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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STATISTICAL ANALYSIS PLAN (SAP)

Flebogamma® 5% DIF / IG1104

Title: A multicenter, prospective, randomised, 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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ABBREVIATIONS

2MWD	Two Minute Walk Distance
6MWD	Six Minute Walk Distance
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDV	Early Discontinuation Visit
FSS	Fatigue Severity Scale
FV	Final Visit
HRQoL	Health-Related Quality of life
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
LOCF-FU	Last Observation in the Follow-Up Period Carried Forward
LS	Least squares
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
MMT	Manual Muscle Testing
mMRC	modified Medical Research Council
NAT	Nucleic acid Amplification Technology
PCS	Physical Component Summary
PD	Protocol Deviation
PP	Per-Protocol
PPS	Post-Polio Syndrome
PT	Preferred Term
QMT	Quantitative Muscle Testing
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SF-36	Short Form 36
SI	Special Interest
SOC	System Organ Class
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug classification Dictionary

TABLE OF CONTENTS

1 DOCUMENT REVISION HISTORY

SAP Version	Effective Date	Description of change
1.0	15Nov2013	Not Applicable
2.0	30Jul2014	1. Removal of the mITT population – in place the PP population was modified to incorporate the definition of the mITT population. 2. Inclusion of additional text to describe the details of the Interim Analysis. 3. Inclusion of age group in the summary of patient demographics. 4. Inclusion of statistical hypotheses for analysis of primary endpoint.
3.0	See left margin	1. Inclusion of text to describe reasons for early termination of the trial and the impact of that decision on the planned analyses 2. Inclusion of algorithms for imputation of partial AE and medication start and stop dates 3. Inclusion of algorithm for calculation of SF-36 sub-scores 4. Update of list of exploratory endpoints to reflect updates to protocol since version 2.0 of this SAP 5. Update to the specification of the primary, secondary and exploratory analyses to reflect

SAP Version	Effective Date	Description of change
		updates to protocol since version 2.0 of this SAP 6. Clarification to the breakdown of summaries of Adverse Events. 7. Inclusion of text to specify re-mapping of PD categories for PDs processed after 16May2022 to original PD categories.

2 INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol IG1104 Version 7.0, dated March 7th, 2022.

Subsequent to the finalization of the protocol, Instituto Grifols S.A. took the decision to prematurely terminate this trial once subjects participating at the time of the decision had completed their study treatment. The early termination resulted from a business decision by Grifols, with no safety concerns regarding the Investigational Product and no changes in the risk/benefit for ongoing subjects participating in the study.

As a commitment to study participants, all subjects that were enrolled at the time of the decision were given the opportunity to complete blinded study drug infusions, continue with treatment visits and be assessed as per protocol. In addition, where feasible and consented by study subject, assessments and procedures to be performed during an early discontinuation visits were to take place after the last investigational product infusion on infusion visit 13. Alternatively, subjects in the follow-up period were to be discontinued as soon as possible.

[redacted]

The purpose of this SAP is to ensure that the statistical methodologies that will be used, and the data listings, summary tables and figures which will be produced, are appropriate and complete to support valid conclusions regarding the study objectives and the completion of Clinical Study Report (CSR).

3 STUDY DESIGN AND OBJECTIVES

3.1 Study Design

This is a phase II/III, 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 subjects with post-polio syndrome (PPS).

This study will consist of two stages. The first stage (Stage 1) is for dose selection, and the second stage (Stage 2) is to establish the superiority (efficacy confirmation) of the selected Stage 1 dose of Flebogamma® 5% DIF in physical performance (Two Minute Walk Distance [2MWD]) as compared to placebo by combining both Stage 1 and Stage 2 data. Safety analysis will be based on the combined data from both stages.

At Stage 1, 126 subjects are planned to be randomized across trial sites located in Canada, Czech Republic, Denmark, Germany, Italy, Netherlands, Poland, Spain and the United States of America. Eligible subjects will be randomized with 1:1:1 ratio into one of three treatment arms:

- Flebogamma® 5% DIF 2 g/kg of body weight
- Flebogamma® 5% DIF 1 g/kg of body weight
- Placebo (Normal Saline Solution)

At the end of Stage 1 (when at least 80% of 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 the pre-defined criteria, one of the two active treatment arms will be selected to continue to Stage 2 of the clinical study.

At Stage 2, a separate cohort of 84 subjects are planned to be randomized with 1:1 ratio into one of two treatment arms:

- Flebogamma® 5% DIF selected dose from Stage 1
- Placebo (Normal Saline Solution)

At both stages, randomization will be stratified by the main part of the body affected (lower extremities or upper extremities). To maintain the blind for the whole study, all subjects will receive the same total dose volume (calculated to be equivalent to 2 g/kg Flebogamma® 5% DIF volume of body weight) for all treatment arms at both stages. Both stages will consist of a screening period (4 weeks), a treatment period (52 weeks), and a follow-up period (24 weeks). The purpose of the follow-up period is to evaluate the sustained effect of Flebogamma® 5% DIF compared to placebo. The total duration of participation for subjects who complete the study will be approximately 80 weeks. The detailed schedule of events summarizing the frequency and timing of the study procedures and schema of study design can be found in the sections 4.5.1 and 4.2 of the protocol, respectively.

3.2 Study Objectives

3.2.1 Primary Efficacy Objectives

The purpose of this study is to evaluate whether intravenous Flebogamma® 5% DIF with monthly infusions (every four weeks) in a 1 year treatment period is superior to placebo in PPS subjects 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 is to select the optimal dose of Flebogamma® 5% DIF.
- At Stage 2, the primary efficacy objective is 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.

3.2.2 Secondary Efficacy Objectives

The secondary efficacy objectives of this study are:

- To evaluate clinical effect of Flebogamma® 5% DIF in PPS subjects by assessing pain, as measured by change in visual analogue scale (VAS) of pain from baseline to the end of the treatment period (Week 52), compared to placebo.
- To evaluate clinical effect of Flebogamma® 5% DIF in PPS subjects by evaluating 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 subjects 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.

3.2.3 Safety Objective

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

4 STUDY VARIABLES

4.1 Efficacy Variables

4.1.1 Primary Efficacy Variable

The primary efficacy variable is physical performance (2MWD) from baseline to the end of the treatment period (Week 52).

4.1.2 Secondary Efficacy Variables

Secondary efficacy variables assessed are:

- Pain (VAS of pain) from baseline to the end of the treatment period (Week 52). VAS correction for different scale sizes are in section 5.1.1.
- Health-related quality of life (SF-36 PCS) from baseline to the end of the treatment period (Week 52).
- Endurance (6MWD) from baseline to the end of the treatment period (Week 52).

4.1.3 Exploratory Efficacy Variables

Exploratory efficacy variables include the change in the following measurements from baseline to the end of the treatment period (Week 52):

- muscle strength of two newly weakened muscle groups (Manual Muscle Testing [MMT] using the modified Medical Research Council [mMRC]) scale,
- muscle strength of two newly weakened muscle groups (Quantitative Muscle Testing [QMT]: Chair Dynamometer was used for lower extremity muscle groups and the results appeared in Newton meters (Nm). Handheld Dynamometer was used for upper extremity muscle groups and the measurement results were presented in Newtons (N)),
- walking activity in daily life (pedometer), (daily walking steps = 7-day steps collected in CRF/7)
- subjects' self-perceived exertion/fatigue level using Borg scale before and after 2MWD and 6MWD assessments,
- fatigue (Fatigue Severity Scale [FSS]),
- HRQoL (SF-36 Mental Component Summary [MCS]).
- and blood inflammatory cytokines (IL-1, IL-4, IL-6, IL-10, IL-13, TNF-alpha, and IFN-gamma)

In addition, change from baseline to assessment visits in the follow-up period (Week 64 Follow-up Visit, Week 76 Final Visit – as indicated below) will be analyzed for the following measurements to explore the sustained effect of Flebogamma® 5% DIF compared to placebo:

- physical performance (2MWD) – week 64 and week 76,
- pain (VAS of pain) – week 64 and week 76,
- HRQoL (SF-36 PCS) – week 64 and week 76,
- endurance (6MWD) – week 64 and week 76,
- muscle strength (MMT using the mMRC scale) – week 76,
- muscle strength (QMT using a dynamometry) – week 76,
- walking activity in daily life (pedometer) – week 76,

- subjects' self-perceived exertion/fatigue level using Borg scale before and after 2MWD and 6MWD assessments – week 64 and week 76,
- fatigue (FSS) – week 76,
- HRQoL (SF-36 MCS) – week 64 and week 76,
- and blood inflammatory cytokines – week 76.

4.2 Safety Variables

The following safety variables will be assessed:

- Adverse Events (AEs), adverse reactions (ARs), suspected adverse drug reactions (ADRs), serious AEs (SAEs), AEs leading to the discontinuation of the study, AE with special interest (AESI), and infusional AEs. Section 11.1 provides definitions of AE endpoints.
- Blood biochemistry (creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP) and total bilirubin (TB)) and cell counts (complete blood count (CBC), including differential leukocyte count)
- Vital signs (heart rate, blood pressure, respiratory rate, and temperature)
- Physical assessments

5 GENERAL STATISTICAL CONSIDERATIONS

Statistical analyses and data presentations will be generated using SAS version 9.2 or higher.

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum and maximum. The minimum and maximum will be presented to the same number of decimal places to which the data were recorded, the mean and median will be presented to 1 decimal place more than the data were recorded and the standard deviation will be presented to 2 decimal places more than the data were recorded.

For categorical variables, descriptive statistics will include counts and percentages per category. Percentages will be presented to 1 decimal place. Percentages of 0 and 100 will be reported as whole numbers (i.e. "0%" and "100%", respectively).

Unless otherwise noted, all statistical inference will be tested at 2-sided with α=0.05. P-values will be presented to 4 decimal places and confidence intervals will be presented to the same number of decimal places as the corresponding point estimate.

Unless otherwise noted, all data collected in the electronic case report forms (eCRFs) or electronically transferred (such as central laboratory data) will be presented in data listings. Subjects will be identified in the data listings by subject number (which includes site number)

and grouped by treatment arm. All summaries and listings will be presented by treatment arm and by study stage (i.e., Stage 1, Stage 2, and Overall) if appropriate.

5.1 Data Handling

Unless otherwise noted, if an observation is missing at a specific scheduled visit/timepoint, the value at that visit will not be imputed and will be set to missing in summary tables.

Baseline will be defined as the measurement taken at the Enrollment Visit (EV)/Infusion Visit 1 (IV1) or the last measurement taken prior to the start of the study treatment if the parameter is not measured at the Enrollment Visit (EV)/Infusion Visit 1 (IV1) or there are multiple observations for the parameter at the Enrollment Visit (EV)/Infusion Visit 1 (IV1).

For table summaries, the data will be presented at the scheduled visits according to protocol. For early terminated subjects, the termination visit occurred at End of Study will be remapped to the subject's next scheduled visit for analysis and summary. Any data collected at the unscheduled visits will be listed in data listings.

5.1.1 VAS Correction

For cases where VAS was recorded on the scale sizes of X(mm) other than 100mm, the VAS score will be recalculated as

$$VAS\_VAS_{recorded} * \frac{100}{X}$$

The tracker file "IG1104_VAS_scale_issue_100_mm.xlsx" includes all the protocol deviations of VAS records with scales other than 100mm. The adjusted VAS score will be implemented for the cases included in the tracker file. The unadjusted and adjusted VAS scores will be presented in the relevant CSR listing with a flag to indicate which VAS scores were adjusted. A footnote will be included to explain the rescaling of the VAS scores.

5.2 Analysis Populations

In this study, three analysis populations are defined as:

Intent to treat (ITT) population

The Intent-to-treat (ITT) population consists of all subjects randomized.

Per-protocol (PP) population

The Per-protocol (PP) population consists of all 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 one post-baseline measures of the 2MWD, and have no critical or major protocol deviations

that might have impact on the primary efficacy assessment (as determined at a data review meeting prior to database lock and unblinding).

Critical/major protocol deviations will include, but not limited to: 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. The critical/major protocol deviations will be identified and documented prior to database lock and the unblinding of the study.

Safety population

The Safety population consists of all subjects who received at least 1 infusion of investigational product (test or placebo).

The validity of a subject for inclusion in each of these three populations (ITT, PP, and Safety) will be assessed at a blinded review meeting before unblinding the study. If any protocol deviations or data issues are identified to justify removing a subject from any analysis population, the decisions and rationales will be documented in a blinded review meeting report.

5.3 Sample Size Considerations

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

Baseline measure of 2MWD in patients with PPS has been estimated in about 120 meters with standard deviation

s 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 [Horemans HL, Nollet F, Beelen A, *et al.*, Stolwijk-Swüste JM, Beelen A, Lankhorst GJ, *et al.*, Horemans HL, Beelen A, Nollet F, *et al*]. 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 2MWT (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%.

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

5.4 Interim Analysis

A formal unblinded interim analysis will be performed to select one of the two active doses for Stage 2 based on primary efficacy endpoint of 2MWD. The interim analysis will be performed when at least 80% of randomised subjects have finished the treatment period of Stage 1. The subjects included in the interim analysis from the data cut are those who have completed the one-year treatment period or who have the 2MWD measurements at the 6-month visit or afterwards. Based on the interim analysis results, the independent DMC will use the pre-specified dose selection rule to select one of the Flebogamma® 5% DIF doses (2 g/kg or 1 g/kg) to continue the Stage 2 of the clinical trial. Given no safety concern for the Flebogamma® 5% DIF doses, 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 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 Flebogamma® 5% DIF 2 g/kg arm is at least 10% relatively higher than Flebogamma® 5% DIF 1 g/kg arm, 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.

The conditional power will be calculated for each active treatment arm vs placebo with the randomization ratio 1:1, using the following formula based on the observed data and parameters estimated at the interim analysis (Chang; 2008):

$$CP(Z,\hat{\delta},s,n_1,n_2) = \Phi\left(\frac{Z\sqrt{\frac{n_1}{2s^2}} - z_{1-\alpha}\sqrt{\frac{n_1}{2s^2}} + \hat{\delta}\left(\frac{n_2}{2s^2}\right)}{\sqrt{\frac{n_2}{2s^2}}}\right) = \Phi\left(Z\sqrt{\frac{n_1}{n_2}} - z_{1-\alpha}\sqrt{\frac{n_1}{n_2}} + \hat{\delta}\sqrt{\frac{n_2}{2s^2}}\right)$$

where Z is the z-test statistics, $\hat{\delta}$ is the estimated mean difference between the treatment arm and placebo, and s is the estimated standard error for the mean of treatment; which are the estimates from the mixed-effect model repeated measures including 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-subject at each visit as a repeated measure. n_1 is the number of subjects included in the interim analysis for the treatment arm at Stage 1 and n_2 is the number of subjects planned to be enrolled for treatment arm at Stage 2.

From the last subject first visit of 80% planned randomized subjects in Stage 1 to the final DMC decision of dose selection for Stage 2, subject enrollment will continue for Stage 1. Depending on the study enrollment rate, there could be more than the rest 20% of planned randomized subjects in Stage 1 enrolled (i.e., over-running) or less than the rest of 20% of

planned randomized subjects in Stage 1 enrolled (i.e., under-running) when the final DMC dose selection is decided.

For over-running scenario, the over-running subjects will be included in the final analysis for Stage 1 and Stage 2 will enroll the number of subjects as planned. It is not anticipated there will be more than 10% of the planned sample size of Stage 1 for over-running subjects. If over-running subjects exceed 10% of the planned sample size for Stage 1, the study enrollment may be paused until the decision of the final dose selection for Stage 2 by DMC.

For under-running scenario, the enrollment for Stage 1 will be stopped and the remaining subjects not randomized in the Stage 1 will be reallocated to Stage 2 and included in the final analysis for Stage 2. In addition, the number of subjects as planned for Stage 2 will still be enrolled so that the entire study will have the same number of randomized subjects as planned. In this case, there will be more subjects in the selected dose and placebo arms than that as planned.

6 SUBJECT DISPOSITION

Subject disposition will include the number of subjects screened, number of randomized subjects, number and percentage of subjects in each analysis population, number and percentage of subjects completing the scheduled treatment of investigational products, number and percentage of subjects completing the study treatment period up to Week 52, and number and percentage of subjects completing the study follow-up period up to Week 76 by treatment arm and by study stage.

The number and percentage of subjects discontinuing early from the study will be summarized for primary reasons of discontinuation. Also, the number and percentage of screening failures will be summarized for primary reasons of ineligibility in a separate table.

Disposition status will be listed for all subjects.

7 PROTOCOL DEVIATIONS

Protocol deviations (PD)s will be identified during the study, evaluated and categorized as Critical, Major or Minor before the database lock. Following process improvement measures to [redacted] (external Contract Research Organization) Clinical Trial Management System for tracking, processing and classification of PDs, classification terms for PDs changed for PDs processed after the 16May2022. In order to ensure a consistent unified categorization of PDs, [redacted] will re-map PDs categorized after 16May2022 to the original categories used prior to the change in classification categories.

The type of protocol deviations will be summarized by treatment arm for each stage and overall.

8 DEMOGRAPHY AND MEDICAL HISTORY

8.1 Demographic and Baseline Characteristics

Demographic and baseline characteristics including sex, race, ethnicity, age, age group (<65 versus >= 65 years old), height, weight and body mass index will be summarized by treatment arm and study stage (individually and combined). Baseline pregnancy test, time since diagnosis of post-polio syndrome(years), time since diagnosis of poliomyelitis(years), IgA levels, IgA antibodies, general health assessment and blood assessment for general health, immunologic function, and viral exposure will be summarized.

Time since diagnosis of post-polio syndrome will be calculated as:

(Subject ICF date – date of diagnosis of post-polio syndrome)/365.25

Time since diagnosis of poliomyelitis will be calculated as:

(Subject ICF date – date of diagnosis of poliomyelitis)/365.25

All demographic and baseline characteristics data will be listed.

8.2 Medical History

Medical history events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 17.1 and summarized by treatment arm, system organ class (SOC) and preferred term (PT).

9 CONCOMITANT MEDICATION AND TREATMENT

9.1 Prior and Concomitant Medication

All medications as documented by the investigator will be coded using ATC classification codes via the World Health Organization Drug classification Dictionary (WHO-DD). All medications will be summarized by treatment arm and sorted alphabetically by medication class (i.e., ATC level 1) and medication sub-class (i.e., ATC level 3). If the ATC level 3 term is missing, the ATC level 2 term will be used in the medication summary table and data listing.

The following convention will be used for missing or partial end date information in order to determine whether a medication is prior or concomitant:

The unknown portions of a medication end date will be assumed to be as late as possible. If a medication end date is incomplete but the month/year of medication end date is prior to the month/year of the start of study treatment, then the medication will be considered a prior medication. If a medication end date is incomplete but the month/year of medication end date is the same as the month/year of the start of study treatment, then the medication will be considered a concomitant medication. All other incomplete medication end dates and all medications with missing end dates will be assumed to be concomitant medications. Start/end

dates reported in the eCRFs will be presented in the listings. Further details of the imputation methods for partial dates is provided in section 12.1.2.

Prior medications are defined as any medication ended prior to the start of study treatment (i.e., start of the first study infusion at Week 0).

Concomitant medications are defined as any medication started on or after the start of study treatment or any medication taken prior to the start of study treatment and continued after the start of study treatment during the study.

9.2 Treatment Compliance

Treatment volume compliance will be calculated as total volume infused * 100% / total volume prepared during the study. The total volume prepared and dispensed by pharmacist is the intended dose volume a subject should be given based on the body weight.

Treatment infusion compliance will be calculated as the number of actual infusions * 100% / number of infusions expected or planned.

The treatment compliance and infusion compliance will be listed and summarized by treatment arm and study stage. Overall compliance (treatment compliance x infusion compliance) will be listed and summarized by treatment arm and study stage. The number of subjects with compliance between 80% and 120% will be calculated.

9.3 Treatment Exposure

For each treatment, the duration of exposure (weeks), number of infusions received, and the total volume infused in liters will be summarized. Duration of exposure is determined by calculating the difference between the start date of last infusion and the start date of first infusion inclusive divided by seven to give the value in weeks [(start date of last infusion– start date of first infusion) + 28]/7, rounding to one decimal place.

10 EFFICACY ANALYSES

Analysis will be performed for each individual stage for the primary endpoint (2MWD) only and the significance of the treatment effect at each stage will be combined to provide an overall assessment of treatment efficacy. For secondary and exploratory endpoints, analyses will be performed over the two stages combined, using the placebo and selected dose of Flebogamma® 5% DIF treatment groups only.

Efficacy analyses will be performed on the ITT population. The ITT analyses will be performed according to the treatment randomized, not the actual treatment received. The primary efficacy analyses will also be performed on the PP population.

10.1 Primary Efficacy Analyses

The primary efficacy variable is physical performance (2MWD) from baseline to the end of the treatment period (Week 52). The primary efficacy variable will be analyzed to compare each active treatment arm to placebo at Week 52 by using mixed-effect model repeated measures (MMRM) method separately for each stage.

The MMRM will include 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-subject at each visit as a repeated measure. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead.

The least-squares means for each treatment arm and its differences along with p-values between Flebogamma® 5% DIF and placebo at Week 52 will be estimated separately for each stage. The sample SAS® code for MMRM model is below:

```
proc mixed data=pp method=ml;
   class Subject Treatment Visit Bodypart;
   model change = Baseline Bodypart Treatment Visit
                  Treatment*Visit / s;
   repeated Visit / type=un subject=Subject r;
   lsmeans Treatment*Visit / pdiff cl;
run;
```

The overall adjusted p-value for the selected dose of Flebogamma® 5% DIF vs placebo at Week 52 will be calculated from the p-values of both Stage 1 and Stage 2 by the method proposed by Posch & Bauer (2005) in order to control the overall type I error rate for testing the equal means between the selected dose and placebo:

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

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 mean change of 2MWD for the selected Flebogamma® 5% DIF dose group and placebo respectively. The superiority will be deemed to have been demonstrated if the two-sided overall adjusted p-value is less than or equal to 0.05 and $\mu_{flebogamma} - \mu_{placebo} > 0$.

Let's assume two active arms A and B (corresponding to 1 g/kg and 2 g/kg of Flebogamma® 5% DIF, respectively) comparing to Placebo in Stage 1 with one active arm (arm B) moving into Stage 2 without loss of generality. Let's denote p_A and p_B as the one-sided p-values in Stage 1 comparing to placebo for treatment A and B, respectively; q is the one-sided p-value in Stage 2 comparing B to placebo; p_{AB} and q_{AB} are the one-sided p-values for testing null hypothesis H_{AB} (i.e., the intersection hypothesis $H_A \cap H_B$) for Stage 1 and Stage 2, respectively. As demonstrated in the paper (Posch & Bauer; 2005) example,

$$p_{AB} = \min(2\,p(1), p(2)), \text{ for ordered p-value } p(1) <= p(2) \quad \text{(Simes test)}$$

$$\text{and } q_{AB}=q.$$

By using the weighted inverse normal combination function, the combination function is:

$$C(x, y) = 1 - \text{probnorm}(v*\text{probit}(1-x)+w*\text{probit}(1-y)),$$

where $v=\text{sqrt}(n_1/(n_1+n_2))$ and $w=\text{sqrt}(n_2/(n_1+n_2))$, n_1 and n_2 are sample size for Stage 1 and Stage 2 for the selected arm and placebo.

The overall adjusted one-sided p-value for hypothesis H_B (i.e., overall efficacy) would be:

$$\text{Overall adjusted one-sided p-value} = \max(C(p_{AB}, q), C(p_B, q)).$$

10.2 Primary Efficacy Sensitivity Analyses

The analysis outlined in section 10.1 will be repeated using the PP population.
The following additional sensitivity analyses will be performed for the ITT population, using placebo and selected dose of Flebogamma® 5% DIF 2MWD data from Stages 1 and 2 combined.

1. An MMRM using the same model used in the primary analysis. Least squares (LS) means and 95% CIs will be presented and plotted by visit and treatment group.

2. An analysis of covariance (ANCOVA) will be performed with change in 2MWD from baseline to 52 Week 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. Data missing at 52 Week will be imputed using the Last (post-baseline) 2MWD Observation Carried Forward [LOCF]. LS means and 95% CIs for treatment effect and treatment comparison at week 52 will be provided

10.3 Secondary Efficacy Analyses

The MMRM and ANCOVA analyses using combined data from Stages 1 and 2, described in section 10.2, will be performed and LS means will be plotted by visit and treatment group for each of the secondary efficacy variables listed in section 4.1.2.

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 will be tested is pre-determined as follows:

1. Pain (VAS of pain) from baseline to the end of the treatment period (Week 52).
2. Health-related quality of life (SF-36 PCS) from baseline to the end of the treatment period (Week 52).
3. Endurance (6MWD) from baseline to the end of the treatment period (Week 52).

The outcome of each subsequent hypothesis tested will be evaluated only if all previously tested null hypotheses have been rejected at a two-sided significance level of 5%.

10.4 Exploratory Efficacy Analyses

With the exception of the Borg scale (which is recorded twice at each relevant visit – pre and post 2MWD and 6MWD), an MMRM analysis using placebo and selected dose of Flebogamma® 5% DIF 2MWD data from Stages 1 and 2 combined, will be performed and LS means will be plotted by visit and treatment group for each of the exploratory efficacy variables listed in section 4.1.3.

Estimates of treatment effect will be presented by a comparison of the mean change in each exploratory parameter from baseline to week 52 for selected dose of Flebogamma® 5% DIF versus Placebo.

Estimates of sustained treatment effect will be presented by a comparison of the mean change in each exploratory parameter from baseline to weeks 64 (where applicable) and 72 for selected dose of Flebogamma® 5% DIF versus Placebo.

The MMRM analysis will be repeated for the Borg scale, but with adjustment for timepoint (pre or post) within each visit. The following estimates of treatment effect will be provided separately for 2MWD and 6MWD:

1. Difference in mean change in Borg scale recorded prior to 2MWD/6MWD, from baseline to week 52 for Flebogamma® 5% DIF versus Placebo.
2. Difference in mean change in Borg scale recorded post 2MWD/6MWD, from baseline to week 52 for Flebogamma® 5% DIF versus Placebo.
3. Difference in mean change in the post-pre Borg scores, from baseline to week 52 for Flebogamma® 5% DIF versus Placebo.

11 SAFETY ANALYSIS

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

11.1 Adverse Events

Analysis of AEs will be primarily focused on a descriptive analysis of AEs, suspected adverse drug reaction (ADRs) and adverse reaction (AR). Safety assessment will be based on the prevalence of suspected ADRs and AR occurred during the clinical trial.

- Suspected ADRs are defined as AEs with a causal relationship to study treatment of "Definitely Related", "Probably Related", "Possibly Related" or "Doubtful/Unlikely Related".
- ARs are defined as AEs with a causal relationship to study treatment of "Definitely Related".

AEs will be classified according to their onset date/time into the following categories:

- Treatment emergent AEs (TEAEs): AEs with an onset date/time between first study treatment date/time and final study visit date or a pre-existing AE that worsens in severity within the same time window.
  TEAEs will be further classified as follows:
  - On-treatment TEAEs: TEAEs with an onset date/time between first study treatment date/time and last study treatment date +4 weeks.
  - Infusional TEAEs: TEAEs with an onset date/time between the start date/time of study treatment infusion and 72 hours post-completion of the infusion of total dose of study treatment during any of the 2-day infusion periods.
  - Post-treatment TEAEs: TEAEs with an onset date/time after the last study treatment date/time +4 weeks.
- non-TEAEs: all other AEs – i.e. AE which occur prior to the start of study treatment.

For the purposes of classifying AEs into the above categories, partial AE start and end dates will be imputed to allow comparison with the study treatment date start and end dates. Section 13.1.1 below presents the imputation rules. Note, the imputed dates will be used for classification purposes only and the original partial AE dates will be presented in data listings.

AEs will be coded using MedDRA dictionary version 17.1 and summarized (stage 1 and stage 2 combined) by treatment group, system organ class (SOC) and preferred term (PT) as follows:

- TEAEs:
  - On-treatment TEAEs
    - overall
    - by maximum severity
    - by maximum causal-relationship
    - SAEs
    - suspected ADRs
    - ARs
    - AESIs
    - suspected ADRs of Special Interest (SI),
    - ARs of SI

  - Post-treatment TEAEs
    - overall
    - SAEs
  - Infusional TEAEs
    - overall
    - SAEs
    - suspected ADRs
- Non-TEAEs

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients with any AE, any AE within each SOC and any AE within each PT (grouped by SOC).

For summaries by maximum severity, if a patient reported more than one AE with the same PT, the AE with the maximum severity will be presented. If the severity of an AE is missing, the severity will be treated as missing in summaries. If a patient reported more than one AE within the same SOC, the patient will be counted only once under the maximum severity within the SOC.

Corresponding reporting rules will be applied for summaries by maximum causal-relationship.

All AEs will be listed by treatment group and subject identifier. In addition, subjects with SAEs and AEs leading to premature discontinuation of treatment period from the study will be individually listed.

11.2 Laboratory Assessments

Blood biochemistry and cell counts data will be collected at the assigned visits according to the protocol and will be stored and/or testing performed by a central laboratory.

The lab parameters will be summarized using number of subjects, mean, standard deviation, median, minimum, and maximum values at each visit for continuous variables, and counts and percentages for categorical variables. Change from baseline to each scheduled post-baseline visit will be summarized for each continuous variable. Shift tables, based on the high/low flags, will also be summarized for each parameter at each visit.

All laboratory data will be presented in data listings.

11.2.1 List of Laboratory Parameters

The following table presents a list of all laboratory parameters tested. The column "Summarize" indicates which laboratory tests will be summarized as described in section 11.2, above. Results for all other tests will be listed only.

Lab category	Lab test	Summarize
CHEMISTRY	ALT (SGPT)	Y

Lab category	Lab test	Summarize
	APTT-FSL-QT	
	AST (SGOT)	Y
	Albumin-BCG	
	Aldolase-335	
	Alkaline Phosphatase-QT	Y
	Calcium (EDTA)	
	Cholesterol (High Performance)	
	Creatine Kinase	
	Creatinine (Rate Blanked)	Y
	D-Dimer	Y
	Direct Bilirubin	Y
	Direct HDL-C 3rd Generation-QT	
	Folate	
	GFR by MDRD-QT	Y
	Haptoglobin-QT	Y
	Indirect Bilirubin	Y
	International Normalized Ratio	
	LDH	Y
	LDL Chol-Friedewald 3rd -QT	
	Magnesium	
	Phosphorus	
	Prothrombin Time	
	Rheumatoid Factor-CL-QT	
	SPE M-spike Qty 1	
	SPE M-spike Qty 2	
	SPE Total M-Protein	
	SPE-M-spike 1(%)-CL	
	SPE-M-spike 2(%)-CL	
	Ser Electrophoresis-Albumin(%)	
	Serum Bicarbonate	
	Serum Chloride	
	Serum Glucose	
	Serum Potassium	
	Serum Sodium	
	Total Bilirubin	Y
	Total Protein	
	Triglycerides (GPO)	
	Urea Nitrogen	
HEMATOLOGY	Atypical Lymphocytes	
	Basophils, Basophils (%)	Y

Lab category	Lab test	Summarize
	Eosinophils, Eosinophils (%)	Y
	Lymphocytes, Lymphocytes (%)	Y
	Monocytes, Monocytes (%)	Y
	Neutrophils, Neutrophils (%)	Y
	Platelets	Y
	Reticulocyte Count %-CL	Y
	WBC	Y
	Anti-Thyroglobulin	
	Free T3	
	Free Thyroxine	
	IFN Gamma	Y
	IL-1	Y
	IL-4	Y
	IL-6	Y
	IL-10	Y
	IL-13	Y
	Immunoglobulin IgA-QT	
	Immunoglobulin IgGQT	
	Immunoglobulin IgMQT	
	Ser Electrophoresis-Albumin	
	Ser Electrophoresis-Alpha 1	
	Ser Electrophoresis-Alpha 2	
	Ser Electrophoresis-Alpha1 (%)	
	Ser Electrophoresis-Alpha2 (%)	
	Ser Electrophoresis-Gamma	
	Ser Electrophoresis-Gamma (%)	
	TNFalpha (-70)-TAT60d-RUO-CL	Y
	TSH 3rd Generation-QT	
	TSH 3rd IS	
	Thyroperoxidase Antibody	
	Total Thyroxine	
	Vitamin B12	
URINALYSIS	Ur Blood	
	Ur Glucose	
	Ur Hyaline Casts/LPF	
	Ur Ketones	
	Ur Leukocyte Esterase	
	Ur Nitrite	
	Ur Protein	
	Ur RBC/HPF	Y

Lab category	Lab test	Summarize
	Ur Renal Tubular Epi Cells	
	Ur Specific Gravity	Y
	Ur Squamous Epithelial Cells	
	Ur Transitional Epi Cells	
	Ur Urobilinogen	
	Ur WBC/HPF	Y
	Ur pH	Y

All parameters indicated as "Y" will be summarized, all other parameters will be listed only.

11.3 Vital Signs

Vital signs are collected over two days (Day 1 and Day 2) at each infusion at following timepoints:

- Day 1/2- 15 mins before start of IV infusion
- Day 1/2- 30 mins after start of IV infusion
- Day 1/2- 60 mins after start of IV infusion
- Day 1/2- 30 mins after completion of IV infusion

The vital signs parameters were recorded heart rate, respiration rate, systolic and diastolic blood pressure and temperature, with timepoint and indication of abnormal or not.

The changes of vital signs from pre-infusion (15 mins before start of IV infusion) to each of the post infusion timepoints will be summarized for each day at each visit.

All vital signs data will be listed.

11.4 Physical Assessments

Abnormal physical assessment findings at screening will be summarized using counts and percentages of subjects, by body system. Entries for 'Other' body systems will be grouped together; a subject with 2 or more 'Other' entries will be counted only once. Counts and percentages of subjects with new or worsening findings post-screening will be presented by treatment group.

All physical assessment data will be listed.

12 CHANGES TO PROTOCOL SPECIFIED ANALYSES

12.1 Exploratory Analysis of Cytokine

In July 2022, Grifols decided to terminate the study early due as a business decision. For this reason, it was also decided that some of the IL-17 and IL23 testing would not be performed. As a result, these parameters will no longer be considered exploratory endpoints as originally planned, and available results for these parameters will be listed only.

13 APPENDICES

13.1 Imputation rules

13.1.1 AE date imputation

The following rules will be applied to impute AE start/end dates when partial AE start/end dates have been recorded. The imputed dates will be used for the determination of treatment emergence of AEs only. The original partial AE dates will be presented in data listings.

AE start date imputation:

AE start date imputation will be based on a comparison of the partial AE start date and the treatment start date. Table 12-1 presents the notation that will be used to describe the rules for imputation of partial AE start dates.

Table 12-1 Notation for imputation of partial AE start dates

	Year	Month	Day
Partial AE start date	YYYY	MON	Not used
Study treatment start date	TRTY	TRTM	Not used

Table 12-2 presents a matrix of rules for the imputation of AE start dates.

Table 12-2 AE start date imputation

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NULL Uncertain	NULL Uncertain	NULL Uncertain	NULL Uncertain
YYYY < TRTY	(D) = 01JULYYYY Before Treatment Start	(C)= 15MONYYYY Before Treatment Start	(C)= 15MONYYYY Before Treatment Start	(C)= 15MONYYYY Before Treatment Start
YYYY = TRTY	(B)= TRTSTD+1 Uncertain	(C)= 15MONYYYY Before Treatment Start	(A)= TRTSTD+1 Uncertain	(A)= 01MONYYYY After Treatment Start
YYYY > TRTY	(E)= 01JANYYYY After Treatment Start	(A)= 01MONYYYY After Treatment Start	(A)= 01MONYYYY After Treatment Start	(A)= 01MONYYYY After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date

LEGEND:		
NULL	No imputation	
(A)	Max(01MONYYYY,TRTSTD+1)	
(B)	TRTSTD+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL (i.e. no imputation).
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

   a. if the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

   b. else, if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

   a. if the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

   b. else, if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:

   a. and the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.

   b. else, if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

   c. else, if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

AE end date imputation:

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

If the AE end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).

If the AE end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, last day of the month, date of death).

If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

Imputed AE date flag

If the year of the imputed date is not equal to YYYY then imputed date flag = Y, else if month of the imputed date is not equal to MON then imputed date flag = M, else if day of the imputed date is not equal to day of original date then imputed date flag = D, else imputed date flag = null. Imputed AE date flags will be created separately for both AE start and end dates.

13.1.2 Prior and concomitant medication date imputation

The following rules will be applied to impute medication start/end dates when partial medication start/end dates have been recorded. The imputed dates will be used to distinguish between prior and concomitant medications only. The original partial medication dates will be presented in data listings.

- The missing day of start date of a medication will be set to the first day of the month that the medication was taken.
- The missing day of end date of a medication will be set to the last day of the month of the occurrence.
- If the start date of a medication is missing both the day and month, the medication start date will be set to January 1 of the year of medication start.
- If the end date of a medication is missing both the day and month, the date will be set to December 31 of the year of occurrence.
- If the start date of a medication is null and the end date is not a complete date, then the start date will be set to the date of the first study visit.
- If the start date of a medication is null and the end date is a complete date
    - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
    - otherwise the start date will be set to the end date of the medication.
- If the end date of a medication is null and the start date is not a complete date, then the end date will be set to the date of the last study visit.
- If the end date of a medication is null and the start date is a complete date
    - and the start date is prior to the date of the last study visit then the end date will be set to the date of the last study visit.

- otherwise, the end date will be set to the start date of the medication

Imputed medication date flag

If the year of the imputed date is not equal to the year of the original medication date then imputed date flag = Y, else if the month of the imputed date is not equal to the month of the original medication date then imputed date flag = M, else if the day of the imputed date is not equal to the day of the original medication date then imputed date flag = D, else imputed date flag = null. Imputed medication date flags will be created separately for both medication start and end dates.

13.1.3 SF-36

The SF-36v2 is a 36-item, self-report survey of functional health and well-being, with 1-week recall period (QualityMetric 2011). Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'Health Transition' item, asks patients to rate how their current state of health compared to their state of health 1 week ago, and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: Physical Functioning (PF), Role Limitations due to Physical Health (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE), and Mental Health (MH). Psychometrically-based physical and mental health component summary scores (PCS and MCS, respectively) are computed from subscale scores to give a broader metric of physical and mental health-related quality of life.

Norm-based scoring (NBS) is used to calculate the eight SF-36v2 subscales and the two component scores. NBS standardizes scale and component scores using the means and standard deviations from a U.S. general population normative sample derived from responses to the internet-based 2009 QualityMetric PRO Norming Study.

The norm-based scores in the U.S. general population have been set to have a mean of 50 and a standard deviation of 10. By using the NBS method, the data in the current study will be scored in relation to U.S. general population norms; therefore, all scores obtained that are below 50 can be interpreted as being below the U.S. general population norm while scores above 50 can be interpreted as above the U.S. general population norm. PCS and MCS scores are each calculated through weighted sums of all 8 scale z-scores. A more detailed description of this scoring process can be found in the SF-36v2 manual (QualityMetric 2011).

Algorithms that allow for the evaluation of SF-36v2 scale and component summary scores in the presence of item-level missing data have been previously developed using a combination of Item Response Theory, mean substitution, and regression methods. A more detailed description of this scoring process, the Missing Score Estimation, can be found in the SF- 6v2 manual (QualityMetric 2011).

Two types of thresholds have been developed for interpretation of SF-36v2 scores. The first type is suitable for comparing group mean scores and is generally referred to as the MCID.

The second type is suitable for interpreting change at the individual level and is referred to as the responder threshold or responder definition (QualityMetric 2011).

14 REFERENCE

1. Chang, Mark. Adaptive design theory and implementation using SAS and R (©2008; Chapman & Hall/CRC Biostatistics series; 22)

2. Posch M, Koenig F, Branson M, et al. Testing and estimation in flexible group sequential designs with adaptive treatment selection. Statistics in Medicine 2005; 24: 3697-3714.

3. Horemans HL, Nollet F, Beelen A, *et al.* Pyridostigmine in postpolio syndrome: no decline in fatigue and limited functional improvement. J Neurol, Neurosurg Psychiatry 2003; 74(12): 1655-1661.

4. Stolwijk-Swüste JM, Beelen A, Lankhorst GJ, *et al.*CARPA study group. SF36 physical functioning scale and 2-minute walk test advocated as core qualifiers to evaluate physical functioning in patients with late-onset sequelae of poliomyelitis. J Rehabil Med 2008; 40(5): 387-394.

5. Horemans HL, Beelen A, Nollet F, *et al.* Reproducibility of walking at self-preferred and maximal speed in patients with postpoliomyelitis syndrome. Arch Phys Med Rehabil 2004; 85(12): 1929-1932.