TITLE PAGE

Protocol Title: A Study to investigate safety and tolerability of Higher infusion rate to shORten the duraTion of FabrazymE infusioN

Protocol Number: LPS17726

Amendment Number: Amendment 2.0 – Protocol Version 3.0

Compound: Agalsidase beta/Fabrazyme®

Brief Title: SHORTEN

Study Phase: 4

Sponsor Name: Sanofi US. Services Inc.

Legal Registered Address:

55 Corporate Drive

Bridgewater, NJ 08807

USA

Regulatory Agency Identifier Numbers:

Registry	ID
IND	007616

Approval Date: 09 Jul 2024

Medical Monitor name and contact information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY			
Document	**Date**	**Substantial**	**Region**
Amendment 2.0	09-Jul-2024	No	Global
Amendment 1.0	20-May-2024	Yes	Global
Original Protocol	22-Jun-2023	-	-

Amendment 2.0 (09 Jul 2024)

Overall Rationale for the Amendment:

This Amendment 2.0 (Protocol version 3.0) was developed for administrative change.

Section # and Name	Description of Change	Brief Rationale
Title page	The name and address of Sponsor was updated as, "Sanofi US. Services Inc. 55 Corporate Drive Bridgewater, NJ 08807 USA"	To correct the administrative error.

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Study to investigate safety and tolerability of Higher infusion rate to shORten the duraTion of FabrazymE infusioN

Registry	ID
IND	007616

Rationale:

This Phase 4 study will evaluate the safety and tolerability of Fabrazyme at current approved dose of 1 mg/kg with increases in the infusion rate and reduced infusion volume. This study aims to generate data to provide the guidance on how infusion rate can be safely increased (ie, infusion duration be reduced) and minimize the burden of the life-long treatment with Fabrazyme.

Objectives, Endpoints, 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 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.

Objectives	Estimand Description/Endpoints
	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 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, 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 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 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.
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	most recent 3 infusions. **Treatment**: Fabrazyme 1 mg/kg Q2W up to the rate tolerated (refer to 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 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 Section 6.2), with oral premedications given 30 minutes prior to each

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	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 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.

Objectives	Estimand Description/Endpoints
	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 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.
Safety • To investigate the influence of increased infusion rate on the safety of Fabrazyme treatment	• Number, severity, and nature of AEs including IARs

Abbreviations: AE = adverse event; FD = Fabry disease; IAR = infusion associated reaction; Q2W = every 2 weeks.

Overall Design:

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.

Screening will be performed up to 4 weeks prior to the first dose of study intervention. Eligible participants will receive treatment for up to 16 weeks and have an End-of-Study Visit 28 weeks after the start of the treatment.

All 4 cohorts of this study will be enrolled simultaneously.

Number of Participants:

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).

Intervention Groups and Duration:

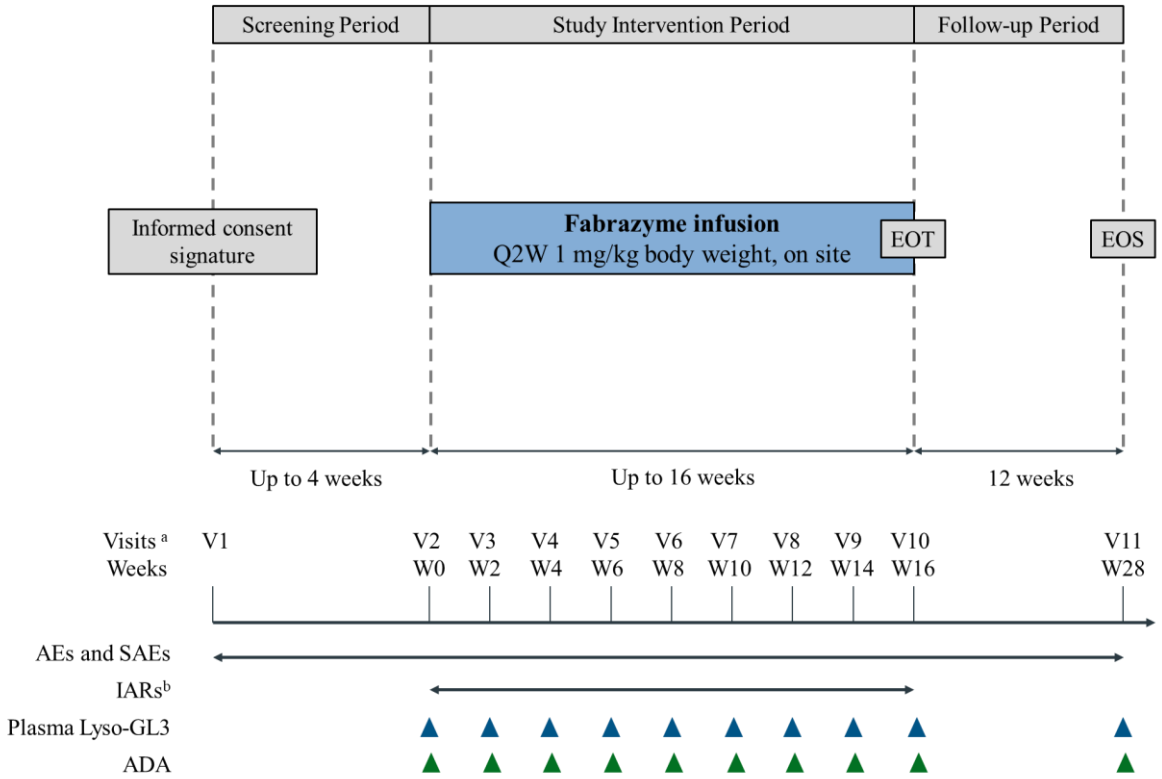
This is a single arm study. All participants will receive Fabrazyme infusions at dose of 1 mg/kg at the study site, for up to 16 weeks (9 infusions). The infusion duration will shorten, and the infusion rate will rise with each successfully tolerated infusion (ie, an infusion completed within a duration not exceeding 120% of planned duration, without IAR), until reaches 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.

Non-investigational prophylactic premedication with acetaminophen (160 mg to 650 mg, depending on age) and one antihistamine (diphenhydramine 25 mg or 12.5 mg, or loratadine 10 mg or 5 mg, or cetirizine 5 mg or 2.5 mg, or fexofenadine 180 mg or 30 mg - doses will depend on age) will be administered to all participants to avoid IARs, 30 minutes prior to each infusion. Dexamethasone (5 mg to 7 mg, depending on age and weight) and montelukast (4 to 10 mg, depending on age) will also be administered as premedication for participants that presents an IAR during the study.

Data Monitoring/Other Committee: No

1.2 Schema

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.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening (Day -28 to Day 1) [a]	Study Intervention Period: up to 16 Weeks [b]			EOS	Notes
		Day 1	Q2W (± 3 days) Except Week 12	At Week 12 (± 3 days) Month 3	At Week 28 (± 3 days) Month 6	
		W0	W2, W4, W6, W8, W10, W14, W16	W12	W28	
	V1	V2	V3, V4, V5, V6, V7, V9, V10 [c]	V8	V11	
Written informed consent and participant's assent (when applicable)/assignment of participant identification number	X					
Inclusion and exclusion criteria	X					
Demography	X					Including but not limited to age, gender, race/ethnicity, and duration of Fabrazyme treatment before entering the study.
Medical history	X					
Current medical conditions	X					
Urine pregnancy test (only for WOCBC)	X					If a urine test cannot be confirmed as negative, a serum pregnancy test is required.

Procedure	Screening (Day -28 to Day 1) [a]	Study Intervention Period: up to 16 Weeks[b]			EOS	Notes
		Day 1	Q2W (± 3 days) Except Week 12	At Week 12 (± 3 days) Month 3	At Week 28 (± 3 days) Month 6	
		W0	W2, W4, W6, W8, W10, W14, W16	W12	W28	
	V1	V2	V3, V4, V5, V6, V7, V9, V10 [c]	V8	V11	
Vital signs and weight	X	X	X	X[d]		Vital signs include body temperature, heart rate, respiratory rate, and blood pressure., which will be assessed before and 1 hour after completion of each study intervention infusion. Refer to Sections 8.2 and 8.4.1.
Plasma Lyso-GL3		X	X	X	X	Blood sampling should be done prior to study intervention infusion. To be done at a central lab.
Serum for anti-agalsidase beta IgG antibody titers		X	X	X	X	Blood sampling should be done prior to study intervention infusion. To be done at a central lab.
Study intervention[b]		X	X	X		
IAR monitoring[e]		←==========		==========→		
AE monitoring	←==========			==========→		
SAE monitoring	←==========			==========→		
Concomitant medication review	←==========			==========→		

Abbreviations: AE = adverse event; EOS = end-of-study; IAR = infusion associated reaction; IgG = immunoglobulin G; lyso-GL3 = globotriaosylsphingosine; Q2W = every 2 weeks; SAE = serious adverse event; V = visit; W = week; WOCBP = women of childbearing potential.

a. The Screening Visit (V1) and Day 1 Visit (V2) can take place on the same day. If that occurs, the procedures planned for both visits should be performed only once, and all the screening procedures must be completed prior to the infusion and other study-required procedures.
b. The Study Intervention Period duration (up to 16 weeks) will depend on the participant's tolerability of the continuous reduction of the infusion duration time. 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. The study intervention will be permanently discontinued if the participant presents a second IAR.
c. Participants may have a different number of visits during the Study Intervention Period. Visits 1, 2, 3, 8 and 11 should happen regardless of the number of infusions a participant receives. All other visits are planned but will occur only if the participant does not present any criteria to permanently discontinue the study intervention, such as having a second IAR, or only until the treatment is not considered completed.
d. Applicable only if the study intervention is administered in this visit. Refer to footnote b.
e. IAR monitoring will be performed only during the Study Intervention Period which can be shorter than 16 weeks for some participants.

Note: If a participant is not able to visit the study site for any reason, they should contact the study site by telephone. Adverse event and concomitant medication details may be collected during a telephone call. It may not be possible to collect all clinical laboratory samples or conduct clinical assessments during this time, but any details should be recorded in the source document and electronic case report form (eCRF). If alternative arrangements can be agreed for the sample collection or clinical assessments, the details should be documented in the eCRF.

2.0 INTRODUCTION

Recombinant human α-galactosidase A (αGAL) (Fabrazyme®, agalsidase beta) has been developed and manufactured by Sanofi. Fabrazyme was approved for the treatment of patients with Fabry disease (FD) by European Agency for the Evaluation of Medicinal Products in 2001 and by Food and Drug Administration in 2003.

2.1 Study Rationale

This Phase 4 study will evaluate the safety and tolerability of Fabrazyme at current approved dose with increased infusion rate and reduced infusion volume. This study aims to generate data to provide guidance on how infusion rate can be safely increased to minimize the burden of the life-long treatment with Fabrazyme.

The infusion rate of Fabrazyme in the Company Core Data Sheet and the labels approved in most countries, including the US, is based on the pivotal Phase 3 study and its extension study data leading to recommended minimum infusion duration of 90 minutes, even when the patients tolerate the infusion very well.

Data from real world [1,2] indicate that infusion durations less than 90 minutes are well tolerated by adult male and female patients. Additionally, the data from Japanese post marketing surveillance study also indicate that young boys with classic FD with body weight <30 kg tolerated up to 1 mg/kg/hour of infusions with Fabrazyme that were completed in 60 minutes [3].

2.2 Background

Fabry disease is a rare, x-linked, genetic disorder caused by mutations in the gene encoding the lysosomal enzyme, αGAL. The resultant enzymatic deficiency leads to the progressive accumulation of glycosphingolipids, most notably globotriaosylceramide (GL3), in lysosomes of a variety of cell types and tissues. Fabry disease is a progressive disorder that takes years to advance to end stage organ failure. Over a period of decades, the progressive accumulation of glycosphingolipids impairs vital organ function, putting patients with FD at risk of developing renal failure, cardiovascular dysfunction, and stroke. Fabry disease management consists of disease-specific treatment with enzyme replacement therapy (ERT), chemical chaperone and symptomatic/adjuvant treatments targeted at preventing and treating disease related symptoms and complications. Fabrazyme (agalsidase beta) is a recombinant human α-galactosidase enzyme approved to be used in patients with FD in over 80 countries/regions.

Fabrazyme showed significant reduction in plasma globotriaosylsphingosine (lyso-GL3) and GL3 levels in clinical trials, indicating that agalsidase beta has a good pharmacodynamic effect on these markers at the recommended dose of 1 mg/kg every 2 weeks (Q2W) [4]. In

addition, when infused at the recommended dose for 6 months, Fabrazyme cleared or reduced GL3 in renal, cardiac, and dermal microvascular endothelia and other cells, with long-term sustained results in most patients evaluated. Specifically, for renal interstitial capillary endothelium, 100% GL3 clearance was achieved (baseline versus Week 26) at the recommended dose. Based on the Phase 3, the Phase 3 extension, and the Phase 4 study results, it was demonstrated that early treatment may alleviate symptoms and prevent further progression of this lethal disease before irreversible damage has occurred [5].

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of Fabrazyme may be found in the US package insert [6].

The Sponsor will immediately notify the Principal Investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

The Sponsor and Investigator may take appropriate urgent safety measures in order to protect the participants of a clinical study against any immediate hazard to their health or safety. If such measures are taken, the Sponsor shall immediately (no later than 3 days from the date the measures are taken) give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

2.3.1 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Fabrazyme		
Anaphylaxis and hypersensitivity reactions	Life-threatening anaphylactic and severe hypersensitivity reactions have been observed in patients during Fabrazyme infusions. In clinical trials and post marketing safety experience with Fabrazyme, approximately 1% of patients developed anaphylactic or severe hypersensitivity reactions during Fabrazyme infusion [6].	Participants with history of significant allergic disease or hypersensitivity to Fabrazyme or other medicinal products will be excluded from this study (Section 5.2). Only participants who had not experienced any IAR during 3 most recent infusions will be included
IARs	In clinical trials of Fabrazyme, 59% of participants experienced IARs during Fabrazyme administration, some of which were severe [6].	IARs are AESI in this study. The incidence and severity of IARs will be closely monitored and evaluated throughout the study. Non-investigational premedication with acetaminophen and one antihistamine will be administered to all participants to avoid IARs prior to each infusion, and dexamethasone and montelukast will be added to the premedication in participants experiencing IARs during the study. All participants will have their infusions in a clinical setting, with direct physician supervision where any reactions can be managed appropriately. In the unpublished data from Japanese post marketing surveillance study, shorter infusion duration was related to lower incidence of IARs as infusion duration was reduced in participants who tolerated longer infusions. By reducing infusion duration only when a participant tolerates longer infusion, the risk of IARs will be minimized.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
AEs	Common adverse reactions which occurred in ≥20% of patients treated with Fabrazyme and >2.5% compared to placebo are upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash [6]. The most common adverse reactions (>20%) in pediatric FD patients, ages 8 to 16 years, were headache, abdominal pain, pharyngitis, fever, nausea, vomiting, rhinitis, diarrhea, arthralgia, and dizziness [6].	The incidence and severity of AEs will be monitored and evaluated throughout the study and will be managed per clinical judgment and institutional standard of care. Anaphylaxis is an AESI in this study. The incidence and severity of anaphylaxis will be closely monitored and evaluated throughout the study.
Study Procedures		
Blood draws	Blood draws have the potential to cause pain, bruising, erythema, bleeding, swelling of the site/vein, hematoma at the injection site, and fainting.	Most symptoms are self-limiting and curtailed by use of appropriate measures. Blood will be drawn in aseptic conditions with the support of medically trained professionals.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; IAR = infusion associated reaction.

2.3.2 Benefit Assessment

The pivotal Phase 3[7] and extension study[8] have demonstrated sustained clearance of GL3 from capillary endothelium in the heart, kidney, and skin, as well as from kidney cell types. Renal function remained stable in most participants. However, the effect of Fabrazyme treatment on kidney function was limited in some participants with advanced renal disease. The results also indicate that patients may achieve reduced pain and enhanced quality of life with ERT. In another double-blind, placebo-controlled study with more advanced disease, the rate of clinical events was substantially lower among Fabrazyme treated participants compared to placebo-treated participants, and this result was consistent across renal, cardiac, and cerebrovascular events.

The results of these studies indicate that Fabrazyme treatment at 1.0 mg/kg Q2W provides clinical benefit in key clinical outcomes in patients with early and advanced FD. Because this condition is slowly progressive, early detection and treatment are critical to achieve the best outcomes.

In the open label pediatric study, clearance of GL3 in superficial skin vascular endothelium was achieved in all participants who had accumulated GL3 at baseline.

Since its approval in 2001, many clinical studies and observational data have been published detailing the clinical benefit of Fabrazyme in adults and children with FD [9, 10].

Fabrazyme-based ERT is a life-long treatment and patients require regular intravenous infusions every 2 weeks, which entails a significant burden for them to bear in addition to the symptoms of the disease [11]. In this study, additionally to the benefit of continuing treatment with Fabrazyme free of charge during the study, the participants will have the opportunity to benefit from shorter infusions, which will decrease the time committed to treatment and potentially increase their quality of life.

2.3.3 Overall Benefit Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with Fabrazyme are justified by the anticipated benefits that may be afforded to participants with FD.

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 presents the primary, secondary, and exploratory objectives and corresponding Estimands or endpoints.

Table 2 Study Objectives and Estimands/Endpoints

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 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.

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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 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.
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Objectives	Estimand Description/Endpoints
	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 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.

Objectives	Estimand Description/Endpoints
	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 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.

4.0 STUDY DESIGN

4.1 Overall Design

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 with increases in the infusion rate and reduced infusion volume.

Up to 14 participants with FD will be enrolled to receive 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.

The study schema is presented in Section 1.2. Screening will be performed up to 4 weeks prior to the first dose of study intervention. All 4 cohorts of this study will be enrolled simultaneously. Enrolled participants will receive treatment for up to 16 weeks (up to 9 infusions) 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.

All participants will receive Fabrazyme infusions at dose of 1 mg/kg at the study site. The participants are not required to stay at the site after completion of the infusion, unless the Investigator considers it medically necessary. The infusion duration will shorten, and the infusion rate will rise with each successfully tolerated infusion (ie, an infusion completed within a duration not exceeding 120% of planned duration, without infusion associated reaction [IAR]), until reaches 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). Guidance for increasing the rate of infusion (and consequently decreasing the infusion duration) are presented in Section 6.2. When the participant successfully reaches the shortest infusion duration planned for the cohort which he/she belongs, 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.

All participants will also receive premedication with an antipyretic and antihistamine to avoid IARs prior to each infusion. Oral steroid and montelukast will also be administered as premedication for the participants that presents an IAR during the study.

4.2 Scientific Rationale for Study Design

A single arm design was selected as the main objective is to evaluate the safety and tolerability of increases in Fabrazyme infusion rate, and within a participant, the longer-lasting infusions might be used as the comparators for the shorter ones. An open label design was selected as all participants will receive the same intervention and the duration of the infusion decreases as the study progresses, which is automatically recognizable to the participants and study personnel.

The population chosen for the study comprises the diversity of patients with FD already treated with Fabrazyme: women, men with classic and non-classic disease, and children.

Standard clinical and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for participants with FD. All clinical and laboratory procedures in this study are standard and generally accepted.

4.3 Justification for Dose

The dose selected for this study of 1 mg/kg body weight given every 2 weeks as an intravenous infusion is the recommended dose as per approved dosage regimen [6].

Fabrazyme will be used according to the US package insert, except for infusion duration and rate, as the main objective of this study is to evaluate shorter infusion durations, and infusion volume. The volume of infusion to be used in this study (50 mL for participants <60 kg and 100 mL for participants ≥60 kg) is within the range that was used in the Phase I/II study [12].

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled visit.

4.5 End of Treatment Definition

The end of treatment is defined when the participant successfully reaches the shortest infusion duration planned for the cohort which he/she belongs to or when the participant experiences a second IAR. At that point, the participant will not receive any further infusion as part of the study, regardless of whether the Study Intervention Period reaches 16 weeks or not (Figure 2 and Figure 3).

4.6 Study Stopping Criteria

4.6.1 Stopping Criteria for Individual Participants

Criteria for discontinuing study intervention for an individual participant and the criteria for discontinuing the study for an individual participant are presented in Section 7.0.

4.6.2 Criteria for Stopping the Study

While no specific criteria have been established for terminating the study prematurely, it remains within the Sponsor's discretion to stop the study, at any time, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will promptly notify the Investigator.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Participants with confirmed diagnosis of FD who are ≥2 and ≤65 years of age at the time of signing the informed consent form (ICF) or assent, if applicable.

    a. Cohort 1: female participants with body weight ≥30 kg who have been treated with Fabrazyme for at least 3 months without IARs during the most recent 3 infusions.

    b. Cohort 2: non-classic male participants with body weight ≥30 kg who have been treated with Fabrazyme for at least 3 months without IARs during the most recent 3 infusions.

    c. Cohort 3: classic male participants with body weight ≥30 kg who have been treated with Fabrazyme for at least 3 months without IARs during the most recent 3 infusions.

    d. Cohort 4: participants with body weight <30 kg who have been treated with Fabrazyme for at least 3 months without IARs during the most recent 3 infusions.

    Note: Classic FD is defined by αGAL level in dried blood spot or leukocyte below 3% of normal value.

2. Women of childbearing potential must use a highly effective method of contraception through the study (refer to Appendix 4 in Section 10.4).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Female participants who are pregnant or breastfeeding.
2. History of significant allergic disease or hypersensitivity to Fabrazyme or other medicinal products.
3. Contraindication to Fabrazyme or any of the premedications or rescue medications (diphenhydramine, loratadine, cetirizine, fexofenadine, acetaminophen, montelukast, dexamethasone).

4. Any other medical condition considered to make the increased infusion rate not tolerable at the Investigator's discretion.

5.3 Lifestyle Considerations

No lifestyle observations are required in this study.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6.0 STUDY INTERVENTIONS AND CONCOMITANT THERAPY

Study intervention is defined as any investigational interventions, marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Interventions Administered

The study has a single arm. All participants will receive 1 mg/kg of body weight of Fabrazyme every 2 weeks at the study site until they reach the shortest infusion duration planned for the cohort they belong to, for up to 16 weeks. The infusion duration and rate will follow the flow presented in Section 6.2.

The participants are not required to stay at the site after completion of the infusion, unless the Investigator considers it medically necessary.

All participants will receive acetaminophen and one antihistamine as non-investigational prophylactic premedication, 30 minutes prior to each infusion. In case of IAR occurrence, 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 study interventions are presented in Table 3 and Table 4 (for the possible antihistamines allowed as premedication).

Table 3 Study Interventions Administered

Intervention Label	Fabrazyme	Acetaminophen	Dexamethasone	Montelukast
Intervention Name	Recombinant human αGAL (agalsidase beta)	Acetaminophen	Dexamethasone	Montelukast
Intervention Description	Fabrazyme 1 mg/kg Q2W	Acetaminophen	Dexamethasone	Montelukast
Type	Biological	Drug	Drug	Drug
Dose Formulation	Lyophilized powder for reconstitution	Tablet (for participants >12 years old) or solution (for participants ≤12 years old)	Tablet or solution (alternative only available for participants <16 years old)	Tablet (for participants ≥15 years old), chewable tablet (for participants up to 14 years old) or oral granules (only for participants <6 years old)
Unit Dose Strength(s)	Nominal value of 35 mg to have 5 mg/mL (35 mg/7 mL) after reconstitution with 7.2 mL of sterile water for infusion	650 mg (tablet), or any approved and commercially available solution	7.5 mg (tablet) or any approved and commercially available solution	10 mg (tablet), 5 mg (chewable tablet) or 4 mg (chewable tablet or oral granules)
Dosage Level(s)	1 mg/kg of body weight, Q2W	According to age: >12 years: 650 mg 12 years: 640 mg 11 years: 480 mg 9-10 years: 400 mg 7-8 years: 320 mg 4-6 years: 240 mg 2-3 years: 160 mg Frequency: 30 minutes prior to each infusion	According to age: Adult: 7.5 mg <16 years: 0.1 mg/kg, maximum of 5 mg Frequency: At an IAR and from this time forward, 30 minutes prior to each new infusion	According to age: ≥15 years: 10 mg 6-14 years: 5 mg <6 years: 4 mg Frequency: At an IAR and from this time forward, 30 minutes prior to each new infusion
Route of Administration	IV infusion	Oral	Oral	Oral
Use	Experimental intervention	Prophylactic premedication	Rescue and prophylactic premedication	Rescue and prophylactic premedication
IMP and NIMP/AMP	IMP	NIMP/AMP	NIMP/AMP	NIMP/AMP

Intervention Label	Fabrazyme	Acetaminophen	Dexamethasone	Montelukast
Sourcing	Provided centrally by the Sponsor	Provided locally by the study site	Provided locally by the study site	Provided locally by the study site
Packaging and Labeling	Study intervention will be provided in a single vial per box (35 mg). Each box will be labeled as required per country requirement	Packaged and labeled as required per country requirement	Packaged and labeled as required per country requirement	Packaged and labeled as required per country requirement

Abbreviations: AMP = auxiliary medicinal product; IAR = infusion associated reaction; IMP = investigational medical product; IV = intravenous; NIMP = non-investigational medical product; Q2W = every 2 weeks; αGAL = α-galactosidase A.

Table 4 Possible Antihistamines Administered as Premedication

Intervention Label	Diphenhydramine	Loratadine	Cetirizine	Fexofenadine
Intervention Name	Diphenhydramine	Loratadine	Cetirizine	Fexofenadine
Intervention Description	Diphenhydramine	Loratadine	Cetirizine	Fexofenadine
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet or solution (alternative only available for participants <12 years old)	Tablet (for participants >6 years old) or chewable tablet (for participants between 2 to 6 years old)	Tablet (for participants >6 years old) or oral solution (for participants between 2 to 6 years old)	Tablet (for participants >12 years old) or oral suspension (for participants between 2 to 12 years old)
Unit Dose Strength(s)	25 mg or 12.5 mg (tablet) or any approved and commercially available solution	10 mg (tablet) or 5 mg (chewable tablet)	5 mg (tablet) or 2.5 mg (oral solution of 1 mg/mL)	180 mg (tablet) or 30 mg (oral suspension of 30 mg/5 mL)
Dosage Level(s)	According to age: ≥12 years: 25 mg <12 years: 12.5 mg Frequency: 30 minutes prior to each infusion	According to age: Adults and children >6 years old: 10 mg 2 to 6 years age: 5 mg Frequency: 30 minutes prior to each infusion	According to age: Adults and children >6 years old: 5 to 10 mg 2 to 6 years age: 2.5 to 5 mg (2.5 mL to 5 mL) Frequency: 30 minutes prior to each infusion	According to age: Adults and children >6 years old: 180 mg 2 to 12 years age: 30 mg (5 mL) Frequency: 30 minutes prior to each infusion

Route of Administration	Oral	Oral	Oral	Oral
Use	Prophylactic premedication	Prophylactic premedication	Prophylactic premedication	Prophylactic premedication
IMP and NIMP/AMP	NIMP/AMP	NIMP/AMP	NIMP/AMP	NIMP/AMP
Sourcing	Provided locally by the study site	Provided locally by the study site	Provided locally by the study site	Provided locally by the study site
Packaging and Labeling	Packaged and labeled as required per country requirement	Packaged and labeled as required per country requirement	Packaged and labeled as required per country requirement	Packaged and labeled as required per country requirement

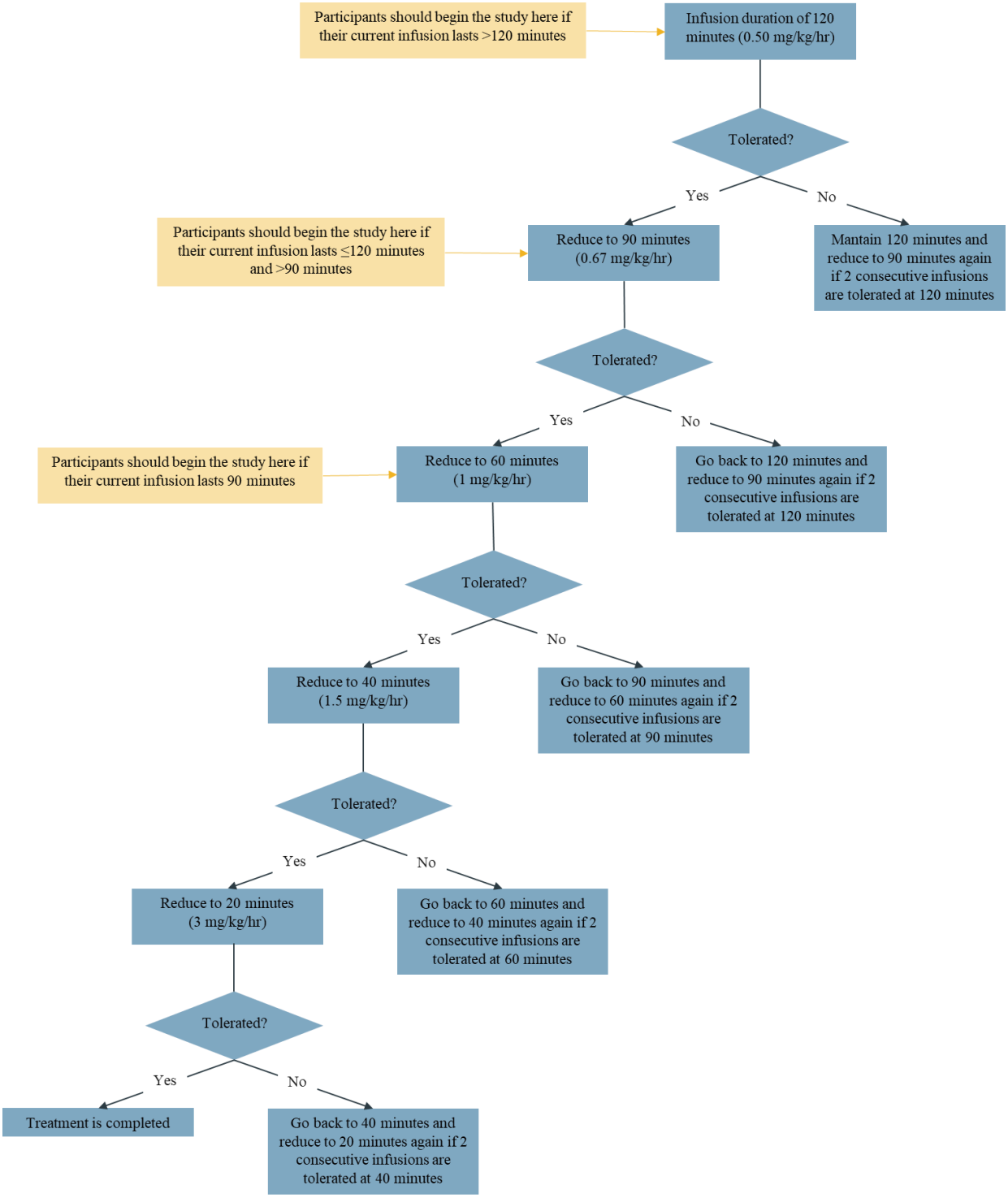
Abbreviations: AMP = auxiliary medicinal product; IMP= investigational medical product; NIMP = non-investigational medical product.

6.2 Infusion Duration Guideline

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

Please note that a participant is considered to tolerate the infusion duration when the infusion is completed within a duration not exceeding 120% of planned duration and no IAR is observed during the infusion.

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

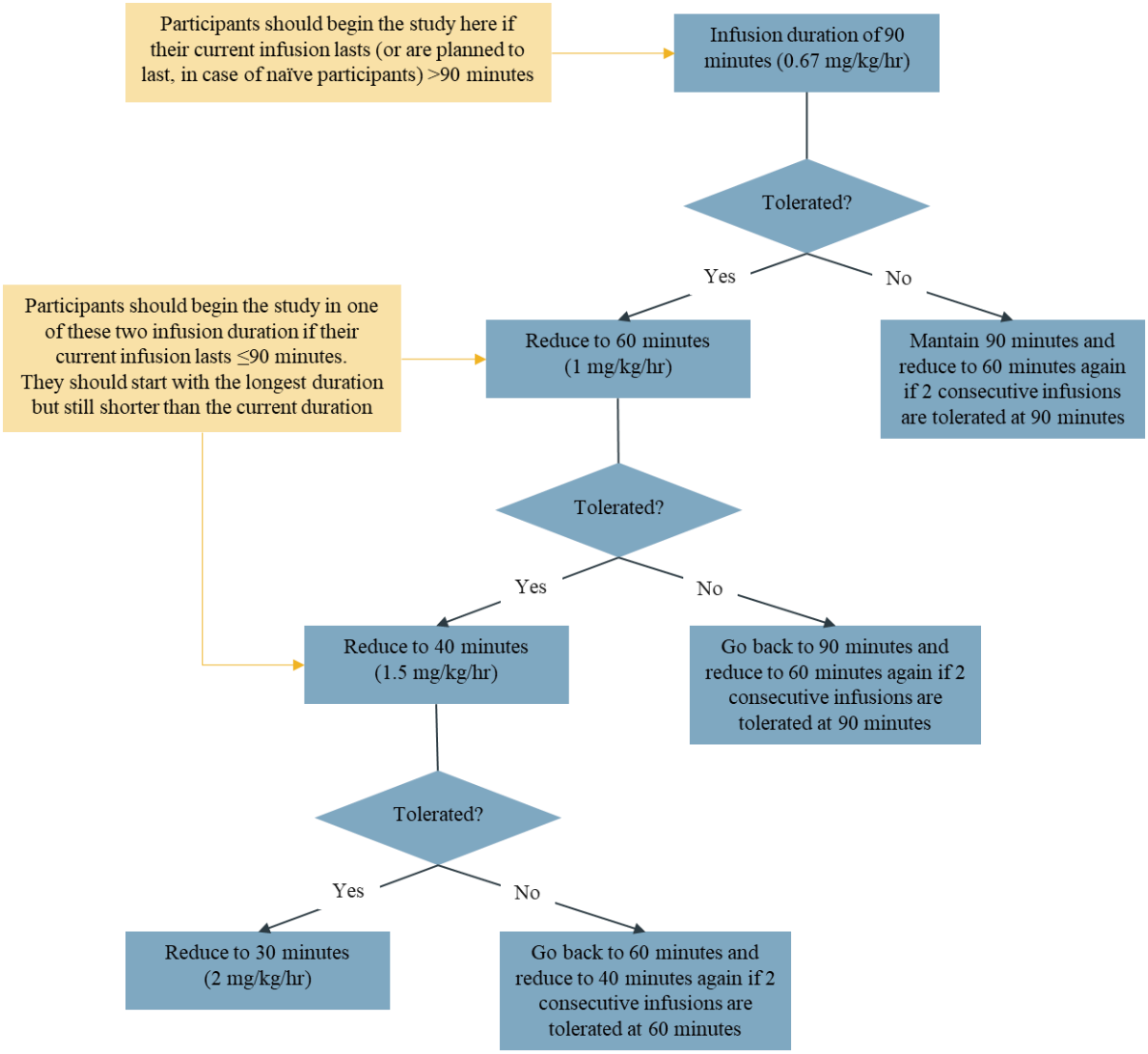


Abbreviations: IAR = infusion associated reaction.

Note: IARs occurring during a single infusion are counted as one IAR. Only when an IAR occurs in relation to a separate infusion will it 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 will it 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.

6.3 Preparation, Handling, Storage, and Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Guidance about reconstitution and dose preparation for Fabrazyme are provided in Appendix 2 (Section 10.2).

Only participants enrolled in the study may receive study intervention, and only authorized study site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study intervention using the Drug Accountability Form. These forms must be available for inspection at any time.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.4 Measures to Minimize Bias: Randomization and Blinding

This is a single arm and open label study. No randomization or blinding will be implemented. The study intervention kits dispensing will not be managed within Interactive Response Technology. To minimize bias, the participant number will be assigned sequentially in the electronic case report form (eCRF) as the participants are enrolled into the study.

6.5 Study Intervention Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRF.

Participants exhibiting poor compliance as assessed by visit attendance for their infusions should be counseled on the importance of good compliance to the study dosing regimen.

Non-compliance is defined as taking less than 80% of study intervention during any evaluation period (visit to visit).

Participants will be dosed at the study site and receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the quantity of study intervention administered to each participant must be maintained and reconciled with study intervention and compliance records. The date, time of

start and stop of each infusion, as well as the dose and total volume infused, will also be recorded.

6.6 Dose Modification

Dose modifications are not planned or allowed in this study. Any dose deviation must be recorded in the eCRF.

6.7 Continued Access to Study Intervention After the End of the Study

The Sponsor will not be responsible for study intervention provision after the end of the treatment phase and after the end of the study. Continuing treatment after the end of the Study Intervention Period will be at the discretion of Investigator or treating physician.

The Sponsor will not provide any additional care to participants after they leave the study because such care should not differ from what is normally expected for participants with FD.

6.8 Treatment of Overdose

Any dose of study intervention greater than the planned and approved dose will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (depending on study intervention half-life).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- For vaccines (if applicable) include brand name and manufacturer (plus lot number if available)

Administration of live or inactivated vaccines is allowed (eg, inactivated influenza vaccines or severe acute respiratory syndrome coronavirus 2 vaccines).

Participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) that may interfere with the study in the opinion of the Investigator and the Sponsor within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Non-investigational premedication with acetaminophen and an antihistaminic will be administered to avoid IARs prior to each infusion. Dexamethasone and montelukast may also be administered as premedication in participants who have experienced an IAR (refer to Section 6.1). All premedications must be recorded as concomitant medication.

6.9.1 Rescue Medicine

In case of IAR occurrence, 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. Both drugs are described in Section 6.1.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.11.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated 12 and 28 weeks after the start of the treatment (ie, Visit 8 [Week 12] and Visit 11, End-of-Study [Week 28], see the SoA in Section 1.3 for data to be collected).

If a participant who does not meet enrollment criteria is inadvertently enrolled, that participant must be discontinued from study intervention and the Sponsor, or Sponsor designee, must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor, or Sponsor designee, to allow the participant to continue in the study.

The participant will be permanently discontinued from the study intervention under the following circumstances:

- Participant's own request.
- Pregnancy.
- Any significant AE/SAE that in the opinion of the Investigator necessitates the participant's being withdrawn.
- When a second IAR occurs (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).
- Specific request from Sponsor.
- Any other information, if in the Investigator's opinion suggests that taking part in the study may not be in the participant's best interest.
- Any major medical finding (eg, abnormal liver function) that in the opinion of the Investigator necessitates the participant's being withdrawn.

Participants who discontinue study intervention will not be replaced, except in the cases where the participant was enrolled in error.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance, or administrative reasons. This is expected to be uncommon.

If participants no longer wish to take the study intervention, they will be encouraged to remain in the study to be evaluated 12 and 28 weeks after the start of the treatment.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study site study records.

Participants who voluntarily withdraw are termed dropouts. Dropouts and participants withdrawn due to protocol violations will not be replaced.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Study site personnel, or an independent third-party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented

and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed at Day 1 to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 55 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Collection of Demographic Characteristics

Demographic parameters including but not limited to age, gender, race/ethnicity, and duration of Fabrazyme treatment before entering the study will be collected at the Screening Visit (refer to SoA in Section 1.3).

Race and ethnicity are typically collected in clinical studies of Fabry disease. Although there is no evidence so far that race/ethnicity may influence the safety and tolerability of faster infusions of Fabrazyme, which are the outcomes investigated in this study, this possibility cannot be ruled out. Gathering data on ethnicity will be informative when interpreting the results from this study and will make it easier to compare the findings with those of other studies.

8.2 Body Weight Measurements

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.

8.3 Efficacy Assessments

Efficacy data will be collected for exploratory purposes, at the planned time points specified in the SoA (Section 1.3).

8.3.1 Plasma Lyso-GL3 Marker

Levels of Lyso-Gb3 will be assessed in the plasma by a central laboratory using standardized and validated methods in addition to applicable calibrated equipment.

Refer to the Laboratory Manual for details regarding collection, processing, storage, and shipment.

8.4 Safety Assessments

8.4.1 Vital Signs

Body temperature, heart rate, respiratory rate, and blood pressure will be assessed before and 1 hour after the completion of each infusion.

Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

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

8.4.2 Clinical Safety Laboratory Tests

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 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.

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.

8.5 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention/ study (see Section 7.0).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.5.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the last scheduled visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours of the Investigator's awareness of the event, as indicated in Section 10.3. The Investigator will submit any updated SAE or AESI data to the Sponsor or designee within 24 hours of their awareness of the updated information.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE, AESI and SAE and the procedures for completing and transmitting safety reports are provided in Section 10.3.

8.5.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs, AESIs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.5.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and adverse events of special interest (AESI) (as defined in Section 8.5.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.5.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the study documents and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.5.5 Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and until end of study.

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant pregnancy and should follow the procedures outlined in Section 10.3.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]) the Investigator will report according to the SAE reporting procedures described in Section 10.3.

The participant will be followed to determine the outcome of the pregnancy (eg, until delivery of baby). The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor or designee.

Any post study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.5.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.5.6 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the safety profile of the study treatment and require close monitoring and rapid communication by the Investigators to the Sponsor. For this study, the following events are considered AESIs:

- **Infusion associated reaction:**
    - In this study, IAR is defined as AEs listed below or any other AEs that the Investigator considers related to Fabrazyme infusion, occurring on same day as infusion and only after infusion has begun. 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.
        - Chills
        - Fever/body temperature increased (objective sign/measurement)
        - Feeling hot/cold (subjective symptom only)
        - Nausea
        - Vomiting
        - Hypertension (following age-appropriate ranges)
        - Acute hypotension (following age-appropriate ranges)
        - Flushing
        - New or worsening (if paresthesia at baseline) paresthesia during infusion or on same day after infusion completion
        - New or worsening (if fatigue at baseline) fatigue during infusion or on same day after infusion completion
        - New or worsening (if pain at baseline) pain during infusion or on same day after infusion completion
        - New or worsening (if dyspnea at baseline) dyspnea during infusion or on same day after infusion completion

- New or worsening (if abdominal pain at baseline) abdominal pain during infusion or on same day after infusion completion
- Headache
- Pruritis
- Chest discomfort
- Urticaria
- Dizziness/lightheadedness
- Decreased alertness/level of consciousness
- Tachycardia (using age-appropriate ranges)
- Hypoxia (oxygen saturation decreased from baseline) during infusion or on same day after infusion completion
- Throat tightness
- Acute facial edema
- Acute rhinitis or nasal congestion during infusion or on same day after infusion completion
- Acute bronchospasm/wheezing
- Tachypnea (using age-appropriate reference ranges) during infusion or on same day after infusion completion
- Palpitations (subjective)

- **Anaphylaxis:**

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled [13]:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following**:

    - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    - Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
    - Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens

2. Acute onset of hypotension[a] or bronchospasm[b] or laryngeal involvement[c] after exposure to a known or highly probable allergen[d] for that patient (minutes to several hours), even in the absence of typical skin involvement.

    a. Hypotension defined as a decrease in systolic blood pressure greater than 30% from that person's baseline, OR

i. Infants and children under 10 years: systolic blood pressure less than (70 mmHg + [2 x age in years])
ii. Adults and children over 10 years: systolic blood pressure less than 90 mmHg.

b. Excluding lower respiratory symptoms triggered by common inhalant allergens or food allergens perceived to cause "inhalational" reactions in the absence of ingestion.

c. Laryngeal symptoms include stridor, vocal changes, odynophagia.

d. An allergen is a substance (usually a protein) capable of triggering an immune response that can result in an allergic reaction. Most allergens act through an immunoglobulin E (IgE) mediated pathway, but some non-allergen triggers can act independent of IgE (for example, via direct activation of mast cells).

All AESIs will be recorded in the eCRF before the next infusion began. An AESI can be serious or non-serious and will be reported as detailed in Section 10.3.

8.6 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.7 Pharmacodynamics

Plasma lyso-GL3 will be evaluated as a pharmacodynamic biomarker in this study. As plasma lyso-GL3 is also being used in this study as a surrogate endpoint of efficacy that is reasonably likely to predict clinical benefit, details are reported in Section 8.3.1.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Plasma lyso-GL3 will be evaluated as a pharmacodynamic biomarker in this study. As plasma lyso-GL3 is also being used in this study as a surrogate endpoint of efficacy that is reasonably likely to predict clinical benefit, details are reported in Section 8.3.1.

8.10 Immunogenicity Assessments

Antibodies to Fabrazyme will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to Fabrazyme and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to Fabrazyme and/or further characterize the immunogenicity of Fabrazyme.

The detection and characterization of antibodies to Fabrazyme will be performed using a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study interventions. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to Fabrazyme.

8.11 Health Economics

Health economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the endpoints including primary, secondary, and exploratory endpoints.

9.1 Statistical Hypotheses

There are no statistical hypotheses.

9.1.1 Multiplicity Adjustment

Multiplicity adjustment is not applicable.

9.2 Analysis Sets

- Enrolled Analysis Set: All participants who sign the ICF.
- Intent-to-Treat Analysis Set: All participants who were enrolled and allocated to study treatment.
- Safety Analysis Set: All participants who receive any amount of study treatment (Fabrazyme). The Safety Analysis Set will be used for all safety analyses.

9.3 Statistical Analyses

9.3.1 General Considerations

All analyses, summaries, and listings will be performed using SAS® software (version 9.4 or higher) unless otherwise noted. All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the SAP.

The analysis of complete data for the study will be performed when all the participants have either completed the study or discontinued early from the study, all data from the study are in the database, and the database is locked.

In general, descriptive statistics of efficacy and safety parameters (result and change from baseline) by scheduled visits will be provided on observed cases, ie, inclusion of only participants having non-missing assessments at a specific visit. 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.

The observation period of safety data will be as follows:

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

- Treatment Emergent (TE) period: The TE period is defined as the time from the first dose of study intervention to the last dose of study intervention + follow-up period.

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

- 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.
- 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.

Baseline definition: Unless otherwise specified, baseline is defined as the last observed value of the parameter of interest prior to the first intake of Fabrazyme in the study period (this includes unscheduled visits).

9.3.2 Primary Endpoint Analysis

Table 5 Primary Endpoint Analysis

Endpoint	Statistical Analysis Methods
% Reduction of infusion duration from prestudy average of recent 3 infusions in participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during recent 3 infusions.	The primary endpoint will be analyzed using descriptive statistic, focusing on median and quantiles of % reduction of infusion duration from prestudy average of recent 3 infusions (pooled all cohorts).
Shortest infusion duration tolerated by each participant in participants with confirmed diagnosis of FD, age 2 to 65 years, Fabrazyme-experienced, treated for at least 3 months without IARs during recent 3 infusions.	The primary endpoint will be analyzed using descriptive statistic, focusing on median and quantiles of the shortest infusion duration tolerated by each participant (pooled all cohorts).

Abbreviations: FD = Fabry disease; IAR = infusion associated reaction.

9.3.3 Secondary Endpoints Analysis

Table 6 Secondary Endpoint Analysis

Endpoint	Statistical Analysis Methods
Participants achieving 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.	The secondary endpoints will be analyzed using descriptive statistics (cohort 1 to 4).
Participants achieving infusion duration shorter than 90 minutes without experiencing a second IAR.	
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 IAR.	
Participants achieving infusion duration shorter than 90 minutes without experiencing any IAR.	
Participants achieving each infusion duration without experiencing any IAR.	
Participants achieving each infusion duration without experiencing a second IAR.	

Abbreviations: IAR = infusion associated reaction.

9.3.4 Exploratory Endpoints Analysis

Table 7 Exploratory Endpoint Analysis

Endpoint	Statistical Analysis Methods
Changes of plasma lyso-GL3 from baseline to 6 months follow-up	The exploratory endpoints will be analyzed using descriptive statistics (cohort 1 to 4).
Changes of the titer of ADA to Fabrazyme from baseline to 6 months follow-up	

Abbreviations: ADA = anti-drug antibody; lyso-GL3 = globotriaosylsphingosine.

9.3.5 Safety Analysis

Safety endpoints include treatment-emergent adverse events, AESI (IARs and anaphylaxis), and vital signs.

For applicable safety variables, both the actual value and the change from the baseline value will be summarized at each visit using the n, mean, SD, median, minimum value, and maximum value. AEs and IARs will be summarized by frequency counts and percentage. Duration of exposure to study intervention and number of injections will be summarized descriptively.

All safety analyses will be performed on the Safety Analysis Set.

9.4 Interim Analysis

No formal interim analysis will be conducted.

9.5 Sample Size Determination

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

10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs, or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the Investigator has not signed the protocol.

10.1.2 Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study site.

If the Investigator/institution retains the services of any individual or party to perform study-related duties and functions, the Investigator/institution should ensure this individual or party

is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3 Financial Disclosure

Investigators and sub investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4 Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the participants in this study. The terms of the insurance will be kept in the study files.

10.1.5 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants (or their legally authorized representatives) and the participant's legal guardian (for children under 16 years old) will be required to provide assent, if applicable, and sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study. Participants who reach legal age of majority after study initiation must reconfirm their participation in the study by giving signed informed consent.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

10.1.6 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.7 Committees Structure

No study committee is involved in this study.

10.1.8 Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to any relevant database a summary of the results of the clinical study within 1 year from the end of the global clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of CRFs will be provided in CRF Completion instruction.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10 Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in ICH GCP Integrated Addendum E6 (R2) Section 1.51 and Section 4.9.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first study site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For study site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.12 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of

multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Reconstitution, Dose Preparation and Storage of Reconstituted Solution of Fabrazyme

The instructions presented below were extracted from Fabrazyme US label [6], when applicable. Sterile Water for Injection, USP, and 0.9% Sodium Chloride Injection, USP, for the reconstitution and dilution are provided by the study site.

Vials are for single use only. Discard any unused product.

Avoid shaking or agitating this product. Do not use filter needles during the preparation of the infusion.

10.2.1 Reconstitution and Dilution (Using Aseptic Technique)

1. Allow Fabrazyme vials and diluent to reach room temperature prior to reconstitution (approximately 30 minutes). The number of 35 mg vials needed is based on the participant's body weight (kg) and the recommended dose of 1 mg/kg.

   Select a number of 35 mg vials so that the total number of mg is equal to or greater than the participant's number of kg of body weight.

2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).

3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.

4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to a total volume based on participant weight specified in Table 8 below. Prior to adding the volume of reconstituted Fabrazyme required for the participant dose, remove an equal volume of 0.9% Sodium Chloride Injection, USP from the infusion bag.

Table 8 Total Infusion Volume Based on Participant Weight

Participant Weight (kg)	Maximum Total Volume (mL)
<60	50
≥60	100

Participant dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabrazyme required for participant dose.

Example: Participant dose = 80 mg. 80 mg ÷ 5 mg/mL = 16 mL of Fabrazyme.

Slowly withdraw the reconstituted solution from each vial up to the total volume required for the participant dose. Inject the reconstituted Fabrazyme solution directly into the Sodium Chloride solution. Do not inject in the airspace within the infusion bag. Discard any vial with unused reconstituted solution.

5. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and agitation.
6. Do not infuse Fabrazyme in the same intravenous line with other products.
7. Administer Fabrazyme using an in-line low protein binding 0.2 μm filter.

10.2.2 Storage of Reconstituted Solution

Use reconstituted and diluted solutions of Fabrazyme immediately. If immediate use is not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with that product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention/treatment, whether considered related to the study intervention/treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (eg, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death • For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate CRF.
b. Is life-threatening • The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • The term congenital anomaly/birth defect means there is suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of an AE is an estimate of the relative severity of the event made by the Investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to study intervention will be considered "related." Events assessed as having no reasonable possibility of being related to study intervention will be considered "unrelated."
- The Investigator will also consult the product prescribing information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the Investigator's awareness of the information.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor or Designee via an Electronic Data Collection System
• The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection system. The study site will enter the event into the electronic data collection system within 24 hours of the Investigator's awareness of the event. • If the electronic system is unavailable, then the study site will use the paper SAE report form (see next section) to report the event and will enter the event into the electronic data collection system as soon as the system becomes available. • After the study is completed at a given study site, the electronic data collection system will be taken offline to prevent the entry of new data or changes to existing data. • If a study site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection system has been taken offline, then the study site can report this information on a paper SAE report form (see next section) to the Sponsor or designee. • Contacts for SAE reporting can be found in eCRF Completion Guidelines.

SAE Reporting to the Sponsor or Designee via Paper SAE Report Form
• The backup mechanism for reporting an SAE to the Sponsor or designee will be the paper SAE report form. The study site will submit the SAE report form, via email, within 24 hours of the Investigator's awareness of the event. Facsimile transmission may be utilized as an alternative mode of submission, if necessary. • Notification of SAE information via telephone does not replace the need for the Investigator to complete, sign and submit the paper SAE report form to the Sponsor or designee within 24 hours of the Investigator's awareness of the event. • Email for SAE reporting via paper report form: phv_iab16602_so@iqvia.com.

10.4 Appendix 4: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a) Documented hysterectomy.
    b) Documented bilateral salpingectomy.
    c) Documented bilateral oophorectomy.

NOTE: Documentation can come from the study site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female:
    a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Pregnancy testing:

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within the screening period before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

10.4.2 Collection of Pregnancy Information

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the

appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the Investigator will report according to the SAE reporting procedures described in Section 10.3.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor or designee as described in Section 10.3. While the Investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Abbreviations and Definitions

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
CFR	Code of Federal Regulations
CI	Confidence interval
CRF	Case report form
eCRF	Electronic case report form
ECG	Electrocardiogram
ERT	Enzyme replacement therapy
FDA	Food and Drug Administration
FD	Fabry disease
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GL3	Globotriaosylceramide
HRT	Hormone replacement therapy
IAR	Infusion associated reaction
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IRB	Institutional Review Board
Lyso-GL3	Globotriaosylsphingosine
Q2W	Every 2 weeks
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SoA	Schedule of activities
TE	Treatment emergent
USP	United States Pharmacopeia
WOCBP	Women of childbearing potential

Abbreviation	Definition
α-GAL	α-galactosidase A

10.6 Appendix 6: Protocol Amendment History

Amendment 1.0 (20-May-2024)

Overall Rationale for the Amendment:

This Amendment 1.0 (Protocol version 2.0) was developed to adjust the study design. Key adjustments include**:**

- Removal of sequential enrollment, based on the observation that infusion durations shortenings for the initial 4 participants in cohorts 1 and 2 were well tolerated, and the risk for cohorts 3 and 4 is deemed low.
- Cohort 5, which previously consisted of ERT-naïve participants and posed the highest risk of not tolerating an infusion duration shorter than 120 minutes, has been excluded from the study.
- Removal of new targets for infusion duration in line with removal of sequential enrollment.
- Removal of formal interim analysis, of which main purpose was to calculate new targets for infusion duration, in line with removal of sequential enrollment.
- Addition of 3 additional options for antihistamine as premedication.
- Addition of anaphylaxis as an adverse event of special interest.
- Clarification that participants are not required to remain at the site after infusion unless medically necessary.
- Addition of notes on body weight measurements.

Additionally, although not described in the below table, the address of Sanofi office headquarters was updated. Minor editorial changes were also made, without impacting the content previously presented.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3.0 Objectives, Endpoints and Estimands	The second primary estimands involving the enzyme replacement therapy (ERT)-naïve population was deleted. The population attribute of all secondary estimands were adjusted to remove the mention on ERT-naïve population. The intercurrent event attribute for all endpoints was adjusted to add "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."	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2-4 parallel. Changes in intercurrent event attribute was made to explicitly add full clarity on management of endpoints in case pre-medications are not given as described within the protocol.
1.1 Synopsis 4.1 Overall Design	The description and flow of the staged enrollment was removed (together with Figure 2) and the following sentence was added "All 4 cohorts of this study will be enrolled simultaneously."	Initial data shows that infusion duration shortening is very well tolerated and participants can reach 20-minute duration without experiencing a single infusion associated reaction (IAR). Considering this, and that cohort 5 (treatment-naïve patients, which has the highest risk of not tolerating shorter infusions) was removed from the study, the risk for the remaining cohorts (2, 3, and 4) not tolerating these shorter infusions is relatively low. Therefore, the study will proceed to enroll all cohorts simultaneously.
1.1 Synopsis 4.1 Overall Design	The number of participants was reduced from 18 to 14, and cohort 5 description was deleted.	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2 to 4 parallel.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design	The below paragraph was edited (deleted text in strikethrough, additions in bold): "The infusion duration will shorten, and the infusion rate will rise with each successfully tolerated infusion (ie, an infusion **completed within a duration not exceeding 120% of planned duration**, without IAR), until reaches 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**)** ~~or, in later cohorts, the new target infusion duration determined based on the results in earlier cohorts~~."	As initial data shows that infusion duration shortening is very well tolerated and participants can reach 20-minute duration without experiencing a single IAR, it is reasonable to assume that the previously defined calculations for new targets for infusion in cohorts 3 and 4 may not be necessary. Hence, the target infusion durations in this study are kept 20 minutes for cohorts 1 to 3 and 30 minutes for cohort 4, without further adjustment. A threshold was added to determine if an infusion is tolerated in the cases in which the actual infusion duration is greater than the planned duration.
1.1 Synopsis	The below paragraph was edited (deleted text in strikethrough, additions in bold): "Non-investigational prophylactic premedication with acetaminophen (160 mg to 650 mg, depending on age) and **one antihistamine (**diphenhydramine 25 mg or 12.5 mg**, or loratadine 10 mg or 5 mg, or cetirizine 5 mg or 2.5 mg, or fexofenadine 180 mg or 30 mg - doses will depend** ~~depending~~ on age) will be administered to all participants to avoid IARs, 30 minutes prior to each infusion."	Additional antihistaminic options have been included in the protocol as premedication. This allows the Investigators to select from the four available H1 blockers.
1.3 Schedule of Activities	Added a cross reference to the new Section 8.2 on the notes for line "Vital signs and weight".	To allow sites to easily identify more details on weight measurements.
2.1 Study Rationale	The term "unpublished" was removed when referring to data from Japanese post-marketing surveillance study, and the appropriate reference from published literature was added.	Adequate literature reference added to support the data described.

Section # and Name	Description of Change	Brief Rationale
2.3.1 Risk Assessment	The following information was added in the mitigation strategy for AEs: "Anaphylaxis is an AESI in this study. The incidence and severity of anaphylaxis will be closely monitored and evaluated throughout the study". Also, the mention to diphenhydramine was changed to "one antihistaminic" in the mitigation strategy text for IARs.	Anaphylaxis was added as an AESI per FDA's comment, not based on a new safety signal. Additional antihistaminic options have been included in the protocol as premedication. This allows the Investigators to select from the four available H1 blockers.
4.1 Overall Design 6.1 Study Interventions Administered	The following sentence was added: "The participants are not required to stay at the site after completion of the infusion, unless the Investigator considers it medically necessary."	To clarify that participants are not required to remain at the site following the completion of the infusion, unless the Investigator deems it medically necessary.
4.2 Scientific Rationale for Study Design	The below paragraphs were edited (deleted text in strikethrough, additions in bold): The population chosen for the study ~~is wide,~~ comprise~~sing~~ the diversity of patients with Fabry Disease (FD) **already treated with Fabrazyme**: women, men with classic and non-classic disease, **and** children. ~~patients already treated with Fabrazyme, and ERT-naïve patients~~. ~~The enrollment and treatment will have a staged enrollment. The study will start with the demographic segment with the lowest risk of experiencing IARs (ie, female participants and non-classic male participants) and the portion with highest risk (ie, ERT naïve participants) will be the last cohort to be enrolled~~. Standard ~~statistical,~~ clinical, and laboratory procedures will be utilized in this study.	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2 to 4 parallel. Also, initial data shows that infusion duration shortening is very well tolerated and participants can reach 20-minute duration without experiencing a single IAR. Considering this, and that cohort 5 (which had the highest risk of not tolerating shorter infusions) was removed from the study, the risk for the remaining cohorts (2, 3, and 4) not tolerating these shorter infusions is relatively low. Therefore, the study will proceed to enroll all cohorts simultaneously.

Section # and Name	Description of Change	Brief Rationale
4.5 End of Treatment Definition	The below paragraphs were edited (deleted text in strikethrough, additions in bold): The end of treatment is defined when the participant successfully reaches the shortest infusion duration planned for the cohort which he/she belongs to **or when the participant experiences a second IAR**. At that point, the participant will not receive any further infusion as part of the study, regardless of whether the Study Intervention Period reaches 16 weeks or not. ~~The Study Intervention Period will be completed in the absence of IAR at Week 10, or at the latest at Week 16~~ (Figure 2 and Figure 3).	Correction on end of treatment definition, as in the absence of any IAR during the treatment period, if the current infusion duration for the participant ≥30 kg is 120 minutes (the shortest possible initial duration), then he/she would complete the treatment at Week 8; if the current infusion duration for the participant <30 kg is 90 minutes (the shortest possible initial duration), then he/she would complete the treatment at Week 6.

Section # and Name	Description of Change	Brief Rationale
4.6.2 Criteria for Stopping the Study	The paragraphs were edited (deleted text in strikethrough, additions in bold): "**While no specific criteria have been established for terminating the study prematurely, it remains within the Sponsor's discretion to stop the study, at any time, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will promptly notify the Investigator.** ~~As detailed in Section 4.1, the duration of the Fabrazyme infusions given during the study will gradually decrease and the infusion rate will gradually increase, up to a minimum duration .that may be calculated during the study (ie, new targets for infusion duration).~~ ~~The study will be stopped without enrolling remaining cohorts if any of the following scenarios involving the new target infusion duration occur:~~ ~~• In case the new target 1 for infusion duration is not shorter than 90 minutes.~~ ~~• In case the new target 2 for infusion duration is not shorter than 90 minutes.~~ ~~• In case the new target 3 for infusion duration is not shorter than 90 minutes.~~"	As initial data shows that infusion duration shortening is very well tolerated and participants can reach 20-minute duration without experiencing a single IAR, it is reasonable to assume that the previously defined calculations for new targets for infusion in cohorts 3 and 4 may no longer be necessary. Consequently, there is no specific criteria for stopping the study related to these new targets.
5.1 Inclusion Criteria	Criterion 1 e. "Cohort 5: ERT-naïve participants" was deleted.	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2 to 4 parallel.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Criterion 3 was adjusted (additions in bold): "3. Contraindication to Fabrazyme or any of the premedications or rescue medications (diphenhydramine, **loratadine, cetirizine, fexofenadine,** acetaminophen, montelukast, dexamethasone).	Adjustment to reflect the new antihistaminic options included in the protocol as premedication. This allows the Investigators to select from the four available H1 blockers.
6.1 Study Interventions Administered	The paragraphs were edited (deleted text in strikethrough, additions in bold): "All participants will receive acetaminophen and ~~diphenhydramine~~ **one antihistamine** as non-investigational prophylactic premedication, 30 minutes prior to each infusion. In case of IAR occurrence, 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. ~~All~~ **The** study interventions are presented in Table 3 **and Table 4 (for the possible antihistamines allowed as premedication)**." Table 4 containing details of possible antihistamines administered as premedication (including diphenhydramine, loratadine, cetirizine and fexofenadine) was added.	Additional antihistaminic options have been included in the protocol as premedication. This allows the Investigators to select from the four available H1 blockers.

Section # and Name	Description of Change	Brief Rationale
6.2 Infusion Duration Guideline	Previous Figure 4 (current Figure 3) Guideline for Decreasing Infusion Duration for Participants <30 kg was updated, removing the mention of naïve participants. The below sentence was adjusted (deleted text in strikethrough, additions in bold): "Please note that a participant **is considered to** tolerate~~s~~ the infusion duration when **the infusion is completed within a duration not exceeding 120% of planned duration and** no IAR is observed during the infusion.	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2 to 4 parallel. A threshold was added to determine if an infusion is tolerated in the cases in which the actual infusion duration is greater than the planned duration.
6.9 Concomitant Therapy	Changed the word "diphenhydramine" to "an antihistaminic" in the paragraph about non-investigational premedication. Additionally, the below sentence was edited (additions in bold): "Dexamethasone and montelukast may also be administered as premedication **in participants who have experienced an IAR** (refer to Section 6.1)."	Additional antihistaminic options have been included in the protocol as premedication. This allows the Investigators to select from the four available H1 blockers. Clarification – no change was made in the conduct previously established.
6.9.1 Rescue Medicine	The below sentence was edited (additions in bold): In case of IAR occurrence, 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**.	Clarification – no change was made in the conduct previously established.
8.2 Body Weight Measurements	Addition of a new section, explaining that the amount of Fabrazyme to be administered is dependent on the participant's weight, and 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.	Section added to describe in more details weight measurements and permit the use of a previous measurement to prepare the current infusion for a participant.

Section # and Name	Description of Change	Brief Rationale
8.5.6 Adverse Events of Special Interest	Anaphylaxis was added as an adverse event of special interest, with a definition according to the World Allergy Organization Anaphylaxis Guidance 2020.	Anaphylaxis was added as an AESI per FDA's comment, not based on a new safety signal.
9.3.1 General Considerations	The following paragraph was deleted: "Two interim analyses will be conducted: the first is when cohorts 1 and 2 completes the study and the second is when cohorts 3 and 4 completes the study." Additionally, the following change was made in the text about categorical data (deleted text in strikethrough, additions in bold): "The change from baseline **in distribution** ~~value~~ for the categorical endpoint will be presented with a shift table; number and percentage of participants will be provided."	As all cohorts will now enroll simultaneously, there is no longer a requirement for interim analysis. Correction.
9.3.2 Primary Endpoint Analysis	The endpoint "% Reduction of infusion duration from initial 120 minutes in participants with confirmed diagnosis of FD, age 2 to 65 years, ERT-naïve" and the correspondent statistical analysis method was deleted from Table 4 Primary Endpoint Analysis. All mentions to ERT-naïve or Cohort 5 were removed from the other primary endpoints.	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2 to 4 parallel.
9.3.3 Secondary Endpoints Analysis 9.3.4 Exploratory Endpoints Analysis	All mentions to Cohort 5 were removed from the statistical analysis methods.	Cohort 5, previously composed of ERT-naïve participants, was removed from the study as a way to mitigate with participant enrollment delay. ERT-naïve patients are considered to have the highest risk of not tolerating shorter infusions. This cohort is removed to minimize increase of risk related to making enrollment of cohorts 2 to 4 parallel.
9.3.5 Safety Analysis	Anaphylaxis was added as an adverse event of special interest (AESI).	Anaphylaxis was added as an AESI per FDA's comment, not based on a new safety signal.

Section # and Name	Description of Change	Brief Rationale
9.4 Interim Analysis	The paragraphs were edited (deleted text in strikethrough, additions in bold): "~~Two interim analyses will be conducted. First interim analysis will take place after cohort 1 and 2 complete the Study Intervention Period. Second interim analysis will take place after cohort 3 and 4 complete the Study Intervention Period.~~ ~~The detailed plan of interim analyses will be specified in the SAP.~~ ~~The first interim analysis outcome will determine the enrollment and infusion rate of cohorts 3 and 4. The second interim analysis will determine the enrollment of cohort 5~~. **No formal interim analysis will be conducted**."	As all cohorts will now enroll simultaneously, there is no longer a requirement for interim analysis of which main purpose was to calculate new targets for infusion duration.

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