STATISTICAL ANALYSIS PLAN

LPS17726

A Study to investigate safety and tolerability of Higher infusion rate to shorten the duration of Fabrazyme infusion

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VERSION NUMBER AND DATE: Final V1.0, 22Oct2024

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final V1.0 (Dated 22Oct2024) for Protocol LSP17726.

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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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LIST OF ABBREVIATIONS

Abbreviation	Term
α-GAL	α-galactosidase A
ADA	Anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
eCRF	Electronic Case Report Form
DBP	Diastolic Blood Pressure
EOS	End-of-Study
EOT	End-of-Treatment
ERT	Enzyme Replacement Therapy
FD	Fabry Disease
IAR	Infusion Associated Reaction
ICE	Intercurrent Event
ICF	Informed Consent Form
IgG	Immunoglobulin G
Kg	Kilogram
lyso-GL3	Globotriaosylsphingosine
MedRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ML	Milliliter
NA	Not Applicable
PCSA	Potentially clinically significant abnormality
Q2W	Every 2 Weeks
QL	Quantification Limit
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SBP	Systolic Blood Pressure

TE	Treatment Emergent
TEAE	Treatment Emergent Adverse Event
V	Visit
W	Week
WHO	World Health Organization
WHODrug	World Health Organization Drug

1 INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of safety and tolerability data for Protocol LPS17726. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 2.0 (Protocol Amendment Number 1.0), dated 20May2024. Changes to statistical considerations previously defined within the protocol are detailed in Section 3.3 'Changes to Analysis from Protocol'.

2 STUDY OBJECTIVES AND ESTIMANDS

Table A - Objectives and Estimands

Objectives	Estimand Description/Endpoints
Primary	
• To investigate the safety and tolerability of the protocol to increase the rate of Fabrazyme infusion with reduced total time and volume of infusion	**Population**: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: % reduction of infusion duration from prestudy average of recent 3 infusions. **Intercurrent events**: A while-on-treatment approach will be applied, where the % reduction of infusion duration will be derived from the infusions actually received. Participants never observed to tolerate any infusion rate will be counted as having zero percent

	reduction. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: Median and quantiles of % reduction of infusion duration from prestudy average of recent 3 infusions.
	Population: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: Shortest infusion duration each participant tolerates. **Intercurrent events**: A while-on-treatment approach will be applied, the shortest infusion duration will be derived from the infusions actually received. Participants never observed to tolerate any infusion rate will be counted as having duration greater than the maximum observed in their treatment group. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: Median and quantiles of the shortest infusion duration each participant tolerates.

Secondary	
• To investigate the proportion of participants achieving the shortest planned duration of infusion time (20 minutes for participants ≥30 kg and 30 minutes for participants <30 kg) without experiencing any or the second IAR	**Population**: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: Binary: Participant achieved the shortest planned duration of infusion time (20 minutes for participants ≥30 kg and 30 minutes for participants <30 kg) without experiencing any IAR. **Intercurrent events**: A while-on-treatment approach will be applied. Participants never observed to tolerate any infusion rate will be counted as not achieving the shortest planned duration. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: Number and % of participants achieving the endpoint.
	Population: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each

	infusion. **Endpoint**: Binary: Participant achieved the shortest planned duration of infusion time (20 minutes for participants ≥30 kg and 30 minutes for participants <30 kg) without experiencing a second IAR. **Intercurrent events**: A while-on-treatment approach will be applied. Participants never observed to tolerate any infusion rate will be counted as not achieving the shortest planned duration. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: Number and % of participants achieving the endpoint.
• To investigate the proportion of participants achieving infusion duration shorter than 90 minutes without experiencing any or the second IAR	**Population**: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: Binary: Participant achieved infusion duration shorter than 90 minutes without experiencing any IAR. **Intercurrent events**: A while-on-treatment approach will be applied. Participants never observed to tolerate any infusion rate will be counted as not achieving the required duration. A treatment policy approach will be applied in case pre-medications are

	not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: Number and % of participants achieving the endpoint.
	Population: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: Binary: Participant achieved infusion duration shorter than 90 minutes. without experiencing a second IAR. **Intercurrent events**: A while-on-treatment approach will be applied. Participants never observed to tolerate any infusion rate will be counted as not achieving the required duration. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: Number and % of participants achieving the endpoint.

• To investigate the number and proportion of participants achieving each infusion duration planned in the study without experiencing any or the second IAR	**Population**: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: Binary, calculated separately for each infusion duration: Participant achieved infusion duration without experiencing any IAR. **Intercurrent events**: A while-on-treatment approach will be applied. Participants never observed to tolerate any infusion rate will be counted as not achieving the required duration for the infusion. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: For each infusion duration, number and % of participants achieving the endpoint.
	Population: Participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during the most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to Protocol Section 6.2), with oral premedications given 30 minutes prior to each infusion. **Endpoint**: Binary, calculated separately for each infusion duration: Participant achieved infusion

	duration without experiencing a second IAR. **Intercurrent events**: A while-on-treatment approach will be applied. Participants never observed to tolerate any infusion rate will be counted as not achieving the required duration for the infusion. A treatment policy approach will be applied in case pre-medications are not given as described within the protocol. No action will be taken for this event for the analysis even when pre-medications are not given as described within the protocol. **Summary measure**: For each infusion duration, number and % of participants achieving the endpoint.
Exploratory	
• To investigate the influence of increased infusion rate on the immunogenicity and efficacy of Fabrazyme treatment	• Changes of plasma lyso-GL3 from baseline to 6 months follow-up • Change of the titer of ADA to Fabrazyme over 6 months follow-up
Safety	
• To investigate the influence of increased infusion rate on the safety of Fabrazyme treatment	• Number, severity, and nature of AEs including IARs

Abbreviations: ADA = anti-drug antibody, AE = adverse event; FD = Fabry disease; IAR = infusion associated reaction; lyso-GL3 = globotriaosylsphingosine; Q2W = every 2 weeks.

3 STUDY DESIGN

3.1 GENERAL DESCRIPTION

This is a Phase 4, prospective, open label, single arm, interventional study, to be conducted in the US, to evaluate the safety and tolerability of Fabrazyme at approved dose of 1 mg/kg and increased infusion rate and reduced infusion volume.

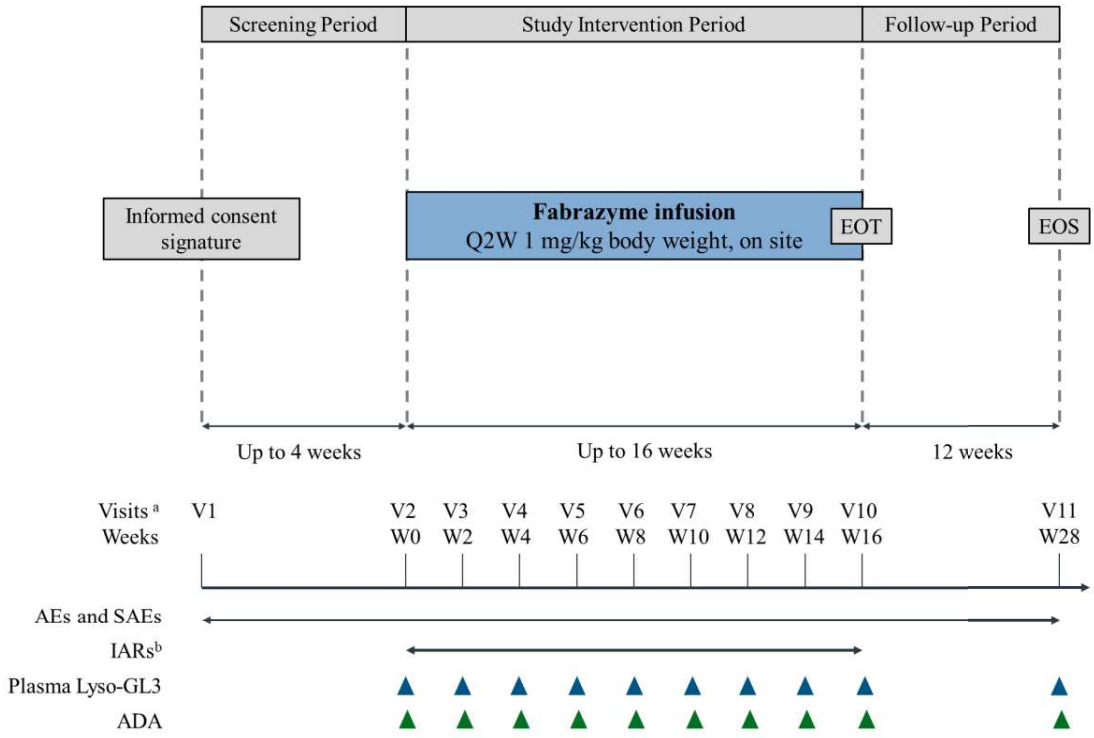
Up to 14 participants with Fabry disease will be enrolled to study intervention in 4 cohorts:

- **Cohort 1:** 3 Fabrazyme experienced female participants (body weight ≥30 kg)
- **Cohort 2:** 3 Fabrazyme experienced non-classic male participants (body weight ≥30 kg)
- **Cohort 3:** 4 Fabrazyme experienced classic male participants (body weight ≥30 kg)
- **Cohort 4:** 4 Fabrazyme experienced participants (body weight <30 kg)

Classic FD is defined by αGAL level in dried blood spot or leukocyte below 3% of normal value and all others are considered as non-classic disease.

Screening will be performed up to 4 weeks prior to the first dose of study intervention. Enrolled participants will receive treatment for up to 16 weeks and have an End-of-Study Visit 28 weeks after the start of the treatment. Participants will undergo visits and study procedures as shown in Schedule of Activities (SoA) presented in Section 1.3 of the protocol. A flow chat illustrating the key components of the study is provided in Figure 1.

Figure 1: Study Schema



Abbreviations: ADA = anti-drug antibody (ie, anti-agalsidase beta IgG antibody); AE = adverse event; AESI = adverse event of special interest; EOS = end-of-study; EOT = end-of-treatment; IAR = infusion associated reaction; lyso-GL3 = globotriaosylsphingosine; Q2W = every 2 weeks; SAE = serious adverse events; V = visit; W = week.

a. V1 and V2 can take place on the same day. The number of visits during the Study Intervention Period (ie, Visits 2 to 10) may differ between participants, as those having a second IARs will discontinue the study intervention, and those who successfully reaches the shortest infusion duration planned for the cohort to which they belong will be considered as treatment completers. All participants will stay in the study for the follow-up visits at Week 12 and Week 28.

b. IARs will be collected only during the Study Intervention Period which can be shorter than 16 weeks for some participants.

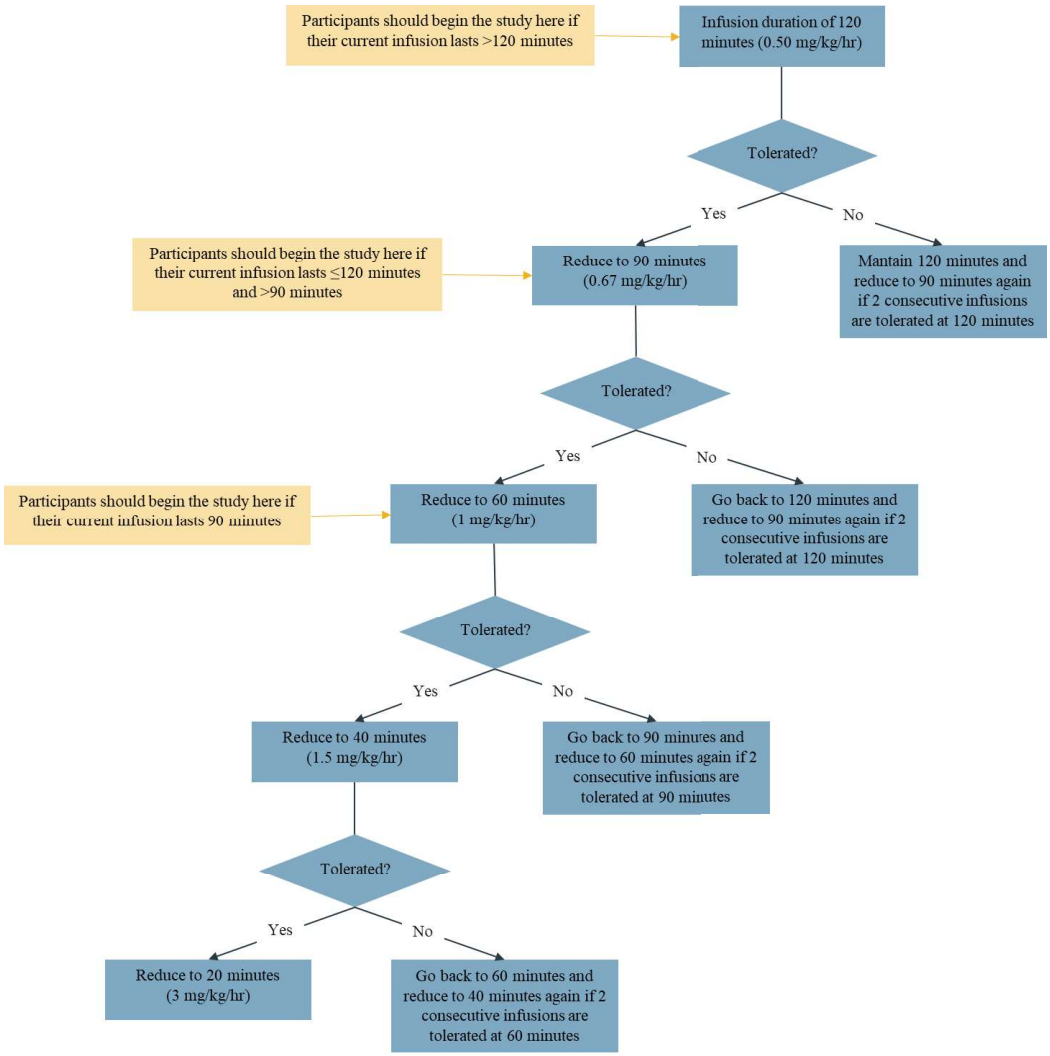
3.1.1 INFUSION DURATION GUIDELINE

All participants will receive Fabrazyme infusions at dose of 1 mg/kg of body weight every 2 weeks at the study site, for up to 16 weeks. The infusion duration will shorten, and the infusion rate will rise with each successfully tolerated infusion, until they reach the minimum infusion duration of 20 minutes for participants in cohorts 1 to 3 (≥30 kg) and 30 minutes for participants in cohort 4 (<30 kg). When the participant successfully reaches the shortest infusion duration planned for the cohort which he/she belongs to, he/she will be considered a treatment completer and will not receive any further infusion as part of the study, regardless of whether the treatment period reaches 16 weeks or not.

Infusion duration tolerated by a participant is an infusion at which they successfully receive an infusion within an actual duration not exceeding 120% of planned duration without an IAR. If the participant receives several infusions at the same planned duration during the treatment period, the infusion duration will be considered tolerated if the last infusion received is without IAR and does not exceed 120% of planned duration.

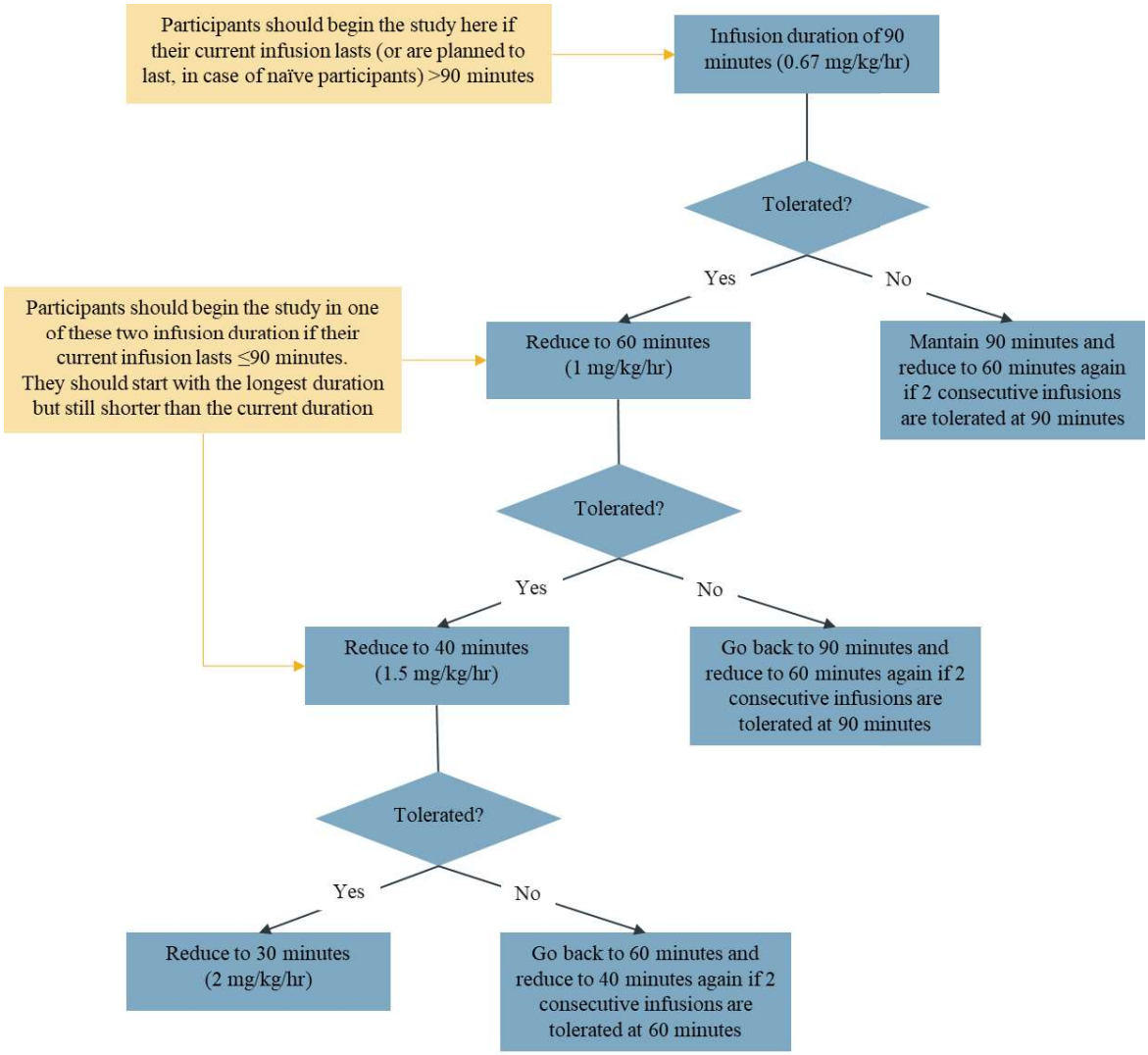
The decrease in the infusion duration for participants in cohorts 1 to 3 (with ≥30 kg body weight) will follow the flow diagram presented in Figure 2. The decrease in the infusion duration for participants in cohort 4 (with <30 kg body weight) will follow the flow diagram presented in Figure 3.

Figure 2: Guideline for Decreasing Infusion Duration for Participants ≥30 kg



Abbreviations: IAR = infusion associated reaction.
Note: IARs occurring during a single infusion are counted as one IAR. Only when an IAR occurs in relation to a separate infusion it will be considered as a second IAR.
Note: When a second IAR occurs, the participant will discontinue study intervention and the previous highest rate tolerated by the participant will be considered as the maximum tolerated rate for this participant.

Figure 3: Guideline for Decreasing Infusion Duration for Participants <30 kg



Abbreviations: IAR = infusion associated reaction.
Note: IARs occurring during a single infusion are counted as one IAR. Only when an IAR occurs in relation to a separate infusion it will be considered as a second IAR.
Note: When a second IAR occurs, the participant will discontinue study intervention and the previous highest rate tolerated by the participant will be considered as the maximum tolerated rate for this participant.

3.2 SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the protocol.

3.3 CHANGES TO ANALYSIS FROM PROTOCOL

The following presents the updated changes to analysis from protocol section 9.0, version 2.0 (Protocol Amendment Number 1.0), dated 20May2024.

Table B - Changes to Analysis from Protocol

Analysis in Protocol	Analysis in SAP
Exploratory Endpoints and Summary Measures **Endpoint**: • Changes of plasma lyso-GL3 from baseline to 6 months follow-up • Change of the titer of ADA to Fabrazyme over 6 months follow-up	**Reason for Update:** ADA analysis will include summaries of ADA attributes, titer, incidence, and kinetics of ADA response. Also, "6 months follow-up" will include "each visit where plasma lyso-GL3 (ng/mL)/ADA titer is recorded" to make it clear that all post-baseline visits will be considered for analysis as per the windowing convention described in Section 6.6 'Windowing Conventions'. Refer to Section 15.3.1 for the full descriptions of derivations and analyses.
Analysis of Continuous and Categorical Data • Continuous data will be summarized using the number of observations available (n, mean, standard deviation [SD], minimum, median, 1st quartile, 3rd quartile, and maximum). Additionally, for the absolute change or percent change from baseline analysis, a 95% confidence interval (CI) will be provided.	**Reason for Update:** Analyses with limited value are removed: The 95% confidence intervals will not be presented due to the small sample size. Shift tables will not be presented. Change from baseline will only be derived for continuous measurements of select variables specified in the SAP. See Section 7: 'Statistical Considerations'

Analysis in Protocol	Analysis in SAP
• Categorical data will be summarized using count and percentage (the percentage of participants in each category relative to the total number of participants in the relevant analysis set or relative to the total number of participants in the relevant analysis set, with assessments available [where appropriate]) in each category. A 95% CI will be provided for the binary endpoint as appropriate. The change from baseline in distribution for the categorical endpoint will be presented with a shift table; number and percentage of participants will be provided.	
Analysis of Cohorts • The data will be summarized per cohort and by pooled cohorts as described in Sections 9.3.2, 9.3.3 and 9.3.4, and where appropriate, per infusion duration.	**Reason for Update:** Data will be summarized by pooled cohorts 1-4 only. This is because there are very few participants within each cohort. See Section 7: 'Statistical Considerations'

4 PLANNED ANALYSES

No formal interim analysis will be conducted.

There will be analysis performed for exploratory purposes as per sponsor discretion.

At no point will the results of the analysis have an impact on the study design with an absence of stopping rules for efficacy and futility.

A Final Analysis is planned for the whole study period (including screening period, study intervention period and follow-up period).

4.1 FINAL ANALYSIS

A Final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, all Participants Reach their End of Study Visit (see Section 6.4 'Derived Timepoints'), the Database is Locked, and the Sponsor Completes Authorization of Analysis Sets.

5 ANALYSIS SETS

Agreement and authorization of participants included and excluded from each analysis set will be conducted prior to database lock.

5.1 PROCESS FOR ANALYSIS SET ASSIGNMENT

The definitions of the analysis sets given below will be used to determine analysis set assignments. Analysis set assignments will be determined prior to Database Lock.

5.2 ENROLLED ANALYSIS SET [ENR]

The Enrolled Analysis Set (ENR) set will contain all participants who sign the ICF.
The enrolled analysis set will be used to analyze participant disposition, inclusion/exclusion of analysis sets post-enrolment and exclusion criteria met and/or inclusion criteria not met for screen failures.

5.3 SAFETY ANALYSIS SET [SAF]

The Safety Analysis Set (SAF) will contain all participants who receive any amount of study drug (Fabrazyme) during study treatment period.

The safety analysis set will be used to analyze all safety and exploratory ADA endpoints.

5.4 INTENT-TO-TREAT ANALYSIS SET [ITT]

The intent-to-treat analysis set (ITT) will contain all participants who were enrolled and allocated to study treatment.

The ITT analysis set will be used to evaluate all primary, secondary and the plasma lyso-GL3 (ng/mL) exploratory endpoint.

6 GENERAL CONSIDERATIONS

6.1 OBSERVATION PERIODS

- Pre-treatment period: The pre-treatment period is defined from when the participant provides informed consent up to the first dose of study intervention.

- Study treatment period: The study treatment period is defined as the time between the first dose of study intervention to the date of the last dose of study intervention. For Adverse Events, this is known as the Treatment Emergent (TE) period

- Post-treatment period: The post-treatment period is defined as the day after the last dose of study intervention until the last follow-up visit.

6.2 REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the date of the first dose of study Fabrazyme after enrolment.

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It 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 date, then: Study Day = (date of event –

reference start date) + 1 (Day 1 is the day of the first dose of study Fabrazyme after enrolment).

- If the date of the event is prior to the reference date, then: Study Day = (date of event – reference start date).

In the situation where the assessment or event date is partial, the date will appear partial in the listings. If the assessment or event date is missing the date will also appear missing in the listings. Study Day and any corresponding durations will not be derived for any missing or partial assessment/event dates and will therefore appear missing in the listings.

6.3 BASELINE

Unless otherwise specified, baseline is defined as the last observed value, including unscheduled visits, prior to the first date and time of study Fabrazyme infusion after enrolment.

If the last non-missing measurement and reference start date and time coincide that measurement will be considered baseline if the assessment is planned per protocol to take place prior to first administration of study medication during the study treatment period.

6.4 DERIVED TIMEPOINTS

For the below definitions a treatment completer is defined as a participant who has either reached the target infusion duration of their cohort or completed the study treatment period and experienced at most 1 IAR. A study completer is defined as a participant who has enrolled into the study through providing informed consent, been allocated to the study treatment, completed the study treatment period, and attended their last follow-up visit.

End of Treatment (EOT) visit is derived for participants who are administered at least one infusion during the study treatment period and is defined as the last recorded visit for which the participant receives study Fabrazyme. For treatment completers this occurs when the participant

either successfully reaches the target infusion duration for the cohort or reaches the end of the study treatment period and does not experience two IARs. For non-treatment completers their EOT visit is defined as the last recorded visit prior to or on treatment discontinuation for any reason.

End of Study (EOS) visit for a participant is defined as their last recorded visit in the study. For study completers their EOS visit will be their last follow-up visit recorded 28 weeks after their first Fabrazyme administration. For non-study completers their EOS visit is defined as their last recorded visit prior to or on study withdrawal. For screen failures their EOS will be recorded as 'Screening'.

6.5 RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit summaries, data will be assigned to visits based on the windowing rules provided in SAP Section 6.6 'Windowing Conventions'. Measurements taken at unscheduled visits (including retests) can be considered for the by-visit summaries (as per the visit windowing rules).

6.6 WINDOWING CONVENTIONS

A windowing convention will be used to determine the analysis visit value for a given measurement. Exploratory Laboratory Parameters and Vital Signs are subject to the following windowing conventions.

All scheduled study visits are defined relative to the reference start date.

Assessments with a partially known or missing assessment date will not be considered for analysis windowing.

Observations that fall outside of a visit window will be identified as "Out of Window" and will be listed only and not used in any by visit summary tables or analyses where visit is used.

6.6.1 EXPLORATORY ENDPOINTS

The windowing convention for the exploratory laboratory measurements are wider to those in the protocol and are provided in the below table.

Table C - Analysis Window for Exploratory Endpoints

Assigned Study Day (Inclusive)		Visit Assigned	Week Assigned	Target Day
From	To			
1	6	Visit 2	Week 0	1
7	21	Visit 3	Week 2	14
22	34	Visit 4	Week 4	28
35	48	Visit 5	Week 6	42
49	62	Visit 6	Week 8	56
63	76	Visit 7	Week 10	70
77	90	Visit 8	Week 12	84
91	104	Visit 9	Week 14	98
105	153	Visit 10	Week 16	112
154	210	Visit 11	Week 28	196

If one or more result for a variable falls within the same visit window, the result with the date closest to (but before) the start date of infusion of the study drug will be used for post-baseline by visit summaries.

6.6.2 VITAL SIGNS

The windowing convention for vital signs are the same as for exploratory endpoints and are provided in the below table.

Table D: Analysis Windows for Vital Signs

Assigned Study Day (Inclusive)		Visit Assigned	Week Assigned	Target Day
From	To			
-28	-1	Screening	Screening	-1
1	6	Visit 2	Week 0	1
7	21	Visit 3	Week 2	14
22	34	Visit 4	Week 4	28
35	48	Visit 5	Week 6	42
49	62	Visit 6	Week 8	56
63	76	Visit 7	Week 10	70
77	90	Visit 8	Week 12	84
91	104	Visit 9	Week 14	98
105	153	Visit 10	Week 16	112
154	210	Visit 11	Week 28	196

If one or more result for a variable falls within the same visit window, the following rules will be applied to select the appropriate value to be used for post-baseline by visit summaries.

Only the vital signs assessed prior or after an infusion of the study drug, on the day of the infusion, are considered. The following rules apply (note that pre-infusion and post-infusion assessments should be considered separately):

- Take the result with the date closest to the target day.
- If two assessment dates are equidistant from the Target Day, take the earlier assessment.
- If more than one assessment is on the same date, take the latest based on time.
- If time is not available and it cannot be determined whether the assessment was prior to or after the infusion, then the result will be considered missing.

6.7 STATISTICAL TESTS

No formal statistical test will be performed in this study.

6.8 COMMON CALCULATIONS

For the below “Visit X" corresponds to post-baseline visits for all X.
For quantitative measurements, change and percent change from baseline will be calculated as:

- Change from baseline at visit X= Test Value at Visit X - Baseline Value
- Percentage change from baseline = 100*(Test Value at Visit X - Baseline Value)/ Baseline Value

Conversion from weight (lb) to weight (kg) is given by:

- Weight (kg) = 0.453592*Weight(lb)

6.9 SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or above.

7 STATISTICAL CONSIDERATIONS

In general unless otherwise specified, descriptive statistics will be provided on observed cases only eg, for by-visit summaries only participants with non-missing values at that visit will be included in the analysis at that visit. Data will be summarized by cohorts 1-4 pooled.
There will be no comparisons between any of the cohorts for all analysis.

The following descriptive statistics will be used as applicable to summarize the study data unless stated otherwise:

- Continuous data will be summarized using the number of observations available (number, arithmetic mean, standard deviation [SD], minimum, median, 1st quartile, 3rd quartile, and maximum).

- Categorical data will be summarized using count and percentage (the percentage of participants in each category relative to the total number of participants in the relevant analysis set or relative to the total number of participants in the relevant analysis set, with assessments available [where appropriate]) in each category.

7.1 MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers.
Data from all centers will be pooled for statistical analyses.

7.2 INTERCURRENT EVENTS (ICE)

The intercurrent events in this study are defined as follows:

- ICE1 = Premature discontinuation of study treatment.
- ICE2 = Pre-medications are not given as described within the protocol.

The handling of the intercurrent events will be as follows:

<u>For primary and secondary endpoints:</u>
Management of ICE1 = A while-on-treatment approach will be applied in case of premature discontinuation of the study treatment, where the value of the endpoint will be derived from the infusions actually received.

Management of ICE2 = A treatment policy approach will be applied in the case pre-medications are not given as described within the protocol, meaning the value for the endpoint of interest will be used regardless of whether different pre-medications are given to those listed within the

protocol, administration of the pre-medications are different to what is provided on the protocol or in an absence of pre-medication being administered.

For exploratory endpoints:

Management of ICE1 = A treatment policy approach will be applied in the case of premature discontinuation of the study treatment, meaning the value for the endpoint of interest will be used regardless of whether study treatment was discontinued prematurely or not.

Management of ICE2 = A treatment policy approach will be applied in the case pre-medications are not given as described within the protocol, meaning the value for the endpoint of interest will be used regardless of whether different pre-medications are given to those listed within the protocol, administration of the pre-medications are different to what is provided on the protocol or in an absence of pre-medication being administered.

7.3 MISSING DATA

7.3.1 PRIMARY, SECONDARY AND EXPLORATORY ENDPOINTS

7.3.1.1 PRIMARY ENDPOINTS

7.3.1.1.1 ACTUAL INFUSION DURATION

If actual infusion duration, see Section 15.1.2, cannot be calculated due to a partial date and/or time combination of any terms in the derivation, including interruption times then the actual duration will be set to the planned duration. Missing or partial dates for infusion start/stop and interruption times will not be imputed.

7.3.1.1.2 ACTUAL SHORTEST TOLERATED INFUSION DURATION

Participants never observed to tolerate any infusion during the study treatment period will have

their actual shortest tolerated duration set to their mean (average) pre-study infusion duration. If all pre-study durations are missing and the participant does not tolerate any infusion during the study treatment period, then shortest tolerated infusion duration will be considered missing.

7.3.1.1.3 Percentage Reduction in Infusion Duration

Percentage reduction of infusion duration, see Section 15.1.2 should be considered missing if all pre-study infusion durations are missing. If at least one is missing (but not all), then available infusion durations will be used.

7.3.1.2 Secondary Endpoints

For all secondary endpoints, see Section 15.2.1, participants never observed to tolerate any infusion rate during the study treatment period will be classified as non-responders ie, "No".

7.3.1.3 Exploratory Endpoints

7.3.1.3.1 Handling of ADA Titers with Missing or Non-numerical Values

If the ADA titer is reported as "<value", then the actual value is imputed as this value. For example, "<100" will be imputed as 100. However, no imputation for missing or non-numerical values will be done.

7.3.1.3.2 Handling of Plasma Lyso-GL3 (ng/ml) with non-Numerical Values

Results below the quantification limit (QL) of 0.3 ng/ml will be imputed to 0.15 (QL/2) for the summary tables and figures. Listings will present the reported value, as"<0.3 (ng/ml)".

7.3.2 Safety Endpoints

No imputation of results will be applied to all safety endpoints.

7.3.2.1 PARTIAL DATES FOR ADVERSE EVENTS AND MEDICATIONS

Partial missing date and/or time will be imputed to determine start/stop date and time for adverse events and medications. Only the collected date, not the imputed will be present in listings. The imputation conventions are specified in Section 20 Appendix 2 - 'Partial Date Conversions'.

7.3.2.2 ADVERSE EVENTS

7.3.2.2.1 INTENSITY

If the intensity is missing for one of the occurrences of an AE, for incidence summaries the intensity will be imputed with the maximal intensity of the other occurrences of the same AE for that participant. If the intensity is missing for all occurrences or if there are no other occurrences, the intensity will be left as missing. Actual values as collected will be presented in overview listings of pre-treatment AEs, All TEAEs and post-treatment AEs.

7.3.2.2.2 RELATIONSHIP

If the relationship to study treatment is missing for a pre-treatment or post-treatment AE, then for incidence summaries a relationship of "not related" will be assigned. If the relationship to study treatment is missing for a TEAE, a relationship of "related" will be assigned. Actual values as collected will be presented in overview listings of pre-treatment AEs, All TEAEs and post-treatment AEs.

7.4 MULTIPLE COMPARISONS/ MULTIPLICITY

Multiplicity adjustment is not applicable as no statistical testing is planned.

7.5 EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8 OUTPUT PRESENTATIONS

Section 19 Appendix 1 - 'Programming Conventions' for Outputs 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, listings, and figures to be provided by IQVIA™ Biostatistics.

Unless otherwise specified, for eCRF data, unknown as presented on summary outputs corresponds to a missing entry on the eCRF.

9 DISPOSITION AND WITHDRAWALS

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

9.1 DISPOSITION

Disposition of participants will be summarized for the Enrolled Analysis Set.
The number of participants in each analysis set (ENR, ITT and SAF) will be summarized by count and percentage over cohorts 1-4 pooled. Percentages will use the ENR analysis set as the denominator. Reasons for exclusion for each analysis set will be presented in a listing.

The number and percentage of screen failure participants using the ENR analysis set as the denominator will be presented. The number of individuals who fail to meet the individual inclusion criteria and/or meet the individual exclusion criteria will be presented using the number of screen fail participants as the denominator. A participant will be counted across multiple criteria if satisfied.

Count and percentage of study/treatment completers will be summarized along with non-completers. For non-completers the reason for discontinuation from study/treatment will also be

summarized. All reasons, including additional comments will be presented in a listing.

Disposition information is recorded in the following eCRF pages:

- End of Study Treatment
- End of Study

9.2 PROTOCOL DEVIATIONS

Protocol Deviations (PDs) identified will recorded in the IQVIA Clinical Trial Management System (CTMS) by IQVIA Clinical, as per the Protocol Deviation Management Plan.

Protocol Deviations (PDs) will be reviewed by the cross functional teams in Sanofi and IQVIA on a regular basis throughout the study.

9.2.1 PROTOCOL DEVIATION SEVERITY CLASSIFICATIONS

- **Critical Protocol Deviation:** A deviation from Protocol-related procedures that threatens integrity of data, adversely affects participants and/or could invalidate acceptability of a project (or part of it).
- **Major Protocol Deviation:** A deviation from Protocol-related procedures that could affect integrity of the data or adversely affect participants.
- **Minor Protocol Deviation:** A deviation from Protocol-related procedures that will not adversely affect participants or data integrity.

9.2.2 ANALYSIS OF PROTOCOL DEVIATIONS

The total number and percentage of participants who record at least one major or critical protocol deviation in the study per classification and category will be provided for cohorts 1-4 pooled for the ITT analysis set. A participant can be counted over several classifications but only once per category. A corresponding listing of all major or critical protocol deviations will be provided per cohort for the ITT analysis set.

Deviations will be presented if the frequency is greater than 0, according to the following categories as per the PD management plan:

- Informed Consent and Process
- Inclusion Criteria
- Exclusion criteria
- Laboratory Assessment
- Study Procedures
- Safety
- Randomization
- Visit Schedule
- IP conditions
- IP preparation
- IP administration
- Administrative
- Training/Delegation non-compliance
- PI oversight
- PI & site staff qualification
- Source documents
- Communication with IRB
- Investigator site file
- Adequate site staff and backup
- Site processes/Site systems
- Safety letters management
- Facilities/Equipment
- Other

10 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic data and baseline characteristics are recorded in the following eCRF pages: Demography, Pregnancy test, Pre-study Fabrazyme Treatment and Vital Signs.

Demographic data and baseline characteristics will be presented for the ITT analysis set.

The following demographic and baseline characteristics will be reported for this study:

- Age (years)
- Age group (Children 2-10 years, Adolescents 11-17 years, Adults 18-65 years)
- Sex (Male, Female, Unknown)
- Ethnic origin (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown)
- Hispanic Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Women of child-bearing potential (Yes, No with reason, Unknown)
- Baseline Weight (kg)
- Baseline Weight by Category (≥30 kg, <30 kg)
- Pre-study Fabrazyme infusions (dose and duration)
- Duration of Fabrazyme treatment pre-study (full months)

Unknown corresponds to either the selection on the CRF or for missing data.

A summary table for cohorts 1-4 pooled will be provided. A corresponding listing per cohort will be provided for all characteristics, where the pre-study Fabrazyme duration and dose will present all records as collected on the eCRF.

11 MEDICAL HISTORY

Medical History conditions are defined as those conditions which stop prior to or at Screening.

Medical History data is captured on the following eCRF page: Current or Medical History Condition where Ongoing is not indicated.

Medical History information will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher depending on the version in effect at IQVIA at time of database lock.

Medical History will be presented for the ITT analysis set and summarized by System Organ Class (SOC) and Preferred Term (PT) for cohorts 1-4 pooled.

There will also be a listing per cohort detailing the SOC, PT, Reported Name per record, along with the corresponding start and end dates recorded.

12 CURRENT MEDICAL CONDITIONS

Current medical conditions are conditions other than the indication being studied which started prior to or at Screening and are ongoing at the date of Screening.

Current medical conditions are captured in the following eCRF page: Current or Medical History Condition where Ongoing is indicated.

Current medical conditions will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher depending on the version in effect at IQVIA at time of database lock.

Current medical conditions will be presented for the ITT analysis set and summarized by System Organ Class (SOC) and Preferred Term (PT) for cohorts 1-4 pooled.

There will also be a listing per cohort detailing the SOC, PT, Reported Name per record, along with the corresponding start and end dates recorded.

13 MEDICATIONS

Non investigational prior, concomitant, and post-treatment medications are captured on the following eCRF page: Concomitant Medications Review.

Pre and rescue medications provided on the protocol are captured on the eCRF page: Pre-Medications and Rescue Medications. In the case a participant is administered an alternative pre or rescue medication to those outlined in the protocol such medications will be captured in the Concomitant Medications Review eCRF page.

All medications will be coded using World Health Organization (WHO) Drug Global dictionary, version B3 March 2023 or higher depending on the version in effect at IQVIA at time of database lock.

13.1 PRIOR, CONCOMITANT AND POST-TREATMENT MEDICATIONS

See Section 20.2, for handling partial dates for medications.

- Prior medications are those which start prior to the first dose of Fabrazyme, regardless of stop date.
- Concomitant medications are those received by the participant concomitantly to Fabrazyme during the study treatment period. The start date of these medications can either be prior to, on or after the first dose of Fabrazyme but not after the date of the last Fabrazyme infusion in the study treatment period. The end date of these medications must be after the first dose of Fabrazyme in the study treatment period or missing (ongoing).
- Post-treatment medications are those which are taken after the last dose of

Fabrazyme in the study treatment period, up to the end of the study, including those with a missing end date (ongoing).

A medication can be classified as a combination of prior, concomitant, and post-treatment if any of the above are satisfied, ie, a medication can be prior, concomitant and post-treatment if the start date is prior to the first dose of Fabrazyme and continues to be taken after the last dose of Fabrazyme (ongoing or stop date is after last dose of Fabrazyme).

If the classification cannot be determined the medication will be considered as prior, concomitant, and post-treatment.

13.2 PRE AND RESCUE MEDICATIONS

All participants will receive acetaminophen and one antihistamine as non-investigational prophylactic premedication, 30 minutes prior to each infusion. In case of IAR occurrence, the participant will receive dexamethasone and montelukast as rescue medication, and both drugs will be given from this time forward as prophylactic premedication, together with acetaminophen and the antihistamine, 30 minutes prior to all further infusions. The interventions are presented in tables 3 and 4 in the protocol.

13.3 ANALYSIS OF MEDICATIONS

Medications will be summarized for the ITT analysis set, by number and percentage of participants in cohorts 1-4 pooled according to Anatomical Class (ATC) drug class (level 1) and Anatomical Therapeutic Class (ATC) drug class (level 3). A medication can be counted over several level 1 categories. In summary outputs multiple medication usage by a participant in the same level 3 category will be counted only once in that category. All medications will be provided in listings per cohort for the ITT analysis set and will include the start and end dates of the medication (if known), reason(s) for why the medication was given, dosage, frequency and route. Medications presented in listings will be coded by Anatomical Class (ATC) drug class (level 1), Therapeutic Class (ATC) drug class (level 3) and preferred name.

14 STUDY MEDICATION COMPLIANCE

Compliance is based on the accumulation of the planned and actual dose (mg/kg) inputs on the Fabrazyme eCRF pages at each visit and is derived and analyzed in accordance with Sections 14.1 and 14.2.

14.1 DERIVATIONS

For each participant, compliance to Fabrazyme is defined as the percentage of the sum of actual dose versus sum of planned dose:

- Compliance (%) = [Sum of Actual dose received (mg/kg) / Sum of Planned dose (mg/kg)]* 100

If actual dose received (mg/kg) is missing for at least one visit, then overall compliance (%) will be missing and categorized as not assessable.

14.2 ANALYSIS OF COMPLIANCE

Compliance will be summarized for cohorts 1-4 pooled as described in Section 7: 'Statistical Considerations' for the SAF analysis set. The count and percentage of participants in the following categories will also be reported:

- <80%
- 80-100%
- >100%
- Not Assessable

A listing by cohort presenting compliance (%) and group will be provided for the SAF. The listing will also include the planned and actual doses (mg/kg) recorded at each visit per participant.

15 ENDPOINT EVALUATION

15.1 PRIMARY ENDPOINTS

15.1.1 PRIMARY ENDPOINT VARIABLE(S)

15.1.1.1 SHORTEST INFUSION DURATION EACH PARTICIPANT TOLERATES

The shortest infusion duration tolerated is the actual shortest duration (highest infusion rate) of a completed infusion tolerated by the participant without experiencing a second IAR.

A completed infusion is an infusion during which the entire amount of the study drug planned to be given at the visit has been delivered to the participant via infusion and the question "Was the infusion adjusted from the planned infusion?" is answered either "Infusion not changed" or "Infusion interrupted" on the Fabrazyme eCRF page. If the infusion was interrupted, it will only be considered completed if it was restarted, ie, the stop time of study drug infusion is later than the stop time of infusion interrupted.

An infusion is considered tolerated if it is completed within an actual duration (excluding any interruptions) not exceeding 120% of planned duration, without IAR. If the participant receives several infusions at the same planned duration during the study treatment period, the infusion duration will be considered tolerated if the last infusion with the duration is tolerated. Data for infusion duration tolerated at each visit (scheduled and unscheduled) is captured on the Fabrazyme eCRF pages.

15.1.1.2 PERCENT REDUCTION OF INFUSION DURATION FROM PRE-STUDY AVERAGE OF RECENT 3 INFUSIONS

Percent reduction is with respect to the shortest tolerated infusion for the participant.

The pre-study infusion duration is derived as the average of the duration of 3 most recent

infusions the participant received prior to participating to this study. Data for pre-study infusion durations are captured on the Pre-Study Fabrazyme Treatment eCRF page.

15.1.2 Derivations

- Infusion Interruption Duration (minutes) = (Interruption Stop Time – Interruption Start Time)
- Actual infusion duration (minutes) = (Infusion Stop Time – Infusion Start Time) – Infusion Interruption Duration (minutes)
- Average of pre-study infusion duration (minutes) = sum of all pre-study infusion duration (minutes) / number of pre-study infusions
- Percentage reduction of infusion duration (%) =100*[(Average of pre-study infusion duration (minutes) – Actual shortest infusion duration tolerated (minutes)] /Average of pre-study infusion duration (minutes)
- Percentage change of infusion duration (%) =100*[Actual shortest infusion duration tolerated (minutes) – Average of pre-study infusion duration (minutes)] /Average of pre-study infusion duration (minutes)

15.1.3 Intercurrent Event Handling and Data Imputation for Primary Endpoint Variable(s)

Refer to Sections 7.2 and 7.3.1.1 for details about intercurrent events and management of missing data.

15.1.4 Analysis of Primary Endpoint Variable(s)

Primary endpoints will be summarized descriptively for cohorts 1-4 pooled for the ITT analysis set. Details of the descriptive statistics is described in Section 7: 'Statistical Considerations'. A

corresponding listing presenting the primary endpoint values will also be provided per cohort for the ITT analysis set.

Each participant's shortest tolerated infusion duration and individual % change in infusion duration will be presented graphically in separate waterfall plots for the ITT analysis set.

For analysis of the primary endpoints IARs will be considered separate only when they are occurring in separate infusions. IARs occurring at multiple time points during a single infusion will be considered as a single IAR.

15.2 SECONDARY ENDPOINTS

15.2.1 SECONDARY VARIABLES

Data for secondary endpoints at each visit (scheduled and unscheduled) are captured on the Fabrazyme eCRF pages.

15.2.1.1 PROPORTION OF PARTICIPANTS ACHIEVING THE SHORTEST PLANNED DURATION OF INFUSION TIME WITHOUT EXPERIENCING ANY OR THE SECOND IAR

To evaluate the objective the following binary variables will be derived for each participant:

- Whether the participant achieved the shortest planned target duration of infusion (20 minutes for participants ≥30 kg and 30 minutes for participants <30 kg) without experiencing a first (ie, any) IAR (yes/no).

- Whether the participant achieved the shortest planned target duration of infusion time (20 minutes for participants ≥30 kg and 30 minutes for participants <30 kg) without experiencing a second IAR (yes/no).

15.2.1.2 PROPORTION OF PARTICIPANTS ACHIEVING INFUSION DURATION SHORTER THAN 90 MINUTES WITHOUT EXPERIENCING ANY OR THE SECOND IAR

To evaluate the objective the following binary variables will be derived for each participant:

- Whether the participant achieved infusion duration shorter than 90 minutes without experiencing a first (ie, any) IAR (yes/no).

  Whether the participant achieved infusion duration shorter than 90 minutes without experiencing a second IAR (yes/no).

A participant will be considered a non-responder ie, "No" if they have an initial planned target duration <90 minutes yet fail to tolerate an infusion during the study treatment period with actual duration <90 minutes. Participants with an initial planned target duration <90 minutes will be considered a responder ie, "Yes" if they tolerate at least one infusion during the study treatment period with actual duration <90 minutes.

15.2.1.3 PROPORTION OF PARTICIPANTS ACHIEVING EACH INFUSION DURATION PLANNED IN THE STUDY WITHOUT EXPERIENCING ANY OR THE SECOND IAR

To evaluate the objective the following binary variables will be derived for each participant:

- Whether the participant tolerated the planned infusion duration without experiencing a first (ie, any) IAR (yes/no), calculated separately per each planned infusion duration.

- Whether the participant tolerated the planned infusion duration without experiencing a second IAR (yes/no), calculated separately per each planned infusion duration.

15.2.2 Intercurrent Event Handling and Data Imputation for Secondary Efficacy Variable(s)

Refer to Sections 7.2 and 7.3.1.2 for details about intercurrent events and management of missing data.

15.2.3 Analysis of Secondary Endpoint Variables

Secondary endpoints will be summarized descriptively, count and percentage, for cohorts 1-4 pooled for the ITT analysis set.

A stacked bar chart split by cohort and planned infusion duration will be provided to summarize objective described in Section 15.2.1.3 and will describe:

- The number of participants who reach the duration without experiencing any IAR.
- The number of participants who have experienced only one IAR .
- The number of participants who have experienced a second IAR

The number of IARs a participant has experienced up to and including the planned infusion duration is displayed.

A listing of participants per cohort presenting their shortest tolerated infusion duration without any IAR will be provided. This listing will also include their shortest tolerated infusion duration without experiencing a second IAR. Responders/Non-responders according to each secondary endpoint will be flagged in listings.

For analysis of the secondary endpoints IARs will be considered separate only when they are occurring in separate infusions. IARs occurring at multiple time points during a single infusion will be considered as a single IAR.

15.3 EXPLORATORY ENDPOINTS

15.3.1 EXPLORATORY ENDPOINT VARIABLES & DERIVATIONS

15.3.1.1 PLASMA LYSO-GL3 (NG/ML)

Plasma lyso-GL3 (ng/mL) will be evaluated as a pharmacodynamic biomarker in this study and is also being used as a surrogate endpoint of efficacy that is reasonably likely to predict clinical benefit.

To evaluate the objective the following variables will be derived:

- Change from baseline of plasma lyso-GL3(ng/mL) at each visit
- Percent change from baseline of plasma lyso-GL3(ng/mL) at each visit

15.3.1.1.1 ANALYSIS OF PLASMA LYSO-GL3 (NG/ML)

Values, changes and percent changes from baseline of plasma lyso-GL3 (ng/mL) at each visit will be summarized descriptively for cohorts 1-4 pooled for the ITT analysis set.

During the study treatment period, only results from the samples taken prior to an infusion of the study drug will be considered. During the post treatment period, all samples will be considered. If time is not available and it cannot be determined the assessment was prior to the infusion, then the result will be considered missing.

Refer to Section 7.3.1.3.2 for handling of non-numerical results.

Percent change from baseline per participant and mean for each cohort will be presented in a spaghetti plot. A Listing of participants' observed values, changes and percent changes of Plasma lyso-GL3 (ng/mL) levels at each visit will be displayed per cohort for the ITT analysis set.

15.3.1.2 IMMUNOGENICITY

15.3.1.2.1 EVALUABLE PARTICIPANTS

Evaluable participants include all SAF participants with at least one sample taken post-baseline (during treatment or follow-up period) that is appropriate for ADA testing with a reportable result (positive, negative, or inconclusive). ADA titers will be determined for ADA-positive samples. Results from the confirmatory assays will be used in tables and figures. All available ADA data will be presented in listings.

15.3.1.2.2 ADA ATTRIBUTES

15.3.1.2.2.1 PRE-EXISTING ADA

Participants with ADA-positive sample at baseline are categorized as participants with pre-existing ADA.
Note that participants whose baseline ADA sample is missing or non-reportable but has at least one post-baseline sample will be considered as without pre-existing ADA for the analysis.

15.3.1.2.2.2 TREATMENT-BOOSTED ADA

Participants with pre-existing ADAs and at least a two-titer step increase in level of ADA titers at any timepoint after first dosing of study Fabrazyme (including follow-up period) are categorized as participants with treatment-boosted ADAs.

15.3.1.2.2.3 TREATMENT-INDUCED ADA

Participants without pre-existing ADA and developed ADA after first dosing of study Fabrazyme (including follow-up period) are categorized as participants with treatment-induced ADAs.

15.3.1.2.3 KINETICS OF ADA RESPONSE

Treatment boosted ADAs are excluded from the analysis of ADA kinetics.

15.3.1.2.3.1 PERSISTENT ADA RESPONSE

Persistent ADA response is defined as treatment-induced ADA detected at two or more timepoints post-baseline (including follow-up period), where the first and last ADA-positive timepoints (irrespective of any negative samples in between) are separated by at least 16 weeks.

15.3.1.2.3.2 TRANSIENT ADA RESPONSE

Transient ADA response is defined as treatment-induced ADA detected at only one timepoint post baseline (excluding the last sampling timepoint) or at two or more timepoints post-baseline (including the follow-up period), where the first and last ADA-positive timepoints (irrespective of any negative samples in between) are separated by less than 16 weeks and the participant's last timepoint is ADA-negative.

15.3.1.2.3.3 INTERMEDIATE ADA RESPONSE

Indeterminate ADA response is defined as when only the last timepoint is ADA-positive and all previous samples are ADA-negative or the last two samples (including follow-up period), separated by less than 16 weeks are positive.

15.3.1.2.4 ADA RESPONSE VARIABLE

ADA Incidence is defined as the proportion of evaluable participants found to have seroconverted (treatment-induced ADAs) or boosted their pre-existing ADA response (treatment-boosted ADAs) at any timepoint during the study period.

- ADA incidence (%) = 100* (number of treatment-boosted ADA participants + treatment-induced ADA participants)/ total number of evaluable participants

15.3.1.2.5 ANALYSIS OF IMMUNOGENICITY

During the study treatment period, only results from the samples taken prior to an infusion of the study drug will be considered. During the post treatment period, all samples will be considered.

If time is not available and it cannot be determined the assessment was prior to the infusion, then the result will be considered missing.

Summary tables for cohorts 1-4 pooled on the SAF analysis set will present:

- Evaluable participants (n)
- Participants with pre-existing ADA (n, %†)
    - Number of participants with treatment-boosted ADA (n, %†) and ADA peak titer (median, min, max)*
- Participants who are ADA negative at baseline (n, %†)
    - Number of participants with treatment-induced ADA (n, %†) and ADA peak titer (median, min, max)*
    - Participants with persistent ADA response (n, %†)
    - Participants with transient ADA response (n, %†)
    - Participants with indeterminate ADA response (n, %†)
- ADA incidence (%†)

† The number of evaluable participants will be the denominator for the percentages.

* ADA peak titer is defined as the highest titer after the first study infusion of Fabrazyme. In case of sparse treatment-boosted or treatment-induced ADA participants (eg, less than 5 participants), ADA peak titer may not be summarized.

Additionally, a summary table of ADA titers per visit will be presented with the following statistics: number, median, Q1, Q3, min, max, and geometric mean along with geometric SD (in case of sparse ADA positive participants, eg, less than 5 participants per visit, the ADA titer may not be descriptively summarized).

Individual ADA titers and median value for the cohorts over time will be presented in a spaghetti

plot in Safety analysis set.
Listing of participants presenting their ADA status (positive, negative, inconclusive) and ADA titer at each visit will be displayed by cohort in Safety analysis set.
If an ADA titer result is reported as non-numerical, it will be imputed as described in Section 7.3.1.3.1 for summary tables and figures. The listing will present the results as reported.

15.3.2 Intercurrent Event Handling and Data Imputation for Exploratory Variable(s)

Refer to Sections 7.2 and 7.3.1.3.1 for details about intercurrent events and management of missing data.

16 Safety Outcomes

16.1 Adverse Events

Adverse Events (AEs) will be coded to a preferred term (PT) and associated primary system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 27.0 or above depending on the version in effect at IQVIA at time of database lock. The information on AEs are captured in eCRF pages: Adverse Events, Adverse Event of Special Interest and Adverse Events of Special Interest-Infusion Associated Reaction. AEs that worsened or became serious are recorded as new records in the eCRF, and as such are counted as separate events for analysis. “Start date (and time)” below refer to the start date (and time) of each AE record.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs with start date (and time) < first dose of Fabrazyme start date/time.
- Treatment-emergent adverse events (TEAEs): AEs with start date (and time) ≥ first dose of Fabrazyme start date/time and <= last dose of study Fabrazyme end date. AEs will be

classified as TEAEs in the case where it's not possible to determine whether they're treatment emergent, refer to Appendix 20.1 - 'Algorithm for Treatment Emergent Adverse Events'.

- Post-treatment AEs: AEs with start date > last dose of study Fabrazyme end date.

16.1.1 Intensity

Intensity is classed as mild/ moderate/ severe. If a participant reports an AE more than once within a SOC/ PT, the AE with the worst-case intensity will be used in the corresponding intensity summaries. In the cases of missing intensity for an AE refer to Section 7.3.2.2.1.

16.1.2 Relationship to Fabrazyme

Relationship, as indicated by the Investigator, is classed as "related", "not related" and "not applicable". If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries. In the cases of missing relationship for an AE refer to Section 7.3.2.2.2.

16.1.3 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded where the Serious Event question is marked as Y on the Adverse Events page of the eCRF.

16.1.4 Adverse events leading to dose modification or interruption (including Dose Reduced, Drug Interrupted, Infusion Rate Decreased)

TEAEs leading to dose modification or interruption of study medication will be identified where action taken with Fabrazyme is either Dose Reduced, Drug Interrupted, or Infusion Rate Decreased on the eCRF Adverse Events page.

16.1.5 Adverse Events leading to permanent treatment withdrawal

TEAEs leading to permanent treatment withdrawal of study medication will be identified where action taken with Fabrazyme is Drug Withdrawal on the eCRF Adverse Events page.

16.1.6 Adverse Events Leading to Death

TEAEs leading to death are those events for which the outcomes are recorded as Fatal on the Adverse Events page of the eCRF.

16.1.7 Adverse Events Of Special Interest

16.1.7.1 Infusion Associated Reaction

In this study, IAR is defined as AEs the Investigator considers related to Fabrazyme infusion, occurring on same day as infusion and only after infusion has begun. Each individual AE occurrence will be considered separate when analyzing Adverse Events.
IARs are events recorded as Adverse Event of Special Interest (Infusion Associated Reaction) on the Adverse Events page of the eCRF.

16.1.7.2 Anaphylaxis

See Protocol Section 8.5.6 for details.

Anaphylaxis are events recorded as Adverse Events of Special Interest (Anaphylaxis) on the Adverse Events page of the eCRF.

16.1.8 Analysis of Adverse Events

Events with missing start/end dates and/or time will be handled according to the rules in Appendix 20.1 - 'Algorithm for Treatment Emergent Adverse Events'.

An overall summary table of all TEAEs will be provided for cohorts 1-4 pooled for the SAF

analysis set and will provide the number and percentage of occurrences along with the total number of events for the following:

For all TEAEs:

- Participants with any TEAE
- Participants with any Severe TEAE
- Participants with any Treatment-Emergent SAE
- Participants with any TEAE leading to Death
- Participants with any TEAE leading to Permanent Discontinuation of Fabrazyme
- Participants with any Treatment-Emergent AESIs: IARs
- Participants with any Treatment-Emergent AESIs: Anaphylaxis
- Participants with any Treatment-Related TEAEs

The AE summaries provided on Table D will be generated with number and percentage of participants experiencing at least one event for the SAF analysis set. Additionally, AE listings in Table E will be provided by cohort for the SAF analysis set.

When evaluating the number of events for participants, multiple occurrences of the same event for the same participant (ie, same SOC and PT) will be as individual events in summary tables. Counts of all AE occurrences will be included in summary tables. All AE occurrences for each participant will be presented in listings.

Table D - Summary Analyses of adverse events

Type of AE	MedDRA levels
All TEAEs	Primary System Organ Class and Preferred Term
TEAEs by Maximal Intensity	Primary System Organ Class and Preferred Term
TEAEs by Worst Relationship to Fabrazyme	Primary System Organ Class and Preferred Term
Treatment Emergent SAEs	Primary System Organ Class and Preferred Term
Treatment Emergent SAEs by Worst Relationship to Fabrazyme	Primary System Organ Class and Preferred Term
TEAEs of Special Interest (IAR)	Primary System Organ Class and Preferred Term

Type of AE	MedDRA levels
All TEAEs	Primary System Organ Class and Preferred Term
TEAEs of Special Interest (Anaphylaxis)	Primary System Organ Class and Preferred Term
TEAE leading to Permanent Full Discontinuation of Study Treatment	Primary System Organ Class and Preferred Term
Pre-treatment Adverse Events	Primary System Organ Class and Preferred Term
Post-treatment Adverse Events	Primary System Organ Class and Preferred Term

Table E - Listings of Adverse Events

Type of AE
All TEAEs
Treatment Emergent Serious Adverse Events (SAEs)
Pre-Treatment Adverse Events
Post-Treatment Adverse Events

16.2 DEATH DETAILS

If any participants die during the study as recorded on the 'death details' page of the eCRF, information available relating to whether an autopsy was performed, the date/time of death along with the primary and secondary cause will be presented in a data listing by cohort for the SAF population.

16.3 LABORATORY EVALUATIONS

Standard clinical and laboratory procedures will be utilized in this study. All clinical and laboratory procedures in this study are standard and generally accepted.

Levels of Lyso-GL3 and ADA will be assessed in the plasma by a central laboratory using standardized and validated methods in addition to applicable calibrated equipment.

There are no clinical safety laboratory tests planned for this study.
During the study, laboratory exams may be requested at the Investigator's discretion according to the individual needs of each participant.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor. If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

16.4 VITAL SIGNS AND WEIGHT

16.4.1 VITAL SIGNS

Vital Signs data at screening is captured in the Vital Sign eCRF page. Vital Signs data captured at each visit post-screening is captured in the Vital Signs (Timepoint) eCRF pages.
Body temperature, heart rate, respiratory rate, and blood pressure will be assessed before and 1 hour after each infusion.

16.4.2 WEIGHT

Weight (kg) will be treated as a vital sign. Weight (kg) data at screening is captured in the Vital Sign eCRF page. Weight (kg) data captured at each visit post-screening is captured in the Vital Signs (Timepoint) eCRF pages.

The amount of Fabrazyme to be administered is dependent on the participant's weight. Before each infusion, the participant must be weighed. If weighing is not possible before each infusion preparation, the site may use the participant's weight obtained for the previous infusion, within 1 month of the date of the infusion.

For analysis only observed weights recorded at the visit as per windowing conventions, see Section 6.6.2, will be presented on outputs. If no record is observed within the window then the value will be considered missing for by visit summaries and presented as missing on listings.

16.4.3 Derivations

For the below "Visit X" corresponds to post-baseline visits for all X.
For quantitative measurements:

- Change from baseline at visit X = Value at Visit X pre-dose – Baseline Value
- Change from pre-to post-dose each visit at visit X = Test Value at Visit X post-dose - Test Value at Visit X pre-dose

To convert temperature (F) to temperature (°C):

- Temperature (°C) = [Temperature (F) – 32] x (5/9)

16.4.4 Vital Signs and Weight Potentially Clinically Significant Abnormality Criteria

Potentially clinically significant abnormality (PCSA) quantitative Vital Signs and weight measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Age Group: ≥18 years old

Variable	Unit	Low	High
SBP	mmHg	≤90 AND change from baseline ≤-20	≥180 AND change from baseline ≥20
DBP	mmHg	≤50 AND change from baseline ≤-15	≥105 AND change from baseline ≥15
Heart rate	Bpm	≤50 AND change from baseline ≤-15	≥120 AND change from baseline ≥15

Variable	Unit	Low	High
Body temperature	˚C	NA	≥38.3 AND change from baseline ≥1.1
Weight	Kg	percentage change from baseline ≤-7.0 %	percentage change from baseline ≥7.0 %

Age Group: 6 to <12 Years Old

Variable	Unit	Low	High
SBP	mmHg	≤80 AND change from baseline ≤-20	≥108 AND change from baseline ≥20
DBP	mmHg	≤48 AND change from baseline ≤-10	≥72 AND change from baseline ≥10
Heart rate	Bpm	≤50 AND change from baseline ≤-20	≥120 AND change from baseline ≥20
Body temperature	˚C	NA	≥38
Weight	Kg	percentage change from baseline ≤-5.0 %	

Age Group: 12 to 18 years old

Variable	Unit	Low	High
SBP	mmHg	≤90 AND change from baseline ≤-20	≥119 AND change from baseline ≥20
DBP	mmHg	≤54 AND change from baseline ≤-10	≥78 AND change from baseline ≥10
Heart rate	Bpm	≤50 AND change from baseline ≤-20	≥120 AND change from baseline ≥20
Body temperature	˚C	NA	≥38
Weight	Kg	percentage change from baseline ≤-5.0 %	

16.4.5 Analysis of Vital Signs and Weight

Vital signs data will be analyzed for the SAF analysis set for the following parameters:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Respiratory rate (bpm)
- Body temperature (°C)
- Weight (kg)

The following summaries based on observed data will be provided for the study treatment period:

- Values at each visit.
- Change from baseline at each visit for pre-dose vital signs.
- Change from pre-dose to post-dose at each visit (for all parameters except weight [kg])
- Incidence of predefined markedly abnormal criteria by age group and parameter.

Participants who have markedly abnormal values in both directions (abnormally high and abnormally low) during the study treatment period for the same parameter will be included in both high and low counts for that parameter.

Corresponding listings will also be provided detailing the above summaries, including the date and time of assessment and reasons if known as to why a scheduled assessment was not conducted. Listings will also include what abnormality is satisfied at each visit pre/post infusion.

17 Sample Size Consideration

There is no sample size calculation. The chosen sample size is based on feasibility considerations.

18 REFERENCES

ICH E9 - *Statistical Principles for Clinical Trials* - Adopted by CPMP, March 1998, issued as CPMP/ICH/363/96/step 5.

ICH E9 (R1) - *addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials* - Adopted by CHMP, February 2000, issued as EMA/CHMP/ICH/436221/2017.

19 APPENDIX 1: PROGRAMMING CONVENTIONS FOR OUTPUTS

19.1 IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following:

19.1.1 FONTS

The font type 'Courier New' will be used for all outputs, with a font size of 8. The font color will be black. Where possible single spacing will be used for all text.

19.1.2 DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

19.1.3 SPELLING FORMAT

English US

19.1.4 PRESENTATION OF TREATMENT GROUPS ON SUMMARY OUTPUTS

For summary outputs, "Cohorts 1-4" will donate cohorts 1-4 pooled.

19.1.5 DECIMAL PLACES AND PRESENTATION OF STATISTICS

The decimal places for this study will use the following rules, unless otherwise stated.

- Value = x dp
- (Arithmetic and Geometric) Mean = x+1 dp
- Standard Deviation = x+2 dp
- Geometric Standard Deviation = x + 2 dp
- Median = x+1 dp

- Q1/Q3 = x+1 dp
- Minimum/Maximum = x dp

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages <0.1 but >0.0 which will be presented as '<0.1' and percentages <100.0 but >99.9 which will be presented as '>99.9'. Percentages of 100% will be presented as 100.0.
Where counts are zero, no percentages will appear in the output.

19.1.6 LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Cohort Number,
- Center-subject ID,
- (Start) Date, where applicable,

When screen failure participants are included on the listing, the cohort will be displayed as 'Screen Failure'.

20 APPENDIX 2: PARTIAL DATE CONVERSIONS

20.1 ALGORITHM FOR TREATMENT EMERGENT ADVERSE EVENTS

AE START DATE/TIME	AE STOP DATE/TIME	ACTION
Missing	Known	If stop date (and time) < first dose of Fabrazyme start date/time, assign as pre-treatment AE. If stop date (and time) ≥ first dose of Fabrazyme start date/time, then assign as TEAE.
Missing	Missing	Assumed TEAE

20.2 ALGORITHM FOR PRIOR/CONCOMITANT AND POST-MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Missing	If stop date is missing then medication is assumed to be ongoing. Assign period based on start date, see Section 13.1.
Partial	Known /Missing	If stop date is missing then medication is assumed to be ongoing. Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown). Assign period based on imputed start date, see Section 13.1.

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < first dose of study Fabrazyme assign as prior. Else if stop date <= last dose of study Fabrazyme date, assign as prior and concomitant. Else if stop date > last dose of study Fabrazyme date, assign as prior, concomitant and post-treatment.
Missing	Missing	If stop date is missing then medication is assumed to be ongoing. Assign as prior, concomitant and post-treatment.