglobin levels <10 g/dL, platelets levels <100,000 /mm3, white blood cells count <3.0 k/µL, and erythrocyte sedimentation rate (ESR) >50 mm/h or twice above normal.
22. Participants with known seropositive to hepatitis C virus (HCV), human immunodeficiency virus (HIV)-1, and/or HIV-2.
23. Participants with a history of intolerance to fructose.

Investigational Product, Dose and Mode of Administration, Batch Number:

Flebogamma 5% DIF was the investigational product being tested, and Normal Saline Solution was 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. The 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) was performed with Flebogamma DIF formulated at 5% (Flebogamma 5% DIF).

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

The lot numbers of Flebogamma 5% DIF used in this study were as follows: A4GEA00531, A4GEB00521, A4GEC01341, A4GED00241, A4GED00931, A4GED01221, A4GED01431, A4GEF00721, IBGK4CECI1, IBGK4HVI11, IBGK4M3M41, IBGK5NGNI1, IBGK6IIIX1, IBGK6LVM11, and IKGK4AEAG1.

Duration of Treatment:

Subject participation (from Screening Visit to the Final Follow-up Visit): up to 80 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable.

Criteria for Evaluation:

Primary Efficacy Variable

Physical performance by 2-minute walking distance (2MWD) from baseline to Week 52.

Secondary Efficacy Variables

- Pain (VAS of pain) from baseline to the end of the treatment period (at the EoTV – Week 52).

- HRQoL (SF-36 PCS) from baseline to the end of the treatment period (at the EoTV – Week 52).
- Endurance (6MWD) from baseline to the end of the treatment period (at the EoTV – Week 52).

Safety:

Safety Variables

- Adverse events (AEs) including treatment emergent AEs (TEAEs) or non-treatment emergent AEs (non-TEAEs), suspected adverse drug reactions (ADRs), serious adverse events (SAEs), AEs leading to the discontinuation of the study, AE with special interest (AESI), and infusional AEs.
- Vital signs during infusions, including temperature (T), respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP)
- Physical assessments
- Blood biochemistry and cell counts, including renal, hepatic and hematological parameters.

Statistical Methods:

Unless otherwise noted, for continuous variables, descriptive statistics include the number of non-missing values, mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics include counts and percentages per category. Unless otherwise noted, all statistical inference were tested at 2-sided with α=0.05.

Unless otherwise noted, all data collected in the eCRFs or electronically transferred (such as central laboratory data) are presented in data listings. Participants are identified in the data listings by participant number (which includes site number) and grouped by treatment arm. All summaries and listings are presented by treatment arm and by study stage (i.e., Stage 1, Stage 2, and overall) if appropriate.

Primary Efficacy Analyses

For the statistical analysis of the primary efficacy endpoint of 2MWD, from baseline to the end of the treatment period (Week 52) for Flebogamma 5% DIF compared to placebo in the ITT population, the treatment difference between Flebogamma 5% DIF and placebo was 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. In Stage 1, the difference between treatment groups in the change in 2MWD, from baseline to the end of the treatment period (Week 52), was tested to determine the treatment effect of Flebogamma 5% DIF 2 g/kg versus placebo and Flebogamma 5% DIF 1 g/kg versus placebo. In Stage 2, the difference between treatment groups in the change in 2MWD, from baseline to the end of the treatment period (Week 52), was tested to determine the treatment effect of the selected dose of Flebogamma 5% DIF from Stage 1 and placebo.

For the selected dose group of Flebogamma 5% DIF (1 g/kg) versus placebo, p-values were obtained from Stage 1 and Stage 2 separately. The overall adjusted p-value was

calculated from the p-values from both Stage 1 and Stage 2 by the method proposed by Posch & Bauer (2005) 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 Flebogamma 5% DIF versus placebo, an analysis of covariance (ANCOVA) method was used 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.

Secondary Analyses

The treatment effect of the selected dose of Flebogamma 5% DIF versus placebo on 2MWD will be explored using MMRM with the combined data from both Stage 1 and Stage 2 together for all participants only in the selected dose of Flebogamma 5% DIF and placebo groups. The same model will be used as was used for the primary MMRM analysis.

The MMRM and ANCOVA analyses will be repeated for each of the secondary efficacy variables with data from the selected dose of Flebogamma 5% DIF and placebo groups over stages 1 stage 2 combined.

A fixed-sequence testing method was employed to address the multiplicity issue for multiple secondary efficacy variables.

Safety Analyses

Safety analyses were based on the Safety Population. All combined safety data from both Stage 1 and Stage 2 were summarized by the treatment arm. Safety analyses were performed according to the actual treatment received.

Determination of Sample Size:

The sample size of this clinical study was calculated based on the primary efficacy endpoint (2MWD) at the end of the treatment period.

Baseline measure of 2MWD in participants with PPS has been estimated at 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. 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) was 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%.

To show the treatment difference of 6 meters in 2MWD with a standard deviation of 11 meters, 99 participants needed to be randomized into 1 of 3 treatment arms in Stage 1 and 66 participants needed to be randomized into 1 of 2 treatment arms in Stage 2. To account for a 20% dropout rate, approximately 126 needed to be randomized into 1 of the 3 treatment arms (42 participant/arm) in Stage 1, and approximately 84 participants into 1 of 2 treatment arms (42 participant/arm) in Stage 2.

SUMMARY OF RESULTS

Disposition, Demographics, and Exposure to Study Drug:

Overall, 191 participants were randomized in the two stages of the study. A total of 126 participants were randomized in Stage 1 across 3 treatment arms 42/group (Flebogamma 5% DIF 2 g/kg; Flebogamma 5% DIF 1 g/kg; placebo), and 65 participants were randomized in Stage 2 to either Flebogamma 5% DIF 1 g/kg (n=33) or placebo (n=32). The DMC opted to move forward with the 1 g/kg Flebogamma DIF dose for Stage 2 and 33 participants were randomized to active; 32 participants to placebo in this stage. Stage 2 of the study was truncated and prematurely terminated by the Sponsor due to a business decision so the planned enrollment of 84 participants was reduced to 65 participants. While all participants on-study were allowed to complete blinded study drug treatment through Week 52, the follow-up period was truncated shorter than 76 weeks to expedite closure of the study for business reasons (12 participants discontinued for this reason).

The disposition of participants for both stages combined is presented in Table 1. It is evident that there was higher attrition during Stage 1 in the Flebogamma 5% DIF 2 g/kg group, about twice the rate of Flebogamma 5% DIF 1 g/kg and placebo, and the majority of premature withdrawals were due to adverse events (AEs) in the higher dose group. Completion of study through the end of Week 52 Treatment Phase was comparable for the Flebogamma 5% DIF 1 g/kg and placebo arms across stages.

Populations for analysis are summarized in Table 2. The Intent-to-treat (ITT) population consisted of all participants randomized. The Per-protocol population was defined as participants in the ITT population who had received at least 8 infusions, without having two consecutive missed infusions of any investigational product (IP) during the treatment period, had baseline and at least one post-baseline measure of the Two Minute Walking Distance, and had no critical or major protocol deviations that might have an impact on the primary efficacy assessment. The Safety population consisted of all participants who received at least 1 infusion of IP (test or placebo).

Table 1 Disposition (both stages combined)

Characteristic	Flebogamma 5% DIF 2 g/kg n(%)	Flebogamma 5% DIF 1 g/kg n(%)	Placebo n(%)	Total n(%)
Participants screened				238
Participants randomized	42	75	74	191
Completed Week 52*	25 (59.5)	60 (80.0)	59 (79.7)	144 (75.4)
Discontinued prior to Week 52*	17 (40.5)	15 (20.0)	15 (20.3)	47 (24.6)
Adverse Event*	10 (23.8)	5 (6.7)	5 (6.8)	20 (10.5)
Withdrawal by Participant*	4 (9.5)	5 (6.7)	6 (8.1)	15 (7.9)
Lost to Follow-up*	0	1 (1.3)	1 (1.4)	2 (1.0)
Death	0	0	0	0

Characteristic	Flebogamma 5% DIF 2 g/kg n(%)	Flebogamma 5% DIF 1 g/kg n(%)	Placebo n(%)	Total n(%)
Physician Decision*	1 (2.4)	0	0	1 (0.5)
Protocol Violation*	2 (4.8)	1 (1.3)	1 (1.4)	4 (2.1)
Other*	0	3 (4.0)	2 (2.7)	5 (2.6)

*Percentages are based on the number of participants randomized.

Table 2 Populations for Analysis

Population	Flebogamma 5% DIF 2 g/kg n(%)	Flebogamma 5% DIF 1 g/kg n(%)	Placebo n(%)
Stage 1			
Intent-to-treat	42	42	42
Per-protocol	24 (57.1)	31 (73.8)	32 (76.2)
Safety	42 (100.0)	42 (100.0)	42 (100.0)
Stage 2			
Intent-to-treat (randomized)	---	33	32
Per-protocol	---	25 (75.8)	25 (78.1)
Safety	---	33 (100.0)	32 (100.0)
Both Stages Combined			
Intent-to-treat	42	75	74
Per-protocol	24 (57.1)	56 (74.7)	57 (77.0)
Safety	42 (100.0)	75 (100.0)	74 (100.0)

There was a balance across arms and study stages in demographic and disease characteristics. The population was almost entirely Caucasian, overall more than half of the participants were women (60.2%), and 49.2% were age 65 years or more. The demographic profile was concordant with the previous endemicity of active polio virus infection before universal vaccination. Overall diagnosis of post-polio syndrome on average was established ~10 years prior to study entry and resulted from acute poliomyelitis that had occurred 61 years before. Only 2 participants had ever received IVIG for post-polio syndrome. The main part of the body that was affected by post-polio syndrome was overwhelmingly the lower extremity in 95% of cases overall across treatment arms and study stages.

Treatment compliance was good whilst participants remained on-study with mean overall compliance ≥ 94.6% in each group. Given the higher discontinuation rate in Stage 1 for the Flebogamma 5% DIF 2 g/kg dose, the duration of exposure in weeks was less for this group (36.58±19.6 weeks), but exposure was similar for the Flebogamma 5% DIF 1 g/kg (45.85±13.63) and placebo groups (45.24±14.57) for both stages combined.

EFFICACY RESULTS:

Primary Efficacy Results:

Although Flebogamma 5% DIF doses showed an improvement in the distance walked with treatment over placebo during Stage 1, based on the prespecified requirement by the Data Monitoring Committee, the Flebogamma 5% DIF 1 g/kg dose was selected for Stage 2. Stage 2 enrollment was truncated to only 65 participants due to business decision (instead

of the 84 participants planned). Participants could walk an average of 11.1 meters more than they could at Baseline following 1 year of monthly 1 g/kg Flebogamma 5% DIF intravenous infusions.

The results of the priori statistical analysis showed a significant improvement in 2MWD for the Flebogamma 5% DIF 1 g/kg group (Posch & Bauer p-value =0.0469), which was more pronounced in the Per Protocol population (Posch & Bauer p-value =0.0206). This statistical significance was further confirmed in a sensitivity analysis of both stages combined with a MMRM p-value of 0.0147 and ANCOVA last-observation carried forward (LOCF) change from baseline to Week 52 p-value of 0.0089 for 2MWD. Table 3 provides the MMRM primary endpoint and sensitivity analyses for the ITT population with both stages combined.

Table 3 Primary Endpoint: Change from Baseline to Week 52 for Two Minute Walking Distance (meters) MMRM Model Primary Analysis (Posch and Bauer) and Combined Stages Sensitivity Analysis (ANCOVA) (ITT population)

	Flebogamma 5% DIF 1 g/kg	**Placebo**
Primary Endpoint Analysis		
Stage 1	**(n=42)**	**(n=42)**
Week 52		
LS Means standard error (SE)	11.12 (3.142)	4.64 (3.172)
95% CI	(4.9, 17.3)	(-1.6, 10.9)
LS Means Difference from Placebo		
LS Means Difference (SE)	6.49 (3.759)	
95% CI	(-1.0, 13.9)	
p-value	0.0870	
Stage 2	**(n=33)**	**(n=32)**
Week 52		
LS Means (SE)	16.81 (3.901)	11.42 (3.864)
95% CI	(9.0, 24.6)	(3.7, 19.2)
LS Means Difference from Placebo		
LS Means Difference (SE)	5.38 (2.933)	
95% CI	(-0.5, 11.3)	
p-value	0.0713	
Posch and Bauer p-value [1]	**0.0469**	
Primary Endpoint Sensitivity Analysis Both Stages Combined		
Week 52	**(n=75)**	**(n=74)**
LS Means (SE)	12.75 (2.496)	6.69 (2.511)
95% CI	(7.82, 17.69)	(1.72, 11.65)
LS Means Difference from Placebo		
LS Means Difference (SE)	6.07 (2.455)	
95% CI	(1.21, 10.92)	
p-value	0.0147	

2MWD = Two Minute Walking Distance; ANCOVA = analysis of covariance; CI = Confidence Interval; LS = Least squares; SE = standard error.

[1] Overall adjusted p-value for the selected dose of Flebogamma 5% DIF vs placebo at Week 52 using the method proposed by Posch & Bauer.

Note: Estimates, standard errors, confidence intervals (CI) and treatment comparisons for the individual stages are based on a mixed-effect model repeated measures (MMRM) of the change from baseline in 2MWD as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and main part of the body affected (lower extremity versus upper extremity) as the fixed effects; baseline 2MWD measure as a covariate; and measures within-patient at each visit as a repeated measure.

Note: The 2MWD measures the distance that a patient can walk at self-preferred speed on an indoor 50-m track for 2 minutes.

Secondary Efficacy Results:

The secondary efficacy variables included a visual analogue scale (VAS) for pain, the physical component summary of the SF-36, and endurance measured by the Six-Minute Walk Distance (6MWD). All secondary endpoints were determined as change from baseline (CFB) to the end of the Treatment Period.

The patient reported outcomes (VAS and SF-36 physical component) did not show statistical significance versus placebo. The VAS for pain diminished in both the Flebogamma 5% DIF 1 g/kg and placebo arms over successive visits with marginal mm difference in decrease between arms. SF-36 physical component scores increased in both arms indicating better health. For these endpoints the salutary numeric change was consistently greater in the Flebogamma 5% DIF arm though the differential versus placebo was small.

The test of endurance 6MWD did show numerical differences though these did not reach statistical significance. The observed increase from baseline in the number of meters patients were able to walk in 6 minutes was twice that for placebo in the Flebogamma 5% DIF 1 g/kg dose group. Participants could walk an average of 31.56 meters farther at the end of 1 year of monthly IV 1 g/kg Flebogamma 5% DIF infusions, which was nearly twice the increment in distance walked relative to placebo over the time interval.

SAFETY RESULTS

A total of 26 participants had SAEs during the study including both Treatment and Follow-up periods. Seven participants had SAEs related to study drug (2 in each of the active treatment arms and 3 in placebo). These included myocardial infarction (participant completed study on 2 g/kg Flebogamma 5% DIF); generalized skin rash (participant discontinued 2 g/kg Flebogamma 5% DIF); pulmonary embolism (participant discontinued 1 g/kg Flebogamma 5% DIF); meningeal irritation (meningism) (participant completed study on 1 g/kg Flebogamma 5% DIF); syncope (placebo – participant continued study); 2 participants with hypertension (placebo – both participants discontinued study.

A total of 22 participants had TEAEs that resulted in premature withdrawal from the study with the highest number of premature discontinuations (10 participants) occurring in the 2 g/kg Flebogamma 5% DIF group. The TEAEs that resulted in discontinuation of > 1 participant in any treatment arm were: nausea (2 participants in the 2 g/kg Flebogamma 5% DIF group [none in other arms]); headache 1 and 3 participants in the 1 g/kg and 2 g/kg Flebogamma 5% DIF groups, respectively (none in placebo); rash in 1 and 2 participants in the 1 g/kg and 2 g/kg Flebogamma 5% DIF groups (none in placebo); and hypertension 2 participants in the placebo group and none in either active arm.

An overall summary of on-treatment TEAEs is provided in Table 4. The TEAEs that occurred in 10% or more of participants in any randomized arm that occurred on-treatment are summarized in Table 5. The pattern of TEAEs was typical of those commonly observed with IVIG administration.

Table 4 Overall Summary of On-Treatment* TEAEs – Both Stages Combined (safety population)

Parameter	Flebogamma 5% DIF 2 g/kg (n=42)	Flebogamma 5% DIF 1 g/kg (n=75)	Placebo (n=74)
Participants with TEAEs	40 (95.2%)	74 (98.7%)	68 (91.9%)
Total number of TEAEs	419	819	492
Participants with suspected ADRs (doubtful/unlikely, possibly, probable or definitely related TEAEs)	38 (90.5%)	67 (89.3%)	52 (70.3%)
Total number of suspected ADRs	335	623	305
Participants with ARs (definitely related)	10 (23.8%)	19 (25.3%)	10 (13.5%)
Total number of ARs	53	80	33
Participants with TEAEs during or within 72 hours of infusion	36 (85.7%)	69 (92.0%)	54 (73.0%)
Total number of temporally associated AEs	289	530	265
Participants with on-treatment SAEs	3 (7.1%)	7 (9.3%)	9 (12.2%)
Total number of on-treatment SAEs	3	8	13
Participants with post-treatment SAEs (during follow-up)	2 (4.8%)	4 (5.3%)	3 (4.1%)
Total number of post-treatment SAEs (during follow-up)	2	4	3
Participants with any AE leading to premature discontinuation during the Treatment Period	8 (19.0%)	5 (6.7%)	4 (5.4%)

*On-treatment TEAEs are included in this table unless otherwise specified. On-treatment TEAEs have an onset date/time between first study treatment date/time and last study treatment date +4 weeks.

Table 5 Summary of On-Treatment* TEAEs Occurring in ≥ 10% of Participants in Any Treatment Group – Both Stages Combined (safety population)

TEAE Preferred Term	Flebogamma 5% DIF 2 g/kg (n=42) n (%)	Flebogamma 5% DIF 1 g/kg (n=75) n (%)	Placebo (n=74) n (%)
Diarrhoea	0	7 (9.3)	8 (10.8)
Nausea	11 (26.2)	13 (17.3)	4 (5.4)
Vomiting	6 (14.3)	5 (6.7)	3 (4.1)
Chills	8 (19.0)	15 (20.0)	2 (2.7)
Fatigue	14 (33.3)	22 (29.3)	20 (27.0)
Influenza like illness	0	10 (13.3)	3 (4.1)
Oedema peripheral	2 (4.8)	3 (4.0)	8 (10.8)

TEAE Preferred Term	Flebogamma 5% DIF 2 g/kg (n=42) n (%)	Flebogamma 5% DIF 1 g/kg (n=75) n (%)	Placebo (n=74) n (%)
Pyrexia	8 (19.0)	13 (17.3)	1 (1.4)
Influenza	4 (9.5)	9 (12.0)	2 (2.7)
Nasopharyngitis	4 (9.5)	8 (10.7)	11 (14.9)
Fall	2 (4.8)	5 (6.7)	8 (10.8)
Blood pressure increased	0	8 (10.7)	0
Arthralgia	8 (19.0)	13 (17.3)	12 (16.2)
Back pain	5 (11.9)	8 (10.7)	6 (8.1)
Myalgia	6 (14.3)	10 (13.3)	3 (4.1)
Pain in extremity	3 (7.1)	10 (13.3)	5 (6.8)
Dizziness	3 (7.1)	4 (5.3)	13 (17.6)
Headache	27 (64.3)	39 (52.0)	23 (31.1)
Rash	1 (2.4)	11 (14.7)	0
Hypertension	7 (16.7)	12 (16.0)	10 (13.5)

*On-treatment TEAEs have an onset date/time between first study treatment date/time and last study treatment date +4 weeks.

CONCLUSION:

- The primary efficacy endpoint of change from baseline in 2MWD for the selected 1 g/kg Flebogamma 5% DIF dose was met and was statistically significant versus placebo in the primary analysis and all sensitivity analyses. Participants could walk an average of 11.1 meters more than they could at Baseline following 1 year of monthly 1 g/kg Flebogamma 5% DIF intravenous infusions, which was more than twice the increment in the placebo group (4.26 meters).
- Among the secondary endpoints, endurance as measured by the 6MWD showed a numerical benefit for Flebogamma 5% DIF although this did not reach statistical significance versus placebo at the end of the Treatment Period. Participants could walk an average of 31.56 meters farther at the end of 1 year of monthly IV 1 g/kg Flebogamma 5% DIF infusions, which was nearly twice the increment in distance walked relative to placebo over the time interval.
- The patient reported secondary outcome measures, VAS and SF-36 physical component did not show a statistically significant difference from placebo for change from baseline to the end of the Treatment Period (Week 52) though numerically slightly favoring Flebogamma 5% DIF 1 g/kg arm.
- Flebogamma 5% DIF was safe and well-tolerated.
- The safety profile is consistent with that known for IVIG administration in other indications.