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

Published: 04-11-2014
Last updated: 21-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON55451

Source
ToetsingOnline

Brief title
Grifols Post-Polio Syndrome

Condition

- Viral infectious disorders
- Spinal cord and nerve root disorders

Synonym
late effects, Post-Poliomyelitis Syndrome; Polio

Research involving
Human

Sponsors and support

Primary sponsor: Instituto Grifols, S.A.
Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: Flebogamma DIF, IGIV, Immunoglobulin, Post-Polio Syndrome

Outcome measures

Primary outcome

Physical performance (2MWD) from baseline to the end of the treatment period

(at End of Treatment Visit [EoTV] * Week 52).

Secondary outcome

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

- evaluating health-related quality of life (HRQoL), as measured by SF-36 PCS,

compared to that of placebo

- endurance, as measured by 6MWD, compared to that of placebo.

Study description

Background summary

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. IVIG
has been widely available in several indications, has a well-documented safety profile and, based on the accumulated experience, it has the potential to be of

benefit in patients with post-polio syndrome.

Study objective

To test whether monthly infusions (every four 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.

Study design

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 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 Flebogamma® 5% DIF in the change in physical performance (Two Minutes 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 three-arm evaluation of two 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, one of the doses of Flebogamma® 5% DIF from the two 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 affected, that is, lower extremities or upper extremities.
Both stages, Stage 1 and Stage 2, will consist of a screening period (4 weeks), a treatment period (52 weeks), and a follow-up period (24 weeks).

Intervention

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.

Study burden and risks

Flebogamma is made from human blood, which may contain infectious agents, such as viruses, that can cause disease. However, the risk that Flebogamma will transmit an infectious agent has been greatly reduced by 1) screening donors for prior exposure to certain viruses, 2) testing for the presence of viral infections and 3) inactivating and/or removing viruses during the manufacturing process. Despite these safety measures, there is a small chance that such products could transmit disease. The main risk for getting a disease from Flebogamma is from infectious agents that cannot yet be detected through the screening process. The optimal dose and IVIG cycle frequency has not been examined in PPS, the rationale for the 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 demyeliating polyradiculoneuropathy (CIDP), which, as PPS, is a slowly progressive disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 BMI less than 30 kg/m2.
4. Subjects who meet the clinical criteria for diagnosis of PPS as set by the March-of-Dimes.
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 two newly weakened muscle groups due to PPS (as defined by medical history), with at least one of them in a lower extremity, as defined by medical history and having a mMRC scale score of 3 or geater 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 whole duration of the study.
10. Subjects who are able to walk a 2MWD of at least 50 meters at the Screening Visit (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

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 them 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 Screening Visit, 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 time 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 mg/dL, platelets levels <100,000/mm3, white blood cells count <3.0 k/*L 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.

Study design

Design

Study phase:	2
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-02-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Flebogamma DIF
Generic name:	Immunoglobuline I.V.

Ethics review

Approved WMO Date:	04-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-04-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-05-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-004503-39-NL
ClinicalTrials.gov	NCT02176863
CCMO	NL49498.018.14