An open-label, single arm, multi-centre, phase II study investigating safety, tolerability, efficacy, pharmacodynamics and pharmacokinetics of imlifidase (IdeS) in patients with Guillain-Barré Syndrome (GBS), in comparison with matched control patients

Published: 08-07-2019
Last updated: 14-03-2025

The objectives of this study are to:• Assess safety and tolerability of imlifidase in combination with standard IVIg treatment in GBS subjects• Evaluate pharmacokinetics of imlifidase• Evaluate pharmacodynamics profile of imlifidase• Evaluate...

Ethical review	Approved WMO
Status	Completed
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON52611

Source
ToetsingOnline

Brief title
Clinical study of imlifidase in patients with Guillain-Barré Syndrome

Condition

- Immune disorders NEC
- Neurological disorders NEC

Synonym

1 - An open-label, single arm, multi-centre, phase II study investigating safety, to ... 13-05-2025

Guillain Barré Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Hansa Biopharma AB
Source(s) of monetary or material Support: Hansa Biopharma AB

Intervention

Keyword: GBS, Guillain-Barré Syndrome, imlifidase

Outcome measures

Primary outcome

Endpoints

• Safety as measured by type, frequency and intensity of Adverse Event (AE) / Serious Adverse Event (SAE) and change from baseline in parameters of clinical laboratory tests, vital signs and Electrocardiograms (ECG)

Secondary outcome

Efficacy as assessed by:

• Proportion of subjects with improvement of one or more grades in disability outcome (on the 6-point GBS disability score [DS]) over time.

• Proportion of subjects with improvement of two or more grades in disability outcome (on the 6-point GBS DS) over time

• Proportion of subjects with improvement of three or more grades in disability outcome (on the 6-point GBS DS) over time

• Change in GBS DS over time

• Proportion of subjects able to walk unaided (GBS DS <= 2) over time

• Time to improvement by at least one, two and three grade(s) on the GBS DS

• Time to walk independently (GBS DS <= 2).

• Time to run (GBS DS <= 1)

• Proportion of subjects that reach GBS DS <= 1 by week 26

• Proportion of subjects with an increase from baseline in R-ODS score

by at least 6 points on the centile metric score over time.

• Proportion of subjects with all R-ODS items above 0 at week 26

• Proportion of subjects requiring mechanical ventilation support (GBS DS 5).

• Days on mechanical ventilation

• Days in hospital and in an ICU

• Changes in MRC sum score over time

• Pharmacokinetics (PK) parameters Cmax, area under the curve (AUC), tmax, t*,

V, Clearance (CL), of imlifidase

• Pharmacodynamics (PD) effect by means of time course of IgG following

administration of imlifidase

Study description

Background summary

Guillain-Barré Syndrome is an acute, paralyzing, inflammatory disease of the peripheral nervous system usually preceded by an infection or other immune stimulation that induces an aberrant autoimmune response targeting peripheral nerves and their spinal roots. It is the most frequent cause of acute neuromuscular weakness in the Western world and can occur at any age. GBS is a rapidly progressive disorder often leading to a severe paralysis of the arms and legs. Most GBS patients have sensory disturbance (tingling or numbness or ataxia) and pain, and some patients have double vision or problems with swallowing. GBS may also paralyse the respiratory muscles, leading to intensive care unit admission and mechanical ventilation. The cause of GBS is believed to

be anti-nerve autoantibody induction by infections that frequently precede the onset of disease.

After onset, GBS patients have highly varying prognoses. Despite modern care, the mortality rate is 3-5%. Two thirds of the patients have severe symptoms resulting in their inability to walk unaided, and 20-30% require mechanical ventilation for a period ranging from weeks to months. Progression of weakness in GBS is usually rapid and reaches a nadir within 4 weeks in the majority of patients, but many develop their maximum deficit within 2 weeks. Even with subsequent recovery from the acute condition, many patients suffer from long-term complications, leaving 20% unable to walk after 6 months.

To treat GBS, both general medical care and immunological treatment are recommended. Supportive care, including monitoring of respiratory function by frequent measurement of vital capacity and other clinical outcomes, is needed to prevent or to manage complications.

Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PE) are the two main treatment options aimed at attenuating the autoreactive humoral immune response. A review performed in 2014 showed that IVIg and PE were equally effective in treating GBS and the frequency of adverse events was similar with either treatment. Unlike many other neurological conditions with an autoimmune basis, patients with GBS do not respond to corticosteroids.

Although both IVIg and PE are effective treatments for GBS, many patients still have a severe disease course and residual deficits, including weakness, sensory signs, fatigue, and pain. Moreover, many patients remain otherwise disabled or severely fatigued. Three to 6 years after onset, the residual damage arising from GBS still has a great impact on quality of life and the ability to perform activities.

In addition, the clinical response to IVIg varies among patients. About 8-16% of GBS patients deteriorate after a standard course of IVIg treatment, even after initial improvement. Therefore, there is a great medical need for a more effective treatment of patients with GBS, in particular for patients with a severe disease course and poor prognosis.

Imlifidase is an immunoglobulin G-degrading enzyme derived from Streptococcus pyogenes that with strict specificity cleaves all four human subclasses of IgG. Imlifidase cleaves human IgG below the hinge region thereby generating one F(ab*)2 fragment and one Fc-fragment which does
not bind to Fc-receptors and does not activate complement. In addition to safety and tolerability, this study is designed to determine the efficacy of intravenous dosing of imlifidase in GBS subjects by comparing their outcomes to matched GBS subjects from the International GBS Outcome Study (IGOS). Pharmacokinetics (PK) and pharmacodynamics (PD) will be determined.

The hypothesis is that the reduction in pathological IgG antibodies may translate into aborted progression, quicker recovery and less severe disease as compared to standard treatment.

Study objective

The objectives of this study are to:
• Assess safety and tolerability of imlifidase in combination with standard IVIg treatment in GBS subjects
• Evaluate pharmacokinetics of imlifidase
• Evaluate pharmacodynamics profile of imlifidase
• Evaluate immunogenicity of imlifidase
• Evaluate efficacy of imlifidase in subjects with GBS
• Evaluate quality of life after imlifidase treatment in subjects with GBS
• Evaluate healthcare resource utilization after imlifidase treatment in subjects with GBS
• Evaluate the contribution of a dose of imlifidase on outcomes with respect to severity of symptoms and recovery time through a comparison with an externally matched cohort of GBS subjects
• Evaluate the effect of imlifidase on exploratory biomarkers

Study design

This is an open-label, single arm, multi-centre, phase II study of imlifidase in combination with standard care IVIg in subjects within 10 days of onset of GBS.
The study will recruit approximately 30 subjects with GBS eligible for IVIg treatment based on current practice (i.e. GBS disability score >3 at time of screening for enrolment and within 10 days of onset of weakness). All subjects will receive imlifidase (Day 1) prior to standard care IVIg.
Data from each subject enrolled in this study will, if feasible, be compared with a matched external control group from the IGOS database (International Guillain-Barré Syndrome Outcome Study, ClinicalTrials.gov Identifier: NCT01582763). If such an indirect comparison study is feasible, details pertaining to the comparison will be outlined in a separate non-interventional study protocol.

A Safety Review Committee (SRC) will be established to evaluate safety and tolerability data. The Committee will meet after the first subject has completed study visit 6 (Day 29); thereafter the SRC will meet after 3, 7 and 12 subjects have completed visit 6 (Day 29). A final SRC meeting will be held at the end of the study. The SRC will schedule a meeting as soon as possible if an important safety issue arises anytime during the conduct of the study. The SRC will comprise of 3 independent physicians. Internal and external experts will be invited to attend the meetings on an ad hoc basis, if any issue arises that requires additional expertise. A working procedure for the SRC will be

described in an SRC Charter.

Intervention

Imlifidase is provided as a freeze-dried powder for concentrate for solution for infusion, 11 mg per vial. After reconstitution with sterile water for injection, the concentrate contains 10 mg/mL imlifidase. The concentrate will be added to 50 mL sodium chloride 9 mg/mL (0.9 %) solution for infusion and administered as an infusion to 0.25 mg/kg.

IVIg is currently the standard of care and will be administered for 5 consecutive days at 0.4 g/kg, starting on Day 3. At least 48 hours after imlifidase dosing and within 14 days of onset of weakness.

Study burden and risks

Study drug
Imlifidase is a study drug that is approved by the authorities for kidney transplant patients but has not yet been approved for this disease.
A total of more than 141 persons have been treated with imlifidase so far.
Imlifidase has previously been tested in two studies in healthy volunteers and eight completed studies in patients with different diseases.
Five patients in total have experienced possible allergic reactions or infusion reactions. This risk will be reduced by giving treatment with anti-allergy medication before the treatment with imlifidase.
As imlifidase removes IgG antibodies, there is an increased risk for infections. To minimise this risk, the patient will receive antibiotics for 14 days.
Decreased levels of IgG may also cause a temporary reduction of vaccine protection for up to four weeks following imlifidase treatment.
The risks of imlifidase for a developing embryo or foetus (an unborn baby) are unknown. Due to this, pregnant women or women who plan to become pregnant during the study cannot participate in this study. Women of childbearing potential will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy.
There may also be other side effects or risks associated with imlifidase that we cannot predict.

Infusion procedure
Infusion is the administration of drugs directly into the bloodstream using intravenous (IV) lines. The infusion procedure may cause some pain and there is a small risk of bleeding, bruising, or infection at the puncture site.

Anti-allergy medication (methylprednisolone and anti-histamine)
The patient will receive a low dose of anti-allergy medication prior to the infusion with imlifidase. Methylprednisolone could cause a temporary increase

in blood pressure and headache. Anti-histamine could cause headache and dry mouth.

Antibiotics
Please ask the study doctor for information regarding any side effects with taking antibiotics, as these may vary depending on what kind of antibiotics that is used at the site where the patient are being treated.

IVIg - standard of care
There is a very small risk of anaphylaxis (closing of the throat) during the infusion with IVIg. Side effects may include headache, muscular pain, low blood pressure, nausea and flushing. These side effects can be corrected by lowing the infusion rate. Other side effects are meningitis, skin reactions (especially eczema), low white blood cells and in very rare occasions blood clot events like stroke or heart attacks.

Tests
Drawing blood may be painful or cause some bruising.
In total, it will be taken less than 500 mL of blood from the patient. This amount does not cause any problems in adults. To compare: a blood donation involves 500 ml of blood being taken each time.

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. Signed Informed Consent obtained before any study-related procedures.
2. Willingness and ability to comply with the protocol.
3. Male or female aged >=18 years at the time of screening.
4. GBS diagnosed according to National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria (Asbury et al. 1990)
5. Onset of weakness due to GBS is not more than 10 days prior to screening.
6. Unable to walk unaided for >10 meters (grade >= 3 on GBS DS).
7. IVIg treatment being considered.
8. Women of child-bearing potential willing or able to use at least one highly effective contraceptive method from the day of treatment until at least 6 months after the dose of imlifidase if not abstinent. In the context of this study, an effective method is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly.
9. Men willing to use double-barrier contraception from the day of treatment until at least 2 months after the dose of imlifidase if not abstinent.

Exclusion criteria

1. Previous treatment with imlifidase.
2. Previous IVIg treatment within 28 days prior to imlifidase treatment.
3. Subjects who are being considered for, or already on, PE.
4. Women of childbearing potential who are not willing to use contraception from the screening visit until at least 180 days following imlifidase dosing.
5. Breastfeeding or pregnancy
6. Clinical evidence of a polyneuropathy of another cause e.g. diabetes mellitus (except mild sensory), alcoholism, vitamin deficiency, or porphyria.
7. Known selective IgA deficiency
8. Hypersensitivity to IVIg or to any of the excipients.
9. Immunosuppressive treatment (e.g. azathioprine, cyclosporine, mycofenolatemofetil, tacrolimus, sirolimus or > 20 mg prednisolone daily) during the last month.
10. Subject known to have a severe concurrent disease, e.g. malignancy, severe cardiovascular disease and severe chronic obstructive pulmonary disease (COPD).
11. Any condition that in the opinion of the investigator could increase the subject*s risk by participating in the study or confound the outcome of the

study.
12. Known mental incapacity or language barriers precluding adequate understanding of the Informed Consent information and the study activities.
13. Subjects with clinical signs of ongoing infection.
14. Subjects who have received other investigational drugs within 5 half-lives prior to imlifidase dosing. A subject will be withdrawn from the study if more than 12 days elapse between the onset of weakness and planned imlifidase administration, thus preventing that the administration of IVIg after imlifidase administration would be later than 14 days after onset of weakness.
15. Present or history of thrombotic thrombocytopenic purpura (TTP), or known familial history of TTP.
16. Positive PCR test for SARS-CoV-2 virus infection.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-02-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Imlifidase
Generic name:	Imlifidase

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-07-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2021
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-09-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	23-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-001059-12-NL
ClinicalTrials.gov	NCT01582763
CCMO	NL69195.078.19