Clinical Study Protocol

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

Clinical Study Protocol No.:	15-HMedIdeS-09
Investigational Medicinal Product:	Imlifidase
Phase:	II
EudraCT Number:	2018-001059-12
Name and Address of Sponsor:	Hansa Biopharma AB P.O. Box 785 SE-220 07 Lund Sweden

Synopsis

Name of Sponsor/Company

Hansa Biopharma AB (hereafter referred to as Hansa Biopharma)

Title of the study

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

Co-ordinating Investigator

[redacted]

Study Site(s)

Approximately 10 to 15 sites in Europe will be included

Planned Study Period	**Clinical Phase**
First subject first visit: Q4 2019 Expected last subject last visit: Q2 2024	Phase II

Background and Scientific Justification for Conducting the Study

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 evaluate the efficacy of intravenous dosing of imlifidase in GBS subjects. 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.

Objectives

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 pharmacodynamic 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

Endpoints

The following endpoints will be evaluated:

- 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)
- 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 scale 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 C_{max}, area under the curve (AUC), t_{max}, $t_{½}$, V, clearance (CL) of imlifidase
- Pharmacodynamics (PD) effect on IgG following administration of imlifidase
- Pharmacodynamics (PD) effect on identified autoantibodies following administration of imlifidase
- Presence of anti-imlifidase antibodies (ADA)
- Quality of Life as measured by EurQol EQ-5D Health Questionnaire at 4 weeks and later

Exploratory Endpoint

- Biomarker evaluation (analysis of anti-ganglioside antibodies and neurofilament light chain levels)

Methodology

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.

Study Procedures/Assessments

Subjects will be followed clinically on days 1-8, 15, 29, 57, 92 and 180 days after imlifidase infusion and additionally with a 360-day telephone contact to assess GBS DS, R-ODS, capture health status in a questionnaire, and AEs.

Disability scores to assess disability status and capture activities and social participation will be evaluated during the study. Blood sampling for safety, pharmacokinetics, and pharmacodynamics will be collected at multiple time points during the study and the subjects will be closely monitored after infusion with imlifidase.

Safety parameters will be measured up to day 180. Concomitant medication will be recorded throughout the study.

Reporting of adverse events will be done from signing of informed consent and throughout the study.

After study completion, all study subjects will be followed up regularly according to clinical practice at the site in question.

Number of subjects

Approximately 30 adult males or females will be included in the study.

Diagnosis and criteria for inclusion/exclusion

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 or 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.
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.

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.

Investigational Medicinal Product(s)

IMP
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 of 0.25 mg/kg.

Non-IMP
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.

Methylprednisolone and antihistamine are administered according to the clinical practice at each site prior to infusion of imlifidase in order to decrease the risk infusion reaction.

Duration of treatment

All subjects will receive a single intravenous infusion of imlifidase over 30 minutes.

Statistical methods

Number of subjects

No formal sample size calculations have been performed for this study. Approximately 30 evaluable subjects are considered sufficient to provide adequate information about the safety and efficacy.

Efficacy evaluation

The clinical outcome of the GBS patients treated with imlifidase and IVIg will be presented using descriptive statistics. In addition, a comparison to an externally matched cohort of GBS subjects treated with IVIg (IGOS database) will, if feasible, be conducted to evaluate the efficacy of imlifidase plus IVIg in combination. If such an indirect comparison study is feasible, details pertaining to the comparison will be outlined in a separate non-interventional study protocol.

Safety evaluation

Safety data will be presented by descriptive statistics.

Protocol Revision History including Summary of Changes

Protocol Version	Date	Including Amendment Type and No.	Overall Rationale for Changes
9.0	27-JUN-2023	Non-substantial amendment No. 08	The planned comparison to an externally matched cohort of GBS subjects will be outlined in a separate non-interventional study protocol. This change leads to modifications to some of the objectives and endpoints in the protocol. Additional baseline and disease characteristic data will be collected from subject's medical records.
8.0	13-DEC-2022	Non-substantial amendment No. 07 (No updated protocol version)	Extension of timeline for study completion. Number of study sites included in the trial updated.
8.0	27-JUN-2022	Non-substantial amendment No. 06 (No updated protocol version)	Extension of timeline for study completion.
8.0	31-JAN-2022	Substantial amendment No. 05	The knowledge of the safety of imlifidase has increased since study initiation and the safety surveillance is standardised across studies. GBS is an acute illness with a well-established standard of care including a close monitoring of the patients. It is therefore considered appropriate to lower the amount of data to be collected in the trial focusing on data needed for the evaluation of safety and disease response to imlifidase treatment. This will make the trial more feasible to perform and free resources for patient care. The infusion rate of the first dose of IVIg has been changed to ensure administration during day and evening shift. Addition of safety sections describing overdose and adverse events of special interest (AESIs). Change in CRO responsible for SAE/SUSAR reporting. Prohibited therapies updated and clarified. Extension of study duration.
7.0	11-JUN-2021	Non-substantial amendment No. 04	Minor modification to the screening procedures to minimise the risk of unnecessary delay of GBS treatment

Protocol Version	**Date**	**Including Amendment Type and No.**	**Overall Rationale for Changes**
6.0	09-OCT-2020	Substantial amendment No. 03	Request from Safety Review Committee: Addition of exclusion criterion
5.0	26-AUG-2020	Substantial amendment No. 02 (France only)	Request from Regulatory Agency: Addition of exclusion criterion Addition of timeframes to administration of antibody-based medicinal products (Submitted and approved in France only)
4.0	14-NOV-2019	Substantial amendment No. 01	Change of exclusion criteria
3.0	13-MAR-2019	N/A	Updates included after input from Regulatory Agency
2.0	22-JAN-2019	N/A	Updates included after input from Regulatory Agency
1.0	16-NOV-2018	N/A – Original Protocol	N/A

Table of Content

List of Tables

List of Figures

Abbreviations

ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMAN	Acute Motor Axonal Neuropathy
AUC	Area Under the Curve
CKD	Chronic Kidney Disease
CL	Clearance
C_{max}	Maximum serum concentration
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQoL EQ-5D Health Questionnaire
FAS	Full Analysis data Set
GBS	Guillain-Barré Syndrome
GBS DS	Guillain-Barré Syndrome disability score
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IdeS	Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IGOS	International Guillain-Barré syndrome Outcome Study
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IVIg	Intravenous Immunoglobulin
MedDRA	The Medical Dictionary for Regulatory Activities
MFS	Miller Fisher Syndrome
MRC	Medical Research Council sum score
NCS	Nerve Conduction Studies
NIMP	Non-Investigational Medicinal Products
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics
PE	Plasma Exchange
PP	Per Protocol
PK	Pharmacokinetics
PQC	Product Quality Complaint
PT	Preferred Term
RA	Regulatory Authority
R-ODS	Rasch- built Overall Disability Scale
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SDV	Source Document Verification
SOC	System Organ Class
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	Terminal half-life
t_{max}	Time to maximum plasma concentration
TTP	Thrombotic thrombocytopenic purpura
V	Distribution volume

1. INTRODUCTION

The company code initially used for the active substance in this project was HMED-IdeS (sometimes abbreviated to IdeS) and thus many reports refer to this name.

The International Non-proprietary Name imlifidase was recently assigned for the active substance, and this name will be used in the following.

1.1 Background

Disease and patient population

Guillain-Barré Syndrome (GBS) is an acute, paralyzing, inflammatory peripheral 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 (Willison et al. 2016). GBS is a rapidly progressive disorder often leading to a severe paresis of the arms and legs. Most GBS patients also have sensory disturbance (tingling or numbness or ataxia) and pain, and some patients have double vision or problems with swallowing. GBS may also involve the respiratory muscles, leading to intensive care unit (ICU) admission and mechanical ventilation.

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 (van Leeuwen et al. 2016), 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 (Willison et al. 2016; van Leeuwen et al. 2016). Even with subsequent to recovery from the acute condition, many patients suffer from long-term complications, leaving 20% unable to walk after 6 months.

There are two major GBS electrophysiological subtypes as determined by Nerve Conduction Studies (NCS) and Electromyography (EMG):

- Demyelinating variant, referred to as acute inflammatory demyelinating polyneuropathy (AIDP)
- Axonal variants with two major subtypes, Acute Motor Axonal Neuropathy (AMAN) and Acute Motor and Sensory Axonal Neuropathy (AMSAN)

Clinically, there are multiple GBS subtypes or variants, with the best known being the Miller Fisher Syndrome (MFS) and the pure motor form (van den Berg et al. 2014; Willison et al. 2016). In addition, GBS is highly variable with respect to disease severity, clinical course and outcome.

Current Treatments

To treat GBS, both general medical care and immunological treatment are indicated. 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

(Willison et al. 2016). Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PE) are the two main treatment options aimed at attenuating the autoreactive humoral immune response. A Cochrane review performed in 2014 (Hughes et al. 2014), showed that IVIg and PE were equally effective in treating GBS, and the frequency of adverse events (AE) 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 clinical deficits, including weakness, sensory signs, fatigue, and pain (van den Berg et al. 2014; Willison et al. 2016; van Leeuwen et al. 2016). 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 (van Doorn et al. 2010).

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 (van Doorn et al. 2010). Therefore, there is a great medical need for a more effective treatment of patients with GBS, in particular for patients with a severe disease and poor prognosis (Walgaard et al. 2011).

1.2 Scientific Rationale

There is growing body of evidence to suggest that GBS is an antibody-mediated disorder in which complement fixing, Immunoglobulin G (IgG) 1/3 subclass, anti-ganglioside antibodies play a major role in the pathogenesis. These antibodies are also directed against epitopes present on peripheral nerves and are induced through the mechanism including molecular mimicry with bacterial lipo-oligosaccharides (Willison et al. 2016; Kieseier et al. 2018). The specificity of these antibodies largely determines the clinical spectrum (pure motor, sensory-motor, MFS, etc.). Current research into the pathogenesis of GBS is primarily focused on identifying humoral immunity and downstream effector pathways, including complement activation.

Imlifidase

Imlifidase is an immunoglobulin G-degrading enzyme derived from *Streptococcus pyogenes* (IdeS) that cleaves all four human subclasses of IgG with strict specificity and comparable efficacy. Imlifidase cleaves human IgG below the hinge region thereby generating one $F(ab')_2$ fragment and one Fc-fragment which does not bind to Fcγ-receptors and does not activate complement. Thus, the proteolytic activity of imlifidase on IgG molecules prevents IgG mediated phagocytosis, antibody-dependent cellular cytotoxicity and complement mediated injury (Winstedt et al. 2015; Jarnum et al. 2017). Imlifidase is highly specific towards IgG; other Ig molecules, i.e. IgA, IgD, IgE and IgM, are not cleaved, and no other substrates have been identified. In addition to the restricted target specificity of imlifidase, the speed of the reaction is a major advantage of the substance. Within a few hours after dosing, the entire intra- and extravascular pool of IgG is fully cleaved into $F(ab')_2$ and Fc fragments, thereby creating a window where IgG levels are kept very low, lasting for approximately one week. It is therefore hypothesised that imlifidase can rapidly and efficiently deplete the autoreactive IgG pool in GBS patients, thereby interrupting the disease process.

Using sera from 15 patients diagnosed with GBS or MFS it was demonstrated that imlifidase efficiently cleaved IgG and blocked complement activation mediated by anti-ganglioside IgG antibodies (Takahashi et al. 2015).

Furthermore, treatment with imlifidase in a rabbit model of AMAN significantly reduced the disruption of Nav channels as well as activated C3 deposition at the anterior spinal root nodes of Ranvier. The clinical recovery of AMAN rabbits was significantly promoted, and there were significantly lower frequencies of axonal degeneration in anterior spinal roots of AMAN rabbits. The data support that imlifidase treatment reduces the anti-ganglioside IgG-mediated impairment in peripheral nerves (Wang et al. 2017).

Six studies with imlifidase have been completed, one in healthy subjects as well as four in sensitized chronic kidney disease (CKD) subjects and one in asymptomatic antibody-mediated thrombotic thrombocytopenic purpura (TTP) subjects.

Two studies with imlifidase are ongoing, one investigator-initiated phase II study to evaluate the efficacy and safety of imlifidase in anti-GBM disease (Glomerular Basement Membrane/Goodpasture's disease) with adverse renal prognosis and one prospective, observational long-term follow up study of patients treated with imlifidase prior to kidney transplantation.

1.3 Study Design and Dose Rationale

This is an open-label, single-arm, multi-center, phase II study of imlifidase added to standard care IVIg in subjects within 10 days of onset of GBS.

Approximately 30 subjects will be included in this study.

In addition to safety and tolerability, another objective of the proposed study is efficacy. Other objectives include pharmacokinetics (PK) and pharmacodynamics (PD).

Eligible subjects must have been diagnosed with GBS and be unable to walk unaided for >10 meters (grade ≥3 on Guillain-Barré Syndrome disability score (GBS DS)). Onset of weakness should be within 10 days before inclusion.

Healthy subjects have been dosed with 0.01-0.24 mg/kg, and patients up to 2 x 0.25 and 1 x 0.5 mg/kg of imlifidase. Rapid and complete cleavage of IgG to $F(ab')_2$ and Fc fragments was demonstrated at a dose of 0.25 mg/kg. In this study, each patient will receive one dose of 0.25 mg/kg imlifidase administered as an intravenous infusion over 30 minutes on Day 1.

A standard 5-day IVIg regimen (0.4 g/kg/day for 5 consecutive days) will be initiated at least 48 hours after imlifidase dosing. As subjects will be included and dosed with imlifidase within 12 days of onset of weakness, IVIg treatment will be initiated in all subjects within 14 days from onset of weakness which is within the time frame for which standard treatment has been shown to have a beneficial effect on the outcome (Hughes et al. 2014).

Based on the current knowledge, including experience from completed and ongoing clinical studies, it is expected that imlifidase will degrade IgG into $F(ab')_2$ and Fc fragments across all compartments allowing a rapid and potent inactivation of any pathological GBS auto-antibodies. This may in turn prevent irreversible nerve damage.

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.

1.4 Benefit/Risk Aspects

The possible benefit for the subject is that the rapid depletion of the IgG pool will interrupt the progressive phase of the disease process and possibly lead to a more rapid and qualitatively better recovery than the standard of care treatment.

An imlifidase dose of 0.25 mg/kg has been selected for this study. The phase I study did not identify any dose limiting factors at the highest tested dose (0.24 mg/kg), and CKD patients in two completed phase II studies were exposed to up to 0.5 mg/kg with acceptable safety profiles.

In order to avoid pregnancies, a pregnancy test will be performed in women of child-bearing potential prior to dosing, and the requirement for highly effective contraception for all subjects is part of the inclusion criteria for this study.

One serious and four non-serious (one of which was in a subject treated with placebo) infusion related reactions regarded as related to treatment have occurred. Signs and symptoms associated with infusion related reactions included, but were not limited to dyspnoea, pharyngeal oedema, sinus tachycardia, chest discomfort and flushing.

To mitigate the risk of infusion related reactions, all subjects will receive methylprednisolone and antihistamine treatment prior to dosing and will be closely monitored during the infusion.

Since imlifidase effectively removes the IgG pool, there may be an increased risk of infection. To minimise the risk for bacterial infections all subjects treated with imlifidase will receive prophylactic antibiotics prior to imlifidase dosing. Subjects will be screened for Hepatitis B,

C, and HIV, and subjects having clinical signs of ongoing infection will be excluded from the study. Subjects will also be screened for SARS-CoV-2, and subjects with a positive test will not be included in the study. As SARS-CoV-2-naïve subjects do not have any IgG antibodies towards the virus, and since imlifidase does not prevent IgG synthesis, administration of imlifidase is not considered to have any impact on patient safety should the subject subsequently become infected with SARS-CoV-2. As IVIg treatment will be started at least 48 hours post dosing of imlifidase, normal IgG levels are expected to be restored shortly after and minimize the risk of infection.

In a previous study with imlifidase in patients with TTP, 2 patients developed rash and arthralgia, with one of the subjects experiencing fever as well. The sponsor cannot exclude that the underlying disease of TTP was a factor in the development of serum sickness in these patients since none of 27 other subjects treated with imlifidase without concomitant immunosuppression showed signs of serum sickness. Of note is that at the time of these events only very low levels of imlifidase were left in circulation, not sufficient to form immune complexes with Anti-Drug Antibody (ADA). Serum sickness has not been observed in toxicology studies.

The rationale for at least 48 hours between imlifidase and IVIg dosing is based on the pharmacokinetic and pharmacodynamic profiles of imlifidase. In addition, in one clinical study (14-HmedIdeS-04) alemtuzumab was given four days post dosing of imlifidase, and in another clinical study (15-HmedIdeS-06) IVIg was given seven days post dosing of imlifidase. As there is no data supporting initiation of IVIg treatment earlier than 48 hours post imlifidase dosing, a subject who deteriorates very quickly during the first 24 hours after imlifidase administration may be treated with PE to remove any remaining imlifidase before initiating IVIg treatment according to standard of care. This decision is made at the discretion of the investigator.

The subjects will be closely monitored for all adverse events. The principal investigators will make sure that sufficient facilities and procedures are available to handle emergency situations including unexpected adverse reactions during the study. Furthermore, all subjects will be included in a long-term safety follow-up approximately 12 months after dosing.

Adverse events after administration of IVIg do occur but are seldom serious. There is a very small risk of anaphylaxis, often in subjects with severe IgA deficiency. Other reported side effects include headache, myalgia, nausea, transient hypotension and flushing (all of which can be corrected by slowing the infusion rate), meningism, aseptic meningitis, skin reactions (especially eczema), neutropenia, worsening of renal failure, and thromboembolic events (Deep vein thrombosis (DVT), Myocardial Infarction (MI) and stroke) attributable to hyperviscosity (Hughes et al. 2014). To reduce the risk of thromboembolic events patients will be managed according to standard of care for GBS, i.e. patients who are unable to walk independently will receive subcutaneous low-molecular-weight heparin.

A guidance for the investigator and Reference Safety Information regarding imlifidase can be found in the Investigator’s Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

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

2.2 Endpoints

The following endpoints will be evaluated:

- Type, frequency and intensity of AE / Serious Adverse Event (SAE) and change from baseline in parameters of clinical laboratory tests, vital signs and Electrocardiograms (ECG)
- Efficacy as assessed by:
    - Proportion of subjects with improvement of one or more grades in disability outcome (on the 6-point GBS 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 scale 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 maximum serum concentration (C_{max}), area under the curve (AUC), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{½}$), V, clearance (CL), of imlifidase
- Pharmacodynamics (PD) effect on IgG following administration of imlifidase
- Pharmacodynamics (PD) effect on identified autoantibodies following administration of imlifidase
- Presence of anti-imlifidase antibodies (ADA)
- Quality of Life as measured by EurQol EQ-5D Health Questionnaire at 4 weeks and later

2.2.1 Exploratory Endpoint

- Biomarker evaluation (analysis of anti-ganglioside antibodies and neurofilament light chain levels)

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

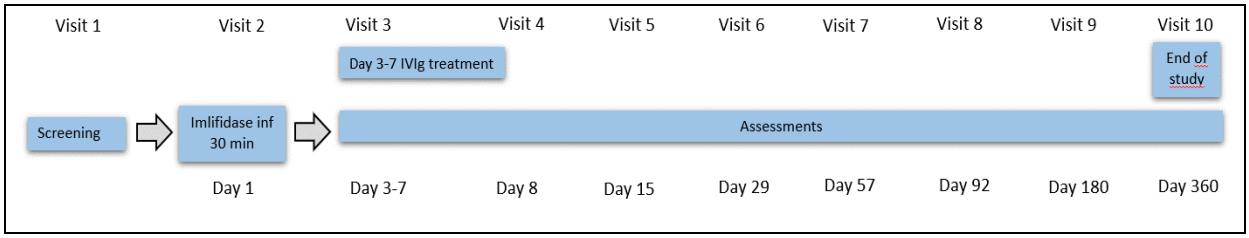


Figure 1. Overview of study design

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.

A detailed analysis plan is contained in the Statistical Analysis Plan (SAP). Data from each subject enrolled in this study will, if feasible, be compared with an external control group consisting of matched subjects from the IGOS database (Jacobs et al. 2017) (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.

3.1.1 Screening

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). Any male or female subject aged ≥18 years who presents with symptoms of GBS will be evaluated for eligibility to enter the study.

3.1.2 Treatment

All subjects will receive imlifidase (Day 1) prior to standard care IVIg (see Section 5.2). Scores to assess disability status and capturing activities and social participation will be evaluated. Blood samples for safety, pharmacokinetics, and pharmacodynamics will be collected, and subjects will be closely monitored after infusion with imlifidase.

3.1.3 Assessment Procedures

The subjects will be followed clinically on Days 1-8, 15, 29, 57, 92 and 180 days after imlifidase infusion and additionally with a 360-day telephone contact to assess GBS DS, R-ODS, capture health status in a questionnaire and AEs.

After study completion, all study subjects will be followed up regularly according to clinical practice at the site in question.

3.2 Safety Review Committee

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.

3.3 Study Timeline

The expected study start is Q4 2019. Expected last subject last visit is Q2 2024 including recruitment and 12 months follow up for included subjects.

3.4 Planned Number of Study Sites and Subjects

This is a multi-center study. Approximately 10 to 15 sites in Europe will be included. Approximately 30 adult male or female subjects will be enrolled in the study.

3.5 End-of-Study

The planned end-of-study is defined as the last telephone contact has been completed (visit 10). Hansa Biopharma will ensure that an end-of-study notification is submitted to the concerned Regulatory Authority (RA) and Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) according to local requirements.

For procedures in case of premature termination or suspension of the study, see Section 13.4.

4. STUDY POPULATION

4.1 Selection Criteria

To be eligible for the study, subjects must meet all inclusion criteria and no exclusion criteria. Those subjects who pass the screening phase of the study will receive imlifidase. Imlifidase administration will commence as soon as possible after consent is obtained (within 24 hours) and within 12 days of onset of weakness due to GBS.

4.2 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 such as:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
        - oral
        - intravaginal
        - transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation
        - oral
        - injectable
        - implantable
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomized partner
    - true abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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.

4.3 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 should not have received other investigational drugs within 5 half-lives prior to imlifidase dosing.
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.

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.

4.4 Method of Assigning Subjects to Treatment Groups

Not applicable since this is a single-arm, non-randomised study.

4.5 Discontinuation of Subjects and Stopping Criteria

A subject will be withdrawn from the study if more than 12 days elapse between the onset of weakness and planned imlifidase administration.

The subjects have the right to withdraw from the study at any time for any reason without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible. The investigator also has the right to withdraw subjects. In either event, the investigator must notify Monitor.

Minor infusion-related reactions have been observed in some patients receiving imlifidase for other indications. These are usually mild and include chest discomfort, flushing, pharyngeal oedema and dyspnea. More severe reactions can occur.

If a minor infusion-related reaction (Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2) is suspected the infusion should be temporarily stopped and the patient should be observed for clinical signs of allergic reactions. If a significant infusion-related reaction or anaphylactic reaction occurs (CTCAE grade 3 or higher) then the imlifidase therapy should be discontinued immediately.

The patient should be treated by the investigator according to local practice for an allergic reaction or a severe allergic reaction/anaphylaxis, respectively. If the symptoms resolve, the infusion can be resumed. If the symptoms persist or worsen, then the drug infusion should not be restarted.

A subject that prematurely discontinues participation must, if possible, be called in for a last visit and undergo the assessments and procedures scheduled for visit 9 (180 days after treatment with imlifidase). Even if the subject is not able to attend, the End-of-Study Form in the electronic Case Report Form (eCRF) must be completed. Subjects who for a medical reason cannot comply with the protocol procedures will be followed by best procedure to retrieve safety and efficacy data.

Subjects withdrawn from the study before visit 6 (29 days after treatment with imlifidase) may be replaced, not using the same subject number, in order to reach approximately 30 evaluable subjects.

5. STUDY TREATMENT

5.1 Investigational Medicinal Product (IMP)

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.

The excipients are: mannitol, polysorbate 80, Tris (tris(hydroxymethyl)aminomethane) buffer and ethylenediaminetetraacetic acid (EDTA). The excipients are all Pharmacopoeial quality.

Imlifidase for infusion will be prepared by the pharmacist or study nurse and the administration will be performed by the study nurse or physician at site. Details on preparation, labelling, administration and accountability of imlifidase are described in the pharmacy manual that will be provided to the site and pharmacy prior to inclusion of the first subject.

All subjects will receive an intravenous dose of imlifidase, 0.25 mg/kg, administered over 30 minutes.

5.1.1 Conditions for Storage and Use

The vials with imlifidase should be stored in a refrigerator at +2°C to +8°C.

For information on preparation, storage and use of the solution for infusion it is referred to the Pharmacy Manual.

The investigator will ensure that the medicinal products always will be stored in appropriate conditions in a secure location. The storage compartment shall be monitored regularly, and the temperature shall be documented.

5.1.2 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed in accordance with Good Manufacturing Practice (GMP) and national regulatory requirements.

5.2 Non-Investigational Medicinal Product(s)

Non-Investigational Medicinal Products (NIMPs) will be sourced from the investigational site pharmacy supply. Essential information about the NIMPs is to be found in the latest version of respective Summary of Product Characteristics.

The subjects will be treated with the following NIMPs (other treatments may be used as required at the investigators discretion):

5.2.1 Prophylactic Antibiotic

Since imlifidase effectively removes the IgG pool, there may be an increased risk of infection. To minimize the risk for bacterial infections all study subjects will receive prophylactic antibiotics for 14 days (e.g. phenoxymethylpenicillin (1 g ×1 orally), amoxicillin (500 mg ×1

orally) or ciprofloxacin (500 mg ×1 orally); in case of penicillin allergy clindamycin (300 mg ×1 orally) can be given). Subjects will be closely monitored for infections and instructed to contact the principal investigator immediately if they have any signs of infection.

5.2.2 Premedication

Premedication with methylprednisolone (1 mg/kg, max 100 mg, iv) and antihistamine (chlorphenamine maleate 10 mg orally, or an equipotent antihistamine) will be administered before imlifidase infusion to prevent/minimise risk of infusion reactions.

5.2.3 Treatment with IVIg

All subjects will receive standard care with IVIg infusion (0.4 g IVIg/kg for consecutive 5 days (total dose 2 g/kg) intravenously, starting on Day 3, ≥48 hours after end of imlifidase administration and within 14 days of onset of weakness.

First dose will be given by starting with a slow infusion rate over 2 hours (at a maximum rate of 0.55 mg/kg/min). If the infusion is well tolerated the infusion rate of the first infusion can be increased according to the site's standard of care for the rest of the infusion. The consecutive doses should follow the site standard of care practice.

The participation in the study will delay the commencement of standard IVIg treatment by at least 48 hours. If a subject deteriorates very quickly during the first 24 hours after imlifidase administration, the subject may be treated with PE to manage the rapid progression of GBS to remove any remaining imlifidase before initiating IVIg treatment according to standard of care. This decision is made at the discretion of the investigator. The subjects will continue in the study according to study schedule.

Premedication if any before first IVIg dose will be given to the subjects according to local clinical standard.

5.2.4 Conditions for Storage and Use

The investigator will ensure that the NIMPs will be stored in appropriate conditions, according to labels, in a secure location with controlled access. The storage compartment shall be monitored regularly, and the temperature shall be documented.

5.3 Blinding

Blinding is not relevant since this is an open-label study, and all subjects will receive the same dose of IMP.

5.4 Compliance, Accountability and Destruction of IMP(s) and NIMP(s)

5.4.1 Compliance

The administration of all medication (including investigational products) will be done by trained study personnel and must be recorded in the appropriate sections of the eCRF. All

investigational treatments must also be documented in the accountability logs. Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, date and time of administration of the investigational product will be checked by the monitor at monitoring visits.

5.4.2 Accountability and Destruction of IMP(s) and NIMP(s)

It is the principal investigator's/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

1. Deliveries are correctly received by a responsible person (e.g. pharmacist or designated study personnel).

2. Deliveries are recorded.

3. All IMP and NIMPs are handled and stored safely and properly.

4. The IMP and NIMP provided for this study will be used only as directed in the study protocol.

5. The study personnel will account for all drugs dispensed and returned. Any discrepancies must be documented, investigated and appropriately resolved.

6. The study pharmacist will maintain and keep the total accountability records. At the end of the study, the pharmacist will return all unused IMPs to Klifo for destruction after it has been checked by monitor unless otherwise agreed with Hansa Biopharma. The used IMP vials will be accounted for and destructed at site, after control by monitor.

5.5 Product Quality Complaints (PQC)

A PQC is a reported defect related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution and/or usage. The defect can be related to the product itself or to the product's label, delivery system, or packaging. Examples of PQCs include but are not limited to contamination, label errors, and delivery system failures.

Hansa Biopharma must be made aware of any PQCs as soon as possible on the day of detection. Hansa Biopharma will assess the impact of the reported defect and take any necessary precautions to ensure the safety of the study subjects and the credibility of the study results. PQCs should be reported using the IMP Issue form to ensure that all relevant information is captured.

5.6 Concomitant Medication and Therapies

Concomitant medication and/or other therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. All concomitant medication and other therapy, including e.g. premedication, prophylactic antibiotics and PE, must be recorded on

the concomitant medication page in the eCRF throughout the study, beginning from screening to end of study. Treatments up to 30 days prior to screening will be recorded in the eCRF. Recorded information will include indication, name of drug, dose (if available), route of administration and start and stop date.

5.7 Prohibited Therapies

Imlifidase specifically cleaves all subclasses of human and rabbit IgG. As a consequence, medicinal products based on human or rabbit IgG may be inactivated if given in connection with imlifidase. For this reason the following restrictions apply:

- intravenous immunoglobulin (IVIg) should not be administered within 48 hours following imlifidase administration
- alemtuzumab, adalimumab, basiliximab, denosumab, etanercept, and rituximab should not be administered within 4 days following imlifidase administration
- rabbit anti-human thymocyte globulin (rATG) and belatacept should not be admininstred within 1 week following imlifidase administration

Of note, equine anti-thymocyte globulin and eculizumab are not cleved by imlifidase and no time interval applies if any of these drugs should be considered necessary for the subject's welfare.

No report of AEs related to incompatibilities with administration of biologics concomitantly with imlifidase has been reported to date.

6. STUDY PROCEDURES

6.1 Study Visits

The total duration of the study, including screening, follow-up visits and long-term follow up will not exceed 13 months. The flow chart for patients enrolled in the study is presented in Table 1.

Visit 1, screening of subject, and visit 2 may be performed at the same day. Assessments included in both visits will then only be performed once, except for GBS disability score that will be assessed again at visit 2 if more than 24 hours elapse between screening and dosing.

Imlifidase administration will be commenced as soon as possible after confirmed eligibility (within 24 hours).

AEs and concomitant medication and other treatments will be collected throughout the study and are not specified for each visit.

The following GBS disease baseline characteristics will be collected whenever first available: GBS variant, GBS subtypes and cranial nerve involvement.

Comorbidities affecting mobility and/or respiration will be collected as part of medical history.

Information on days on mechanical ventilation, days in hospital, days in an ICU and reason for ICU admittance will be collected from screening to Day 180.

Visit 1, Screening

All subjects considered for the study will be informed about the study the anticipated benefits and theoretical risks verbally and in writing and must give their written consent before screening or any other study procedure is performed.

The screening visit will include to the following:

- Signing of Informed Consent form
- Demographics (age, sex and race)
- Medical history (including symptom onset time)
- Physical examination
- Vital signs (blood pressure & pulse, respiratory frequency, oxygen saturation, body temperature)
- Height and weight
- Serology (HIV, Hep B and C)
- Evaluation of SARS-CoV-2 virus PCR-test analysis performed at hospital admission or later

- Pregnancy test (serum)
- Safety local laboratory (Clinical Chemistry, Haematology and Urinalysis)
- GBS DS, MRC sum score and R-ODS scale
- Concomitant medication
- Check of inclusion and exclusion criteria

Visit 2 (Imlifidase treatment), Day 1 and Day 2

The following activities and assessments will be performed on Day 1**, prior to dosing with imlifidase**:

- Vital signs (blood pressure & pulse, respiratory frequency, oxygen saturation, and body temperature)
- Safety local laboratory (Clinical Chemistry, Haematology, and Urinalysis)
- PD and ADA
- Exploratory biomarkers
- GBS DS only if more than 24 hours have elapsed between screening and dosing

Premedication prior to dosing with imlifidase:

Methylprednisolone and antihistamine, see Section 5.2.2.

Predose prophylactic antibiotic treatment:

Antibiotics for prophylaxis will be administered to all subjects according to Section 5.2.1. Treatment with antibiotics will start before imlifidase administration and continue for 14 days.

Imlifidase dosing:

All subjects will receive an intravenous infusion of imlifidase (0.25 mg/kg) over 30 minutes.

The following activities and assessments will be performed on Day 1 **after start of imlifidase:**

- The subjects should be observed for 2 hours after end of imlifidase infusion.
- Vital signs (blood pressure & pulse, respiratory frequency, oxygen saturation, and body temperature) at 1 and 2 h after end of imlifidase infusion.

The following activities should be done at **Day 2:**

- Safety local laboratory (Clinical Chemistry, Haematology, and Urinalysis)
- PD and ADA within 24 hours after start of imlifidase infusion
- Exploratory biomarkers within 24 hours after start of imlifidase infusion
- GBS DS and MRC sum score

Visit 3 (IVIg treatment), Day 3-7

All subjects will receive standard care IVIg infusion starting Day 3, at least 48 hours after end of the imlifidase infusion (0.4 g IVIg/kg for 5 days [total dose 2 g/kg]), see Section 5.2.3 for details on infusion rate etc.

The following activities and assessments will be performed in the morning **before start of IVIg infusion:**

- Safety local laboratory (Clinical Chemistry, Haematology, and Urinalysis), Day 3
- PD and ADA, Day 3
- Exploratory biomarkers, Day 3
- GBS DS and MRC sum score Days 3, 4, 5, 6 and 7

Visit 4, Day 8 (+2 days)

The following activities and assessments will be performed:

- Vital signs (blood pressure & pulse, respiratory frequency, and oxygen saturation)
- Safety local laboratory (Clinical Chemistry, Haematology, and Urinalysis)
- PD and ADA
- Exploratory biomarkers
- GBS DS, R-ODS, and MRC sum score
- EurQol EQ-5D Health Questionnaire

Visit 5, Day 15 (±2 days)

The following activities and assessments will be performed:

- Vital signs (blood pressure & pulse, respiratory frequency, and oxygen saturation)
- Safety local laboratory (Clinical Chemistry, Haematology, and Urinalysis)
- PD and ADA
- Exploratory biomarkers
- NCS (optional)
- GBS DS, R-ODS and MRC sum score
- EurQol EQ-5D Health Questionnaire

Visit 6, Day 29 (±3 days)

The following activities and assessments will be performed:

- Vital signs (blood pressure & pulse, respiratory frequency, and oxygen saturation)
- Safety local laboratory (Clinical Chemistry, Haematology, and Urinalysis)
- ADA
- Exploratory biomarkers
- NCS (optional)
- GBS DS, R-ODS and MRC sum score
- EurQol EQ-5D Health Questionnaire

Visit 7, Day 57 (±4 days) and Visit 8, Day 92 (±4 days)

The following activities and assessments will be performed:

- ADA
- Exploratory biomarkers
- GBS DS, R-ODS and MRC sum score
- EurQol EQ-5D Health Questionnaire

Visit 9, Day 180 (+14 days)

The last on-site visit will be performed 180 days after infusion of imlifidase.

The following activities and assessments will be performed:

- Physical examination
- Pregnancy test (serum)
- ADA
- Exploratory biomarkers
- GBS DS, R-ODS and MRC sum score
- EurQol EQ-5D Health Questionnaire
- Confirm that the diagnosis is still GBS (yes/no), if no, specify which primary diagnosis the patient has been given

Visit 10 End-of-study, Day 360 (Telephone Contact) (+14 days)

A telephone contact for safety evaluation will be performed approximately 12 months (Day 360) after infusion of imlifidase.

The following activities and assessments will be performed:

- AE and Concomitant Medication
- GBS DS and R-ODS scale
- EurQol EQ-5D Health Questionnaire
- Confirm that the diagnosis is still GBS (yes/no), if no, specify which primary diagnosis the patient has been given

6.2 Flow Chart

Table 1. Study Flow Chart

Visit Number	**1**	**2**		**3**					**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Screening	Imlifidase treatment		IVIg treatment					Assessments						End of study
Day		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**29**	**57**	**92**	**180**	**360**
Assessment / Time window									**+2d**	**±2d**	**±3d**	**±4d**	**±4d**	**+14d**	**+14d**
Informed consent	X														
Inclusion and exclusion criteria	X														
Demographics	X														
Medical history	X														
Physical examination	X													X	
Blood pressure & pulse	X	X[a]							X	X	X				
Respiratory frequency & oxygen saturation	X	X[a]							X	X	X				
Body temp.	X	X[a]													
Weight	X														
Height	X														
Serology (HIV, HBV and HCV)	X														
SARS-CoV-2	X														

Table 1. Study Flow Chart

Visit Number	**1**	**2**		**3**					**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Screening	Imlifidase treatment		IVIg treatment					Assessments						End of study
Day		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**29**	**57**	**92**	**180**	**360**
Assessment / Time window									**+2d**	**±2d**	**±3d**	**±4d**	**±4d**	**+14d**	**+14d**
Pregnancy test in serum	X													X	
Clinical chemistry, Haematology	X[h]	X[b]	X	X[c]					X	X	X				
Urinalysis	X[h]	X[b]	X	X[c]					X	X	X				
Premedication before imlifidase infusion		X[d]													
Prophylactic antibiotics		X[d]													
Imlifidase IV infusion over 30 min		X[d]													
IVIg				X[e]	X[e]	X[e]	X[e]	X[e]							
PK (imlifidase concentration)[i]		To be completed ONLY if PK sampling initiated according to Protocol Ver.7.0[i]													
PD (IgG)		X[b]	X[f]	X[c]					X	X					
ADA		X[b]	X[f]	X[c]					X	X	X	X	X	X	
Biomarker sampling		X[b]	X[f]	X[c]					X	X	X	X	X	X	
NCS (optional)										X	X				
GBS disability score	X	X[g]	X	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X	X	X	X	X
R-ODS scale	X								X	X	X	X	X	X	X
MRC sum score	X		X	X[c]	X[c]	X[c]	X[c]	X[c]	X	X	X	X	X	X	
EurQol EQ-5D									X	X	X	X	X	X	X
GBS baseline disease information[j]	X														
Confirmation of GBS diagnosis														X	X
Days in hospital/ICU[k]	X ---------- X														
Days on mechanical ventilation[k]	X ---------- X														
Concomitant medication	Throughout the study														

Table 1. Study Flow Chart

Visit Number	**1**	**2**		**3**					**4**	**5**	**6**	**7**	**8**	**9**	**10**
	Screening	Imlifidase treatment		IVIg treatment					Assessments						End of study
Day		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**29**	**57**	**92**	**180**	**360**
Assessment / Time window									**+2d**	**±2d**	**±3d**	**±4d**	**±4d**	**+14d**	**+14d**
Adverse Event	Throughout the study														

[a] Before imlifidase and 1 and 2 hours after end of imlifidase dosing. The patient will be observed for 2 hours after end of imlifidase infusion, longer if medically indicated. If the patient is without infusion related symptoms and vital signs are normal the observation period ends 2 hours after end of infusion.
[b] Predose at Day 1
[c] Before start of IVIg infusion
[d] Imlifidase infusion IV preceded by predefined premedication (methylprednisolone and antihistamine) and start of prophylactic treatment with antibiotics. Treatment with antibiotics will continue for 14 days.
[e] IVIg (0.4 g/kg) infusion will be given for 5 days (total dose 2 g/kg) starting Day 3, at least 48 hours after end of the imlifidase infusion, see Section 5.2.3 for details on infusion rate etc.
[f] Within 24 hours after start of imlifidase administration
[g] Baseline GBS disability score will be assessed if more than 24 hours elapse between screening and imlifidase administration
[h] Collection of safety laboratory samples to be done within 7 days prior to inclusion
[i] PK sampling to be completed ONLY if initiated in accordance with Protocol Ver. 7.0. Sampling timepoints: Predose, 29 min (±1 min), 1 hour (±5 min), 2 hours (±15 min), 6 hours (±30 min), 24 hours at visit 2 and before start of IVIg infusion at Day 3, 4, 5, 6 and 7 (±2 hours)
[j] Data regarding GBS variant, GBS subtypes and cranial nerve involvement will be collected when first available
[k] Data regarding days on mechanical ventilation, days in hospital, days in ICU and reason for ICU admittance will be collected from screening up until Day 180

7. STUDY ASSESSMENTS

All sampling, shipping and analysing of laboratory samples will be detailed in the laboratory manual.

7.1 Assessments Related to Endpoints

7.1.1 GBS Disability Score (GBS DS)

The GBS DS will be assessed at all visits for all subjects. GBS DS is a widely accepted and easily obtainable scoring system to assess disability status of GBS subjects.

The score is as follows:

0 = Healthy

1 = Minor symptoms and capable of running (subjects must be asked to run)

2 = Able to walk independently 10 meters or more but unable to run

3 = Able to walk more than 10 meters across an open space with help

4 = Bedridden or chair bound

5 = Needing mechanical ventilation

6 = Dead

7.1.2 Rasch-Built Linearly Weighted Overall Disability Scale (R-ODS)

R-ODS will be assessed at Screening, Days 8, 15, 29, 57, 92, 180, and 360 for all patients.

R-ODS is a linearly weighted disease specific scale, which captures activities and social participation limitation in patients with immune-mediated neuropathies, including GBS (van Nes et al. 2011). The final questionnaire comprises 24 items ranging from ability to read a book or newspaper (as the easiest item to accomplish) to ability to run (most difficult item to accomplish).

The response options for each item are:

0 = Not possible

1 = Possible with effort

2 = Easy to perform

The obtained raw summed score is subsequently translated to a convenient centile metric ranging from 0 (most severe disability) to 100 (no disability at all) that can be analysed in an analysis of covariance model (ANCOVA) model.

7.1.3 Medical Research Council sum score (MRC sum score)

MRC will be assessed at all visits except for Days 1 and 360 for all patients.

The MRC sum score is widely used to assess the motor impairment in subjects with peripheral neuropathies. It is a sum score of power in six muscle groups on each side

(abduction of arm, flexion of forearm, extension of the wrist, hip flexion, and extension of knee and dorsal flexion of the foot). The sum of these scores ranges from 0 (total paralysis) to 60 (normal power). It gives very valuable information about the muscle strength, especially when patient in bed bound and ventilated (Kleyweg et al. 1991). Change in MRC sum score helps in identification of GBS patients with treatment related fluctuation or exacerbation.

The individual MRC grades are defined as follows:

0 = No visible contraction

1 = Visible contraction without movement of the limb

2 = Movement of the limb but not against gravity

3 = Movement against gravity (almost full range)

4 = Movement against gravity and resistance

5 = Normal

7.1.4 Pharmacokinetics (PK)

No PK sampling will be done after Protocol Ver. 8.0 is approved unless PK sampling has been initiated to a patient in accordance with previous version of the protocol. If so collection of PK samples should continue for a full PK profile.

7.1.5 Pharmacodynamics (PD)

Samples for the determination of IgG levels in serum (PD) will be taken during study as described below. The date and actual time of collection of each sample will be recorded in the eCRF. Full details of the analytical method used will be detailed in a separate bioanalytical report and the analysis results will be collected in the clinical database.

Samples for PD determination will be taken:

- Day 1: predose
- Day 2: within 24 hours after start of imlifidase administration
- Day 3: before start of IVIg
- Days 8 and 15

7.1.6 Immunogenicity (ADA)

Samples for the determination of anti-drug antibody (ADA) levels in serum will be taken during study as described below. The date and time of collection of each sample will be recorded in the eCRF. [redacted] Full details of the analytical method used, and the analysis results will be detailed in a separate bioanalytical report.

Serum samples for the determination of ADA levels will be taken:

- Day 1: predose
- Day 2: within 24 hours after start of imlifidase administration

- Day 3: before start of IVIg
- Days 8, 15, 29, 57, 92 and 180

7.1.7 Days in Hospital and Days in an ICU

Number of days in hospital and number of days in ICU from screening up until Day 180 will be collected. Reason for admittance to ICU will be collected as: worsening of GBS, study procedure/according to site standard practice, infection or other.

7.1.8 Mechanical Ventilation

Number of days on mechanical ventilation from screening up until Day 180 will be collected.

7.1.9 Exploratory Biomarkers

Blood samples for exploratory biomarkers including autoantibodies and other inflammatory factors will be collected:

- Day 1: predose
- Day 2: within 24 hours after start of imlifidase administration
- Day 3: before start of IVIg
- Days 8, 15, 29, 57, 92, and 180

7.1.10 EurQol EQ-5D-5L Health Questionnaire

EQ-5D-5L is a standardised measure of health status developed to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of a descriptive system and an EQ Visual Analogue scale (EQ VAS) and EQ-5D-5L is designed for self-completion by respondents. The questionnaire is cognitively undemanding and taking only a few minutes to complete. EQ-5D-5L will be completed by the participating subjects at Days 8, 15, 29, 57, 92, 180, and 360.

7.2 Safety Assessments Related to Endpoints

7.2.1 Adverse Events

AEs will be recorded during the study period, from obtaining the informed consent until end-of-study visit 10. For further information on definitions and reporting of AEs and SAEs, see Section 9.

7.2.2 Safety Local Laboratory

Blood samples for safety laboratory evaluations of clinical chemistry and haematology parameters will be collected during study as described below. Actual sampling time will be recorded. Clinically significant abnormal findings will be reported as AEs. Findings at the

screening visit will be recorded in the medical history section in the eCRF. Clinical chemistry and haematology will be analysed locally.

Urine samples for safety evaluations will be taken as described below. Samples will be measured with dipstick and analysed locally. In case of abnormal results, a microscopic test will be measured.

The investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether abnormal results are non-clinically or clinically significant.

The following parameters will be collected:

- Clinical chemistry:
    - P-alanine aminotransferase (ALT), P-gamma glutamyl transferase, P-alkaline phosphate, P-bilirubin total, P-creatinine, P-potassium, P-albumin, P-calcium, P-immunoglobulin G (IgG)
- Haematology:
    - B-haemoglobin, B-haematocrit, B-white blood cell count, B-neutrophils (absolute count), B-lymphocytes (absolute count), B-eosinophiles (absolute count), B-platelet count
- Urinalysis(dipstick):
    - U-glucose, U-haemoglobin, U-protein, U-pH

Time of collection:

- All the above analyses:
    - At screening within 7 days prior to inclusion
    - Day 1: Prior to imlifidase administration
    - Days 2, 3 (prior to IVIg infusion), 8, 15 and 29

7.2.3 Physical Examination

A complete physical examination will be performed at screening and Day 180 (visit 9) and include an assessment of the following: general appearance, head and neck, lymph nodes, abdomen, musculo-skeletal, cardiovascular, respiratory and gross neurological examination. The physical examination shall be performed by an investigator.

7.2.4 Vital Signs

Blood pressure, pulse rate, respiratory frequency, oxygen saturation and body temperature will be assessed at:

- Screening

- Day 1:
    - Predose
    - 1 and 2 hours after end of imlifidase dosing
- Days 8, 15, and 29 (all except body temperature)

At Day 1 the subject will be observed for 2 hours after end of imlifidase infusion, longer if medically indicated. If the subject is without infusion related symptoms and vital signs are normal the observation period ends 2 hours after end of infusion.

Systolic and diastolic blood pressure will be measured after the subject has been in supine position for at least 5 minutes. All recordings will be performed using validated standard equipment. Clinically significant abnormal findings will be reported as AEs.

7.2.5 ECG

No ECGs will be collected.

7.3 Other Assessments

7.3.1 Demographics and Baseline data

Information about gender, race and age at inclusion, weight and height will be collected at the screening visit for each subject. Measurements should be taken without shoes and overcoat.

7.3.2 Baseline GBS Disease Information

The following information will be collected when first available:

- GBS variant (pure motor GBS, pharyngeal-cervical-branchial weakness, Miller Fisher syndrome [no limb weakness], Miller Fisher-GBS overlap syndrome, pure sensory GBS, ataxic form, other)
- Cranial nerve involvement
- Electrophysiology classification of subtypes (acute motor axonal neuropathy [AMAN], acute inflammatory demyelinating neuropathy [AIDP], unresponsive nerves, responsive nerves but not classifiable [equivocal], normal).

7.3.3 Serology

Determination of HIV-1 and HIV-2 antibodies, hepatitis B surface-antigen and hepatitis C virus antibodies will be performed at screening.

7.3.4 Pregnancy Test

Serum β-hCG will be determined for all female subjects at screening and on Day 180 (visit 9), using validated standard methods.

7.3.5 Medical History

Information regarding medical history will be collected at the screening visit for each subject and recorded in the eCRF. Medical history will include information regarding any comorbidities affecting mobility and/or respiration.

7.3.6 Nerve Conduction Study (NCS)

If assessed, nerve conduction study (NCS) will be measured at Days 15 and 29. NCS is performed using standard techniques at least on one side of the body. The skin temperature should be controlled and maintained between 32 °C and 34 °C. The NCS includes median, ulnar, peroneal, and tibial motor responses and superficial radial, and sural sensory responses. The median nerve is stimulated at the wrist, antecubital fossa, and responses are recorded over the abductor pollicis brevis. The ulnar nerve is stimulated at the wrist, below the elbow, and responses are recorded over the abductor digiti minimi. The peroneal nerve is stimulated at the ankle, fibular head, and responses are recorded over the extensor digitorum brevis. The tibial nerve is stimulated at the ankle and popliteal fossa, and responses are recorded over the abductor hallucis. Measurements include distal latency, negative peak duration, baseline-to-peak amplitude, conduction velocity, and minimum F-wave latencies. To define conduction block (CB), we used the consensus criteria of the American Association of Electrodiagnostic Medicine (Olney et al. 2003).

7.3.7 SARS-CoV-2 virus PCR-test

At the screening visit an evaluation of the result of the SARS-CoV-2 virus PCR-test, performed at hospital admission or later, will be done.

8. BIOLOGICAL SAMPLING PROCEDURES

8.1 Handling, Storage and Destruction of Biological Samples

Safety samples will be disposed after analyses according to local laboratory practice.

PK, PD, ADA and biomarker samples may be stored for at maximum of 5 years after completion of the study report.

Details on handling of biological samples are described in the laboratory manual that will be provided to the site prior to inclusion of the first subject.

8.2 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their life cycle.

The principal investigator keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed.

Hansa Biopharma keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

8.3 Withdrawal of Informed Consent for Biological Samples

If a subject withdraws consent to the use of biological samples, the samples will be disposed/destroyed, if not already analysed and documented.

The principal investigator:

- Will ensure that subject withdrawal of informed consent is notified immediately to Hansa Biopharma.
- Will ensure that biological samples from that subject, if stored at the study site, are immediately identified, disposed/destructed and the action documented.
- Will ensure the local laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed, and the action documented returned to the study site.

Hansa Biopharma ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed, and the action documented returned to the study site.

In the event that analysis/research has already been performed, Hansa Biopharma will retain the results and associated data for regulatory reasons, but these will not be used in any subsequent analyses.

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Relationship to the study drug will be deemed as not related, unlikely, possible or probable. An undesirable medical condition can be symptoms (e.g., nausea and chest pain), signs (e.g., tachycardia and enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings and electrocardiograms).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

9.1.2 Serious Adverse Event

An SAE is an AE or suspected adverse reaction that is considered "serious" if, in the view of either the investigator or Hansa Biopharma, it results in any of the following outcomes:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening event: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or Hansa Biopharma, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Disability is defined as a substantial disruption in a person’s ability to conduct normal life functions.

Hospitalisation: Admittance to an emergency room for observation without being admitted to the hospital may be considered to be an AE but is not considered as an SAE. However, complications that occur during hospitalization are AEs, and if a complication prolongs hospitalisation, the event is considered serious.

The death of a subject is *per se* not an event but an outcome, but the cause of the death is.

9.2 Collection and Recording of Adverse Events

In clinical studies, an AE/SAE can occur at any time after signing of the informed consent until the end of the study, including run-in or washout periods, even if no study treatment has been administered, e.g., an AE can be related to a procedure in the protocol.

AEs will therefore be collected on the AE eCRF from the time of signing of the informed consent and throughout the study including the follow-up period.

Adverse events can be collected by:

- The subject's response to questions about his/her health (a standard non-leading question such as "Have you had any health problems since you were last asked/your last visit?")
- Symptoms spontaneously reported by the subject
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities
- Other information relating to the subject's health becoming known to the investigator (e.g. hospitalisation)

9.2.1 Variables

The following variables will be recorded in the eCRF for each AE; description of the AE, the date and time (if applicable) when the AE started and stopped, severity based on Common Terminology Criteria for Adverse Events grading (CTCAE v. 4.03) whether the AE is serious or not, causality assessment, action taken and outcome.

9.2.1.1 Causality Assessment

For each reported AE the investigator will make an assessment of the relationship of the event to study procedures and/or IMP using the following criteria.

- **Unrelated:** applicable to an AE that occurs when the subject was not exposed to study treatment or another cause is obvious.
- **Unlikely to be related:** applicable to an AE that meets the following criteria
    - Does not follow a reasonable temporal sequence from study drug dosing
    - May readily have been produced by the subject's clinical state, environmental, or toxic factors, or other therapy administered to the subject
- **Possibly related:** applicable to AEs where connection with dosing of study drug appears unlikely but cannot be ruled out. Applicable to AEs where
    - It follows a reasonable temporal sequence dosing with study drug
    - It follows a known pattern of response to study drug dosing (based on previous studies)

- **Probably related**: applicable to AEs that are considered, with a high degree of certainty, to be related to the study drug. Applicable to AEs where
  - It follows a reasonable temporal sequence study drug dosing
  - It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy
  - It follows a known pattern of response to study drug dosing (based on previous data).
- For SAEs causal relationship will also be assessed for any study procedure.

9.2.2 Adverse Events Based on Signs and Symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms, for example: congestive heart failure rather than low ejection fraction. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom not part of the diagnosis will be recorded separately, for example: congestive heart failure and conjunctivitis.

9.2.3 Adverse Events Based on Examinations and Tests

If lab values are judged as clinically significant and/or a treatment has been given, they will be captured as AEs and if SAE criteria are fulfilled they will also be SAEs.

If vital signs are judged as clinically significant and/or require a treatment, then they will be captured as AEs and if SAE criteria are fulfilled they will also be SAEs.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE and if SAE criteria is fulfilled they will also be SAEs.

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia *versus* low haemoglobin value).

9.2.4 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the investigator until stabilization, for as long as medically indicated or the overall clinical outcome of the subject is known, unless the subject is documented as "lost to follow-up". All SAEs and AEs leading to discontinuation should be followed until the event resolves or stabilizes.

Reasonable attempts to obtain this information must be made and documented. Hansa Biopharma retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.2.5 Reporting of Serious Adverse Events

All SAEs must be reported, whether considered related to the investigational product, or to the study procedure(s), on a separate SAE form. In the Adverse Event form, it will be added that the AE is considered serious. SAEs will be recorded from the time of informed consent.

An assigned Contract Research Organisation (CRO), [redacted], will be responsible for reporting all SAEs to RA in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), and local regulations. Hansa Biopharma or [redacted] will be responsible for reporting to IEC/IRBs.

As soon as the investigator is aware of a potential SAE he/she should contact [redacted] by e-mail and in any case no later than 24 hours after the knowledge of such a case. At the time of initial reporting the investigator must provide as a minimum requirement, subject number, and birth date, description of the SAE and a preliminary assessment of causality.

Contact Information:	
CRO:	[redacted]
e-mail:	[redacted]

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Hansa Biopharma and monitor of any follow-up information on a previously reported SAE immediately but no later than within 24 hours of when he or she becomes aware of it. The monitor or Hansa Biopharma will advise the investigator/study site personnel how to proceed.

The SAE reporting procedures are detailed in the study specific Safety Management Plan. This plan is an agreement between Hansa Biopharma and [redacted].

9.2.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to RAs. A suspected serious adverse reaction is any SAE for which there is a reasonable possibility that the investigational product caused the adverse event. A serious adverse reaction is considered "unexpected" if it is not listed in the reference safety information section of the investigator brochure or is not listed at the specificity or severity that has been observed.

SUSARs with an outcome of death or which are life threatening must be reported to the relevant RAs within 7 calendar days, all other SUSARs must be submitted within 15 calendar days. [redacted] will be responsible for ensuring reporting all SUSARs to RAs in accordance with ICH GCP, CT-3, and local regulations.

The CRO managing the trial sites is responsible for informing all participating trial investigators and ethics committees of any SUSAR on an expedited basis and in accordance with applicable regulations.

In addition, Hansa Biopharma is responsible for ensuring information about all SUSAR to all investigators, IRB, and ethics committees, as applicable, in all other ongoing studies involving imlifidase. The SUSAR reporting procedures are detailed in the study Safety

Management Plan. This plan is an agreement between the Hansa Biopharma, and [redacted].

9.3 Pregnancy and Pregnancy Outcome

Pregnancy is an exclusion criterion and a pregnancy test are performed at the screening visit and prior to infusion of the imlifidase. A pregnancy test is also performed at visit 9.

If a subject becomes pregnant after receiving the dose of imlifidase, the subject will continue in the study according to study protocol, if possible. A Pregnancy Report Form must be sent by the investigator to [redacted] at the latest within two weeks of learning of the pregnancy. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) will be followed up on the Pregnancy Report Form even after the subject has completed or discontinued the study. [redacted] will follow up on pregnancy outcome 4 weeks after the projected due date.

Pregnancy itself is not considered an AE or SAE, but any event occurring during pregnancy that meets serious criteria must be reported to Hansa Biopharma and will be handled as a SAE. Spontaneous abortions, congenital abnormalities/birth defects are always considered to be SAEs and will be reported and followed up in accordance with other SAEs. Any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the study drug by the investigator will be reported to Hansa Biopharma (or designee).

9.4 Overdose

An overdose is a dose in excess of the dose specified in the protocol. There are no data on overdosing of imlifidase. There is no known antidote, but depletion of IgG can be restored with IVIg. In the event of an overdose the patient should be monitored closely and treated symptomatically. This should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF
- An overdose without associated symptoms is only reported in the patient file

9.5 Adverse Events of Special Interest

The following events will be assessed as adverse events of special interest (AESI):

- Infusion-related reactions that occurs within 48 hours of imlifidase treatment
- All AEs resulting in interruption (pause and/or discontinuation) of imlifidase dose (exempted are all interruptions due to problems with e.g. infusion line or pump
- Severe or serious infections within 30 days after imlifidase administration

All events (irrespective of severity) that results in interruption of imlifidase dose should be reported within 24 hours as described for SAEs (see Section 9.2.5).

10. STUDY MANAGEMENT

10.1 Pre-Study Activities

Before the first subject is enrolled into the study, it may be necessary for a representative of Hansa Biopharma to visit the investigational study site for a pre-study visit to:

- Determine the adequacy of the facilities to give Hansa Biopharma information about whether the study centre has knowledge, enough time, a sufficient subject pool, and sufficient training to manage the study in a good way in terms of subject inclusion, subject handling, data and overall study management.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities regarding protocol adherence and the responsibilities of Hansa Biopharma or its representatives.

Before the first subject is entered into the study, a Hansa Biopharma representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and train them in any study specific procedures and system(s) utilized at a site initiation visit.

The principal investigator will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

10.2 Monitoring of the Study

During the study, a Hansa Biopharma representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, ICH GCP, data are being accurately and timely recorded in the eCRFs, and IMP accountability checks are being performed.
- Perform Source Data Verification (SDV) (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects.
- If a subject withdraws informed consent to the use of their biological samples; ensure this is reported to Hansa Biopharma and biological samples are identified, disposed/destructed accordingly, and the action is documented, and reported to the subject.

Hansa Biopharma and its representatives will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct. Details about monitoring are specified in a study specific monitoring plan.

10.3 Source Data

Source data is defined in ICH GCP. Except for SAEs, which must always be source data verified the extent to which SDV will be carried out must be decided, specified and detailed in the Monitoring Plan. For all data recorded, the source document must be defined in a source document agreement at each study site. There must only be one source defined at any time for any data elements.

10.4 Audit and Inspection

The investigator will make all the study-related source data and records available at any time to Quality Assurance auditor(s) mandated by Hansa Biopharma, or to domestic/foreign regulatory inspectors or representatives from IECs/IRBs who may audit/inspect the study.

The main purposes of an audit or inspection are to assess compliance with the study protocol and the principles of ICH GCP and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Documents that authorised Hansa Biopharma representatives and representatives from RAs and IECs/IRBs may wish to inspect their medical records. During audits/inspections the auditors/inspectors may copy relevant parts of the medical records. No personal identification apart from the screening/randomisation number will appear on these copies.

The investigator should notify Hansa Biopharma without any delay of any inspection by a RA or IEC/IRB.

10.5 Study Agreements

The principal investigator must comply with all the terms, conditions, and obligations of the clinical study agreement for this study. In the event of any inconsistency between this clinical study protocol and the clinical study agreement, the clinical study protocol will prevail.

Agreements between Hansa Biopharma and the principal investigator must be in place before any study-related procedures can take place, or subjects be enrolled.

11. DATA MANAGEMENT

At clean file, data from visit 1 to 9 will be evaluated and reported in the Clinical Study Report (CSR). Data from visit 10 will be reported separately as an addendum to the CSR.

11.1 Case Report Form

An eCRF system provided by a CRO will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Hansa Biopharma and vendor procedures, in accordance with regulatory and system requirements.

After the study database is declared clean and released to the statistician, a final copy of the database will be stored at Hansa Biopharma. The investigator will also receive a copy of the study site's final and locked data (including audit trail, electronic signature, meta data and queries) as write-protected PDF-files produced by the CRO. The PDF-files will be stored on a CD/DVD or other applicable media and will be provided to the investigator before access to the eCRF is revoked.

11.2 Provider of Data Management

All data management procedures will be outsourced to a CRO. Activities will be specified in a Data Management Plan prepared by the CRO and reviewed and approved by Hansa Biopharma. The plan will be issued before data collection begins and will describe all functions, processes and specifications for data collection, cleaning and validation.

11.3 Coding

For medical coding of AEs, medical history and concomitant medication the most recent versions of the Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug Dictionary will be used at study closure (unless decided otherwise by Hansa Biopharma).

The coding will be outsourced to a CRO. All coding performed will be approved by Hansa Biopharma prior to study closure/database lock.

11.4 Handling of External Data

If central laboratories or other external data transfers from vendors to Hansa Biopharma will be transmitted, it will be performed in a secure environment according to a Data Transfer Specification.

12. STATISTICAL METHODS

The detailed analysis plan is contained in the SAP. The statistical analyses will be outsourced to a CRO. Prior to database lock, a SAP with details on statistical analysis and data presentation will be written. No formal statistical hypothesis testing will be performed in this study.

The data from the clinical assessments, including demographics and other baseline characteristics, will be summarised and listed by time point using descriptive techniques. Summary statistics (n, arithmetic mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables (absolute values at each time point and, if relevant, changes from baseline) and counts and, if relevant, percentages will be presented for categorical variables.

12.1 Analysis Sets

Compliance and all baseline characteristics (demographics, GBS disease information, medical history, prior and concomitant medication, and physical examination) will be presented for all analysis sets.

12.1.1 Full Analysis Set (FAS)

The FAS comprises data from all dosed subjects having a confirmed GBS diagnosis, i.e., subjects having change in diagnosis during the course of the study will be excluded. The FAS will be used for presentation of efficacy endpoints.

12.1.2 PK/PD Analysis Set

The PK/PD analysis data set comprises data from all dosed subjects, with at least one PK or PD data point available post-baseline. The PK/PD analysis set will be used for presentation of pharmacokinetic and pharmacodynamic endpoints.

12.1.3 Safety Analysis Set

The safety analysis set comprises all treated subjects and will be used for presentation of safety endpoints.

12.2 Subject Characteristics

12.2.1 Subject Disposition

The subject disposition will present number of subjects as enrolled, completed, withdrawn overall and by reason for withdrawal and finally by each of the analysis sets. The number of subjects screened but not found eligible will be stated in the trial report but otherwise not accounted for. Subjects enrolled but not dosed will be regarded as screening failures.

12.2.2 Demographics and Other Baseline Characteristics

The subject demographics and other baseline characteristics will be listed and summarised.

12.2.3 Recent and Concomitant Medication

Recent and concomitant medication will be summarised by anatomical therapeutic chemical (ATC) code and generic drug name.

12.2.4 Exposure and Compliance

Exposure and compliance will be calculated per subject and listed.

12.3 Statistical Analysis of Endpoints

No formal statistical hypothesis testing will be performed in the study.

12.3.1 Analysis of Adverse Events

AEs will be coded according to the latest version of the MedDRA. All data will be listed by subject. Only treatment emergent AEs will be presented in summary tables. Separate data listing will be provided for AEs that are defined as pre-treatment or post-treatment emergent.

12.3.1.1 Pre-treatment Adverse Event

A pre-treatment adverse event is any untoward medical occurrence arising or observed between signing of informed consent and administration of the IMP.

12.3.1.2 Treatment Emergent Adverse Event

A treatment emergent adverse event is any adverse event occurring after the administration of the IMP and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after administration of the IMP and within the time of residual drug effect.

The time of residual drug effect is the estimated period after the administration of the IMP, where the effect of the product is still considered to be present based on pharmacokinetic, pharmacodynamic or other substance characteristics. The residual drug effect is generally accepted to be 5 times the terminal half-life. The terminal half-life of imlifidase is expected to be within the range of approx. 100 hours, i.e. in this study the residual drug effect is likely to be well within the Day 29 assessments, but since this is the first administration of imlifidase to GBS subjects, all AEs occurring up to Day 29 are regarded as treatment emergent.

12.3.1.3 Post-treatment Emergent Adverse Events

A post-treatment emergent adverse event is any adverse event occurring after the time of residual drug effect of the IMP, i.e. between the end of the treatment period visit 6 and visit 10.

12.3.2 Overview of Treatment Emergent Adverse Events

A treatment emergent AE summary table will be presented. The table will include, the number of subjects reporting an AE, the percentage of subjects with an AE and the number of events reported, for the following categories:

- All AEs
- Severe AEs
- SAEs
- Adverse Drug Reactions (ADR)
- AEs leading to withdrawal
- Deaths

ADRs are defined as events that are considered to be possibly or probably related to IMP as judged by the Investigator.

12.3.2.1 Incidence of Treatment Emergent Adverse Events

Summary tables will be prepared for the incidence of treatment emergent AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT), presenting number of subjects reporting an AE, the percentage of subjects (%) with an AE and the number of events reported. Summary tables will be prepared for:

- All treatment emergent AEs by SOC and PT
- AEs by causality
- AEs by intensity
- ADRs by SOC and PT
- ADRs by intensity

Missing values will be treated as missing except for causality, intensity, seriousness and outcome of an AE, in which case, a “worst case” approach will be taken. Thus, if causality is missing, the AE will be regarded as related to the IMP, if intensity of the AE is missing, it will be taken to be severe, if seriousness is missing, the AE will be considered to be an SAE and if the outcome is missing and no date of outcome is present, the outcome is regarded as “not yet recovered”.

12.3.2.2 Serious Adverse Events, Deaths, and Other Significant Adverse Events

Separate listings will be provided for SAEs, deaths, and other significant AEs if any such event occurs.

12.3.3 Analysis of Other Safety Variables

12.3.3.1 Vital Signs

Vital signs will be presented by assessment (time) for each parameter and summarised, including absolute change and percentage change from treatment period baseline. Shift tables will be presented from baseline to end of residual drug effect, i.e. Day 29. Any changes from normal/low to high or from normal/high to low during these periods will be counted as a shift and will be summarised.

12.3.3.2 Clinical Chemistry, Haematology and Urinalysis

Clinical chemistry, haematology and urinalysis parameters will be presented in the same way as the vital sign parameters.

12.3.3.3 Electrocardiography

ECGs will be categorised as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant” (as judged by the Investigator) and listed by subject.

12.3.4 Efficacy

The clinical outcome of the GBS subjects treated with imlifidase and IVIg will be presented as outlined below and as further described in the SAP. Additional analyses, such as a comparison with a matched external control group will be outlined in a separate non-interventional study protocol and corresponding SAP.

12.3.4.1 Proportion of subjects with improvement of one, two, three or more grades on the GBS DS

The proportion of subjects with improvement of at least one, two or three grades, respectively, on the GBS DS will be presented using descriptive statistics by time point.

12.3.4.2 Change in GBS DS

Actual values and changes from baseline will be presented using descriptive statistics by time point.

12.3.4.3 Proportion of subjects able to walk unaided (GBS DS ≤ 2)

Proportion of subjects able to walk unaided (GBS DS ≤ 2) will be presented using descriptive statistics by time point.

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

Time to improvement by at least one, two and three grade(s), respectively, on the GBS DS will be presented using Kaplan-Meier curves.

12.3.4.5 Time to walk independently (GBS DS ≤ 2)

Time to walk independently (GBS DS ≤ 2) will be presented using Kaplan-Meier curves.

12.3.4.6 Time to run (GBS DS ≤ 1)

Time to run (GBS DS ≤ 1) will be presented using Kaplan-Meier curves.

12.3.4.7 Proportion of subjects that reach GBS DS ≤ 1 by week 26

Proportion of subjects that reach GBS DS ≤ 1 by week 26 will be presented using descriptive statistics.

12.3.4.8 Proportion of subjects with an increase from baseline in R-ODS scale

Proportion of subjects with an increase from baseline in R-ODS scale by at least 6 points on the centile metric score will be presented using descriptive statistics by time point. Actual values and change from baseline will be presented using descriptive statistics by time point.

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

Proportion of subjects with all R-ODS items above 0 at week 26 will be presented using descriptive statistics.

12.3.4.10 Proportion of subjects requiring mechanical ventilation support

Proportion of subjects requiring mechanical ventilation support (GBS DS 5) will be presented using descriptive statistics by time point.

12.3.4.11 Days on mechanical ventilation

Days on mechanical ventilation will be presented using descriptive statistics.

12.3.4.12 Days in hospital and days in an ICU

Days in hospital, days in an ICU and reason for admittance to ICU will be presented using descriptive statistics.

12.3.4.13 Change in MRC sum score

Actual values and changes from baseline will be presented using descriptive statistics by time point.

12.3.4.14 Quality of Life – EQ-5D-5L

Change in quality of life EQ-5D-5L score will be presented using descriptive statistics by time point.

12.3.5 Pharmacokinetics

The PK parameters will be calculated using the software WinNonlin® (Pharsight Corporation, US). Non-compartmental analysis (NCA) or compartment calculations will be used for PK evaluation. Actual sampling time points relative to dosing will be used in the PK calculations for each patient and on the individual plots of plasma concentration versus time.

Plasma concentration values below lower limit of quantification (LLOQ) and missing values (e.g. no blood sample collected, or no value obtained at analysis) will be excluded from the PK parameter calculation.

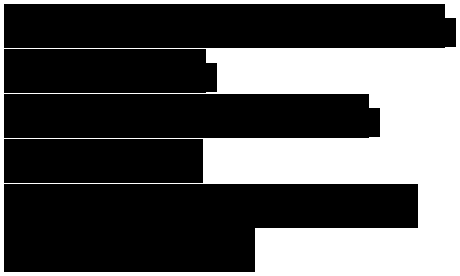
PK parameters will be estimated based on measurements of the plasma concentration-time data of imlifidase, and the following parameters will be estimated (but not limited to), if possible: AUC, $\%AUC_{extrap}$, C_{max}, t_{max}, $t_{½}$, CL, V_z.

PK parameters will be presented with number of measurements, number of missing data, mean, standard deviation, median, minimum, maximum, geometric mean. For $t_{½}$, the harmonic mean will be listed instead of the geometric mean. For t_{max} the geometric mean and the CV% will be omitted.

12.3.6 Pharmacodynamics

The PD data will be summarised and presented graphically as mean profiles and by patient profiles.

The SDS-PAGE bioanalytical report will include a qualitative description of results, and the outcome will be scored according to the following, listed, and summarised:



The relationship between imlifidase concentration and IgG cleavage will be presented graphically.

12.3.7 Anti-drug Antibodies

Presence of ADAs will be presented using descriptive statistics by time point.

12.4 Statistical Analysis of Exploratory Endpoint(s)

Exploratory biomarkers will be presented by descriptive statistics.

12.5 Determination of Sample Size

No formal sample size calculations have been performed for this study. Approximately 30 evaluable subjects are considered sufficient to provide adequate information about the safety and efficacy.

12.6 Evaluability of Subjects for Analysis

Major protocol violations such as significant non-compliance or other serious unforeseen violations deemed to invalidate the data collected for the purposes of the study may lead to exclusion of the data from analysis. In case of minor protocol violations, data will not be excluded from the data analysis. The rating of protocol violations in ‘minor’ and ‘major’ will be decided on the basis of a review of the data before declaration of ‘clean file’ and database lock.

13. CHANGES IN STUDY CONDUCT OR PLANNED ANALYSES

Any changes and deviations to plans described in the protocol and in the SAP must be documented.

13.1 Protocol Amendment(s)

Any change to this protocol will be documented in a protocol amendment, issued by Hansa Biopharma, and agreed upon by the investigator and Hansa Biopharma prior to its implementation. Protocol Amendments and documents updated as a result of the Protocol Amendment must not be implemented until all approvals (IEC/IRB and RAs, if applicable) have been obtained.

Changes to the protocol to eliminate immediate hazard(s) to study subjects may be implemented prior to IEC(s)/IRB(s) and RA approval.

13.2 Protocol Deviations

Under working conditions, deviations from the protocol may occur. If deviations from the protocol occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed, discussed and documented. Deviation reports and supporting documentation will be kept in the investigator site file and the study master file.

13.3 Statistical Analysis Plan

Any changes to the SAP will be described in the Clinical Study Report and/or in the Statistical Report.

13.4 Premature Termination or Suspension of the Study

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the subjects and should assure appropriate therapy and follow-up.

If the investigator terminates or suspends a study without prior agreement of Hansa Biopharma, the investigator should inform the Institution where applicable. The investigator/institution should promptly inform Hansa Biopharma and should provide Hansa Biopharma with a detailed written explanation of the termination or suspension. If Hansa Biopharma terminates or suspends a Study, the investigator should promptly inform the Institution where applicable. In both cases Hansa Biopharma will promptly inform the RA and IEC and provide them with a detailed written explanation of the termination or suspension.

If the RA or IEC terminates or suspends its approval/favourable opinion of a study, Hansa Biopharma should inform the investigators and institutions (where applicable) and provide them with a detailed written explanation of the termination or suspension.

14. REPORTING AND PUBLICATION

14.1 Clinical Study Report

The main analyses for the clinical study report (CSR) will be based on all data when all patients have had visit 9 (Day 180). Data from visit 10 (Day 360) will be reported as an addendum to the CSR. The full CSR including addendum will be available within one year after end of study (for definition see Section 3.5).

14.2 Confidentiality and Data Ownership

Any confidential information relating to the IMP or the study, including any data and results from the study will be the exclusive property of Hansa Biopharma. The investigator and any other persons involved in the study will protect the confidentiality of the proprietary information belonging to Hansa Biopharma.

14.3 Publications

14.3.1 Publication Policy

At the end of the study, one or more manuscripts for joint publication will be prepared in collaboration between the investigator(s) offered authorship and Hansa Biopharma.

Any external CRO or laboratory involved in the conduct of this study has no publication rights regarding the study.

14.4 Public Disclosure

The study will be registered in a public clinical trials registry e.g. the U.S. National Institutes of Health register ClinicalTrials.gov and EU Clinical Trials Register.

15. ETHICAL AND REGULATORY ASPECTS

15.1 Ethical Conduct of the Study

This study will be conducted in accordance with ICH GCP, approved protocol and any amendment and applicable regulatory requirements.

The responsibilities of Hansa Biopharma, the monitor and the investigator are defined in the ICH GCP guideline and applicable regulatory requirements in the country where the study takes place.

15.2 Liabilities and Insurance

Hansa Biopharma is, as sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a study subject for injury arising from the subject's participation in the study.

15.3 Independent Ethics Committee(s) and Institutional Review Boards

All ethical and regulatory approvals must be available before a subject is exposed to any study-related procedure, including screening tests for eligibility.

According to applicable regulatory requirements Hansa Biopharma will:

- obtain approval from or notify the relevant (IECs) of the protocol, any amendments, the Subject Information Sheet/Informed Consent Form and any advertisements etc.
- send periodic updates to the IEC(s) if applicable
- provide investigator(s) with an accurate and complete record of all submissions to the local IEC. The copies should be filed in the investigator site file.

Hansa Biopharma will keep an updated list of submission and approval dates of all documents submitted to IEC(s).

15.4 Regulatory Authority(ies)

Before initiating the clinical study, Hansa Biopharma and the investigator, if required by the applicable regulatory requirement(s), should submit any required application to the appropriate Regulatory Authorities (RA) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s) to begin the study. Any notification/submission should be dated and contain sufficient information to identify the protocol.

Hansa Biopharma will keep an updated list of submission and approval dates of all documents submitted to RAs.

15.5 Subject Information and Informed Consent

Before any study-related activities and in agreement with applicable regulatory requirements, the investigator must give the subject oral and written information about the study in a form that the subject can understand. Investigator must ensure that the subject is fully informed about the aims, procedures, potential risks, any discomforts and expected benefits of the study. Before consenting, the subject must be left with ample time to consider and to pose questions.

It must be emphasised that participation is voluntary and that the subject has the right to withdraw from the study at any time without prejudice.

In cases where the subject is deemed to have capacity, but physical disability prevents them from signing the personal consent form, the procedure for information and consent will be followed in compliance with local regulations, which could involve a designated authorised person to consent on behalf of the subject.

The original, signed Informed Consent Forms must be kept in the investigator site file.

The subject will receive a copy of the Subject Information and his/her signed Informed Consent Form.

If new information becomes available that may be relevant to the study subject's willingness to continue participation in the study, a new Subject Information and Informed Consent Form will be forwarded to the IEC(s)/IRB(s) (and RAs, if required). The study subjects will be informed about this new information and re-consent will be obtained.

15.6 Subject Participation Card

The subject will be provided with a subject participation card bearing the following information:

That he/she is participating in a clinical study (incl. study code).

That he/she has been treated with study drug.

The name and phone number of the investigator (could be phone number to the department of the investigator, when used in emergency situations).

The subject will be asked to keep the subject participation card in their possession at all times during the study and to return it at the last study visit, if applicable.

Include statement whether each subject's primary care physician will be notified of their participation in the study by the investigator, if the subject agrees.

15.7 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and Hansa Biopharma and their agents. This confidentiality is extended to cover testing of

biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of Hansa Biopharma.

The study monitors, or other authorized representatives of Hansa Biopharma may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such record.

16. ARCHIVING

16.1 Retention of Clinical Study Site Documentation

The investigator is responsible for maintaining all the records, which enable the conduct of the study at the site to be fully understood, in compliance with ICH GCP. The study documentation including all the relevant correspondence should be kept by the investigator for at least 25 years or longer if so required by local law after the completion or discontinuation of the study, if no further instructions are given by Hansa Biopharma.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous eCRF data for Hansa Biopharma. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 25 years or longer if so required by local law after the completion or discontinuation of the study.

No study site document may be destroyed without prior written agreement between the investigator and Hansa Biopharma. Should the investigator elect to assign the study documents to another party, or move them to another location, Hansa Biopharma must be notified. If the investigator retires and the documents can no longer be archived by the site, Hansa Biopharma can arrange having the investigator site file archived at an external archive.

16.2 Study Master File

Hansa Biopharma will archive the Study Master File in accordance with ICH GCP and applicable regulatory requirements.

17. REFERENCES

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18. ATTACHMENT

18.1 Protocol Amendment 08