Statistical analysis plan

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

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List of abbreviations and definition of terms

ADA	Anti-Drug Antibody
ADaM	Analysis data model
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the concentration versus time curve
BP	Blood pressure
CI	Confidence interval
CL	Clearance of imlifidase
C_{max}	Maximum observed concentration
CSR	Clinical Study Report
ECG	Electrocardiography
EQ-5D-5L	EuroQoL EQ-5D Health Questionnaire
FAS	Full analysis set
GBS	Guillain-Barré Syndrome
GBS DS	Guillain-Barré Syndrome disability score
ICU	Intensive Care Unit
IdeS	Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*
IMP	Investigational medicinal product
IVIg	Intravenous Immunoglobulin
LLOQ	Lower limit of quantification
mEGOS	Modified Erasmus GBS Outcome Score
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council sum score
NCS	Nerve Conduction Studies
PD	Pharmacodynamics
PE	Plasma Exchange
PK	Pharmacokinetics
PKPDAS	PK/PD analysis set
PT	Preferred term
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study data tabulation model
SE	Standard error
SOC	System organ class
TEAE	Treatment emergent adverse event
T_{max}	Time of observed C_{max}
$t_{½}$	Half-life
V	Volume of central compartment
Vss	Volume of distribution at steady-state
Vz	Volume of distribution during the elimination phase

1 Introduction

Guillain-Barré Syndrome (GBS) 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. 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.

After onset, GBS patients have a mortality rate of 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 patients, but the majority develop their maximum deficit within 2 weeks.

To treat GBS, both general medical care and immunological treatment are recommended. Intravenous Immunoglobulin (IVIg) and Plasma Exchange (PE) are the two main treatments. 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.

This study is designed to evaluate the safety, tolerability, and efficacy of intravenous dosing of imlifidase in GBS subjects. Additionally, pharmacokinetics (PK) and pharmacodynamics (PD) will be assessed.

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.

This document presents the planned statistical analyses for Hansa Biopharma AB, study 15-HMedIdeS-09: 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.

This statistical analysis plan is based on the trial protocol version 7.0 (dated 11JUN2021), version 8.0 (dated 31JAN2022) and version 9.0 (dated 27JUN2023).

In case of deviations from the SAP, explanations will be provided in the Clinical Study Report (CSR).

1.1 Study objectives and endpoints

1.1.1 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 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.

1.1.2 Endpoints

1.1.2.1 Efficacy

The efficacy endpoints are the following:

- GBS Disability Score (DS):
  - Proportion of subjects with improvement of one or more grades in disability outcome (on the 6-point GBS DS) over time (i.e., at all post-baseline visits)
  - Proportion of subjects with improvement of two or more grades in disability outcome (on the 6-point GBS DS) over time (i.e., at all post-baseline visits)
  - Proportion of subjects with improvement of three or more grades in disability outcome (on the 6-point GBS DS) over time (i.e., at all post-baseline visits)
  - Change in GBS DS over time (i.e., at all post-baseline visits)
  - Proportion of subjects able to walk unaided (GBS DS ≤ 2) over time (i.e., at all post-baseline visits)
  - Time (days) to improvement by at least one, two and three grade(s) on the GBS DS
  - Time (days) to walk independently (GBS DS ≤ 2)
  - Proportion of subjects that reach GBS DS ≤ 1 by week 26
  - Time (days) to run (GBS DS ≤ 1)
- Rasch-built Overall Disability Scale (R-ODS):
  - Proportion of subjects with an increase from baseline in R-ODS scale by at least 6 points on the centile metric score over time (i.e., at all post-baseline visits)
  - Proportion of subjects with all R-ODS items above 0 at week 26
- Change in MRC sum score over time (i.e., at all post-baseline visits).
- Ventilation support (GBS DS 5):

- Proportion of subjects requiring mechanical ventilation support (GBS DS 5) (i.e., at all visits)
- Time (days) on mechanical ventilation

- Time (days) in hospital and in an ICU
- Quality of life as measured by EurQol EQ-5D Health Questionnaire (EQ-5D-5L) at 4 weeks and later.

1.1.2.2 Safety

Safety will be assessed by:

- Adverse events:
  - All AEs
  - TEAEs
  - Severe AEs (AEs having CTCAE grade ≥ 3)
  - SAEs
  - Adverse Drug Reactions (ADR) defined as TEAEs related to study treatment (Possibly or Probably Related AEs)
  - AEs leading to withdrawal
- Deaths
- Adverse events of special interest (AESI), defined as
  - 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

- Presence of anti-imlifidase antibodies (ADA)

- Laboratory tests:
  - 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

  - Urinanalysis:

    U-glucose, U-haemoglobin, U-protein, U-pH, U-urobilinogen, U-protein, U-ketone, U-bilirubin.

- Vital signs (Blood pressure, pulse rate, respiratory frequency, oxygen saturation and body temperature)

- Physical examination (include an assessment of the following: general appearance, head and neck, lymph nodes, abdomen, musculo-skeletal, cardiovascular, respiratory and gross neurological examination)

- Electrocardiography (ECG) (categorised as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”, as judged by the Investigator), only collected up to protocol version 7.0 (inclusive).

1.1.2.3 Pharmacokinetics (PK) and Pharmacodynamics (PD)

PD and PK will additionally be evaluated as endpoints:

- 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

- PD effect on IgG following administration of imlifidase

- PD effect on identified autoantibodies regarded as GBS disease specific following administration of imlifidase.

To note, identification of post-infusion antibodies is described in section 1.1.2.4.

1.1.2.4 Exploratory Endpoint

Biomarker assessment (analysis of anti-ganglioside antibodies and neurofilament light chain levels) will be evaluated as an exploratory endpoint.

2 Study design

The study 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 (adult males or females) 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).

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 (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. This data will be handled according to a separate SAP.

2.1 Overview of study procedures

All subjects will receive imlifidase (Day 1) prior to standard of care IVIg. Disability scores to assess disability status and capture 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.

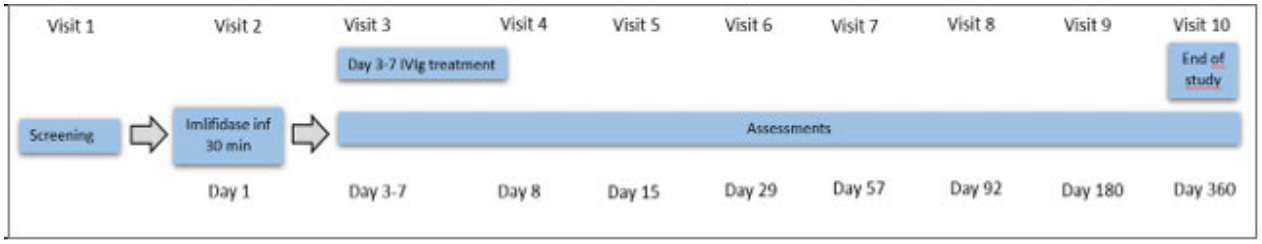
Subjects will be followed clinically on days 1-8, 15, 29, 57, 92 and 180 days after imlifidase infusion and additionally with a 360-day telephone contact to assess GBS DS, R-ODS, capture health status in a questionnaire, and AEs.

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.

Figure 1. Overview of study



The planned tests are summarised in the **Study Flow Chart Table** outlined in the study protocol.

Note, schedule of Study Flow Chart (i.e., assessments and procedures) may change between protocol versions, please refer to corresponding schedule relevant for each protocol version.

2.2 Determination of sample size

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

2.3 Blinding

Blinding is not relevant since this is an open-label study, and all subjects will receive a dose of imlifidase, 0.25mg/kg.

2.4 Data pre-processing

Difference between the value at each assessment and value at baseline for the efficacy parameters as an absolute change and percentage change will be calculated as:

$$Absolute\ change\ at\ visit\ x = Value\ at\ visit\ x - value\ at\ baseline.$$

$$Change\ in\ \%\ at\ visit\ x = \frac{absolute\ change\ at\ visit\ x}{value\ at\ baseline} \cdot 100.$$

The proportion of subjects with improvement since baseline at each visit will be calculated as:

$$Proportion\ at\ visit\ x = \frac{number\ of\ subjects\ with\ improvement\ at\ visit\ x}{number\ of\ subjects\ at\ baseline}.$$

Mean difference from baseline to each visit will be calculated as:

$$Mean\ difference\ at\ visit\ x = \frac{sum\ of\ absolute\ change\ from\ baseline\ at\ visit\ x}{number\ of\ subjects\ at\ visit\ x}.$$

3 Analysis sets

3.1 Full analysis set

The full analysis set (FAS) consists of data from all dosed subjects having a confirmed GBS diagnosis, i.e., subjects re-evaluated and having change in diagnosis (incorrectly diagnosed with GBS at study entry) will be excluded.

The FAS will be used for presentation of efficacy endpoints.

3.2 PK/PD analysis set

The PK/PD analysis set (PKPDAS) 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.

3.3 Safety analysis set

All treated subjects are included in the safety analysis set (SAF).

The safety analysis set will be used for presentation of safety endpoints.

4 Statistical analyses and presentation of data

4.1 General considerations

In general, FAS, PKPDAS and SAF will be used for presentation of all baseline characteristics (demographics, GBS disease information, medical history, prior and concomitant medication, and physical examination), FAS will be used for efficacy endpoints, SAF will be used for exposure and compliance and safety endpoints and PKPDAS will be used for pharmacokinetic and pharmacodynamic endpoints.

Listings to be presented for all subjects, if not otherwise specified in the corresponding TFL shell.

4.1.1 Data presentation

No statistical testing will be performed. Results from analyses will be presented with estimates and 95% confidence intervals (CIs). For log-transformed analyses, the anti-log transformation will be applied before presentation.

No adjustments for multiple testing will be done, since no statistical testing will be performed.

Numerical data will be presented in summary tables by number of subjects, arithmetic mean, median, standard deviation (SD), minimum and maximum. When numerical data are recorded at different time points, absolute values at each time point and changes from baseline may be presented in the summary tables.

Categorical data will be presented by number and percent of subjects as well as number of events (where applicable).

Summaries and analysis of data will in general be presented for all subjects included in the analysis set, unless otherwise specified in the output shell.

All data will be listed by subject and time point (if applicable).

4.1.2 Baseline definition

Baseline value is defined as the last non-missing assessment before the subjects start on the treatment. Change from baseline will be calculated as the difference between values for a given timepoint after baseline and baseline values (timepoint after baseline value minus baseline value). If the post-baseline value or baseline value are missing, then the change from baseline will also be missing.

4.1.3 Data imputation

In general, missing data will remain as missing and the missing values will not be imputed. There are some exceptions described below.

Dates for adverse event and concomitant medication

Missing or partial start dates for AEs and concomitant medication data will be handled in the following way:

- If the start date is totally missing, the date will still be missing.
- If the start date is partial where only month and year are given, then the two cases are considered:
  1. If the available partial date (month and year) is before the month and year of treatment start date, then the AE/medication will be considered as pre-treatment and the date will be imputed as the end date of the month.
  2. If the available partial date does not indicate that the AE/medication has started before the treatment start, then the AE/medication will be considered as treatment emergent/concomitant or post-treatment emergent, as follows:
     - If month is same as month of treatment start date or the month right after the month of treatment start date, then the AE is treatment emergent.
     - Else if month is after month of treatment start date, then the AE is post-treatment emergent.
     - For medications, if the available partial date does not indicate that the medication has started before the treatment start, then it will be considered as concomitant.

     The date will be imputed as the start (1st) of the month (if the month and year is after the month and year of the treatment start date) or treatment start date (if the month and year is same as month and year of the treatment start date).
- If the start date is partial where only the year is given, then the two cases are considered:
  3. If the available partial date (year) is clearly before the year of treatment start date, then the start date is imputed as last day of the year (i.e. 31 December).
  4. If the available partial date (year) is equal to or after the year of treatment start date, then the start date will be imputed as start of the year (1st January YYYY) (if the year is not same as that of the treatment start date) or treatment start date (if the year is same as the treatment start date).
- For the partial end dates, similar procedure will be used as for the start dates. The only difference is the imputation for missing days and months. Missing days is imputed to the end of the month (instead of the start of the month) or at the date of study discontinuation/completion, whichever occurs first. If only year is available, the end date is set to 31st December YYYY or at the date of study discontinuation/completion, whichever occurs first. It will be checked that the imputed end dates fall after the corresponding start dates.

All completely missing end dates will be missing.

The partial dates as reported will be presented in the listings. The imputed dates purpose is for deriving the corresponding flags for relation to start/end of IMP (e.g. TEAE flagging) and study days, when applicable.

4.2 Subject disposition

Subjects enrolled but not dosed will be regarded as screening failures.

Subjects screened but not found eligible will be stated in the trial report but otherwise not accounted for.

A table will present the subject disposition as number of subjects screened, enrolled, GBS not confirmed at 6 months, GBS not confirmed at 12 months, screen failures, completed (6 months follow-up visit and 12 months follow-up visit, respectively), withdrawn overall and by reason for withdrawal and by subjects in each of the analysis sets.

4.3 Protocol deviations

Deviations from the protocol, as continuously tracked by investigator and sponsor, will be classified as ‘minor’ or ‘major’. The final classification of the deviations will be done before the database lock.

All protocol deviations will be summarised with frequency and percentage for each category of protocol deviation, for both FAS and safety analysis sets. The protocol deviations will also be listed by subject.

4.4 Demographics and other baseline characteristics

The demographics are age at screening date, sex, and race.

Medication will be classified according to WHODrug Global B3 dictionary version 2018Q3.

Summary tables will be performed for:

- Demographics (including age (years), sex, race, height, weight and BMI before IMP intake)
- Medical history or concomitant illness as reported at study entry
- Baseline GBS characteristics and GBS symptoms, including:
    - Presence of diarrhoea (<4 weeks from screening)
    - Onset of weakness due to GBS
    - Days from onset of weakness until imlifidase administration
    - GBS variant type at screening
    - Electrophysiology classification of subtype the subject has according to JJ Sejver et al. (Vaccine 2011; 29: 599-612)
    - Status of cranial involvement
    - Medical history of disease affecting mobility (yes/no)

  - Medical history of disease affecting respiration (yes/no)

- Pre-medication to prevent/minimise risk of infusion reactions (methylprednisolone and antihistamine or an equipotent antihistamine) before imlifidase infusion
- Medication to minimise the risk for bacterial infections (prophylactic antibiotics), summarizing all prophylactic antibiotics the subjects had during the first 14 days after imlifidase administration (including prophylactic antibiotics given in day before imlifidase administration and in same day as the imlifidase administration).
- Prior medication, summarizing all medications the subjects had before the study (prior to start of study treatment)
- Concomitant medication, summarizing all medications the subjects had throughout the study (following start of study treatment), considering the following tables:
  - All concomitant medications
  - Concomitant medication during Day 1 – 29
  - Concomitant medications during Day 30 – End of study

Note: prior and concomitant medication will exclude 'Pre-medication to prevent/minimise risk of infusion reactions before imlifidase infusion' and 'Medication to minimise the risk for bacterial infections'.

Listings will be provided including the values for each subject of:

- Subject disposition (enrolled, completed, withdrawn (reason for withdrawal) for each analysis set (FAS, SAF and PKPDAS).
- Demographics (including age (years), sex, race)
- Medical history as reported at study entry (system organ class (SOC) and preferred term (PT))
- GBS disease information at study entry
- Baseline GBS characteristics
- Pre-medication to prevent/minimise risk of infusion reactions (methylprednisolone and antihistamine or an equipotent antihistamine) before imlifidase infusion
- Prophylactic antibiotics (flag in if during the first 14 days after imlifidase treatment).
- Prior medication (anatomical therapeutic chemical (ATC) code and generic drug name)
- Concomitant medication (anatomical therapeutic chemical (ATC) code and generic drug name)
- Serology (HIV-1 and HIV-2 antibodies, hepatitis B surface-antigen and hepatitis C virus antibodies performed at screening)

4.5 Compliance and exposure

A summary table will be presented for exposure and compliance. The table will summarise the exposure (total dose of imlifidase, actual dose of imlifidase in mg/kg, total grams of IVIg given per dose, total grams of IVIg given to the subject, number of IVIg doses) and compliance (percent of planned dose of imlifidase compared to actual, percent of number IVIg doses compare to planned*).

*As per protocol, all subjects are planned to receive standard care with IVIg infusion (0.4 g IVIg/kg/day for consecutive 5 days).

Compliance and the drug exposure will be also presented in a listing by subject. In addition, listings will be presented to show drug administration details of imlifidase and IVIg.

4.6 Subgroups

If deemed appropriate, the following subgroups might be considered for specific subgroup analysis. If so, the subgroup analysis will be defined at a later stage in a separate document.

The following subgroups might be considered:

- [redacted]
- Electrophysiology classification subgroup: subjects with acute motor axonal neuropathy (AMAN)/ acute motor and sensory axonal neuropathy (AMSAN) and subjects with acute inflammatory demyelinating neuropathy (AIDP).
- [redacted]

The above defined subgroups will be listed and summarized (number and percentage of subjects in each category of subgroup) on the FAS.

4.7 Efficacy analysis

4.7.1 GBS Disability Score (GBS DS)

The GBS Disability Score (GBS DS) used for the efficacy endpoints will be assessed for all subjects as per the schedule of assessments. The score is defined 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

Summary statistics will be presented in tables for the actual values and absolute change from baseline by time point. Also, shift tables will be presented to show the change from baseline as compared to post-baseline visits for the GBS DS.

In addition, the number and percentages of subjects with improvement of at least one, two or three grades, respectively, on the GBS DS will be presented by time point.

Similarly, the number and percentage of subjects able to walk unaided (GBS DS ≤ 2) and run (GBS DS ≤ 1), respectively, will be presented by time point.

Lastly, the following Kaplan-Meier analysis summary tables and plots will be presented:

- Time to improvement by at least one grade on the GBS DS
- Time to improvement by at least two grades on the GBS DS
- Time to improvement by at least three grades on the GBS DS
- Time to walk independently (GBS DS ≤ 2)
- Time to run (GBS DS ≤ 1)

Study end/discontinuation will be considered as censoring for subjects that do not have the event. In addition, the survival function will start at 0, since all these are “positive” events.

For each endpoint two separate Kaplan-Meier plots will be presented, one up to Day 29 (collected part of Visit 6) and one up to Day 360 (collected as part of Visit 10), including the subjects at risk at specific timepoints. Also censored observations will be marked as such on the plot.

The summary tables for the corresponding Kaplan-Meier analysis will include the following for specific timepoints up to Day 360: subjects at risk, number of subjects with events, censored observations, proportion estimates and associated pointwise 95% confidence interval (CI).

A separate table will present the number of subjects included in the analysis with corresponding number of events, number of censored observations and summary statistics for the time to event (minimum, maximum, median and associated 95% CI, quartiles).

Additionally, a swimmer plot will be created to show change in GBS DS over time up to Day 92 (collected as part of Visit 8). Subjects will be shown as rows on y-axis, time on x-axis, each subject having a bar that is coloured according to latest GBS DS.

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

The response options for each item of the Rasch-Built Linearly Weighted Overall Disability Scale (R-ODS) used for the efficacy endpoints will be assessed for all subjects as per the schedule of assessments. 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), as described in Appendix 2, which will be used for summary statistics and analyses. To note, the centile metric will be calculated only if all 24 items have data, otherwise this will be missing.

Summary statistics will be presented in tables for the actual values and absolute change from baseline by time point for the centile metric.

In addition, the number and percentages 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.

Similarly, the number and percentages of subjects with all R-ODS items above 0 at week 26 will be presented.

4.7.3 Medical Research Council sum score (MRC sum score)

The Medical Research Council sum score (MRC sum score) used for the efficacy endpoints will be assessed for all subjects as per the schedule of assessments. It is a sum score of power in six muscle groups on each side (summing all the obtained scores of each muscle groups on each side). The sum of these scores ranges from 0 (total paralysis) to 60 (normal power). The individual MRC grades are defined as:

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

Summary statistics will be presented in tables for the actual values and absolute change from baseline for MRC sum score by time point. MRC sum score will be calculated only if all 12 scores of each muscle groups on each side have data, otherwise this will be missing.

In addition, representing proximal and distal muscles outcomes, summary statistics (both actual values and absolute change from baseline) will be presented for the following four subgroups of the MRC score (sub-scores), calculated as an average of the included items, by time point:

- abduction of arm + flexion of forearm for both sides
- extension of the wrist for both sides
- hip flexion + extension of knee at both sides
- dorsal flexion of the foot for both sides

Sub-scores including one muscle group will be calculated if both sides have scores, sub-scores including two muscle groups will be calculated if both muscle groups have scores from at least one side. This does mean that the MRC sum score may be missing even though some sub-scores are calculated (due to available data for the scores in particular muscle groups).

Individual subject plots will be created showing both MRC sub-scores and GBS DS over time up to Day 92 (collected as part of Visit 8). The graph will show time since imlifidase administration on x-axis, MRC sub-scores over time will be represented as a line, GBS DS as a bar coloured according to latest GBS DS. Additional events of interest will be included on the plot: onset date of worsening of GBS (captured as AE: any AE with reporter term stating 'FACIAL PARALYSIS', or AE coded preferred term of 'Neuropathy peripheral' or 'Respiratory failure' with corresponding reported term suggesting worsening/deterioration of GBS), start and stop dates for ICU admission(s).

4.7.4 Ventilator support and days in hospital and days in an ICU

The number and percentage of subjects requiring mechanical ventilation support (GBS DS 5) will be presented by time point.

In addition, summary statistics will be presented in three separate tables for the number of days on mechanical ventilation and number of days in hospital and in an ICU. The number of days in an ICU is a subset of number of days in hospital.

The total number of days on mechanical ventilation and total number of days in hospital and in an ICU will be calculated for each subject considering the following formula:

> Total number of days on mechanical ventilator = Sum of [(End date of mechanical ventilation – Start date of mechanical ventilation) + 1]
>
> Total number of days in hospital = Sum of [(End date in hospital – Start date in hospital) + 1]
>
> Total number of days in an ICU = Sum of [(End date in an ICU – Start date in an ICU) + 1],

including each period the subject was on mechanical ventilator in hospital and in an ICU between administration of IMP to Day 180. As periods can overlap (new period starting at the same date that previous period ended) it will be ensured that no day is counted twice.

Also, the number and percentage of subjects that were at ICU or on mechanical ventilator at time of imlifidase administration will be presented in a separate table on the FAS, part of the baseline characteristics section.

Details about the mechanical ventilation support, hospital admission and days in an ICU will be presented in separate listings.

4.7.5 EurQol EQ-5D-5L Health Questionnaire

Quality of Life is used for assessment of efficacy and is measured by EuroQol EQ-5D Health Questionnaire. The EQ-5D-5L consists of 5 individual items (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and an EQ Visual Analogue scale (EQ VAS) and EQ-5D-5L is designed for self-completion by respondents. EQ-5D-5L will be completed by the participating subjects as per the schedule of assessments.

Summary statistics will be presented in a table for the VAS score by time point. Also, all individual items will be summarized using frequency counts and associated percentages for all time points in a separate table.

4.8 Safety

Safety data will be presented by descriptive statistics in tables and in listings for each subject. Safety parameters will be evaluated for the safety analysis data set.

4.8.1 Adverse events

According to the protocol, an AE is defined as 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).

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

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

A Serious Adverse Event (SAE) is defined as an AE which fulfills any of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient 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, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE, but not the procedure itself.

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

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

Summary tables will be presented for all AEs and TEAEs, respectively. For each of the AE categories below, the number of subjects reporting an AE, the percentage of subjects with an AE and the number of events reported:

- All AEs
- TEAEs
- All non-TEAEs divided in pre- and post-TEAE
- AEs having CTCAE grade ≥ 3
- TEAEs having CTCAE grade ≥ 3
- All non-TEAE having CTCAE grade ≥ 3 divided in pre- and post-TEAE
- SAEs
- Serious TEAEs
- Adverse Drug Reactions (ADR) defined as TEAEs related to study treatment (i.e., Possibly or Probably Related AEs)
- AEs leading to withdrawal
- TEAEs leading to withdrawal
- AEs leading to death
- AEs of special interest (AESI).

Summary tables will be prepared for the incidence of all AEs and TEAEs, respectively, 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 AEs by SOC and PT
- All TEAEs by SOC and PT
- All pre-TEAEs by SOC and PT

- All post-TEAEs by SOC and PT
- AEs by SOC, PT and causality (related/not-related)
- TEAEs by SOC, PT and causality (related/not-related)
- Pre-TEAE by SOC, PT and causality (related/not-related)
- Post-TEAE by SOC, PT and causality (related/not-related)
- AEs by SOC, PT and intensity
- TEAEs by SOC, PT and intensity
- Pre-TEAE by SOC, PT and intensity
- Post-TEAE by SOC, PT and intensity
- TEADRs by SOC and PT
- Post-Treatment emergent ADRs by SOC and PT
- TEADRs by SOC and PT and intensity
- Post-Treatment emergent ADR by SOC, PT and 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 as an SAE and if the outcome is missing and no date of outcome is present, the outcome is regarded as "not yet recovered".

Listing will be provided for:

- All AEs
- TEAEs
- Pre-treatment AEs
- Post-treatment emergent AEs
- AEs having CTCAE grade ≥ 3 divided in Pre-TEAE, TEAE and Post-TEAEs
- SAEs divided in Pre-TEAE, TEAE and Post-TEAEs
- Adverse Drug Reactions (ADR) divided in TEAE and Post-TEAEs
- AEs leading to withdrawal divided in Pre-TEAE, TEAE and Post-TEAEs
- Deaths (ie AEs leading to death) divided in Pre-TEAE, TEAE and Post-TEAEs
- Adverse events of special interest (AESI) divided in TEAE and Post-TEAEs

4.8.2 Other safety endpoints

4.8.2.1 Anti-imlifidase antibodies (ADA)

Presence of anti-imlifidase antibodies (ADA) will be assessed. The long-term effect of treatment will be evaluated by presenting summary statistics for each time point, for antibodies anti-imlifidase IgG (ADA) values. A listing will also present the ADA results collected over time by time point.

Antibodies anti-imlifidase IgG (ADA) values below lower limit of quantification (LLOQ) will be imputed using the limit itself.

Boxplots corresponding to the ADA results collected over time will be presented by time point. Also, individual plots will be presented for each subject to show the ADA results over time point in two separate set of plots: one up to Day 29 (collected part of Visit 6) and one up to Day 180 (collected part of Visit 9).

4.8.2.2 Vital signs

Vital signs will be presented by visit (i.e., time point) for each parameter and summarised, including absolute change from baseline. Shift tables will be presented from baseline to all planned time points until 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. The results will be flagged as Low (L)/High (H) as per the criteria defined in Appendix 3.

In addition, separate listings containing vital signs data will be presented by subject.

The vital signs assessment part of visit 3, 7 and 9 has only been collected up to protocol version 7.0 (inclusive). Results from these visits will only be presented in the listing.

4.8.2.3 Clinical Chemistry, Haematology and Urinalysis

Laboratory tests will be summarised and presented in tables similarly as the vital signs parameters. In addition, shift tables for normal, abnormal and not clinically significant, abnormal and clinically significant results will be presented for all clinical chemistry and haematology laboratory parameters from baseline to all planned time points until end of residual drug effect, i.e. Day 29. Similar shift tables will be presented also for urinalysis parameters from baseline to all planned time points until end of residual drug effect, i.e. Day 29. Listings containing laboratory test data will be presented by subject. Abnormal clinically significant values will be flagged in listings.

The safety laboratory assessment part of visit 7 and 9 has only been collected up to protocol version 7.0 (inclusive). Results from these visits will only be presented in the listings.

4.8.2.4 Electrocardiography (ECG)

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

4.8.2.5 Physical examination

A complete physical examination will be performed at screening and Day 180 (visit 9). The physical examination will be listed by subject.

4.9 Other endpoints

4.9.1 Anti-ganglioside antibodies

Biomarker assessment (analysis of anti-ganglioside antibodies and neurofilament light chain levels) will be evaluated as an exploratory endpoint.

Pre-dose samples will be screened for anti-ganglioside antibodies and presented in a table as positive or negative. The anti-ganglioside antibodies data will be listed by subject.

Neurofilament light chain levels will be summarized in a table and presented in a listing by subject. In addition, neurofilament light chain levels will be presented both as mean plot and individual subject plots to show the change over time.

Moreover, a separate plot will show anti-ganglioside antibodies titers per subject over time up to Day 92 (collected as part of Visit 8) together with the swimmer plot of the GBS disability scores and the subgroup MRC scores on FAS.

4.9.2 Pharmacokinetics and Pharmacodynamics

PK sampling has only been done up to protocol version 7.0 (inclusive). If PK sampling were initiated in accordance with the previous version of the protocol after Protocol Version 8.0 was approved, collection of PK samples were to continue for the full imlifidase PK profile.

Plasma concentrations of imlifidase will be summarized with number of measurements, number below LLOQ, number of missing data, mean, standard deviation, median, minimum, maximum, geometric mean and CV (%) by time points and presented graphically as mean profiles and by subject profiles. No formal analysis of "outliers" is planned. If the actual time differs more than 20% from the nominal time for a value, that value will not be included in the figure for the mean concentrations.

Plasma concentrations will be presented both as mean plot (both in linear and log-scale) and individual subject plots to show the change over time.

Pharmacokinetics (PK) parameters will be estimated based on measurements of the plasma concentration-time data of imlifidase. The following parameters will be estimated, if possible, but not limited to:

- Maximum serum concentration (C_{max})
- Area under the curve (AUC)
- Time to maximum plasma concentration (t_{max})
- Terminal half-life ($t_{½}$)
- Distribution volume (V_z)
- Volume of distribution, steady state (Vss)
- Volume of central compartment (V)
- Clearance (CL) of imlifidase.

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

Plasma concentration values below lower limit of quantification (LLOQ) will be imputed as 0 for descriptive statistics, LLOQ/2 in plots and excluded from PK parameter calculations. Missing values (e.g. no blood sample collected, or no value obtained at analysis) will not be imputed for plasma concentrations descriptive statistics or PK parameter calculations.

In addition, the PK concentrations and PK parameters will be presented in separate listings by subject.

Pharmacodynamics (PD) will be assessed by:

- Effect on IgG following administration of imlifidase
- Effect on identified autoantibodies following administration of imlifidase.
- IgG fragment analysis using SDS-PAGE

The IgG below LLOQ will be imputed using the limit itself for the summary statistics and the plots.

The IgG data will be summarised in tables and presented graphically as mean profiles. Individual data will be plotted over time.

Anti-ganglioside autoantibodies titer data results of Negative will be imputed to 500 for the summary statistics and the plots.

Anti-ganglioside autoantibodies titer data will be summarised in tables and presented graphically over time as mean profiles for each ganglioside antibody and in a mean summary graph with all anti-ganglioside antibodies, if data allows. Individual data will be plotted over time.

IgG and identified autoantibodies will additionally be presented in listings.

SDS-PAGE score data of intact IgG, scIgG and IgG fragments in serum will be presented by subjects and summarised by time point in a table.

4.9.3 Pregnancy test

Serum β-hCG will be determined for all female subjects at screening and on Day 180 (visit 9). All pregnancy test results will be presented in a listing by subject.

4.9.4 Nerve conduction study (NCS)

Nerve conduction study (NCS) might be measured at Days 15 and 29. NCS is performed using standard techniques at least on one side of the body.

The NCS assessments details will be included only in the SDTM datasets (ie will not be presented in the TFLs).

4.9.5 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.

SARS-CoV-2 virus PCR-test assessments details will be presented in a listing by subject.

5 Interim analyses

No interim analyses are planned.

The main analyses for the CSR will be based on all data up to and including visit 9 (Day 180). To note, at time of the main analysis some subjects will have also the visit 10 (Day 360) performed, ie will have completed the study. All data available at time of database lock will be included in the main analyses, meaning that some subjects will have completed the study.

Remaining data from visit 10 (Day 360) will be included in an addendum to the CSR.

6 Deviations from protocol analysis

The following changes have been considered in current SAP as compared to study protocol:

- Minor wording on the FAS definition as compared to protocol. Change has been made in order to make the definition clearer.
- Percentage change from baseline summaries will be not presented for the vital signs and laboratory assessment results (ie clinical chemistry, haematology and urinalysis).
- The main analyses for the CSR will be based on all data included in the database at time of database lock, including visit 10 (Day 360) data for subjects that reached that stage (ie completed the study).

7 Quality control

ADaM data sets will be based on the SDTM data sets. The programming of the ADaM datasets will be performed in SAS and QC of the programs will include

- Independent code review
- QC of SDTM input data vs output in ADaM or listings

Tables, listings and figures (TLF) will be created by SAS programs and based on the ADaM data sets. To note, if only listings are planned to be presented on a particular data (ie no tables and figures) then that can be created using the SDTM data sets.

The programming of TLFs will be reviewed by an independent person.

SAS Viya version 3.5 or later, will be used for data handling and presentation.

8 Layout of output

The output will follow [redacted] standard output templates. Tables, figures and listings will be prepared as individual RTF (Rich text format) files. Separate Word documents will be created for tables (called 14.x), figures (called 14.x), and listings (called 16.x) respectively.

Margins and font will be chosen to respect the requirements for filing with EMA (European medicines agency) and FDA (the US Food and drug administration).

In the page header of each table/listing, a table/listing number followed by the title of the table/listing will be presented. After the title line, optional sub-title or population information can be presented. Footnotes will be put in the footer at the bottom of the page.

SAS program name, name of output file, location of files and date of creation of each table/listing/figure will appear below the output. Page number will appear on the top right corner and sponsor name and status (draft/final) on the top left of the header of each page for each table/listing/figure.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

9 Appendixes

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2 Appendix 2 - Centile metric score calculated for the R-ODS

The following nomogram allows the translation of raw sum scores of the final R-ODS (range 0 to 48) to logits or to a centile metric score with values ranging from 0 (most severe activity and social participation restrictions) to 100 (no activity and social participation limitations). Rasch analysis calculates the corresponding logits and centile metric.

R-ODS summed raw score	Rasch person location (logits)	centile metric
0	-6.95	0
1	-6.03	6
2	-5.36	11
3	-4.87	14
4	-4.48	16
5	-4.14	19
6	-3.84	21
7	-3.57	22
8	-3.32	24
9	-3.09	26
10	-2.87	27
11	-2.66	28
12	-2.46	30
13	-2.26	31
14	-2.07	32
15	-1.88	34
16	-1.70	35
17	-1.52	36
18	-1.33	37
19	-1.15	39
20	-0.97	40
21	-0.79	41
22	-0.61	42
23	-0.42	43
24	-0.24	45
25	-0.05	46
26	0.14	47
27	0.34	48
28	0.53	50
29	0.73	51
30	0.94	52
31	1.15	54
32	1.36	55
33	1.58	57
34	1.81	58
35	2.04	60
36	2.28	61
37	2.54	63

38	2.80	65
39	3.09	67
40	3.40	69
41	3.74	71
42	4.11	73
43	4.54	76
44	5.03	80
45	5.59	83
46	6.25	88
47	7.07	93
48	8.11	100

9.3 Appendix 3 - Vital Sign Parameters Normal Ranges

All vital signs measurement results below/above the normal range will be flagged as Low (L)/High (H) results, as per criteria defined below:

Vital Sign Parameter	Lower range	Upper range
Systolic Blood Pressure (mmHg)	less than 120	140 or higher
Diastolic Blood Pressure (mmHg)	less than 80	90 or higher
Oxygen Saturation (%)	less than 95	NA
Pulse Rate (beats/min)	less than 60	100 or higher
Respiratory Rate (breaths/min)	less than 12	20 or higher
Body Temperature (C)	less than 36.4	37.8 or higher

10 Change log

Version	Effective date	Reason for revision
1.0	14-SEP-2023	Finalized as v1.0.
2.0	21-FEB-2024	Finalized as v2.0 (updated during main analysis).