STATISTICAL ANALYSIS PLAN

BIO-AGA-Fase III-001

Phase III, Open-label, Switch Over Trial of the Efficacy and Safety of Agalsidase Beta Biosidus (AGA BETA BS) in Fabry Disease Patients Previously Stabilized with Fabrazyme®.

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 08May2025) for Protocol BIO-AGA-Fase III-001 Version 6.0 dated 22Apr2024

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
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LIST OF ABBREVIATIONS

Abbreviation	Term
ADL	Activities of Daily Living
AE	Adverse event
AGA BETA BS	Agalsidase Beta Biosidus
Anti-AGA	Anti-Agalsidase antibodies
BPI-short form	Brief Pain Inventory short form
CI	Confidence interval
COVID-19	Coronavirus disease 2019
ECG	Electrocardiogram
eCRF	Electronic case report form
IARs	Infusion-associated reactions
FD	Fabry disease
FSH	Follicle-stimulating hormone
ICF	Informed Consent Form
ITT	Intent to Treat
IV	Intravenous
PP	Per Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAF	Safety
SD	Standard deviation
Rand -36	36-Item Short Form Health Survey
SoA	Schedule of activities
WOCBP	Women of childbearing potential

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of Safety, Efficacy, and other relevant data for protocol BIO-AGA-Fase III-001. It describes the data to be summarized and analyzed, including specifics of the statistical analysis to be performed. This statistical analysis plan (SAP) is based on protocol version 6.0 dated 22APR2024.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of the study is to evaluate the equivalence in efficacy between AGA BETA BS and Fabrazyme® after 6 months of treatment in patients with Fabry disease previously stabilized with Fabrazyme®, by measuring disease biomarker.

2.2 Secondary Objectives

- To evaluate the difference in efficacy between AGA BETA BS and Fabrazyme® after 1 year of treatment in patients with Fabry disease previously stabilized with Fabrazyme®, by measuring disease biomarker.
- To compare the pain severity before and after the treatment with AGA BETA BS in patients with Fabry disease previously stabilized with Fabrazyme®, as measured by the BPI-short form.
- To compare the impact of pain on daily functions before and after the treatment with AGA BETA BS in patients with Fabry disease previously stabilized with Fabrazyme®, as measured by the BPI-short form.
- To compare the patients' perception of their own health before and after the treatment with AGA BETA BS in patients with Fabry disease previously stabilized with Fabrazyme®, as measured by the Rand -36.

2.3 Exploratory Objective

Not Applicable

2.4 Safety Objectives

To characterize the safety of AGA BETA BS treatment in patients with Fabry disease previously stabilized with Fabrazyme®.

2.5 Primary Efficacy Endpoints & Derivation(s)

Mean Serum Lyso-Gb3 marker ratio after 26 weeks of treatment, defined as serum level of the marker Lyso-Gb3 after 26 weeks (6 months) divided by serum level of the marker Lyso-Gb3 at baseline.

2.6 Secondary Efficacy Endpoints & Derivations

- Mean serum Lyso-Gb3 marker ratio after 54 weeks of treatment, defined as serum level of the marker Lyso-Gb3 after 54 weeks (12 months) divided by serum level of the marker Lyso-Gb3 at baseline.
- Change from baseline in pain severity as assessed by BPI-short form pain severity items scores after 26 and 54 weeks of treatment.
- Change from baseline in pain interference as assessed by BPI-short form pain interference items scores after 26 and 54 weeks of treatment.
- Change from baseline in Rand -36 scores after 26 and 54 weeks of treatment.

2.7 Safety Endpoints & Derivations

- Evaluation of general health based on the analysis of laboratory values for hematology and clinical chemistry from blood samples collected at baseline and after 14, 26, and 54 weeks of treatment.
- Evaluation of renal function based on the analysis of laboratory values for BUN, eGFR, urine albumin-creatinine ratio, electrolytes, and phosphate, from blood and urine samples collected at baseline and after 14, 26, and 54 weeks of treatment.
- Evaluation of cardiac function based on the analysis of electrocardiogram and bidimensional echocardiogram exams performed at baseline and after 26 and 54 weeks of treatment.
- Evaluation of immunogenicity based on the analysis of anti-AGA levels from blood samples collected at baseline and after 14, 26, and 54 weeks of treatment.
- Analysis of data obtained from clinical and physical assessments, and from reported adverse events and infusion-related reactions throughout the clinical trial.

3 STUDY DESIGN

3.1 General Description

BIO-AGA-Fase III-001 is a Phase III, prospective, multicenter, open-label, single-group, baseline-controlled, switch over clinical trial to evaluate the efficacy and safety of AGA BETA BS in patients with FD already treated and previously stabilized with Fabrazyme®.
The study will be conducted in 2 parts: a 5-week Lead-in period (period 1) and 54-week treatment period (period 2).
Details regarding Lead-in period and treatment period are provided below:

1. Lead-in period: all participants will receive 2 intravenous (IV) infusions of Fabrazyme®, provided by Biosidus, at a dose of 1 mg/kg of body mass, with 14 days between doses. The participant's baseline status will be assessed at the end of this period.

2. Treatment period: all participants will switch treatment to AGA BETA BS, administered at dose of 1 mg/kg of body mass, infused every 2 weeks as an IV infusion, for up to 54 weeks. Participants will receive a total of 27 infusions.

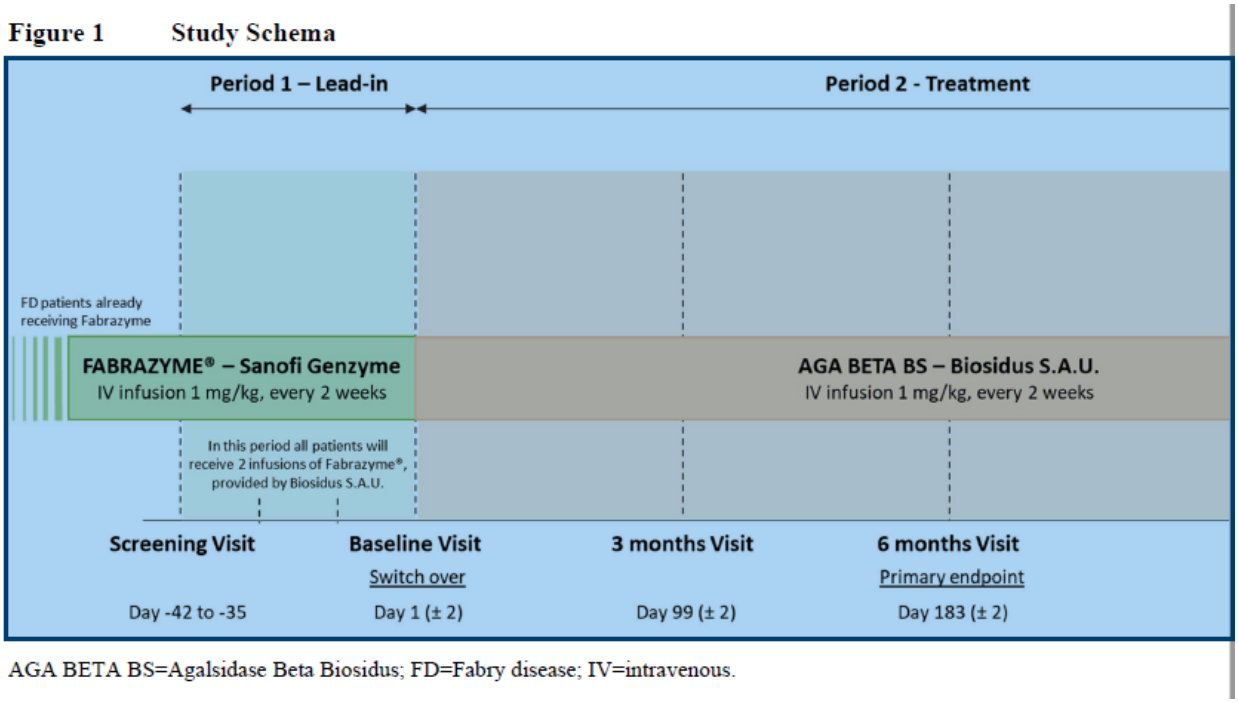
The design of this study is based on that used for the only biosimilar approved in an ICH member country (Japan). In both, a "patient's own historical control" is used as a control, in which the efficacy of AGA BETA BS is measured by comparing the value of the surrogate marker (Lyso-Gb3) at baseline - after at least 6 months of treatment with Fabrazyme® - compared to the value at 6 and 12 months of treatment with AGA BETA BS. This will be a paired comparison that maximizes the ability to detect variations in treatment efficacy.
Number of Patients:
A total of up to 20 patients are planned for the study. Patients will have previous diagnosis of FD, will be aged at least 18 years and no more than 60 years, will have received Fabrazyme® for at least 6 months, with treatment compliance of at least 80% of the prescribed dose during the last 3 months, and with disease status considered clinically stabilized, at the Investigators' discretion. At least 50% of the patients will be male with classic FD phenotype. The remaining percentage will consist of male late onset and classic women FD phenotype. Patients with chronic kidney disease in stage 3b, 4 or 5, who have suffered a clinical cardiovascular or cerebrovascular event in the last 6 months, who have acute kidney injury in the last 12 months or who have clinically significant unstable cardiac disease will be excluded from the trial.

Intervention Groups and Duration:

All patients will receive 2 doses of Fabrazyme® first, administered as an IV infusion at a dose of 1.0 mg/kg of body weight with 14 days between doses. After that, all patients will receive AGA

BETA BS, administered at dose of 1 mg/kg of body weight, infused every 2 weeks as an IV infusion, for up to 54 weeks (27 infusions).
1. non-investigational prophylactic pretreatment with antihistamine will be administered at the Investigator's discretion to avoid infusion-associated reactions during the study, except during the first 2 infusions in period 2 in which administration will be compulsory. The antihistamine will be loratadine 10 mg, 1 to 2 hours before infusion, oral route. Furthermore, patients must remain in observation at the study center for at least 1 hour after each infusion during the first four AGA BETA BS infusions. In subsequent infusions, the center staff will contact each patient within 24 hours after infusion to check their clinical condition.

Figure1: Study Design



AGA BETA BS=Agalsidase Beta Biosidus; FD=Fabry disease; IV=intravenous.

3.2 Schedule of Events

Schedule of events can be found in protocol section 1.3(Schedule of activities)

3.3 Changes to Analysis from Protocol

As per Latest protocol amendment (V6.0, dated 22 Apr2024), the data for Lyso-GB3 is collected from "Serum" instead of "Plasma". Thus, "Plasma" was expected to be replaced by "Serum" in

all protocol. However, during protocol amendment in some sections this change was missed to be updated. Hence, all phrases suggesting "plasma" in TLF mock shells and SAP are modified to "Serum".

4 PLANNED ANALYSES

The following analyses will be performed for this study:

4.1 Sample Size Re-estimation (SSR)

A sample size re-estimation is planned to be carried out when 50% of the total number of participants is reached. The objective is to recalculate the sample size according to the pooled variability (% co-efficient of variation) observed so far.

4.2 Interim Analysis of Primary Efficacy Variable

This document provided in Appendix 4 presents the interim analysis of the primary efficacy variable, the mean serum Lyso-Gb3 marker ratio after 26 weeks of treatment. This ratio is defined as the serum level of Lyso-Gb3 after 26 weeks divided by the baseline serum level, based on the Intent to Treat (ITT) population.

Results are summarized in two tables:

Table 14.2.3.1.1: Descriptive statistics for serum Lyso-Gb3 marker data.
Table 14.2.1.1.1: Primary analysis of the primary efficacy variable.

Out of 21 patients in the ITT population, 2 discontinued before the treatment period and are excluded from this analysis. Additionally, one patient (BIO-AGA-FaseIII-001-03-02) had serum Lyso-Gb3 data at both baseline and week 26 visits, but their treatment start date was before the baseline visit. Therefore, this assessment does not qualify as a baseline record and is excluded from the summary statistics and primary analysis. Thus, the primary analysis is performed on 18 patients from the ITT population.

This interim analysis provides preliminary information and should not be regarded as the final outcome. It focuses exclusively on the primary endpoint, the mean serum Lyso-Gb3 marker ratio after 26 weeks of treatment. A complete analysis will be conducted at the study's conclusion. The

sponsor will assess the clinical significance of these results. IQVIA recommends refraining from making major decisions until the final study report is completed and available.

As part of the final interim analysis (*pre-CSR analysis*) and to better cover certain aspects of the Safety of the ongoing Phase III clinical study, below outputs will be considered as pert of report:

- **Table 14.3.1.5.1**: Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)
- **Table 14.3.1.6.1**: Adverse Events by System Organ Class and Preferred Term for Infusion Associated Reactions (Safety Population)
- **Table 14.3.2.4.1**: Summary for Echocardiogram Parameter Results by Visit (Safety Population)
- **Table 14.3.2.4.2**: Summary for Electrocardiogram (ECG) Parameter Results by Visit (Safety Population)
- **Table 14.3.2.1.4**: Summary of Laboratory Values – Renal Function Parameters by Visit under Treatment Period (Safety Population)

4.3 Final Analysis

Final analysis will be performed when all active patients complete the Week 54 assessment visit. The efficacy endpoints up to week 54 and all available safety and efficacy data will be analyzed using the methods described in the analysis plan.

5 ANALYSIS POPULATIONS

Agreement and authorization of patients from Screened population included/excluded from each analysis Population will be conducted prior to the unblinding of the study.

5.1 Screened Population

Screened Population consists of all patients from screened population who provide informed consent for this study.

5.2 Enrolled Population (ENR)

Enrolled Population consists of all patients from screened population who meet all eligibility criteria for this study.

5.3 Intent To Treat Population (ITT)

Intent to Treat Population will include all patients from enrolled population who are part of the Lead-in period (Period 1). The ITT Population will be used for efficacy analyses.

5.4 Safety Population (SAF)

Safety Population will include all patients from ITT population who receive at least one dose of study treatment (AGA BETA BS). The Safety Population will be used for all safety analyses.

5.5 Per Protocol Population (PP)

Per Protocol set will include all participants who satisfactorily complete the study and comply with the requirements of the protocol. It is a subset of the ITT population without any major/Critical protocol deviations impacting the primary endpoint of the study.

6 GENERAL CONSIDERATIONS

All descriptive statistics will be presented by study medication.
Categorical data will be described using absolute and relative frequencies (n and %). Percentages will be presented to 1 decimal place. Continuous data will be summarized using the descriptive statistics (n, mean, standard deviation [SD], quartiles (Q1, Q3), minimum, median, and maximum). The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures, and listings, as specified in APPENDIX 1. Minimum and maximum values will be reported with the same precision as the unit of measure.
Inferential statistics are described in primary and secondary efficacy sections of this SAP.
Relevant raw and derived variables will be listed in by-patient data listings, sorted by study medication and patient number.

6.1 Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.
Reference start date is defined as the day of the first dose of study medication i.e. first intravenous (IV) infusion of AGA BETA BS in Treatment period (period 1), (Day 1 is the day of the first dose of study medication: AGA BETA BS) and will appear in every listing where an assessment date or event date appears.
If the date of the event is on or after the reference start date, then:
Study Day = (date of event – reference start date) + 1.
If the date of the event is prior to the reference start date, then:
Study Day = (date of event – reference start date).
In the situation where the event date is partial or missing, study day, and any corresponding durations will appear partial or missing in the listings.

6.2 Baseline

Unless otherwise specified, baseline is defined as the last observed value of the parameter of interest prior to the first intake of AGA BETA BS (this includes unscheduled visits). In the case where the date of last non-missing measurement and the reference start date coincide, then collection time, where available, will be compared with the first dose time to determine whether the measurement is pre-baseline or post-baseline. If time is not available or if assessment time coincides with reference start time, the measurement will be considered pre-baseline, but adverse events (AEs), medications commencing on the reference start date will be considered post-baseline.
Any assessment collected prior to intake of AGA BETA BS will be part of Lead-in period.

6.3 Derived Timepoints

Not Applicable

6.4 Retests, Unscheduled Visits and Early Termination Data

In general, for by visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

In case of retest (same visit number assigned), the latest available measurement for that visit will be used for by visit summaries but will contribute to the EOS and EOT values.
Listings will include scheduled, unscheduled, retest and early discontinuation data.
All patients who discontinued from treatment and study will be listed and the reasons for discontinuation will be tabulated.

6.5 Windowing Conventions

Not Applicable

6.6 Statistical Tests

The default significant level will be (5%) confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7 Common Calculations

For quantitative measurements, change from baseline at visit X will be calculated as:

- Test Value at Visit X – Baseline Value

For quantitative measurements, percentage change from baseline at visit X will be calculated as

- ((Value at post-baseline visit X-Baseline value)/Baseline value)*100

6.8 Software Version

All statistical analyses including PK and ADA, summaries and listings will be generated using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina). Graphics may be prepared using the same version of SAS.

7 STATISTICAL CONSIDERATIONS

7.1 Adjustments for Covariates and Factors to be Included in Analyses

Not Applicable

7.2 Multicenter Studies

This study will be conducted by multiple investigators at 5 Sites.

7.3 Missing Data

All data obtained in evaluable patients will be used in the analysis. Missing data for the primary endpoint, secondary endpoints will not be imputed.

8 OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9 DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

9.1 Disposition

All patients who provide informed consent and those who enter lead-in period will be accounted and presented for SCR population by treatment group and period.
The number of patients Screened, screen failed, number of enrolled, Entering Lead-in period, completing Lead-in period, discontinued during Lead-in period, Entering Treatment period, completing Treatment period, discontinued during Treatment period, reasons for Treatment discontinuation, completed or discontinued from study with the reasons for premature study discontinuation will be summarized by treatment group using incidence and percentage (n and %).
The number of patients included in each analysis population will be summarized by ENR population. The confirmation of the analysis population will be finalized at a data review meeting with the Sponsor prior to final database lock. Any excluded patients will be listed and a summary of the main reason(s) for exclusion will be provided. Reason(s) for exclusion can be protocol deviations that affect the validity of efficacy outcome or treatment of the patient.
Inclusion/exclusion criteria exceptions, i.e. those patients who met exclusion criteria or who did not meet inclusion criteria but were included in the study and received treatment, will be listed by ENR Population.

A detailed patient wise listing will be provided for Disposition for SCR population. It will include the details for screened, completed etc with reasons for discontinuation.

10 PROTOCOL DEVIATIONS

Protocol deviations are the deviations from the procedure outlined in the protocol. All the Protocol Deviations (PDs) will be summarized using the ITT population as obtained from Clinical Trial Management System (CTMS) logs. PDs will be identified and discussed with the Investigator/Sponsor in PD review discussion to categorize them, and to finalize analysis population assignment.
Any PDs will be categorized into critical, major and minor protocol deviations and will be summarized based on severity categories. Critical, Major and Minor protocol deviations having impact on primary analysis will be considered while finalizing the Per Protocol (PP) Analysis population. PDs log will be used for reporting purpose in tables. PDs will be summarized based by type and severity for lead-in period and Treatment period. A by patient listing with the specific details for all protocol deviations will be provided.

11 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT population.
No statistical testing will be carried out for demographic or other baseline characteristics.
Categorical data will be summarized as frequencies, percentages and continuous data as descriptive statistics. Descriptive statistics for the following demographic and other baseline characteristics will be reported:

- Age,
- Gender
- Child Bearing potential for female patients
- Race
- Ethnicity (Hispanic or Latin origin)
- Body weight
- Height
- BMI

12 MEDICAL AND DISEASE HISTORY

Medical history will be presented and summarized for ITT population and coded using MedDRA version 25.1 and will be recorded at the Screening visit.
Medical History conditions are defined as those conditions which stop prior to screening or at screening. All Events captured on medical history page will be included in medical history summary irrespective on end date status.
Medical history will be summarized and presented with count and percentage by SOC (System organ class) and PT (Preferred Term) wise.
Patient wise listing of medical history will be provided. Also listing for disease history will be provided separately.

13 MEDICATIONS

Medications will be presented and summarized using WHO DD Sept 2022 Global version.

- Prior medications are medications which started and stopped prior to first dose of study medication (AGA BETA BS) and will be presented only for Fabrazyme® for Lead-in period.
- Concomitant medications are medications which started prior to, on or after the first dose of study medication (AGA BETA BS) and ended on or after the date of first dose of study medication or were ongoing at the end of the study.

Concomitant medications will be presented only for AGA BETA BS for Treatment Period.
A combined patient wise listing for prior and concomitant medication will be provided for ITT population. Concomitant medications which will be summarized using counts and percentages by Period, treatment group.
Patients are counted only once in each therapeutic class category, and only once in each preferred term category.
Prior and concomitant medication will be summarized by Anatomical Therapeutic Chemical level 3 categories and preferred name. Prior medications will be summarized using the ITT, and concomitant medications will be summarized using the SAF.

See appendix 1 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

14 STUDY MEDICATION EXPOSURE

Exposure to study Fabrazyme/ AGA BETA BS in weeks will be presented and summarized for the ITT population for Lead-in Period and Treatment Period respectively.
Duration of exposure (in weeks), no. of IP administrations, Number of patients exposed to IP week wise, Volume of dose administered will be summarized descriptively for Lead-in period and Treatment period.
Derivation for Duration of exposure is explained in section 14.1.

14.1 Derivations:(Exposure)

Duration of exposure (Weeks) = (Date of last study medication administration – Date of first study medication administration + 1)/7
If the last medication date is unknown, then the latest patients visit date will be considered for calculation of duration of exposure for the respective period. Duration of exposure will be calculated separately for Lead-in Period and Treatment period and date of study medications administration will be considered as date of administration of Fabrazyme®/AGA BETA BS depending on the study period.
Derivation for Overall compliance is explained in section 15.1

15 STUDY MEDICATION COMPLIANCE

Compliance to Fabrazyme/ AGA BETA BS will be presented and summarized for the ITT Population based on Lead-in Period and Treatment Period.
Non-compliance is defined as taking less than 80% of study treatment during respective evaluation period (visit to visit).
Overall compliance and class of compliance (Compliant/Non-compliant) will be presented with respect to treatment groups for respective period.

15.1 Derivations:(Compliance)

The formula used for calculation Overall Compliance will be as follows:
Overall Compliance (%)= (Total amount (mg) of actual doses received in each period / total amount (mg) of planned doses in each period) * 100.
Compliance will be calculated separately for Lead-in Period and Treatment period respectively.

16 EFFICACY OUTCOMES

16.1 Sample Size Re-estimation (SSR)

A SSR was planned to be carried out when 50% of the total number of participants is reached. The detailed description of the SSR is defined below**.**

- Number of Evaluable subjects: 11 Patients were part of Intent to treat population.
- Number of subjects included for SSR: 11 Evaluable patients with Lyso GB3 data were included for SSR.
- Co-efficient of Variation estimate for Lyso-GB3: The CV (%) is estimated to be 17.9% % for 11 included patients.
- Sample size calculation based on CV estimates from the bullets above calculated using nQuery(Version 2.0.1.0): Sample size was estimated based on patient pooled variability (CV) of XX.X% (Refer to Appendix 4 SSR Report
- Assuming the true difference between AGA BETA BS and Fabrazyme is no greater than 20%, 16 Patients per group are needed to have to at least a power of 80% at type I error of 5% to obtain 95% confidence intervals for the ratio of serum level of Lyso-Gb3 marker at week 26 and serum level of the marker LysoGb3 at baseline to lie completely within the range 80% to 125% and a dropout rate of 20%.

16.2 Primary Efficacy

To evaluate the equivalence in efficacy between AGA BETA BS and Fabrazyme® after 6 Months of treatment in patients with Fabry disease previously stabilized with Fabrazyme®, by measuring disease biomarker.

The primary efficacy variable is

16.2.1 Intercurrent Event Handling and Data Imputation for Primary Efficacy Variable(s)

Not Applicable

16.2.2 Primary Analysis of Primary Efficacy Variable(s)

The primary analysis of the primary efficacy variable will be performed based on both ITT population and PP populations.
The primary efficacy analysis will aim to demonstrate the equivalence in efficacy based on the mean serum Lyso-Gb3 marker ratio after 26 weeks of treatment, considering Serum level of the marker Lyso-Gb3 after 26 weeks divided by plasma level of the marker Lyso-Gb3 at baseline
The primary objective of this study is to test the hypothesis that:
H0: Ratio of serum level of Lyso-Gb3 marker at week 26 and serum level of the marker LysoGb3 at baseline is less than 80% or greater than 125%. This means that there is a difference between AGA BETA BS (Test) and Fabrazyme® (Reference) after 6 months.

H1: Ratio of serum level of Lyso-Gb3 marker at week 26 and serum level of the marker Lyso-Gb3 at baseline is in between 80% and 125%. This means that there is no difference between AGA BETA BS (Test) and Fabrazyme® (Reference) after 6 months.
Mathematically,

H0: $(\mu T / \mu R) <= 0.80$ or $(\mu T / \mu R) >= 1.25$
H1: $0.80 < (\mu T / \mu R) < 1.25$

where μT /μR represent the ratio of means of plasma level of Lyso-Gb3 marker at week 26 and mean of plasma level of the marker LysoGb3 at baseline indicating a difference between AGA BETA BS (Test) and Fabrazyme® (Reference)
A paired t-test will be fit to the log-transformed mean of Lyso-GB3 Marker Baseline value and Lyso-GB3 Marker after 26 weeks of treatment . Equivalence will be declared if the 95% CI for the postbaseline and baseline ratio of plasma level of the marker LysoGb3 is entirely contained within the prespecified equivalence margin of 80% to 125% for the ITT population.

Mean change from baseline of plasma Lyso-Gb3 after 26 weeks of treatment will be calculated and a 95% CI for the difference will be computed. The mean change from baseline and its CI will be exponentiated to obtain the ratio of the means between after 26 weeks of treatment and baseline and its 95% CI. Equivalence will be determined if the 95%CI for the postbaseline and baseline ratio lies completely within the range 0.80 to 1.25 for the ITT population.
Analysis will be performed based on both ITT population and PP population. Descriptive statistics will be presented for the actual and change from baseline data for phenotype wise (classic Fabry males, later onset Fabry males, and Fabry females) and overall, for ITT and PP population.
Patient Profile for Lyso-GB3 Marker by Visit and Lyso-GB3 Marker (Week 26 and Week 54) will be presented as a figure.

16.3 Secondary Efficacy

The secondary efficacy analyses will be performed for the ITT population and PP population.

16.3.1 Analysis of Secondary Efficacy Endpoints

- Mean serum Lyso-Gb3 marker ratio after 54 weeks of treatment will be analyzed in an analogous way to the primary endpoint. No equivalence testing will be performed. Additionally, p-value will be presented for secondary efficacy analysis. Analysis will be based on both ITT population and PP Population.

- Pain severity and impact of pain on daily functions will be assessed through BPI Questionnaire based on the methods provided in Appendix 3 (BPI) .
  Endpoint will be evaluated for average scores, across each of the domain item (Pain severity and Pain interference items) and descriptive statistics will be presented using actual and change from baseline after 26 weeks and 54 weeks of treatment for ITT Population.

- The change in health perception before and after treatment with AGA BETA BS in participants with FD previously stabilized with Fabrazyme® will be measured by the Rand -36. Descriptive statistics will be presented using actual and change from baseline data for Rand -36 scores at week 26 and week 54 for ITT Population. Additionally, Scores will be classified into different domain items namely physical functioning, Bodily Pain, general health, vitality, social functioning, role physical, Role Emotional and Mental health based on methods provided in appendix (Rand-36).

16.4 Exploratory Efficacy

Not Applicable.

17 SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF population or ITT population.
For Safety variables, formal statistical comparisons between treatment groups will not be performed.

17.1 Adverse Events

All Adverse Events (AE) recorded in study will be coded using the MedDRA central coding dictionary version 25.1.
An AE will be defined as a treatment-emergent adverse event (TEAE) if they start on or after the date of the first dose of AGA BETA BS and would be counted only under treatment period and Non-TEAEs under Lead-in period in treatment period.
See Appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.
Adverse events collected during the trial will be summarized by treatment groups and Period based on SAF population. Adverse events Listings will be presented for ITT population.
The number of AE and the number and percentage of patients experiencing AE will be summarized by severity and relationship to the Fabrazyme® and AGA BETA BS.
SAEs and AEs leading to premature study discontinuation will be summarized.
Listings will be provided for AEs based on severity and relationship to study medication.
Listings will be provided for AEs, SAE and AEs leading to discontinuation from study.

17.1.1 All AEs

An overview of AE summary will be provided for both Lead-in period and Treatment period with the No. of events and n (%).
Following points will be considered in overview of AE
At least one

- AE
- Treatment related AE
- Severe AE
- Serious AE
- AE leading to discontinuation of study medication
- AE leading to Death
- Infusion Associated reactions
- Serious events
- AEs with maximum severity
- Relationship to Treatment (Study Medication)
- Action taken with AGA BETA BS and Fabrazyme®
- AEs by Outcome

Incidence of AEs will be presented by System Organ class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication (AGA BETA BS) for Treatment period.

The number of patients with incidence of AE in two groups will be summarized and presented with frequency and percentage n (%) for Treatment period.

17.1.1.1 Severity

Severity is classed as mild, moderate, severe. AEs starting after the first dose of Fabrazyme/AGA BETA BS with a missing intensity will be classified as severe. If a patient reports a TEAE more than once within that SOC/PT, the AE with the greatest intensity will be used in the corresponding intensity summaries.

17.1.1.2 Relationship to Study Medication

Relationship, as indicated by the investigator, is classed as “Related”, ”Not related”.
AEs starting after the first dose of Fabrazyme/AGA BETA BS with a missing relationship will be classified as “Related”. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst-case relationship to study medication (AGA BETA BS) will be used in the corresponding summaries.

17.1.2 AEs Leading to Discontinuation of Study Medication

AEs leading to permanent discontinuation of patient will be identified by using Action taken as Discontinued in the CRF under Adverse Event.
AEs leading to discontinuation of patients from treatment will be listed with the reasons for discontinuation.

17.1.3 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as” Serious” on the Adverse Events page of the (e)CRF.
A summary of serious AEs by SOC and PT will be prepared.
Serious adverse event (SAEs) leading to patient discontinuation will be summarized.
See appendix 1 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case;i.e. treatment emergent.
SAE will be listed, and summary will be provided for treatment period.

17.1.4 Adverse Events Leading to Death

Adverse Events Leading to death will be presented as a listing for ITT population.

17.1.5 Infusion Associated reaction(IAR)

An AE related to the infusion of study drug is referred to as an Infusion associated reaction (IAR) and will be identified by patients recording is the event an Infusion-Associated Reaction (IAR)? as “Yes”. ADR will be summarized by SOC/ PT and presented as listing.

17.2 Deaths

Deaths during the study presented in a data listing for ITT population.

17.3 Laboratory Evaluations

Results from the central laboratory and local laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Coagulation, Urinalysis, and Renal Functions (blood urea nitrogen, eGFR, urine albumin-creatinine ratio, electrolytes(Sodium, Potassium, Bicarbonate, Chlorine, Magnesium, Calcium), and phosphate from blood and Urine Samples).
Quantitative laboratory measurements reported as “< X”, i.e. below the lower limit of quantification (BLQ), or “> X”, i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as “< X” or “> X” in the listings.
Laboratory tests which will be included in summaries are provided below:

- **Hematology**: Complete hemogram, %Reticulocytes, Platelet count, White blood cell count with differential, Red blood cell count, Neutrophils, Hemoglobin, Lymphocytes, Hematocrit, Monocytes, Red blood cell indices, Eosinophils, Mean corpuscular volume, Basophils, Mean corpuscular hemoglobin, Mean cell hemoglobin concentration.
- **Chemistry**:, Creatinine, Total cholesterol, Cholesterol LDL, Cholesterol HDL, Triglycerides, Glycemia, Total bilirubin, Alkaline phosphatase, Direct bilirubin, Total proteins, Aspartate aminotransferase, Albumin, Alanine aminotransferase, Gamma glutamyl transferase
- **Urinalysis**: First morning urine(visual exam, dipstick test and microscopic exam (color, clarity, pH, specific gravity, glycose, blood, ketones, protein, urobilinogen, bilirubin, leukocyte esterase, nitrite, blood, white blood cells, red blood cells, epithelial cells, crystals, and casts).

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- The count and percentage of patients for Urinalysis (Discrete measurements)
- Incidence of abnormal values according to Clinical significance criteria

17.3.1 Laboratory Specific Derivations

Not Applicable

17.3.2 Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

17.4 ECG Evaluations

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. Results for ECG will be presented under SAF.
The following ECG parameters will be reported for this study:

- Heart Rate (beats/min)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- Overall ECG Evaluation (Investigator's judgment):

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- The count and percentage of patients for overall ECG interpretation will be provided as follows
- Normal
- Abnormal, Not Clinically Significant (NCS)
- Abnormal, Clinically Significant (CS)

A patient wise listing of 12 Lead ECG findings will be provided.

17.5 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart (Bpm)
- Respiratory Rate (resp/min)
- Body Temperature (axillary) (ºC)
- Weight (Kg)
- BMI (kg/m2)

The following summaries will be provided for vital signs data:

- Actual and change in vital signs by visit.
- Listing of patients' vital signs.

For all measurements including before and hourly during the infusions, blood pressure, heart rate, and respiratory rate will be assessed in a sitting position after 5 minutes rest for the patient in a quiet setting without distractions (eg, television, cell phones), with a device previously calibrated or as determined by the manufacturer.

Three readings of blood pressure and heart rate will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.

Data from both Vital signs and Vital Signs Dosing page of CRF will be presented for SAF population for average reading for applicable parameters.

17.6 Immunogenicity Assessments

Results for Immunogenicity analysis will be presented under SAF population. The following analyses will be performed: Number and frequency of patients with ADA Neutralization Results to AGA BETA BS sampling results by visit

o Negative
o Positive
o Not Done

Descriptive statistics for percentage neutralization will be provided for all available parameters at protocol specified visits using Number of patients available at each assessment visit, Arithmetic Mean, Median, Minimum Maximum, quartiles and Geometric Mean. Summaries for both Actual and change from baseline will be presented. For geometric mean, the mean and the 95% CIs will be calculated on log transformed data , with subsequent antilog transformations applied.

17.7 Physical Examination

A patient wise listing of physical examination findings as collected in eCRF will be provided on SAF.

17.8 Echocardiogram

Results from the Echocardiogram will be included in the reporting of this study. Results for Echocardiogram will be presented under SAF.
The following Echocardiogram parameters will be reported for this study:

- Thickness of the Left Ventricular Wall
- Left Ventricular Mass index
- Left ventricular ejection fraction
- Overall Evaluation

The following summaries will be provided for Echocardiogram data:

- Actual and change from baseline by visit (for quantitative measurements)
- The count and percentage of patients for overall Echocardiogram interpretation will be provided as follows

  Normal
  Abnormal, Not Clinically Significant (NCS)
  Abnormal, Clinically Significant (CS)

A patient wise listing of Echocardiogram findings will be provided.

17.9 Other Safety Assessments

A listing will be provided for female patients for Pregnancy Test. Details indicating visit, test type (Serum/Urine) and Test results would be provided for ITT population.

18 DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:
Comments
phone contact
Registration RD
Check Questions
Questionnaires Status QS
Date of Visit

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

19 REFERENCES

YZAA1358- BIO-AGA-Fase III-001_Protocol_Amendment_v6_ April 22, 2024

https://static.medicine.iupui.edu/divisions/rheu/content/physicians/BRIEF_PAIN_INVENTORY.pdf

- **https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html**

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

This appendix (including the example layout) is optional, depending on the customer. Include if there are no customer guidelines; otherwise reference customer guidelines.
IQVIA Output Conventions
Outputs will be presented according to the following:
Abbreviations
ASCII American standard code for information interchange file format
CGM Computer graphics metafile
ODS Output Delivery System
RTF Rich text file format
Introduction
This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. These standards should be used in the absence of customer specific standards.
Output File Naming Conventions
File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.
As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg T14_3_01_1.rtf)
Paper Size, Orientation and Margins
The size of paper will be Letter for the United States, otherwise A4.
The page orientation should preferably be landscape, but portrait is also permitted.
Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.
The number of columns per page (linesize) should be 145 for A4 and 134 for Letter.
The number of rows per page (pagesize) should be 49 for A4 and 51 for Letter.
Fonts
The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No bolding, underlining or italics should be permitted.
Single spacing should be used for all text.

Figures should have a default font of “Times Roman”, “Helvetica”, or “Courier New”.
This can be achieved by using the following options in SAS:
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof97l
gaccess = gsasfile;
filename gsasfile "….cgm";
Header Information
Headers should be defined as follows:
• The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
• The customer’s name and protocol number should appear in row 1, left-aligned
• The output identification number should appear in row 2, centered
• The output title should start in row 3, centered
• The output population should appear in row 4, centered.
• Row 5 should be a continuous row of underscores (‘_’) (the number of underscores should equal the linesize)
• Row 6 should be a blank line
• Mixed case should be used for titles
• The output titles should be designed so that they are arranged consistently through all outputs. For example, content (eg Vital Signs) followed by metric (eg Change from Baseline) e.g. Vital Signs – Change from Baseline.
• Titles should not contain quotation marks or footnote references
• The column headings should be underlined with a row of underscores (‘_’)
• Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
• Column headings containing numbers should be centered
• Column headings should be in sentence case
• In general, the population count should appear in the column header in the form “(N=XXX)”
• “Statistic” should be the column header over n, Mean, SE, n (%) etc.
• As a rule, all columns should have column headings.
Table and Listing Output Conventions
General:
• The first row in the body of the table or listing should be blank

• The left-hand column should start in column 1. No indenting or centering of the output should occur.
• Rounding should be done with the SAS function ROUND.
• Numbers in tables should be rounded, not truncated.
• Alphanumeric output should be left aligned.
• Numbers should be decimal point aligned.
• Whole numbers should be right aligned.
• Text values should be left aligned.
• The first letter of a text entry should be capitalized
• Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
• The study drug should appear first in tables with treatments as columns
• In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization, unless the customer specifically requests it.
• If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
• The width of the entire output should match the line size

Univariate Statistics:
• Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
• Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
• If the original data has N decimal places, then the summary statistics should have the following decimal places:
Minimum and maximum: N
Mean, median and CV%: N + 1
SD: N + 2

Frequencies and percentages (n and %):
• Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
77 (100.0%)
50 (64.9%)
0 (0.0%)
• Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be

presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
Eg (<0.1%)
(6.8%)
(>99.9%)
Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
• Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:
• As a rule confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
• Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
• Boundary values of confidence intervals should be separated by a comma.
• Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
• An example is given below:
(-0.12, -0.10)
(9.54, 12.91)

P-values:
• P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:
• Ratios should be reported to one more decimal place than the original data.

Spacing:
• There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:
• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

• A “0” should be used to indicate a zero frequency.
• A blank will be used to indicate missing data in an end-of-text table or patient listing.
Figure Output Conventions
• Figures should be provided in RTF files.
• The image should be clear and of high quality when viewed in the Word document, and when printed.
• In general, boxes around the figures should be used.
Footnote Information
Footers should be defined as follows:
• A continuous line of underscores (‘_’) will follow the body of the table or listing prior to any footnotes at the bottom of the page
• Table footnotes should appear directly after the body of the table
• The program path and name and version number (if applicable) should appear as footnote 1 at the bottom of the page
• The date/time stamp should appear as footnote 2 at the bottom of the page
• Footnotes should be left-aligned.
• Footnotes should be in sentence case.
• Only “typewriter” symbols are permitted – eg “*”, “$”, “#”, “@”, “&” and “+”.
• The choice of footnote symbols should be consistent. E.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.
• If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
• The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the first footnote, right aligned

Ordering of footnotes should be as follows:

1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes
• Common notes from table to table should appear in the same order.
• The symbols should appear in the same order as what they are defined in the table or listing, from left to right.
Programming Instructions

Programming instructions must appear at the end of each table or listing shell. Programming instructions, where necessary, should begin with the words “Programming Note” followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.
Dates & Times
Depending on data available, dates and times will take the form DDMMMYYYY:hh:mm.
Spelling Format
English UK.
Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US (or English UK) .

Presentation of Treatment Groups and Periods

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group: For Tables, Listings and Graphs
Lead in Period: Fabrazyme®
Treatment Period: AGA BETA BS

For outputs, visits will be represented as follows and in that order:

Long Name (default)
Screening
Week 1
Week 1 (Every 14 days)
Week 99
Week 183
Week 379

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):
Treatment group
Patient ID,
Date (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE. If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE. If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE. If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior. If stop date >= study med start date and start date <= study med end date, assign as concomitant If stop date >= study med start date and start date > study med end date, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= study med end date, assign as concomitant If start date > study med end date, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior. If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior. If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. EFFICACY DETAILS

Rand-36

Scoring the 36-Item Health Survey is a two-step process.
First, pre-coded numeric values are recoded per the scoring key given in Table 1.
Note that all items are scored so that a high score defines a more favorable health state.
In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved.
In step 2, items in the same scale are averaged together to create the 8 scale scores.
Table 2 lists the items averaged together to create each scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores.
Hence, scale scores represent the average for all items in the scale that the respondent answered.

Table:1

Item numbers	Change original response category *	To recoded value of:
1, 2, 20, 22, 34, 36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100
13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40

	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

Table 2:

Scale	Number of items	After recoding per Table 1, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31
Emotional well-being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22
General health	5	1 33 34 35 36

BPI Scores

The Brief Pain Inventory (BPI) rapidly assesses the severity of pain and its impact on functioning.
It uses a 0 to 10 numeric rating scales for item rating.

Pain severity score and Pain interference score:
(a) Pain Severity Score = Mean of items 3-6 (pain at its worst, pain at its least, average Pain and current pain)
(b)Pain Interference Score = Mean of items 9A-9G (interference of pain with: general activity, mood, walking, normal work, relations, sleep, enjoyment of life)
Additionally, BPI scores will be summed and averaged across all 9 items to provide total scores and average scores.

Questionnaires:

36-Item Short Form Survey Instrument (S

BPI-SF_English-24h _Original_CURRENT.

APPENDIX 4. SAMPLE SIZE RE-ESTIMATION

Biosidus_YZAA1358_
Sample Size Reestima