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AMENDED CLINICAL TRIAL PROTOCOL NO. 08

COMPOUND: Fabrazyme®/agalsidase beta/GZ419828

A Multicenter, Multinational Study of the Effects of Fabrazyme® (agalsidase beta) Treatment on Lactation and Infants

STUDY NUMBER: AGAL02603/MSC12868

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1 SYNOPSIS

NAME OF COMPANY Sanofi Genzyme 500 Kendall Street Cambridge, MA 02142 **NAME OF FINISHED PRODUCT** Fabrazyme **NAME OF ACTIVE INGREDIENT** agalsidase beta	**SUMMARY TABLE** Referring to Part…… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

TITLE:
A Multicenter, Multinational Study of the Effects of Fabrazyme® (agalsidase beta) Treatment on Lactation and Infants

PROTOCOL NO.: AGAL02603 / MSC12868

INVESTIGATOR/STUDY CENTERS:
Investigators at approximately 10 multinational study centers will participate.

OBJECTIVES:

The objectives of this study are:

1. To determine whether αGAL (alpha-galactosidase A) activity is present in the breast milk of mothers with Fabry disease who are being treated with Fabrazyme during lactation.
2. To measure breast milk production and composition (volume, protein and fat content) in women with Fabry disease who receive Fabrazyme during lactation.
3. To determine whether Fabrazyme affects the growth, development, and immunologic response of infants born to mothers with Fabry disease who receive Fabrazyme during lactation.

METHODOLOGY:
This is a multicenter, multinational study of the potential effects of Fabrazyme on lactation and on the growth, development, and immunologic response of infants born to mothers with Fabry disease who are treated with Fabrazyme during lactation. Pregnant women who received Fabrazyme at any point during their pregnancy can be enrolled in the study. If woman is not receiving treatment with Fabrazyme at the Baseline visit, mother should start treatment with Fabrazyme between the delivery and Month 1 visit.

Mother: Breast milk will be collected at Months 1, 3, and 6 immediately prior to Fabrazyme infusion, just after the end of the infusion, and 2 hours after the end of the infusion. Breast milk samples will be analyzed for volume, presence of αGAL activity, total fat content, and total protein concentration. Blood samples from the mother will be drawn for pharmacokinetic (PK) analysis prior to each breast milk collection. Lactation status, adverse events (AEs), and concomitant medications will be collected at every visit. If infant genotyping is performed on the umbilical blood cord sample at Baseline visit, a buccal cell sample will be obtained from the mother to rule out contamination of the cord blood sample with maternal DNA (deoxyribonucleic acid) (maternal cell contamination (MCC) analysis). The following data items will be collected through the Registry: medical history (including Fabrazyme status during pregnancy), pregnancy outcome, serum immunoglobulin G (IgG) antibodies, and genotyping.

Infant: If the parent(s)/legal guardian(s) consents to infant participation, the infant's growth and development will be assessed at Months 1, 2, 3, and 6, then at 6-month intervals through Month 24. The infant may also be tested for the formation or continued presence of IgG (immunoglobulin G) and IgM (immunoglobulin M) antibodies to recombinant human α galactosidase A (r-hαGAL) at Baseline, Months 2, 6, and 12 and for genotype at Baseline.

NUMBER OF SUBJECTS:
Mothers: Approximately 10 mothers and up to 10 infants will be enrolled in this study.

NAME OF COMPANY Sanofi Genzyme 500 Kendall Street Cambridge, MA 02142 **NAME OF FINISHED PRODUCT** Fabrazyme **NAME OF ACTIVE INGREDIENT** agalsidase beta	**SUMMARY TABLE** Referring to Part…… of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

DIAGNOSIS/INCLUSION-EXCLUSION CRITERIA:

Inclusion Criteria - Mothers must meet the following criteria to be enrolled in this study:

I 01. provide signed written informed consent to participate in this study,

I 02. be enrolled in the Fabry Registry and receiving Fabrazyme while lactating,

I 03. agree to adhere to the Fabry Registry recommended schedule of assessments for medical history, pregnancy outcome, genotyping, and antibody testing, and

I 04. agree to adhere to the schedule of evaluations for this study.

Inclusion Criteria - Infants must meet the following criteria to be enrolled in this study:

I 05. have the signed written informed consent of the parent(s)/legal guardian(s) to participate in this study,

I 06. be born to a mother who is receiving Fabrazyme during lactation,

I 07. be receiving breast milk from the mother, and

I 08. have the agreement of the parent(s)/legal guardian(s) to adhere to the schedule of evaluations for this study.

Exclusion Criteria

The mother and infant will be excluded from this study if the mother has received an investigational drug within 30 days prior to study enrollment.

DOSE/ROUTE/REGIMEN:

Mothers receive Fabrazyme treatment (commercially available) at their prescribed dose and regimen as determined by their treating physician.

REFERENCE TREATMENT: No reference treatment will be used in this study.

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CRITERIA FOR EVALUATION:

Mother

- Efficacy: Efficacy will not be measured in this study.
- Pharmacokinetics: Blood and breast milk samples will be taken from the mother at Months 1, 3, and 6 for measurement of αGAL concentrations (if mother is lactating at the time of the evaluation and is receiving Fabrazyme therapy). Blood samples will be collected prior to each breast milk collection as follows: sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection; sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection. Breast milk samples will be collected after each plasma collection for PK testing as follows: sample 1: immediately prior to Fabrazyme infusion and after plasma collection; sample 2: immediately after Fabrazyme infusion and after plasma collection; and sample 3: 2 hours after Fabrazyme infusion and after plasma collection. The volume of breast milk expressed from each timepoint (immediately prior to infusion, from infusion start until end of infusion, and from end of infusion until 2 hours post-infusion) will be recorded and summarized.
- Breast Milk: Samples of expressed breast milk will be collected by pump at Months 1, 3, and 6 (if mother is lactating at the time of the evaluation and continues to receive Fabrazyme therapy) for PK assessment as above. Additionally, the volume, fat content, and protein content of breast milk samples will be determined.
- Safety: The IgG antibody titers and incidence of adverse events (AEs) occurring in mothers enrolled in this study will be summarized.

Infant

- Efficacy: Efficacy will not be measured in this study.
- Immunoglobulins: At birth, a sample of umbilical cord blood will be collected to determine the infant's Baseline anti- r-hαGAL IgM and IgG titers. Testing for presence of IgG and IgM antibodies will also occur at Month 2, 6, and 12.
- Development: The infant's growth and development will be monitored from birth to Month 24 through physical exams and the Denver II Developmental Screening Test.
- Safety: The incidence of adverse events occurring in infants enrolled in this study will be summarized.

Genotype testing: will be conducted for all participating infants on umbilical cord blood to determine diagnosis of Fabry disease. In cases when umbilical blood cord sample is not collected at the Baseline visit, genotyping of the infant enrolled for full participation could be performed on the additional blood sample collected at visit month 12. If genotyping of the infant is performed as a part of standard care prior to visit month 12, this result will be recorded by Investigator in the CRF (Case Report Form).

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STATISTICAL AND ANALYTICAL PLANS:

Statistical Methods:

Data collected in this study will be analyzed using descriptive statistics and reported using summary tables, graphs, figures, and/or patient data listings. No hypothesis testing will be performed. Details of the statistical analysis will be specified in the Statistical Analysis Plan.

Study Variables

Mother: The following study variables from the mothers will be summarized:

- Plasma αGAL activity
- Milk αGAL to plasma αGAL ratio;
- The levels of αGAL activity, volume, total fat and protein content in breast milk samples;
- Lactation status;
- Frequency of AEs, coded using the Medical Dictionary for Regulatory Activities (MedDRA);
- Concomitant medications received.

Each lactating woman will serve as her own control, with pre-infusion and post-infusion breast milk samples. The following data will be collected through the Registry and summarized:

- Medical history (including Fabrazyme status during pregnancy);
- Genotyping;
- Pregnancy outcomes;
- IgG antibody.

Infant: The following study variables from the infants will be summarized:

- Medical history;
- Physical exam;
- Gender;
- Apgar scores at 1 minute and 5 minutes after birth;
- Denver II Developmental Screening Test;
- IgM antibody titer to r-hαGAL;
- IgG antibody titer to r-hαGAL;
- Genotype;
- Frequency of AEs, coded using MedDRA;
- Concomitant medications received.

Sample Size: No formal statistical sample size calculations were performed for this study. The sample size of approximately 10 mothers and up to 10 infants is based upon 1) the availability of mothers to study lactation in this rare disease and 2) the availability of infants whose parents or legal guardians consent to their participation in this study.

Interim Analysis: After 5 mothers have contributed breast milk samples to this study, an interim analysis of αGAL activity in the breast milk will be performed. [redacted]

In addition, status of this study will be summarized annually as part of the Fabry Registry Program Annual Report.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

AE:	adverse event
AUC:	area under the concentration-time curve
CHO:	Chinese Hamster Ovary
C_{max}:	maximum concentration
CRF:	case report form
DNA:	deoxyribonucleic acid
GCP:	Good Clinical Practice
GL-3:	globotriasylceramide
HEENT:	head, ears, eyes, nose, and throat
IAR:	infusion-associated reactions
ICH:	International Conference on Harmonization
IEC:	independent ethics committee
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IRB:	institutional review board
MCC:	Maternal Cell Contamination
MedDRA:	Medical Dictionary for Regulatory Activities
PK:	pharmacokinetics
q2w:	every two weeks
r-hαGAL:	recombinant human alpha galactosidase A
SAE:	serious adverse event
SOM:	Study Operations Manual
SOP:	Standard Operating Procedure
US:	United States
αGAL:	alpha-galactosidase A

4 INTRODUCTION AND RATIONALE

α-Galactosidase A (αGAL) is a lysosomal hydrolase enzyme responsible for the metabolism of globotriaosylceramide (GL-3), the enzyme's major glycosphingolipid substrate. In Fabry disease, an inherited deficiency of αGAL leads to widespread deposition of GL-3, and to a lesser extent other α-galactoside-containing glycolipids, in the heart(1), kidney(2), liver(3), skin(4), and intestines.(5)

The major clinical signs and symptoms of Fabry disease include skin lesions, benign corneal and lenticular opacities, excruciating acral pain, paresthesias, autonomic dysfunction, cardiac disease, and renal failure.(6) Progressive glycolipid deposition in the microvasculature lead to failure of target organs resulting in death in the third to fifth decades of life prior to the advent of kidney dialysis and renal transplantation. Because the X-chromosome carries the αGAL gene, most affected patients are hemizygous males, although some heterozygous females can also be affected due to lyonization (random inactivation of 1 X-chromosome).(7)

Fabrazyme® has been approved in more than 40 countries, including the European Union, Australia, Canada, Japan, and the United States (US). Genzyme has manufactured a recombinant form of human α-galactosidase A (r-hαGAL; agalsidase beta) to provide replacement enzyme to patients with Fabry disease.

More detailed information regarding the preclinical and clinical safety, including a complete listing of adverse events (AEs) and serious adverse events (SAEs), as well as efficacy of Fabrazyme is provided in the Investigator Brochure and/or product labeling.

4.1 SUMMARY OF BENEFITS

Immediate benefits for infants enrolled in the study include the possible early diagnosis of Fabry disease, awareness of which can lead to early treatment of the disease. Information collected regarding the potential effects of Fabrazyme on growth and development of infants and lactation of mothers is expected to be useful in planning the use of Fabrazyme therapy for female patients of child-bearing potential.

4.2 SUMMARY OF RISKS

The r-hαGAL enzyme (Fabrazyme) is a highly purified form of human αGAL, made by recombinant DNA technology. It is well known that immune response may occur following treatment with exogenous human proteins. In the setting of an endogenous enzyme deficiency, infusion of an exogenous recombinant enzyme to patients' naïve to the normal enzyme is expected to cause antibody response to the enzyme. Of the 177 patients evaluated in 7 clinical studies in which a Fabrazyme dose of 1 mg/kg every two weeks (q2w) was used for the duration of the study, the majority developed IgG (immunoglobulin G) antibodies to Fabrazyme: 84% of 163 males and 43% of 14 females seroconverted. Seroconversion occurred in a mean (SD) time of 194.5 (130.24) days for the 6 females compared to 76.2 (71.16) days for the 124 males. Of the

143 seropositive patients, the majority (a combined total of 66%) exhibit either consistently low titers or declining titers over time. Continued safe treatment with Fabrazyme has not been precluded by IgG antibody development. Across the 7 pooled clinical studies of Fabry patients treated with Fabrazyme 1 mg/kg q2w, the most common drug-related AEs were infusion associated reactions (IARs, defined as drug- related events occurring on the day of the infusion). The most common IARs included chills, pyrexia, nausea, feeling cold, headache, vomiting, paraesthesia, blood pressure increased, flushing, feeling hot, chest discomfort, pruritus, body temperature increased, urticaria, fatigue and somnolence. Most IARs were mild to moderate in intensity and non-serious.

There is no adequate safety data for the use of Fabrazyme in pregnant or lactating women or the possible effects on their infants. It is not known if Fabrazyme passes through the placenta to the embryo or if it is excreted in breast milk. Maternal IgG antibodies may be passively transferred transplacentally or via breast milk to the fetus/infant. Whether maternal administration of Fabrazyme can lead to an IgG and/or IgM (immunoglobulin M) antibody response to Fabrazyme by the fetus/infant is not known.

Some study specific procedures may cause increased risk to the mother or infant, eg, risks associated with phlebotomy include fainting, hematoma, excessive bleeding, or infection.

[redacted]

A small number of patients have experienced anaphylactoid reactions some of which were considered life-threatening. Signs or symptoms of possible anaphylactoid reactions have included events of localized angioedema, generalized urticaria, bronchospasm, and hypotension. The risks and benefits of re-administering Fabrazyme following a severe hypersensitivity or anaphylactoid reaction should be carefully considered.

A complete overview of the safety profile of Fabrazyme can be found in the Investigator's Brochure and/or product labeling.

5 STUDY OBJECTIVES

The objectives of this study are:

1. To determine whether αGAL activity is present in the breast milk of mothers with Fabry disease who are being treated with Fabrazyme during lactation.
2. To measure breast milk production and composition (volume, protein and fat content) in women with Fabry disease who receive Fabrazyme during lactation.
3. To determine whether Fabrazyme affects the growth, development, and immunologic response of infants born to mothers with Fabry disease who receive Fabrazyme during lactation.

6 INVESTIGATIONAL PLAN

6.1 STUDY DESIGN

This is a phase 4, multicenter, multinational study of the effects of Fabrazyme on lactation and on the growth, development, and immunologic response of infants born to mothers with Fabry disease who are treated with Fabrazyme during lactation. There are 3 participation scenarios: mother/infant full participation, mother full participation/infant development only, and mother full participation/infant no participation (see Section 9.1).

Whether or not the mother continues to lactate will be assessed at each visit. Breast milk will be collected at Months 1, 3, and 6 immediately prior to Fabrazyme infusion, just after the end of the infusion, and 2 hours after the end of the infusion. Breast milk samples will be analyzed for volume, presence of αGAL activity, total fat content, and total protein concentration. Blood samples from the mother will be drawn for pharmacokinetic (PK) analysis prior to each breast milk collection. If infant genotyping is performed on the umbilical blood cord sample collected at Baseline visit, a buccal cell sample will be obtained from the mother to rule out contamination of the cord blood sample with maternal DNA.

If the parent(s)/legal guardian(s) consent to infant participation, the infant's growth and development will be assessed. The infant may also be tested for the formation or continued presence of serum IgG and IgM antibodies to r-hαGAL and for genotype.

For the purposes of this study, the mother and the infant will each be considered a study patient. The mother must be enrolled in the Fabry Registry and will be followed using the Fabry Registry assessment schedule and CRFs as well as this study's CRF. During this study, infants will be evaluated, ie, the infant may be tested for IgG and IgM antibodies to r-hαGAL at birth and Months 2, 6, and 12 and will be tested developmentally at each visit for 24 months, or until the parent(s)/legal guardian(s) withdraws consent and discontinues the infant's study participation, the infant is discontinued from the study by the Investigator (see Section 7.3.1), or the study is terminated (see Section 7.3.2).

If the mother is no longer lactating, the mother will discontinue this study but continue to be followed in the Fabry Registry. The infant will be followed for development only for the remainder of this 24 month study.

6.2 STUDY RATIONALE

It is anticipated that with Fabrazyme becoming widely available, more women of childbearing age with Fabry disease will receive Fabrazyme. It is not known whether Fabrazyme is excreted in human milk and there is limited data involving infants of mothers receiving Fabrazyme during lactation. This study is being conducted 1) to determine whether αGAL is present in the breast milk of mothers with Fabry disease who receive Fabrazyme during lactation; 2) to measure breast milk production and composition (volume and protein and fat content) in women with Fabry

disease who receive Fabrazyme during lactation; and 3) to determine whether Fabrazyme affects the growth, development, and immunologic response of infants born to these mothers. Antibody formation to r-hαGAL in infants will be monitored postpartum for up to 1 year (Month 12). Blood samples for maternal PK analysis will be drawn to assess the clearance of αGAL post-partum and during the lactating period for up to Month 6. Data on concomitant medications and AEs for both mothers and infants will also be collected at each visit and coded using Medical Dictionary for Regulatory Activities (MedDRA).

6.2.1 Dosing Regimen

Mothers who are receiving Fabrazyme during lactation will continue to receive Fabrazyme treatment (commercially available) during study participation at their prescribed dosage regimen as determined by their treating physician. Each Fabrazyme infusion will be prepared in the standard approved manner (refer to appropriate country labeling information).

6.2.2 Study Duration

This study will last for up to 2 years (24 months).

If the mother is no longer lactating or the mother is no longer receiving Fabrazyme treatment, the mother will discontinue this study but continue to be followed in the Fabry Registry. The infant will be followed, for development only, for the remainder of this 24 month study.

6.2.3 Study Population

Females treated with Fabrazyme while lactating and their infants will be eligible for enrollment into this study. Pregnant women who received Fabrazyme at any point during their pregnancy can be enrolled in the study. If woman is not receiving treatment with Fabrazyme at the Baseline visit, mother should start treatment with Fabrazyme between the delivery and Month 1 visit. Females being treated with Fabrazyme infusion during lactation will have to provide signed written informed consent for themselves and for their infant to participate as study patients prior to any protocol-related procedures being performed.

7 PATIENT POPULATION AND SELECTION

Approximately 10 females and up to 10 of their infants (who must be receiving breast milk while the mother is receiving Fabrazyme therapy) will be enrolled in this study, at approximately 10 study centers. Mothers will receive Fabrazyme treatment as part of the standard of care of Fabry disease and will be followed through the Fabry Registry.

7.1 INCLUSION CRITERIA

Mothers must meet the following criteria to be enrolled in this study:

1. provide signed written informed consent to participate in this study,
2. be enrolled in the Fabry Registry* and receiving Fabrazyme while lactating,
3. agree to adhere to the Fabry Registry recommended schedule of assessments for medical history, pregnancy outcome, genotyping, and antibody testing, and
4. agree to adhere to the schedule of evaluations (Table 1, Table 2, or Table 3) for this study.

*The Fabry Registry is a global, observational, and voluntary program for patients with Fabry disease, intended to explore and define the natural course and clinical characteristics of the disease as well as to track and characterize response to treatments.

Infants must meet the following criteria to be enrolled in this study:

1. have the signed written informed consent of the parent(s)/legal guardian(s) to participate in this study,
2. be born to a mother who is receiving Fabrazyme during lactation,
3. be receiving breast milk from the mother, and
4. have the agreement of the parent(s)/legal guardian(s) to adhere to the schedule of evaluations (Table 1 or Table 2) for this study.

7.2 EXCLUSION CRITERIA

The mother and infant will be excluded from this study if the mother has received an investigational drug within 30 days prior to study enrollment.

7.3 WITHDRAWAL CRITERIA

7.3.1 Patient Withdrawal

The mother (or the legal guardian acting on behalf of the infant and/or the mother) is free to withdraw consent and discontinue her participation as well as the infant's participation in the study at any time, without prejudice to further treatment. The mother and infant's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a patient from the study:

Mother:

- The mother is uncooperative/noncompliant and will not adhere to study responsibilities, including failure to appear at scheduled study visits, or failure to undergo study assessments, and/or failure to comply with the Registry schedule of assessments.
- The mother was erroneously included in the study.
- The mother experiences an intolerable AE.
- The mother stops lactating.
- The study is terminated by the Sponsor.

Infant:

- The mother and/or infant was erroneously included in the study.
- The infant experiences an intolerable AE.
- The study is terminated by the Sponsor.

If the mother and/or the infant discontinues participation in the study, or their participation is discontinued by the Investigator, the mother and/or infant's legal guardian should be contacted by the Study Investigator in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs. Whenever possible the patient should return to the study site for the final clinical assessments as specified in Section 9.1.1.8, Section 9.1.2.8, or Section 9.1.3.4, as appropriate. The Study Investigator will describe the reason for discontinuation on the appropriate CRF.

7.3.2 Study or Site Termination

If the Sponsor, Study Investigator, Medical Monitor, or regulatory authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Sponsor, Study Investigator, and Medical Monitor. Conditions that may warrant termination of the study or study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue the study;
- Failure of the Study Investigator to comply with pertinent regulatory authority regulations;
- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or regulatory authorities; or
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in applicable local regulations and Sponsor Standard Operating Procedures (SOPs).

8 STUDY TREATMENTS

8.1 TREATMENTS ADMINISTERED

Mothers will receive Fabrazyme treatment (commercially available) at their currently prescribed dosage regimen as determined by their treating physician. The Fabrazyme infusions will be prepared in the standard approved manner (refer to appropriate country labeling information).

8.2 INVESTIGATIONAL PRODUCT

8.2.1 Investigational Product Description and Preparation

Description: recombinant human α-galactosidase A (r-hαGAL; Fabrazyme) is produced by mammalian cell culture technology using a Chinese Hamster Ovary (CHO) cell line.

Chemical Name: recombinant human α-galactosidase A (r-hαGAL)

CAS Registry Number: 104138-64-9

USAN (WHO/INN): agalsidase beta

Chemical Structure: r-hαGAL is comprised of two subunits of 398 amino acids (approximately 51 kD), each of which contains three N-linked glycosylation sites. α-galactosidase A catalyzes the hydrolysis of GL-3 and other α-galactyl-terminated neutral glycosphingolipids, such as galabiosylceramide and blood group B substances to ceramide dihexoside and galactose.

Molecular Weight: r-hαGAL is a homodimeric glycoprotein with a molecular weight of approximately 100 kD.

Commercial Fabrazyme is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP. Each 35 mg vial contains 37 mg of agalsidase beta, as well as 222 mg mannitol, 20.4 mg sodium phosphate monobasic monohydrate, and 59.2 mg sodium phosphate dibasic heptahydrate. Following reconstitution as directed, 35 mg of agalsidase beta (7 mL) may be extracted from each 35 mg vial. Each 5 mg vial contains 5.5 mg of agalsidase beta, as well as 33.0 mg mannitol, 3.0 mg sodium phosphate monobasic monohydrate, and 8.8 mg sodium phosphate dibasic heptahydrate. Following reconstitution as directed, 5 mg of agalsidase beta (1 mL) may be extracted from each 5 mg vial.

8.2.2 Packaging and Labeling

Commercially supplied Fabrazyme is to be used.

8.2.3 Drug Storage

All drug supplies must be kept in a secure place with restricted access and stored at 2° to 8°C.

8.2.4 Study Drug Accountability

Not applicable.

8.3 PATIENT NUMBERING

After the mother has signed written informed consent for her and her infant to participate, the infant will be assigned a unique 5-digit identification number, which will consist of a 3 digit assigned site number and 2 digit sequential patient number, beginning with 01. The mother's patient identification number will be the number assigned to her through the Fabry Registry.

8.4 PACKAGING AND LABELING

Refer to appropriate country labeling information for packaging and labeling information for Fabrazyme.

8.5 PRIOR AND CONCOMITANT MEDICATIONS

All medications taken by the mother and all medications taken by the infant from the time the Informed Consent Form is signed until the end of study participation will be recorded on the Concomitant Medication CRF.

8.6 BLINDING AND RANDOMIZATION

Not applicable for this open-label study.

9 EFFICACY, PHARMACOKINETICS, AND SAFETY VARIABLES

Efficacy will not be measured in this study.

The effects of Fabrazyme treatment on lactation and infants will be monitored continuously throughout study participation and will be assessed in terms of incidence of AEs, concomitant medication, immunogenicity testing, vital signs, and physical examination results including the infant's growth and development. Pharmacokinetics testing will be conducted on the mother's plasma and breast milk.

Refer to Table 1, Table 2, or Table 3 for the schedules of assessments (mother/infant full participation, mother full participation/infant development only, and mother full participation/infant no participation, respectively).

9.1 MEASUREMENTS ASSESSED AND STUDY FLOWCHART

After obtaining signed, written informed consent, the study will be conducted as outlined in the following sections. Table 1 summarizes the schedules of study evaluations at each study visit for mothers and infants enrolled for full participation (eg, full/full participation through Month 24). If the mother is enrolled for full participation but the infant is enrolled only for developmental assessments (eg, full/development) (see Table 2), the mother and infant schedules are the same as full/full participation, except the infant blood samples are omitted. If only the mother is participating in the study (eg, full/no) (see Table 3), her assessment schedule is the same as full participation except study participation is stopped and considered complete at Month 6. Refer to the Study Operations Manual (SOM) for guidelines regarding test assessments and procedures for handling/shipment of all laboratory samples.

The timing of study procedures will be based on calendar weeks starting with Baseline; defined for the mother as during the month prior to delivery and at birth for the infant. Thus Month 1 is 1 month postpartum. The study procedures and assessments are scheduled so that the maximum time the mother and the infant may participate in the study is approximately 24 months.

Table 1 - Schedule of Study Evaluations - Mother (Full Participation) and Infant (Full Participation)

Evaluations	Baseline[a]	Months Postpartum[b]						
		1	2	3	6	12	18	24/End of Study
Mother								
Written Informed Consent	X							
Confirm Registry Enrollment	X							
Blood Samples for PK Testing		X[c]		X[c]	X[c]			
Breast Milk Samples for PK, αGAL activity, volume, and protein and fat content[d]		X[e]		X[e]	X[e]			
Lactation Status	X[f]	X	X	X	X	X	X	X
Buccal Cell Sample	X[h, j]							
Concomitant Medications Review	Continuous Monitoring							
Adverse Events Assessment	Continuous Monitoring							
Infant								
Written Informed Consent (provided by parent[s]/legal guardian[s])	X							
Medical History	X							
Physical Examination	X[g]	X	X	X	X	X	X	X
Denver II Developmental Screening Test		X	X	X	X	X	X	X
Record Receiving Breast Milk Status	X	X	X	X	X	X	X	X
Blood Samples for Antibodies to r-hαGAL	X[h]		X		X	X[i]		
Blood sample for Genotyping	X[h,i]							
Concomitant Medications Review	Continuous Monitoring							
Adverse Events Assessment	Continuous Monitoring							

Evaluations	Baseline[a]	Months Postpartum[b]						
		1	2	3	6	12	18	24/End of Study

a Baseline is defined as within 1 month prior to delivery (mother) and at birth (infant).
b All visits will be within ±7 days of the scheduled visit.
c Blood samples will be collected prior to each breast milk collection as follows: sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection; sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.
d The mother must be lactating and receiving Fabrazyme therapy during the evaluation period.
e Breast milk samples will be collected after each plasma collection for PK testing as follows: sample 1: immediately prior to Fabrazyme infusion and after plasma collection; sample 2: immediately after Fabrazyme infusion and after plasma collection; and sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
f At baseline, record plans for breast milk feeding.
g Includes Apgar score assessed at 1 minute and 5 minutes after birth.
h Blood samples for Baseline IgG and IgM antibodies to r-hαGAL and genotyping of the infant will be obtained from umbilical cord immediately after birth. A buccal cell sample will be obtained (by buccal swab) from the mother to rule out contamination of the cord blood sample with maternal DNA (maternal cell contamination analysis).
i In cases when umbilical blood cord sample is not collected at the Baseline visit, genotyping of the infant could be performed on the additional blood sample collected at visit month 12.
j At birth, in case when umbilical cord blood sample was collected.

Table 2 - Schedule of Study Evaluations - Mother (Full Participation) and Infant (Development Participation)

Evaluations	Baseline[a]	Months Postpartum[b]						
		1	2	3	6	12	18	24/End of Study
Mother								
Written Informed Consent	X							
Confirm Registry Enrollment	X							
Blood Samples for PK Testing		X[c]		X[c]	X[c]			
Breast Milk Samples for PK, αGAL activity, volume, and protein and fat content[d]		X[e]		X[e]	X[e]			
Lactation Status	X[f]	X	X	X	X	X	X	X
Buccal Cell Sample	X[h, i]							
Concomitant Medications Review	Continuous Monitoring							
Adverse Events Assessment	Continuous Monitoring							
Infant								
Written Informed Consent (provided by parent[s]/legal guardian[s])	X							
Medical History	X							
Physical Examination	X[g]	X	X	X	X	X	X	X
Denver II Developmental Screening Test		X	X	X	X	X	X	X
Record Receiving Breast Milk Status	X	X	X	X	X	X	X	X
Blood sample for Genotyping	X[h]							
Concomitant Medications Review	Continuous Monitoring							
Adverse Events Assessment	Continuous Monitoring							

a Baseline is defined as within 1 month prior to delivery (mother) and at birth (infant).
b All visits will be within ±7 days of the scheduled visit.
c Blood samples will be collected prior to each breast milk collection as follows: sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection; sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.
d The mother must be lactating and receiving Fabrazyme therapy during the evaluation period.
e Breast milk samples will be collected after each plasma collection for PK testing as follows: sample 1: immediately prior to Fabrazyme infusion and after plasma collection; sample 2: immediately after Fabrazyme infusion and after plasma collection; and sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
f At baseline, record plans for breast milk feeding.
g Includes Apgar score assessed at 1 minute and 5 minutes after birth.
h Blood sample for genotyping of the infant will be obtained from umbilical cord blood immediately after birth. A buccal cell sample will be obtained (by buccal swab) from the mother to rule out contamination of the cord blood sample with maternal DNA (maternal cell contamination analysis).
i At birth, in case when umbilical cord blood sample was collected.

Table 3 - Schedule of Study Evaluations - Mother (Full Participation) Infant (No Participation)

Evaluations	Baseline[a]	Months Postpartum[b]		
		1	3	6/ End of Study
Mother				
Written Informed Consent	X			
Confirm Registry Enrollment	X			
Blood Samples for PK Testing		X[c]	X[c]	X[c]
Breast Milk Samples for PK, αGAL activity, volume, and protein and fat content[d]		X[e]	X[e]	X[e]
Lactation Status	X	X	X	X
Concomitant Medications Review	Continuous Monitoring			
Adverse Events Assessment	Continuous Monitoring			

a Baseline is defined as within 1 month prior to delivery (mother) and at birth (infant).

b All visits will be within ±7 days of the scheduled visit.

c Blood samples will be collected prior to each breast milk collection as follows: sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection; sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

d The mother must be lactating and receiving Fabrazyme therapy during the evaluation period.

e Breast milk samples will be collected after each plasma collection for PK testing as follows: sample 1: immediately prior to Fabrazyme infusion and after plasma collection; sample 2: immediately after Fabrazyme infusion and after plasma collection; and sample 3: 2 hours after Fabrazyme infusion and after plasma collection..

9.1.1 Tests and Procedures for Mother Full Participation and Infant Full Participation

9.1.1.1 Baseline (Full/Full Participation)

The following assessments will be completed at Baseline: Mother (within 1 month prior to the infant's birth):

- Provide signed, written informed consent (Note: mothers must also be enrolled in the Fabry Registry with a signed written informed consent maintained within the Registry.)
- Record plans for feeding the infant breast milk.
- Collect buccal cell sample by buccal swab for MCC analysis at birth if umbilical cord blood sample was collected for genotyping of the infant.
- Record AEs on the study CRF, from the time of signing the study informed consent.
- Record concomitant medications on the study CRF, from the time of signing informed consent.

Infant (at birth):

- Parent(s)/legal guardian(s) provide signed written informed consent for the infant. (May be collected/provided prior to birth.)
- Record the Apgar score at 1 minute and 5 minutes after birth.
- Collect umbilical cord blood sample for IgG and IgM antibodies to r-hαGAL and for genotyping.
- Record the medical history and conduct a physical examination.
- Record status of receiving breast milk.
- Record AEs, from birth.
- Record concomitant medications, from the time the informed consent is signed/or from birth.

9.1.1.2 Month One (Full/Full Participation)

The following assessments will be completed at Month 1 (1 month ±7 days postpartum):

Mother:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection; sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.1.3 Month Two (Full/Full Participation)

The following assessments will be completed at Month 2 (2 months ±7 days postpartum):

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Collect a blood sample for IgG and IgM antibodies to r-hαGAL.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.1.4 Month Three (Full/Full Participation)

The following assessments will be completed at Month 3 (3 months ±7 days postpartum):

Mother:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.
- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.1.5 Month Six (Full/Full Participation)

The following assessments will be completed at Month 6 (6 months ±7 days postpartum):

Mother:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Collect a blood sample for IgG and IgM antibodies to r-hαGAL.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.1.6 Month Twelve (Full/Full Participation)

The following assessments will be completed at Month 12 (12 months ±7 days postpartum):

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Collect a blood sample for IgG and IgM antibodies to r-hαGAL.
- Collect a blood sample for genotyping (only if umbilical blood cord sample was not collected at the Baseline visit and infant genotyping was not performed as a part of standard care prior to visit month 12).
- Record AEs.
- Record concomitant medications.

9.1.1.7 Month Eighteen (Full/Full Participation)

The following assessments will be completed at Month 18 (18 months ±7 days postpartum):

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.1.8 Month Twenty-four/End of Study (Full/Full Participation)

The following assessments will be completed at Month 24 (24 months ±7 days postpartum) or at early withdrawal:

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2 Tests and Procedures for Mother Full Participation and Infant Development

9.1.2.1 Baseline (Full/Development Participation)

The following assessments will be completed at Baseline:

Mother (within 1 month prior to the infant's birth):

- Provide signed, written informed consent (Note: mothers must also be enrolled in the Fabry Registry with a signed written informed consent maintained within the Registry.)
- Record plans for feeding the infant breast milk.
- Collect buccal cell sample by buccal swab for MCC analysis at birth if umbilical cord blood sample was collected for genotyping of the infant.
- Record AEs on the study CRF, from the time of signing the study informed consent.
- Record concomitant medications on the study CRF, from the time of signing informed consent.

Infant (at birth):

- Parent(s)/legal guardian(s) provide signed written informed consent for the infant.
- Record the Apgar score at 1 minute and 5 minutes after birth.
- Collect umbilical cord blood sample for genotyping.
- Record the medical history and conduct a physical examination.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.2 Month One (Full/Development Participation)

The following assessments will be completed at Month 1 (1 month ±7 days postpartum):

Mother:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.
- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;

- sample 2: immediately after Fabrazyme infusion and after plasma collection; and
- sample 3: 2 hours after Fabrazyme infusion and after plasma collection.

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.3 Month Two (Full/Development Participation)

The following assessments will be completed at Month 2 (2 months ±7 days postpartum):

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.4 Month Three (Full/Development Participation)

The following assessments will be completed at Month 3 (3 months ±7 days postpartum):

Mother:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.5 Month Six (Full/Development Participation)

The following assessments will be completed at Month 6 (6 months ±7 days postpartum):

Mother:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.
- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.6 Month Twelve (Full/Development Participation)

The following assessments will be completed at Month 12 (12 months ±7 days postpartum):

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.7 Month Eighteen (Full/Development Participation)

The following assessments will be completed at Month 18 (18 months ±7 days postpartum):

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.2.8 Month Twenty-four/End of Study (Full/Development Participation)

The following assessments will be completed at Month 24 (24 months ±7 days postpartum) or at early withdrawal:

Mother:

- Record lactation status.
- Record AEs.
- Record concomitant medications.

Infant:

- Conduct a physical examination.
- Administer the Denver II Developmental Screening Test.
- Record status of receiving breast milk.
- Record AEs.
- Record concomitant medications.

9.1.3 Tests and Procedures for Mother (Full Participation) Infant (No Participation)

9.1.3.1 Baseline (Full/No Participation)

The following assessments will be completed at Baseline:

Mother (within 1 month prior to the infant's birth):

- Provide signed, written informed consent (Note: mothers must also be enrolled in the Fabry Registry with a signed written informed consent maintained within the Registry.)
- Record plans for feeding the infant breast milk.
- Record AEs on the study CRF, from the time of signing the study informed consent.
- Record concomitant medications on the study CRF, from the time of signing informed consent.

9.1.3.2 Month One (Full/No Participation)

The following assessments will be completed at Month 1 (1 month ±7 days postpartum):

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

9.1.3.3 Month Three (Full/No Participation)

The following assessments will be completed at Month 3 (3 months ±7 days postpartum):

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.
- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

9.1.3.4 Month Six/End of Study (Full/No Participation)

The following assessments will be completed at Month 6 (6 months ±7 days postpartum) or at early withdrawal:

- Collect blood samples for PK testing prior to each breast milk collection as follows:
  - sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection;
  - sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and
  - sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

- Collect breast milk samples for presence of αGAL as well as measurement of volume and fat and protein levels after each plasma collection for PK testing as follows:
  - sample 1: immediately prior to Fabrazyme infusion and after plasma collection;
  - sample 2: immediately after Fabrazyme infusion and after plasma collection; and
  - sample 3: 2 hours after Fabrazyme infusion and after plasma collection.
- Record lactation status.
- Record AEs.
- Record concomitant medications.

9.2 EFFICACY ASSESSMENTS

Not Applicable.

9.3 PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic Sampling

Blood and breast milk samples will be taken from the mother for measurement of αGAL concentrations. Sample collection, processing, and shipping instructions are provided in the SOM.

Blood samples will be taken from the mother at Months 1, 3, and 6 for PK testing (if mother is lactating at the time of the evaluation and is receiving Fabrazyme therapy). Blood samples will be collected prior to each breast milk collection as follows: sample 1: immediately prior to Fabrazyme infusion and prior to breast milk collection; sample 2: just prior to the end of Fabrazyme infusion and prior to breast milk collection; and sample 3: 2 hours after Fabrazyme infusion and prior to breast milk collection.

Bioanalytical Method.

[redacted]

Pharmacokinetic parameters

The following pharmacokinetic parameters will be calculated, using noncompartmental methods from plasma αGAL concentrations and milk αGAL concentrations

- maximum plasma concentration observed (C_{max}) in plasma and milk
- area under the plasma αGAL concentration versus time curve calculated using the trapezoidal method from 0 to 2 hours post end of infusion ($AUC_{0\text{-}2\ plasma}$).

- The amount of αGAL in milk calculated as the product of αGAL activity times the milk volume
- area under the milk αGAL concentration versus time curve calculated using the trapezoidal method from 0 to 2 hours post end of infusion ($AUC_{0\text{-}2\ milk}$).
- Lactation clearance determined in the 0-2 hours interval, according to the following equation : amount of αGAL excreted over the sampling period divided by the AUC during the sampling period

The milk to plasma ratio for $AUC_{0\text{-}2}$ will also be computed.

9.4 SAFETY ASSESSMENTS AND OTHER MEASUREMENTS

9.4.1 Adverse Events

An AE is any undesirable physical, psychological, or behavioral effect experienced by a patient or subject during their participation in an investigational study whether or not product-related. This includes any untoward signs or symptoms experienced by the mother and/or infant from the time of signing of the informed consent until completion of the study. AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously demonstrated by the infant and/or observed by the mother, guardian, investigator, or medical staff.
- Laboratory abnormalities of clinical significance.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the study medication are not considered AEs after treatment unless they reoccur after the patient has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

All AEs ongoing at the time of withdrawal, study termination, or study completion require a follow up at approximately 28 days after discontinuation of study participation. The Investigator will be asked to follow-up on all SAEs that were ongoing at the time of withdrawal, termination or completion until resolution, until both the sponsor and investigator agree follow-up is deemed no longer medically necessary or until the patient is lost to follow-up.

If any new SAEs are identified during the course of this follow-up of ongoing SAEs, additional follow-up of these new SAEs may be performed. The Investigator and sponsor will determine if the follow-up is clinically warranted and relevant to the evaluation of the safety of the trial treatment or until patient is lost to follow up. The investigator must follow patients with AEs until their condition resolves or stabilizes. Certain conditions that are not expected to resolve, such as metastatic cancer, need not be followed indefinitely by the investigator.

9.4.2 Serious Adverse Events

SAEs will be recorded from signed consent through the Month 24 visit (or through the Month 6 visit if only the mother is participating in the study). For patients who discontinue prematurely from the study, SAEs will be reported from signed consent through the last patient study visit. A serious adverse event is defined as any AE that results in any of the following outcomes:

- Death
- Life-threatening experience
- Required or prolonged inpatient hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical events, based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above

Life-threatening experience: any AE that places the patient, in the view of the reporter, at immediate risk of death from the AE as it occurred, ie, does not include an AE that had it occurred in a more severe form might have caused death.

Persistent or significant disability/incapacity: the AE that resulted in a substantial disruption of a person's ability to conduct normal life functions.

Important medical events based upon appropriate medical judgment, that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above: an AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The Investigator will be asked to assess the severity of the adverse drug/biologic event using the following categories: Mild, Moderate, and Severe. This assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar types of events observed in clinical practice. Below are listed guidelines for severity assessment:

Mild: Symptom(s) barely noticeable to the subject/patient or does not make the subject/patient uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate: Symptom(s) of a sufficient severity to make the subject/patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.

Severe: Symptom(s) of a sufficient severity to cause the subject/patient severe discomfort. Severity may cause cessation of treatment with the study drug. Treatment for symptom(s) may be given.

9.4.3 Adverse Event and Serious Adverse Event Reporting

All SAEs will be documented on the study CRF and reported within 24 hours of the Study Investigator's knowledge of the event, even if the experience does not appear to be related to Fabrazyme. The following central global contact information should be used for reporting to the Sponsor's Global Pharmacovigilance and Epidemiology (GPE):

Fax: +33 1 60 49 70 70

Email: CL-CPV-receipt@sanofi.com

For all SAEs, a detailed written description that includes copies of relevant patient records, autopsy reports, and other documents will be sent to Sponsor's Global Pharmacovigilance and Epidemiology (GPE) Department as directed above.

During the course of the study, Sanofi Genzyme is responsible for reporting in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate, and to the Investigators. Additionally, Sanofi Genzyme is responsible for expedited reporting of all SAEs that are expected and at least reasonably related to the study drug to the regulatory authorities, according to the local regulations.

9.4.4 Clinical Laboratory Tests

Not applicable.

9.4.5 Concomitant Medications

A concomitant medication is any medication, prescription or over the counter, taken by a patient during their participation in an investigational study. All medications taken from the time of signing the Informed Consent through to study completion will be recorded on the CRF. In addition, at every visit, the site personnel will record any medication used by the patient since a previous visit.

Administration of concomitant medication(s) signals that an AE should be recorded.

9.4.6 Status of Lactation/Receiving Breast Milk

Whether or not the mother is lactating will be recorded at each visit on the mother's CRF.

If the infant is participating in this study, whether or not the infant is receiving breast milk will be recorded at each visit on the infant's CRF.

9.4.7 Breast Milk Samples

Breast milk samples of mothers receiving Fabrazyme will be tested for αGAL activity, volume, and fat and protein content. Since αGAL is a protein, it is a normal component of breast milk and it is possible that the women enrolled in the study naturally produce αGAL in the breast milk samples. The current assay cannot differentiate between endogenous αGAL and Fabrazyme. As breast milk samples are not available prior to the mother having started Fabrazyme therapy, breast milk samples will be tested just prior to the Fabrazyme infusion and at timed intervals as specified above (see Section 9.3) to see if there is an increase in the αGAL levels in breast milk.

Each breast milk collection should first be measured for total volume. An aliquot of each breast milk sample collected at the site is to be set aside for testing and the remainder of the sample may be fed to the infant. Refer to the SOM for further details on breast milk sampling.

9.4.8 Physical Examination

Each infant physical examination will include the following physical observations: Length; Weight; Head Circumference; Vital Signs; General Appearance; Skin; Head, Ears, Eyes, Nose, and Throat (HEENT); Lymph Nodes; Heart; Lungs; Abdomen; Extremities/Joints; Neurological; Mental Status; and External Genitalia.

If clinically significant worsening of the physical examination assessments compared to Baseline is noted, the change will be documented as an AE on the AE CRF and will be followed as an AE consistent with the procedures outlined in Section 9.4.1. Clinical significance is defined as any variation in physical findings that has medical relevance resulting in an alteration in medical care.

The infant's Apgar score will be determined at 1 minute and 5 minutes after birth.

9.4.9 Developmental Assessment

The Denver II Developmental Screening Test will be used as an evaluation tool for developmental abnormalities. The Denver II Developmental Screening Test is used to evaluate 4 developmental areas: personal-social, fine motor, language, and gross motor. Information regarding the Denver II Developmental Screening Test is provided in the SOM. If the assessment is abnormal, more in-depth testing will be undertaken based on the local standards of care.

9.4.10 Genotype Testing

Genotype testing will be conducted for all participating infants on umbilical cord blood to determine diagnosis of Fabry disease. Buccal cells will be collected from the mother by buccal swab to rule out contamination of the cord blood sample with maternal DNA (MCC analysis). The basic premise of the MCC test is the comparison of highly polymorphic short tandem repeat loci between the maternal and fetal DNA samples following polymerase chain reaction.(8)

In cases when umbilical blood cord sample is not collected at the Baseline visit, genotyping of the infant enrolled for full participation could be performed on the additional blood sample collected at visit month 12. If genotyping of the infant is performed as a part of standard care prior to visit month 12, this result will be recorded by Investigator in the CRF.

Blood and buccal cell sample collection, processing, and shipping instructions are provided in the SOM.

9.4.11 Immunogenicity Testing

Immunogenicity testing will be conducted in those infants with parent(s)/legal guardian(s) consent. Blood collection, processing, and shipping instructions for infant blood samples for antibodies (IgG and IgM) to r-hαGAL are provided in the SOM.

9.4.12 Safety Follow-Up

Study sites will attempt to reach all study participants by telephone approximately 28 days after the final study procedures are completed, to conduct concomitant medication and adverse experience/event assessment.

10 DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

10.1 RECORDING OF DATA

All required data will be recorded in the CRF provided by Genzyme. All missing data will be explained. If a space is blank because the item was not done, the item will be marked "ND." If the item is unknown, the item will be marked "UNK." If the item is not applicable to the individual case, the space will be marked "NA." If the item is not available, it will be marked "NAV." All entries will be recorded in black ink. Any erroneous entries made on the CRFs will be crossed out with a single line, initialed and dated, and the correct entry, if appropriate, will be recorded. Errors may not be erased and whiteout may not be used.

10.2 DATA QUALITY ASSURANCE

The CRFs will be reviewed by a clinical monitor from Genzyme or designee for completeness and accuracy. Source document verification will be performed. The data will also be reviewed internally by Genzyme data management or designee and if necessary, the investigational sites will be queried for corrections and/or clarifications.

10.3 DATA MANAGEMENT

The format and content of the CRF will be approved by Genzyme or designee prior to the start of the trial. Genzyme or designee will be responsible for database creation and management of data from other sources (eg, non-safety specialty lab data).

Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of patient data for analysis will be determined by appropriate clinical and statistical personnel. Any exclusion will be documented. Protocol deviations will be tracked by Genzyme or its designee.

11 STATISTICAL METHODS AND PLANNED ANALYSES

11.1 GENERAL CONSIDERATIONS

Genzyme will be responsible for data entry and editing, reviewing all the information in the CRFs, statistical analysis, and generation of the clinical report.

Clinical data will be double-entered and validated in an Oracle database using Clintrial 4.5.

The Genzyme Biomedical Data and Informatics will perform the statistical analysis of the data derived from this study. The analysis will be performed using the SAS® statistical software system. (9)(10) The status of this study will be summarized annually as part of the Fabry Registry Program Annual Report.

Any missing or invalid data will not be replaced or imputed.

Data collected in this study will be reported using summary tables, graphs, figures, and/or patient data listings.

No hypothesis testing will be performed.

11.2 DETERMINATION OF SAMPLE SIZE

No formal statistical sample size calculations were performed for this study. The sample size of approximately 10 mothers and up to 10 infants is based upon 1) the availability of mothers to study lactation in this rare disease and 2) the availability of infants whose parents or legal guardians consent to their participation in this study.

11.3 ANALYSIS POPULATIONS

The patient populations will consist of all the mothers and all the infants who were enrolled in the study.

11.4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic and Baseline characteristics data will be summarized for the mothers and for the infants.

11.5 PATIENT ACCOUNTABILITY

Data from all patients who are enrolled in the study will be included in the summary of patient accountability. The frequency and percentage of patients who are enrolled in the study, attended each visit, are discontinued from the study, and completed the study will be summarized for the mothers and for the infants.

11.6 STUDY TREATMENT USAGE AND COMPLIANCE

Not applicable.

11.7 EFFICACY ANALYSIS

Not applicable.

11.8 SAFETY ANALYSIS

The following study variables will be summarized as appropriate for the mothers:

- Medical history (including Fabrazyme status during pregnancy)
- Genotyping
- Pregnancy outcome
- IgG antibody status
- Lactation status
- Plasma and breast milk PK testing
- The level of αGAL, volume, and fat and protein content in breast milk samples
- Frequency of AEs
- Frequency of concomitant medications

The following study variables will be summarized as appropriate for the infants:

- Medical history
- Physical examination
- Gender
- Genotype
- Apgar score at 1 minute and 5 minutes after birth
- Denver II Developmental Screening Test
- IgM antibodies to r-hαGAL – presence, time to development, level of titers present
- IgG antibodies to r-hαGAL – presence, time to development, level of titers present
- Frequency of AEs
- Frequency of concomitant medications

11.9 INTERIM ANALYSIS

After 5 mothers have contributed breast milk samples to this study, an interim analysis of αGAL activity in the breast milk will be performed. [redacted]

In addition, the status of this study will be summarized annually as part of the Fabry Registry Program Annual Report and the Fabrazyme Post-Marketing Commitment Annual Report.

11.10 PHARMACOKINETICS ANALYSIS

Because of the limited sampling schedule, the only PK parameters that will be reported are maximum concentration (C_{max}) and area under the plasma αGAL concentration-time curve (AUC) from 0 to 2 hours post end of infusion (AUC_{0-2}). A more complete PK profile is not being done because it is not the objective of the study to characterize the pharmacokinetics of αGAL in lactating mothers.

Lactation clearance will be determined using the same calculations used to assess renal clearance. Breast milk will be collected at Baseline (sample 1) to empty each breast of milk, at end of infusion (sample 2), and 2 hours post-dose (sample 3). The amount of αGAL will be calculated as the product of αGAL activity times the milk volume. AUC from Baseline to 2 hours after the end of infusion will be calculated using a linear trapezoid. Lactation clearance will be estimated as the amount of αGAL excreted over the sampling period divided by the AUC during the sampling period. The milk to plasma ratio calculated as the AUC_{milk} to AUC_{plasma} from time 0 (sample 2) to 2 hours after the end of infusion (sample 3) will also be computed.

12 SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP). These requirements are stated in "Guidance for Good Clinical Practice," International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and national regulations.

12.1 INSTITUTIONAL AND ETHICAL REVIEW

This protocol and patient informed consent form must be reviewed and approved by an IRB or IEC complying with the national regulations and the guidelines of the ICH before enrollment of patients. A copy of the letter or certificate of approval from the IRB or IEC and the approved consent form must be received by Genzyme prior to initiation of the study.

12.2 CHANGES TO THE CONDUCT OF THE STUDY OR PROTOCOL

No change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Genzyme. All changes must be documented by signed protocol amendments. If changes to the design of the study are made, the amendment must be submitted to and approved by the IRB, IEC, or any other appropriate regulatory authority, signed by the Investigator, and returned to Genzyme.

12.3 INVESTIGATOR'S RESPONSIBILITIES

12.3.1 Patient Informed Consent

Before a patient's participation in the clinical trial, study informed consent forms for mother and parents/legal guardian, where required by law separate genetic informed consent forms for mother and parents/legal guardian will be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of each signed and dated written informed consent form will be provided to the patient.

The informed consent form and where required by law the separate genetic informed consent form used by the investigator for obtaining the patient's informed consent must be reviewed and approved by the sponsor before submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion. Upon approval by the IRB or IEC, the Investigator must furnish the Sponsor with: (1) a photocopy of the approved informed consent and (2) a copy of the letter stating formal approval has been granted by the institution, prior to initiation of the study.

Signed, written informed consent from the infant's parent(s) or legal guardian(s) is required prior to enrollment in the study. It is the responsibility of the Investigator to obtain such consent.

12.3.2 Case Report Forms

CRFs will be filled out legibly and completely (black ballpoint pen). Refer to Section 10.1 for further guidance on completion of CRFs.

The original CRFs will be provided to Genzyme. A copy of the CRFs will be maintained in the Investigator's file. Designated site personnel must complete CRFs in a timely manner.

Illegible or incomplete entries will be returned and queried to the Investigator for clarification.

Patient records in connection with the study, including patient charts, laboratory data, etc. will be made available to Genzyme for review.

12.3.3 Record Retention

The investigator must maintain confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents.

The investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements will be taken into account in the event that a longer period is required.

The investigator must notify the sponsor before destroying any study essential documents following the clinical trial completion or discontinuation.

If the investigator's personal situation is such that archiving can no longer be ensured by him/her, the investigator shall inform the sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

12.3.4 Monitoring

A representative of Genzyme will visit the Investigator periodically for the purpose of monitoring the progress of this study in accordance with national regulations and ICH-GCP guidelines. It is the responsibility of the Investigator to be present or available for consultation during such scheduled monitoring visits. During these routine visits, all data pertaining to a patient's participation in this clinical investigation must be made available to the monitor.

Genzyme personnel or their designee may perform an audit at any time during or after completion of the clinical study. All study-related documentation must be made available to the designated auditor.

In addition, a representative of a regulatory agency may choose to inspect a study center at any time prior to, during, or after completion of the clinical study. A Genzyme representative will be available to assist in the preparation for such an inspection. All pertinent study data should be made available to the regulatory authority for verification, audit, or inspection purposes.

12.3.5 Materials Control

There will be no clinical trial supplies provided for this study.

For specific information concerning warnings, precautions, and contraindications, the Investigator is asked to refer to the appropriate section of the Investigator Brochure and/or product labeling. Because of the possibility of AEs, a fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should be immediately available.

12.3.6 Disclosure of Data

All information obtained during the conduct of this study will be regarded as confidential and written permission from Genzyme is required prior to disclosing any information relative to this study. Manuscripts prepared for publication will be in accordance with the policy previously presented by Genzyme to the Investigator. Submission to the Sponsor for review and comment prior to submission to the publisher will be required. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.

12.3.7 Clinical Study Report

If deemed appropriate by the Sponsor, an Investigator may be designated to sign the completed clinical study report at the end of this study.

13 REFERENCES

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]		