CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103979Orig1s5309

Trade Name:	FABRAZYME
Generic or Proper Name:	agalsidase beta
Sponsor:	Genzyme Corporation
Approval Date:	March 11, 2021
Indication:	Fabrazyme is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

CENTER FOR DRUG EVALUATION AND RESEARCH

103979Orig1s5309

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Officer/Employee List	
Multidiscipline Review(s) • **Summary Review** • **Office Director** • **Cross Discipline Team Leader** • **Clinical** • **Non-Clinical** • **Statistical** • **Clinical Pharmacology**	**X**
Product Quality Review(s)	
Clinical Microbiology / Virology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103979Orig1s5309

APPROVAL LETTER

BLA 103979/S-5309

SUPPLEMENT APPROVAL

Genzyme Corporation
Attention: Hiren Patel
Sr Manager, US, Global Regulatory Affairs
50 Binney Street
Cambridge, MA 02142

Dear Mr. Patel:

Please refer to your supplemental biologics license application (sBLA), dated and received February 14, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Fabrazyme (agalsidase beta).

We acknowledge receipt of your major amendment dated November 24, 2020, which extended the goal date by three months.

This Prior Approval supplemental biologics application provides for the traditional approval of Fabrazyme for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT

This supplemental application contained the final report for the following postmarketing requirement listed in the May 13, 2008, complete response/postapproval postmarketing requirement letter.

2421-2 Genzyme commits to performing additional analyses of the data obtained in the registry of patients with Fabry disease being treated with Agalsidase beta that was established to obtain long-term clinical status information. Additional analyses of the registry data are to be performed for the purpose of establishing the clinical benefit of Fabrazyme on progression of renal disease and other end-organ disease endpoints in patients with Fabry disease. Additional analyses to be performed include the following:

a) Progression of renal disease, including assessment of time of onset of proteinuria, hypertension, chronic renal insufficiency, end-stage renal disease, and death.
b) Exploration of the effects of endogenous αGAL activity and genetic mutations on progression of renal disease, the occurrence of significant clinical events, and the development of anti-recombinant-human-αGAL (anti-r-hαGAL) IgG antibodies.
c) Progression of renal disease by age of initiation of ERT with Fabrazyme for age groups such as <10 years of age, ≥10 to <15 years of age, ≥15 to 20 years of age, and in 10 year increments at >20 years of age.
d) Progression of renal disease by treatment administered, including ERT with Fabrazyme or no treatment. Reports will include data on patients who have received other Fabry specific treatments
e) Progression of renal disease by GFR status (≥60 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2) at initiation of ERT with Fabrazyme.
f) Time of first significant clinical event.
g) Analysis of anti-r-hαGAL IgG antibodies titers on the progression of renal disease and the occurrence of significant clinical events.

A final analysis plan for the registry study protocol will be submitted to CDER by October 25, 2008. The final study report under this registry will be submitted to CDER by July 30, 2021.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there is a postmarketing commitment listed in the April 24, 2003, approval letter that is still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Michael G. White, PhD, Chief, Project Management Staff, at 240-402-6149.

Sincerely,

{See appended electronic signature page}

Patroula Smpokou, M.D.
Deputy Director
Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Center for Drug Evaluation and Research

ENCLOSURE:

- Content of Labeling
    - Prescribing Information

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATROULA I SMPOKOU
03/11/2021 11:17:53 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103979Orig1s5309

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FABRAZYME safely and effectively. See full prescribing information for FABRAZYME.

FABRAZYME (agalsidase beta) for injection, for intravenous use
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	3/2021
Warnings and Precautions (5.1, 5.2)	3/2021

----------INDICATIONS AND USAGE----------

Fabrazyme is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. (2.1)
- Ensure appropriate medical support is available when Fabrazyme is administered because of the potential for anaphylaxis and severe infusion-associated reactions. (2.1, 5.1, 5.2)
- Administer antipyretics prior to infusion. (2.1)
- See the full prescribing information for the recommended infusion rate. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 5 mg or 35 mg lyophilized cake or powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylactic and severe hypersensitivity reactions have occurred during Fabrazyme infusions. If severe hypersensitivity or anaphylactic reactions occur, immediately discontinue the infusion and provide necessary emergency treatment. Readministration to patients who have previously experienced severe or serious hypersensitivity reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel with appropriate medical support measures readily available. (5.1)
- Infusion-Associated Reactions: Pretreat patients who experience infusion-associated reactions with an antipyretic and antihistamine. If an infusion-associated reaction occurs, decrease the infusion rate, temporarily stop the infusion, and consider administration of additional antipyretics, antihistamines, and/or steroids. If a severe infusion-associated reaction occurs, discontinue the infusion and initiate appropriate anaphylaxis treatment. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20%) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fabrazyme® is indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every two weeks as an intravenous infusion.
- Infusion rate:
  - The initial intravenous infusion rate is 0.25 mg/min (15 mg/hour). Slow the infusion rate in the event of infusion-associated reactions *[see Warnings and Precautions (5.2)]*.
  - For patients > 30 kg, after patient tolerance to the infusion is well established, increase the infusion rate in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hour) with each subsequent infusion. The minimum infusion duration is 1.5 hours (based on individual patient tolerability).
  - For patients weighing < 30 kg, the maximum infusion rate is 0.25 mg/minute (15 mg/hour).
- Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available when Fabrazyme is administered *[see Warnings and Precautions (5.2)]*.
- Administer antipyretics prior to infusion of Fabrazyme *[see Warnings and Precautions (5.2)]*.
- Rechallenge: Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully rechallenged with Fabrazyme. The initial rechallenge administration should be a low dose at a lower infusion rate, e.g., ½ the therapeutic dose (0.5 mg/kg) at 1/25 of the initial standard recommended rate (0.01 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/minute), as tolerated *[see Adverse Reactions (6.2)]*.

2.2 Preparation and Administration Instructions

Fabrazyme does not contain any preservatives. 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.

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 and 5 mg vials needed is based on the patient's body weight (kg) and the recommended dose of 1 mg/kg.

   Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the patient'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).

   Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 1.1 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 5 mg, 1 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 patient weight specified in Table 1 below. Prior to adding the volume of reconstituted Fabrazyme required for the patient dose, remove an equal volume of 0.9% Sodium Chloride Injection, USP from the infusion bag.

   Table 1 Total Infusion Volume Based on Patient Weight

Patient Weight (kg)	Minimum Total Volume (mL)
≤35	50
35.1 to 70	100
70.1 to 100	250
>100	500

   Patient dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabrazyme required for patient dose

   Example: Patient 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 patient 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.

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).

3 DOSAGE FORMS AND STRENGTHS

For injection: 5 mg or 35 mg of agalsidase beta as a white to off-white, lyophilized cake or powder in a single-dose vial for reconstitution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Hypersensitivity Reactions

In clinical trials and postmarketing safety experience with Fabrazyme, approximately 1% of patients developed anaphylactic or severe hypersensitivity reactions during Fabrazyme infusion.

In clinical trials with Fabrazyme, 10 of 238 patients developed IgE antibodies or skin test reactivity specific to Fabrazyme. Two of six patients in the rechallenge study discontinued treatment with Fabrazyme prematurely due to recurrent infusion-associated reactions. Four serious infusion-associated reactions occurred in three patients during Fabrazyme infusions, including bronchospasm, urticaria, hypotension, and development of Fabrazyme-specific antibodies. Other infusion-associated reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus.

Higher incidences of hypersensitivity reactions were observed in adult patients with persistent anti-Fabrazyme antibodies and in adult patients with high antibody titer compared to that in antibody negative adult patients *[see Adverse Reactions (6.2)]*.

Life-threatening anaphylactic and severe hypersensitivity reactions have been observed in patients during Fabrazyme infusions. Reactions have included localized angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension, generalized urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion. Interventions have included cardiopulmonary resuscitation, oxygen supplementation, intravenous fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and intravenous corticosteroids.

If anaphylactic or severe hypersensitivity reactions occur, immediately discontinue the administration of Fabrazyme and initiate necessary emergency treatment. Because of the potential for severe hypersensitivity reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

The risks and benefits of readministering Fabrazyme following an anaphylactic or severe hypersensitivity reaction should be considered. If a decision is made to readminister the product, ensure that appropriate medical emergency support is available *[see Dosage and Administration (2.1) and Adverse Reactions (6.2)]*.

Physicians should consider testing for IgE antibodies in patients who experienced suspected hypersensitivity reactions and consider the risks and benefits of continued treatment in patients with anti-Fabrazyme IgE antibodies. There are no marketed tests for antibodies against Fabrazyme. If testing is warranted, contact Genzyme Corporation at 1-800-745-4447.

Patients who have had a positive skin test to Fabrazyme or who have tested positive for Fabrazyme-specific IgE antibody have been rechallenged with Fabrazyme using a rechallenge

protocol. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available *[see Dosage and Administration (2.1) and Adverse Reactions (6.2)]*.

5.2 Infusion-Associated Reactions

In clinical trials of Fabrazyme, 59% of patients experienced infusion-associated reactions during Fabrazyme administration, some of which were severe. Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion. The incidence of infusion-associated reactions was higher in patients who were positive for anti-Fabrazyme antibodies than in patients who were negative for anti-Fabrazyme antibodies *[see Adverse Reactions (6.2)]*.

Severe infusion-associated reactions experienced by more than one patient in clinical trials of Fabrazyme included chills, vomiting, hypotension, and paresthesia. Other infusion-associated reactions included pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, urticaria, bradycardia, and somnolence *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

Most patients in clinical trials were pretreated with acetaminophen. In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion-associated reactions occurred in some patients after receiving pretreatment with antipyretics, antihistamines, and oral steroids. Infusion-associated reactions tended to decline in frequency with continued use of Fabrazyme. However, infusion-associated reactions may still occur despite extended duration of Fabrazyme treatment. If an infusion-associated reaction occurs, decrease the infusion rate, temporarily stop the infusion, and consider administrating additional antipyretics, antihistamines, and/or steroids. If severe infusion-associated reactions occur, discontinue administration of Fabrazyme immediately and initiate appropriate medical treatment. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated.

Because of the potential for severe infusion-associated reactions, ensure appropriate medical support measures are readily available when Fabrazyme is administered. Monitor closely patients who have experienced infusion-associated reactions when readministering Fabrazyme. Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion-associated reactions. Monitor closely patients with compromised cardiac function if Fabrazyme is administered to these patients *[see Warnings and Precautions (5.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Anaphylaxis and Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Infusion-Associated Reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in patients in clinical practice.

The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1 mg/kg Fabrazyme every two weeks in two separate double-blind, placebo-controlled clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58 patients enrolled in one of the two studies continued into an open-label extension study of Fabrazyme treatment for up to 54 additional months. Patients were treated with antipyretics and antihistamines prior to the infusions.

Most Common Adverse Reactions

Table 2 enumerates adverse reactions that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2) *[see Clinical Studies (14)]*. The most common adverse reactions reported with Fabrazyme were infusion-associated reactions, (Fabrazyme 59% vs placebo 27%) some of which were severe (Fabrazyme 5.0% vs placebo 1.7%). Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion.

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. Table 2 lists the common adverse reactions (≥ 5%):

Table 2: Summary of Common Adverse Reactions* in Clinical Trials (Study 1 and 2) of Patients with Fabry Disease

Adverse Reaction	Fabrazyme (n=80) %	Placebo (n=60) %
Upper respiratory tract infection[a]	53	42
Chills[b]	49	13
Pyrexia	39	22
Headache	39	28
Cough	33	25
Paresthesia	31	18
Fatigue	24	17
Peripheral edema	21	7
Dizziness	21	8
Rash	20	10
Pain in extremity	19	8
Myalgia[c]	18	7
Lower respiratory tract infection	18	7
Pain	16	13
Back pain	16	10
Hypertension	14	5
Pruritus	10	3
Tachycardia	9	3
Excoriation	9	2
Increased blood creatinine	9	5
Tinnitus	8	3

Adverse Reaction	Fabrazyme (n=80) %	Placebo (n=60) %
Dyspnea	8	2
Fall	6	3
Burning sensation	6	0
Anxiety	6	3
Depression	6	2
Wheezing	6	0
Hypoacusis	5	0
Chest discomfort	5	2
Fungal infection	5	0
Viral infection	5	0
Hot flush	5	0

* Reported at rate of at least 5% in Fabrazyme-treated patients and greater than 2 5% compared to placebo-treated patients.
a Includes reports of upper respiratory infection, nasal congestion, sinusitis, respiratory tract congestion, and pharyngitis.
b Includes reports of chills and feeling cold.
c Includes reports of myalgia and muscle spasms.

Most infusion-associated reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids.

Adverse Reactions in Pediatric Patients

In Study 3, the safety profile of Fabrazyme in pediatric Fabry disease patients, ages 8 to 16 years, was similar to that seen in adults. The most common adverse reactions (>20%) were headache, abdominal pain, pharyngitis, fever, nausea, vomiting, rhinitis, diarrhea, arthralgia, and dizziness *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Fabrazyme in the studies described below with the incidence of antibodies in other studies or to other agalsidase beta products may be misleading.

Patients with classic Fabry disease in Study 1, Study 2, and extension studies were tested at multiple time points for antibodies to agalsidase beta during the 55 to 58-month period. Approximately 83% (110 of 133) of adult patients receiving agalsidase beta developed antibodies; 77% (102/133) of patients developed neutralizing antibody (NAb) that inhibited *in vitro* agalsidase beta catalytic activity, which declined over time, and 6% (8/133) of patients developed NAb that inhibited cellular uptake. In pediatric patients with Fabry disease in Study 3 receiving the recommended dose who were 8 to <16 years of age, antibodies to agalsidase beta were detected in approximately 69% (11/16) of patients. Most patients who developed antibodies did so within the first 3 months of treatment. Antibody titers generally declined over time. Approximately 18% of adult patients who developed antibodies became antibody-negative by 74

weeks (median time) from the time of seroconversion; however, none of the pediatric patients became antibody negative. Female patients generally had lower incidence of antibodies and lower antibody titers compared to male patients. In Study 5, patients with truncating *GLA* mutations had higher incidence of antibodies and higher antibody titers compared to patients with nontruncating *GLA* mutations. Patients with plasma α-galactosidase A activity ≤1.5 nmol/hr/mL had higher incidence of antibodies and higher antibody titers compared to patients with plasma α-galactosidase A activity >1.5 nmol/hr/mL.

In general, over 90% of adult and pediatric patients treated with agalsidase beta achieved and maintained normalization of plasma globotriaosylceramide (GL-3) levels irrespective of developing antibodies to agalsidase beta.

Study 4 was an open-label, rechallenge study to evaluate the safety of Fabrazyme treatment in patients who had a positive skin test to Fabrazyme or who had tested positive for Fabrazyme-specific IgE antibodies. In this study, six adult male patients, who had experienced multiple or recurrent infusion-associated reactions during previous clinical trials of Fabrazyme, were rechallenged with Fabrazyme administered as a graded infusion for up to 52 weeks of treatment. The initial two rechallenge doses of Fabrazyme were administered as a 0.5 mg/kg dose per week at an initial infusion rate of 0.01 mg/min for the first 30 minutes (1/25th the usually recommended maximum infusion rate). The infusion rate was doubled every 30 minutes thereafter, as tolerated, for the remainder of the infusion up to a maximum rate of 0.25 mg/min. If the patient tolerated the infusion, the dose was increased to 1 mg/kg every two weeks, and the infusion rate was increased by slow upwards titration *[see Dosage and Administration (2.1)]*. Pretreatment was not permitted for at least the first 4 infusions in order to allow early recognition of acute systemic hypersensitivity reactions. Four of the six patients treated in this study received at least 26 weeks of Fabrazyme (2 patients received 26 weeks and 2 patients received 52 weeks), and two patients discontinued prematurely due to recurrent infusion-associated reactions *[see Warnings and Precautions (5.1, 5.2)]*.

Testing for IgE antibodies was performed in approximately 60 patients in clinical trials who experienced moderate to severe infusion-associated reactions or in whom mast cell activation was suspected. Seven of these patients tested positive for Fabrazyme-specific IgE antibodies or had a positive skin test to Fabrazyme. Patients who have had a positive skin test to Fabrazyme, or who have tested positive for Fabrazyme-specific IgE antibodies in clinical trials with Fabrazyme have been rechallenged *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1, 5.2)]*.

The incidences of hypersensitivity reactions were 51% (41/80) and 60% (25/42) in adult patients with persistent anti-Fabrazyme antibodies and in adult patients with high antibody titer, respectively, compared to 30% (7/23) in antibody-negative adult patients *[see Warnings and Precautions (5.1)]*.

The incidence of infusion-associated reactions was 76% (84/110) in antibody positive adult patients compared to 30% (7/23) in antibody negative adult patients. The incidence of infusion-associated reactions was 46% (5/11) in antibody positive pediatric patients compared to 20% (1/5) in antibody negative pediatric patients *[see Warnings and Precautions (5.2)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Fabrazyme. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Cardiovascular:* cardiorespiratory arrest, cardiac failure, myocardial infarction, palpitations
- *Hypersensitivity reactions:* anaphylaxis *[see Warnings and Precautions (5.1)]*, localized angioedema (including auricular swelling, eye swelling, dysphagia, lip swelling, edema, pharyngeal edema, face swelling, and swollen tongue), and bronchospasm
- *General:* hyperhidrosis, asthenia, infusion site reaction
- *Lymphatic:* lymphadenopathy
- *Musculoskeletal:* arthralgia
- *Neurologic:* cerebrovascular accident, hypoesthesia, oral hypoesthesia
- *Pulmonary*: respiratory failure, hypoxia
- *Renal:* renal failure
- *Vascular:* leukocytoclastic vasculitis

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

Pregnant women and women of reproductive potential should be encouraged to enroll in the Fabry patient registry. The registry will monitor the effect of Fabrazyme on pregnant women and their offspring. For more information, visit www.registrynxt.com or call 1-800-745-4447, extension 15500.

Risk Summary

Available data from postmarketing case reports and case series with Fabrazyme use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Reproduction studies performed in rats at doses up to 68 times the human dose have revealed no evidence of effects on embryo-fetal development *(see Data)*.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

The effects of agalsidase beta on embryo-fetal development in rats were evaluated at doses of 3, 10, and 30 mg/kg/day (up to 68 times the human dose of 1 mg/kg every 2 weeks on a body surface area basis) during gestation days 7 to 17. Hepatocellular necrosis consistent with

accumulation of test article was evident in maternal livers in the 10 and 30 mg/kg/day groups (23 and 68 times the human dose on a body surface area basis). There were no adverse effects of agalsidase beta on embryo-fetal development in rats.

8.2 Lactation

Risk Summary

There are no data on the presence of agalsidase beta in either human or animal milk, the effects of the drug on the breastfed infant, or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Fabrazyme and any potential adverse effects on the breastfed child from Fabrazyme or from the underlying maternal condition.

Lactating women with Fabry disease treated with Fabrazyme should be encouraged to enroll in the Fabry registry *[see Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Fabrazyme have been established in pediatric patients based on adequate and well-controlled studies in adults, a single-arm, open-label study in 16 pediatric patients with Fabry disease aged 8 to 16 years, and additional data in 24 patients with Fabry disease aged 2 to 7 years *[see Clinical Pharmacology (12.2) and Clinical Studies (14)]*.

The overall safety profile of Fabrazyme was similar between the pediatric and the adult population *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

8.5 Geriatric Use

Clinical studies of Fabrazyme did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Agalsidase beta is a recombinant human α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Purified agalsidase beta is a homodimeric glycoprotein with a molecular weight of approximately 100 kD. The mature protein is comprised of two subunits of 398 amino acids (approximately 51 kD), each of which contains three N-linked glycosylation sites. The enzyme 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. The specific activity of agalsidase beta is approximately 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1 μmole of a synthetic substrate, p-nitrophenyl-α-D-galactopyranoside, per minute under the assay conditions).

Agalsidase beta is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system.

Fabrazyme (agalsidase beta) for injection is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, preservative-free, 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fabrazyme (agalsidase beta) provides an exogenous source of α-galactosidase A in Fabry disease patients. Agalsidase beta is internalized and transported into lysosomes where it exerts enzymatic activity and reduces accumulated GL-3.

12.2 Pharmacodynamics

In Study 1, baseline mean values for plasma GL-3 were similar in the Fabrazyme (14.4 µg/mL) and the placebo (14.7 µg/mL) treatment groups. In the Fabrazyme treatment group, all 29 patients experienced normalization of plasma GL-3 levels (≤7.03 µg/mL) and they maintained normal plasma GL-3 levels for up to 60 months of treatment. Follow-up heart and kidney biopsies were assessed at month 54 in only 8 of the 44 patients, which showed sustained GL-3 clearance in the capillary endothelium of the kidney in 8 patients, and sustained GL-3 clearance in the capillary endothelium of the heart in 6 patients. The reduction in tissue GL-3 is summarized in the clinical studies section (Table 4) *[see Clinical Studies (14)]*.

In Study 2, patients in the Fabrazyme treatment group had mean plasma GL-3 levels that decreased from 9.0 µg/mL at baseline (N=49) to 4.8 µg/mL at one year (N=37) and 4.8 µg/mL at two years (N=18). In the placebo group, the mean plasma GL-3 was 9.1 µg/mL at baseline (N=31), 8.8 µg/mL at one year (N=21), and 9.4 µg/mL at two years (N=7).

In Study 3, at baseline, all 14 males had elevated plasma GL-3 levels (i.e., >7.03 µg/mL), whereas the two female patients had normal plasma GL-3 levels. At weeks 24 and 48 of treatment, all 14 males had plasma GL-3 within the normal range. The two female patients' plasma GL-3 levels remained normal through study week 48. Histological evaluation of the capillary endothelium (vasculature), deep vessel endothelium, deep vessel smooth muscle cells, and perineurium of biopsied skin was conducted using histochemistry with light microscopy. Scoring was on a scale of 0 to 3 (0 defined as none; 1 as mild, 2 as moderate, and 3 as severe). At baseline, 12 of the 14 males had GL-3 inclusions present on skin biopsy (scores 1, 2, or 3) and all 12 achieved GL-3 inclusion scores of 0 at weeks 24 and 48 of treatment. The two females had no GL-3 inclusions in skin at baseline.

In Study 5, in an analysis of 24 Fabrazyme-treated pediatric patients with Fabry disease aged 2 to <8 years at Fabrazyme initiation and with elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, plasma GL-3 levels fell within the normal range (i.e., ≤7.03 µg/mL) in 91% (20/22), 95% (18/19), and 92% (12/13) of patients at 6, 12, and 24 months, respectively.

12.3 Pharmacokinetics

The pharmacokinetics of Fabrazyme in clinical studies with adult and pediatric patients with Fabry disease are summarized in Table 3.

Fabrazyme exhibited nonlinear pharmacokinetics following intravenous infusions at 0.3 (30% of the approved recommended dosage), 1 mg/kg, and 3 mg/kg (3 times the approved recommended dosage) in adult patients. The area under the plasma concentration-time curve (AUC_{inf}) and the maximum plasma concentration (C_{max}) increased greater than dose proportional with increasing doses. The AUC_{inf} and C_{max} following multiple dose administrations were comparable to their values at the first dose.

In pediatric patients 8 to 16 years of age with body weight ranging from 27 to 65 kg, the AUC_{inf} and C_{max} following multiple dose administrations were higher compared to their values at the first dose. The increased plasma concentrations following multiple dose administrations in pediatric patients could be due to formation of anti-drug antibodies; however, such impact was not observed in adult patients *[see Adverse Reactions (6.2) and Use in Specific Populations (8.4)]*.

Table 3: Fabrazyme Pharmacokinetic Summary

Dose	Regimen	Mean Infusion Length (min)	Infusion number (n= patients)	AUC_{inf} μg min/mL	C_{max} μg/mL	Half-life min	CL mL/min/ kg	Vss* mL/kg
Study FB9702-01: Phase 1/2 Study in Adult Patients with Fabry Disease								
0.3 mg/kg	q14 days × 5	132	1 (n=3)	79 ± 24	0.6 ± 0.2	92 ± 27	4.1 ± 1.2	225 ± 62
		128	5 (n=3)	74 ± 30	0.6 ± 0.2	78 ± 67	4.6 ± 2.2	330 ± 231
1 mg/kg	q14 days × 5	115	1 (n=3)	496 ± 137	5.0 ± 1.1	67 ± 12	2.1 ± 0.7	112 ± 13
		120	5 (n=2)	466 ± 382	4.74 ± 4.3	45 ± 3	3.2 ± 2.6	243 ± 236
3 mg/kg	q14 days × 5	129	1 (n=2)	4168 ± 1401	29.7 ± 14.6	102 ± 4	0.8 ± 0.3	81 ± 45
		300	5 (n=2)	4327 ± 2074	19.8 ± 5.8	87 ± 21	0.8 ± 0.4	165 ± 80
Study 1: Phase 3 Study in Adult Patients with Fabry Disease								
1 mg/kg	q14 days × 11	280	1-3 (n=11)	649 ± 226	3.5 ± 1.6	89 ± 20	1.8 ± 0.8	120 ± 80
		280	7 (n=11)	372 ± 223	2.1 ± 1.14	82 ± 25	4.9 ± 5.6	570 ± 710
		300	11 (n=11)	784 ± 521	3.5 ± 2.2	119 ± 49	2.3 ± 2.2	280 ± 230
Study 3: Phase 2 Study in Pediatric Patients with Fabry Disease								
1 mg/kg	q14 days × 24	208	1 (n=8-9)	344 ± 307	2.2 ± 1.9	86 ± 27	5.8 ± 4.6	1097 ± 912
		111	12 (n=15)	1007 ± 688	4.9 ± 2.4	130 ± 41	1.6 ± 1.2	292 ± 185
		108	24 (n=9-10)	1238 ± 547	7.1 ± 4.4	151 ± 59	1.1 ± 0.8	247 ± 146

*Vss = volume of distribution at steady state
All data reported as the mean ± standard deviation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies to assess the carcinogenic or mutagenic potential of Fabrazyme. A study to evaluate the effects of agalsidase beta on fertility and general

reproduction was performed in male and female rats at doses up to 10 mg/kg/day (23 times the human dose, on a body surface area basis). There were no adverse effects of agalsidase beta on fertility and early embryonic development in rats.

14 CLINICAL STUDIES

The safety and efficacy of Fabrazyme were assessed in four clinical studies in patients with Fabry disease and one matched analysis based on data from observational studies.

Study 1 was a randomized, double-blind, placebo-controlled, multinational, multicenter study of 58 patients with Fabry disease (56 males and 2 females), ages 16 to 61 years, all naive to enzyme replacement therapy *[see Clinical Pharmacology (12.2)]*. Patients were randomized 1:1 to receive either Fabrazyme 1 mg/kg every 2 weeks or placebo for 20 weeks. Patients had a median age of 24 years in the placebo group and 33 years in the Fabrazyme group at baseline. At baseline, all patients had plasma αGAL activity below the detection limit and 79% had leukocyte αGAL activity below the detection limit. The median plasma GL-3 at baseline was 14.4 ng/uL in the placebo group and 14.7 ng/uL in the Fabrazyme group with the overall range of <1.2 to 36 ng/uL. The median eGFR at baseline was 98.5 mL/hr in the placebo group and 83.0 mL/hr in the Fabrazyme group (overall range 24 to 153 mL/hr). All patients were pretreated with acetaminophen and an antihistamine. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion-associated reactions. Tissue biopsy specimens (kidney, heart, skin) were evaluated at baseline and at week 20 by light microscopy for the presence and number of GL-3 inclusions using a semi-quantitative methodology. Renal interstitial capillaries were scored based on the number of GL-3 inclusions on a scale of 0 to 3 (0 defined as “nearly none” or “trace,” 1 defined as “mild,” 2 defined as “moderate,” and 3 defined as “severe”). The primary endpoint was the proportion of patients in either group with a renal capillary GL-3 inclusion score of zero at week 20. In the Fabrazyme group, 20 of 29 (69%) patients achieved a score of zero while 0 of 29 placebo-treated patients achieved a score of zero ($p<0.001$). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin (Table 4). All 58 patients who completed Study 1 were subsequently treated with Fabrazyme 1 mg/kg every two weeks in an open-label extension study. After six months of open-label treatment, most patients with available biopsy data achieved a GL-3 inclusion score of 0 in capillary endothelium (Table 4).

Table 4: Proportion of Patients with Tissue GL-3 Inclusion Score of Zero (Study 1 and Open Label Treatment)

	20 weeks of randomized treatment in Study 1		**6 months of Fabrazyme open-label treatment**	
	Placebo (n=29)	Fabrazyme (n=29)	Placebo/Fabrazyme (n=29)*	Fabrazyme/Fabrazyme (n=29)*
Kidney	0/29	20/29	24/24	23/25
Heart	1/29	21/29	13/18	19/22
Skin	1/29	29/29	25/26	26/27

* Results reported where biopsies were available.

Study 2 was a randomized (2:1 Fabrazyme to placebo), double-blind, placebo-controlled, multinational, multicenter study of 82 patients (72 males and 10 females) with Fabry disease, all naive to enzyme replacement therapy *[see Clinical Pharmacology (12.2)]*. Of the 82 enrolled patients, 51 and 31 patients were randomized to the Fabrazyme and placebo groups, respectively.

Patients were 20 to 72 years of age with a median age of 45 years at baseline, a median age of 36 years at Fabry disease diagnosis, and at a median of 10 years at symptom onset. The median plasma GL-3 at baseline was 9.3 ug/mL in the placebo group and 8.9 ug/mL in the Fabrazyme group with the overall range of 2.8 to 18.9 ug/mL. At baseline, patients had median plasma αGAL activity 1.5 nmol/hour/mL (range: 0 to 1.5), leukocyte αGAL activity 1.8 nmol/hour/mL (range: 0 to 4.0), eGFR 52 mL/min/1.73 m^2 (range: 25 to 113), and protein to creatinine ratio 0.9 mg/mg (range: 0 to 7.3). Patients received either 1 mg/kg Fabrazyme IV or placebo every two weeks for up to 35 months (median follow up 18.5 months). The primary efficacy endpoint was the time to first occurrence of a clinically significant event (renal, cardiac, or cerebrovascular event, or death). A total of 14 of 51 (28%) Fabrazyme-treated patients and 13 of 31 (42%) placebo-treated patients experienced a clinically significant event (HR 0.57, 95% CI: 0.27, 1.22).

Study 3 (Pediatric Study) was an open-label, single-arm, multinational, multicenter study in 16 pediatric patients with Fabry disease (14 males, 2 females), aged 8 to 16 years (median 12 years) *[see Clinical Pharmacology (12.2)]*. At baseline, patients had median plasma αGAL activity 0.2 nmol/hour/mL (range: 0.0, 2.0) and median leukocyte αGAL activity 0.5 nmol/hour/mg (range: 0.0, 12.5). All 14 males had elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, whereas the two females had normal plasma GL-3 levels. Median eGFR was normal (112.1 mL/min/1.73 m^2) at baseline and did not change during treatment, and median urinary protein was 151.0 mg/24 hr (range: 70.0, 431.0). All patients received Fabrazyme 1 mg/kg every two weeks for up to 48 weeks.

Study 5 was a long-term, observational study assessing the rate of decline in renal function (eGFR slope) in 122 patients with Fabry disease aged 16 years and older treated with Fabrazyme. Treated patients were matched 1:1 based on age (at Fabrazyme initiation), sex, Fabry disease subtype (classic or non-classic), and baseline eGFR to a historical cohort of untreated patients with Fabry disease. The median follow-up time was 3 years in the untreated group and 4.5 years in the treated group (maximum follow-up time 5 years in both groups). In the matched cohort, the median age (at Fabrazyme initiation) was 35 years, 72% of patients were male, 84% of patients had the classic Fabry disease subtype, and the median baseline eGFR was 93 mL/min/1.73 m^2. The estimated mean eGFR slope was -1.5 mL/min/1.73 m^2/year in the Fabrazyme-treated group and -3.2 mL/min/1.73 m^2/year in the untreated group (eGFR slope difference: 1.7 mL/min/1.73 m^2/year; 95% CI: 0.5, 3.0).

16 HOW SUPPLIED/STORAGE AND HANDLING

Fabrazyme (agalsidase beta) for injection is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-dose vials.

35 mg vial: NDC 58468-0040-1

5 mg vial: NDC 58468-0041-1

Refrigerate vials of Fabrazyme at 2°C to 8°C (36°F to 46°F). Do not use Fabrazyme after the expiration date on the vial.

This product contains no preservatives. Reconstituted and diluted solutions of Fabrazyme should be used 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) *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Patient Registry

Inform patients that a Registry has been established in order to better understand the variability and progression of Fabry disease in the population as a whole and in women *[see Use in Specific Populations (8.1)]*, and to monitor and evaluate long-term treatment effects of Fabrazyme. The Registry will also monitor the effect of Fabrazyme on pregnant women and their offspring. Encourage patients to participate. Advise patients that their participation is voluntary and may involve long-term follow-up. For more information, visit www.registrynxt.com or call 1-800-745-4447, extension 15500.

Manufactured by:
Genzyme Corporation
50 Binney Street
Cambridge, MA 02142
U.S. License Number: 1596

Fabrazyme and Genzyme are registered trademarks of Genzyme Corporation.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103979Orig1s5309

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

sBLA Multi-Disciplinary Review and Evaluation

Application Type	Prior Approval Supplemental BLA (efficacy)
Application Number	BLA 103979/ S-5309
Priority or Standard	Standard
Submission Date	February 14, 2020
Received Date	February 14, 2020
PDUFA Goal Date	March 14, 2021 (including major amendment)
Division/Office	Division of Rare Diseases and Medical Genetics/ Office of New Drugs
Review Completion Date	March 11, 2021
Established Name	Agalsidase beta
Trade Name	Fabrazyme
Pharmacologic Class	Enzyme replacement therapy
Applicant	Sanofi Genzyme
Dosage form	Lyophilized powder for reconstitution
Applicant proposed Dosing Regimen	1 mg/kg IV every 2 weeks
Applicant Proposed Indication	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term	16652001 Fabry disease (disorder)
Recommendation on Regulatory Action	approval
Final Indication	treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease
Final SNOMED CT Indication Disease Term	16652001 Fabry disease (disorder)
Final Dosing Regimen	1 mg/kg IV every 2 weeks

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Nicolas Kong/ Michael G. White
Nonclinical Reviewer	N/A
Nonclinical Team Leader	N/A
Office of Clinical Pharmacology Reviewer	Xiaouhui Li
Office of Clinical Pharmacology Team Leader	Jie Wang
Clinical Reviewer	Anita Zaidi
Clinical Team Leader	Anita Zaidi
Statistical Reviewer	Therri Usher
Statistical Team Leader	Yan Wang
Cross-Disciplinary Team Leader	Anita Zaidi
Deputy Division Director	Patroula Smpokou

Consultants (see separate consultation reviews in DARRTS):

- Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE)
- Division of Epidemiology I, OSE
- Division of Cardiology and Nephrology, Office of New Drugs
- Division of Pediatrics and Maternal Health, Office of New Drugs

Signatures

Signature page is attached to the review

Glossary

ACEI	angiotensin-converting enzyme inhibitor
ADA	anti-drug antibodies
AE	adverse event
ARB	angiotensin receptor blocker
AUC	area under the curve
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CI	confidence interval
Cr	creatinine
eGFR	estimated glomerular filtration rate
ERT	enzyme replacement therapy
ESRD	end-stage renal disease
FD	Fabry disease
FDA	Food and Drug Administration
FSS	Fabrazyme Scoring System
GLA	alpha galactosidase A gene
GL-3	globotriaosylceramide
IAB	Independent Adjudication Board
IAR	infusion-associated reaction
ITT	intent to treat
IV	intravenous
LM	light microscopy
Lyso-GL-3	globotriaosylsphingosine
NAb	neutralizing antibodies
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PP	per protocol
PTC	peritubular capillaries
Q2W	every two weeks
SAP	statistical analysis plan
sBLA	supplemental Biologic License Application
SE	surrogate endpoint

1. Executive Summary

1.1. Introduction

Fabrazyme (agalsidase beta) is a recombinant human α-galactosidase (α-GAL) A enzyme which acts as an exogenous source of the deficient/absent endogenous α-GAL A enzyme in Fabry disease (FD), a rare, serious, monogenic inborn error of glycosphingolipid metabolism. This single enzymatic deficiency leads to progressive intralysosomal accumulation of the undegraded glycosphingolipids globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-GL-3) causing progressive cellular dysfunction, tissue damage, and organ impairment. Tissue and circulating levels of GL-3 and lyso-GL-3 are consistently elevated in patients with FD and the degree of that elevation typically relates to the degree of tissue damage and the severity of the disease manifestations in particular organs, such as the kidneys (Germain 2010). Reduction in biopsied renal peritubular capillary GL-3 inclusions was previously used as a surrogate endpoint supporting accelerated approval of products intended for treatment of FD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for Fabrazyme was previously established based on the demonstration of a large and statistically significant treatment effect on the surrogate endpoint (SE) of relative clearance/substantial reduction of accumulated globotriaosylceramide (GL-3) in biopsied renal peritubular capillaries (specifically, the achievement of a score of zero on light microscopy using the Fabrazyme Scoring System) in the randomized, placebo-controlled, phase 3 trial AGAL-1-002-98. At the time of approval, it was determined that this renal histologic endpoint was reasonably likely to predict clinical benefit and, thus, formed the basis for Fabrazyme's accelerated approval. New evidence submitted in this application includes long-term, observational data suggesting that treatment with Fabrazyme may be associated with slower renal disease progression (eGFR slope) in Fabrazyme-treated vs untreated Fabry disease (FD) patients as well as several published studies establishing the central pathophysiological role of tissue GL-3 accumulation in FD which has progressive, detrimental effects on tissue structure and organ function in FD. This new evidence was considered together with previous findings from the randomized, placebo-controlled clinical trial AGAL-008-00 which suggested a comparatively favorable clinical effect of Fabrazyme vs placebo on the incidence of Fabry-associated clinical events (renal, cardiac, cerebrovascular events, or death). Based on the preponderance of the available scientific evidence, we conclude that the renal histologic SE, which was used as the basis for accelerated approval previously, is sufficiently validated and can predict clinical benefit in this development program. As such, the observed treatment effect on this SE which previously established substantial evidence of effectiveness for Fabrazyme's accelerated approval, can now form the basis for the product's full (traditional) approval.

Overall, the scientific evidence supporting the surrogacy of the renal histologic endpoint for full approval of Fabrazyme in this application includes the following:

- Published literature collectively showing that: a) accumulation of GL-3 is toxic to tissues, b) GL-3 accumulates in tissues/organs which exhibit structural damage and functional impairment due to Fabry disease, and c) GL-3 accumulation in affected tissues correlates with tissue and end-organ damage and functional impairment.
- Analyses of data from the Fabrazyme clinical studies showing that: a) Fabrazyme substantially reduced accumulated GL-3 in biopsied capillary endothelium of skin and heart in treated adults and of skin in pediatric patients, and b) Fabrazyme substantially reduced accumulated GL-3 in biopsied peritubular renal capillaries in treated adult patients as evidenced by the relative reduction of GL-3 inclusion burden to a score of zero (no/minimal GL-3 inclusions) on light microscopy using the Fabrazyme Scoring System in a majority of Fabrazyme-treated patients compared to no placebo patients in trial AGAL-1-002-98.
- Exploratory analyses of clinical data from the phase 4, randomized, placebo-controlled clinical trial AGAL-008-00 that lend support to a favorable clinical effect of Fabrazyme on the incidence of Fabry-associated clinical events (renal, cardiac, cerebrovascular events, or death).
- Exploratory analyses of clinical data from a long-term, observational study showing that Fabrazyme treatment may be associated with a slower decline in renal function (based on eGFR slope) compared to no treatment in adults with Fabry disease who were matched on important baseline predictive variables.

The safety profile of Fabrazyme is well-characterized over the approximately 18 years since its accelerated approval through previous clinical trial safety assessments and extensive post-marketing safety surveillance. Common adverse reactions associated with the use of Fabrazyme generally include hypersensitivity reactions and infusion-associated reactions, both consistent with the expected hypersensitivity to this foreign protein. These known safety risks can be adequately mitigated through product labeling and further evaluated through routine pharmacovigilance.

In summary, we conclude that Fabrazyme's demonstrated clinical benefit outweighs the known safety risks when used as recommended in the approved labeling and we, recommend its full approval for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

1.3. Benefit-Risk Assessment

Fabry disease (FD) is a rare and serious inborn error of glycosphingolipid metabolism characterized by deficiency of a single lysosomal enzyme, alpha-galactosidase A. This single enzyme defect leads to progressive accumulation of the upstream metabolite (substrate) globotriaosylceramide (GL-3) due to the enzymatic block in the pathway of its degradation. The major clinical manifestations, which are chronically progressive, severely debilitating, and sometimes life-threatening, include chronic renal impairment leading to renal failure, myocardial infarction and arrhythmias leading to sudden death, strokes, and chronic neuropathic pain and gastrointestinal dysmotility.

Fabrazyme is a recombinant, human alpha-galactosidase A enzyme that replaces the deficient enzyme in FD. Fabrazyme was granted accelerated approval in 2003 based on a reduction in GL-3 deposition in renal peritubular capillaries, a surrogate endpoint that FDA determined was reasonably likely to predict clinical benefit. In this supplemental application, the Applicant has submitted evidence accrued since the Fabrazyme approval that, in the context of this rare disease, sufficiently establishes that the GL-3 deposition reductions with Fabrazyme do, in fact, predict clinical benefit, supporting full approval. This evidence consists of (1) data showing that accumulation of GL-3 is toxic to tissue, that GL-3 accumulates in tissues where Fabry disease causes structural damage and functional loss, and that GL-3 accumulation correlates with tissue damage, (2) data showing that Fabrazyme reduces or clears GL-3 from the capillary endothelium of the skin and heart, in addition to the data available at the time of approval that showed Fabrazyme substantially reduces GL-3 from peritubular renal capillaries (as evidenced by reduction of GL-3 to a score of zero on light microscopy in a majority of the renal biopsies from treated patients), exploratory analyses from a second randomized, placebo-controlled clinical trial (AGAL-008-00) that lends support to an effect of Fabrazyme on the incidence of Fabry-associated clinical events (renal, cardiac, cerebrovascular events, or death), and exploratory analyses from a longer-term observational study showing that Fabrazyme treatment was associated with slower decline in renal function compared to no treatment in Fabry disease patients matched on important baseline predictive variables. The entirety of this evidence in the context of a rare disease supports a conclusion that Fabrazyme's dramatic effect on the surrogate endpoint of accumulated GL-3 substrate in biopsied renal peritubular capillaries, does in fact, predict clinical benefit in the treatment of adult and pediatric patients with Fabry disease.

Safety: the Applicant submitted a large database of post-marketing safety data collected from voluntary reports. The safety data of the completed trials was previously reviewed and included in the product's approved label. Overall, there were no new serious safety risks identified through post-marketing surveillance. In all, the most common adverse reactions include hypersensitivity reactions and infusion-associated reactions from the product's immunogenicity as a foreign protein.

Benefit-Risk determination: the entirety of the submitted scientific evidence demonstrates the clinical benefit of Fabrazyme in adult and pediatric patients with FD (as described above and in detail in section 8), which outweighs the known and well-characterized safety risks associated with the use of the product. This favorable benefit-risk assessment supports the full approval of Fabrazyme for the proposed

indication.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Fabry disease (FD) is a rare, X-linked, slowly progressive, monogenic disease caused by the deficiency of the lysosomal enzyme alpha-galactosidase A (alpha-Gal A) which breaks down the glycosphingolipid globotriaosylceramide (GL-3) in lysosomes. • Progressive intralysosomal accumulation of the substrates GL-3 and its related product lyso-GL-3 in affected tissues cause tissue damage and organ dysfunction with progressive and life-threatening complications (e.g. chronic renal failure, cardiac arrhythmias, myocardial infarction, sudden death, stroke). • Both males and females are affected. The disease course is heterogeneous, especially in females, and generally depends on the amount of residual alpha-Gal A enzyme activity in males and females and on the degree of X-inactivation in affected tissues in females.	• FD is a serious and rare disease with chronic, life-threatening complications. • GL-3 and lyso-GL-3 are the tissue-toxic intermediates which accumulate in affected tissues and mediate the disease pathophysiological mechanism. • Reduction of accumulated GL-3 in affected tissues is expected to ameliorate and/or prevent the clinical effects from the cellular and tissue damage and organ dyfunction caused by this single enzyme deficiency.
Current Treatment Options	• Fabrazyme has been approved under the accelerated approval pathway since 2003 based on histological clearance of the substrate GL-3 in cells of biopsied renal, cardiac, and skin tissues. • Fabrazyme constitutes standard of care therapy and is the only therapy approved for FD patients of all ages and regardless of underlying gene mutation. • Galafold, a chaperone small molecule drug, was approved under accelerated approval for adults with FD who have specific gene mutations (predominantly missense mutations, which are found largely in patients with mild, late-onset FD) that are "amenable" to treatment with the drug based on results of an in vitro assay (human embryonic kidney assay).	• Enzyme replacement therapy (ERT) provides an exogenous source of the deficient enzyme which works to break down the accumulated GL-3 in lysosomes and prevents further accumulation in affected tissues. • Both currently approved treatments, Fabrazyme and Galafold, a targeted chaperone for a limited Fabry subpopulation, were approved under accelerated approval with clinical benefit still unverified.

Benefit	• Fabrazyme was granted accelerated approval based on substantial reduction/clearance of the disease substrate GL-3 in renal peritubular capillaries in treated patients vs placebo patients in a phase 3, randomized, double-blind, placebo-controlled trial (trial AGAL-1-002-98). After 6 months of treatment, 20/29 (69%) patients in the treatment group had a slide score of 0 (signifying no visible inclusions), whereas 0/29 patients in the placebo group had a slide score of 0.
	• Since the accelerated approval, additional evidence has accrued, that in its entirety, supports a conclusion that the surrogate endpoint used for Fabrazyme's accelerated approval now appears to predict clinical benefit and, thus, support the product's full approval. This evidence includes:
	  • 15 published studies, including in-vivo, in-vitro data and case reports that have shown that the substrate GL-3 deposition leads to damage to the tissue that it accumulates in and that the degree of deposition correlates with the degree of tissue damage.
	  • Exploratory analyses from Trial AGAL-008-00, a post-approval, phase 4, randomized, double-blind, placebo-controlled trial that lends support to the treatment effect of Fabrazyme on a composite of clinical events relevant to this disease (renal, cardiac, stroke, death). The primary analysis showed a HR 0.57; 95% CI: 0.27-1.22; p 0.14) for Fabrazyme compared to placebo. The estimated HR when excluding two patients with transient increases in creatinine (unlikely to be indicative of a renal event as defined in the primary endpoint) was 0.48 (95% CI: 0.22, 1.04) favoring Fabrazyme.
	  • Exploratory analyses from a long-term observational study showing a smaller decline in the mean estimated glomerular filtration rate (eGFR) slope of -1.5 mL/ min/1.73m^2/year in the Fabrazyme-treated patients and -3.2 mL/ min/1.73m^2/year in the untreated patients suggesting slower decline in renal function in patients treated with Fabrazyme compared to those who were not.
		• Substantial evidence of effectiveness has previously been established for Fabrazyme at the time of its accelerated approval.
		• In the context of this rare disease, the entirety of the accrued scientific evidence since Fabrazyme's approval presented in this sBLA in conjunction with data from all Fabrazyme clinical studies adequately support that Fabrazyme's large treatment effect on the renal histologic surrogate endpoint is predictive of clinical benefit in the Fabrazyme development program.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No new controlled safety data from trials were submitted for review in this application • Post-marketing safety reports and safety data from the Fabry Registry study were reviewed and those align with the known adverse reactions of Fabrazyme including hypersensitivity and infusion-associated reactions.	• There are no new serious or unexpected adverse reactions identified through post-marketing surveillance. • Routine pharmacovigilance is sufficient to monitor the safety of the product post-approval.

1.4. Patient Experience Data Relevant to This Application

☐	The patient experience data that were submitted as part of the application include:		Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data	
	☐	Qualitative studies	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
X	**Patient experience data was not submitted in this application**		

2. Therapeutic Context

2.1. Analysis of Condition

Fabry disease is an X-linked, slowly progressive, lysosomal storage disease affecting both males and females. With an estimated incidence of 1:40,000 to 1:117,000 (Germain 2010), it is the second most common lysosomal storage disorder after Gaucher disease. FD is caused by galactosidase α gene (GLA) mutations (referred to as variants) resulting in complete or partial deficiency of the lysosomal enzyme alpha-galactosidase A (alpha-Gal A) which breaks down glycosphingolipids within the lysosomes. The enzyme deficiency causes progressive intralysosomal accumulation of the substrate glycosphingolipids globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-GL3) in tissues such as vascular endothelial, epithelial, smooth muscle, and ganglion cells (Spada et al. 2006). Organs primarily affected in FD include the kidneys, cardiovascular system, cerebrovascular system, gastrointestinal tract, peripheral nerves, and skin.

FD spans a spectrum of disease severity ranging from severe, early-onset disease (classic FD) to later-onset, milder disease (late-onset FD) to even asymptomatic individuals (some heterozygous females). The first clinical manifestations in the classic, early-onset form in males typically appear in childhood around age 5 years with development of diarrhea or abdominal pain, neuropathic pain crises, and/or hypo/anhidrosis. Females with FD typically present at age 9 years and exhibit high variability in symptoms and age of onset. Typically, chronic renal insufficiency (initially manifesting as proteinuria, on average appearing in the 20s in classic FD males) slowly progresses to renal failure and end stage renal disease. Gradual decline in renal function and the development of azotemia typically occur in the third to fifth decades and are managed with hemodialysis and renal transplantation (Spada et al. 2006). Males with classic FD with untreated end-stage renal disease (ESRD) typically die in their early 40s (Waldek and Feriozzi 2014). Major causes of mortality in FD include life-threatening cardiovascular and cerebrovascular complications. The cardiovascular manifestations can include hypertension, left ventricular hypertrophy, and ischemic heart disease which can progress to heart failure, myocardial infarction or arrhythmias (Patel et al. 2011). Cardiac disease is progressive and is typically present in most males with classic FD by middle age. Certain cardiac phenotypes can develop hypertrophic cardiomyopathy that may lead to cardiovascular events. Cardiac manifestations tend to occur earlier in affected males than in females (Linhart et al. 2007). The disease course in late-onset FD is highly variable with some patients experiencing severe manifestations and a more rapid rate of disease progression, while others only have mild or slowly progressive symptoms over their lifetime. Typically, affected males experience more severe disease manifestations and a faster rate of disease progression than affected females due to the X-linked nature of the disease. Some affected females may be asymptomatic or only experience few or mild symptoms over their lifetime and have a later disease onset. Other females may develop severe symptoms, although usually at a later age than affected males (Spada et al. 2006). Disease manifestations in females with FD depend on the degree of X-

inactivation (which is random) of the allele carrying the FD mutation. In females in which the abnormal allele is inactive in relevant tissues, disease manifestations may be milder or appear later in life or not at all.

2.2. Analysis of Current Treatment Options

Galafold (migalastat) is an α-galactosidase A (α-Gal A) pharmacological chaperone that was approved under the accelerated approval regulations, 21 CFR 314.510 (subpart H) in 2018 in the United States and is indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable GLA variant based on in-vitro assay data. It is given as an oral dose of 123mg every other day. The phase 3 trial of Galafold included patients with a diagnosis of FD with a GLA variant responsive to Galafold based on the clinical trial human embryonic kidney assay. Treatment with Galafold resulted in a greater reduction in GL-3 deposition in the KIC endothelial cells, as assessed by renal biopsy using the BLISS methodology, after 6 months of treatment, compared to placebo. The indication was approved under accelerated approval based on reduction in kidney interstitial capillary cell globotriaosylceramide (KIC GL-3) substrate.

Other Products (Approved Outside of the United States)

Replagal (agalsidase alpha) is a recombinant human alpha-Gal A enzyme (containing modified mannose residues) approved in multiple countries including in Europe, Australia, Canada, and Japan for long-term treatment of FD.

Fabagal (agalsidase-beta) is a recombinant analogue of human alpha-galactosidase A and is produced by recombinant DNA technology using Chinese hamster ovary cell culture. Fabagal was approved in South Korea for long term treatment of patients with FD.

3. Regulatory Background

Fabrazyme received accelerated approval on April 24, 2003 based on trial AGAL-1-002-98, a phase 3, placebo-controlled, randomized, double blind trial in 58 patients with FD treated over 20 weeks. Fabrazyme is indicated for the treatment of patients with Fabry disease. The approval decision was based on clearance of GL-3 (surrogate endpoint) in capillary endothelial cells of biopsied renal tissue in trial AGAL-1-002-98. As a postmarketing requirement (PMR), the Applicant conducted a phase 4 randomized, double-blind, placebo-controlled clinical trial (AGAL-008-00) in 82 patients with FD with a primary endpoint of time to first occurrence of a clinically significant renal, cardiac, or cerebrovascular event or death. Essential design elements and results of this trial are summarized in sections 8.2.2 and 8.2.3 of this review. (b) (4)

(b) (4)

. At that time, a revised PMC #2 (new PMC #7) was agreed upon with the Applicant as a requirement for the accelerated approval and was issued as follows:

> *"Genzyme commits to performing additional analyses of the data obtained in the registry of patients with Fabry disease being treated with Agalsidase beta that was established to obtain long-term clinical status information. Additional analyses of the registry data are to be performed for the purpose of establishing the clinical benefit of Fabrazyme on progression of renal disease and other end-organ disease endpoints in patients with Fabry disease. Additional analyses to be performed include the following: a. Progression of renal disease, including assessment of time of onset of proteinuria, hypertension, chronic renal insufficiency, end-stage renal disease, and death. b. Exploration of the effects of endogenous alpha GAL activity and genetic mutations on progression of renal disease, the occurrence of significant clinical events, and the development of anti-recombinant-human-alpha GAL (anti-rh alpha GAL) IgG antibodies. c. Progression of renal disease by age of initiation of enzyme replacement therapy (ERT) with Fabrazyme for age groups such as <10 years of age, greater than or equal to 10 to <15 years of age, greater than or equal to 15 to 20 years of age, and in 10-year increments at >20 years of age. d. Progression of renal disease by treatment administered, including ERT with Fabrazyme or no treatment. Reports will include data on patients who have received other Fabry specific treatments e. Progression of renal disease by glomerular filtration rate status (>60 ml/min/1.73 m2 or <60 ml/min/1.73 m2) at initiation of ERT with Fabrazyme. f. Time of first significant clinical event. g. Analysis of anti-rh alpha GAL IgG antibodies titers on the progression of renal disease and the occurrence of significant clinical events. A final analysis plan for the registry study protocol will be submitted to CDER by October 25, 2008. The final study report under this registry will be submitted to CDER by July 30, 2021."*

The indication was expanded to include pediatric patients in 2006 after the submission of the results of pediatric trial AGAL-016-01 which evaluated pediatric patients with FD who were 8 years and older.

Table 1. Key Regulatory History

Date	Outcome
1/19/1988	Orphan drug designation granted
5/8/1998	Fast Track designation granted
6/3/2000	BLA submission for accelerated approval (data package from trial AGAL 1-002-98)
1/13/2003	AC meeting: voted 14 to 1 that the surrogate endpoint of GL-3 clearance from capillary endothelium of the kidney was reasonably likely to predict clinical benefit in FD
4/24/2003	Accelerated approval
(b) (4)	(b) (4)
9/29/2006	sBLA submission (data package from pediatric trial AGAL-016-01): indication expanded to include pediatric patients with FD
(b) (4)	(b) (4)
5/21/2019	Pre-sBLA meeting for full approval (data package from all completed trials. long-term, observational data, scientific evidence validating the surrogate endpoint)

Source: Applicant table with reviewer edits (2.5 Clinical Overview Appendix 2)
Abbreviations: AC = Advisory Committee; CR = complete response; FD = Fabry disease; GL-3 = globotriaosylceramide

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

Not applicable.

5. Nonclinical Pharmacology/Toxicology

Not applicable.

6. Clinical Pharmacology

6.1. Executive Summary

Fabrazyme (agalsidase beta) is a recombinant, human α-galactosidase A, previously approved via the accelerated approval pathway for the treatment of patients with Fabry disease. The approved dosage regimen in both adult and pediatric patients is 1 mg/kg administered every two weeks (Q2W) as an intravenous (IV) infusion.

In this sBLA, the Applicant provided a summary of pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity data of agalsidase beta in clinical studies in adult and pediatric patients > 8 years old with Fabry disease (b) (4). The Applicant

additionally submitted the results from the extension period of the phase 3 clinical trial and the required postmarketing confirmatory phase 4 clinical trial and its extension trial in adults as well as the Fabry Registry in adults and pediatric ≥2 years old. See section 7.1 for description of the clinical studies that supported the current supplemental BLA. This clinical pharmacology review focuses on the assessment of the immunogenicity data submitted in the sBLA. The clinical pharmacology review team defers the determination of whether the current sBLA supports the full approval of BLA 103979 to the clinical review team.

The key clinical pharmacology findings are summarized in Table 2.

Table 2. Summary of Clinical Pharmacology Review

Review Issues	Findings and Comments
Pharmacodynamics	Reductions of GL-3 in plasma and in capillary endothelium of kidney, heart, and skin were observed in patients with Fabry disease after treatment with Fabrazyme.
General dosing instructions	The currently approved dosing regimen of agalsidase beta (1 mg/kg IV Q2W) was studied in adult and pediatric patients with Fabry disease in the phase 3/4 clinical trials (AGAL-1-002-98 and AGAL-008-00) and their extension studies in adults and in the phase 2 clinical trial (AGAL-016-01) in pediatric patients > 8 years old as well as the Fabry Registry. The Applicant did not propose any update to the currently approved dosing regimen in this sBLA.
Immunogenicity	**Immunogenicity incidence:** The immunogenicity incidence is summarized in Table 4 (section 6.2.1). **Impact on PK:** Increased plasma concentrations of agalsidase beta were observed following multiple dose administrations in pediatric patients with Fabry disease possibly due to formation of anti-drug antibodies (ADA); however, such impact was not observed in adult patients. **Impact on PD:** In adult and pediatric patients with Fabry disease, the elevated plasma GL-3 levels declined with the agalsidase beta treatment. Development of ADA did not have clinically significant impact on plasma GL-3 reduction in adult patients (pooled phase 3/4 studies) or pediatric patients (study AGAL-016-01). **Impact on efficacy:** In adult patients with Fabry disease in clinical trials, there was no clear evidence indicating that development of ADA was associated with reduced effectiveness of agalsidase beta. **Impact on safety:** Subjects who developed ADA appeared to be more likely to experience infusion-associated reaction and hypersensitivity compared to subjects who were ADA negative in adult patients with Fabry disease.

Abbreviations: GL-3 = globotriaosylceramide; PD = pharmacodynamic; PK = pharmacokinetic; Q2W = every two weeks

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action and Pharmacodynamics

Agalsidase beta provides an exogenous source of α-galactosidase A in Fabry disease patients. Agalsidase beta is internalized and transported into lysosomes where it exerts enzymatic activity and reduces accumulated GL-3. Reductions of GL-3 in plasma and in capillary endothelium of kidney, heart, and skin were observed in patients with Fabry disease.

Pharmacokinetics

The PK of agalsidase beta in adult and pediatric (8 to <16 years old) patients with Fabry disease receiving the approved dosing regimen of 1 mg/kg IV Q2W are summarized in Table 3.

Table 3. Pharmacokinetics of Agalsidase Beta Following IV Administration of 1 mg/kg Q2W

Infusion Length (min)	Infusion Number (n=patients)	AUC_{inf} (μg min/mL)	C_{max} (μg/mL)	T_{max} (min)	Half-life (min)	CL (mL/min)	Vss (L)
Adult patients (phase 3 trial AGAL-1-002-98)							
280	1-3 (n=11)	649 ± 226	3.5 ± 1.6	250	89 ± 20	119 ± 63	8.3 ± 5.9
280	7 (n=11)	372 ± 223	2.1 ± 1.1	270	82 ± 25	345 ± 465	40.8 ± 58.0
300	11 (n=11)	784 ± 521	3.5 ± 2.2	282	119 ± 49	153 ± 156	18.7 ± 16.0
Pediatric patients (pediatric trial AGAL-016-01)							
272	1 (n=8-9)	561 ± 327	2.2 ± 1.9	266	43 ± 11	93 ± 48	2.5 ± 1.0
189	13 (n=15)	1087 ± 560	4.9 ± 2.4	194	131 ± 52	50 ± 28	4.2 ± 1.7
172	25 (n=9-10)	1206 ± 493	7.1 ± 4.4	189	302 ± 129	42 ± 26	6.3 ± 3.1

Source: Table 4 in Summary of Clinical Pharmacology Studies for adults and Table 3 and Appendix 11.7 in AGAL-016-01 PK Report FINAL
All data are reported as the mean ± standard deviation except for the infusion time and Tmax for which the median is reported. For pediatric trial, the table includes all patients whether they seroconverted or not. The PK parameters summarized in Table 3 were derived using compartmental methods. Of note, the current section 12.3 of the product labeling uses the PK parameters derived using non-partmental methods.
Abbreviations: AUC = area under the curve; CL = clearance; Q2W = every two weeks; Vss = volume of distribution at steady state

Immunogenicity

The incidences of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) in adult and pediatric patients in the clinical trials and in the Fabry Registry are summarized in Table 4. Of note, for the ADA testing of immunogenicity samples collected in the Fabry Registry, the polyclonal antibody in the Enzyme-Linked Immunosorbent Assay was replaced by a monoclonal antibody as the detection agent, which resulted in fewer ADA positive samples. Also note that samples for immunogenicity assessment were collected less frequent in the Fabry Registry as compared to clinical trials. Therefore, comparison of the ADA incidence in the Fabry Registry with the incidence in clinical trials may be misleading. The clinical impact of immunogenicity on PK, PD, efficacy and safety are summarized in Table 2.

Table 4. Immunogenicity Incidences for ADA and NAb in Adult and Pediatric Patients With Fabry Disease

Population	Parameter	Clinical Trials	Fabry Registry
Adults	ADA	83% (110/133)	48% (383/805)
	Persistent ADA	60% (80/133)	28% (226/805)
	ADA titer ≥12800[#]	32% (42/133)	9% (69/805)
	NAb enzyme activity inhibition	93% (102/110)	75% (38/51)
		63% (69/110) persistent	57% (29/51) persistent
	NAb cellular uptake inhibition	7% (8/110)	NA
Pediatrics*	ADA	69% (11/16)	55% (86/157)
	Persistent ADA	38% (6/16)	36% (57/157)
	ADA titer ≥12800[#]	0	18% (28/157)
	NAb enzyme activity inhibition		70% (7/10)
		NA	70% (7/10) persistent

Source: Tables 17, 18, 25, 55, 59, and 68 in Immunogenicity Report
*Pediatric patients in clinical trials were 8 to <16 years old and received the recommended dose of 1.0 mg/kg IV Q2W. Pediatric patients in the Fabry Registry were 2 to <16 years old.
The ADA titer cut point of 12800 represented approximately the fourth quartile of ADA titers for the Phase 3 and Phase 4 evaluable adult patient population.
Abbreviations: ADA = anti-drug ant bodies; NA = not applicable; NAb = neutralizing ant bodies; Q2W = every two weeks

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The pharmacologic activity, pharmacokinetics, and clinical pharmacology of agalsidase beta that are relevant to the interpretation of benefit and risk are summarized in Table 5. Of note, the PK and PD results described below are based on the Applicant's current clinical pharmacology summary and do not represent reviewer's new analysis results because the relevant clinical pharmacology studies have been submitted and reviewed previously under the BLA. This clinical pharmacology review focuses on the assessment of the immunogenicity data.

Table 5. Summary of Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Fabrazyme (agalsidase beta) is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme.
Mechanism of action	Fabrazyme provides an exogenous source of α-galactosidase A in Fabry disease patients. Agalsidase beta is internalized and transported into lysosomes where it exerts enzymatic activity and reduces accumulated GL-3
Active moieties	Agalsidase beta
	General Information
Bioanalysis	The bioanalytical methods for pharmacokinetic (PK) and pharmacodynamic (PD) samples were developed and validated. Enzymatic assay for quantification of agalsidase beta activity in plasma LC-MS/MS for measuring plasma GL-3
Drug exposure at steady state following the therapeutic dosing regimen	The PK of agalsidase beta are summarized in Table 3.
Range of effective dosage(s) or exposure	The recommended dose of agalsidase beta is 1 mg/kg every two weeks administered via IV infusion.
	Absorption
Bioavailability	The determination of bioavailability of agalsidase beta is not necessary since agalsidase beta is administered via IV infusion.
T_{max}	The T_{max} is expected to be reached approximately at the end of the IV infusion.
	Distribution
Volume of distribution	Following 1 mg/kg IV infusion in Fabry disease patients, the mean volume of distribution during elimination phase was 8.3 L in adults and 2.5 L in pediatrics after single dose and ranging from 19 to 41 L in adults and 4.2 to 6.3 L in pediatrics following multiple IV infusions administered every two weeks.
	Elimination
Clearance	Following a single dose 1 mg/kg IV infusion in Fabry disease patients, the mean clearance of agalsidase beta was 119 mL/min in adults and 93 mL/min in pediatrics. The mean clearance of agalsidase beta was 153 to 345 mL/min and 42 to 50 mL/min, respectively, for adult and pediatric patients following 1 mg/kg IV Q2W multiple administrations.
Half-life	Following a single dose 1 mg/kg IV infusion in Fabry disease patients, the mean elimination half-life (t1/2) of agalsidase beta was 89 min in adults and 43 min in pediatrics. The mean elimination half-life (t1/2) of agalsidase beta was 82 to 119 min and 131 to 302 min, respectively, for adult and pediatric patients with Fabry disease after following 1 mg/kg IV Q2W multiple administrations.
Metabolic pathway(s)	The metabolic pathway of agalsidase beta has not been characterized. As a lysosomal neutral glycosphingolipid-specific enzyme, agalsidase beta is expected to be degraded via peptide hydrolysis in a manner similar to endogenous protein.
	Intrinsic Factors and Specific Populations
Body weight, age, and sex	The recommended dosage regimen of agalsidase beta is based on body weight. Age and sex were not considered clinically significant covariates with respect to drug exposure in adults or pediatric patients.
Renal impairment Hepatic impairment	No studies were conducted to evaluate the effect of renal impairment or hepatic impairment on the PK of agalsidase beta.

Characteristic	Drug Information
	Pharmacodynamics
Pharmacodynamics	Reductions of GL-3 in plasma and in capillary endothelium of kidney, heart, and skin were observed in patients with Fabry disease after treatment with agalsidase beta.
	Immunogenicity
Bioanalysis	The bioanalytical methods for immunogenicity samples in human serum were developed and validated. Monoclonal ELISA for detecting anti-agalsidase beta antibodies. A cell-based assay and an enzymatic activity assay for detecting neutralizing antibodies.
Incidence	Adult patients in clinical trials. Among 133 evaluable subjects for up to 74 months, 83% (110/133) of patients treated with agalsidase beta developed ADA and 60% (80/133) had persistent ADA response (i.e., peak titer >800 and remained ADA positive through the final assessment). Most ADAs developed within the first 3 months of treatment. Among the subjects who developed ADA, approximately 93% (77% of all subjects) had positive neutralizing antibodies (NAb) that inhibited in vitro catalytic activity and 7% (6% of all subjects) developed NAb that inhibited in vitro enzyme uptake into cells (all inhibited catalytic activity). Pediatrics (8 to <16 years old) in clinical trial. The incidence for ADA was 69% (11/16) following treatment with agalsidase beta for up to 48 months. Approximately 38% (6/16) patients had persistent ADA response. Pediatrics (2 to <16 years old) in Registry. Incidence for ADA was 55% among the 157 evaluable pediatric patients with Fabry disease receiving the agalsidase beta treatment for a median duration of 89 months. Among the 10 patients who were evaluated for NAb, 7 patients were positive for NAb inhibiting catalytic activity and all 7 developed persistent NAb response.
Clinical impact	The clinical impacts of immunogenicity on PK, PD, efficacy and safety are summarized in Table 2. See section 6.3.2 for detailed information.

Abbreviations: ADA = anti-drug ant bodies; ELISA = Enzyme-Linked Immunosorbent Assays GL-3 = globotriaosylceramide; IV = intravenous; LC-MS/MS = liquid chromatography with tandem mass spectrometry; Q2W = every two weeks

6.3.2. Clinical Pharmacology Questions

What are the pharmacodynamic results of Fabrazyme in clinical trials and in the Fabry Registry?

Reductions of GL-3 in plasma and in capillary endothelium of kidney, heart, and skin were observed in patients with Fabry disease after treatment with Fabrazyme. This section provides updated PD results of plasma GL-3 responses in clinical trials and in the Fabry Registry.

In adults following Fabrazyme treatment at 1 mg/kg IV Q2W in the Phase 4 study (Trial AGAL-008-00), 76% (37/49) and 81% (25/31) patients had elevated plasma GL-3 levels above the normal range (>7.03 µg/mL) at baseline for the Fabrazyme and placebo treatment group, respectively. After treatment, the majority of patients in the Fabrazyme treatment group had normal plasma GL-3 levels, whereas most patients in the placebo treatment group had elevated plasma GL-3 values throughout the study. From Month 6 through the final blinded visit at Month 35, the proportion of patients with elevated plasma GL-3 levels were 5% to 20% for the

Fabrazyme group and 68% to 100% for the placebo group. The mean plasma GL-3 levels were decreased to the normal range (≤7.03 μg/mL) as early as within 3 months of treatment and remained within the normal range up to 35 months at the end of the trial. The mean plasma GL-3 level was 9.0 μg/mL at baseline and 4.8 μg/mL and 4.8 μg/mL, respectively, at 1 year and 2 years following agalsidase beta treatment. The mean plasma GL-3 levels were largely unchanged for the placebo group throughout the trial. The PD effect on plasma GL-3 reduction was maintained with agalsidase beta treatment during the additional treatment period in the extension trial.

A similar pattern of plasma GL-3 reduction was observed in pediatric patients (8 to 16 years old) in the pediatric clinical trial. All 14 (out of 16) patients who had elevated plasma GL-3 levels at baseline achieved the normal levels by Week 20 and maintained the PD effect until the end of the trial. The remaining two patients had normal plasma GL-3 levels at baseline and maintained normal plasma GL-3 levels during the trial.

Among the pediatric patients (2 to <16 years old) receiving Fabrazyme treatment in the Fabry Registry, reduction of plasma GL-3 levels was observed within the first 6 months of treatment. Approximately 17% of the patients (2 to <8 years old) and 50% of the patients (8 to <16 years old) had baseline plasma GL-3 levels within the normal range, compared to 92% to 93% and 96% to 100%, respectively, at month 6 through month 24 following Fabrazyme treatment.

What are the incidence of immunogenicity and the clinical impacts of immunogenicity?

Immunogenicity

Immunogenicity of agalsidase beta was assessed in clinical trials (pivotal Phase 3 Trial AGAL-1-002-98 and its extension study AGAL-005-99, Phase 4 confirmatory Trial AGAL-008-00 and its extension study, and Phase 2 pediatric trial AGAL-016-01) and the Fabry Registry.

- Clinical Trial Population: included all agalsidase beta treated patients with at least 2 ADA assessments post-baseline (post agalsidase beta treatment).
- Fabry Registry Population (longitudinal): included agalsidase beta treated patients with at least 2 ADA assessments after agalsidase beta initiation (at least 1 of which is ≥3 months post treatment initiation) in adults (≥ 16 years old) and pediatric patients (2 to <16 years old). The minimum ADA follow-up period of ≥3 months was chosen based on the median time to seroconversion identified in the Phase 3 and 4 clinical trials.

The Applicant used the following definitions to classify subject ADA status. The confirmed ADA positive samples in adults were also evaluated for NAb by two assays: catalytic activity

inhibition assay and cellular update inhibition assay. In the Fabry Registry, selective patients who were ADA positive with elevated plasma GL-3 levels were evaluated for NAb.

- Always negative (ADA-): The patient was ADA negative at all visits after agalsidase beta treatment.
- Ever positive ADA (ADA+): Patient had at least one positive treatment-induced ADAs after agalsidase beta treatment, which was further sub-classified.
  - Low response: Patient had a peak titer ≤ 800 and positive at final assessment
  - Tolerized: A patient was ADA positive, but subsequently became ADA negative, and remained ADA negative through the final assessment
  - Persistent ADA: ADA peak titer was >800 and remained ADA positive through the final assessment

The ADA and NAb incidences in adult and pediatric patients in the clinical trials and in the Fabry Registry are summarized in Table 4. In clinical trials, the ADA incidence was 83% (110/133) and 69% (11/16) in adult and pediatric patients treated with agalsidase beta, respectively. The median times to appearance of ADA were 12 weeks and 8 weeks in adult and pediatric patients, respectively. In adult patients, the incidences for NAb among the ADA positive subjects were 93% (102/110). Approximately 38% (42/110) of the ADA positive adult patients but none of the pediatric patients had ADA titer values of ≥ 12800. The ADA titer cut point of 12800 represented approximately the fourth quartiles of ADA titers for the Phase 3 and Phase 4 evaluable adult patient population.

In the Registry, the incidence of ADA was 48% (383/805) and 55% (86/157) in the adult and pediatric patients, respectively. Among the selective patients evaluated for NAb (who were ADA positive and had elevated plasma GL-3), the incidences for NAb were 75% (38/51) and 70% (7/10) in adult and pediatric patients, respectively. Approximately 18% (69/383) and 33% (28/86) of the ADA positive subjects in adult and pediatric patients, respectively, had ADA titer values of ≥ 12800.

Additionally, female patients had lower ADA and NAb incidence and lower antibody titers compared to male patients in general. Patients with truncating GLA mutations had a higher incidence of ADA response compared to patients with non-truncating GLA mutations. The incidence of ADA response was higher in patients with low plasma αGAL activity (≤1.5 nmol/hr/mL) compared with patients with higher plasma αGAL activity (>1.5 nmol/hr/mL). See Clinical Pharmacology Appendices for additional immunogenicity incidence summaries.

Clinical Impacts of Immunogenicity

Impact of Immunogenicity on Pharmacokinetics

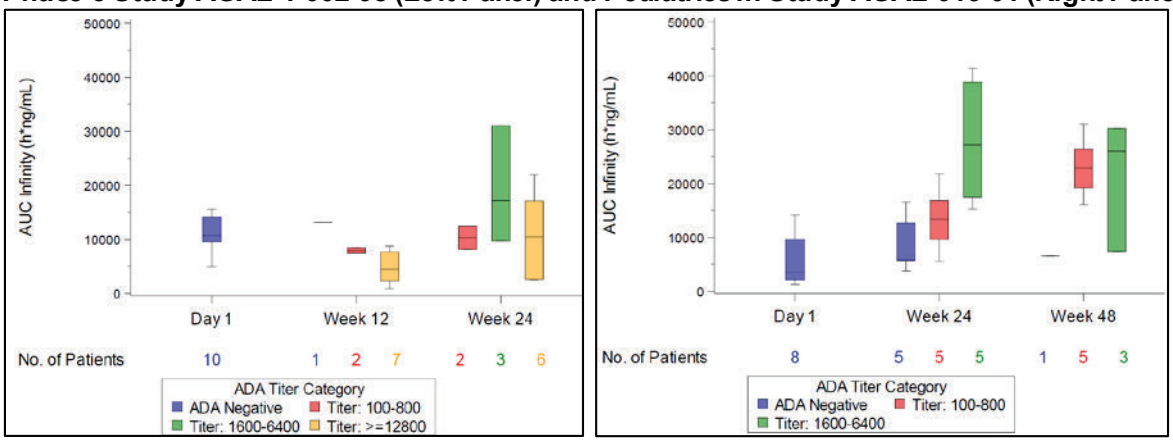
Given the increased variability in PK following multiple dose administration compared to the initial dosing, the small number of ADA- subjects, and inconsistent PK patterns following

repeated dosing in adult and pediatric patients, it is not feasible to make definite conclusions regarding the impact of ADA development on PK of agalsidase beta.

In adult patients with Fabry disease in study AGAL-1-002-98, the area under the curve (AUC) of agalsidase beta at Week 12 in the ADA positive patients was lower than the AUC in the ADA negative patient at Week 12 (N=1) and also lower than the AUC in negative patients on Day 1. However, the AUC of agalsidase beta appeared to be similar between the ADA positive patients at Week 24 and the AUC in ADA negative patients on Day 1 and Week 12 (Figure 1, left panel).

In pediatric patients with Fabry disease in study AGAL-016-01, the AUC of agalsidase beta was increased in the ADA positive patients compared to the ADA negative patients at both Week 24 and Week 48 (Figure 1, right panel). Increased plasma concentrations of agalsidase beta were observed following multiple dose administrations in pediatric patients with Fabry disease as compared to the first dose, which is possibly due to formation of ADA; however, such impact was not observed in adult patients.

Figure 1. AUC of Agalsidase Beta by Subject ADA Status and ADA Titer Categories in Adults in Phase 3 Study AGAL-1-002-98 (Left Panel) and Pediatrics in Study AGAL-016-01 (Right Panel)



Source: Figures 11 and 13 of Immunogenicity Report
Abbreviations: ADA = anti-drug ant bodies; AUC = area under the curve

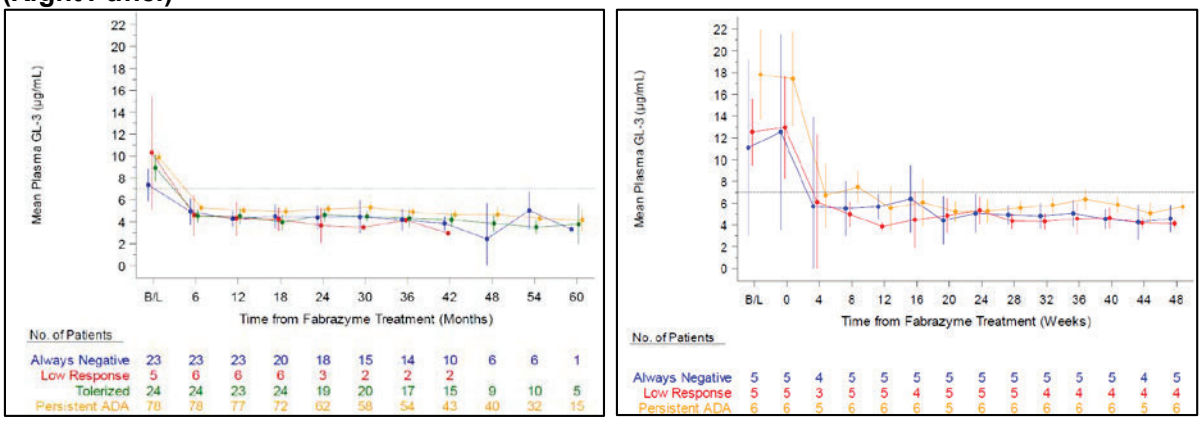
Impact of Immunogenicity on Pharmacodynamics

Plasma GL-3 was used as a PD endpoint for the assessment of immunogenicity impact on effectiveness of Fabrazyme. Because reduction of plasma GL-3 is directly related to the mechanism of action of Fabrazyme, it is considered a more sensitive endpoint to assess immunogenicity impact than clinical endpoint that measures function. The impact of ADA on plasma GL-3 was evaluated in clinical trials and the Fabry Registry.

Reduction of plasma GL-3 was observed in adult and pediatric patients with Fabry disease in the clinical trials. Development of ADA did not have an impact on plasma GL-3 reduction in either adult patient population (pooled Phase 3 and Phase 4) or pediatric patient population in the clinical studies (Figure 2). The development of NAb, as measured by enzyme activity inhibition

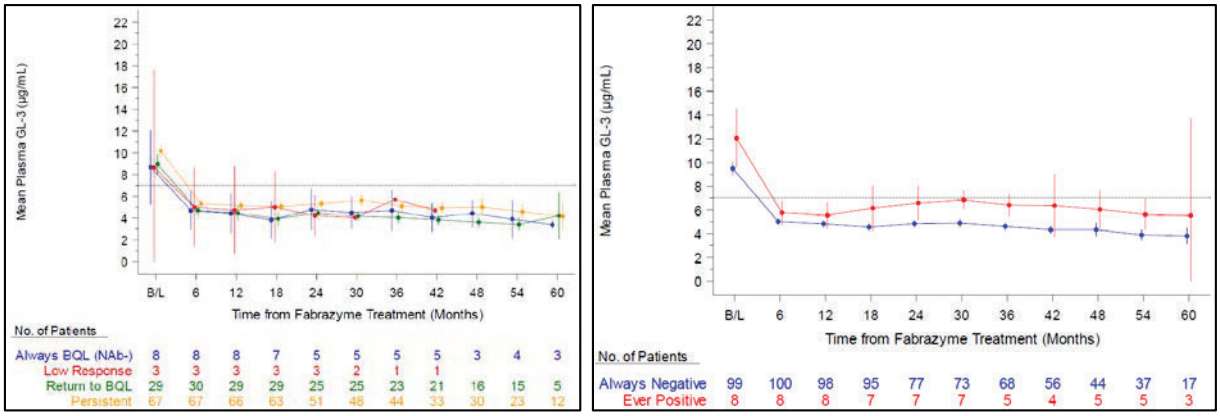
in vitro, did not have a clinically significant impact on plasma GL-3 reduction. Although the subjects who developed NAb, as measured by cellular uptake inhibition in vitro, appeared to have relatively higher mean plasma GL-3 levels than NAb negative subjects, the plasma GL-3 levels in NAb positive subjects generally remained within the normal range (Figure 3).

Figure 2. Mean (95% CI) Plasma GL-3 Time Course by Subject ADA Status in Adults in Pooled Studies AGAL-1-002-98 and AGAL-008-00 (Left Panel) and in Pediatrics in Study AGAL-016-01 (Right Panel)



Source: Figures 19 and 21 in Immunogenicity Report
Note: Reference line at 7.03 µg/mL represents the upper limit of normal.
Abbreviations: ADA = anti-drug antibodies; CI = confidence interval; GL-3 = globotriaosylceramide

Figure 3. Mean (95% CI) Plasma GL-3 Time Course by Subject NAb Status Measured by Enzyme Activity (Left Panel) and NAb Status Measured by Cellular Uptake (Right Panel) in Adults in Pooled Studies AGAL-1-002-98 and AGAL-008-00 and Their Extension Studies

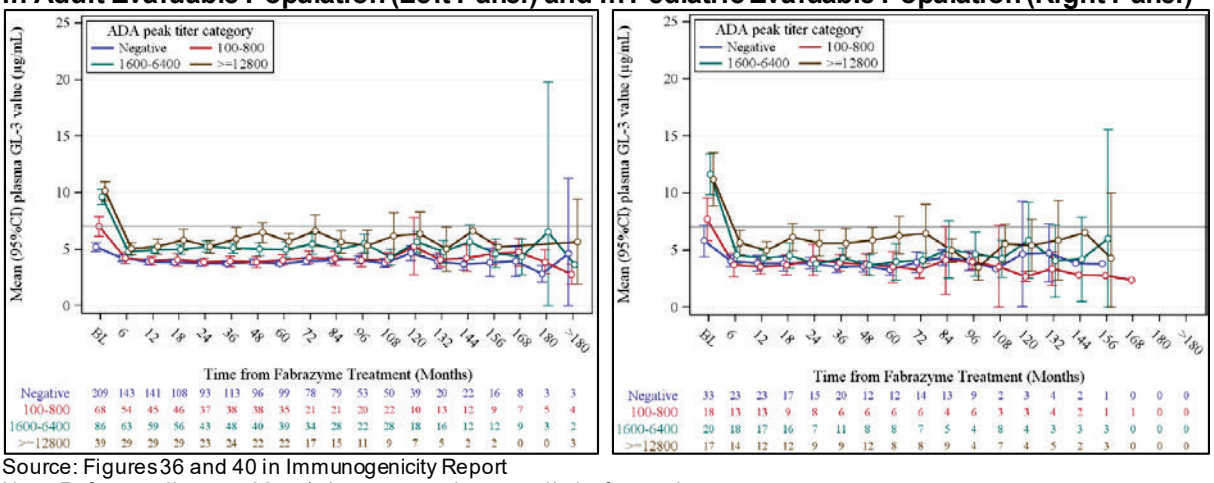


Source: Figures 24 and 25 in Immunogenicity Report
Note: Reference line at 7.03 µg/mL represents the upper limit of normal.
Abbreviations: BQL = below quantifiable limit; CI = confidence interval; GL-3 = globotriaosylceramide; NAb = neutralizing antibodies

In the Fabry Registry, reduction of plasma GL-3 was observed in adult and pediatric patients with Fabry disease treated with Fabrazyme. The majority of patients achieved plasma GL-3 levels within the normal range by Month 6. Although subjects with very high ADA titer (e.g., ≥12800) appeared to have relatively higher mean plasma GL-3 levels compared to lower ADA

titer categories, the reduction of plasma GL-3 was maintained and the plasma GL-3 levels were within the normal range through the end of the studies irrespective of ADA titer response category in both adult and pediatric patient populations (Figure 4).

Figure 4. Mean (95% CI) Plasma GL-3 Time Course by ADA Peak Titer Category in Fabry Registry in Adult Evaluable Population (Left Panel) and in Pediatric Evaluable Population (Right Panel)



Source: Figures 36 and 40 in Immunogenicity Report
Note: Reference line at 7.03 µg/mL represents the upper limit of normal.
Abbreviations: ADA = anti-drug antibodies; CI = confidence interval; GL-3 = globotriaosylceramide

Impact of Immunogenicity on Efficacy

The impact of immunogenicity on efficacy was assessed based on clinical events (i.e., clinically significant renal, cardiac, or cerebrovascular event, or death) in agalsidase beta treated patients in the Phase 4 population (including both the double blind and the open label extension period) by their ADA and NAb response categories. The results, as summarized in Table 6, do not show a clear evidence of negative impact of immunogenicity on efficacy due to small number of subjects in each immunogenicity response category. The percentage of patients with clinical events was slightly higher in patients who developed ADA and those who did not develop ADA, 40% (23/58) vs 35% (6/17). In patients who had peak ADA titer ≥12800, the percentage of patients with clinical events was higher compared to other ADA peak titer subgroups. Notably, all 3 patients with positive NAb inhibiting cellular uptake had clinical events; however, patients with positive NAb inhibiting enzyme activity had lower clinical events than patient who were NAb negative.

Table 6. Summary Of Clinical Events in Fabrazyme-Treated Patients by ADA/NAb Status: Phase 4 Population

Subject Immunogenicity Status	Number of Patients	Number (%) of Patients With Clinical Events
Overall	75	29 (39%)
ADA negative	17	6 (35%)
ADA positive	58	23 (40%)
ADA peak titer		
100-800	17	7 (41%)
1600-6400	31	10 (32%)
≥12800	10	6 (60%)
NAb (enzyme activity)		
NAb negative	3	2 (67%)
NAb positive	55	21 (38%)
NAb (cellular uptake)		
NAb negative	55	20 (36%)
NAb positive	3	3 (100%)

Source: Table 37 in Immunogenicity Report
Abbreviations: ADA = anti-drug ant bodies; NAb = neutralizing antibodies

Impact of Immunogenicity on Safety

The impacts of immunogenicity on safety were evaluated in the clinical trials, i.e., adult studies AGAL-1-002-98, AGAL-008-00, and their extensions, and pediatric study AGAL-016-01.

In the pooled adult population, the incidence of infusion associated reactions (IARs) was higher in patients who developed ADA compared to those who were ADA negative (Table 7). The incidence of IARs was also higher in patients with ADA peak titer ≥12800 and ADA peak titer within 1600-6400 compared to patients with ADA peak titer within 100-800. In addition, the incidence of hypersensitivity was higher in ADA positive patients compared to patients with ADA negative status (Table 7).

Table 7. Adverse Events of IAR and Hypersensitivity by ADA Response Type in Pooled Adult Patient Population

TE-Adverse Event, n (%)	Negative (N=23)	ADA Peak Titer Category 100-800 (N=25)	1600-6400 (N=43)	>=12800 (N=42)	Overall (N=133)
IAR	7 (30)	13 (52)	36 (84)	35 (83)	91 (68)
Hypersensitivity	7 (30)	13 (52)	17 (40)	25 (60)	62 (47)

Source: Reviewer's summary based on Table 47 and Appendix 2, 3.5.2.1 in Immunogenicity Report
Abbreviations: ADA = anti-drug ant bodies; IAR = infusion-associated reaction

In the pediatric patient population, a trend of higher incidence of IARs was observed in patients who were ADA positive compared to the ADA negative patients (Table 8). No clear impact of ADA on the incidence of hypersensitivity was observed.

Table 8. Adverse Events of IAR and Hypersensitivity by ADA Response Type in Pediatric Patient Population

TE-Adverse Event, n (%)	Negative (N=5)	ADA Peak Titer Category 100-800 (N=5)	1600-6400 (N=43)	>=12800 (N=0)	Overall (N=16)
IAR	1 (20)	2 (40)	3 (50)	0	6 (38)
Hypersensitivity	2 (40)	2 (40)	2 (33)	0	6 (38)

Source: Reviewer's summary based on Table 47 and Appendix 2, 3.5.2.2 in Immunogenicity Report
Abbreviations: ADA = anti-drug ant bodies; IAR = infusion-associated reaction

7. Sources of Clinical Data and Review Strategy

7.1. Main Clinical Studies in Fabrazyme Development Program

Table 9. Clinical Studies (Fabrazyme Dosed at 1 mg/kg IV Every 2 Weeks in All Studies)

Study	Study Type	Design	Efficacy Endpoints	Population
AGAL-1-002-98	Phase 3 trial	Randomized (1:1), double-blind, placebo controlled; 20 weeks	Clearance of GL-3 (score of 0) in interstitial capillaries of biopsied renal interstitial capillaries (surrogate endpoint); plasma GL-3	N=58 Patients ≥ 16 years old with classic, early-onset FD
AGAL-008-00	Phase 4 trial	Randomized (2:1), double-blind, placebo controlled; maximum 35 months (median 18 months)	Time to first occurrence of renal, cardiac or cerebrovascular events, or death; eGFR slope; plasma GL-3	N=82 Adults with classic, early-onset FD and mild to moderate renal impairment
AGAL-016-01	Phase 2 trial	Open label, single-arm; 48 weeks	skin GL-3 (at 24 weeks); plasma GL-3	N=16 Children with classic, early-onset FD, 8-16 years old
Fabry Registry/ Natural History Matched Analyses	Observational (retrospective cohort) study	Treated patients followed in Fabry Registry matched to historical control cohort; maximum 5 years (median 4 years)	eGFR slope; plasma GL-3	N=244 Patients ≥ 2 years old with FD

Source: Applicant table with reviewer edits (2.5 Clinical Overview Appendix 1)
Abbreviations: eGFR = estimated glomerular filtration rate; FD = Fabry disease; GL-3 = globotriaosylceramide

Table 10. Published Studies on the Effect of GL-3 Accumulation in Tissues (since 2003)

Publication	Population	Study Design	Intervention	Results
1	Human microvascular cardiac endothelial cells (ECs)	In vitro	ECs incubated with GL-3	GL-3 inhibited eNOS expression by 28% and 43% (p =0.002 and p=0.001)
2	Peripheral Blood mononuclear cells (PBMC) from 29 Fabry patients and 15 healthy controls	In vitro	PBMC incubated with GL-3	PBMC from Fabry patients presented with a higher proinflammatory cytokine expression and production. Normal cells displayed same proinflammatory profile when cultured in presence of GL-3
3	Human podocyte cell line with knocked-down GLA	In vitro		A-Gal A deficient podocytes suggested activation of autophagic cellular machinery Increased number of autophagosomes in GL-3 laden podocytes
4	GLA knock-out mice Biobanked plasma from classic FD patients compared to matched healthy controls Human vascular endothelial cells fused with A549 cells	In vitro and in vivo		GL-3 accumulation associated in >60% reduction in eNOS activity in cell culture Levels of 3NT (specific marker for reactive nitrogen species) was six-fold elevated in plasma samples from classic fabry patients compared with control (p<0.01)
5	Kidney biopsies in 15 adult, ERT-naïve FD patients	Cross-sectional		GL-3 present in epithelial tubular cells, epithelial bowman cells, endothelial glomerular cells Positive staining for TGF-β1 found in proximal tubular cells
6	9 renal biopsies in symptomatic FD patients	Cross sectional		LM showed Glomerular, interstitial and vascular changes in nearly all patients EM showed podocyte inclusions, foot-process effacements. Mesangial and glomerular endothelial cell inclusions found in all patients

Publication	Population	Study Design	Intervention	Results
7	Renal biopsies from 35 males and 24 females with mild Fabry nephropathy	Cross sectional		Males had greater podocyte vacuolization, proximal tubule, peritubular capillary, and vascular intimal inclusions than females
8	Review article that included autopsy studies from Kaye et al 1988; Kahn 1973 and Gadoth et al 1988	Expert consensus panel		Swollen dorsal root ganglion cells; GL-3 storage in substantia nigra, anterior horn cells, degeneration of nerve fibers in dorsal root entry zone and substantia gelatinosa of the spinal cord
9	Renal biopsies from 14 ERT naïve fabry patients compared to 9 healthy living kidney donors	Cross-sectional, observational		Podocyte GL-3 inclusion volume density increased with age (p=0.001) in parallel with podocyte foot process width (p=0.01) Foot process width and podocyte GL-3 inclusion volume density correlated with proteinuria (p=0.008)
10	Renal biopsies from 55 males with classic fabry disease And 7 healthy living kidney donors	Cross-sectional		GL-3 accumulation associated with podocyte injury and loss as evidenced by increased foot process width (p=0.004) Increased podocyte LG-3 volume fraction and foot process width were associated with increasing proteinuria (p=0.003 and p=0.007, respectively) as well as decreasing GFR
11	16 pediatric Fabry disease patients aged 8 to 16 years of age 12 with skin biopsy	Multicenter open label study	1mg/kg Fabrazyme every 2 weeks	12 patients exhibited GL-3 deposits in superficial dermal capillary endothelium. Complete clearance of GL-3 was observed at week 24 for the 12 patients.

Publication	Population	Study Design	Intervention	Results
12	Renal biopsy of 12 fabry patients	Longitudinal, interventional	Treated with agalsidase alfa or agalsidase beta	Regression analysis showed significant correlation between podocyte GL-3 inclusion clearance and reduction in albumin to creatinine ratio (p=0.001)

Source: prepared by reviewer
[1] (Namdar et al. 2012)
[2] (De Francesco et al. 2013)
[3] (Liebau et al. 2013)
[4] (Shu et al. 2014)
[5] (Rozenfeld et al. 2020)
[6] (Tondel et al. 2008)
[7] (Fogo et al. 2010)
[8] (Politei et al. 2016)
[9] (Najafian et al. 2011)
[10] (Najafian et al. 2020)
[11] (Wraith et al. 2008)
[12] (Tondel et al. 2013)
Abbreviations: EM = electron microscopy; ERT = enzyme-replacement therapy; GFR = glomerular filtration rate; GL-3 = globotriaosylceramide; LM = light microscopy

7.2. Review Strategy

For this BLA efficacy review, published literature was reviewed to assess the effect of the accumulation of GL-3 on the structure and function of organs affected in FD. Data on Fabry associated clinical events and eGFR slope (as an indicator of renal function) were also analyzed from the phase 4 trial AGAL-008 and the Fabry registry respectively. (b) (4) [redacted] For the observational data analyses (Fabry Registry/Narual History Matched Analysis), the review team focused on the primary endpoint (eGRF slope) in 122 treated patients and 122 untreated patients who were 1:1 matched on age, sex, FD phenotype, and baseline eGFR. For the eGFR slope, this review does not discuss the Applicant's matched analyses on age, sex, and FD phenotype because they did not include baseline eGFR as a matching variable and showed significant imbalance between the treatment groups in baseline eGFR. The submitted post marketing safety reports spanning approximately 18 years of post-marketing safety experience were reviewed for purposes of the safety assessment and for updating pertinent sections of the label.

8. Statistical and Clinical Evaluation

8.1. Efficacy Evaluation: Renal PTC GL-3 Reduction to Score of Zero on LM as a Surrogate Endpoint for Full Approval

Fabrazyme received accelerated approval in 2003 based on the results from trial AGAL-1-002-98, as the evidence was sufficient at that time to conclude that achievement of a histological score of zero (using the Fabrazyme Scoring System; FSS), indicating no visible GL-3 inclusions, in biopsied renal peritubular capillaries from patients in trial AGAL-1-002-98 was reasonably likely to predict clinical (renal) benefit in that population. See section 8.2.1 and the original BLA review for more information regarding the FSS methodology. Since 2003, a considerable body of evidence has accumulated on the role of this SE in Fabry disease, i.e. the achievement of complete/near complete clearance (score of zero on LM using the FSS) of GL-3 inclusions in renal peritubular capillaries (PTC). This body of evidence which includes a number of published studies is summarized in this section. Overall, the scientific evidence, summarized by the Applicant, includes evidence that accumulation of GL-3 is toxic to renal tissue, that GL-3 accumulates in all tissues where Fabry disease causes structural damage and functional loss including the kidneys, that GL-3 accumulation correlates with renal tissue damage, and that Fabrazyme removes GL-3 from biopsied renal, skin, and heart tissues. In addition, as detailed in section 8.2, treatment with Fabrazyme at the approved dose was associated with favorable trends in the incidence of clinical events (renal, cardiac, cerebrovascular events, or death) in trial AGAL-008-00, a phase 4 randomized trial, and a favorable effect on eGFR slope (a marker of renal function) in the observational study. This evidence as a whole supports that the observed treatment effect of Fabrazyme in trial AGAL-1-002-98 (achievement of score of zero on LM using the FSS after 20 weeks of treatment in biopsied renal PTC in treated patients) predicts clinical benefit in this population and is, thus, a SE able to support full (traditional) approval for Fabrazyme in this sBLA.

A. Cellular and Tissue Toxicity of Accumulated GL-3

Since Fabrazyme was granted accelerated approval in 2003, multiple studies have been published demonstrating that GL-3 is tissue-toxic when it accumulates. In vitro data show that GL-3 increases inflammatory biomarkers such as cyclooxygenase-2 and decreases anti-inflammatory biomarkers such as homeostatic nitric oxide synthase in cardiac epithelial cells (Namdar et al. 2012). A proinflammatory cytokine profile was found to be expressed in the peripheral blood mononuclear cells in Fabry disease patients compared to normal controls. GL-3 was also found to induce the same inflammatory profile in normal cells. (De Francesco et al. 2013) GL-3 accumulation in podocytes led to an increase in autophagy and a decrease of mTOR and AKT signaling which led to podocyte damage (Liebau et al. 2013). In the *GLA* knockout mouse model , an increase in GL-3 content led to eNOS dysregulation, decreased nitric oxide bioavailability and increased 3NT, a marker of reactive nitrogen species. This caused a marked increase in endothelial dysfunction and vasculopathy manifesting as oxidant-induced thrombosis. Plasma samples from 13 male patients with untreated, classic Fabry disease were

also found to have a six-fold higher 3NT concentration compared to age-matched controls further supporting the correlation of GL-3 accumulation with endothelial dysfunction (Shu et al. 2014). Fifteen renal biopsies from treatment naïve Fabry adult patients with proteinuria revealed enlarged and vacuolated podocytes and mesangial cells in all samples with global glomerular sclerosis present in 7 of 15 Fabry patients. The presence of interstitial fibrosis was identified in 12 of 15 patients. Immunohistochemical staining of GL3 showed GL3 expression in epithelial tubular cells, epithelial bowman cells, endothelial glomerular cells, podocytes and mesangial cells. It also confirmed that GL3 deposits led to vacuolization of cells. Positive staining for TGF-B1 (potent profibrogenic cytokine) was found in the proximal tubular epithelial cells in all the fabry biopsies (Rozenfeld et al. 2020).

B. GL-3 Accumulation is Universally Present in Tissues With Fabry-Related Structural Damage and Functional Loss

That GL-3 accumulates in tissues with structural damage and functional loss in Fabry patients was reasonably well-understood in 2003 and was an important line of evidence in the FDA's decision to grant accelerated approval on that basis. Autopsy data from Fabry patients suggested that GL-3 accumulates in cardiac muscle fibers, vascular smooth muscle, endothelium, mitral valve connective tissue, and the dorsal root ganglia (Ferrans et al. 1969; Gadoth and Sandbank 1983). Baseline renal biopsies from n=58 patients enrolled in trial AGAL-1-002-98 established that GL-3 accumulates in nearly all renal cell types including vascular endothelial cells, vascular smooth muscle cells, mesangial cells and interstitial cells, with particularly dense accumulations in podocytes and distal tubular epithelial cells. Otologic histopathology described from autopsy data in 2 Fabry disease patients with sensorineural hearing loss found GL-3 accumulation in the vascular endothelial cells and ganglion cells in the ear (Schachern et al. 1989).

Since Fabrazyme was granted accelerated approval in 2003, additional evidence has emerged that GL-3 accumulates in all tissues with structural and functional loss in Fabry patients. GL-3 accumulation was found in podocytes and distal tubules in renal biopsies from 9 adolescent patients with Fabry disease (mean age 13.5 years) (Tondel et al. 2008). Arteriopathy which may indicate potentially progressive vascular disease were found in 5 of 9 patients. A cross-sectional study assessing renal biopsies in 35 males and 24 females found vacuolization of podocytes with males having greater vacuolization and GL-3 inclusions than females. Proximal tubule, peritubular capillary and vascular intimal inclusions and arteriolar hyalinosis was also seen (Fogo et al. 2010). Histopathological examination of GL-3 within the central and peripheral nervous system found GL-3 accumulation in the dorsal root ganglion, substantia nigra and anterior horn cells with degeneration of nerve fibers in the dorsal root entry zone and substantia gelatinosa of the spinal cord (Politei et al. 2016).

C. Degree of GL-3 Accumulation Correlates With Degree of Renal Tissue Damage

Whether or not the degree of GL-3 accumulations is correlated with degree of tissue damage was not well understood when Fabrazyme was granted accelerated approval in 2003. Since

then, several important findings have been published establishing that link. Proteinuria has since been found to be a risk factor for worsening renal disease (January 2013). Renal biopsies that were obtained in 14 untreated Fabry disease patients with median age of 12 years were compared to nine normal living kidney donor controls. Fabry disease biopsies showed GL-3 inclusions in all glomerular cell types. The volume fraction of GL-3 inclusions in the podocyte increased with age, as did podocyte foot process width. Segmental foot process effacement was present in all glomeruli. The volume fraction and foot process width correlated directly with proteinuria (Najafian et al. 2011). A cross sectional study assessed renal biopsies performed on 55 treatment-naïve males (mean age 27 years) with classic Fabry disease and found that the proportion of podocyte cytoplasm that was occupied by GL3 inclusions increased with age up to about age 27, suggesting that the rate of GL3 accumulation exceeds the rate of podocyte cellular enlargement which leads to podocyte loss. In 33 subjects with documented plasma and leukocyte α-GAL A activity values, there was a direct relationship between α gal A deficiency and podocyte loss. Urine protein excretion ratio also correlated with increasing podocyte GL3 volume (Najafian et al. 2020).

D. Fabrazyme Removes Accumulated GL-3 From Fabry Target Tissues

Results from trial AGAL-1-002-98 showed that Fabrazyme removes accumulated GL-3 in renal peritubular capillaries and formed the basis of the FDA's decision to grant accelerated approval in 2003. A statistically significant difference between treatment groups favored Fabrazyme treated patients compared to placebo. Fabrazyme also reduced GL-3 inclusions in the vascular endothelium of biopsied heart and skin in adults and of skin in pediatric patients (see primary BLA review for more information). Since then, additional evidence has emerged establishing that Fabrazyme removes GL-3 from Fabry target tissues. The phase 3 extension trial AGAL-005-99 showed reduction of the substrate from capillary endothelium of the kidney, skin, and heart in patients who transitioned to Fabrazyme from placebo. In the pediatric study AGAL-016-01 in 16 patients aged 8-16 years of age, skin biopsies after 24 weeks of treatment with Fabrazyme showed clearance of GL-3 from the superficial dermal capillary endothelium (Wraith et al. 2008). Longitudinal data that evaluated renal biopsies before and after an average of 5 years of ERT showed a clearance of GL-3 inclusions in podocytes, glomerular endothelial cells and mesangial cells. In addition to complete clearance of podocyte inclusions, there was also a decrease in podocyte effacement and microalbuminuria (Tondel et al. 2013).

E. Treatment With Fabrazyme in Clinical Studies was Associated With Favorable Histologic and Clinical Effects

Completed clinical studies in the Fabrazyme development program (see section 8.2) showed that treatment with Fabrazyme was associated with a large and statistically significant reduction to a score of zero (on LM) of GL-3 inclusions in patients treated in trial AGAL-1-002-98 which supported Fabrazyme's accelerated approval. Since then, treatment with Fabrazyme was associated with favorable clinical effects on the incidence of clinically significant events (compared to placebo in trial AGAL-008-00) and on the rate of progression of renal disease

(eGFR slope; compared to untreated historical patients in the long-term observational study/ matched analyses). This evidence is described in detail in section 8.2. New data submitted in this application include eGFR data from the long-term observational study which were reviewed for the first time and are described in detail in sections 8.2.4 and 8.2.5.

8.2. Efficacy Evaluation: Fabrazyme Clinical Studies

8.2.1. Trial AGAL-1-002-98

Trial AGAL 1-002-98 was a multicenter, placebo-controlled, double-blind, randomized trial that evaluated patients with Fabry disease. Patients aged ≥ 16 years old with a clinical presentation consistent with Fabry disease and a plasma α gal activity of <1.5nmol/hr/ml or leukocyte α gal activity of <4 nmol/hr/mg were randomized to receive 0.9-1.1mg/kg of Fabrazyme or placebo every 2 weeks for 20 weeks. There were 29 patients randomized to placebo and 29 patients randomized to treatment. The primary endpoint was the proportion of patients in each group with a score of zero on accumulation of the GL-3 substrate in the capillary endothelium of the kidney (using the FSS – see below) at 20 weeks. Secondary endpoints included quantitation of GL-3 accumulation in the capillary endothelium of the heart and skin as determined by light microscopy comparing baseline to 20 weeks. The FSS methodology consisted of all capillaries on each slide that were individually examined and received grades of 0, trace, 1, 2, or 3 based on imaging within the endothelium: score of "0" signified no visible inclusions, "trace" signified a single inclusion, "1" signified multiple discrete inclusions, "2" signified single or multiple aggregates of inclusions and "3" signified aggregates of inclusions large enough or numerous enough to cause a clear distortion of the luminal surface. A slide score of 0 would be obtained if more than 50% of capillaries had a capillary score of 0. At baseline, only one patient in the treatment group had a slide score of 0. At the end of treatment, 20 (69%) patients in the treatment group had a slide score of 0, whereas no patients in the placebo group had a slide score of 0. Skin and heart biopsies showed a similar trend as the kidney biopsies. The following tables (Table 11, Table 12, and Table 13) show the baseline and end-of-study (Week 20) scores and the results of the primary and secondary endpoints.

Table 11. Trial AGAL-1-002-98: Renal Slide Scores at Baseline and Week 20

	Baseline		Week 20	
Slide Score	Placebo (N=29)	Fabrazyme (N=29)	Placebo (N=29)	Fabrazyme (N=29)
0	0	1	0 (0%)	20 (69%)
1	4	7	7 (24%)	8 (28%)
2	15	14	11 (38%)	0 (0%)
3	10	7	11 (38%)	1 ** (3%)
			p-value < 0.001	

Source: Fabrazyme 2003 BLA review
** Subject 307, attributed a worst-case score in the absence of an end-of-trial biopsy.

Table 12. Trial AGAL-1-002-98: Proportion of Patients With Zero Score in the Capillary Endothelium of Kidney at Week 20

	Placebo (N=29)	Fabrazyme (N=29)
Zero	0 (0%)	20 (69%)
Non-zero	29 (100%)	9 (31%)
Odds ratio (95% CI)	0.008 (0.00, 0.14) p-value < 0.001	

Source: Fabrazyme 2003 BLA review

Table 13. Trial AGAL-1-002-98: Proportion of Patients With Zero Score in the Capillary Endothelium of Heart and Skin at Week 20

	Placebo (N=29)	Fabrazyme (N=29)
Heart	1/29	21/29
Skin	1/29	29/29

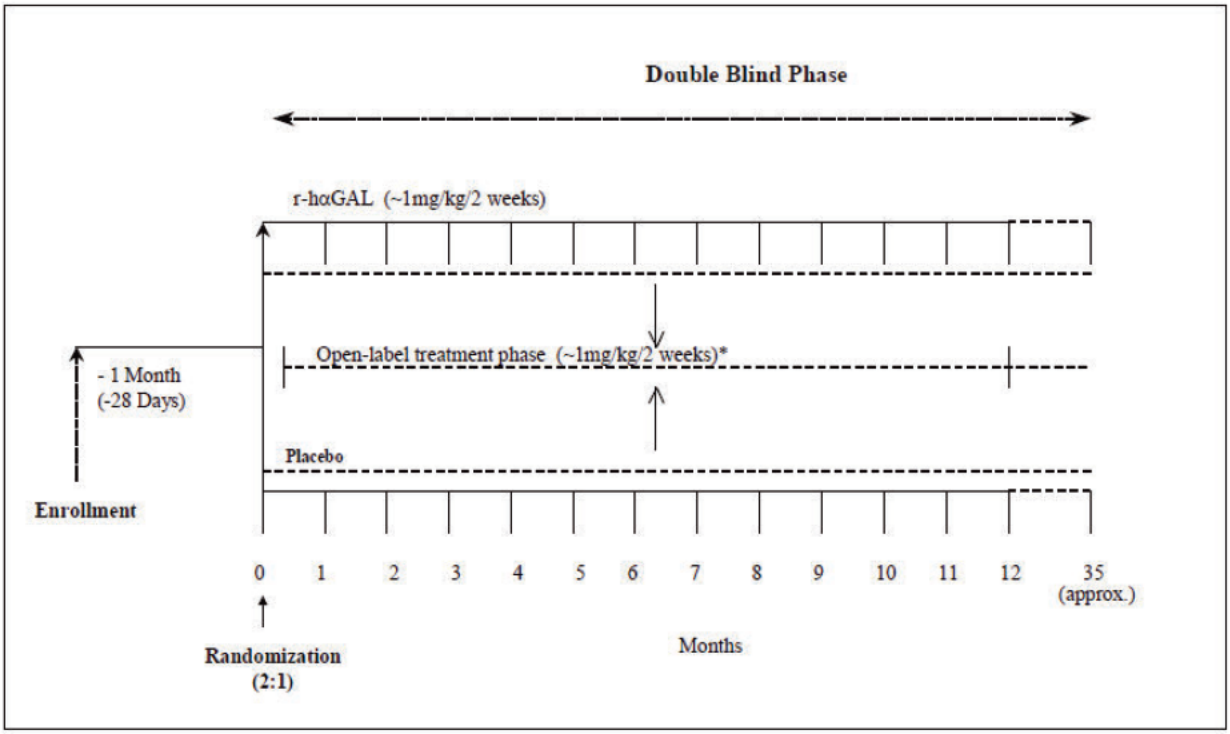
Source: Fabrazyme 2003 BLA review

Conclusions

Overall, Trial AGAL-1-002-98, which supported Fabrazyme's accelerated approval, showed a statistically significant and substantial relative reduction of accumulated GL-3 in the renal peritubular capillaries (PTC) compared to placebo ($p<0.001$) over 20 weeks of randomized treatment. At the time of approval, the review team determined that Fabrazyme exerted a strong treatment effect on the renal histological endpoint that was used as a surrogate endpoint reasonably likely to predict clinical benefit. This evidence supports substantial evidence of effectiveness for the accelerated (in 2003) and the full approval (now) of the product.

8.2.2. Trial AGAL-008-00

Figure 5. AGAL-008-00 Trial Design



Source: trial AGAL-008 protocol

Trial AGAL-008-00 (Figure 5) was the required postmarketing confirmatory randomized, placebo-controlled phase 4 trial which evaluated Fabrazyme 1mg/kg IV every 2 weeks in patients with Fabry disease and mild to moderate renal disease. Patients were randomized 2:1 to either Fabrazyme or placebo for a maximum of 35 months. This was followed by an open label extension phase 4 extension trial (AGAL-2503) during which all patients received Fabrazyme. (b) (4)

Inclusion Criteria:

Males and females ≥16 years of age with a diagnosis of Fabry disease (documented plasma α-galactosidase A [αGAL] activity <1.5 nmol/hr/mL or leukocyte αGAL activity <4 nmol/hr/mg), clinical presentation consistent with Fabry disease (e.g., angiokeratoma, "Fabry pain," decreased sweating, corneal opacities, or other), and documented renal disease by one or more of the following: two consecutive serum creatinine (Cr) measurements >1.2 and <3 mg/dL AND the two values within 15% of each other, OR, if the patient's serum Cr was <1.2 mg/dL, then an estimated Cr clearance <80 mL/min (using the Cockroft-Gault formula) AND the two values are within 15% of each other.

Exclusion Criteria:

Undergone or were scheduled for kidney transplantation or were on dialysis; any of the following: acute renal failure, diabetes mellitus or presence of confounding renal disease; history of transient ischemic attack or ischemic stroke within three months of trial entry, current critical coronary artery disease, congestive heart failure (Class III or IV New York Heart Association classification); residual neurological deficit that would confound the detection of new events; serious intercurrent illness or extenuating circumstance that would preclude trial participation; had previously received enzyme replacement therapy for the treatment of Fabry disease.

Primary Efficacy Endpoint: Time to First Occurrence of a Clinically Significant Renal, Cardiac, or Cerebrovascular Event, or Death.

Clinically significant events were defined as:

- Renal event: 33% increase in serum Cr from baseline (mean of last two serum Cr observations during the Screening period), or progression to end-stage renal disease defined as the requirement for chronic dialysis (continuing for >40 days) or renal transplantation
- Cardiac event: myocardial infarction, or a significant change in cardiac status requiring new surgical or medical intervention, including: unstable angina accompanied by electrocardiogram change that results in hospital admission, worsening congestive heart failure requiring hospitalization for IV drug administration, or symptomatic arrhythmia requiring medication, pacemaker, cardioversion or defibrillator implantation,
- Cerebrovascular event: stroke or transient ischemic attack
- Death due to any cause

All potential events were reviewed and adjudicated by a blinded three-member Independent Adjudication Board (IAB) that consisted of a nephrologist, cardiologist and neurologist. If a patient from either treatment arm experienced a clinically significant event that the principal investigator felt met the criteria for the primary endpoint, the IAB reviewed the event and if the event was confirmed as meeting the primary endpoint, the principal investigator and the medical monitor had the option to enter the patient into open-label treatment. The review team agrees with the addition of the IAB to provide a secondary blinded evaluation for confirmation of the clinically significant events as related to Fabry disease progression.

Secondary Endpoints

- Progression of renal disease as measured by the difference in the post-baseline slope of the reciprocal of the serum creatinine (1/serum Cr) between the two treatment groups
- Difference in time to first renal event between the two treatment groups

- Neuropathic pain as assessed by Question 12 of the Brief Pain Inventory questionnaire ("pain at its worst" in the past week) from pre-infusion to final visit
- Difference in post-baseline slopes of eGFR between the two groups

Statistical Analysis Plan

The intent-to-treat (ITT) population was the primary analysis population for the primary endpoint and included all randomized patients. Analyses using the ITT population defined treatment group as the patient's randomized treatment. The ITT efficacy population only included data collected while on blinded therapy and excluded data collected after first occurrence of one of the composite clinical events, withdrawal, or use of unblinded therapy. The per-protocol (PP) population was defined as those in the ITT population that did not miss more than 20% of trial drug infusions and that did not have major protocol violations. Analyses using the PP population defined treatment group as the patient's received treatment. The As-Treated population was defined as all randomized patients but utilized the patient's received treatment, rather than randomized treatment. The primary endpoint was assessed using a two-sided log-rank test at the 5% significance level. Patients that withdrew, were lost to follow-up, or began taking commercially available therapy before the occurrence of the primary endpoint were censored at the date of the withdrawal, loss to follow-up, or therapy switch. If a patient completed the trial without a clinical event, then the patient was censored at the date of trial completion. No missing values were imputed for the primary endpoint. Supportive analyses of the primary endpoint included Kaplan-Meier estimates displayed in a figure and summarization of the time to first occurrence of the primary endpoint within each treatment group.

The statistical analysis plan (SAP) pre-specified the following supplemental analyses:

- For the primary endpoint: a Cox proportional hazard model to estimate the hazard ratio and corresponding 95% confidence interval (CI) and p-value, adjusting for treatment group, baseline age and baseline serum creatinine
- Gehan's two-sided weighted log-rank test to assess differences in the time to first occurrence of a 33% increase in serum creatinine between treatment groups
- Excluding "greater than 40 days on dialysis" as a renal event in the composite clinical event endpoint
- Assessment of each component of the composite clinical event endpoint – cardiovascular, cerebrovascular, renal, and death
  - Descriptive statistics by treatment group for each component
  - Kaplan-Meier curves for each component
- A per protocol analysis: This analysis excluded any clinically significant event that occurred within three months of randomization. Any patient that has an event within the three months was considered censored at the event date.
- Assessment of the renal event endpoint using multiple imputation based on a matched historical dataset for patients randomized to placebo that withdrew or began taking commercially available therapy prior to a clinical event

To assess differences in eGFR slopes between treatment groups, a linear mixed effects model was used to estimate individual patients' eGFR slope. The mixed effects model included both fixed and random effects for intercept and slope, modeled by time as a continuous measure. A Wilcoxon rank-sum test was used on the individual predicted eGFR slopes, obtained from the linear mixed effects model, in order to assess differences in the distribution between treatment groups. Supplemental analyses utilized quadratic fixed and random effects in the linear mixed effects model.

It should be noted that p-values and 95% CIs in Section 8.2.3 are nominal and presented for descriptive use only given that the pre-defined primary efficacy analysis of the primary endpoint did not yield a statistically significant result (p-value >0.05).

Protocol Amendments

The protocol amendments were reviewed and do not appear to negatively impact the trial conduct or efficacy evaluations.

8.2.3. Trial AGAL-008-00 Results

Compliance With Good Clinical Practices

The protocol was designed and conducted, recorded, and reported in compliance with the principles of Good Clinical Practice regulations.

Financial Disclosure

The Applicant provided a signed copy of FDA form 3454 disclosing all financial interests and arrangements of clinical investigators. The Applicant certifies that it did not enter into any financial arrangement with the Clinical Investigators whereby the value of compensation to the investigator/physicians could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Applicant also certifies that each listed Clinical Investigator required to disclose to the Applicant whether the investigator/physicians had a proprietary interest in the tested product (property or other financial interest including, but not limited to a patent, trademark, copyright or licensing agreement) as defined in 21 CFR 54.2(c), did not disclose any such interests.

Patient Disposition

Seventy-one of the 82 randomized patients (87%) completed the trial. Of the remaining 11 patients: Three discontinued due to hypersensitivity concerns [Two patients (Fabrazyme) were withdrawn from the trial for a positive IgE and for a positive skin test; one patient (Fabrazyme) was withdrawn due to an inconclusive skin test]; three patients (one placebo and two Fabrazyme) who did not meet the primary endpoint voluntarily withdrew from the trial; two patients (one placebo and one Fabrazyme) withdrew after reaching the primary endpoint; three

patients (Fabrazyme) who reached the primary endpoint switched to open-label therapy once Fabrazyme was commercially available. Among the 27 patients (14 Fabrazyme, 13 placebo) who met the primary endpoint, 22 of these 27 patients (10 Fabrazyme, 12 placebo) switched to open-label therapy. The remaining five patients were not transitioned; one patient withdrew, one patient was not confirmed as having a primary endpoint until after the trial was completed, and three patients died (PE, cardiac arrest after a stroke, and cardiac arrest).

Protocol Violations/Deviations

Five patients missed ≥ 20% infusions, two patients received the wrong medication and one patient did not meet "clinical presentation of Fabry disease" but received a waiver for treatment due to fabry disease noted on renal biopsy. The violations occurred before unblinding and therefore were excluded from the per protocol population and did not impact the efficacy analysis.

Demographic and Other Baseline Characteristics

The population was predominantly male (72 of 82 patients, 88%; Table 14) and Caucasian (72 patients, 88%).

Table 14. Trial AGAL-008-00, Baseline Demographics

Characteristic	Fabrazyme (N=51)	Placebo (N=31)
Age, years		
Mean (SD)	47 (10)	44 (9)
Median	45	44
Min, Max	21, 73	21, 62
Sex, n (%)		
Female	6 (12)	4 (13)
Male	45(88)	27(87)

Source: Table prepared by the Division of Biometrics (DB) IV, Office of Biostatistics review team using analysis datasets (bcov_3) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

Baseline Fabry disease characteristics showed similar age at Fabry symptom diagnosis in both groups (mean of 35 years in Fabrazyme and 33 years in the placebo group; Table 14). All patients had evidence of a low αGAL level at trial entry. Mean serum Cr and estimated glomerular filtration rate were the same in both groups, consistent with mild to moderate renal disease at baseline. Differences between the two groups were notable in that patients randomized to treatment with Fabrazyme had higher mean baseline proteinuria (1.5 mg/mg) compared to placebo (1.2 mg/mg). The difference in baseline proteinuria is important as proteinuria is a strong prognostic indicator for progression of renal disease in general and in Fabry disease in specific, with patients with higher levels of urinary protein tending to have a poorer prognosis (Waldek and Feriozzi 2014). Also notable is a higher mean and median baseline plasma and leukocyte αGAL enzyme level in the placebo group compared to Fabrazyme indicating that patients in placebo group had milder disease and may have had slower disease progression. Key baseline characteristics are presented below in Table 15.

Table 15. Trial AGAL-008-00, Key Baseline Characteristics

Characteristic		Fabrazyme (N=51)	Placebo (N=31)
Age at FD diagnosis (years)	**n=81**	**n=51**	**n=30**
	Mean (SD)	35 (14)	33 (12)
	Median	37	34
	Min, Max	5, 67	11, 55
Plasma GL-3 (ug/mL)	**n=80**	**n=49**	**n=31**
	Mean (SD)	9	9
	Median	9	9
	Min, Max	3, 19	4, 17
Plasma αGAL activity (nmol/hour/mL)	**n=45**	**n=29**	**n=16**
	Mean (SD)	0.9 (0.6)	1.3 (0.5)
	Median	0.9	1.5
	Min, Max	0, 1.5	0, 1.5
Leukocyte αGAL activity (nmol/hour/mL)	**n=37**	**n=22**	**n=15**
	Mean (SD)	2.1 (1.5)	2.4 (1.6)
	Median	1.6	2.8
	Min, Max	0, 4.0	0, 4.0
Serum Cr (mg/dL)	**n=82**	**n=51**	**n=31**
	Mean (SD)	1.6 (0.5)	1.6 (0.5)
	Median	1.5	1.5
	Min, Max	0.8, 2.8	0.9, 2.9
Estimated GFR ($mL/min/1.73m^2$)	**n=82**	**n=51**	**n=31**
	Mean (SD)	53 (18)	52 (18)
	Median	54	50
	Min, Max	27, 113	25, 97
Proteinuria*	**n=82**	**n=51**	**n=31**
	Mean (SD)	1.5 (1.5)	1.2 (1.4)
	Median	0.9	0.7
	Min, Max	0, 7.3	0, 6.0
Follow-up time (months)	**n=82**	**n=51**	**n=31**
	Mean (SD)	19.6 (8.4)	17.4 (8.8)
	Median	19.8	17.5
	Min, Max	0.9, 35.1	0.3, 31.3

Source: Applicant table with reviewer edits (trial report AGAL-008-00 Part A (p86/11551).
* Urine protein: urine creatinine ratio; mg/mg
Abbreviations: Cr = creatinine; FD = Fabry disease; GFR = glomerular filtration rate; GL-3 = globotriaosylceramide

Concomitant Medications

The most commonly reported concomitant medications include analgesics, such as paracetamol (80 patients), ibuprofen (43 patients), and aspirin (37 patients). Approximately 2/3 of concomitant medications were pre-medication for drug infusion, which were used by 79 of 82 patients. There were no obvious differences between the two treatment groups in types and frequency of medication use.

Primary Endpoint: Time to First Occurrence of a Clinically Significant Event (Renal, Cardiac, Cerebrovascular Event or Stroke)

Unless otherwise stated, the results presented in this subsection have been replicated and confirmed by the review team.

Out of the 82 patients enrolled and randomized in AGAL-008-00, 13 (41.9%) patients in the placebo arm and 14 (27.4%) patients in the Fabrazyme arm experienced a clinical event within the composite clinical event endpoint (Table 16). Of the 27 subjects who experienced a clinical event, 17 (63.0%) experienced a renal event; all 17 subjects experienced a 33% increase in serum creatinine. In the placebo arm, seven subjects experienced a renal event, four subjects experienced a cardiac event (three arrhythmia and one angina), and two subjects experienced a cerebrovascular event (stroke). In the Fabrazyme arm, ten patients experienced a renal event, three subjects experienced a cardiac event (one myocardial infarction and two arrhythmia), and one subject died.

The estimated (unadjusted) HR in the ITT population was 0.57 (95% CI: 0.27, 1.22; p 0.14). Figure 6 depicts the Kaplan-Meier estimates of the primary endpoint for each treatment arm.

Favorable trends for Fabrazyme were seen across the renal, cardiac and cerebrovascular components of the composite events (Figure 8), supporting the primary efficacy analysis results.

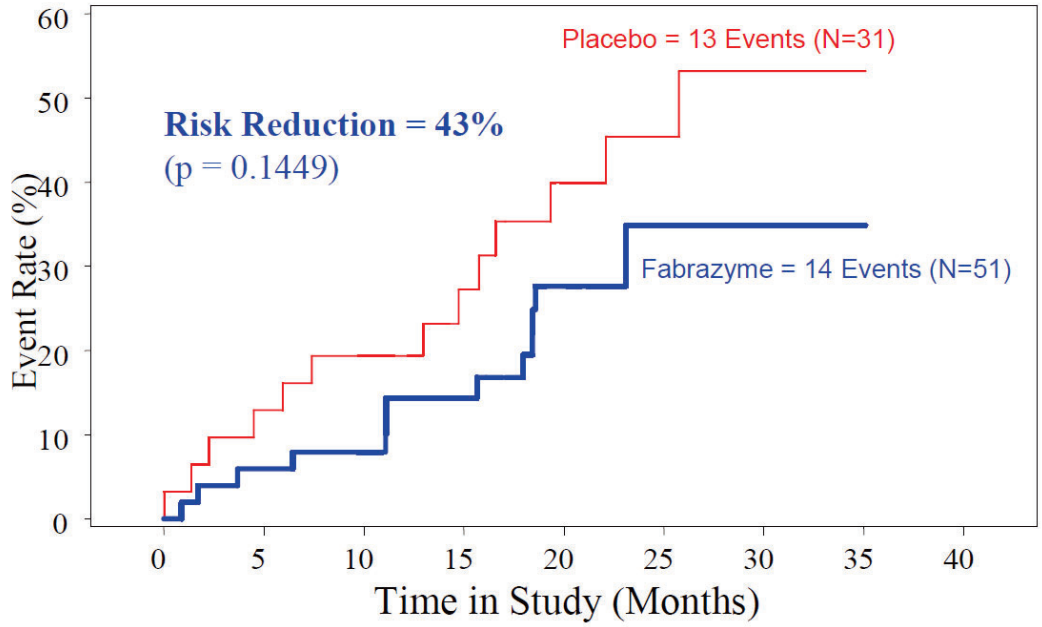
The clinical study report details a (post-hoc) analysis that excluded two patients, patients (b) (6) and (b) (6), whom the Applicant describes as having had a transient acute increase in serum creatinine that normalized and hence did not indicate progression of renal disease. No explanation was discovered for Patient (b) (6). Patient (b) (6) "had been placed on new medications in the two weeks preceding the occurrence of the primary endpoint, which may have accounted for the acute rise in serum creatinine." The review team agrees that an acute and transient increase in serum creatinine is not consistent with renal disease progression which is chronic and non-reversible (i.e. clinically significant renal event). The estimated unadjusted HR after excluding the two patients was 0.48 (95% CI: 0.22, 1.04; p=0.06) and 0.44 (95% CI: 0.19, 1.00; p=0.04) in the ITT and PP populations, respectively. The estimated HR after adjusting for baseline proteinuria was 0.37 (95% CI: 0.16, 0.85; p=0.02) and 0.29 (95% CI: 0.11, 0.73; p<0.01) in the ITT and PP populations, respectively. Figure 7 depicts the Kaplan-Meier estimates of the primary endpoint for each treatment arm after excluding these two patients.

Table 16. AGAL-008-00 Primary Efficacy Analysis Results (ITT Population)

	Fabrazyme (N=51) n (%)	Placebo (N=31) n (%)	Hazard Ratio (95% CI) (Unadjusted Analysis)
Number of clinical events	14 (28)	13 (42)	0.57 (0.27, 1.22); p=0.14
Renal[1]	10 (20)	7 (23)	
Cardiovascular[2]	3 (6)	4 (13)	
Cerebrovascular[3]	0	2 (6)	
All-cause mortality[4]	1 (2)	0	

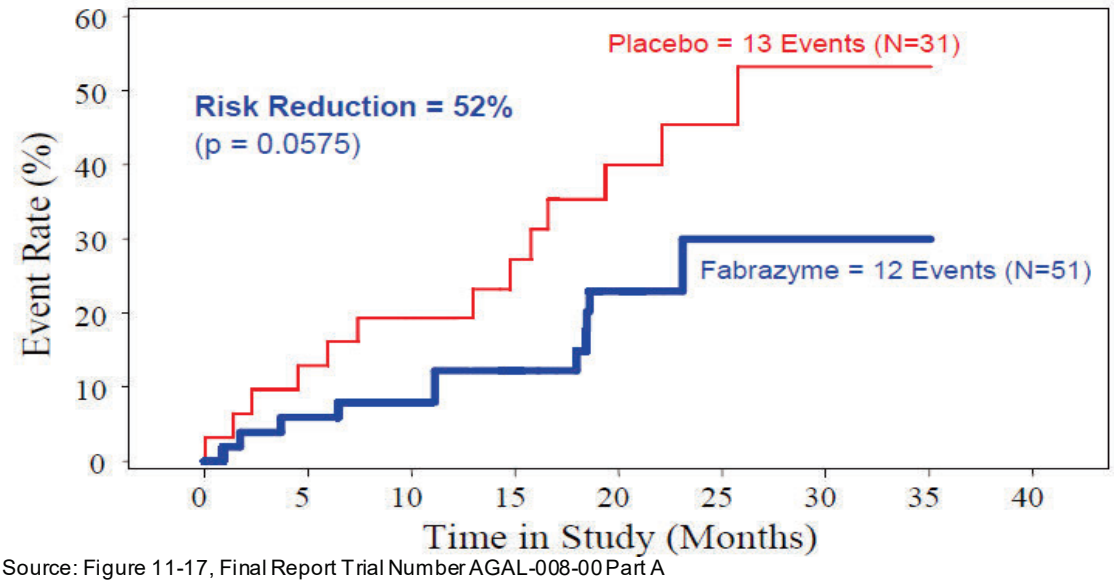
Source: Table prepared by the DB IV review team using analysis datasets (bcov_3 and event_1) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
[1] All observed renal events were 33% increases in serum creatinine from baseline.
[2] Of the three observed cardiovascular events in Fabrazyme-treated patients, two were arrythmias and one was a myocardial infarction. Of the four observed cardiovascular events in placebo-treated patients, three were arrythmias and one was angina.
[3] All observed cerebrovascular events were strokes.
[4] The observed death was due to cardiac arrest
Abbreviations: CI = confidence interval; ITT = intent-to-treat

Figure 6. AGAL-008-00 Kaplan-Meier Estimate of Time to First Occurrence of a Clinically Significant Event (ITT Population)



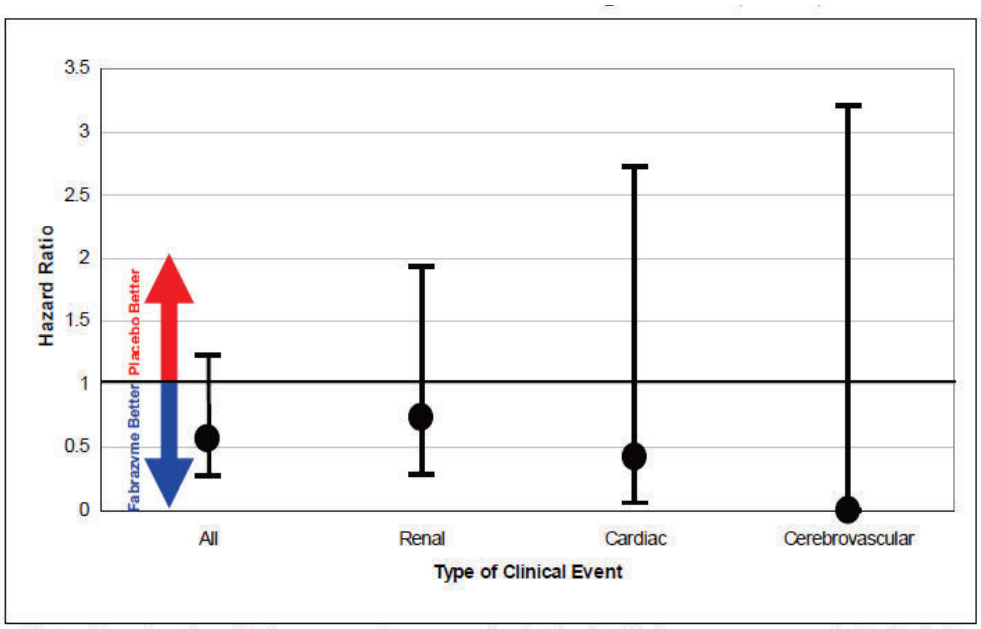
Source: Figure 11-5, Final Report Trial Number AGAL-008-00 Part A
Abbreviations: ITT = intent-to-treat

Figure 7. AGAL-008-00 Kaplan-Meier Estimate of Time to First Occurrence of a Clinically Significant Event (ITT Population Excluding Patients (b) (6) and (b) (6))



Source: Figure 11-17, Final Report Trial Number AGAL-008-00 Part A
Abbreviations: ITT = intent-to-treat

Figure 8. AGAL-008-00 Hazard Ratios by Type of Clinical Event in the Composite Primary Endpoint With 95% CI (ITT Population)



Note: One death, which was a primary endpoint in the Fabrazyme group, is included in the analysis of "All" primary endpoints.

Source: Figure 11-6, Final Report Trial Number AGAL-008-00 Part A
Abbreviations: CI = confidence interval; ITT = intent-to-treat

The clinical study report included a post-hoc analysis of the primary endpoint that adjusted for baseline proteinuria given a small imbalance on this parameter between the 2 groups. When adjusting for baseline proteinuria, the estimated HR in the ITT population was 0.47 (95% CI: 0.21, 1.03), corresponding to a 53% risk reduction with a p-value of 0.06. In the PP population, the estimated HR after adjusting for baseline proteinuria was 0.39 (95% CI: 0.16, 0.93), corresponding to a 61% risk reduction, with a p-value of 0.03.

The subgroup analyses by baseline proteinuria (≤ 1 vs. >1 mg/mg; Table 17), eGFR (< 60 vs. ≥ 60 mL/min/1.73 m^2; Table 18), and time of FD diagnosis (≤ 5 vs. >5 years; Table 19) supported the overall efficacy analysis, showing a favorable trend on the composite clinical event. The estimated HRs were consistently lower in patients who were at less advanced stages of renal disease or treated earlier after FD diagnosis. The HR was 0.43 (95% CI: 0.14, 1.35; p=0.14) in patients with baseline proteinuria ≤ 1 mg/mg and 0.66 (95% CI: 0.23, 1.87; p=0.41) in patients with baseline proteinuria > 1 mg/mg. The HR (adjusted for proteinuria) was 0.23 (95% CI: 0.04, 1.53; p=0.13) in patients with baseline eGFR ≥ 60 mL/min/1.73m^2 and 0.64 (95% CI: 0.26, 1.56; p=0.33) in patients with baseline eGFR < 60 mL/min/1.73m^2 (Figure 9). The HR (adjusted for proteinuria) was 0.23 (95% CI: 0.05, 1.03; p=0.05) in patients with time of FD diagnosis ≤ 5 years and 0.60 (95% CI: 0.22, 1.64; p=0.32) in patients with time of FD diagnosis > 5 years (Figure 9).

Table 17. AGAL-008-00 Primary Endpoint: Subgroup Analyses by Baseline Proteinuria

	All (ITT Population)		Baseline Proteinuria ≤ 1.0 mg/mg		Baseline Proteinuria > 1.0 mg/mg	
	Fabrazyme (n=51)	Placebo (n=31)	Fabrazyme (n=29)	Placebo (n=21)	Fabrazyme (n=22)	Placebo (n=10)
Number of Events	14 (27.5%)	13 (41.9%)	5 (17.2%)	7 (33.3%)	9 (40.9%)	6 (60.0%)
Treatment Difference: Hazard Ratio						
Unadjusted	0.58 (0.27, 1.23); p=0.15		0.43 (0.14, 1.35); p=0.14		0.66 (0.23, 1.87); p=0.41	

Source: Table prepared by the DB IV review team using analysis datasets (bcov_3 and event_1) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
Abbreviations: ITT = intent-to-treat

Table 18. AGAL-008-00 Primary Endpoint: Subgroup Analyses by Baseline eGFR

	All (ITT Population)		Baseline eGFR < 60 mL/min/1.73m^2		Baseline eGFR ≥ 60 mL/min/1.73m^2	
	Fabrazyme (n=51)	Placebo (n=31)	Fabrazyme (n=33)	Placebo (n=22)	Fabrazyme (n=18)	Placebo (n=9)
Number of Events	14 (27.5%)	13 (41.9%)	12 (36.4%)	10 (45.5%)	2 (11.1%)	3 (33.3%)
Treatment Difference: Hazard Ratio						
Unadjusted	0.58 (0.27, 1.23); p=0.15		0.81 (0.35, 1.89); p=0.63		0.25 (0.04, 1.54); p=0.14	
Adjusted for BL proteinuria	0.47 (0.21, 1.03); p=0.06		0.64 (0.26, 1.56); p=0.33		0.23 (0.04, 1.53); p=0.13	

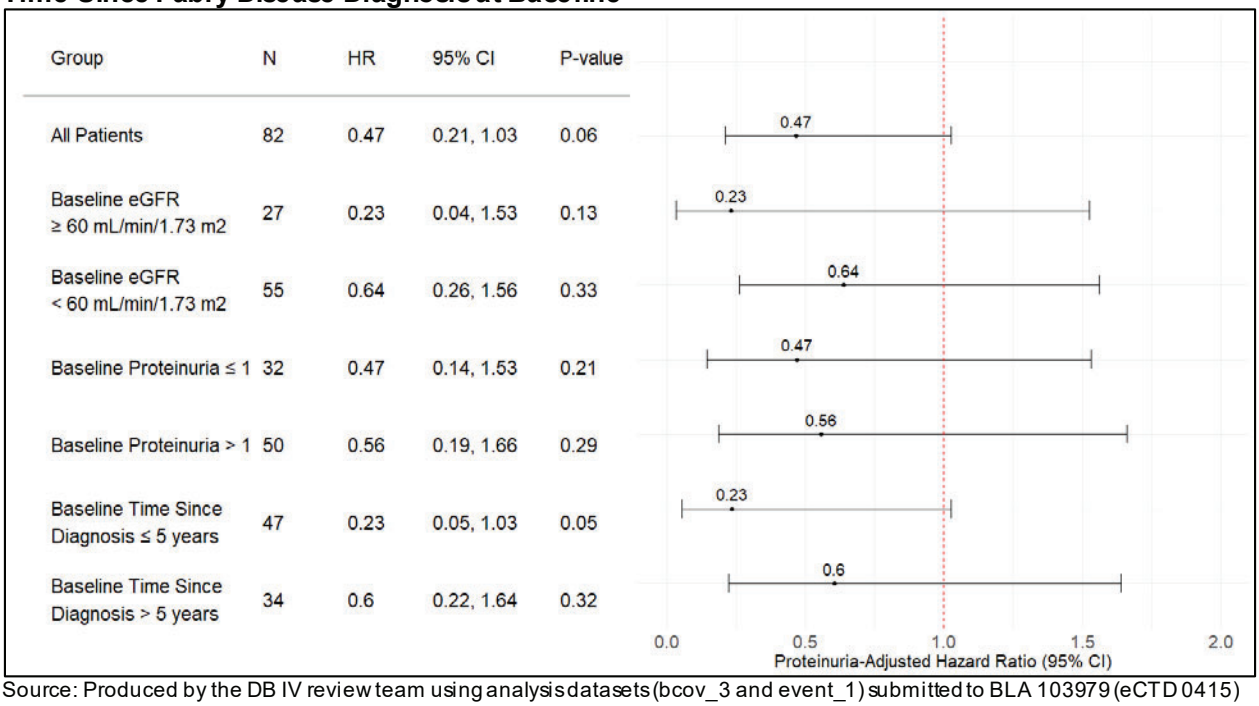
Source: Table prepared by the DB IV review team using analysis datasets (bcov_3 and event_1) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
Abbreviations: eGFR = estimated glomerular filtration rate; ITT = intent-to-treat

Table 19. AGAL-008-00 Primary Endpoint: Subgroup Analyses by Time Since Fabry Diagnosis

	All (ITT Population)		Within 5 Years of Diagnosis at BL		More Than 5 Years Since Diagnosis at BL	
	Fabrazyme (n=51)	Placebo (n=31)	Fabrazyme (n=20)	Placebo (n=14)	Fabrazyme (n=31)	Placebo (n=16)
Number of Events	14 (27.5%)	13 (41.9%)	5 (25.0%)	6 (42.8%)	9 (29.0%)	7 (43.8%)
Treatment Difference: Hazard Ratio						
Unadjusted	0.58 (0.27, 1.23); p=0.15		0.42 (0.13, 1.39); p=0.14		0.66 (0.24, 1.76); p=0.40	
Adjusted for BL proteinuria	0.47 (0.21, 1.03); p=0.06		0.23 (0.05, 1.03); p=0.05		0.60 (0.22, 1.64); p=0.32	

Source: Table prepared by the DB IV review team using analysis datasets (bcov_3 and event_1) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
Abbreviations: BL = baseline; ITT = intent-to-treat

Figure 9. AGAL-008-00 Primary Endpoint: Hazard Ratios (95% CI) Adjusted for Baseline Proteinuria for the Overall Population and Subgroups by Baseline eGFR, Baseline Proteinuria, and Time Since Fabry Disease Diagnosis at Baseline



Source: Produced by the DB IV review team using analysis datasets (bcov_3 and event_1) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio

Data Quality and Integrity

The quality of the submitted datasets was sufficient for review. Additionally, the clinical trial report for AGAL-008-00 contains a section regarding data quality assurance that describes the Applicant's data review process.

Secondary Endpoints: Time to First Renal Event, eGFR Slope

Time to First Renal Event

The time to first renal event endpoint assessed only the events in the composite clinical event endpoint that were renal in nature. Renal events after the first event in the composite clinical event endpoint were not included in the time to first renal event endpoint, as many patients transitioned to open-label Fabrazyme treatment after the first clinical event. All of the renal events in this endpoint were 33% increases in serum creatinine. Among the subjects of AGAL-008-00, ten and seven subjects in the Fabrazyme and placebo arms, respectively, experienced a renal event as the first event of the composite clinical event endpoint. The estimated hazard ratio for the time to first renal event endpoint in the ITT population was 0.73 (95% CI: 0.28, 1.93; p=0.53). The clinical trial report notes that after adjusting for baseline proteinuria and excluding the renal events observed in Patients (b) (6) and (b) (6), whom the Applicant asserts "did not have true progression of chronic renal insufficiency," the estimated hazard ratio was 0.33 (95% CI: 0.11, 1.03; p=0.06).

eGFR slope

Regarding eGFR slope, the overall treatment difference was minimal (Table 20). Patients in the placebo group had a mean decline in eGFR of 3.6 mL/min/1.73m^2/year while patients in the Fabrazyme group had a mean decline in eGFR of 3.3 mL/min/1.73m^2/year, with a treatment difference of 0.4 (95% CI: -1.0, 1.7; p=0.54). However, a favorable trend for Fabrazyme was seen in patients with baseline eGFR ≥ 60 mL/min/1.73m^2. For this subgroup, the mean decline in eGFR was 5.1 mL/min/1.73m^2/year in the placebo group and 1.5 mL/min/1.73 m^2/year in the Fabrazyme group, with a treatment difference of 3.5 (95% CI: 0.54, 6.51; p=0.03) favoring Fabrazyme. This favorable subgroup analysis for the eGFR slope aligned with the subgroup analysis for the primary endpoint. As shown in Table 18, for this subgroup, the estimated hazard ratio was 0.25 (95% CI: 0.04, 1.54; p=0.14) for the risk of composite clinically significant events.

Table 20. AGAL-008-00 eGFR Slope: Overall and Subgroup Analyses by Baseline eGFR

	All Patients		Baseline eGFR > 60 mL/min/1.73m^2	
	Fabrazyme (n=51)	Placebo (n=31)	Fabrazyme (n=18)	Placebo (n=9)
Mean (SD)	-3.25 (2.92)	-3.62 (3.38)	-1.51 (2.85)	-5.09 (3.52)
Median	-3.27	-3.59	-1.92	-4.16
Difference (95% CI)	0.39 (-0.98, 1.72); p=0.54		3.54 (0.54, 6.51); p=0.03	

Source: Tables 14.2.2-2 and 14.2.2-9 of CSR. Data collected after the first date of occurrence of a clinical event, or of receiving unblinded therapy was excluded. Patient slope was estimated from a linear random effects model.
Nominal p-values were presented and based on Wilcoxon Rank Sum test.
Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate

Dose Response

Not assessed.

Conclusions

In Trial AGAL-008-00, the primary efficacy analysis showed that Fabrazyme-treated patients had a numerically lower rate of clinically significant events (renal, cardiac, cerebrovascular event, or death) compared to placebo-treated (HR 0.57, 95% CI: 0.27, 1.22, p = 0.14), with consistent results across the renal, cardiac and cerebrovascular components of the composite events when assessed individually. A stronger favorable effect was seen in patients with less advanced renal disease at baseline. (b) (4)

.

The trial appears to have been underpowered to demonstrate a statistically significant result (at the conventional $p \leq 0.05$ statistical significance threshold) on the primary endpoint due to its small sample size in this rare disease (82 patients) and the small number of clinical events observed in the trial (lower than previously expected). Considering the strong pharmacodynamic effect of Fabrazyme on reducing and even normalizing tissue and plasma GL-3 in this and the previous randomized trial, the favorable trends for efficacy of Fabrazyme over placebo in the primary endpoint in this trial seem unlikely to be due to chance in this trial. Based on the observed treatment effect in this trial, a new randomized trial would require more than 350 patients (2:1 randomization ratio) to have 80% power to demonstrate a statistically significant ($p < 0.05$) treatment effect on the same primary endpoint. This would not be feasible given that Fabry disease is a rare condition and treatment with Fabrazyme is considered standard of care therapy (Ortiz et al. 2018). In addition, the conduct of a new randomized, placebo-controlled clinical trial would not be considered ethical in this context. As such, there is no realistic expectation of collecting additional controlled data in a new randomized, placebo-controlled trial in the future to resolve the uncertainties raised from this trial.

8.2.4. Observational Study: Fabry Registry/Natural History Matched Analysis

The Applicant's submission in this sBLA included a SAP entitled "Fabry Registry/Natural History Matched Data" and the corresponding study report entitled "Effectiveness of Fabrazyme: Fabry Registry/ Natural History Matched Analysis." These matched analyses aimed to demonstrate a treatment benefit of Fabrazyme in slowing the decline of eGFR and in reducing the risk of clinically significant events based on the data from Fabrazyme-treated patients in the Fabry Registry matched to untreated FD patients in study AGAL-014-01 (Natural History study). The Applicant conducted this observational study to fulfill the revised Post-Marketing Commitment (PMC 2421-2). This revised PMC was included in the Agency's complete response letter on 13-May-2008 and contained the following statements: "Sanofi Genzyme committed to performing additional analyses of the data in the Fabry Registry of patients with Fabry disease being

treated with agalsidase beta that was established to obtain long-term clinical status information. Additional analyses of the Fabry Registry data are to be performed for the purpose of establishing the clinical benefit of agalsidase beta on progression of renal disease and other end-organ disease endpoints in patients with Fabry disease."

Fabry Disease Registry (Treated Patients)

The Fabry disease registry is an international, multi-center, longitudinal, observational and voluntary program for patients with Fabry disease designed to track the natural history and outcomes of patients. This long-term program occurred over 15 years. Males and females with a confirmed diagnosis of Fabry disease (defined as a documented deficiency in plasma or leukocyte αGAL enzyme activity and/or mutation in the αGAL A gene) were eligible to participate. The registry began enrollment in 2001 and, as of January 2018, a total of 6,099 unique patients with FD (treated with Fabrazyme or untreated with Fabrazyme) have enrolled. The registry database was designed to collect a variety of baseline and follow-up data obtained through routine clinical and laboratory assessments. All data submissions were voluntary and there were no pre-determined follow-up periods for data collection. The patients underwent clinical assessments and received standard-of-care treatment as determined by the patient's physician.

Natural History Study AGAL-014-01 (Untreated Patients; Historical Control Group)

AGAL-014-01 was an international, multicenter retrospective study that created a historical cohort of patients with a diagnosis of Fabry disease during their lifetimes or at the time of their death and not treated with Fabrazyme. Patients were excluded if they had other "obvious and confounding" renal disease (i.e. diabetic nephropathy, SLE, or other well-established disorder) at FD diagnosis or other major disease (e.g. cancer, HIV/AIDS, significant organic disease) at FD diagnosis. Medical records dating from 1944 through 2002 were abstracted from 447 unique patients in order to characterize the natural history of Fabry disease including the occurrence of renal, cardiac, cerebrovascular events and mortality in Fabry patients. This natural history study provides the patient population for all historical control patients in the present analyses.

Study Eligibility Criteria

Inclusion Criteria

Treated population:

- Agalsidase beta as first Fabry disease treatment
- For patients who switched to an alternative treatment, the data after the switch were excluded
- Non-missing date of the first treatment
- Did not have a neutral allelic variant in the GLA gene
- No renal event (dialysis or renal transplant) prior to initiation of Fabrazyme
- ≥ 16 years of age at the time of treatment initiation

- Non-missing baseline eGFR and at least 1 follow-up eGFR measurement in between 6 months to 5 years of baseline
- Untreated population:
- Non-missing symptom onset date
- Did not have a neutral allelic variant in the GLA gene
- At least 1 eGFR measurement between symptom onset and initiation of therapy or end of follow-up
- No renal event (dialysis or renal transplant) prior to the first eGFR measurement
- At least 2 consecutive eGFR measurements within 6 months to 5 years from each other

Exclusion Criteria

Treated population:

- Missing date of birth
- Missing gender
- On dialysis or received a renal transplant prior to the initiation of Fabrazyme
- Had a genotype indicating a neutral allelic variant in the GLA gene (i.e. A143T, P60L, D313Y, R118C, T385A, IVS0-10 C>T, or the complex haplotype: IVS0-10 C>T/IVS4-16A>G/IVS6-22C>T)

Untreated population:

- Missing date of birth
- Missing gender
- Had confounding renal disease at Fabry disease diagnosis (i.e. diabetic nephropathy, systemic lupus erythematosus, or other well-established disorder)
- Had other major disease at Fabry disease diagnosis (e.g. cancer, HIV, or AIDS)
- Had genotype indicating a neutral allelic variant in the GLA gene (i.e., A143T, P60L, D313Y, R118C, T385A, IVS0-10 C>T, or the complex haplotype: IVS0-10 C>T/IVS4-16A>G/IVS6-22C>T)
- Unknown symptom onset date

Study Endpoints

The primary endpoint was the slope of eGFR estimated using eGFR data collected over a maximum follow-up time period of 5-years (median follow-up time of 3.9 years). The eGFR for adult patients (≥16 years of age) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at each point in follow-up where serum creatinine (Scr) was available. The following excerpts are from the SAP (Figure 10):

Figure 10. CKD-EPI Formula

$$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where:

- Scr in mg/dL,
- $\kappa = 0.7$ for females and 0.9 for males,
- $\alpha = -0.329$ for females and -0.411 for males,
- 1.018 [if female] = 1.1018 if gender is female and 1.0 otherwise
- 1.159 [if black] = 1.159 if race is black and 1.0 otherwise
- min indicates the minimum of Scr/κ or 1, and
- max indicates the maximum of Scr/κ or 1

eGFR is expressed in units of mL/min/1.73 m².

Scr was measured by assays at the local investigative site and reported to the Fabry Registry for the treated population. When values are reported in units other than mg/dL, Scr is converted to a standardized unit of mg/dL using the following conversion factors: (1) µmol/L to mg/dL by dividing by a conversion factor of 88.4; (2) mmol/L to mg/dL, by multiplying by a conversion factor of 11.31; and (3) mg/L to mg/dL by dividing by a conversion factor of 10. Data on Scr measurements in the Natural History study were extracted from medical records and these measurements were conducted via local assays. Scr units in the Natural History study were similarly converted to mg/dL to allow for uniform calculation of eGFR across the two studies.

Source: Applicant's statistical analysis plan
Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = estimated glomerular filtration rate; Scr = serum creatinine

The secondary endpoint was time to first post-baseline event that occurred in any of the following 4 categories:

- Cardiovascular: congestive heart failure, atrial fibrillation, ventricular tachycardia, pacemaker, bypass graft, angioplasty, balloon pump, stent, defibrillator
- Cerebrovascular: hemorrhagic stroke, ischemic stroke
- Renal: chronic dialysis (> 40 days), renal transplantation
- Death: all-cause

Statistical Analysis Plan

Primary Efficacy Endpoint (eGFR Slope)

For the primary efficacy endpoint (eGFR slope), the primary analysis population included Fabry Registry and Natural History study patients ≥16 years of age who were 1:1 and X:X matched on age, gender, and FD phenotype (dbFGP/aGAL definition). In the 1:1 matched analysis, an untreated patient could serve as a control for only one treated patient. In the X:X matched analysis, an untreated patient could serve as a control for multiple treated patients. (b) (4)

(b) (4)

However, the above-mentioned analyses had a significant imbalance between the treatment groups in baseline eGFR, the most significant prognostic factor (Arends et al. 2017). Thus, the results of these analyses might have limited interpretation and are not discussed in this review. For a detailed evaluation of these analyses, please refer to the separate reviews by the Division of Epidemiology I (Office of Surveillance and Epidemiology, CDER) (DARRTS references ID 4694419 and 4734057). These reviews concluded that these matched analyses provide supplementary (supporting) evidence and align with results from Trial AGAL-008-00. The review team agreed with this conclusion.

According to the SAP, the Applicant also conducted a sensitivity analysis of eGFR slope based on the data of 122 treated patients and 122 untreated patients who were matched 1:1 on age at Fabrazyme initiation (index age), sex, FD phenotype, and **baseline eGFR** (these patients are referred to as the main analysis population thereafter). This matched analysis was the focus of the review team's efficacy evaluation. The details of the matching algorithm are presented in Section 14.4.

According to the SAP, the data from untreated and treated patients were analyzed separately to estimate eGFR slopes within each treatment group using a linear mixed effect model that included fixed and random effects for both intercept and slope. For comparing eGFR slopes between the treatment groups, the data from the untreated and treated patients were combined and analyzed using a linear model that included fixed and random effects for both intercept and slope, and fixed effects for treatment and treatment-by-time interaction (time was a continuous variable). Although the Applicant provided 95% CIs and p-values for the estimated eGFR slope within each treatment group, for the comparison of the eGFR slopes between the treatment groups, the Applicant presented only the p-values. The review team calculated 95% CI for the treatment difference in eGFR slopes. The review team's analyses results are presented in Table 31. The p-values for these analyses are nominal and presented as descriptive statistics.

Table 21. Primary Endpoint (eGFR Slope): Matched Analyses on Age at Fabrazyme Initiation, Sex, and FD Phenotype (Primary Analysis Population)

			Treatment Difference	
	Untreated	Treated	95% CI	p-value
1:1 Matched Analysis (N=124:124)	-2.8	-1.4	1.4 (0.2, 2.6)	0.02
X:X Matched Analysis (N=124:1138)	-3.0	-1.7	1.3 (0.7, 2.0)	<0.001

Source: Table prepared by DBIV review team using the analysis datasets (adgfm11 and adgfmxx) submitted to BLA 103979 (eCTD 0415) for the matched analysis on February 14, 2020.
Abbreviations: eGFR = estimated glomerular filtration rate; FD = Fabry disease

Secondary Efficacy Endpoint (Time to First Occurrence of the Composite of Clinical Events)

For the secondary endpoint, according to the SAP, only 1:1 and X:X matched analyses on age, sex, and FD phenotype were conducted. (b) (4)

However, these analyses showed significant imbalances between the treatment groups in age at FD symptom onset and age at FD diagnosis. Thus, these analyses results might have limited interpretation and will not be discussed in this review. For a detailed evaluation of these analyses, please refer to the reviews by the Division of Epidemiology I (Office of Surveillance and Epidemiology, CDER).

Table 22. Secondary Efficacy Endpoint (Clinically Significant Events): Matched Analyses on Age at Fabrazyme Initiation, Sex, and FD Phenotype (Primary Analysis Population)

	Incidence Rate per 1000 Person-Years		Hazard Ratio
	Untreated	Treated	(95% CI; p-value)
1:1 Matched Analysis (N=233:233)	80.9	39.1	0.41 (0.22, 0.74; p=0.003)
X:X Matched Analysis (N=233:1754)	69.2	49.2	0.67 (0.49, 0.90; p=0.008)

Source: Table prepared by DBIV review team using the analysis datasets (adev1to1 and adevxtox) submitted to BLA 103979 (eCTD 0415) for the matched analysis on February 14, 2020.
Abbreviations: CI = confidence interval; FD = Fabry disease

8.2.5. Observational Study Results

Compliance With Good Clinical Practice

According to the Applicant (p14 of Clinical overview), "the natural history trial (AGLA-014-01) and the Fabry Registry were designed, conducted, recorded and reported in compliance with the principles of good clinical practice as required by the International Conference on Harmonisation E6 Guideline for Good Clinical Practice. The studies also meet the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Applicant, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC."

Financial Disclosures

The Applicant provided a signed copy of FDA form 3454 disclosing all financial interests and arrangements of clinical investigators. There was no financial interest reported with the Natural History trial (AGAL-014-01). In the Fabry Registry, the Applicant collected financial disclosure information for 210 actively participating investigators. The Applicant collected financial disclosure information for 44% (63/142) of the inactive investigators. The Applicant was unable to obtain a complete financial disclosure form from 56% (79/142) of inactive investigators as 12 were deceased and 67 were retired and/or left the site and/or did not answer. A total of 32 investigators reported financial interests. The Applicant certifies that each listed clinical

investigator required to disclose to the Applicant whether the investigator/physician had a proprietary interest in the tested product (property or other financial interest including, but not limited to a patent, trademark, copyright or licensing agreement) as defined in 21 CFR 54.2(c), did not disclose any such interests.

Baseline Demographic and Other Characteristics

The main analysis population consisted of 122 pairs of treated and untreated patients who were matched on age at Fabrazyme initiation (index age), sex, FD phenotype, and baseline eGFR. In this population, the two treatment groups were well balanced in the four matching variables (Table 23). The mean age at Fabrazyme initiation was 35 years. The proportion of male patients was 72%. The proportion of patients with a classic FD phenotype was 84%. The mean baseline eGFR was 91 mL/min/1.73m^2.

However, an imbalance in the mean (median) age at FD symptom onset was observed: 12.3 (9.5) years for the untreated and 14.4 (10.2) years for the treated groups. This imbalance might be a marker of less severity of FD for the treated patients and thus might favor the treated group for the efficacy evaluation. To evaluate the potential impact of this imbalance, the review team conducted analysis for the subgroup of patients (referred to as the secondary analysis population thereafter) by excluding the 12 pairs who were in the top 10% in the difference in age at FD symptom onset, calculated as the age for the treated patient subtracted by the age of the untreated patient. These 12 pairs had the largest difference in age at FD symptom onset favoring the treated patients (i.e., the treated patients had an older age at symptom onset than their matched untreated patients). These 12 pairs were excluded from the main analysis population so that the resultant subpopulation would not have an imbalance between the treatment groups in mean and median age at FD symptom onset favoring the treated group.

In the secondary analysis population (110 patients in each group), the two groups were comparable in the four matching variables as well as age at FD diagnosis (Table 23). In addition, the mean age at FD symptom onset in the untreated group was two years older than the treated group (13 years for untreated vs. 11 years for treated) and median age at symptom onset was similar (9.6 years for untreated vs. 9.5 years for treated); this imbalance might suggest less severity of FD for the untreated patients and thus might not favor the treated group for the efficacy evaluation.

Table 23. Summary Statistics of Matching Prognostic Variables (Index Age, Sex, and FD Phenotype, and Baseline eGFR), Age at FD Diagnosis, and Age at Symptom Onset

		Main Analysis Population		Secondary Analysis Population	
Characteristic		Untreated (N=122)	Treated (N=122)	Untreated (N=110)	Treated (N=110)
Age at FD baseline (index age; years)	Mean (SD)	34.5 (10.3)	35.0 (10.3)	33.3 (9.8)	33.6 (9.8)
	Median	35.5	34.7	33.5	33.6
	Min, Max	16, 58.5	16, 57	16, 57	16, 57

Characteristic		Main Analysis Population		Secondary Analysis Population	
		Untreated (N=122)	Treated (N=122)	Untreated (N=110)	Treated (N=110)
Sex		n (%)	n (%)	n (%)	n (%)
	Male	88 (72)	88 (72)	79 (72)	79 (72)
	Female	34 (28)	34 (28)	31 (28)	31 (28)
FD phenotype		n (%)	n (%)	n (%)	n (%)
	Classic	103 (84)	103 (84)	93 (84.5)	93 (84.5)
	Other/missing	19 (16)	19 (16)	17 (15.5)	17 (15.5)
Baseline eGFR (mL/min/1.73m^2)	Mean (SD)	91 (30)	91 (30)	93 (29.5)	93 (29.1)
	Median	93	93	98.6	97.8
	Min, Max	13, 148	17, 148	13, 148	18, 148
Age at FD diagnosis (years)		N=117	N=121	N=105	N=109
	Mean (SD)	25.1 (12.8)	26.8 (14.1)	24.2 (12.7)	24.9 (13.3)
	Median	25.1	27.4	24.3	24.5
	Min, Max	0.0, 57.5	0.0, 56.5	0.0, 54.8	0.0, 56.5
Age at symptom onset (years)		N=122	N=103	N=110	N=91
	Mean (SD)	12.3 (10.1)	14.4 (12.2)	12.7 (10.3)	10.7 (6.9)
	Median	9.5	10.2	9.6	9.5
	Min, Max	0.0, 55.9	0.0, 51.9	2.2, 55.9	0.0, 46.6

Source: Table prepared by DBIV review team using the analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) for the matched analysis on June 5, 2020. *One pair with discordant baseline eGFR (untreated > 60 and treated < 60) was not included in the two subgroups.
NOTE: Age at baseline in the matched analysis is defined as age of Fabrazyme initiation.
Abbreviations: eGFR = estimated glomerular filtration rate; FD = Fabry disease;

To evaluate the significance of baseline eGFR as a prognostic factor, for both the secondary matched analysis population and the randomized population of Trial AGAL-008-00, the review team calculated the mean and median values of baseline eGFR, age at FD diagnosis, and age at FD symptom onset. As shown in Table 25, compared with age at symptom onset and age at FD diagnosis, baseline eGFR was the most consistent and prognostically-important factor with respect to the renal disease progression risk. This observation was consistent with the finding in the article by (Arends et al. 2017). In this article, the authors stated that baseline eGFR was the most significant prognostic factor for FD.

Review team's comments*: According to KDIGO 2012 (January 2013), eGFR categories and proteinuria categories in chronic kidney disease are defined as follows (Table 24):*

Table 24. eGFR and Proteinuria Categories in Chronic Kidney Disease

	eGFR (mL/min/1.73m^2)
G1: normal or high	≥ 90
G2: mildly decreased	≥ 60 to 89
G3a: mildly to moderately decreased	≥ 45 to 59
G3b: moderately to severely decreased	≥ 30 to 44
G4: severely decreased	≥ 15 to 29
G5: kidney failure	<15
	Proteinuria (mg/mg)
Normal to mildly increased	< 0.15
Moderately increased	0.15 – 0.5
Severely increased	> 0.5

Source: KDIGO 2012
Abbreviations: eGFR = estimated glomerular filtration rate

In the secondary matched analysis population, the mean baseline eGFR was above 90 mL/min/1.73m^2 and was significantly higher than the mean baseline eGFR of 53 mL/min/1.73m^2 in Trial AGAL-008-00 (Table 25).

Regarding the category of eGFR ≥ 90 mL/min/1.73m^2, the matched analysis population had 55% of patients who had baseline eGFR in this category and their mean baseline eGFR was 115 mL/min/1.73m^2 (Table 26). On the other hand, Trial AGAL-008-00 had only three (4%) patients who had baseline eGFR in this category, with mean baseline eGFR of 100 mL/min/1.73m^2, mean baseline proteinuria of 0.14, and mean baseline serum creatinine of 1.0 mg/dL.

Thus, overall the matched analysis population was at a much less advanced FD disease stage compared with the study population of Trial AGAL-008-00. A majority of the patients (such as those with baseline eGFR ≥ 90 mL/min/1.73m^2) in the matched analysis population would be expected to have a normal or only mildly increased proteinuria if their proteinuria data were measured using the same method as in Trial AGAL-008-00. Additionally, in Trial AGAL-008-00, among the 27 patients who had experienced a clinically significant event, 22 patients had a baseline eGFR from 27 to 59 mL/min/1.73m^2 and 5 patients had a baseline eGFR from 60-71 mL/min/1.73m^2 (Figure 11). These observations indicated that a majority of the patients (such as those with baseline eGFR ≥ 90 mL/min/1.73m^2) in the matched analysis population were at very low risk of experiencing clinically significant events.

Table 25. Mean (Median) of Baseline eGFR, Age at FD Symptom Onset, Age at FD Diagnosis: Subgroups Defined by Baseline eGFR (≥ 60 vs < 60 mL/min/1.73m^2) (Secondary Matched Analysis Population; Trial AGAL-008-00)

	Baseline eGFR ≥ 60 mL/min/1.73m^2		Baseline eGFR < 60 mL/min/1.73m^2		
Secondary Matched Analysis Population					
	Untreated (N=93)	**Treated (N=93)**	**Untreated (N=16)**	**Treated (N=16)**	**Overall* (N=110:110)**
eGFR at baseline	101.9 (106.1)	102.4 (103.7)	43.5 (47.8)	43.2 (46.7)	93.2 (98.0)
Age at symptom onset (y)	12.4 (9.5)	10.3 (9.8)	13.9 (11.7)	14.5 (7.7)	11.8 (9.6)
Age at FD diagnosis (y)	22.1 (22.9)	22.7 (22.2)	34.6 (37.6)	35.8 (34.3)	24.6 (24.4)
Age at baseline (y)	-	32.2 (32.2)	-	41.5 (40.8)	33.6 (33.6)

	Baseline eGFR ≥ 60 mL/min/1.73m²		Baseline eGFR < 60 mL/min/1.73m²		
Trial AGAL-008-00					
	Placebo (N=9)	**Fabrazyme (N=18)**	**Placebo (N=22)**	**Fabrazyme (N=33)**	**Overall (N=51:31)**
eGFR	74.0 (67.8)	71.8 (69.4)	43.6 (44.5)	42.8 (42.4)	52.8 (51.9)
Age at symptom onset (y)	7.7 (8.5)	12.0 (9.0)	11.8 (9.0)	16.6 (11.0)	13.5 (10)
Age at FD diagnosis (y)	32.0 (32.0)	30.3 (33.0)	33.9 (34.0)	37.2 (37)	34.2 (36.0)
Age at baseline (y)	39.9 (43.1)	48.1 (45.2)	46.1 (44.9)	46.2 (44.7)	45.9 (44.8)
Serum creatinine (mg/dL)	1.2 (1.3)	1.1 (1.2)	1.8 (1.7)	1.9 (1.9)	1.6 (1.5)
Proteinuria (mg/mg)	0.4 (0.2)	0.6 (0.6)	1.4 (0.9)	1.9 (1.5)	1.3 (0.9)

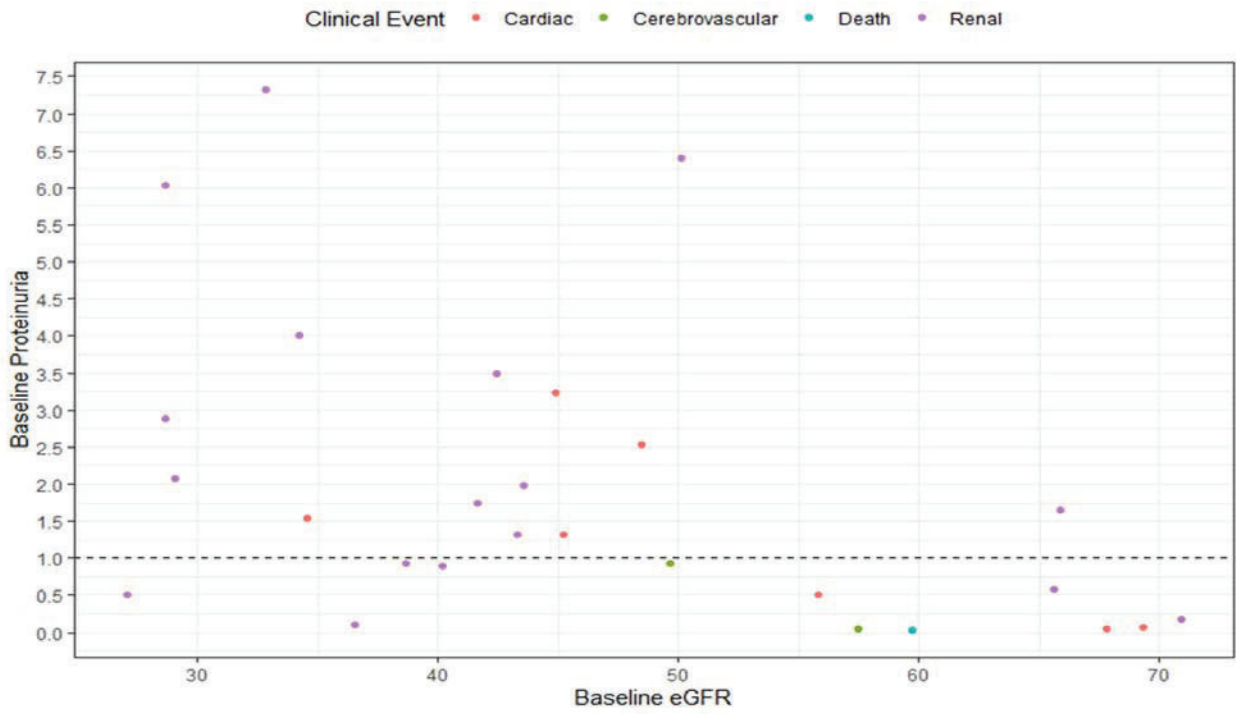
Source: Table prepared by DBIV review team using the analysis datasets submitted to BLA 103979 (eCTD 0415) for trial AGAL-008-00 on February 14, 2020 and the analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) for the matched analysis on June 5, 2020. *One pair with discordant baseline eGFR (untreated > 60 and treated < 60) was not included in the two subgroups
Abbreviations: eGFR = estimated glomerular filtration rate; FD = Fabry disease

Table 26. Mean (Median) of Baseline eGFR, Age at FD Symptom Onset, Age at FD Diagnosis: Subgroups Defined by Baseline eGFR (≥ 90 vs ≥ 60 to < 90 mL/min/1.73m²) (Secondary Matched Analysis Population; Trial AGAL-008-00)

	Baseline eGFR ≥ 90 mL/min/1.73m²		Baseline eGFR ≥ 60 to < 90 mL/min/1.73m²		
Secondary Matched Analysis Population					
	Untreated (N=60)	**Treated (N=60)**	**Untreated (N=28)**	**Treated (N=28)**	**Overall* (N=110:110)**
eGFR	115.6 (113.6)	115.2 (114.7)	75.6 (77.0)	76.9 (77.0)	93.2 (98.0)
Age at symptom onset (y)	10.7 (9.6)	10.3 (8.5)	16.5 (8.7)	10.5 (10.9)	11.8 (9.6)
Age at FD diagnosis (y)	18.8 (19.8)	21.1 (22.1)	28.8 (30.8)	25.8 (26.3)	24.6 (24.4)
Age at baseline (y)	-	29.0 (27.4)	-	39.0 (39.0)	33.6 (33.6)
Trial AGAL-008-00					
	Placebo (N=2)†	**Fabrazyme (N=1)†**	**Placebo (N=7)**	**Fabrazyme (N=17)**	**Overall (N=51:31)**
eGFR	97.3, 90.6	112.7	68.3 (67.7)	69.4 (69.3)	52.8 (51.9)
Age at symptom onset (y)	5.0, 4.0	5.0	9.3 (9.0)	12.5 (9.5)	13.5 (10)
Age at FD diagnosis (y)	44, 15	41.0	32.7 (32.0)	29.7 (31.0)	34.2 (36.0)
Age at baseline (y)	44.3, 26.2	41.9	41.2 (43.1)	48.5 (45.3)	45.9 (44.8)
Serum creatinine (mg/dL)	0.9, 1.1	0.8	1.3 (1.3)	1.1 (1.2)	1.6 (1.5)
Proteinuria (mg/mg)	0.15, 0.16	0.1	0.5 (0.3)	0.6 (0.6)	1.3 (0.9)

Source:: Table prepared by DBIV review team using the analysis datasets submitted to BLA 103979 (eCTD 0415) for trial AGAL-008-00 on February 14, 2020 and the analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) for the matched analysis on June 5, 2020.
† These two columns presented the data listing of the individual patients since there were only 3 patients in Trial AGAL-008-00 who had baseline eGFR ≥ 90 mL/min/1.73m².
Abbreviations: eGFR = estimated glomerular filtration rate; FD = Fabry disease

Figure 11. Scatter Plot of Baseline eGFR and Baseline Proteinuria for the Patients Who Experienced a Clinically Significant Event (Trial AGAL-008-00)



Source: Produced by the DB IV review team using analysis datasets (bcov_3 and event_1) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
Abbreviations: eGFR = estimated glomerular filtration rate

For both the main and secondary analysis populations, imbalances between the treatment groups were observed in the following variables: baseline urinary protein concentration category, baseline calendar year, geographical region, use status of angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB), and follow-up time. For simplicity, the following discussion focused on the secondary analysis population.

Baseline urinary protein concentration category: The untreated group had significantly more missing data (41%) compared with the treated group (26%). This imbalance was likely driven by the different nature of the real-world data source: the data of untreated patients came from a natural history study that collected data retrospectively from patients' medical charts and the data of treated patients came from the registry study that was prospectively designed and encouraged participating physicians to follow a "Recommended Schedule of Assessments" for data collection. For patients who did not have missing data, 74% in the untreated group and 82% in the treated group had a urinary protein category of negative (0 mg/dL to <30 mg/dL) or "1+(≥30mg/dL to <100 mg/dL)" (Table 27). The treated group had a higher proportion (62%) of patients who had a negative category compared with the untreated group (48%). This imbalance was likely driven by the amount of missing data as explained below.

For the patients who had missing protein data in both treatment groups, their median values of baseline eGFR were over 100 mL/min/1.73 m^2 and much closer to those for the patients who had a negative protein category than to those for the patients who had a category of "1+(≥30mg/dL to <100 mg/dL)" (Table 28). Thus, it is reasonable to expect that most of those patients who had missing protein data would have a negative protein category if their data were available.

The urinary protein concentration categories were derived based on five data sources: (1) 24-hour urine protein, (2) spot urine protein, (3) 24-hour albumin, (4) sport urine albumin, and (5) dipstick urine protein (Table 27). For the untreated patients, the protein categories were derived based on 24-hour urine protein or dipstick; on the other hand, for the treated patients, the protein categories were derived mainly based on 24-hour urine protein or spot urine protein. Thus, part of the observed imbalance between the treatment groups in the non-missing protein categories might be due to different data sources and or measurement errors.

Given the comparability between the two treatment groups in six important prognostic variables (age at Fabrazyme initiation, baseline eGFR, sex, phenotype, age at FD symptom onset, and age at FD diagnosis), it is reasonable to expect that there would be no relevant imbalance in baseline urinary protein concentration categories between the treatment groups if missing data were not present and the urine protein outcomes were assessed using a standardized measurement method.

Nevertheless, to examine potential impact of the observed imbalances in baseline urinary protein categories, the review team conducted efficacy analyses for the following subgroups:

- Matched patients who had a same protein category
- Matched patients who had a negative protein category
- Matched patients who had different protein categories (missing data were excluded)
- Matched patients who had missing protein categories

These subgroup analyses indicate that the imbalances between the treatment groups in baseline urinary protein categories were not factors in favor of the treated group (See Section 'Matched Analyses Results of eGFR Slope').

Table 27. Baseline Urinary Protein Concentration Categories and Source

	Main Analysis Population		Secondary Analysis Population	
	Untreated (N=122)	Treated (N=122)	Untreated (N=110)	Treated (N=110)
Baseline urinary protein concentration category	N=69	N=93	N=65	N=81
Negative (0 mg/dL to <30 mg/dL)	33 (47.8)	56 (60.2)	31 (47.7)	50 (61.7)
1+ (≥30mg/dL to <100 mg/dL)	17 (24.6)	26 (28.0)	17 (26.2)	21 (25.9)
2+ (≥100mg/dL to <300 mg/dL)	10 (14.5)	10 (10.8)	9 (13.9)	9 (11.1)
3+ or higher (≥300mg/dL)	9 (13.0)	1 (1.1)	8 (12.3)	1 (1.2)

	Main Analysis Population		Secondary Analysis Population	
	Untreated (N=122)	Treated (N=122)	Untreated (N=110)	Treated (N=110)
Baseline urinary protein concentration source				
24-hour urine protein	32 (46.4)	51 (54.8)	29 (44.6)	44 (54.3)
Spot urine protein	0	39 (41.9)	0	34 (42.0)
24-hour urine albumin	0	2 (2.2)	0	2 (2.5)
Spot urine albumin	0	1 (1.1)	0	1 (1.2)
Dipstick urine protein	37 (53.6)	0	36 (55.4)	0

Source: Table prepared by DBIV review team using the analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) for the matched analysis on June 5, 2020.

Table 28. Baseline eGFR by Baseline Urinary Protein Concentration Category (Secondary Analysis Population)

Baseline Urinary Protein Concentration Category	Untreated (N=110)		Treated (N=110)	
	n	Median	n	Median
Missing	45	101	29	108
Negative (0 mg/dL to <30 mg/dL)	31	111	50	101
1+ (≥30mg/dL to <100 mg/dL)	17	77	21	86
2+ (≥100mg/dL to <300 mg/dL)	9	79	9	67
3+ or higher (≥300mg/dL)	8	64	1	92

Source: Table prepared by DBIV review team using the analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) for the matched analysis on June 5, 2020.
Abbreviations: eGFR = estimated glomerular filtration rate

Baseline calendar year: Baseline calendar year ranged from 1971 to 2001 for the untreated patients and 1998 to 2015 for the treated patients. While 86% of the untreated patients had a baseline calendar year < 2000, 86% of the treated patients had a baseline calendar year ≥ 2000 (Table 29). This imbalance was expected since Fabrazyme received accelerated approval in 2003.

To examine potential impact of the imbalance in baseline calendar year, the review team conducted efficacy analyses for following subgroups:

- Matched patients who had a same baseline calendar year
- Matched patients who had different baseline calendar years
- Matched patients whose baseline calendar years were within 5 years
- Matched patients whose baseline calendar years were more than 5 years apart
- Matched patients who had non-overlap baseline calendar years: >2001 for treated and <1998 for untreated

These subgroup analyses indicate that the imbalance between the treatment groups in baseline calendar year was not a factor in favor of the treated group (See Section 'Matched Analyses Results of eGFR Slope').

Geographical Region: The untreated group had more patients (88%) from North America compared to the treated group (65%). To examine potential impact of the imbalance in baseline calendar year, the review team conducted efficacy analyses for the following subgroups:

- Matched patients who had the same geographical region
- Matched patients who had different geographical region

ACEI/ARB Use Status: This derived variable had two values: (1) "Yes" for patients whose medical charts recorded ACEI/ARB as concomitant medications and (2) "No/Unknown" for patients whose medical charts did not record use of ACEI/ARB. More patients (65%) in the treated group had reported use of ACEI/ARB during follow-up time than the untreated group (28%).

To examine potential impact of this imbalance, the review team conducted efficacy analyses for the following subgroups:

- Matched patients who had "Yes" ACEI/ARB use status
- Matched patients who had "No/Unknown" ACEI/ARB use status
- Matched patients who had different use status of ACEI/ARB

These analyses indicate that the imbalance between the treatment groups in ACEI/ARB use status was not a factor in favor of the treated group (See Section 'Matched Analyses Results of eGFR Slope').

Follow-up time: While the average number of eGFR assessments per patient per year was comparable (two assessments per year) between the two treatment groups, the treated group had a longer median follow-up time (4.5 years) compared with the untreated group (2.9 years).

To examine potential impact of the imbalance in follow-up time, the review team conducted efficacy analyses for the following two subgroups:

- Matched patients whose difference in follow-up time was within 1.5 years (this subgroup was referred to as having concordant follow-up time). In this subgroup, the two treatment groups had comparable median follow-up time (about 4 years; Table 29).
- Matched patients whose difference in follow-up time was more than 1.5 years apart (this subgroup was referred to as having discordant follow-up time). In this subgroup, the treated patients had a much longer median follow-up time (4.6 years) than the untreated patients (1.7 years).

The review team's subgroup analyses indicate that the imbalance between the treatment groups in follow-up time was not a factor in favor of the treated group (See Section 'Matched Analyses Results of eGFR Slope').

Table 29. Baseline Calendar Year and Other Characteristics For 1:1 Matches on Age, Sex, and FD Phenotype, and Baseline eGFR

Characteristic		Main Analysis Population		Secondary Analysis Population	
		Untreated (N=122)	Treated (N=122)	Untreated (N=110)	Treated (N=110)
Calendar year at baseline		n (%)	n (%)	n (%)	n (%)
	1970-1989	24 (19.6)	0	22 (20)	0
	1990-1994	28 (23.0)	0	23 (20.9)	0
	1995-1999	51 (41.8)	15 (12.3)	49 (44.6)	15 (13.6)
	2000-2004	19 (15.6)	66 (54.1)	16 (14.6)	62 (56.4)
	2005-2015	0	41 (33.6)	0	33 (30.0)
Geographical Region†		n (%)	n (%)	n (%)	n (%)
	North America	109 (89)	75 (61)	97 (88)	71 (65)
	Europe	13 (11)	34 (28)	13 (12)	29 (26)
	Asia	0	7 (6)	0	5 (5)
	South America	0	6 (5)	0	5 (5)
Reported ACEI/ARB use at any time during follow-up	Yes	34 (28)	79 (65)	31 (28)	71 (65)
	No/Unknown	88 (72)	43 (35)	79 (72)	39 (35)
Matched patients with different ACEI/ARB use status		N=75	N=75	N=66	N=66
	Yes	15 (20)	60 (80)	13 (20)	53 (80)
	No/Unknown	60 (80)	15 (20)	53 (80)	13 (20)
No. eGFR assessments per patient per year	Mean (SD)	2.2 (1.6)	2.1 (1.3)	2.2 (1.7)	2.1 (1.3)
	Median	1.9	1.6	1.8	1.6
	Min, Max	0.4, 9.8	0.6, 8.1	0.4, 9.8	0.6, 8.1
No. eGFR assessments per patient	Mean (SD)	5.2 (4.2)	8.8 (6.8)	5.1 (3.9)	8.8 (6.8)
	Median	4	6	4	6
	Min, Max	2, 29	2, 40	2, 29	2, 40
Follow-up time (year)	Mean (SD)	2.8 (1.4)	4.1 (1.0)	2.8 (1.4)	4.1 (1.0)
	Median	2.9	4.5	2.9	4.5
	Min, Max	0.5, 5.0	0.7, 5.0	0.5, 5.0	0.7, 5.0
Matched patients with concordant follow-up time* (year)		N=53	N=53	N=49	N=49
	Mean (SD)	3.7 (1.0)	3.9 (1.0)	3.8 (1.0)	3.9 (1.0)
	Median	4.0	4.2	4.0	4.1
	Min, Max	1.1, 5.0	1.2, 5.0	1.1, 5.0	1.1 5.0
Matched patients with discordant follow-up time** (year)		N=69	N=69	N=61	N=61
	Mean (SD)	2.1 (1.2)	4.2 (0.9)	2.0 (1.1)	4.2 (0.9)
	Median	1.7	4.6	1.7	4.6
	Min, Max	0.7, 5.0	0.7, 5.0	0.5, 4.9	0.7, 5.0

Source: Table prepared by the Division of Biometrics (DB) IV, Office of Biostatistics review team using analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) on June 5, 2020.

† North America included Canada and United States; Asia included Australia, Korea, and Taiwan; South America included Argentina, Brazil, and Chile; Europe included Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Sweden, and United Kingdom.

* Patients with concordant follow-up time included all matched patients whose difference in follow-up time was ≤ 1.5 years.

** Patients with discordant follow-up time included all matched patients whose difference in follow-up time was > 1.5 years.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; FD = Fabry disease

Matched Analyses Results: eGFR Slope

The main analysis showed a clinically and statistically significant treatment effect of Fabrazyme in slowing eGFR decline inn treated patients compared to untreated patients (Table 31). On

average, the decline in eGFR for the Fabrazyme-treated patients was reduced by 53% compared to the matched untreated patients. The estimated mean eGFR slope was -1.5 mL/min /1.73m^2/year in the Fabrazyme-treated group and -3.2 mL/min/1.73m^2 /year in the untreated group. The estimated treatment difference was 1.7 mL/min/1.73m^2/year (95% CI: 0.5, 3.0; p=0.007; N=122:122) favoring the Fabrazyme group. This improvement in the annualized rate of eGFR for the Fabrazyme-treated patients is clinically significant because it indicates an improvement of 8.5 mL/min/1.73m^2 in eGFR over a 5-year period.

The overall analysis results for the secondary analysis population were similar to the main analysis results supporting the robustness of the main analysis results in this observational study. Furthermore, the robustness of the main analysis results is further supported by numerous subgroup analyses, as outlined below, in the secondary analysis population (Table 31). Of note, nominal p-values are presented as descriptive statistics for FDA's analyses.

i. A favorable treatment effect of Fabrazyme was seen for both male and female patients.

For male patients, the treatment difference in mean eGFR slopes was 1.6 (95% CI: -0.0,3.3; p=0.06; N=79:79) mL/min/1.73m^2/year; for female patients, the treatment difference was 2.7 (95% CI: 0.5, 4.9; p=0.02; N=31:31) mL/min/1.73m^2/year.

ii. A favorable treatment effect of Fabrazyme was seen for both matched patients with classic (early-onset, severe) FD phenotype and matched patients with phenotype of "other/unclassified/missing."

For patients with classic FD phenotype, the treatment difference in mean eGFR slopes was 1.5 (95% CI: -0.1, 3.0; p=0.06; N=93:93) mL/min/1.73m^2/year; for patients with phenotype of "other/unclassified /missing", the treatment difference was 2.8 (95% CI: -0.9, 6.5; p=0.13; N=17:17) mL/min/1.73m^2/year.

iii. A greater favorable treatment effect of Fabrazyme was seen in matched patients with baseline eGFR ≥ 60 mL/min/1.73m^2 than in matched patients with baseline eGFR < 60 mL/min/1.73m^2.

For matched patients who had baseline eGFR ≥ 60 mL/min/1.73m^2, the treatment difference in mean eGFR slopes was 1.7 (95% CI: 0.2, 3.1; p=0.02; N=93:93) mL/min/1.73m^2/year; for matched patients who had baseline eGFR < 60 mL/min/1.73m^2, the treatment difference was 0.8 (95% CI: -5.1, 6.8; p=0.78; N=16:16) mL/min/1.73m^2/year. These results corroborated the findings in Trial AGAL-008-00 for patients with baseline eGFR ≥ 60 mL/min/1.73m^2 although this trial had a much lower baseline eGFR than the matched analysis population (median baseline eGFR value was 104-106 mL/min/1.73m^2 in the matched analysis population and 68-69 mL/min/1.73m^2 in Trial AGAL-008-00; Table 25).

iv. A greater favorable treatment effect of Fabrazyme was seen in matched patients with baseline eGFR ≥ 90 mL/min/1.73m^2 than in matched patients with baseline eGFR ≥ 60 to < 90 mL/min/1.73m^2.

For matched patients who had baseline eGFR ≥ 90 mL/min/1.73m^2, the treatment difference in mean eGFR slopes was 2.2 (95% CI: 0.5, 3.9; p=0.01; N=60:60) mL/min/1.73m^2/year. For matched patients who had baseline eGFR ≥ 60 to <90 mL/min/1.73m^2, the treatment difference was 1.3 (95% CI: -1.7, 4.3; p=0.40; N=28:28) mL/min/1.73m^2/year. These subgroup analyses shown a larger treatment effect of Fabrazyme in patients at less advanced disease stage and thus further confirmed the findings in Trial AGAL-008-00.

v. A favorable treatment effect of Fabrazyme was seen in both matched patients with the same geographical region and matched patients with different geographical region.

For matched patients who had the same geographical region, the treatment difference in mean eGFR slopes was 1.4 (95% CI: -0.5, 3.3; p=0.15; N=68:68) mL/min/1.73m^2/year. For matched patients who had different geographical regions, the treatment difference was 2.0 (95% CI: 0.1, 4.1; p=0.04; N=42:42) mL/min/ 1.73m^2/year.

vi. A favorable treatment effect of Fabrazyme was seen in both matched patients with the same baseline urinary protein concentration categories (concordant) and matched patients with different baseline urinary protein concentration categories (discordant).

For matched patients who had the same (concordant) baseline urinary protein concentration category, the treatment difference in mean eGFR slopes was 1.5 (95% CI: -1.6, 4.6; p=0.35; N=24:24) mL/min/1.73m^2/year. For matched patients who had "Negative" protein category, the treatment difference in mean eGFR slopes was 1.7 (95% CI: -1.8, 5.1; p=0.33; N=18:18) mL/min/1.73m^2/year. For matched patients who had missing data on protein categories, the treatment difference in mean eGFR slopes was 3.4 (95% CI: -1.1, 8.0; p=0.13; N=14:14) mL/min/1.73m^2/year. For matched patients who had different protein categories, the treatment difference was 0.7 (95% CI: -1.6, 3.0; p=0.52; N=26:26) mL/min/1.73m^2/year and was much smaller than the estimated treatment difference for the matched patients who had the same protein category.

These subgroup analyses results indicate the following: (1) the overall efficacy results were not driven by the matched patients who had different baseline urinary protein concentration categories, and (2) the observed imbalance in urinary protein concentration categories between the treatment groups (see Section 'Baseline Demographic and Other Characteristics') was not a factor that favored the treated group.

vii. A favorable treatment effect of Fabrazyme was seen in both matched patients with the same baseline calendar year and matched patients with different baseline calendar years.

For matched patients who had the same baseline calendar year, the treatment difference in mean eGFR slopes was 2.7 (95% CI: -1.1, 6.4; p=0.16; N=18:18) mL/min/1.73m^2/year. For matched patients who had different baseline calendar years, the treatment difference was 1.5 (95% CI: 0.0, 3.0; p=0.05; N=92:92) mL/min/1.73m^2/year.

As noted in Section 'Baseline Demographic and Other Characteristics', the baseline calendar year ranged from 1971 to 2001 for the untreated patients and 1998 to 2015 for the treated patients. Thus, the two treatment groups had non-overlap calendar years for two time periods: <1998 and >2001. For matched patients who had non-overlap baseline calendar years (>2001 for treated patients and <1998 for untreated patients), the treatment difference in mean eGFR slopes was 1.0 (95% CI: -0.6, 2.7; p=0.22; N=58:58) mL/min/1.73m^2/year and was smaller than the estimated treatment difference of 2.7 for the matched patients who had the same baseline calendar year.

For matched patients whose baseline calendar years were within 5 years, the treatment difference in mean eGFR slopes was 2.0 (95% CI: -0.7, 4.7; p=0.15; N=36:36) mL/min/1.73 m^2/year. For matched patients whose baseline calendar years were more than 5 years apart, the treatment difference in mean eGFR slopes was 1.6 (95% CI: -0.1, 3.2; p=0.06; N=74:74) mL/min/1.73m^2/year.

These subgroup analyses results indicated that the observed imbalance in baseline calendar years between the treatment groups (See Section 'Baseline Demographic and Other Characteristics') was not a factor in favor of the treated group.

viii. A favorable treatment effect of Fabrazyme was seen in both matched patients with same ACEI/ARB use status and matched patients with different ACEI/ARB use status.

For matched patients who had "Yes" ACEI/ARB use status, the treatment difference in mean eGFR slopes was 1.9 (95% CI: -1.3, 5.1; p= 0.24; N=18:18) mL/min/1.73m^2/year. For matched patients who had "No/Unknown" ACEI/ARB use status, the treatment difference in mean eGFR slopes was 2.3 (95% CI: -0.2, 4.8; p= 0.07; N=26:26) mL/min/1.73m^2/year. For matched patients who had different ACEI/ARB use status, the treatment difference was 1.2 (95% CI: -0.7, 3.1; p= 0.21; N=66:66) mL/min/1.73m^2/year.

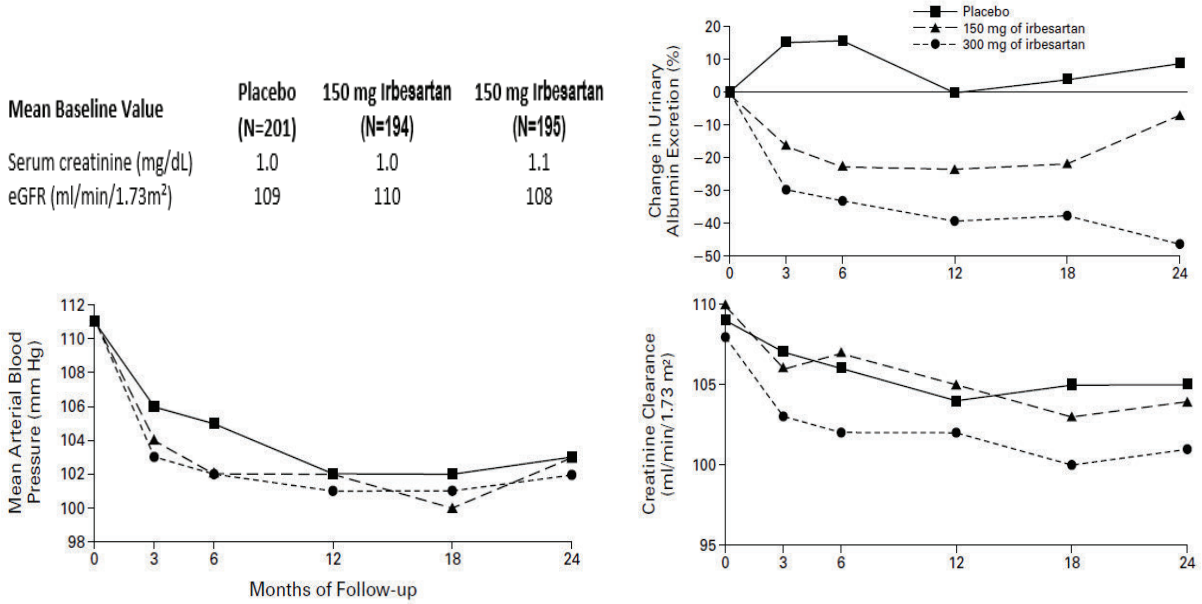
These subgroup analysis results indicated that the overall efficacy results were not driven by the matched patients with different ACEI/ARB use status and the observed imbalance in ACEI/ARB use status between the treatment groups (see Table 29 of Section 'Baseline Demographic and Other Characteristics') was not a factor in favor of the treated group.

Review team's comments: *ACEI/ARB are recommended as adjunctive therapies in the renal management of adult patients with Fabry disease (Ortiz et al. 2018) despite not being approved specifically for this use. The general treatment goal with ACEI/ARB treatment in FD is to reduce urinary protein excretion to less than 500 mg/day based on the belief that the beneficial effects of ACEI/ARB for more common forms of proteinuric kidney disease can be extrapolated to the treatment of Fabry nephropathy (Jain and Warnock 2011). The renoprotective effects of ACEI/ARB for more common forms of proteinuric kidney disease have been reported in numerous articles. However, it appears that the renoprotective effects of ACEI/ARB were only established in patients with overt nephropathy and at high risk of renal disease progression. For example, in articles by Lewis et al and Brenner et al, the studied patients had a mean baseline serum creatinine of 1.7 mg/dL or a mean baseline urinary albumin:creatinine ratio of 1.9 (g/g) and were at high risk for renal disease progression (Brenner et al. 2001; Lewis et al. 2001). The placebo-treated patientsin these articles had an incidence rate above 20% for the composite events (doubling of the baseline serum creatinine concentration, ESRD, or death) and an incidence rate of ESRD above 10% at 24 months. On the other hand, the placebo-treated patients in Trial AGAL-008-00 had zero events of ESRD. Thus, the patients in the articles represented a very different population than the FD patient population in Trial AGAL-008-00 and in the observational study (matched analyses). Consequently, it is unclear whether the reported renoprotective effects of ACEI/ARB use in patients at high risk of renal disease progression (as in the articles above) can be extrapolated to a positive effect of ACEI/ARB use on the eGFR endpoint in FD and, by extension, in the matched analysis populations who were at low risk of renal disease progression. As such, it does not appear that, based on the current state of knowledge, the use of ACEI/ARB in the two analysis populations in this observational study is a confounder or that it affects the results or conclusions to any significant degree. This conclusion also aligns with the following published findings:*

- *(Parving et al. 2001). Parving et al presented the results of a randomized placebo-controlled trial in patients with type 2 diabetes and microalbuminuria. This trial had three treatment arms: placebo, 150 mg, and 300 mg of irbesartan. The trial patients had a similar mean baseline eGFR of 109 mL/min/1.73 m^2 and a similar mean baseline serum creatinine of 1.1 mg/dL as those patients in the matched analysis population who had a baseline eGFR ≥ 60 mL/min/1.73m^2 (Table 25). This trial showed no benefit on eGFR in the irbesartan-treated patients although it showed albuminuria-lowing effect of irbesartan (See Figure 12).*

Figure 12. eGFR, Serum Creatinine, and Albuminuria in Irbesartan-Treated Patients

Mean Baseline Value	Placebo (N=201)	150 mg Irbesartan (N=194)	150 mg Irbesartan (N=195)
Serum creatinine (mg/dL)	1.0	1.0	1.1
eGFR (ml/min/1.73m²)	109	110	108



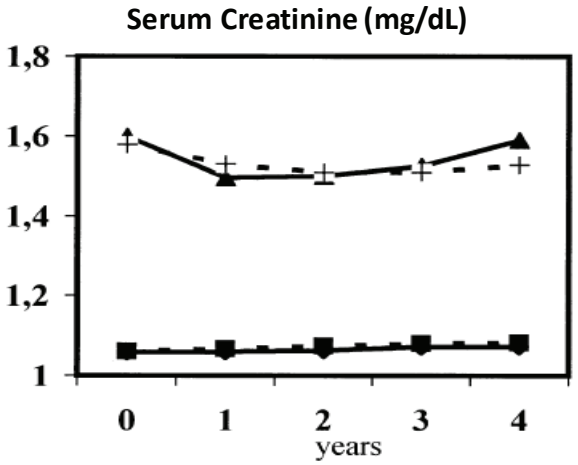
Source: (Parving et al. 2001)
Abbreviations: eGFR = estimated glomerular filtration rate

- *(Mann et al. 2003). Mann et al reported the results of a randomized placebo-controlled trial in type 2 diabetes with and without microalbuminuria. This trial had two treatment arms (placebo and 10 mg of ramipril) and a similar mean baseline serum creatinine (about 1.1 mg/dL) as those patients in Trial AGAL-008-00 who had a baseline eGFR ≥ 60 mL/min/1.73m² (Table 25). This trial showed no benefit on eGFR and serum creatinine in ramipril-treated patients (See Figure 13). Of note: The trial patients were at low risk of renal disease progression as the authors stated that major renal events (dialysis, doubling of serum creatinine level) were uncommon in their trial.*

Figure 13. eGFR and Serum Creatine in Ramipril-Treated Patients

Mean eGFR (ml/min)*	Placebo (N=1765)	Ramipril (N=1806)
Baseline	78.2	78.6
At Year 4	75.7	74.9
Change from baseline at Year 4	-4.4†	-4.5†

Dotted lines for ramipril-treated patients.
Solid lines for placebo-treated patients.
Lower 2 lines for all patients
Upper 2 lines for patients with renal insufficiency defined as serum creatinine level ≥1.4 mg/dL at baseline.



Source: (Mann et al. 2003)
* Calculated using Cockcroft-Gault formula
† Based on observed data
Abbreviations: eGFR = estimated glomerular filtration rate

- *(Beck et al. 2015). This article reported that ACEI/ARB use had no significant impact on the eGFR slope in Fabry patients (Table 30):*

Table 30. Fabry Patients Treated With Agalsidase Alfa

	Used ACEI/ARB (N=164)	Did Not Use ACEI/ARB (N=104)
eGFR slope (95% CI) (mL/min/1.73m^2/year)	-1.37 (-1.81, -0.94)	-1.48 (-3.15, 0.19)

Source: (Beck et al. 2015)
Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; eGFR = estimated glomerular filtration rate

ix. A favorable treatment effect of Fabrazyme was seen in both matched patients with concordant follow-up times and matched patients with discordant follow-up times.

For matched patients with concordant follow-up time (mean follow-up time 4 years in both groups), the treatment difference in mean eGFR slope was 1.5 (95% CI: -0.5, 3.6; p=0.14; N=49:49) mL/min/1.73m^2/year. For matched patients with discordant follow-up time (mean follow-up time 4.2 years for treated and 1.7 years for untreated patients), the treatment difference in mean eGFR slope was 1.6 (95% CI: -0.4, 3.5; p=0.11; N=61:61) mL/min/1.73m^2/year. These subgroup analysis results indicate that the overall efficacy results were not driven by the matched patients with discordant follow-up time.

To further evaluate the potential impact of imbalance in follow-up time between the two groups, the review team conducted three sensitivity analyses: (1) based on eGFR data up to 2 years, (2) based on eGFR data up to 3 years, and (3) based on eGFR data up to 4 years. These

sensitivity analysis results also align with and support the main analysis results and produced the estimated treatment difference in mean eGFR slope (mL/min/1.73m^2/year) as follows:

- 3.3 (95% CI: 0.1, 6.4; p=0.04; N=110:110) based on 2-year eGFR data,
- 2.7 (95% CI: 0.5, 4.8; p=0.02; N=110:110) based on 3-year eGFR data,
- 1.8 (95% CI: 0.2, 3.4; p=0.03; N=110:110) based on 4-year eGFR data.

Table 31. eGFR Slope: 1:1 Matched Analyses on Age at Fabrazyme Initiation, Sex, FD Phenotype, and Baseline eGFR

			Treatment Difference	
Characteristic	**Untreated**	**Treated**	**95% CI**	**P-value†**
Applicant's Analysis: Main Analysis Population (122:122)	-3.2	-1.5	1.7 (0.5, 3.0)	0.0073
FDA's Analysis based on Secondary Analysis Population				
All matched patients (110:110)	-3.3	-1.6	1.7 (0.3, 3.0)	0.0182
Males (79:79)	-3.9	-2.3	1.6 (0.0, 3.3)	0.0560
Females (31:31)	-2.3	0.4	2.7 (0.5, 4.9)	0.0191
Males with Classic FD (74:74)	-3.6	-2.2	1.4 (-0.3, 3.1)	0.0968
Phenotype: Classic FD (93:93)	-3.2	-1.7	1.5 (-0.0, 3.0)	0.0575
Phenotype: Other/Unclassified/Missing (17:17)	-3.6	-0.8	2.8 (-0.9, 6.5)	0.1302
Baseline eGFR ≥ 60 mL/min/1.73 m^2 (93:93)	-2.8	-1.1	1.7 (0.2, 3.1)	0.0244
Baseline eGFR < 60 mL/min/1.73 m^2 (16:16)	-7.0	-6.2	0.8 (-5.1, 6.8)	0.7766
Baseline eGFR ≥ 90 mL/min/1.73 m^2 (60:60)	-3.9	-1.7	2.2 (0.5, 3.9)	0.0106
Baseline eGFR ≥ 60 & <90 mL/min/1.73 m^2 (28:28)	-1.4	0.1	1.3 (-1.7, 4.3)	0.3968
Matched patients with "Negative" baseline urinary protein concentration category (18:18)	-3.7	-2.0	1.7 (-1.8, 5.1)	0.3298
Matched patients with same non-missing baseline urinary protein concentration categories (24:24)	-4.4	-2.9	1.5 (-1.6, 4.6)	0.3454
Matched patients with missing baseline urinary protein concentration categories (14/14)	-5.3	-1.9	3.4 (-1.1, 8.0)	0.1336
Matched patients with different baseline urinary protein concentration categories (26:26)	-2.7	-2.0	0.7 (-1.6, 3.0)	0.5173
Matched patients with the same geographical region (68:68)	-3.1	-1.7	1.4 (-0.5, 3.3)	0.1450
Matched patients with different geographical region (42:42)	-3.3	-1.3	2.0 (0.1, 4.1)	0.0435
Matched patients with the same baseline calendar year (18:18)	-3.8	-1.1	2.7 (-1.1, 6.4)	0.1612
Matched patients with different baseline calendar year (92:92)	-3.1	-1.6	1.5 (0.0, 3.0)	0.0499
Matched patients with different baseline calendar year: >2001 for treated and < 1998 for untreated (58:58)	-2.6	-1.6	1.0 (-0.6, 2.7)	0.2175
Matched patients whose baseline calendar years were within 5 years (36:36)	-3.8	-1.8	2.0 (-0.7, 4.7)	0.1457
Matched patients whose baseline calendar years were more than 5 years apart (74:74)	-3.1	-1.5	1.6 (-0.1, 3.2)	0.0591
Matched patients with "**Yes**" for ACEI/ARB use status (18:18)	-4.4	-2.5	1.9 (-1.3, 5.1)	0.2378

Characteristic	Untreated	Treated	Treatment Difference 95% CI	Treatment Difference P-value†
Matched patients with "**No/Unknown**" for ACEI/ARB use status (26:26)	-3.0	-0.7	2.3 (-0.2, 4.8)	0.0693
Matched patients with different ACEI/ARB use status (66/66)	-2.9	-1.7	1.2 (-0.7, 3.1)	0.2145
Matched patients with concordant follow-up time* (49:49)	-3.5	-1.8	1.5 (-0.5, 3.6)	0.1378
Matched patients with discordant follow-up time** (61:61)	-3.0	-1.4	1.6 (-0.4, 3.5)	0.1119
Matched patients with follow-up time truncated to 2 years (110:110)	-3.4	-0.1	3.3 (0.1, 6.4)	0.0412
Matched patients with follow-up time truncated to 3 years (110:110)	-3.9	-1.2	2.7 (0.5, 4.8)	0.0152
Matched patients with follow-up time truncated to 4 years (110:110)	-3.5	-1.7	1.8 (0.2, 3.4)	0.0304

Source: Table prepared by DBIV review team using analysis datasets (ad11bgfr and adbgfm11) submitted to BLA 103979 (eCTD 0426) on June 5, 2020.
* Patients with concordant follow-up time included all matched patients whose difference in follow-up time was ≤ 1.5 years; in this subgroup analysis, the mean follow-up time was 4 years in both treatment groups.
** Patients with discordant follow-up time included all matched patients whose difference in follow-up time was > 1.5 years; in this subgroup analysis, the mean follow-up was 4 years for the treated group and 2 years for untreated group.
† Nominal p-values were presented for FDA's analyses.
Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; eGFR = estimated glomerular filtration rate; FD = Fabry disease

Conclusions

The main matched analysis of retrospective observational data on eGFR slope compared Fabrazyme-treated patients to a non-contemporaneous (historical) external cohort of FD patients not treated with Fabrazyme. This analysis was based on eGFR data in 122 Fabrazyme-treated patients and 122 untreated patients matched 1:1 on four significant prognostic variables: age (at Fabrazyme initiation), sex, FD phenotype (classic vs non-classic subtype), and baseline eGFR. This analysis showed that estimated mean eGFR slope was -1.5 mL/min /1.73m^2/year in the Fabrazyme-treated group and -3.2 mL/min/1.73m^2/year in the untreated group with an estimated treatment difference of 1.7 (95% CI: 0.5, 3.0) mL/min/1.73 m^2/year favoring the Fabrazyme group. Assuming that eGFR decline in Fabry disease continues at the same rate over a patient's lifetime, we expect a treatment difference of about 8.5 mL/min/1.73m^2 in eGFR over a 5-year period which would be a clinically significant improvement over the untreated renal disease course over a patient's lifetime.

The noted imbalances between the two groups (age at FD symptom onset, baseline proteinuria concentration categories, baseline calendar year, geographic region, ACEI/ARB use status, and follow-up time), discussed in detail in Sections 'Baseline Demographic and Other Characteristics' and 'Matched Analyses Results of eGFR Slope,' do not alter the generally favorable effect observed on eGFR slope in patients treated with Fabrazyme in this observational study. In addition, the overall results in this study were further corroborated by results in numerous subgroups, including: (1) matched patients with baseline eGFR ≥ 60 to <90 mL/min/1.73 m^2, (2) matched patients with baseline eGFR ≥ 90 mL/min /1.73m^2, (3) matched patients with concordant baseline proteinuria concentration categories, (4) matched patients

with discordant baseline proteinuria concentration categories, (5) matched patients with concordant baseline calendar year, (6) matched patients with discordant baseline calendar year, (7) matched patients with concordant ACEI/ARB use status, (9) matched patients with discordant ACEI/ARB use status, (10) matched patients with concordant follow-up time, and (11) matched patients with discordant follow-up time. These subgroup analyses provide support for the robustness of the main analysis results which demonstrate a favorable treatment effect of Fabrazyme on the rate of renal function decline as compared to untreated FD patients.

Overall, the efficacy results of this observational study are considered in this application together with data collected in the Fabrazyme clinical trials and with published literature on the role and significance of GL-3 accumulation in affected tissues. This evidence in its totality confirms that the previously demonstrated large treatment effect of Fabrazyme on the renal histological surrogate endpoint is clinically meaningful and clinically beneficial.

8.3. Safety Evaluation

No new safety studies or clinical trials were submitted for review in this application. Refer to previous clinical reviews for BLA 103979 from 2003, 2006 and 2008 and the Fabrazyme label for pre-approval safety information and reviews. The focus of this safety review is on data collected in the post-marketing setting. Refer to the DPV review for details of the independent safety assessment using the FDA Adverse Event Reporting System (FAERS) database.

8.3.1. Safety Review Approach

Post marketing safety reports were submitted by the Applicant and reviewed from August 3, 2001 through August 31, 2018 from the Sanofi worldwide safety database which contained all healthcare professional-reported or consumer-reported case reports from both solicited reporting (including clinical trials and patient support programs) and voluntary spontaneous reporting.

Overall Exposure

The number of patients exposed to agalsidase beta from July 3, 2001 through July 31, 2018 was 4,779 patients. Due to the nature of postmarketing safety data, it is not possible to summarize or present data by the number of unique patients.

Categorization of Adverse Events

The Sanofi worldwide safety database contains all healthcare professional-reported or consumer-reported case reports from both solicited reporting (including clinical trials and patient support programs) and voluntary spontaneous reporting that meet the criteria for a valid case. Spontaneous reports in the post marketing setting are categorized as unsolicited. The database was searched for all cases involving the use of agalsidase beta. The events reported for all cases were coded using the Medical Dictionary for Regulatory Activities. Sanofi

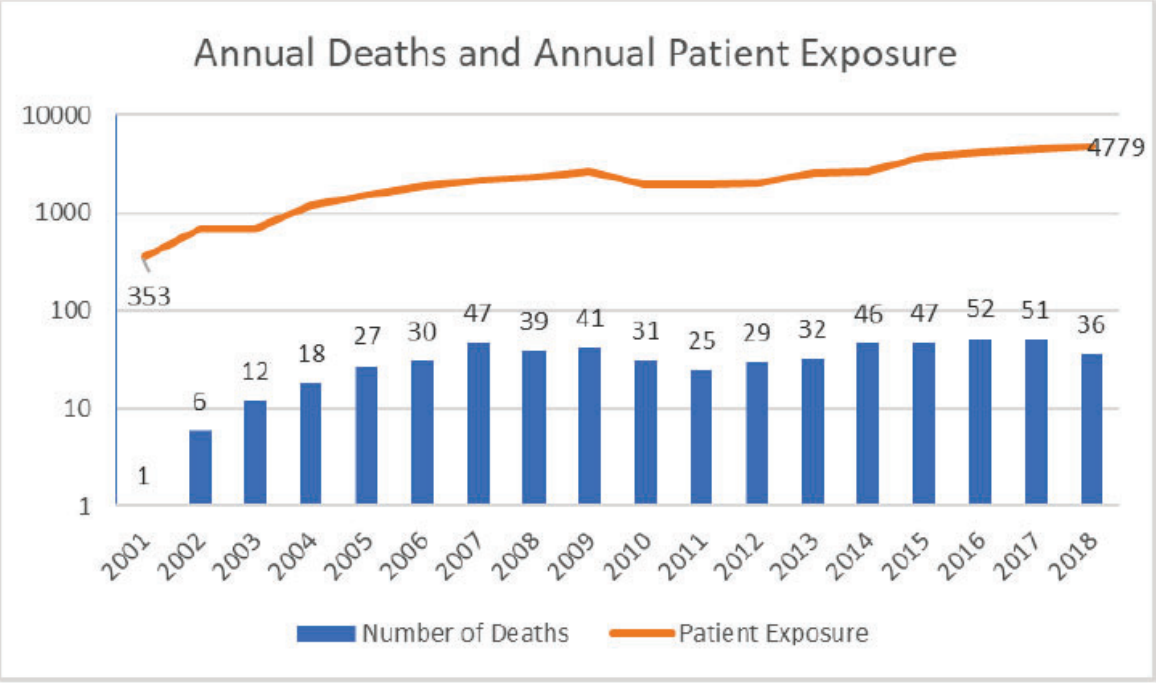
Genzyme directed physicians to report adverse events (AEs) according to the requirement from the drug safety monitoring institutions in each country and request physicians participating in the Fabry Registry to report all adverse drug reactions associated with the product within 24 hours of the physician's first knowledge. Treatment-emergent AEs were defined as AEs that started during or after the first agalsidase beta infusion. Frequency of AEs and the unique number of patients who had each AE were presented for each body system or system organ class and each preferred term. For the summary of AEs by severity and by relationship to treatment, patient incidence was presented, that is, if a patient experienced multiple AEs, only the most severe event or the most intense relationship to treatment was counted within a particular preferred term or system organ class.

8.3.2. Safety Results

Deaths

993 events corresponding to 641 case narratives were reviewed. Of the 641 fatal cases reported to the Sanofi safety database, there were 570 cases reported with a death date that occurred within the interval Aug 3, 2001 and July 31, 2018. An analysis of yearly death and exposure is graphically presented in Figure 14.

Figure 14. Annual Deaths and Annual Patient Exposure



Source: Applicant's postmarketing Safety Report 2019 p132/2413

The most frequently reported fatal outcomes were cardiac arrest 43/993(4.3%), cerebrovascular accident 36/993(3.6%) and cardiac failure 33/993 (3.3%) (Table 32).

Table 32. Fatal Events (>1%)

Fatal Event by Preferred Term	Total, n(%) N=993
Total number of fatal events reported	993 (100)
Death	166 (16.7)
Cardiac arrest	43 (4.3)
Cerebrovascular event	36 (3.6)
Cardiac failure	33 (3.3)
Sepsis	27 (2.7)
Myocardial infarction	24 (2.4)
Pneumonia	24 (2.4)
Cardio-respiratory arrest	21 (2.1)
Multiple organ dysfunction	17 (1.7)
Cardiac disorder	16 (1.6)
Sudden death	15 (1.5)
Cardiac failure congestive	14 (1.4)
Completed suicide	12 (1.2)
Disease progression	12 (1.2)
Renal failure	12 (1.2)
Septic shock	11 (1.1)

Source: Applicant'stable with reviewer'sedits

All deaths were in adults except 2 pediatric cases including a 2-day old neonate from Brazil whose mother-initiated treatment with Fabrazyme in (b) (6). The patient was exposed to Fabrazyme via transplacental route during the mother's pregnancy. In (b) (6), the patient's mother underwent cesarean section due to aminorrhexis at 28-week gestation. Two days after birth, the premature neonate (patient) died of "cardiac arrest" and a 2-year-old male in Taiwan who initiated treatment with Fabrazyme in (b) (6). Day of the last infusion was (b) (6). After an unknown number of days after the last dose, the patient experienced nasopharyngitis, reported as "cold" and was hospitalized. On (b) (6), the patient experienced a "sudden fever", lost consciousness and expired on the same day. It was unclear if an autopsy was performed. Neither death is likely to be related to Fabrazyme.

Serious Adverse Events

The most frequently reported serious adverse events included cerebrovascular accident (2.6%), pyrexia (2.1%) and end stage renal disease (2.1%) (Table 33). The most frequently reported serious adverse events are documented in the post marketing section of the Fabrazyme label.

Table 33. Most Frequent Serious Adverse Events (>1%)

Serious Event by Preferred Term	Total, n (%) N=12,255
Cerebrovascular accident	323 (2.6)
Pyrexia	257 (2.1)
End-stage renal disease	255(2.1)
Dyspnea	216(1.8)
Atrial fibrillation	208(1.7)
Pneumonia	188(1.5)
Pain	176(1.4)
Death	168 (1.4)
Chest pain	155(1.3)
Cardiac disorder	152(1.2)
Myocardial infarction	144(1.2)
Renal failure	142(1.2)
Transient ischemic attack	141(1.2)
Chills	138(1.1)
Vomiting	134(1.1)
Renal impairment	125(1.0)

Source: Applicant'stable with reviewer'sedits

Adverse Events

The most frequently reported adverse events included pyrexia (3.3%), chills (3.3%) and pain (2.7%) (Table 34).

Table 34. Most Frequently Reported Adverse Events (>1%)

Adverse Event	Total, n(%) N=47637
Pyrexia	1592 (3.3)
Chills	1550 (3.3)
Pain	1295 (2.7)
Headache	1088 (2.3)
Malaise	1067 (2.2)
Fatigue	1047 (2.2)
Nausea	1008 (2.1)
Pain in extremity	970 (2.0)
Vomiting	884 (1.9)
Dyspnea	768 (1.6)
Cough	615 (1.3)
Dizziness	604 (1.3)
Diarrhea	571 (1.2)
Influenza	504 (1.1)
Nasopharyngitis	484 (1.0)
Chest pain	482 (1.0)

Source: Applicant'stable with reviewer'sedits

Although pain was a more common adverse event in the post-marketing setting than was seen in the clinical trials, the term is broad and may be associated with other adverse events that have otherwise been noted in the label. Otherwise, adverse events in the post-marketing setting were found to be similar to what was seen in the clinical trials.

Immunogenicity

Hypersensitivity reactions represented 8.2% of all global events. The most frequently reported adverse events related to hypersensitivity were pruritis (11.8%) infusion related reaction (11.6%) rash (11.4%) and urticaria (10.9%). Serious adverse events reactions made up of 14.9% of all hypersensitivity reactions with urticaria (9.1%) anaphylaxis (6.9%) and infusion related reaction (5.3%) most common serious AE related to hypersensitivity. Pediatric events represented 7% (3404/47637) of the total reported global events. Of the pediatric adverse events reported, hypersensitivity accounted for 434(12.7%) events, anaphylaxis with 7(0.8%) events and 1422(41.8%) events with infusion-associated reaction. Of note, infusion-associated reactions were reported at a higher rate than the adult population. However, it is unclear whether the pediatric data was more voluntarily reported than adult adverse events. No other important differences between adverse events were reported between the adult population and the pediatric population.

Safety Conclusions

The post-marketing safety experience reveals a safety profile consistent with the product label with no new serious or unexpected adverse events. Safety data is not provided for patients aged less than 2 years, therefore safety cannot be assessed in pediatric patients who are younger than 2 years of age. No additional safety updates to the label are indicated based on this safety review. The product is approved for ages 2 years and older given the lack of safety data in this age group and the fact that Fabry disease is rarely diagnosed in children younger than 2 years of age.

8.4. Conclusions and Recommendations

The determination for full approval of Fabrazyme in this application is based on the large body of scientific evidence that has acrrued since its approval on the role and effects of tissue GL-3 accumulation in conjunction with newly submitted comparative eGFR data from a long-term observational study (sections 8.2.4 and 8.2.5). This evidence in its entirety shows that the substantial reduction of GL-3 substrate in the renal peritubular capillaries achieved by Fabrazyme predicts clinical benefit in this development program and this SE is now sufficient for a full approval decision. We considered the following data:

- Multiple published in-vivo and in-vitro studies have found that the GL-3 substrate is toxic to tissue, causing damage to organ systems. The degree of accumulation of the substrate appears to correlate with the degree of damage in renal tissue. This provides a clinically meaningful link of the effect of GL-3 accumulation on organ dysfunction in patients with Fabry disease.

- Data showing that Fabrazyme reduces or clears GL-3 from the capillary endothelium of the skin and heart, in addition to the data available at the time of approval that showed Fabrazyme substantially reduces GL-3 from peritubular renal capillaries (as evidenced by

reduction of GL-3 to a score of zero on light microscopy in a majority of the renal biopsies from treated patients).

- Exploratory analyses from a second randomized, placebo-controlled clinical trial (AGAL-008-00) that lends support to an effect of Fabrazyme on the incidence of Fabry-associated clinical events (renal, cardiac, cerebrovascular events, or death).

- Exploratory analyses from a long-term observational study showing that Fabrazyme treatment was associated with slower decline in renal function compared to no treatment in Fabry disease patients matched on important baseline predictive variables.

Based on careful review of the submitted evidence as a whole and these conclusions, we consider this sBLA package sufficient to support validation of the previously used renal histologic SE in this specific clinical development program and the entirety of the available data are adequate for an approval decision.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee was not necessary and was not held for this application.

10. Labeling Recommendations

See agreed-upon final labeling

11. Risk Evaluation and Mitigation Strategies (REMS)

The safety profile of the product is well-characterized and the recognized serious safety risks associated with immunogenicity can be addressed adequately through clinical monitoring and medical management. No REMS are necessary.

12. Postmarketing Requirements and Commitments

No new PMRs or PMCs are warranted.

The Applicant has submitted all relevant data and analyses as requested in the revised PMR #2 (PMR 2421-2) which has been reviewed by the Division. As such, PMR 2421-2 is considered fulfilled.

13. Deputy Division Director (DRDMG) Comments

I concur with the review team's recommendation for full (traditional) approval of Fabrazyme for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease. New data submitted in this application includes: a) a series of published studies (in vitro and in vivo studies, clinical epidemiologic studies) establishing that GL-3 accumulation plays a fundamental pathophysiologic role in FD and the toxic effects of accumulated GL-3 in target tissues disturb tissue structure and organ function in Fabry disease; and b) long-term, observational data which show that Fabrazyme treatment may be associated with a slower rate of decline in renal function in Fabrazyme-treated vs untreated FD patients who were appropriately matched on clinically important baseline predictive factors. This newly submitted evidence was considered in this application along with the previously observed favorable effects of Fabrazyme on the incidence of clinically significant Fabry-associated events in the phase 4, post-marketing, randomized, placebo-controlled trial. In conclusion, the preponderance of the scientific evidence now supports that the previously demonstrated large and statistically significant treatment effect of Fabrazyme on the renal histological surrogate endpoint in the phase 3 randomized, placebo-controlled trial (that established substantial evidence of effectiveness of the product) predicts clinical benefit in this development program and in the specific FD patient population and is adequate to form the basis for full approval of Farbazyme in FD.

14. Appendices

14.1. References

Arends, M, M Biegstraaten, DA Hughes, A Mehta, PM Elliott, D Oder, OT Watkinson, FM Vaz, ABP van Kuilenburg, C Wanner, and CEM Hollak, 2017, Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: Analysis of prognostic factors, PLoS One, 12(8):e0182379.

Beck, M, D Hughes, C Kampmann, S Larroque, A Mehta, G Pintos-Morell, U Ramaswami, M West, A Wijatyk, R Giugliani, and G Fabry Outcome Survey Study, 2015, Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis, Mol Genet Metab Rep, 3:21-27.

Brenner, BM, ME Cooper, D de Zeeuw, WF Keane, WE Mitch, HH Parving, G Remuzzi, SM Snapinn, Z Zhang, S Shahinfar, and RS Investigators, 2001, Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy, N Engl J Med, 345(12):861-869.

De Francesco, PN, JM Mucci, R Ceci, CA Fossati, and PA Rozenfeld, 2013, Fabry disease peripheral blood immune cells release inflammatory cytokines: role of globotriaosylceramide, Mol Genet Metab, 109(1):93-99.

Ferrans, VJ, RG Hibbs, and CD Burda, 1969, The heart in Fabry's disease. A histochemical and electron microscopic study, Am J Cardiol, 24(1):95-110.

Fogo, AB, L Bostad, E Svarstad, WJ Cook, S Moll, F Barbey, L Geldenhuys, M West, D Ferluga, B Vujkovac, AJ Howie, A Burns, R Reeve, S Waldek, LH Noel, JP Grunfeld, C Valbuena, JP Oliveira, J Muller, F Breunig, X Zhang, DG Warnock, and N all members of the International Study Group of Fabry, 2010, Scoring system for renal pathology in Fabry disease: report of the International Study Group of Fabry Nephropathy (ISGFN), Nephrol Dial Transplant, 25(7):2168-2177.

Gadoth, N and U Sandbank, 1983, Involvement of dorsal root ganglia in Fabry's disease, J Med Genet, 20(4):309-312.

Germain, DP, 2010, Fabry disease, Orphanet J Rare Dis, 5:30.

Jain, G and DG Warnock, 2011, Blood pressure, proteinuria and nephropathy in Fabry disease, Nephron Clin Pract, 118(1):c43-48.

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (January 2013)

Lewis, EJ, LG Hunsicker, WR Clarke, T Berl, MA Pohl, JB Lewis, E Ritz, RC Atkins, R Rohde, I Raz, and G Collaborative Study, 2001, Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes, N Engl J Med, 345(12):851-860.

Liebau, MC, F Braun, K Hopker, C Weitbrecht, V Bartels, RU Muller, S Brodesser, MA Saleem, T Benzing, B Schermer, M Cybulla, and CE Kurschat, 2013, Dysregulated autophagy contributes to podocyte damage in Fabry's disease, PLoS One, 8(5):e63506.

Linhart, A, C Kampmann, JL Zamorano, G Sunder-Plassmann, M Beck, A Mehta, PM Elliott, and FOSI European, 2007, Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey, Eur Heart J, 28(10):1228-1235.

Mann, JF, HC Gerstein, QL Yi, J Franke, EM Lonn, BJ Hoogwerf, A Rashkow, S Yusuf, and H Investigators, 2003, Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study, Am J Kidney Dis, 42(5):936-942.

Najafian, B, E Svarstad, L Bostad, MC Gubler, C Tondel, C Whitley, and M Mauer, 2011, Progressive podocyte injury and globotriaosylceramide (GL-3) accumulation in young patients with Fabry disease, Kidney Int, 79(6):663-670.

Najafian, B, C Tondel, E Svarstad, MC Gubler, JP Oliveira, and M Mauer, 2020, Accumulation of Globotriaosylceramide in Podocytes in Fabry Nephropathy Is Associated with Progressive Podocyte Loss, J Am Soc Nephrol, 31(4):865-875.

Namdar, M, C Gebhard, R Studiger, Y Shi, P Mocharla, C Schmied, P Brugada, TF Luscher, and GG Camici, 2012, Globotriaosylsphingosine accumulation and not alpha-galactosidase-A deficiency causes endothelial dysfunction in Fabry disease, PLoS One, 7(4):e36373.

Ortiz, A, DP Germain, RJ Desnick, J Politei, M Mauer, A Burlina, C Eng, RJ Hopkin, D Laney, A Linhart, S Waldek, E Wallace, F Weidemann, and WR Wilcox, 2018, Fabry disease revisited: Management and treatment recommendations for adult patients, Mol Genet Metab, 123(4):416-427.

Parving, HH, H Lehnert, J Brochner-Mortensen, R Gomis, S Andersen, P Arner, D Irbesartan in Patients with Type, and G Microalbuminuria Study, 2001, The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes, N Engl J Med, 345(12):870-878.

Patel, MR, F Cecchi, M Cizmarik, I Kantola, A Linhart, K Nicholls, J Strotmann, J Tallaj, TC Tran, ML West, D Beitner-Johnson, and A Abiose, 2011, Cardiovascular events in patients with fabry disease natural history data from the fabry registry, J Am Coll Cardiol, 57(9):1093-1099.

Politei, JM, D Bouhassira, DP Germain, C Goizet, A Guerrero-Sola, MJ Hilz, EJ Hutton, A Karaa, R Liguori, N Uceyler, LK Zeltzer, and A Burlina, 2016, Pain in Fabry Disease: Practical Recommendations for Diagnosis and Treatment, CNS Neurosci Ther, 22(7):568-576.

Rozenfeld, PA, M de Los Angeles Bolla, P Quieto, A Pisani, S Feriozzi, P Neuman, and C Bondar, 2020, Pathogenesis of Fabry nephropathy: The pathways leading to fibrosis, Mol Genet Metab, 129(2):132-141.

Schachern, PA, DA Shea, MM Paparella, and TH Yoon, 1989, Otologic histopathology of Fabry's disease, Ann Otol Rhinol Laryngol, 98(5 Pt 1):359-363.

Shu, L, A Vivekanandan-Giri, S Pennathur, BE Smid, JM Aerts, CE Hollak, and JA Shayman, 2014, Establishing 3-nitrotyrosine as a biomarker for the vasculopathy of Fabry disease, Kidney Int, 86(1):58-66.

Spada, M, S Pagliardini, M Yasuda, T Tukel, G Thiagarajan, H Sakuraba, A Ponzone, and RJ Desnick, 2006, High incidence of later-onset fabry disease revealed by newborn screening, Am J Hum Genet, 79(1):31-40.

Tondel, C, L Bostad, A Hirth, and E Svarstad, 2008, Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria, Am J Kidney Dis, 51(5):767-776.

Tondel, C, L Bostad, KK Larsen, A Hirth, BE Vikse, G Houge, and E Svarstad, 2013, Agalsidase benefits renal histology in young patients with Fabry disease, J Am Soc Nephrol, 24(1):137-148.

Waldek, S and S Feriozzi, 2014, Fabry nephropathy: a review - how can we optimize the management of Fabry nephropathy?, BMC Nephrol, 15:72.

Wraith, JE, A Tylki-Szymanska, N Guffon, YH Lien, M Tsimaratos, A Vellodi, and DP Germain, 2008, Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease, J Pediatr, 152(4):563-570, 570 e561.

14.2. Financial Disclosures

See section 7.1.

Table 35. Covered Clinical Trial: Trial AGAL-008-00

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 122		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the trial where the value could be influenced by the outcome of the trial: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered trial: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 119		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 36. Covered Clinical Study: Fabry Natural History Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 84		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the trial where the value could be influenced by the outcome of the trial: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered trial: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 84		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Table 37. Covered Clinical Study: Fabry Disease Registry

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 352		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 39		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the trial where the value could be influenced by the outcome of the trial: 2 Significant payments of other sorts: 37 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered trial: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 315		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.3. Clinical Pharmacology Appendices (Technical Documents Supporting OCP Recommendations)

14.3.1. Summaries of Immunogenicity Data in Clinical Trials and Fabry Registry

The immunogenicity data from the following clinical studies and the Fabry Registry are included in the sBLA to support the immunogenicity assessment of Fabrazyme:

- Trial AGAL-1-002-98: A pivotal phase 3 randomized, placebo-controlled, double-blind trial in patients with Fabry disease who had received no prior treatment with agalsidase beta. Fifty-eight subjects (29 per group) were treated with either agalsidase beta (1 mg/kg) or placebo every 2 weeks for 6 months.
- Trial AGAL-005-99: An open-label Phase 3 extension trial. Patients received Fabrazyme 1.0 mg/kg intravenous (IV) q2w for 54 months.
- Trial AGAL-008-00: A Phase 4 confirmatory, randomized, placebo-controlled, double-blind trial in patients with Fabry disease. Patients randomized to agalsidase beta received 1 mg/kg of agalsidase beta IV q2w for 35 months. A total of 82 patients were enrolled and randomized to agalsidase beta (51 patients) or placebo (31 patients).
- Trial AGAL-02503: An open-label Phase 4 extension trial. Patients received 1.0 mg/kg q2w of agalsidase beta for an additional 18 months.
- Trial AGAL-016-01: A Phase 2 open-label trial in pediatric patients (8 to 16 years old at the time of the first infusion) with Fabry disease who had received no previous treatment with agalsidase beta. A total of 16 patients (14 males and 2 females) received 1.0 mg/kg agalsidase beta IV q2w for up to 48 weeks.
- Trial AGAL- 06207/EFC12821: A phase 3b randomized, multicenter, open-label, parallel group study that evaluated two alternative low doses of Fabrazyme (0.5 mg/kg q2w and 1.0 mg/kg q4w) in treatment-naïve male pediatric patients (≥5 to ≤18 years of age) with Fabry disease.
- Fabry Registry (NCT00196742): An ongoing global, observational program. All patients with Fabry disease are eligible to participate.

Immunogenicity Incidences

Immunogenicity incidences for anti-drug antibodies (ADA) in adult patients in the clinical trials are summarized in Table 38. ADA positive samples in adult patients in the clinical trials were analyzed to determine neutralizing antibodies (NAb) with two in-vitro assays (inhibition of enzyme activity and inhibition of enzyme uptake into cells). The NAb results are summarized Table 39. Immunogenicity incidences for ADA in pediatric patients in the clinical trials are summarized in Table 40.

Immunogenicity incidences for ADA in adult patients in the Fabry Registry are summarized in Table 41. Immunogenicity incidences for ADA in pediatric patients in the Fabry Registry are summarized in Table 42. Immunogenicity incidences for ADA in adult patients in the Fabry Registry by Fabry mutation category are summarized in Table 43. Immunogenicity incidences

for ADA in adult patients in the Fabry Registry by plasma αGAL level are summarized in Table 44.

The overall ADA and NAb incidences in pooled clinical trials and Fabry registry are summarized in Table 45. and Table 46.

Impact of Immunogenicity on Progression of Renal Disease and the Occurrence of Clinical Events in Fabry Registry

In the Fabry Registry, serum creatinine was measured for the calculation of glomerular filtration rate and eGFR is expressed in units of mL/min/1.73 m^2. There was no eGFR analyses performed for the pediatric population. The eGFR slope was obtained by fitting a regression line using baseline and post baseline data. The analyses of the impact of ADA on eGFR are limited by the small number of eGFR and ADA assessments per patient during the long-term follow-up. The distribution of eGFR slope overlapped across the ADA response types (Figure 15). A summary of the eGFR slope based on linear mixed effect (LME) models by ADA and NAb categories is shown in Table 47. In general, the observed eGFR slope was higher (less decline) in patients who were ADA negative compared to patients who were ADA positive. Because more severe phenotype was associated with higher incidences of ADA formation in patients with Fabry disease, the eGFR slope and ADA response correlation should be interpreted with caution. Also note that the patients with available NAb data are based on a selected subset of patients with high level plasma GL-3. A trend of higher % of patients with clinical events was also observed in ADA-positive patients than in ADA negative patients (Table 48).

Table 38. Summary of ADA in Adult Patients With Fabry Disease in Clinical Trials

	Phase 3			Phase 4			Pooled
Parameter/Category	**Male (N=56)**	**Female (N=2)**	**Overall (N=58)**	**Male (N=66)**	**Female (N=9)**	**Overall (N=75)**	**Overall (N=133)**
ADA response n(%)							
ADA+[a]	51 (91)	1 (50)	52 (90)	53 (80)	5 (56)	58 (77)	110 (83)
Low response[b]	1 (2)	0	1 (2)	5 (8)	0	5 (7)	6 (5)
Tolerized[c]	9 (16)	1 (50)	10 (17)	9 (14)	5 (56)	14 (19)	24 (18)
Persistent[d]	41 (73)	0	41 (71)	39 (59)	0	39 (52)	80 (60)
Prior positive	1 (2)	0	1 (2)	1 (2)	0	1 (1)	2 (2)
Time to ADA sero-conversion onset (week) Median (min, max)	6 (2, 109)	31 (31, 31)	6 (2, 109)	12 (6, 24)	24.4 (12, 63)	12 (6, 63)	12 (2, 109)

	Phase 3			Phase 4			Pooled
Parameter/Category	Male (N=56)	Female (N=2)	Overall (N=58)	Male (N=66)	Female (N=9)	Overall (N=75)	Overall (N=133)
Time to ADA tolerized from seroconversion (week)[f]	79	74	76	73	72	72	74
Median (min, max)	(54, 234)	(74, 74)	(54, 234)	(10, 174)	(10, 148)	(10, 174)	(10, 234)
Duration of positive ADA (weeks)[e,g]	236		236	133		133	177
Median (min, max)	(12, 272)	NC	(12, 272)	(24, 212)	NC	(24, 212)	(12, 272)

Source: Tables 2.1.1, 2.1.2, 2.1.3 in Appendix 1 of Immunogenicity Report
[a] If the patient had at least one positive ADA assessment
[b] If the patient's peak titer is ≤800 and remains positive at final assessment
[c] If the patient was seroconverted and had negative ADA at the final assessment
[d] If the patient's peak titer is >800 and remains positive at final assessment
[e] Exclude the patient with positive ADA prior to Fabrazyme treatment
[f] Time to ADA tolerized = (date of tolerized - date of initial seroconversion)/7
[g] Duration of positive ADA = (last date of ADA positive - date of initial seroconversion)/7, calculated for patients who ever positive without tolerized
Abbreviations: ADA = anti-drug ant bodies; NC = not counted

Table 39. Summary of NAb in Adult Patients With Fabry Disease in Clinical Trials

	Phase 3			Phase 4			Pooled
Parameter/Category	Male (N=56)	Female (N=2)	Overall (N=58)	Male (N=66)	Female (N=9)	Overall (N=75)	Overall (N=133)
NAb Response type category, n(%)							
Positive NAb catalytic activity inhibition	47 (84)	0	47 (81)	52 (79)	3 (33)	55 (73)	102 (77)
Low response[a]	0	0	0	1 (2)	2 (22)	3 (4)	3 (2)
Return to BQL[b]	18 (32)	0	18 (31)	11 (17)	1 (11)	12 (16)	30 (23)
Persistent[c]	29 (52)	0	29 (50)	40 (61)	0	40 (53)	69 (52)
Positive NAb cellular uptake inhibition	5 (9)	0	5 (9)	3 (5)	0	3 (4)	8 (6)
Only positive in catalytic activity inhibition	42 (75)	0	42 (72)	49 (74)	3 (33)	52 (69)	94 (71)
Only positive in cellular uptake inhibition	0	0	0	0	0	0	0
Positive in both catalytic activity & cellular uptake inhibition	5 (9)	0	5 (9)	3 (5)	0	3 (4)	8 (6)
Time to positive NAb catalytic activity inhibition (week)	18		18	12	112	12	12
Median (min, max)	(4, 52)	NC	(4, 52)	(4, 72)	(63, 137)	(4, 137)	(4, 137)
Time to positive NAb cellular uptake inhibition (week)	80		80	60		60	71
Median (min, max)	(53, 249)	NC	(53, 249)	(60, 84)	NC	(60, 84)	(53, 249)

Source: Tables 2.13.1, 2.13.2, 2.13.3 in Appendix 1 of Immunogenicity Report
[a] Low response defined as having peak value ≤0.9 and still above BQL at the final assessment positive.
[b] Return to BQL: if the patient was ever NAb+ and return to BQL at the final visit.
[c] Persistent: if peak value is >0.9 and the final assessment is positive
Abbreviations: ADA = anti-drug ant bodies; BQL = below quantifiable limit; NAb = neutralizing ant bodies; NC = not counted

Table 40. Summary of ADA in Pediatric Patients With Fabry Disease in Clinical Trials

	Phase 2 Trial AGAL-016-01			Phase 3 Trial AGAL-06207/EFC12821		
Parameter/Category	Male (N=14)	Female (N=2)	Overall (N=16)	Male, 0.5mg/kg Q2W (N=16)	Male, 1.0mg/kg Q4W (N=15)	Overall (N=31)
ADA response n(%)						
ADA+[a]	11 (79)	0	11 (69)	12 (75)	13 (87)	25 (81)
Low response[b]	5 (36)	0)	5 (31)	1 (6)	1 (7)	2 (7)
Tolerized[c]	0	0	0	5 (31.3)	1 (6.7)	6 (19)
Persistent[d]	6 (43)	0	6 (38)	6 (38)	11 (73)	17 (55)
Prior positive	0	0	0			
Time to ADA seroconversion onset (week)	8		8	9	12	10
Median (min, max)	(4, 16)	NC	(4, 16)	(4, 41)	(4, 80)	(4, 80)
Time to ADA tolerized from seroconversion (weeks)				68	157	70
Median (min, max)	NC	NC	NC	(39, 200)	(157, 157)	(39, 200)
Duration of positive ADA (weeks)	41		41	253	250	251
Median (min, max)	(20, 46)	NC	(20, 46)	(248, 257)	(20, 256)	(20, 257)

Source: Tables 18 and 19 in Immunogenicity Report
[a] If the patient had at least one positive ADA assessment
[b] If the patient's peak titer is ≤800 and remains positive at final assessment
[c] If the patient was seroconverted and had negative ADA at the final assessment
[d] If the patient's peak titer is >800 and remains positive at final assessment.
Abbreviations: ADA = anti-drug ant bodies; Q2W = every two weeks; Q4W = every four weeks

Table 41. Summary of ADA in Adult Patients in Fabry Registry (Longitudinal Population)

	Adults in Fabry Registry (Longitudinal)		
Parameter/Category	Male (N=469)	Female (N=336)	Overall (N=805)
ADA response n(%)			
ADA+[a]	333 (71)	50 (15)	383 (48)
Low response[b]	47 (10)	20 (6)	67 (8)
Tolerized[c]	66 (14)	24 (7)	90 (11)
Persistent[d]	220 (47)	6 (1.8)	226 (28)
Positive at baseline	3 (0.6)	1 (0.3)	4 (0.5)
Time to ADA seroconversion onset (week)	32.9	81.7	37.4
Median (min, max)	(1.6, 801)	(12.0, 729)	(1.6, 801)
Time to ADA tolerized from seroconversion (weeks)	196	55	134
Median (min, max)	(13, 655)	(12, 602)	(12.0, 654.9)
Duration of positive ADA (weeks)	194	72	193
Median (min, max)	(0, 736)	(0, 490)	(0, 736)

Source: Table 55 in Immunogenicity Report
[a] If the patient had at least one positive ADA assessment post baseline
[b] If the patient's peak titer is ≤800 and remains positive at final assessment
[c] If the patient had at least one ADA positive assessment post baseline, but negative at final assessment
[d] If the patient's peak titer is >800 and remains positive at final assessment
Abbreviations: ADA = anti-drug ant bodies

Table 42. Summary of ADA in Pediatric Patients in Fabry Registry (Longitudinal Population)

	Pediatrics in Fabry Registry (Longitudinal)		
Parameter/Category	**Male (N=116)**	**Female (N=41)**	**Overall (N=157)**
ADA response n(%)			
ADA+[a]	82 (71)	4 (10)	86 (55)
Low response[b]	11 (10)	3 (7)	14 (9)
Tolerized[c]	14 (12)	1 (2)	15 (10)
Persistent[d]	57 (49)	0	57 (36)
Prior positive	1 (1)	0	1 (1)
Time to ADA seroconversion onset (week)	16	85	17
Median (min, max)	(6, 324)	(16, 164)	(6, 324)
Time to ADA tolerized from seroconversion (week)	127	53	125
Median (min, max)	(13, 505)	(53, 53)	(13, 505)
Duration of positive ADA (weeks)	252	28	200
Median (min, max)	(0, 711)	(0, 130)	(0, 711)

Source: Table 68 in Immunogenicity Report
[a] If the patient had at least one positive ADA assessment
[b] If the patient's peak titer is ≤800 and remains positive at final assessment
[c] If the patient was seroconverted and had negative ADA at the final assessment
[d] If the patient's peak titer is >800 and remains positive at final assessment.
Abbreviations: ADA = anti-drug ant bodies

Table 43. Summary of ADA by Mutation Category in Fabry Registry (Longitudinal Population)

	Mutation Category			
Parameter/Category	**Truncating (N=259)**	**Non-Truncating (N=455)**	**Other/Unspecified (N=14)**	**Missing (N=77)**
ADA response n(%)				
ADA+[a]	150 (58)	187(41)	6 (43)	40 (52)
Low response[b]	18 (7)	43 (10)	1 (7)	5 (7)
Tolerized[c]	28 (111)	53 (12)	1 (7)	8 (10)
Persistent[d]	104 (40)	91 (20)	4 (29)	27 (35)
ADA peak titer category				
100-800	40 (15)	85 (19)	2 (14)	11 (14)
1600-6400	67 (26)	91 (20)	2 (14)	16 (21)
≥12800	43 (17)	11 (2)	2 (14)	13 (17)

Source: Tables 57 of Immunogenicity Report
[a] If the patient had at least one positive ADA assessment
[b] If the patient's peak titer is ≤800 and remains positive at final assessment
[c] If the patient was seroconverted and had negative ADA at the final assessment
[d] If the patient's peak titer is >800 and remains positive at final assessment
Abbreviations: ADA = anti-drug ant bodies;

Table 44. Summary of ADA by Plasma αGAL Level in Fabry Registry (Longitudinal Population)

	Plasma αGAL Level (nmol/hr/mL)					
	≤1.5		<1.5 to <2.4		≥2.4	
Parameter/Category	Male (N=175)	Female (N=9)	Male (N=7)	Female (N=21)	Male (N=13)	Female (N=90)
ADA response n(%)						
ADA+	129 (74)	4 (44)	3 (43)	1 (5)	9 (69)	15 (17)
ADA peak titer						
100-800	32 (18)	1 (11)	0	1 (5)	4 (31)	13 (14)
1600-6400	67 (38)	3 (33)	3 (43)	0	5 (39)	2 (2)
≥12800	30 (17)	0	0	0	0	0

Source: Tables 58 of Immunogenicity Report
Abbreviations: ADA = anti-drug ant bodies

Table 45. Summary of ADA Incidences in Pooled Clinical Studies and Fabry Registry

Population	Clinical Studies	Registry
Adults	83% (110/133)	48% (383/805)
Pediatrics	69% (11/16)*	55% (86/157)

Source: Tables 17, 18, 55, and 68 in Immunogenicity Report
*Phase 2 pediatric trial receiving the recommended dose of 1.0 mg/kg q2w
Abbreviations: ADA = anti-drug ant bodies

Table 46. Summary of NAb Incidences in Pooled Clinical Studies

	NAb In Vitro Assay	
	Catalytic Inhibition	Cellular Update Inhibition
Adults	77% (102/133)	6% (8/133)

Source: Table 25 in Immunogenicity Report
Abbreviations: NAb = neutralizing antibodies

Table 47. eGFR Slope by ADA and NAb Status in Fabry Registry (Longitudinal Population)

Parameter/Category	Number of Patients	Mean (SE) Estimated eGFR Slope (mL/min/1.73m^2 per Year)
ADA always negative	307	-0.845 (0.178)
ADA ever positive	285	-2.255 (0.170)
ADA persistent and had 50% of assessments with titer ≥12800	17	-3.549 (0.619)
NAb catalytic inhibition high peak (>14.8)	13	-3.795 (0.643)
NAb catalytic inhibition persistent	23	-4.064 (0.510)

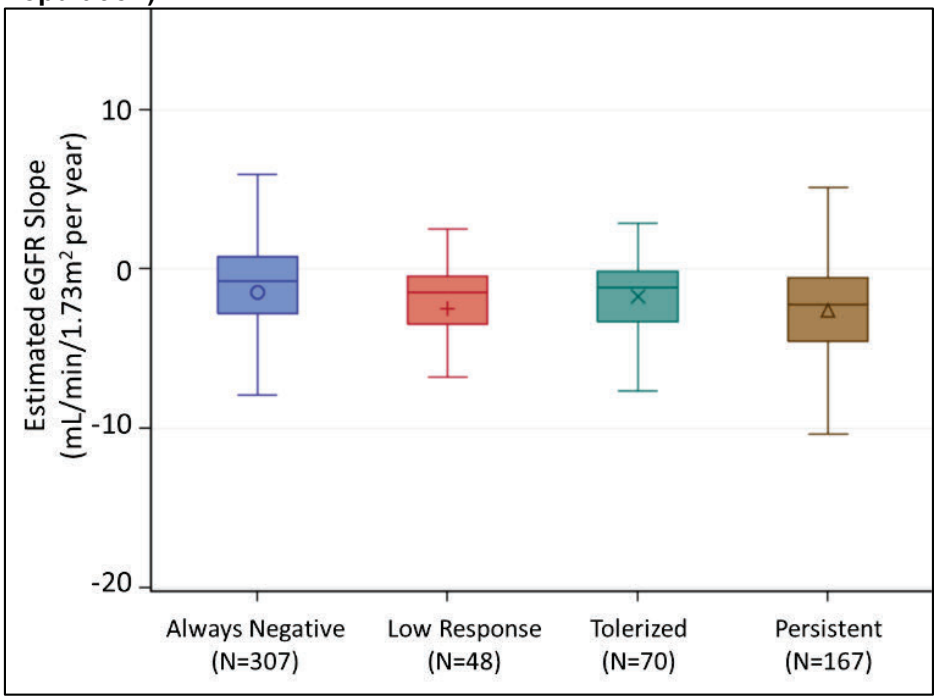
Source: Table 63 in Immunogenicity Report
Abbreviations: ADA = anti-drug ant bodies; NAb = neutralizing antibodies

Table 48. Clinical Outcomes by ADA and NAb Status in Fabry Registry (Longitudinal Population)

Parameter/Category	Number of Patients	Number of Patients With Events (%)
ADA always negative	375	93 (24.8)
ADA ever positive	355	114 (32.1)
ADA persistent and had 50% of assessments with titer ≥12800	22	5 (22.7)
NAb catalytic inhibition high peak (>14.8)	13	5 (38.5)
NAb catalytic inhibition persistent	28	12 (42.9)

Source: Table 64 in Immunogenicity Report
Abbreviations: ADA = anti-drug antibodies; NAb = neutralizing antibodies

Figure 15. eGFR Slope by ADA Response Type Category in Fabry Registry (Longitudinal Population)



Source: Figure 38 in Immunogenicity Report
Abbreviations: ADA = anti-drug antibodies; eGFR = estimated glomerular filtration rate

14.3.2. Immunogenicity Literature Review

The Applicant conducted a systematic literature review of published data of Fabrazyme for the treatment of patients with Fabry disease. A total of 56 studies (71 publications) were included in the literature review, including 12 interventional studies and 44 observational studies. Clinical efficacy and effectiveness outcomes were reported in 52 studies (67 publications) and immunogenicity outcomes were reported in 22 studies (26 publications). Most studies were conducted in adult patients.

The key literature findings by the Applicant regarding the impact of immunogenicity on the effectiveness and efficacy of Fabrazyme are summarized below:

- Multiple studies have shown that the development of ADA generally had no significant impact on the effectiveness of Fabrazyme at the approved dose of 1.0 mg/kg administered every two weeks. Some studies indicated that a potential for reduced effectiveness by ADA could be more appreciable at lower doses of Fabrazyme (e.g., <1.0 mg/kg).
- Fabrazyme-treated patients experienced estimated glomerular filtration rate (eGFR) benefits even in the presence of ADA. Differences in the incidence of clinical events based on serostatus are generally not observed in Fabry patients treated with Fabrazyme.
- The effect of ADA on PD biomarkers was reported in a few studies. Most studies reported successful clearance of tissue globotriaosylceramide (GL-3) despite the presence of ADA. Some studies reported no association between ADA and plasma GL-3 levels. However, it was also reported in some studies that high titer ADA was associated with increased GL-3 depositions in skin and slightly increased plasma GL-3 levels.

14.4. Matching Algorithm for eGFR Slope (Age, Gender, FD Phenotype, and Baseline eGFR) in Observational Study (sections 8.2.4 and 8.2.5)

Prior to carrying out the statistical analyses, the treated adult population is matched by gender (male, female), age (±5 years), phenotype according to dbFGP/αGAL definition (Classic, Late-onset, Other/Unclassified/Missing), and baseline eGFR (±5 ml min/1.73m^2), with the untreated adult population as follows:

A. The eGFR measures of all untreated patients that satisfied the inclusion and exclusion criteria [of the analysis] are compiled into a dataset.
B. Visits where the eGFR measures were collected prior to symptom onset or post dialysis initiation or renal transplant are excluded.
C. Only visits that have at least one additional eGFR measurement during follow-up (i.e., >0.5 to ≤5 years from baseline) are selected as potential baseline measurements.
D. The resulting dataset of untreated patients consists of one observation per patient-visit and is sorted by patient ID and age at eGFR assessment.
E. Each untreated patient in the dataset is assigned a random number from the uniform(0, 1) distribution.
F. For each treated patient satisfying the inclusion/exclusion criteria in [this analysis], a dataset consisting of the patient id, gender, age at initiation of Fabrazyme (the "index age"), and the baseline eGFR value is created (one observation per patient).
G. The first treated patient in the resulting dataset from part F is selected. All untreated patients of the same gender and phenotype as this treated patient who have an eGFR measurement within ±5 years of the "index age" and within ±5 ml/min/1.73m^2 of the "baseline eGFR value" of the treated patient are selected as a possible match to the first treated patient.

H. The untreated candidates that are true candidates for matching from part G are then are then sorted by the random number assigned in part E. The first untreated patient, after the sort, is selected as the match to the treated patient.
I. A "1" is added to the selected untreated match's random number, which lowers the probability the same untreated patient is selected as a match for subsequent treated patients. This is done in order to give a wider range of untreated patients selected for the final matched dataset.
J. The above process from part F through part I is repeated for all treated patients, and all available eGFR measures from the "index age" to 5 years post-baseline are used in the analyses for the treated patients.

The resulting dataset is labeled the "X:X" match; i.e., it contains all treated patients and all untreated patients to which they were matched where an untreated patient may be matched to >1 treated patient.

A dataset labeled "1:1" match is also created from the X:X match. In this dataset, only one occurrence of each untreated patient and a treated patient to which they were matched are included. Specifically, the occurrence of the untreated patient with the longest follow-up period, along with the untreated patient's treated match, is selected from the pool of available matched pairs. The longest follow-up period of the untreated patient is selected for the 1:1 matched dataset in order to increase the comparability of the untreated and treated patients with respect to length of follow-up.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATROULA I SMPOKOU
03/11/2021 10:54:41 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103979Orig1s5309

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 26, 2021

To: Michael White, PhD, Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for FABRAZYME (agalsidase beta) injection, for intravenous use

BLA: 103979 / Supplement 5309

In response to DRDMG consult request dated June 30, 2020, OPDP has reviewed the proposed product labeling (PI) for FABRAZYME (agalsidase beta) injection, for intravenous use. This supplement (S5309) pertains to the PAS for the treatment of Fabry Disease.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRDMG (Michael White) on February 17, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ADEWALE A ADELEYE
02/26/2021 05:25:29 PM

MEMORANDUM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 25, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 103979/S-5309
Product Name and Strength:	Fabrazyme (agalsidase beta) for injection, 5 mg and 35mg vials
Applicant/Sponsor Name:	Sanofi Genzyme
OSE RCM #:	2021-325
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

Sanofi Genzyme submitted a supplement for Fabrazyme (agalsidase beta) for injection to satisfy and fulfill post marketing commitment(PMC)2421-2. Subsequently, Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the Fabrazyme prescribing information (PI) for areas of vulnerability that may lead to medication errors. There were no proposed changes to the carton labeling and container labels.

2 CONCLUSION

We reviewed the proposed changes to the PI and did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED FEBRUARY 14, 2020

Prescribing information received on February 14, 2020:
\\CDSESUB1\evsprod\bla103979\0415\m1\us\annotatedpi.docx

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
02/25/2021 01:20:38 PM

IDALIA E RYCHLIK
02/25/2021 02:01:23 PM

Division of Cardiology and Nephrology
Consultation for the Division of Rare Diseases and Medical Genetics

From: Kirtida Mistry, Physician, Division of Cardiology and Nephrology (DCN)
Through: Aliza Thompson, Deputy Director, DCN
To: Nicolas Kong, Regulatory Project Manager, Division of Rare Diseases and Medical Genetics (DRDMG)

This memorandum serves to close out the consult for BLA 103979/S5309 (agalsidase beta, Fabrazyme®, for the treatment of Fabry disease) dated March 5, 2020.

Reason for consult:
Fabrazyme® (agalsidase beta) is a recombinant human α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Fabrazyme received accelerated approval for the treatment of Fabry disease in 2003 based on a reduction in globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. To verify the treatment benefit, the applicant completed a phase 4, randomized, double-blind, placebo-controlled trial (AGAL-008-00) in patients with Fabry disease with mild to moderate kidney disease who had not received prior enzyme replacement therapy. Participants could continue treatment in an extension study (AGAL02503). AGAL-008-00 failed to show a statistically significant improvement for the primary endpoint and the Agency indicated that additional data would be needed to verify the benefit.

On February 14, 2020, Sanofi-Genzyme submitted an efficacy supplement to fulfill a postmarketing commitment (PMC 2421-2) and obtain traditional approval of Fabrazyme. The efficacy supplement is primarily based on data from matched analyses of the Fabry Registry (NCT00196742) and Natural History Study (AGAL-014-01). DRDMG requested input from DCN on interpretation of the estimated glomerular filtration rate (eGFR) endpoint data.

DCN response:
Drs. Mistry and Thompson participated in discussions as needed.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIRTIDA MISTRY
02/08/2021 09:06:45 AM

ALIZA M THOMPSON
02/08/2021 09:56:23 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Version Date:	November 5, 2020
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Shetarra Walker, MD, MSCR, Acting Medical Team Leader, DPMH John J. Alexander, MD, MPH, Deputy Director DPMH
BLA Number:	103,979
Sponsor:	Genzyme
Drug:	Fabrazyme (agalsidase beta)
Current Indication:	(b) (4)
Proposed Indication:	
Dosage Form and Route of Administration:	5 or 35 mg lyophilized cake or powder, single use vial for reconstitution in sterile water for intravenous (IV) administration
Dosing regimen:	1 mg/kg body weight infused every 2 weeks. Initial infusion rate is no more than 0.25 mg/min (15 mg/hour). For patients ≥30 kg, rate may be increased by increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hour) with each subsequent infusion. Maximum infusion rate for patients weighing < 30 kg, is 0.25 mg/minute (15 mg/hour).
Division Consult Request:	The Division of Rare Diseases and Medical Genetics (DRDMG) requests DPMH assistance with section 8.4 of labeling for this product which was originally marketed under accelerated approval.

Regulatory Background

On January 19, 1998 Fabrazyme (agalsidase beta) received orphan drug designation for use in patients with Fabry disease.

On April 24, 2003, Fabrazyme received accelerated approval to reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types in patients with Fabry disease (FD).

There are no required studies under the Pediatric Research Equity Act and no pediatric written request was issued.

As a condition of accelerated approval, the sponsor committed to undertake a follow-up clinical study to establish clinical effectiveness (PMC 2421-2).

Disease Background

This disease summary is taken from the Online Mendelian Inheritance in Man (OMIM) website (entry #: 301500; Fabry disease)[1] and a recent consensus review.[2] Fabrazyme is an enzyme replacement therapy (ERT) for alpha- (α–) galactosidase deficiency [Fabry disease (FD), also called Anderson-Fabry disease]. FD is a rare, x-linked recessive, lysosomal storage disorder from mutations at Xa22.1. Most patients have inherited mutations rather than *de novo* mutations. Patients cannot degrade/eliminate sphingolipids which leads to build-up of globotriaosylceramide in blood vessels and other organs. The build-up of sphingolipids leads to severe acroparesthesias (as early as 2 years); severe abdominal-pelvic pain mimicking 'surgical abdomen' such as appendicitis (present as early as 2 years); albuminuria (as early as 7 years) with pathologic proteinuria (presenting from 14 to 20 years) progressing to end stage renal disease (ESRD); abnormal electrocardiogram with T-wave inversion (presenting as early as 4 years) and infiltration cardiac muscle fibers with cardiomyopathy; retinal vascular pathology (present at 4 years); angiokeratoma (present at 4 years), and fatigue. GL-3 deposition is found *in utero* and has been confirmed on fetopsy.

Registry data from 2009[3] reported male life expectancy of 58.2 years compared with 74.7 years in the general population of the United States, and female life expectancy of 75.4 years compared with 80.0 years in the United States general population. Nevertheless, deaths in the 3rd and 4th decades are not uncommon and may occur due to cerebrovascular accidents, major acute cardiac events, or complications of ESRD. Affected hemizygous females have been reported. FD screening is part of many newborn screening programs.

Historically, patients came to attention in 2nd to early 4th decade after a therapeutic odyssey for nondescript complaints. With newborn screening (NBS) in some, but not all, states/municipalities, many individuals are diagnosed near birth while still pre-symptomatic. Screening of newborns, particularly newborn siblings of affected probands, is warranted.

PMR 2421-2

"Genzyme commits to performing additional analyses of the data obtained in the registry of patients with Fabry disease being treated with Agalsidase beta that was established to obtain long-term clinical

[1] OMIM entry #: 301500: Fabry disease. https://www.omim.org/entry/301500. Website accessed October 16, 2020.
[2] Hopkin RJ, Jefferies JL, Laney DA, et al. The management and treatment of children with Fabry disease: A United States-based perspective. Molecular Genetics and Medicine 2016. 117: 104-113.
[3] Waldek S., Patel MR., Bankiazemi M., et al. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet. Med. 11: 790-796, 2009.

status information. Additional analyses of the registry data are to be performed for the purpose of establishing the clinical benefit of Fabrazyme on progression of renal disease and other end-organ disease endpoints in patients with Fabry disease. Additional analyses to be performed include the following:

a. Progression of renal disease, including assessment of time of onset of proteinuria, hypertension, chronic renal insufficiency, end-stage renal disease, and death.

b. Exploration of the effects of endogenous alphaGAL activity and genetic mutations on progression of renal disease, the occurrence of significant clinical events, and the development of anti-recombinant-human-alphaGAL (anti-rh-alphaGAL) IgG antibodies.

c. Progression of renal disease by age of initiation of ERT with Fabrazyme for age groups such as <10 years of age, greater than or equal to 10 to <15 years of age, greater than or equal to 15 to 20 years of age, and in 10-year increments at >20 years of age.

d. Progression of renal disease by treatment administered, including ERT with Fabrazyme or no treatment. Reports will include data on patients who have received other Fabry specific treatments.

e. Progression of renal disease by GFR status (>60 ml/min/1.73 m^2 or <60 ml/min/1.73 m^2) at initiation of ERT with Fabrazyme.

f. Time of first significant clinical event.

g. Analysis of anti-rh-alphaGAL IgG antibodies titers on the progression of renal disease and the occurrence of significant clinical events."

A final analysis plan for the registry study protocol was to be submitted to CDER by October 25, 2008. The final study report under this registry was to be submitted to CDER by July 30, 2021.

The current supplement is primarily based on the long-term real-word data (RWD) from matched analyses of the Fabry Registry (NCT00196742) and Natural History study (AGAL-014-01), which the sponsor believes establishes adequate real-world evidence (RWE) to fulfill PMR 2421-2.

Labeling Review

DPMH's labeling recommendations focus on sections 1 (Indications and Usage) and 8.4 (Pediatric Use). Review of the remaining sections is deferred to DRDMG and other disciplines (e.g., Clinical Pharmacology). Proposed changes for section 2 (Dosage and Administration) intended to clarify prior dosing language are similar to current labeling and are not discussed in this review.

This review is based on labeling, including prior revisions from other disciplines, available on October 15, 2020. Newly proposed text (from other FDA disciplines or from the sponsor) is in **bold blue**. Text which DPMH recommends deleting is noted by ~~strike-out~~, and text which DPMH recommends adding is noted in **bold red**. The comments below were provided to DRDMG on November 4, 2020.

The reader is directed to the final negotiated label which may reflect changes not discussed in this document.

Reviewer comment 1: As noted above, the submission is based on analyses of RWD Fabry Registry (NCT00196742) and a natural history study (AGAL-014-01). At the labeling meeting October 14, 2020, DRDMG stated that CDER's Medical Policy and Program Review Council RWE subcommittee agreed that the RWE study alone does not provide adequate scientific evidence to establish the product's efficacy alone but does provide supporting evidence that aligns with AGAL-008 (adult confirmatory trial). The major concern was that the comparison of a registry study to a historical

control can lead to selection bias and issues with temporality which make it challenging for any type of causal inference because of the question around isolation of the treatment effect. Per DRDMG, the RWE subcommittee did not comment on the quality or acceptability of registry data for patients younger than 8 years. Additional details are found in the DRDMG clinical review.

While the key requirement of the PMC was to establish the clinical benefit of Fabrazyme on progression of renal disease and other end-organ disease endpoints in affected patients, all specified endpoints appear exploratory and based on FDA's understanding of the disease at the time the PMC was issued.

If the pre-specified data elements were not appropriately collected and reported, the PMC would be considered not fulfilled. However, if DRDMG determines that the specified data elements were collected and reported in appropriate fashion, the PMC might be considered fulfilled even if DRDMG concludes the endpoints are not clinically meaningful given current understanding of the disease, irrespective of any determination regarding changing the type of approval.

Alternatively, if the endpoint data were collected and reported in an appropriate fashion, are suggestive of clinical benefit, and are consistent with a body of published literature suggesting longer time to adverse events (e.g., death) in treated patients compared to historical controls, DRDMG could consider the PMC fulfilled based on a totality of available evidence and convert the approval from accelerated to 'traditional approval.'

Regarding pediatric literature, Spada et al[4] performed a systematic review of original articles reporting outcomes of enzyme replacement therapy (ERT) in pediatric patients with Fabry disease treated with ERT [agalsidase beta (Fabrazyme; BLA 103,979) or agalsidase beta (Replagal, approved in Europe but not in the United States)]. The authors concluded that ERT "can significantly clear GL-3 accumulation, ameliorate the early symptoms of Fabry disease, and improve quality of life." None of the publications describes use of Fabrazyme in patients younger than 8 years. Limitations of the evidence-based review for Fabrazyme included:

- *One single-arm trial (Grade 1C evidence; endpoints plasma GL-3, dermal GL-3, eGFR, proteinuria, ECG, GI outcomes, QoL), in 16 patients (14 male, two female). This publication appears to describe patient data previously submitted to the BLA.[5]*
- *Two retrospective observational studies (Grade 3 evidence) clinical trial.[6,7] Both publications report use of labeled doses. Neither publication provides pharmacokinetic (PK) data.*
    - *Borgwardt et al[3] describe use in a retrospective cohort review of 10 pediatric patients (6 male, 4 female) from 9 to 16 years of age, followed for up to 8 years. Age at first ERT was 9 to 16 years. All patients began treatment with Fabrazyme as early as 2003; however, six of 10 patients switched to Replagal in 2010 and 2011 due to a worldwide shortage of Fabrazyme.*

[4] Spada M, Baron R, Elliott PM, et al. The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease – A systematic literature review by a European panel of experts. Molecular Genetics and Metabolism 126 (2019) 212–223.
[5] Wraith JE, Tylki-Szymanska A, Guffon N, et al. Safety and Efficacy of Enzyme Replacement Therapy with Agalsidase Beta: An International, Open-label Study in Pediatric Patients with Fabry Disease. J Pediatr 2008; 152:563-70.
[6] Borgwardt L, Feldt-Rasmussen U, Rasmussen AK, et al. Fabry disease in children: agalsidase-beta enzyme replacement therapy. Clin Genet 2013: 83: 432–438.
[7] Kim Jh, Lee BH, Cho JH, et al. Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes. Journal of Human Genetics (2016) 61, 923–929.

- *Kim et al[4] describe use in 19 patients including 4 pediatric males (8.4 to 16.6 years of age at diagnosis), 11 adult males, and 4 heterozygous females. Age at diagnosis was 0 to 13 years. In adult males, the rate of decline in estimate glomerular filtration rate (eGFR) slowed after introduction of ERT and was inversely related to baseline proteinuria (that is, earlier treatment had greater effect).*

- *Eight case reports/series including one Grade 4 case series and 7 Grade 5 case reports.*

1 Indications and Usage

The original indication ["Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types"] is replaced by:

(b) (4)

Reviewer comment: The original indication does not specify the indicated ages. DRDMG is considering if specifying the age in the indication statement is warranted. DRDMG has been unable to locate the administrative record for study AGAL-016-01 supplement 5058, which provided safety and efficacy data for pediatric patients 8 years and older. DRDMG is therefore unable to comment on any internal discussions from that prior review which may or may not have occurred regarding the ages for whom the drug should be indicated.

The following options for the indication can be considered regarding age under the assumption that data are otherwise adequate to support conversion to a traditional approval. A brief framework follows each possible indication statement. A discussion of the relevant considerations follows the list.

a) Indicate for patients 8 years and older:

"Fabrazyme is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for treatment of patients 8 years and older with Fabry disease."

This option is reasonable if DRDMG concludes the submitted postmarket data in 29 pediatric patients 2 to less than 8 years suggests that those patients do worse than expected compared to a control group. This wording is consistent with current labeling guidelines.

b) Indicate for patients 2 years and older:

"Fabrazyme is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for treatment of patients 2 years and older with Fabry disease."

This option is reasonable if DRDMG concludes the submitted postmarket data for pediatric patients 2 to less than 8 years show sustained decreases in plasma GL-3 and that decreases in plasma GL-3 are supportive of clinical benefit. Improvement in a clinical endpoint, preferably in the submission or possibly in peer-reviewed literature, could further support this rationale but might not be needed. This wording may also be viewed as consistent with current labeling guidelines because the language would reflect supportive data.

c) Indicate for all patients:

"Fabrazyme is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for treatment of patients with Fabry disease."

This option is reasonable if DRDMG concludes the submitted postmarket data in 29 pediatric patients 2 to less than 8 years show sustained decreases in plasma GL-3 and if DRDMG determines there are reliable reports of clinical benefit with Fabrazyme use in patients younger than 2 years. Additionally, the drug would remain available for use for clinicians who determine the drug is likely to be effective and needed in patients younger than 2 years.

As of the team meeting of November 3, 2020, DRDMG prefers either option (b) or (c) above.

Discussion: Limiting indication statements to the age groups for whom drugs have been studied is consistent with current labeling practices. However, FDA occasionally considers 'time and extent of use' to support pediatric labeling when safety information is available even in the absence of PK data and efficacy data. Nevertheless, such instances have generally involved imaging agents, such as barium sulfate, which are indicated for diagnostic purposes rather than for treatment.

While DPMH identified no reports of use of Fabrazyme in children younger than 8 years were identified on a PubMed literature search on October 16, 2020, the sponsor submits registry data for 100 patients younger than 16 years, 29 of whom were between 2 and < 8 years. DRDMG does not currently believe the submitted pediatric endpoint data (reduction in GL-3) would be adequate to support indicating the drug in patients less than 8 years.

DRDMG should consider if restricting the indication statement to patients 8 years and older would place undue burden on younger patients for whom clinicians conclude that ERT is effective and warranted. DPMH identified recent consensus recommendations supporting ERT intervention for end organ involvement at 5 years of age for asymptomatic (i.e., pre-symptomatic) males and at 12 to 15 years of age for asymptomatic females. These recommendations support ERT administration for males 7 years of age and older.[8] Other consensus guidelines recommend ERT for any symptomatic patient of either sex at any age even if diagnosis is based solely on laboratory findings; these guidelines appear to reference data from the sponsor's registry and several authors reported relationships with the manufacturers of Fabrazyme and Replagal.[9]

8.4 Pediatric Use

The sponsor's proposed language is presented first followed by DRDMG's suggested language and then language recommended by DPMH.

Sponsor:

The safety and effectiveness of Fabrazyme have been established in pediatric patients (b) (4) (b) (4).

(b) (4)

[8] Germain DP, Fouilhoux A, Cecramer S, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet. 2019 Aug; 96(2): 107–117.
[9] Hopkin RJ, et al. Ibid.

(b) (4)

DRDMG:

(b) (4)

DPMH Proposal:

The safety and effectiveness of Fabrazyme have been established in pediatric patients **based on adequate and well-controlled studies in adults,** (b) (4), open-label study in 16 pediatric patients with Fabry disease, **and additional data in** (b) (4) (b) (4)

The overall safety profile was similar between the pediatric and the adult population [see Adverse Reactions (6.2), and Clinical Studies (14)].

(b) (4)

Reviewer comment: If DRDMG concludes that data from patients younger than 8 years are acceptable, DPMH offers the above language for section 8.4 and recommends retaining a description of use in patients 2 to 7 years in sections 6 (Adverse Reactions) and 14 (Clinical Studies).

As noted under the discussion of the indication statement, if data as supportive of use in pediatric patients 2 and older, DRDMG may also consider not specifying age in the indication statement to allow for use in the rare instance where a clinician concludes the drug is likely to be affective and necessary in younger patients.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ETHAN D HAUSMAN
11/05/2020 06:51:34 AM

SHETARRA E WALKER
11/05/2020 09:03:39 AM

JOHN J ALEXANDER
11/05/2020 09:57:03 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 26, 2021

To: Michael White, PhD, Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for FABRAZYME (agalsidase beta) injection, for intravenous use

BLA: 103979 / Supplement 5309

In response to DRDMG consult request dated June 30, 2020, OPDP has reviewed the proposed product labeling (PI) for FABRAZYME (agalsidase beta) injection, for intravenous use. This supplement (S5309) pertains to the PAS for the treatment of Fabry Disease.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRDMG (Michael White) on February 17, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ADEWALE A ADELEYE
02/26/2021 05:25:29 PM

MEMORANDUM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 25, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 103979/S-5309
Product Name and Strength:	Fabrazyme (agalsidase beta) for injection, 5 mg and 35mg vials
Applicant/Sponsor Name:	Sanofi Genzyme
OSE RCM #:	2021-325
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

Sanofi Genzyme submitted a supplement for Fabrazyme (agalsidase beta) for injection to satisfy and fulfill post marketing commitment(PMC)2421-2. Subsequently, Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the Fabrazyme prescribing information (PI) for areas of vulnerability that may lead to medication errors. There were no proposed changes to the carton labeling and container labels.

2 CONCLUSION

We reviewed the proposed changes to the PI and did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED FEBRUARY 14, 2020

Prescribing information received on February 14, 2020:
\\CDSESUB1\evsprod\bla103979\0415\m1\us\annotatedpi.docx

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
02/25/2021 01:20:38 PM

IDALIA E RYCHLIK
02/25/2021 02:01:23 PM

Division of Cardiology and Nephrology
Consultation for the Division of Rare Diseases and Medical Genetics

From: Kirtida Mistry, Physician, Division of Cardiology and Nephrology (DCN)
Through: Aliza Thompson, Deputy Director, DCN
To: Nicolas Kong, Regulatory Project Manager, Division of Rare Diseases and Medical Genetics (DRDMG)

This memorandum serves to close out the consult for BLA 103979/S5309 (agalsidase beta, Fabrazyme®, for the treatment of Fabry disease) dated March 5, 2020.

Reason for consult:
Fabrazyme® (agalsidase beta) is a recombinant human α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Fabrazyme received accelerated approval for the treatment of Fabry disease in 2003 based on a reduction in globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. To verify the treatment benefit, the applicant completed a phase 4, randomized, double-blind, placebo-controlled trial (AGAL-008-00) in patients with Fabry disease with mild to moderate kidney disease who had not received prior enzyme replacement therapy. Participants could continue treatment in an extension study (AGAL02503). AGAL-008-00 failed to show a statistically significant improvement for the primary endpoint and the Agency indicated that additional data would be needed to verify the benefit.

On February 14, 2020, Sanofi-Genzyme submitted an efficacy supplement to fulfill a postmarketing commitment (PMC 2421-2) and obtain traditional approval of Fabrazyme. The efficacy supplement is primarily based on data from matched analyses of the Fabry Registry (NCT00196742) and Natural History Study (AGAL-014-01). DRDMG requested input from DCN on interpretation of the estimated glomerular filtration rate (eGFR) endpoint data.

DCN response:
Drs. Mistry and Thompson participated in discussions as needed.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIRTIDA MISTRY
02/08/2021 09:06:45 AM

ALIZA M THOMPSON
02/08/2021 09:56:23 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Real-World Evidence (RWE) Review (ADDENDUM)

Date:	January 21, 2021
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD MA Division of Epidemiology I
Associate Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Associate Director for RWE	Jie (Jenni) Li, PhD Office of Pharmacovigilance and Epidemiology
Drug Name:	Agalsidase beta (Fabrazyme®)
Subject:	Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01)
Application Type/Number:	BLA 103979 Efficacy Supplement-5309 (eCTD 0415)
Applicant/sponsor:	Sanofi Genzyme
OSE RCM #:	2020-438

The Division of Epidemiology I (DEPI) prepared this Addendum to explain the meaning of a term (*low-level evidence*) appearing in an earlier DEPI Real-World Evidence (RWE) Review for agalsidase beta (Fabrazyme®) BLA 103979 Efficacy Supplement-5309.[a]

Agalsidase beta is an intravenous enzyme replacement therapy (ERT) for Fabry disease, a heterogeneous X-linked lysosomal storage disorder caused by galactosidase alpha gene (*GLA*) mutation and resultant galactosidase alpha enzyme (αGAL) deficiency. BLA 103979 S-5309 presented, as supporting evidence for clinical effectiveness, a study report from *Fabry Registry / Natural History Matched Analysis*.

Matched Analysis used separate data sources to identify treated and untreated patients, (1) *Fabry Disease Registry* and (2) *Epidemiologic Study of Natural History of Fabry Disease*, respectively.

DEPI's review of Matched Analysis concluded that "results from analyses using a non-contemporaneous (historical) external comparison group provided *low-level evidence* [emphasis added] for possible treatment benefit from agalsidase beta" (p. 4). DEPI suggested a meaning for *low-level evidence* by stating that Matched Analysis used "a study design expected to produce (at best) *low-level evidence* [emphasis added] for treatment efficacy because of major inferential threats related to possible non-comparability of treated and untreated groups (despite matching on important determinants of outcome)" (p. 31). Here, DEPI explicitly and purposefully linked *low-level evidence* to matters intrinsic to study design.

The notion of a research design hierarchy might provide context for understanding DEPI's use of *low-level evidence*. The U.S. Preventive Services Task Force, for example, uses the following **Hierarchy of Research Design** to address "key questions of benefits and harms."[b]

I. Properly powered and conducted RCT; well-conducted systematic review or meta-analysis of homogeneous RCTs.

II-1. Well-designed controlled trial without randomization.

II-2. Well-designed cohort or case-control analysis study.

II-3. Multiple time-series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude.

III. Opinions of respected authorities, based on clinical experience; descriptive studies or case

---

[a] Weissfeld, JL, C Callahan, W Hua, and J Li, Epidemiology Real-World Evidence (RWE) Review, Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01) filed under BLA 103979 on October 30, 2020 (DARRTS Reference ID: 4694419).

[b] U.S. Preventive Services Task Force, Procedure Manual, December 2015, accessed https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/inline-files/procedure-manual-2020_3.pdf on December 22, 2020, p. 27.

reports; reports of expert committees.

Low-level evidence refers to DEPI's assessment of Matched Analysis as a Level II-3 study, one level inferior to a "well-designed cohort or case-control study" (Level II-2) and one level superior to simple "descriptive studies" (Level III). Specifically, DEPI assessed Matched Analysis as an enhanced descriptive study (in *Fabry Disease Registry*) with an external non-contemporaneous reference (*Epidemiologic Study of Natural History of Fabry Disease*). The latter study provides information FDA might use to address whether observations in *Fabry Disease Registry* yielded results of large magnitude. In this context, Matched Analysis resembles the Task Force's example for a Level II-3 study, *i.e.*, an uncontrolled study yielding results of large magnitude.

In an RWE Review Framework (prepared for the RWE Subcommittee to the Medical Policy and Program Review Council), DEPI again referred to Matched Analysis as a study "expected to produce (at best) *low-level evidence* for treatment efficacy.[c] Despite this finding of *low-level evidence*, the Framework (Section I.i) also concluded that "the completed RWE study provides *supplementary (supporting) evidence* [emphasis added] that aligns with results from AGAL-008-00, a completed Phase 4 placebo-controlled clinical trial of agalsidase beta in patients with Fabry disease."

Referring to low-level evidence as supplementary (supporting) evidence might appear paradoxical. The Framework (Section I.i) resolves this apparent paradox by explaining that "the completed RWE study *alone* [emphasis added] does not provide adequate scientific evidence to address the regulatory need." Here, the Framework understood the regulatory need as a requirement for substantial evidence demonstrating the effectiveness for agalsidase beta.[d] Matched analysis does provide confirmatory evidence as defined by the FDA Guidance (*i.e.*, Matched Analysis provides *part* of the substantial evidence of effectiveness to support a marketing application).[e]

On a second point requiring clarification, the Framework (Section 1.f) refers to "high patient attrition (primarily due to criteria for study inclusion)" as a secondary threat to the validity of Matched Analysis. DEPI clarifies that sample loss due to matching on patient characteristics does not necessarily threaten (internal) validity. For Matched Analysis, however, missing data contributed to the attrition in the number of study-eligible patients from *Fabry Disease Registry* and *Epidemiologic Study of Natural History of Fabry Disease*.

CC: Dal Pan G / Ball R / Blum M / Li J / Pinheiro S / Sandhu S / Hua W / Callahan C / Lerro

---

[c] See, Epidemiology Real-World Evidence (RWE) Review, APPENDIX 5, Section I f.

[d] Food and Drug Administration, Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, Guidance for Industry, December 2019, accessed at https://www fda.gov/media/133660/download on December 22, 2020.

[e] Ibid., pp. 10-11.

C / Booth B / Dunson A / Sun S / Calloway P (OSE)

Wang Y / Usher T (DB-IV)

Joffe H / Smpokou P / Zaidi A / Kong N (DRDM)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
01/21/2021 09:43:37 AM

CATHERINE L CALLAHAN
01/21/2021 09:54:31 AM

WEI HUA
01/21/2021 10:26:24 AM

JIE J LI
01/21/2021 10:40:06 AM

Date: 11-19-2020

To: Dr. Jie Wang, CDER/OTS/OCP/DTPM

From: Amy S. Rosenberg, MD, OBP, CDER

Re: Fabry Disease Literature Review: Considerations for PMCs/PMRs

While the literature review provided by the sponsor appeared to be detailed, the analysis, as it contributed to the conclusions, had key flaws including the following:

- the literature survey did not include some key papers
- they failed to focus on studies in which neutralizing antibodies (NABs) were evaluated in addition to more global anti-drug antibodies (ADA)
- they failed to consider the specificity and functional effects of NABS as they impact enzyme uptake and/or enzyme activity including studies in which uptake inhibition was recently demonstrated
- they did not analyze results according to the titers of ADA, neutralizing activity, and enzyme uptake inhibition.
- they failed to factor the immense heterogeneity of disease and of critical additional patient background factors in comparisons of the effects of ADA/NABS on clinical outcomes

State of the Research/Comments on Literature Review

There are no validated surrogate biomarkers with which to evaluate the impact of ADA (titers, isotypes, specificities) or NABs, despite the frequent measure of the unvalidated substrate endpoint GL3 or lyso-GB3. Importantly, Fabry is a highly heterogeneous and rare disease, with clinical endpoints often taking decades to develop. Thus, without substantial long term follow up, the effects of ADA and NABs may not be clear.

Analysis of Specific Studies Cited in the Literature Review

(*Mauhin et al, 2018 – Deep characterization of the anti-drug antibodies developed in Fabry disease patients, a prospective analysis from the French multicenter cohort FFABRY* (*Mauhin et al. Orphanet Journal of Rare Diseases (2018) 13:127 https://doi.org/10.1186/s13023-018-0877-4)* As regards this publication, in which no difference was found in clinical endpoints between ADA/NAB positive and negative patients, this was only a three year study, clearly not sufficiently long in view of the heterogeneity of the patient population and time to potentially reach clinical endpoints.

Despite the claim that ADA/NAB status did not affect clinical outcome, the following flaws in this conclusion have been noted, not only by this reviewer but by Lenders and Brand (Neutralizing anti-drug antibodies in Fabry disease have no obvious clinical impact? Malte Lenders, Boris Schmitz, Stefan-Martin Brand and Eva Brand. Lenders et al. Orphanet Journal of Rare Diseases (2018) 13:171: https://doi.org/10.1186/s13023-018-0916-1) who state: “In their cohort, Mauhin and colleagues found no differences between antibody-positive and antibody-negative in non-renal-transplanted patients. Of note, these data are difficult to interpret since the neutralizing impact of the antibodies was not considered, individual slopes were not calculated (only one time-point), and patients with severe renal impairment were excluded from the analysis. The latter point is of specific interest since antibody-positive compared to negative patients presented with a significantly higher frequency for dialysis and renal transplantation (6 [33.3%] vs 1 [3.7%]; p = 0.012)”. Thus, this publication lacks the critical evaluation needed to support the position of the lack of effect of ADA/NABs on clinical outcome.

In contrast, the Germain 2007 paper (*J Am Soc Nephrol* 18: 1547–1557, 2007. doi: 10.1681/ASN.2006080816), followed patients for 54

months and assessed substrate accumulation over time but did not stratify by ADA level. Given that substrate accumulation is not a validated endpoint, but more importantly, the very high drop out rate for patients undergoing cardiac and renal evaluation of substrate levels at month 54 vs month 6 (from 49 patients at month 6 to only 8 at 54 months for kidney capillary endothelial; from 40 patients at month 6 to 8 at month 54), and the failure to correlate ADA/NAB level with outcome on this evaluation, this study is of very limited value. The immense drop off in patient enrollment may reflect the loss of patients with relatively poor outcomes and persistence of a very small number with slower/more mild disease.

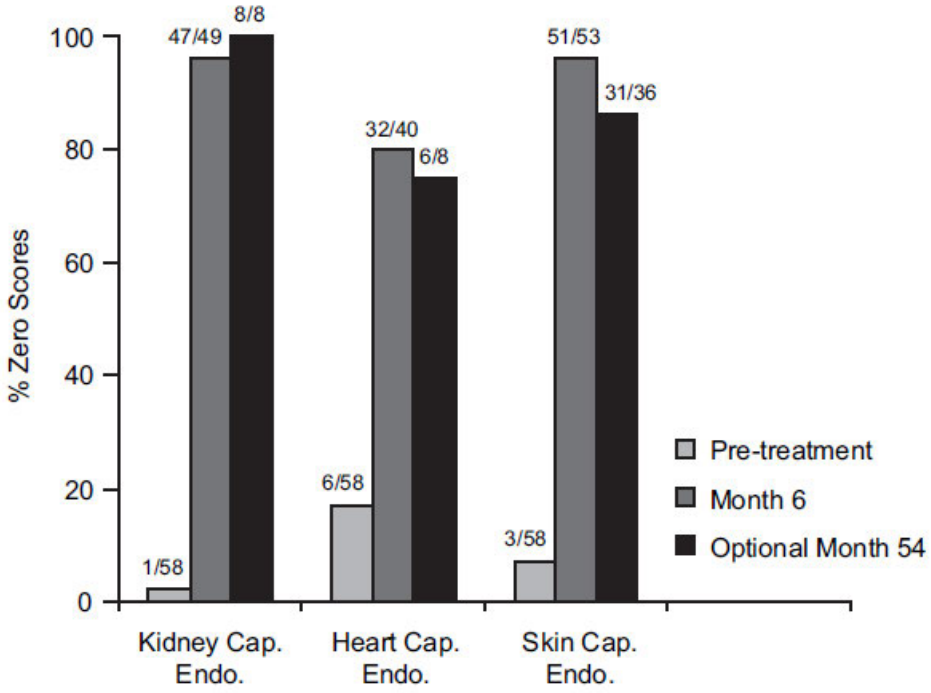


Figure 2. Globotriaosylceramide (GL-3) clearance from kidney, heart, and skin capillary endothelium in all patients. Histologic specimens that were obtained at pretreatment, month 6, and month 54 (optional for kidney and heart) were evaluated for the presence of GL-3. Results show that for the majority of patients, initial GL-3 clearance (score of 0) seen at month 6 was maintained during the 54-mo treatment period. Numbers above bar graphs represent the number of patients with zero scores out of the total number evaluated. cap. endo., capillary endothelium.

Eto Study of Japanese Fabry Patients (J. Inherit. Metab.Dis. 28 (2005) 575-583)

This study enrolled 13 patients and the total span of the study was only 20 weeks. "The renal efficacy end point was the proportion of patients with a zero score for GL-3 deposits at week 20 (11 infusions); of note, this is a non-validated surrogate endpoint. Additional tissue efficacy end points included microvascular endothelial deposits of GL-3 in the heart, skin and other kidney cell types. Although it was reported that 85% of patients seroconverted

with a mean seroconversion time of 63 days, that is the only information on ADA in this study: no report of titers, isotypes, or neutralizing activities. Thus, this study does not have data that are informative regarding the effects of ADA on clinical outcome.

Benichou et al, 2009 – A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease

This publication failed to assess neutralizing capacity of antibodies, patient heterogeneity factors that could strongly play into clinical outcomes such as those elucidated in the Lenders et al 2016 publication (review to follow) including the following: age, duration of ERT, prescription of angiotensin aldosterone system blockers, *nonsense mutations*, body weight, systolic and diastolic blood pressure.

Nonetheless this publication uncovered a strong correlation between ADA titer and accumulation of substrate in dermal capillaries, a potential surrogate endpoint for capillaries in critical tissues such as kidney: “A statistically significant association was found between anti-aGAL IgG titers and observation of some GL-3 deposition in the dermal capillary endothelial cells of skin during treatment, suggesting that GL-3 clearance may be partially impaired in some patients with high antibody titers.”

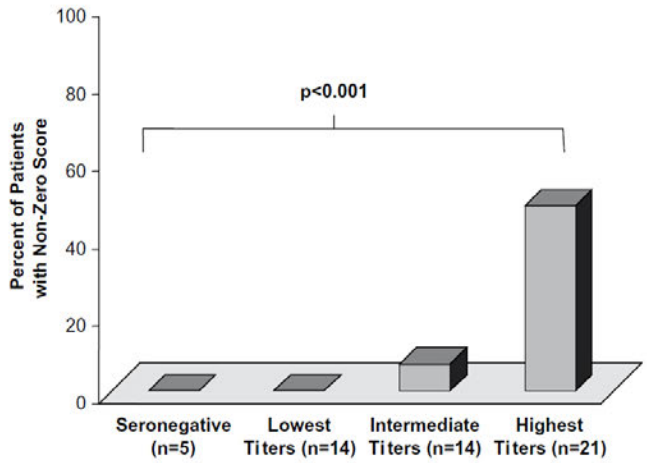


Fig. 4. Occurrence of non-zero scores for GL-3 accumulation in the dermal capillary endothelium during ERT in male patients stratified by peak titer of anti-αGAL IgG antibodies. A median of 6 (range, 1–7) skin biopsies were evaluated per patient during treatment in the Phase 3 studies. The proportion of patients with one or more non-zero scores during treatment was statistically different among the peak titer subgroups ($p < 0.001$).

Of the critical publications the authors fail to cite is that of Lenders et al. Serum-Mediated Inhibition of Enzyme Replacement Therapy in Fabry Disease (J Am Soc Nephrol 27: 256–264, 2016. doi: 10.1681/ASN.2014121226). This is the gold standard of reviews of the issue of ADA/NABs as they affect clinical outcome in Fabry Disease as it factors in patient heterogeneity and key background factors affecting outcome. The lit review authors discounted this publication because it did not delineate patients treated with agalsidase-alpha vs beta and thus the issue of dosage effect as alpha is administered at 0.2mg/kg vs beta at 1.0mg/kg. However, the basic principles remain unaltered and a follow up paper by Lenders et al (*Lenders et al, 2018 – Dose-dependent effect of enzyme replacement therapy on neutralizing antidrug antibody titers and clinical outcome in patients with Fabry disease)* does evaluate the effect of dosage in the context of ADA/NABs offering a potential approach to surmounting the inhibitor effects of ADA/NABs on treatment outcome.

In this non-reviewed but vital publication, in vitro serum-inhibition measurement was as defined as >50% ERT inhibition and provided new evidence for an association between ERT inhibition and more severe end-organ manifestations. Although their initial analysis failed to reveal a relationship between ADA/NAB status and clinical outcomes, when numerous background factors were factored into the analysis in a multivariate analysis there was a significant correlation uncovered between ADA/NAB and clinical outcome. According to the authors, “However, multivariate regression analysis with adjustment for age, duration of ERT in months, body weight, the prescription of RAAS blockers, nonsense mutations, and systolic and diastolic BP showed significantly increased LV mass in ADA/NAB positive (ERTi+) vs negative patients (P=0.02)”. Moreover, this analysis as extended to renal function also revealed a correlation: “Multivariate regression analysis with adjustment for age, duration of ERT, presence of nonsense mutations, and the prescription of diuretics and RAAS blockers confirmed that ERTi+ patients had severely decreased eGFR determined by creatinine-based Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula compared with ERTi– patients (P=0.04;see table below). The same model without correction for nonsense mutations revealed similar results”

Thus, in this highly heterogeneous disease, taking into account differences in key background factors uncovered a strong effect of

NABs on key clinical outcome measures.

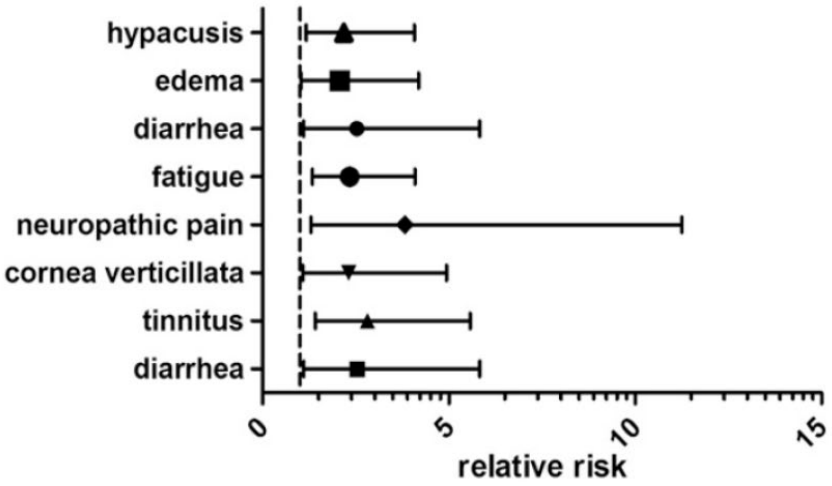
Measures	ERT^{i}– (n=23)	ERT^{i}+ (n=18)	*P* Value	Δ estimate
LV_{mass}/BSA, g/m^2	71.5 ± 8.1	105.8 ± 9.4	0.02	34.4 ± 13.8
RWT, cm	0.42 ± 0.05	0.57 ± 0.06	0.07	0.15 ± 0.08
eGFR, ml/min per 1.73 m^2	93.3 ± 8.9	64.1 ± 9.9	0.04	–29.3 ± 13.3

The mixed model approach for LV mass and RWT calculations was adjusted for age, duration of ERT, prescription of angiotensin aldosterone system blockers, *nonsense mutations*, body weight, systolic and diastolic blood pressure. Patients with renal transplantation and hyperfiltration were excluded from calculations.

Moreover, a 5-year retrospective analysis revealed sharp differences between ADA/NAB positive vs negative patients with ADA negative patients having no statistically significant change in key parameter (eg EGFR, MSSI, DS3), while ADA positive patients showed significant loss in these measures over this timeframe:

Measures	5-year retrospective	Inhibition status assessment	*P* Value	Change (95% CI)
ERT^{i}– *n*=12, age: 43.4617.9 yr				
eGFR, ml/min per 1.73 m^2	79.3 ± 33.8	72.6 ± 36.2	0.24	26.7 (–18.7 to 5.3)
Hyperfiltration, *n*	3 (25.0)	3 (25.0)	0.99	
NTX, *n*	0 (0.0)	0 (0.0)	0.99	
MSSI	12.8 ± 8.5	14.7 ± 8.5	0.21	1.8 (–1.2 to 4.9)
DS3	16.4 ± 9.2	17.1 ± 9.3	0.77	0.7 (–4.2 to 5.5)
ERT^{i}+ *n*=12, age: 41.369.5 yr				
eGFR, ml/min per 1.73 m^2	79.3 ± 35.9	66.0 ± 42.3	0.03	13.3 (– 24.7 to 1.8)
Hyperfiltration, *n*	2 (16.7)	3 (25.0)	0.99	
NTX, *n*	0 (0.0)	1 (8.3)	0.99	
MSSI	14.6 ± 9.5	19.0 ± 12.2	0.01	4.4 (1.3 to 7.6)
DS3	16.0 ± 7.7	22.2 ± 12.3	0.02	6.2 (1.0 to 11.3)

Finally, key quality of life indices were also found to be strongly affected by the presence of NABS. These should not be minimized, as those noted can severely impact quality of life. Nor should the incidence of and prophylaxis for IARs, which are higher in ADA positive patients be minimized as these responses necessitate debilitating treatment with potent anti-histamines and steroids every two weeks prior to treatment.



Forest plot of increased risks of ERTi+ (ADA+) compared with (ADAneg/ERTi–) men with FD.

Risk Mitigation

Given the clear evidence of the diminution of clinical effect by ADA/NABs to agalsidase, mitigation strategies become critical. Initially, these should be targeted to patients at highest risk of developing high titer neutralizing antibodies as are patients with nonsense and other knock out mutations (essentially CRIM negative).

As such, there are two mitigation strategies to consider:

1) Dosing over ADA responses

2) Immune Tolerance Induction

As regards the first strategy, this is extensively covered by a most well investigated approach, the publication of which was included in the literature review provided by the sponsor:

Lenders et al, 2018 – Dose-dependent effect of enzyme replacement therapy on neutralizing antidrug antibody titers and clinical outcome in patients with Fabry disease (J Am Soc Nephrol 29: 2879–2889, 2018. https://doi.org/10.1681/ASN.2018070740)

In this approach, the authors evaluated patient sera 30 minutes following administration of their routine dose of agalsidase (11 with agalsidase-alpha, 15 with agalsidase-beta) to detect whether the amount of infused enzyme saturated neutralizing ADA titers, hypothesizing that patients whose ADA are saturated and who thus have excess free agalsidase after infusion (capable therefore of binding to target endothelial cells the principal source of disease pathology), as compared to those whose ADA are not saturated (ie those who have antibody excess sopping up all of the agalsidase and leaving none unbound to bind to target endothelial sites, benefit from a better clinical outcome. They found patients who indeed had ADA excess (red) and thus predicted not to have free agalsidase (red) and those whose ADA were saturated and predicted to have free agalsidase following ADA saturation (green):

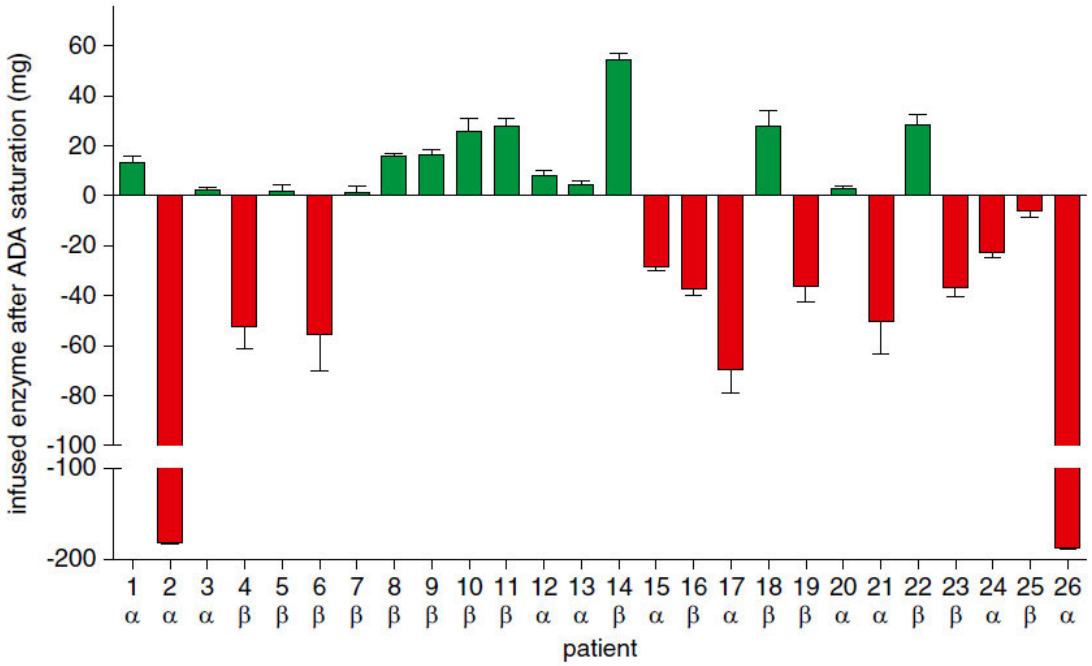


Fig legend: Antibody titer determination allows a classification in saturated and not saturated patients during infusion. Positive values represent residual infused enzyme after ADA saturation (green, agalsidase excess). Negative values represent additional theoretical infused enzyme necessary to saturate ADA titers (red, antibody excess).

Though at baseline both groups presented with comparable eGFR and lyso-Gb3 levels, the ADA saturated group of patients (n=14, 53.8%) presented with a loss of eGFR of -3.06 +/- 2.0ml/min per1.73m2 per year (P<0.001), a stable interventricular septum thickness, and a significant decrease of plasma lyso-Gb3 levels (-24.9 +/-35.0 ng/ml per year, P<0.001) over time (Figure 3). By contrast, not saturated patients (n=12, 46.2%) presented with a steeper decline of eGFR (-4.86 +/-4.0 ml/min per 1.73 m2 per year, P=0.004), a significant increase in interventricular septum thickness (these patients had increased interventricular septal thickness at baseline compared to saturated patients) compared to saturated and a trend for decreasing plasma lyso-Gb3 values (-7.9+/-18.8 ng/ml per year, P=0.32) over time (see figure below), indicating that ADA saturation and thus free agalsidase status during infusion might be beneficial in terms of clinical outcome and less severe disease progression of affected patients which they further explored by dose increases in patients whose ADA had not been

saturated.

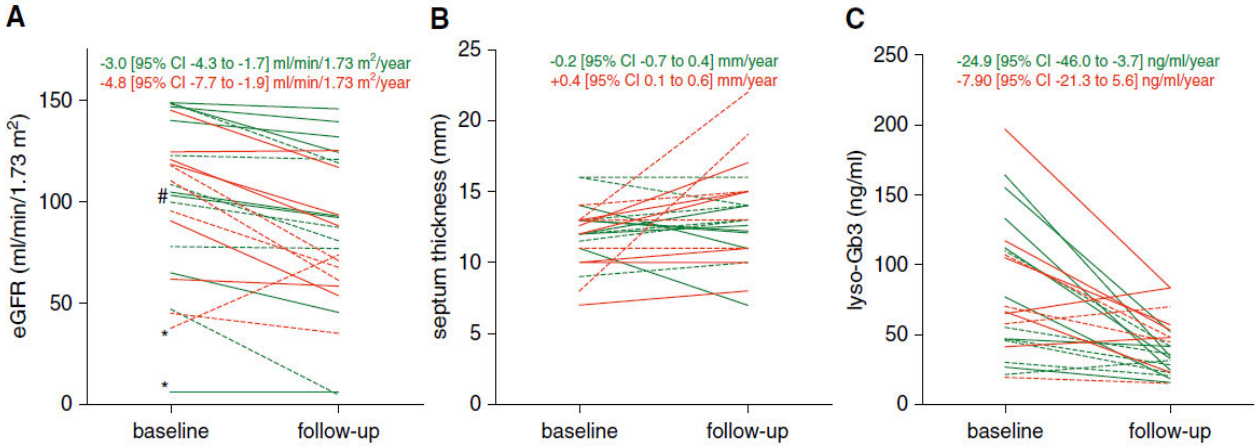
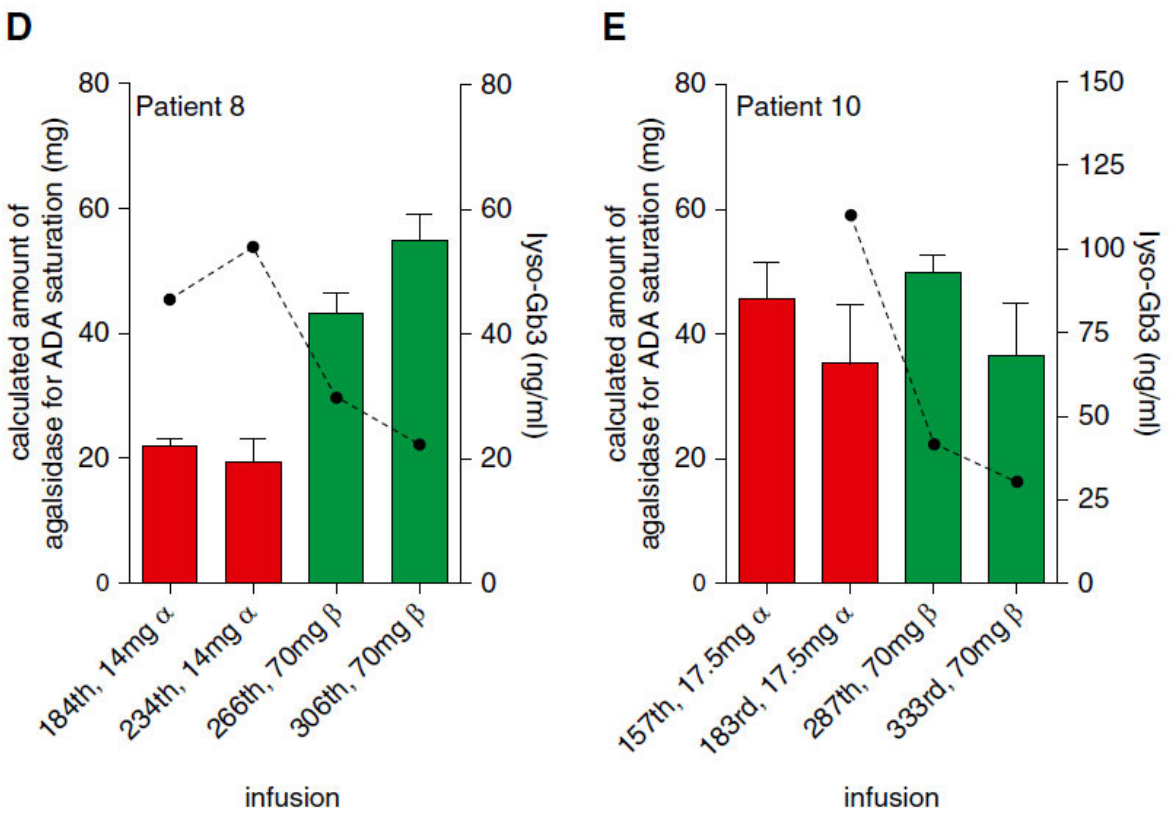


Figure 3. Antibody saturation due to enzyme excess is associated with better outcomes over time. (A) Change in eGFR. (B) Change of interventricular septum thickness. (C) Change of plasma lyso-Gb3 levels. Green lines: saturated patients with agalsidase excess during infusion. Red lines: not saturated patients with antibody excess (agalsidase deficit) during infusion. Solid lines represent ERT-naïve patients at baseline. * indicates patients excluded for eGFR calculations because of renal transplantation or dialysis. # indicates a patient excluded from eGFR calculation because of newly adjusted renin-angiotensin-aldosterone system blockers. 95% CI, 95% confidence interval.

They found that increases in dose often surmounted ADA saturation, but that in some patients this was accompanied by an increase in ADA titers. Best case scenario is illustrated below in patients D and E in which dose increases increased ADA but not to a level in which ADA remained unsaturated (D), or failed to increase ADA level, thus preserving ADA saturation (E).



(D) Long-term effect of dose increase due to product switch (260th infusion) resulted in increased ADA titers, but titers could be saturated. (E) Long-term effect of dose increase (185th infusion) resulted in stable ADA titers, which could be saturated. Green bars indicate saturation (agalsidase excess), red bars indicate no saturation (antibody excess) during infusion. Dotted lines represent plasma lyso-Gb3 levels.

Though this approach may be a reasonable way to enhance efficacy in the face of ADA, there are caveats to this approach principally stemming from an increase in ADA titers leading to increased risk of serious outcomes pertaining to the following:

- facilitate epitope spread, induce different or more robust neutralizing activity
- Immune complex mediated disease
- More severe infusion type reactions

In fact, immune complex mediated disease has been observed in attempts to tolerize immune responses to therapeutic proteins by delivering higher doses of ERT or coagulation factor in the setting of

robust antibody responses to Pompe Disease (Nephrotic syndrome complicating aglucosidase replacement therapy for Pompe disease. Hunley T et al Pediatrics 2004;114:e532–e535) and to Factor IX replacement therapy (Membranous glomerulonephritis and nephrosis post factor IX infusions in hemophilia B. Dharnidharka VR et al Pediatr Nephrol (1998) 12:654–657).

Potential PMC/PMRs

The first mitigation option would be to employ the ADA saturation evaluation for each patient per above. To implement this approach as a PMR/PMC, the sponsor would need to commit to evaluating each ADA/NAB positive patient for antibody saturation (per the above analysis) while receiving their respective product to establish a safe and effective dose in the face of ADA. It would also require intensive monitoring for ADA titer, neutralization activity, epitope specificity and more intensive renal function monitoring to ensure immune complex glomerulonephritis does not occur and worsen renal outcomes. The most relevant patient population would be classical males with nonsense or other obliterating mutations.

The second option is immune tolerance induction. This has been accomplished safely for CRIM negative patients with Pompe Disease, a devastating muscle wasting disease which encompasses a much more fragile population than that of the Fabry patients of interest here. For Pompe, infants are treated with a limited course of rituximab, methotrexate and IVIG with induction of tolerance with the first treatment course in the vast majority of patients (Sustained immune tolerance induction in enzyme replacement therapy-treated CRIM-negative patients with infantile Pompe disease. Kishnani PS et al JCI Insight 2017. 2(16):e94328. doi: 10.1172/jci.insight.94328) Clinicaltrials.gov NCT01665326.

Given the older age of onset and the lesser fragility of Fabry patients at diagnosis and the fact that most patients will have already been vaccinated and thus protected from many extrinsic infections, there are diminished concerns regarding the transient immune suppression. Moreover, even treatment with a limited course of low dose methotrexate diminished immune responses to ERT in Pompe patients and could be of consideration. Both of these approaches to tolerance

should be a strong consideration. Alternative antigen specific or antigen target tolerance treatments could be evaluated by the sponsor for fitness in this setting.

This approach may offer patients benefits above and beyond overdosing as it would avoid immune complex generation and boosting of NAB/ADA responses. Thus, for tolerized patients the only factors limiting efficacy would be the therapeutic's access to and ability to enter critical target endothelial cells as the product was not designed specifically to target endothelial cell and its potency in reducing substrate.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLAS KONG
11/23/2020 09:23:38 AM

AMY S ROSENBERG
11/23/2020 04:59:06 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Literature Review

Date:	October 30, 2020
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD MA Division of Epidemiology I
Associate Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Associate Director for RWE	Jie (Jenni) Li, PhD Office of Pharmacovigilance and Epidemiology
Drug Name:	agalsidase beta (Fabrazyme®)
Subject:	Systematic Literature Review of Fabrazyme for the Treatment of Fabry Disease
Application Type/Number:	BLA 103979 Efficacy Supplement-5309 (eCTD 0415)
Applicant/sponsor:	Sanofi Genzyme
OSE RCM #:	2020-438

TABLE OF CONTENTS

EXECUTIVE SUMMARY

To assist decision-making in the Division of Rare Disease and Medical Genetics (DRDMG), the Division of Epidemiology I (DEPI) assessed methods and procedures used by a Sponsor to identify literature that might support an efficacy supplement for agalsidase beta (Fabrazyme®).

The efficacy supplement (BLA 103979 S-5309) concerns agalsidase beta, an intravenous enzyme replacement therapy for Fabry disease, a heterogeneous X-linked lysosomal storage disorder. Fabry disease classically presents with symptoms in childhood, proteinuria in early adulthood, and premature death from renal failure, heart failure, cardiac arrhythmia, or stroke.

BLA 103979 obtained accelerated FDA-approval in April 2003. Now, BLA 103979 S-5309 presents a "totality of evidence" as possible grounds for traditional approval (full approval). As supporting evidence, BLA 103979 S-5309 includes a Technical Report from a *Systematic Literature Review of Fabrazyme for the Treatment of Fabry Disease*.

The Technical Report presented 71 literature reports (articles) with evidence from 56 studies of outcomes in Fabry disease patients treated with agalsidase beta. To identify literature that might support real-world evidence presented elsewhere in BLA 103979 S-5309, DEPI assessed six clinical trials (including three single-arm trials) and 14 observational studies with findings recorded by the Technical Report in a renal outcome category, the primary efficacy endpoint for *Fabry Registry/Natural History Matched Analysis* (DIREGC07006/AGAL-014-01).

DEPI determined that the Sponsor used acceptably rigorous, systematic, and transparent methods to prepare the Technical Report. DEPI validated the integrity of the Technical Report by completing an independent literature search and checking data presented by the Technical Report in the renal outcome category. However, DEPI found scant evidence for beneficial effects from agalsidase beta on outcomes in a renal outcome category. (b) (4)

DEPI recommends that DRDMG accept the Technical Report as a complete representation of evidence currently available in medical literature about the effectiveness of treatment with agalsidase beta in patients with Fabry's disease.

1 INTRODUCTION

1.1 Background

To assist decision-making in the Division of Rare Disease and Medical Genetics (DRDMG), the Division of Epidemiology I (DEPI) assessed methods and procedures used by a Sponsor to identify literature that might support an efficacy supplement for agalsidase beta (Fabrazyme®).

The efficacy supplement (BLA 103979 S-5309) concerns agalsidase beta, an intravenous enzyme replacement therapy (ERT) for Fabry disease, a heterogeneous X-linked lysosomal storage

disorder caused by galactosidase alpha (*GLA*) mutation. Fabry disease classically presents with symptoms in childhood, proteinuria in early adulthood, and premature death from renal failure, heart failure, cardiac arrhythmia, or stroke.

BLA 103979 received accelerated approval in April 2003 because of double-blind placebo-controlled randomized clinical trials demonstrating an effect of agalsidase beta on "globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types."[1] Now, BLA 103979 S-5309 presents a "totality of evidence" as possible grounds for traditional approval, with principal sources of evidence including,

- AGAL-1-002-98, a Phase 3 placebo-controlled clinical trial with surrogate endpoint.
- AGAL-008-00, a Phase 4 placebo-controlled clinical trial with clinical endpoints.
- DIREGC07006/AGAL-014-01, a matched analysis using real-world data from the *Fabry Disease Registry* (DIREGC07006) and an *Epidemiologic Study of the Natural History of Fabry Disease* (AGAL-014-01).[2]

To support these three principal sources of evidence, BLA 103979 S-5309 includes a Technical Report from a *Systematic Literature Review of Fabrazyme for the Treatment of Fabry Disease*.

1.2 Regulatory History

Three pre-application meetings between DRDMG and the Sponsor (Sanofi) touched on literature as a source of evidence that might support traditional approval for agalsidase beta.

- On November 29, 2017, DRDMG and Sanofi discussed a systemic review of 50 articles published before October 2016.[3] Without information about "the natural history of the disease in a similar/suitably matched population," DRDMG found "it difficult to draw conclusions about Fabrazyme's effectiveness from the cited observational and registry studies."[4]
- On January 18, 2019, DRDMG advised that "a comprehensive review of rigorously performed studies/trials from the published literature" might significantly enhance an

---

[1] Prescribing Information, FABRAZYME (agalsidase beta) for injection, revised12/2018, accessed at Drugs@FDA on July 9, 2020.

[2] For DEPI's review of DIREGC07006/AGAL-014-01, see, Weissfeld JL, C Callahan, W Hua, Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01), filed under BLA 103979 on <PENDING> (DARRTS Reference ID: <PENDING>).

[3] Excerpta Medica, Fabrazyme Efficacy Systematic Literature Review – Clinical Events, GFR, and Cardiac Outcomes, submitted as appendix2.pdf to BLA 103979 (eCTD 0358) on October 25, 2017.

[4] Meeting Minutes, filed under BLA 103979 on December 12, 2017 (DARRTS Reference ID: 4193821).

application for traditional approval.[5]

- On May 21, 2019, DRDMG suggested that Sanofi might specify methods and procedures for identifying, selecting, characterizing, summarizing, and discussing evidence from literature by providing DRDMG with a protocol for a Systemic Literature Review.[6] Sanofi responded by agreeing to submit a Systematic Literature Review of Fabrazyme treatment efficacy and immunogenicity. Sanofi agreed to format this review "in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)."

2 REVIEW METHODS AND MATERIALS

DEPI assessed, a Technical Report from a *Systematic Literature Review of Fabrazyme for the Treatment of Fabry Disease* (October 29, 2019, Version Final), submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

To guide its assessment, DEPI used the 2009 Checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (accessed at http://www.prisma-statement.org/ on July 1, 2020).

Seeking literature support for DIREGC07006/AGAL-014-01 (matched analysis with eGFR change as primary efficacy endpoint), DEPI restricted in-depth analysis of the Technical Report to evidence presented in the renal outcome category.

3 REVIEW RESULTS

3.1 Objective

Sanofi submitted a Technical Report from a Systematic Literature Review (SLR) "to support the supplemental BLA (sBLA) submission to the FDA for full approval."[7] See **APPENDIX 1** for page references in the Technical Report to PRISMA Checklist items.

3.2 SLR Methods

3.2.1 Study eligibility

The SLR sought full-length English-language study reports (articles) published in 2000 or later. The SLR covered studies that used any research design to assess outcomes in Fabry disease patients (any age) treated with agalsidase beta (with or without comparator). The SLR divided

[5] Meeting Request – Written Responses, filed under BLA 103979 on January 18, 2019 (DARRTS Reference ID: 4378266).

[6] Meeting Minutes, filed under BLA 103979 on June 3, 2019 (DARRTS Reference ID: 4442233).

[7] Technical Report, p. 14.

evidence into 11 outcome categories (with references to SLR tables of evidence):

1. Renal outcomes (SLR Tables 6-10) – serum creatinine, kidney function (glomerular filtration rate, GFR), proteinuria, and renal events (*e.g.*, dialysis or kidney transplantation).

2. Myocardial morphology or mass (SLR Tables 11-12) – left ventricular mass or wall thickness.

3. Cardiac outcomes (SLR Tables 13-16) – cardiac events (*e.g.*, arrhythmia, infarction, or angina).

4. Cerebrovascular outcomes (SLR Table 17-19) – white matter lesions on magnetic resonance imaging (MRI) and cerebrovascular events (*e.g.*, stroke or transient ischemic attack).

5. Composite outcomes (SLR Table 20) – any endpoint combining outcomes from two or more categories.

6. Mortality (SLR Table 21) – death due to any cause and death from clinical events related to Fabry disease.

7. Clinical outcome assessments (SLR Tables 22-24) – pain, quality of life, Fabry disease severity, and gastrointestinal symptoms.

8. Biomarkers (SLR Table 25-30) – plasma globotriaosylceramide (GL-3), lyso-GL-3, urine GL-3, and podocyte GL-3.

9. Immunogenicity (SLR Table 31) – anti-drug and neutralizing antibodies.

10. Infusion-associated reactions (SLR Tables 32-33).

11. Hypersensitivity and allergic reactions (SLR Table 34-35).

3.2.2 Literature search

The SLR used terms connected to Fabry disease, ERT, and immunogenicity to search EMBASE, MEDLINE, and the Cochrane Central Registry of Controlled Trials.[8] With help provided by a third individual when needed to resolve disagreement, two individuals, working independently, screened citation abstracts and assessed full-text articles for eligibility.

The SLR screened abstracts for 1,263 unique citations and assessed full-text for 192 articles. The SLR subsequently excluded 129 articles to leave 63 eligible articles.[9] The SLR augmented

[8] EMBASE and MEDLINE searched on May 29, 2019.

[9] See Technical Report (Appendix C) for references to excluded articles by reason excluded.

these 63 articles with eight additional articles identified through other means.[10]

3.2.3 Data extraction

With help provided by a third individual when needed to resolve disagreement, two individuals, working independently, extracted the following items of information from 71 eligible articles [1-71]:

- Study characteristics – study name, year, authors, design, phase, blinding, study location, inclusion criteria, exclusion criteria, follow-up period, sample size, outcome definitions, subgroup availability, and study quality assessment.[11]

- Baseline patient characteristics – sample size, age, sex, race and ethnicity, proportion treatment naïve, Fabry disease phenotype, and baseline renal function (renal event history, proteinuria, GFR, and chronic kidney disease stage).

- Intervention characteristics – treatment regimen, treatment dose, method of administration, frequency of administration, duration of treatment, and prior therapies.

- Effectiveness outcomes – cardiac events, cardiac morphology, cardiac mass, cerebrovascular events, renal events, kidney function, mortality, gastrointestinal symptoms, disease severity, quality of life, pain, and biomarkers (GL-3 or lyso-GL-3 in blood, urine, or tissue).

- Immunogenicity outcomes – anti-drug antibodies, neutralizing antibodies, IgG antibodies, serum-mediated inhibition, infusion-associated reactions, hypersensitivity reactions, allergic reactions, and anaphylaxis.

3.2.4 Presentation of results

The 71 eligible articles referenced 56 studies. Presentations of information from these 56 studies included:

- Tabular summarizes of study design, baseline patient characteristics, and Fabry disease treatments (Technical Report, Tables 3-5).

- Narrative summaries of key studies (Technical Report, Section 4.5).

- Bulleted, narrative, and tabular summaries of agalsidase beta treatment effectiveness (Technical Report, Sections 4.6).

---

[10] Hand search of references lists for key articles or supplemental database search recommended by FDA.

[11] Randomized clinical trials assessed for quality by Cochran Risk-of-Bias Tool and non-randomized studies assessed for quality by Newcastle-Ottawa scale.

- Bulleted, narrative, and tabular summaries of immune-related reactions to agalsidase beta (Technical Report, Sections 4.7).

3.2.5 Synthesis

The SLR assessed evidence using non-quantitative methods (b) (4) [redacted]

3.3 DEPI Analysis

3.3.1 Literature search

To assess the procedure used to identify articles for the Technical Report, DEPI used terms connected to Fabry disease and ERT to identify 1,343 PubMed references (as of July 2, 2020) to articles published in 2000 or later.[13] DEPI's search captured (1) 71 of 71 articles covered by SLR [1-71], (2) two SLR-referenced articles available in database sources after the SLR search date [72, 73], and (3) 43 of 48 full-text articles excluded from SLR for cause [74-116].

On top of these 116 articles (including 34 published in 2016 or later), DEPI's updated search identified 307 references to English-language articles published in 2016 or later (**APPENDIX 2**).[14] DEPI screened the titles and abstracts for these 307 additional references to select 17 articles for examination of full text. To complement the Technical Report, this full-text examination identified three articles (summarized below) with information about agalsidase beta and an outcome of interest [117-119].

- **Trimarchi 2019** [117] assessed podocyturia and urinary CD80 in N=45 Fabry disease patients, including N=22 on agalsidase beta 1 mg/kg for at least 12 months. In analyses unadjusted for age or sex, **Trimarchi 2019** observed lower eGFR (120 *vs.* 141 ml/min/1.73 m^2) and higher urinary protein to creatinine ratio (0.11 *vs.* 0.06 g/g) in patients on ERT as agalsidase beta *vs.* patients not on ERT.

- **Lenders 2020** [118] observed N=78 patients with follow-up available after receiving agalsidase beta 1 mg/kg for at least 12 months.[15] During follow-up, 17 patients continued on agalsidase beta, 22 patients switched to agalsidase alfa, and 39 patients switched to

---

[12] Technical Report, Executive Summary, page 12.

[13] PubMed Query: (Fabry) AND (((ERT OR "enzyme replacement") OR (agalsidase)) OR ("alpha-galactosidase/therapeutic use"[MeSH Terms]))

[14] Range (published in 2016 or later) chosen to extend the systematic literature review submitted to BLA 103979 (eCTD 0358) on October 25, 2017. This earlier review covered literature published up to September 28, 2016. See FOOTNOTE 3.

[15] A recently published article containing results that overlap with an article covered by the Technical Report. See **Kramer 2018** [67].

agalsidase alfa before switching back to agalsidase beta. Table 1 summarizes a kidney function outcome in a subset that excluded patients with kidney transplant or on dialysis at beginning of follow-up.

Table 1: Rate of change in estimated glomerular filtration rate (eGFR, mean±95% confidence-interval half-width, mL/min/1.73 m^2/y), by treatment period and sex.

	Men		Women	
Treatment period	N	eGFR change	N	eGFR change
agalsidase beta	8	-2.9 ± 1.6	3	1.6 ± 4.2
agalsidase alfa	12	-2.9 ± 2.7	5	0.8 ± 4.5
agalsidase alfa before switchback	16	-1.3 ± 5.8	15	-0.1 ± 3.2

SOURCE: **Lenders 2020** [118], Table 1.

- **Wanner 2020** [119] identified adult women in the Fabry Disease Registry with cardiac morphology or kidney function assessed at least twice (≥2 years apart) both before and after initiating agalsidase beta at the recommended dose. Table 2 summarizes results from piecewise linear mixed models adjusted for baseline age.

Table 2: Age-adjusted rates of change for three outcomes in adult women before and after initiating treatment with agalsidase beta (Fabry Disease Registry).

			Observation Period		Difference	
Outcome	Units of Measurement	N	Before	After	Estimate	95% CI
LVPWT	mm/year	38	0.29	-0.13	-0.42	-0.69, -0.15
IVST	mm/year	38	0.33	0.02	-0.31	-0.66, 0.04
eGFR	mL/min/1.73 m^2/year	86	-0.83	-0.96	-0.13	-1.15, 0.89

SOURCE: **Wanner 2020** [119], Table S1.
ABBREVIATIONS: CI – confidence interval; LVPWT – left ventricular posterior wall thickness; IVST – interventricular septal thickness; eGFR – estimated glomerular filtration rate.

3.3.2 Data presentation

SLR identified 71 literature reports (articles) from 56 studies of agalsidase beta, including 12 clinical studies (19 articles [1-3, 8, 9, 11, 16-18, 20, 22, 26, 27, 29, 34, 48, 55, 57, 61]), 38 observational studies (46 articles [4, 5, 12-15, 19, 23-25, 28, 30-33, 35-47, 49-54, 58-60, 62-64, 66-71]), and 6 case series (6 articles [6, 7, 10, 21, 56, 65]). To summarize these articles, the Technical Report organized findings in 11 outcome categories (Table 3).

Table 3: Number of studies reporting results from treatment with agalsidase beta, by outcome category and study design.

Outcome Category	**Clinical Study**	**Observa-tional Study**	**Case Series**
Overall	12	38	6
Renal outcomes	6	14	4
Myocardial morphology or mass	6	20	2
Cardiac outcomes	6	5	1

Outcome Category	Clinical Study	Observa-tional Study	Case Series
Cerebrovascular outcomes	4	9	0
Composite outcomes	3	5	0
Mortality	3	3	1
Clinical outcome assessments	5	18	3
Biomarkers	9	10	3
Immunogenicity	8	11	2
Infusion-associated reactions	7	10	2
Hypersensitivity and allergic reactions	3	3	1

SOURCE: Technical Report, Table D3.

BLA 103979 S-5309 presents real-world evidence from DIREGC07006/AGAL-014-01, a matched analysis with eGFR change as primary efficacy endpoint.[16] To identify literature that might support the primary efficacy endpoint from matched analysis, DEPI assessed the 6 clinical and 14 observational studies with findings recorded by the Technical Report in the renal outcome category.

The Technical Report presented renal outcomes from six clinical studies (trials).

1. The **International Collaborative Fabry Study Group** published placebo-controlled results from Sanofi's Phase 3 trial with surrogate endpoint (AGAL-1-002-98) [2] and uncontrolled long-term results from Sanofi's subsequent open-label extension (AGAL-005-99) [9, 18, 55].

2. The **Fabry Disease Clinical Trial Study Group** published placebo-controlled results from Sanofi's Phase 3 trial with clinical endpoints (AGAL-008-00) [17].

3. **Lubanda 2009** [29] published results from Sanofi's single-arm trial of agalsidase beta 1.0 mg/kg for 6 months followed by 0.3 mg/kg for 18 months (AGAL-017-01).

4. **Wraith 2008** [26] published results from Sanofi's 48-week single-arm pediatric trial of agalsidase beta (AGAL-016-01).

5. **Tahir 2007** [20] published results from a 30-month single-arm trial of agalsidase beta 1.0 mg/kg in N=11 patients maintained on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

6. **Vedder 2007** [22] randomized N=34 adult patients to same-dose (0.2 mg/kg) agalsidase alfa or agalsidase beta for up to 24 months. Table 4 summarizes change in GFR by treatment group.

Table 4: Change in glomerular filtration rate (GFR; by iothalamate/hippuran or iohexol infusion) after 1

[16] Weissfeld, *op. cit.*

and 2 years of treatment with same-dose (0.2 mg/kg) agalsidase beta or agalsidase alfa.

		Results at 1 year					Results at 2 years				
			GFR ↓					GFR ↓			
Treatment group	N	N_0	n	%	RR	95% CI	N_0	n	%	RR	95% CI
agalsidase alfa	18	16	6	37.5	REF		11	4	36.4	REF	
agalsidase beta	16	13	5	38.5	1.03	0.40-2.61	10	7	70.0	1.92	0.80-4.64

SOURCE: Analysis by DEPI using raw data in **Vedder 2007** [22], Table 2.
ABBREVIATIONS: GFR ↓ – follow-up GFR < baseline GFR; RR – relative risk; CI – confidence interval; N – number randomized patients included in overall analysis; N_0 – number of patients with GFR measured at both baseline and the indicated follow-up timepoint (1 or 2 years); n – number of patients with follow-up GFR < baseline GFR.

The Technical Report presented renal outcomes from 14 observational studies.

1. In Korea, **Choi 2008** [23] followed N=11 patients (age 13-48 years) treated with agalsidase beta 1 mg/kg for 4-27 months.

2. At two centers in Germany, **Vedder 2008** [25] stratified data by antibody status to report GFR change after 12 months of treatment with (1) agalsidase beta 1 mg/kg (N=18) or (2) agalsidase alfa or beta 0.2 mg/kg (N=30).

3. In Italy, **Imbriaco 2009** [28] assessed 11 adults before and after 29-58 months of treatment with agalsidase beta (1 mg/kg). Pre-treatment proteinuria "had resolved in five out of eight patients."

4. In Japan, **Tsuboi 2012 & 2014** [40, 53] assessed N=11 adults before and after switch from agalsidase beta (1 mg/kg) to agalsidase alfa.

5. Using the Fabry Disease Registry, **Warnock 2012** [41] identified proteinuria as an important factor associated with more rapid eGFR decline in N=151 men (mean age 38.7 years) and N=62 women (mean age 43.0 years) maintained on agalsidase beta ≈1 mg/kg for ≥2 years.

6. In Italy, **Pisani 2013** [45] assessed N=10 adults before ERT (mean eGFR 92.4 mL/min/1.73 m^2), after ≥48 months on agalsidase beta 1 mg/kg (mean eGFR 91.3 mL/min/1.73 m^2), and ≥20 months after subsequent switch to agalsidase alfa (mean eGFR 90.3 mL/min/1.73 m^2).

7. In Taiwan, **Lin 2014** [50] tracked eGFR in N=8 male patients (age 14-65 years) before and after switch from agalsidase beta (1 mg/kg) to agalsidase alfa.

8. In Argentina, **Politei 2014** [49] tracked eGFR in N=6 patients (67% male, age 17-50 years) during 10 years of treatment with agalsidase beta (1 mg/kg).

9. **Weidemann 2013** [47] followed N=40 adult patients (mean age 40 years; 78% male; median 6.0-year follow-up in survivors) treated with agalsidase beta (1 mg/kg) at a single center in Germany. Kidney function (GFR by ^{99}Tc-DTPA) declined in men (mean -2.4 mL/min/y) and women (mean -1.9 mL/min/y) despite treatment with agalsidase beta. Four proteinuric

patients (baseline GFR 22-81 mL/min) progressed to end-stage renal disease. For comparison, **Weidemann 2013** used the Fabry Disease Registry to identify adults "not treated with ERT because of problems with reimbursement in their countries of residence." **Weidemann 2013** matched treated and untreated patients on year of birth, sex, chronic kidney disease stage, and history of transient ischemic attack. A composite outcome (defined as progression to dialysis, stroke, or death) occurred in 13 treated and 21 and untreated patients. Using this composite outcome, a Cox regression estimated treatment benefit from agalsidase beta, hazard ratio (HR) 0.68, 95% confidence interval (CI) 0.33-1.39, p-value = 0.284.

10. Using the Fabry Disease Registry, **Hopkins 2016** [58] followed N=969 men (mean age 35.0 years, median 4.3-year follow-up on treatment) and N=442 women (mean age 44.0 years, median 3.2-year follow-up on treatment) starting agalsidase beta at ≈1 mg/kg. **Hopkins 2016** recorded 65 and 11 renal events (dialysis or kidney transplantation) during treatment in men and women, respectively.

11. In Korea, **Kim 2016** [59] tracked eGFR in N=19 patients during long-term treatment (≥5 years) with agalsidase beta.

12. **Ripeau 2017** [64] tracked eGFR for 24 months in N=33 patients (age 10-51 years) in Argentina or Venezuela after switch from agalsidase beta (1 mg/kg) to agalsidase alfa (0.2 mg/kg).

13. Combining data from three centers in Germany (Berlin, Munster, and Wurzburg), **Kramer 2018** [67] observed N=112 patients (62% male, mean age 45 years) with follow-up available after receiving agalsidase beta 1 mg/kg for at least 12 months. During follow-up, 37 patients continued on agalsidase beta, 38 patients switched to agalsidase alfa, and 37 patients switched to agalsidase alfa before switching back to agalsidase beta. Table 5 summarizes a kidney function outcome in a subset that excluded patients with kidney transplant or on dialysis at beginning of follow-up. According to statistical tests (one-way analysis of variance; p-value < 0.05), kidney function declined less rapidly during periods of treatment with agalsidase beta as compared to periods of treatment with agalsidase alfa.

Table 5: Rate of change in estimated glomerular filtration rate calculated by Chronic Kidney Disease-Epidemiology Collaboration equation (CKD-EPI eGFR, mean ± standard deviation, mL/min/1.73 m^2/y), by treatment period (≥12 months).

		CKD-EPI eGFR
Treatment	N	mean ± SD
Period 1		
agalsidase beta	25	5.0 ± 14.2
agalsidase alfa	28	-7.2 ± 9.3
agalsidase alfa before switchback	32	-5.6 ± 7.7
Period 2		

Treatment	N	CKD-EPI eGFR mean ± SD
agalsidase beta	25	-3.2 ± 11.2
agalsidase alfa	28	-8.1 ± 12.1
agalsidase beta after switchback	32	-1.3 ± 6.2

SOURCE: **Kramer 2018 [67]**, Table 4.

14. Combining data from the Canadian Fabry Disease Initiative [52] and three centers in Europe (Netherlands, U.K, and Germany), **Arends 2018** [66] followed N=139 patients (56% male, mean age 45 years, 82% classical Fabry phenotype) during treatment with agalsidase beta (1 mg/kg) and N=248 patients (47% male, mean age 45 years, 66% classical Fabry phenotype) during treatment with agalsidase alfa (0.2 mg/kg).[17] In 337 adult patients (all ERT naïve at baseline), a linear mixed model compared agalsidase alfa and agalsidase beta groups for eGFR change over time (Table 6).

Table 6: Treatment difference (agalsidase alfa *vs.* agalsidase beta) in temporal eGFR change, results from a linear mixed model with statistical controls for sex and Fabry disease phenotype.

Baseline eGFR	**Difference in eGFR slope ($\beta_{alfa-beta}$) mL/min/1.73 m^2/y**		**p-value**
	Estimate	**95% CI**	
≥60 mL/min/1.73 m^2	-0.12	-0.76, 0.51	0.70
<60 mL/min/1.73 m^2	-0.85	-2.31, 0.62	0.26

SOURCE: **Arends 2018** [66].
ABBREVIATIONS: eGFR – estimated glomerular filtration rate; CI – confidence interval.

4 DISCUSSION

Acting on FDA advice,[18] Sanofi submitted a Technical Report from a Systematic Literature Review (SLR) to enhance BLA 103979 S-5309, an application seeking traditional approval for agalsidase beta (Fabrazyme®). BLA 103979 received accelerated approval in 2003 because of double-blind placebo-controlled randomized clinical trials demonstrating an effect of agalsidase beta on "globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types."[19] As a condition for traditional approval, FDA now seeks evidence showing a favorable effect from agalsidase beta on a clinically valued endpoint, such as

[17] Median 4.9-year follow-up, overall.

[18] Meeting Minutes, filed under BLA 103979 on December 12, 2017 (DARRTS Reference ID: 4193821).

[19] Prescribing Information, FABRAZYME (agalsidase beta) for injection, revised12/2018, accessed at Drugs@FDA on July 9, 2020.

progression of chronic kidney disease.

To this end, the Technical Report presented 71 literature reports (articles) with evidence from 56 studies of outcomes in Fabry disease patients treated with agalsidase beta. The Technical Report used acceptably rigorous, systematic, and transparent methods to (1) search three electronic bibliographic databases, (2) identify articles eligible for review, and (3) extract evidence about treatment-related outcomes in 11 categories (Section 3.2.1 Study eligibility). In comprehensive fashion, the Technical Report presented findings as bulleted, narrative, and tabular summaries of evidence. DEPI validated the integrity of the Technical Report by completing an independent literature search (Section 3.3.1 Literature search) and checking data presented by the Technical Report in the renal outcome category (Section 3.3.2 Data presentation).

As evidence for effectiveness, the Technical Report asserted that studies show "stabilization of renal and cardiac parameters" in patients treated with agalsidase beta.[20] The Technical Report reached this conclusion not through quantitative and objective synthesis of evidence from adequate and well-controlled studies, but rather through qualitative and subjective assessment of evidence from studies mostly without adequate controls for comparison.

To demonstrate the limited evidence available in literature, Table 7 lists the 20 studies (6 trials and 14 observational) providing evidence about agalsidase beta effectiveness in the renal outcome category. This list includes four Sanofi-sponsored trials with Clinical Study Reports (CSRs) separately available for FDA review. The Sanofi-sponsored trials with CSRs include two placebo-controlled trials (AGAL-1-002-98 [2] and AGAL-008-00 [17]) and two single-arm trials (AGAL-016-01 [26] and AGAL-017-01 [29]). (b) (4) . A renal event, 33% increase in serum creatinine or end-stage renal disease, occurred in 10 of 51 treated patients and 7 of 31 untreated patients during the placebo-controlled phase of AGAL-008-00, HR 0.49 (adjusted for baseline proteinuria), 95% CI 0.17-1.4, p-value = 0.18 [17]. The two remaining trials include a (1) single-arm trial with 11 patients (**Wraith 2008** [26]) and (2) two-armed trial suggesting inferior GFR outcome at two years in patients treated with agalsidase beta instead of agalsidase alfa (**Vedder 2007** [22]; Table 4).

Table 7: Six trials and 14 observational studies with evidence for agalsidase beta effectiveness in the renal outcome category.

STUDY	DESIGN	COMPARATOR
International Collaborative Fabry Study [2, 9, 18, 55]	TRIAL	PLACEBO
Fabry Disease Clinical Trial Study Group [17]	TRIAL	PLACEBO
Lubanda 2009 [29]	TRIAL	NONE
Wraith 2008 [26]	TRIAL	NONE
Tahir 2007 [20]	TRIAL	NONE
Vedder 2007 [22]	TRIAL	AGALSIDASE ALFA

[20] Technical Report, Executive Summary, page 12.

STUDY	DESIGN	COMPARATOR
Weidemann 2013 [47]	OBS	UNTREATED
Arends 2018 [66]	OBS	AGALSIDASE ALFA
Vedder 2008 [25]	OBS	LOW-DOSE ERT
Kramer 2018 [67]	OBS	SWITCH
Tsuboi 2012 & 2014 [40, 53]	OBS	CROSSOVER SWITCH
Pisani 2013 [45]	OBS	CROSSOVER SWITCH
Lin 2014 [50]	OBS	CROSSOVER SWITCH
Imbriaco 2009 [28]	OBS	CROSSOVER
Choi 2008 [23]	OBS	NONE
Warnock 2012 [41]	OBS	NONE
Politei 2014 [49]	OBS	NONE
Hopkins 2016 [58]	OBS	NONE
Kim 2016 [59]	OBS	NONE
Ripeau 2017 [64]	OBS	NONE

SOURCE: Table prepared by DEPI from primary literature sources.
LEGEND: CROSSOVER – crossover from no treatment to agalsidase alfa; SWITCH – crossover from agalsidase beta to agalsidase alfa.

DEPI assessed observational studies according to comparator design.

- Six observational studies assessed renal outcomes in treated cohorts without comparator (**Choi 2008** [23], **Warnock 2012** [41], **Politei 2014** [49], **Hopkins 2016** [58], **Kim 2016** [59], and **Ripeau 2017** [64]). Of note, kidney function deteriorated (eGFR slope < -1.2 mL/min/1.73 m^2/y) despite treatment with agalsidase beta in 113 of 151 men (74.8%) from the Fabry Disease Registry (**Warnock 2012** [41]).

- Assessing a renal outcome before and after crossover from no treatment to treatment with agalsidase beta, one observational study (**Imbriaco 2009** [28]) described resolution of proteinuria in 5 of 8 patients (a possibly unexpected finding [41]).

- Three crossover studies with 29 patients in total observed seemingly similar renal outcomes during treatment with agalsidase beta and subsequently during treatment with agalsidase alfa (**Tsuboi 2012 & 2014** [40, 53], **Pisani 2013** [45], and **Lin 2014** [50]).

- One observational study reported a better renal outcome in patients continued on agalsidase beta compared to patients switched from agalsidase beta to agalsidase alfa (**Kramer 2018** [67]; Table 5). Similar articles used some of the patients studied in **Kramer 2018** to report results that possibly permit a different conclusion about the relative effectiveness of agalsidase beta *vs.* agalsidase alfa. (See **Weidemann 2014** [54], **Lenders 2016** [60], and **Lenders 2020** [118], Table 1). Factors related to the reason patients switched therapy might explain findings in **Kramer 2018**.

- **Vedder 2008** [25] compared GFR change in N=48 patients grouped by ERT dose. **Vedder 2008** reported that renal function "remained stable over the 24 months" in seven men switched ("because of progression of disease") from low-dose ERT (agalsidase beta or agalsidase alfa) to standard-dose agalsidase beta (1.0 mg/kg).

- One observational study with active comparator suggested a better renal outcome from agalsidase beta than agalsidase alfa in patients with advanced pre-ERT chronic kidney disease (eGFR <60 mL/min/1.73 m^2), difference in eGFR slope (agalsidase alfa *vs.* agalsidase beta), -0.85 mL/min/1.73 m^2/y, p-value = 0.26 (**Arends 2018** [66]; Table 6).

- One observational study (**Weidemann 2013** [47]) used a matched untreated comparator (Fabry Disease Registry) and composite endpoint (dialysis, stroke, or death) to suggest treatment benefit from agalsidase beta, HR 0.68, 95% CI 0.33-1.39, p-value = 0.28.

As noted above, the Technical Report presented results as bulleted, narrative, and tabular summaries without formal meta-analysis. Unfortunately, extreme heterogeneity in design, patient selection, and outcome definition across studies precludes meaningful data synthesis by meta-analysis [120]. In place of quantitative synthesis, DEPI's qualitatively assessed individual studies to find scant evidence for beneficial effects from agalsidase beta on renal outcomes. However, the absence of strong evidence does not necessarily mean that agalsidase beta is "ineffective or clinically useless" [121]. Rather, investigators plausibly faced practical challenges that thwarted adequately powered and well controlled studies of therapeutic interventions in Fabry disease, a rare genetic disorder with long and variable disease course.

Seeking literature support for DIREGC07006/AGAL-014-01 (matched analysis with eGFR change as primary efficacy endpoint), DEPI restricted in-depth analysis of the Technical Report to evidence presented in the renal outcome category. Therefore, DEPI's conclusions might not apply to other outcomes addressed in the Technical Report.

5 CONCLUSION

Sanofi used acceptably rigorous, systematic, and transparent methods to prepare a Technical Report, which presented evidence in medical literature about outcomes from treatment with agalsidase beta in patients with Fabry's disease. DEPI found scant evidence in the articles cited by the Technical Report for beneficial effects from agalsidase beta on renal outcomes. (b) (4)

6 RECOMMENDATIONS

DEPI recommends that DRDMG accept the Technical Report as a complete representation of evidence currently available in medical literature about the effectiveness of treatment with agalsidase beta in patients with Fabry's disease.

7 REFERENCES

1. Eng CM, Banikazemi M, Gordon RE, et al. A phase 1/2 clinical trial of enzyme replacement in fabry disease: Pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet. 2001 Mar;**68**(3):711-22.

2. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med. 2001 Jul 5;**345**(1):9-16.

3. Thurberg BL, Rennke H, Colvin RB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int. 2002 Dec;**62**(6):1933-46.

4. Weidemann F, Breunig F, Beer M, et al. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: A prospective strain rate imaging study. Circulation. 2003 Sep 16;**108**(11):1299-301.

5. Linthorst GE, Hollak CE, Donker-Koopman WE, Strijland A, Aerts JM. Enzyme therapy for Fabry disease: Neutralizing antibodies toward agalsidase alpha and beta. Kidney Int. 2004 Oct;**66**(4):1589-95.

6. Mills K, Vellodi A, Morris P, et al. Monitoring the clinical and biochemical response to enzyme replacement therapy in three children with Fabry disease. Eur J Pediatr. 2004 Oct;**163**(10):595-603.

7. Siamopoulos KC. Fabry disease: Kidney involvement and enzyme replacement therapy. Kidney Int. 2004 Feb;**65**(2):744-53.

8. Spinelli L, Pisani A, Sabbatini M, et al. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. Clin Genet. 2004 Aug;**66**(2):158-65.

9. Wilcox WR, Banikazemi M, Guffon N, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004 Jul;**75**(1):65-74.

10. Banikazemi M, Ullman T, Desnick RJ. Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy. Mol Genet Metab. 2005 Aug;**85**(4):255-9.

11. Eto Y, Ohashi T, Utsunomiya Y, et al. Enzyme replacement therapy in Japanese Fabry disease patients: The results of a phase 2 bridging study. J Inherit Metab Dis. 2005;**28**(4):575-83.

12. Pisani A, Spinelli L, Sabbatini M, et al. Enzyme replacement therapy in Fabry disease patients undergoing dialysis: Effects on quality of life and organ involvement. Am J Kidney Dis. 2005 Jul;**46**(1):120-7.

13. Beer M, Weidemann F, Breunig F, et al. Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy. Am J Cardiol. 2006 May 15;**97**(10):1515-8.

14. Breunig F, Weidemann F, Strotmann J, Knoll A, Wanner C. Clinical benefit of enzyme replacement therapy in Fabry disease. Kidney Int. 2006 Apr;**69**(7):1216-21.

15. Elliott PM, Kindler H, Shah JS, et al. Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. Heart. 2006 Mar;**92**(3):357-60.

16. Kalliokoski RJ, Kantola I, Kalliokoski KK, et al. The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease. J Inherit Metab Dis. 2006 Feb;**29**(1):112-8.

17. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: A randomized trial. Ann Intern Med. 2007 Jan 16;**146**(2):77-86.

18. Germain DP, Waldek S, Banikazemi M, et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J Am Soc Nephrol. 2007 May;**18**(5):1547-57.

19. Ohashi T, Sakuma M, Kitagawa T, Suzuki K, Ishige N, Eto Y. Influence of antibody formation on reduction of globotriaosylceramide (GL-3) in urine from Fabry patients during agalsidase beta therapy. Mol Genet Metab. 2007 Nov;**92**(3):271-3.

20. Tahir H, Jackson LL, Warnock DG. Antiproteinuric therapy and fabry nephropathy: Sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-beta. J Am Soc Nephrol. 2007 Sep;**18**(9):2609-17.

21. Tsuboi K. Enzyme replacement therapy in patients with Fabry's disease. J Int Med Res. 2007 Jul-Aug;**35**(4):574-81.

22. Vedder AC, Linthorst GE, Houge G, et al. Treatment of Fabry disease: Outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg. PLoS One. 2007 Jul 11;**2**(7):e598.

23. Choi JH, Cho YM, Suh KS, et al. Short-term efficacy of enzyme replacement therapy in Korean patients with Fabry disease. J Korean Med Sci. 2008 Apr;**23**(2):243-50.

24. Koskenvuo JW, Hartiala JJ, Nuutila P, et al. Twenty-four-month alpha-galactosidase A replacement therapy in Fabry disease has only minimal effects on symptoms and cardiovascular parameters. J Inherit Metab Dis. 2008 Jun;**31**(3):432-41.

25. Vedder AC, Breunig F, Donker-Koopman WE, et al. Treatment of Fabry disease with

different dosing regimens of agalsidase: Effects on antibody formation and GL-3. Mol Genet Metab. 2008 Jul;**94**(3):319-25.

26. Wraith JE, Tylki-Szymanska A, Guffon N, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. J Pediatr. 2008 Apr;**152**(4):563-70, 70 e1.

27. Benichou B, Goyal S, Sung C, Norfleet AM, O'Brien F. A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease. Mol Genet Metab. 2009 Jan;**96**(1):4-12.

28. Imbriaco M, Pisani A, Spinelli L, et al. Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: A prospective long-term cardiac magnetic resonance imaging study. Heart. 2009 Jul;**95**(13):1103-7.

29. Lubanda JC, Anijalg E, Bzduch V, Thurberg BL, Benichou B, Tylki-Szymanska A. Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease. Genet Med. 2009 Apr;**11**(4):256-64.

30. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: Evidence for a better outcome with early treatment. Circulation. 2009 Feb 3;**119**(4):524-9.

31. Watt T, Burlina AP, Cazzorla C, et al. Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: Findings from the Fabry Registry. Genet Med. 2010 Nov;**12**(11):703-12.

32. Machann W, Breunig F, Weidemann F, et al. Cardiac energy metabolism is disturbed in Fabry disease and improves with enzyme replacement therapy using recombinant human galactosidase A. Eur J Heart Fail. 2011 Mar;**13**(3):278-83.

33. van Breemen MJ, Rombach SM, Dekker N, et al. Reduction of elevated plasma globotriaosylsphingosine in patients with classic Fabry disease following enzyme replacement therapy. Biochim Biophys Acta. 2011 Jan;**1812**(1):70-6.

34. Wuest W, Machann W, Breunig F, et al. Right ventricular involvement in patients with Fabry's disease and the effect of enzyme replacement therapy. Rofo. 2011 Nov;**183**(11):1037-42.

35. Collin C, Briet M, Tran TC, et al. Long-term changes in arterial structure and function and left ventricular geometry after enzyme replacement therapy in patients affected with Fabry disease. Eur J Prev Cardiol. 2012 Feb;**19**(1):43-54.

36. Koeppe S, Neubauer H, Breunig F, et al. MR-based analysis of regional cardiac function in

relation to cellular integrity in Fabry disease. Int J Cardiol. 2012 Sep 20;**160**(1):53-8.

37. Messalli G, Imbriaco M, Avitabile G, et al. Role of cardiac MRI in evaluating patients with Anderson-Fabry disease: Assessing cardiac effects of long-term enzyme replacement therapy. Radiol Med. 2012 Feb;**117**(1):19-28.

38. Motwani M, Banypersad S, Woolfson P, Waldek S. Enzyme replacement therapy improves cardiac features and severity of Fabry disease. Mol Genet Metab. 2012 Sep;**107**(1-2):197-202.

39. Rombach SM, Aerts JM, Poorthuis BJ, et al. Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome. PLoS One. 2012;**7**(10):e47805.

40. Tsuboi K, Yamamoto H. Clinical observation of patients with Fabry disease after switching from agalsidase beta (Fabrazyme) to agalsidase alfa (Replagal). Genet Med. 2012 Sep;**14**(9):779-86.

41. Warnock DG, Ortiz A, Mauer M, et al. Renal outcomes of agalsidase beta treatment for Fabry disease: Role of proteinuria and timing of treatment initiation. Nephrol Dial Transplant. 2012 Mar;**27**(3):1042-9.

42. Wilcox WR, Linthorst GE, Germain DP, et al. Anti-alpha-galactosidase A antibody response to agalsidase beta treatment: Data from the Fabry Registry. Mol Genet Metab. 2012 Mar;**105**(3):443-9.

43. Borgwardt L, Feldt-Rasmussen U, Rasmussen AK, Ballegaard M, Meldgaard Lund A. Fabry disease in children: Agalsidase-beta enzyme replacement therapy. Clin Genet. 2013 May;**83**(5):432-8.

44. Germain DP, Weidemann F, Abiose A, et al. Analysis of left ventricular mass in untreated men and in men treated with agalsidase-beta: Data from the Fabry Registry. Genet Med. 2013 Dec;**15**(12):958-65.

45. Pisani A, Spinelli L, Visciano B, et al. Effects of switching from agalsidase beta to agalsidase alfa in 10 patients with Anderson-Fabry disease. JIMD Rep. 2013;**9**:41-8.

46. Tondel C, Bostad L, Larsen KK, et al. Agalsidase benefits renal histology in young patients with Fabry disease. J Am Soc Nephrol. 2013 Jan;**24**(1):137-48.

47. Weidemann F, Niemann M, Stork S, et al. Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: Evidence for disease progression towards serious complications. J Intern Med. 2013 Oct;**274**(4):331-41.

48. Fellgiebel A, Gartenschlager M, Wildberger K, Scheurich A, Desnick RJ, Sims K. Enzyme

replacement therapy stabilized white matter lesion progression in Fabry disease. Cerebrovasc Dis. 2014;**38**(6):448-56.

49. Politei J, Amartino H, Schenone BA, et al. Fabry disease: Multidisciplinary evaluation after 10 years of treatment with agalsidase beta. JIMD Rep. 2014;**16**:7-14.

50. Lin HY, Huang YH, Liao HC, et al. Clinical observations on enzyme replacement therapy in patients with Fabry disease and the switch from agalsidase beta to agalsidase alfa. J Chin Med Assoc. 2014 Apr;**77**(4):190-7.

51. Rigoldi M, Concolino D, Morrone A, et al. Intrafamilial phenotypic variability in four families with Anderson-Fabry disease. Clin Genet. 2014 Sep;**86**(3):258-63.

52. Sirrs SM, Bichet DG, Casey R, et al. Outcomes of patients treated through the Canadian Fabry disease initiative. Mol Genet Metab. 2014 Apr;**111**(4):499-506.

53. Tsuboi K, Yamamoto H. Clinical course of patients with Fabry disease who were switched from agalsidase-beta to agalsidase-alpha. Genet Med. 2014 Oct;**16**(10):766-72.

54. Weidemann F, Kramer J, Duning T, et al. Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch. J Am Soc Nephrol. 2014 Apr;**25**(4):837-49.

55. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015 May;**52**(5):353-8.

56. Senocak Tasci E, Bicik Z. Safe and successful treatment with agalsidase beta during pregnancy in Fabry disease. Iran J Kidney Dis. 2015 Sep;**9**(5):406-8.

57. Goker-Alpan O, Gambello MJ, Maegawa GH, et al. Reduction of plasma globotriaosylsphingosine levels after switching from agalsidase alfa to agalsidase beta as enzyme replacement therapy for Fabry disease. JIMD Rep. 2016;**25**:95-106.

58. Hopkin RJ, Cabrera G, Charrow J, et al. Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: Data from the Fabry Registry. Mol Genet Metab. 2016 Sep;**119**(1-2):151-9.

59. Kim JH, Lee BH, Hyang Cho J, et al. Long-term enzyme replacement therapy for Fabry disease: Efficacy and unmet needs in cardiac and renal outcomes. J Hum Genet. 2016 Nov;**61**(11):923-9.

60. Lenders M, Canaan-Kuhl S, Kramer J, et al. Patients with Fabry disease after enzyme replacement therapy dose reduction and switch-2-year follow-up. J Am Soc Nephrol. 2016 Mar;**27**(3):952-62.

61. Najafian B, Tondel C, Svarstad E, Sokolovkiy A, Smith K, Mauer M. One year of enzyme replacement therapy reduces globotriaosylceramide inclusions in podocytes in male adult patients with Fabry disease. PLoS One. 2016;**11**(4):e0152812.

62. Ortiz A, Abiose A, Bichet DG, et al. Time to treatment benefit for adult patients with Fabry disease receiving agalsidase beta: Data from the Fabry Registry. J Med Genet. 2016 Jul;**53**(7):495-502.

63. Politei J, Schenone AB, Cabrera G, Heguilen R, Szlago M. Fabry disease and enzyme replacement therapy in classic patients with same mutation: Different formulations--different outcome? Clin Genet. 2016 Jan;**89**(1):88-92.

64. Ripeau D, Amartino H, Cedrolla M, et al. Switch from agalsidase beta to agalsidase alfa in the enzyme replacement therapy of patients with Fabry disease in Latin America. Medicina (B Aires). 2017;**77**(3):173-9.

65. Skrunes R, Svarstad E, Kampevold Larsen K, Leh S, Tondel C. Reaccumulation of globotriaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients. Nephrol Dial Transplant. 2017 May 1;**32**(5):807-13.

66. Arends M, Biegstraaten M, Wanner C, et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: An international cohort study. J Med Genet. 2018 May;**55**(5):351-8.

67. Kramer J, Lenders M, Canaan-Kuhl S, et al. Fabry disease under enzyme replacement therapy-new insights in efficacy of different dosages. Nephrol Dial Transplant. 2018 Aug 1;**33**(8):1362-72.

68. Lenders M, Neusser LP, Rudnicki M, et al. Dose-dependent effect of enzyme replacement therapy on neutralizing antidrug antibody titers and clinical outcome in patients with Fabry disease. J Am Soc Nephrol. 2018 Dec;**29**(12):2879-89.

69. Lenders M, Schmitz B, Brand SM, Foell D, Brand E. Characterization of drug-neutralizing antibodies in patients with Fabry disease during infusion. J Allergy Clin Immunol. 2018 Jun;**141**(6):2289-92 e7.

70. Mauhin W, Lidove O, Amelin D, et al. Deep characterization of the anti-drug antibodies developed in Fabry disease patients, A prospective analysis from the French multicenter cohort FFABRY. Orphanet J Rare Dis. 2018 Jul 31;**13**(1):127.

71. Wilcox WR, Feldt-Rasmussen U, Martins AM, et al. Improvement of Fabry disease-related gastrointestinal symptoms in a significant proportion of female patients treated with agalsidase beta: Data from the Fabry Registry. JIMD Rep. 2018;**38**:45-51.

72. Limgala RP, Jennelle T, Plassmeyer M, et al. Altered immune phenotypes in subjects with

Fabry disease and responses to switching from agalsidase alfa to agalsidase beta. Am J Transl Res. 2019;**11**(3):1683-96.

73. Ramaswami U, Bichet DG, Clarke LA, et al. Low-dose agalsidase beta treatment in male pediatric patients with Fabry disease: A 5-year randomized controlled trial. Mol Genet Metab. 2019 May;**127**(1):86-94.

74. Moore DF, Altarescu G, Herscovitch P, Schiffmann R. Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease. BMC Neurol. 2002 Jun 18;**2**:4.

75. Baehner F, Kampmann C, Whybra C, Miebach E, Wiethoff CM, Beck M. Enzyme replacement therapy in heterozygous females with Fabry disease: results of a phase IIIB study. J Inherit Metab Dis. 2003;**26**(7):617-27.

76. Guffon N, Fouilhoux A. Clinical benefit in Fabry patients given enzyme replacement therapy--a case series. J Inherit Metab Dis. 2004;**27**(2):221-7.

77. Hilz MJ, Brys M, Marthol H, Stemper B, Dütsch M. Enzyme replacement therapy improves function of C-, Adelta-, and Abeta-nerve fibers in Fabry neuropathy. Neurology. 2004 Apr 13;**62**(7):1066-72.

78. Jardim L, Vedolin L, Schwartz IV, et al. CNS involvement in Fabry disease: Clinical and imaging studies before and after 12 months of enzyme replacement therapy. J Inherit Metab Dis. 2004;**27**(2):229-40.

79. Mignani R, Panichi V, Giudicissi A, et al. Enzyme replacement therapy with agalsidase beta in kidney transplant patients with Fabry disease: A pilot study. Kidney Int. 2004 Apr;**65**(4):1381-5.

80. Cabrera-Salazar MA, O'Rourke E, Charria-Ortiz G, Barranger JA. Radiological evidence of early cerebral microvascular disease in young children with Fabry disease. J Pediatr. 2005 Jul;**147**(1):102-5.

81. Faggiano A, Pisani A, Milone F, et al. Endocrine dysfunction in patients with Fabry disease. J Clin Endocrinol Metab. 2006 Nov;**91**(11):4319-25.

82. Hoffmann B, Schwarz M, Mehta A, Keshav S. Gastrointestinal symptoms in 342 patients with Fabry disease: Prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol. 2007 Dec;**5**(12):1447-53.

83. Schiffmann R, Askari H, Timmons M, et al. Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing. J Am Soc Nephrol. 2007 May;**18**(5):1576-83.

84. Bodensteiner D, Scott CR, Sims KB, Shepherd GM, Cintron RD, Germain DP. Successful

reinstitution of agalsidase beta therapy in Fabry disease patients with previous IgE-antibody or skin-test reactivity to the recombinant enzyme. Genet Med. 2008 May;**10**(5):353-8.

85. Kovacevic-Preradovic T, Zuber M, Attenhofer Jost CH, et al. Anderson-Fabry disease: Long-term echocardiographic follow-up under enzyme replacement therapy. Eur J Echocardiogr. 2008 Nov;**9**(6):729-35.

86. Mignani R, Feriozzi S, Pisani A, et al. Agalsidase therapy in patients with Fabry disease on renal replacement therapy: A nationwide study in Italy. Nephrol Dial Transplant. 2008 May;**23**(5):1628-35.

87. Möhrenschlager M, Ollert M, Ring J. A study on serum IgE and clinical symptomatology of atopy in patients suffering from the lysosomal storage disorder Fabry disease. J Eur Acad Dermatol Venereol. 2008 Jun;**22**(6):692-5.

88. Pintos-Morell G, Beck M. Fabry disease in children and the effects of enzyme replacement treatment. Eur J Pediatr. 2009 Nov;**168**(11):1355-63.

89. Niemann M, Breunig F, Beer M, et al. Tei index in Fabry disease. J Am Soc Echocardiogr. 2011 Sep;**24**(9):1026-32.

90. Smid BE, Rombach SM, Aerts JM, et al. Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients. Orphanet J Rare Dis. 2011 Oct 31;**6**:69.

91. Engelen MA, Brand E, Baumeister TB, et al. Effects of enzyme replacement therapy in adult patients with Fabry disease on cardiac structure and function: A retrospective cohort study of the Fabry Munster Study (FaMuS) data. BMJ Open. 2012;**2**(6).

92. Fujii H, Kono K, Yamamoto T, et al. Effect of enzyme replacement therapy on serum asymmetric dimethylarginine levels, coronary flow reserve and left ventricular hypertrophy in patients with Fabry disease. Clin Kidney J. 2012 Dec;**5**(6):512-8.

93. Rombach SM, van den Bogaard B, de Groot E, et al. Vascular aspects of Fabry disease in relation to clinical manifestations and elevations in plasma globotriaosylsphingosine. Hypertension. 2012 Oct;**60**(4):998-1005.

94. Furujo M, Kubo T, Kobayashi M, Ohashi T. Enzyme replacement therapy in two Japanese siblings with Fabry disease, and its effectiveness on angiokeratoma and neuropathic pain. Mol Genet Metab. 2013 Nov;**110**(3):405-10.

95. Lin HY, Liu HC, Huang YH, et al. Effects of enzyme replacement therapy for cardiac-type Fabry patients with a Chinese hotspot late-onset Fabry mutation (IVS4+919G>A). BMJ Open. 2013;**3**(7).

96. Rombach SM, Smid BE, Bouwman MG, Linthorst GE, Dijkgraaf MG, Hollak CE. Long

term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain. Orphanet J Rare Dis. 2013 Mar 25;**8**:47.

97. Anderson LJ, Wyatt KM, Henley W, et al. Long-term effectiveness of enzyme replacement therapy in Fabry disease: results from the NCS-LSD cohort study. J Inherit Metab Dis. 2014 Nov;**37**(6):969-78.

98. Prabakaran T, Birn H, Bibby BM, et al. Long-term enzyme replacement therapy is associated with reduced proteinuria and preserved proximal tubular function in women with Fabry disease. Nephrol Dial Transplant. 2014 Mar;**29**(3):619-25.

99. Wijburg FA, Bénichou B, Bichet DG, et al. Characterization of early disease status in treatment-naive male paediatric patients with Fabry disease enrolled in a randomized clinical trial. PLoS One. 2015;**10**(5):e0124987.

100. Biancini GB, Jacques CE, Hammerschmidt T, et al. Biomolecules damage and redox status abnormalities in Fabry patients before and during enzyme replacement therapy. Clin Chim Acta. 2016 Oct 1;**461**:41-6.

101. Chen KH, Chien Y, Wang KL, et al. Evaluation of proinflammatory prognostic biomarkers for Fabry cardiomyopathy with enzyme replacement therapy. Can J Cardiol. 2016 Oct;**32**(10):1221.e1-.e9.

102. Lenders M, Hennermann JB, Kurschat C, et al. Multicenter Female Fabry Study (MFFS) - clinical survey on current treatment of females with Fabry disease. Orphanet J Rare Dis. 2016 Jun 29;**11**(1):88.

103. Lenders M, Stypmann J, Duning T, Schmitz B, Brand SM, Brand E. Serum-mediated inhibition of enzyme replacement therapy in Fabry disease. J Am Soc Nephrol. 2016 Jan;**27**(1):256-64.

104. Trimarchi H, Canzonieri R, Schiel A, et al. Podocyturia is significantly elevated in untreated vs treated Fabry adult patients. J Nephrol. 2016 Dec;**29**(6):791-7.

105. Arends M, Biegstraaten M, Hughes DA, et al. Retrospective study of long-term outcomes of enzyme replacement therapy in Fabry disease: Analysis of prognostic factors. PLoS One. 2017;**12**(8):e0182379.

106. Arends M, Wijburg FA, Wanner C, et al. Favourable effect of early versus late start of enzyme replacement therapy on plasma globotriaosylsphingosine levels in men with classical Fabry disease. Mol Genet Metab. 2017 Jun;**121**(2):157-61.

107. Cabrera G, Politei J, Antongiovani N, Amartino H. Effectiveness of enzyme replacement therapy in Fabry disease: Long term experience in Argentina. Mol Genet Metab Rep. 2017 Jun;**11**:65-8.

108. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet. 2017 Apr;**54**(4):288-96.

109. Lenders M, Schmitz B, Stypmann J, et al. Renal function predicts long-term outcome on enzyme replacement therapy in patients with Fabry disease. Nephrol Dial Transplant. 2017 Dec 1;**32**(12):2090-7.

110. Madsen CV, Bundgaard H, Rasmussen Å K, et al. Echocardiographic and clinical findings in patients with Fabry disease during long-term enzyme replacement therapy: a nationwide Danish cohort study. Scand Cardiovasc J. 2017 Aug;**51**(4):207-16.

111. Nowak A, Koch G, Huynh-Do U, Siegenthaler M, Marti HP, Pfister M. Disease progression modeling to evaluate the effects of enzyme replacement therapy on kidney function in adult patients with the classic phenotype of Fabry disease. Kidney Blood Press Res. 2017;**42**(1):1-15.

112. Skrunes R, Tøndel C, Leh S, et al. Long-term dose-dependent agalsidase effects on kidney histology in Fabry disease. Clin J Am Soc Nephrol. 2017 Sep 7;**12**(9):1470-9.

113. Hongo K, Ito K, Date T, et al. The beneficial effects of long-term enzyme replacement therapy on cardiac involvement in Japanese Fabry patients. Mol Genet Metab. 2018 Jun;**124**(2):143-51.

114. Lin CJ, Chien YH, Lai TS, et al. Results of Fabry disease screening in male pre-end stage renal disease patients with unknown etiology found through the platform of a chronic kidney disease education program in a northern Taiwan medical center. Kidney Blood Press Res. 2018;**43**(5):1636-45.

115. Sakuraba H, Togawa T, Tsukimura T, Kato H. Plasma lyso-Gb3: A biomarker for monitoring Fabry patients during enzyme replacement therapy. Clin Exp Nephrol. 2018 Aug;**22**(4):843-9.

116. van der Veen SJ, van Kuilenburg ABP, Hollak CEM, Kaijen PHP, Voorberg J, Langeveld M. Antibodies against recombinant alpha-galactosidase A in Fabry disease: Subclass analysis and impact on response to treatment. Mol Genet Metab. 2019 Feb;**126**(2):162-8.

117. Trimarchi H, Canzonieri R, Costales-Collaguazo C, et al. Early decrease in the podocalyxin to synaptopodin ratio in urinary Fabry podocytes. Clin Kidney J. 2019 Feb;**12**(1):53-60.

118. Lenders M, Nordbeck P, Canaan-Kühl S, et al. Treatment switch in Fabry disease - a matter of dose? J Med Genet. 2020 Jun 10.

119. Wanner C, Feldt-Rasmussen U, Jovanovic A, et al. Cardiomyopathy and kidney function in agalsidase beta-treated female Fabry patients: A pre-treatment vs. post-treatment analysis.

ESC Heart Fail. 2020 Jun;**7**(3):825-34.

120. Elliott PM, Germain DP, Hilz MJ, Spada M, Wanner C, Falissard B. Why systematic literature reviews in Fabry disease should include all published evidence. Eur J Med Genet. 2019 Oct;**62**(10):103702.

121. El Dib R, Gomaa H, Ortiz A, Politei J, Kapoor A, Barreto F. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. PLoS One. 2017;**12**(3):e0173358.

CC: Dal Pan G / Ball R / Blum M / Li J / Pinheiro S / Sandhu S / Hua W / Callahan C / Lerro C / Booth B / Dunson A / Sun S / Calloway P (OSE)

Wang Y / Usher T (DB-IV)

Joffe H / Smpokou P / Zaidi A / Kong N (DRDMG)

APPENDIX 1: PRISMA Checklist

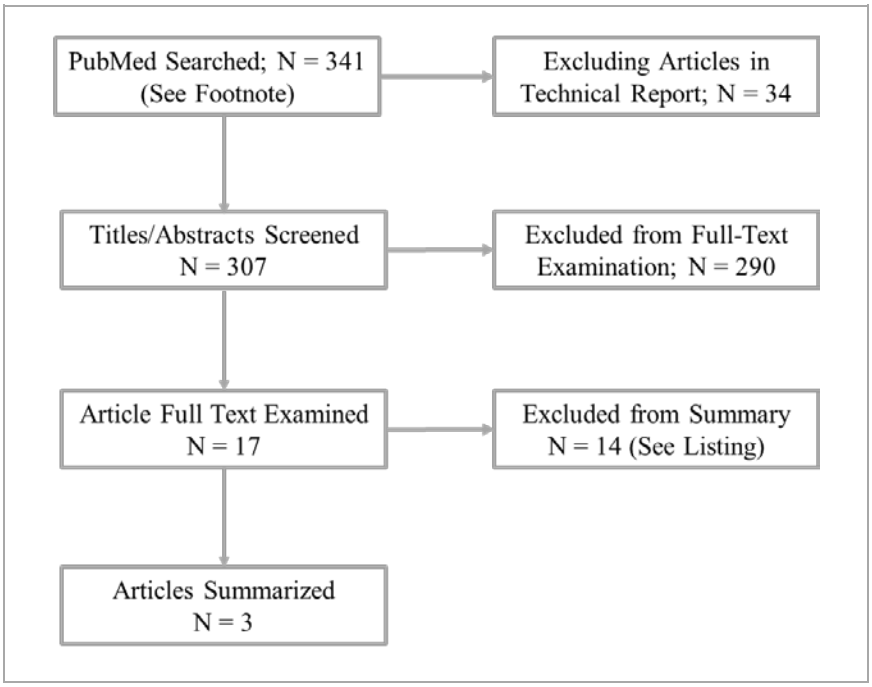
Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	6-12
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	13
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	14-15 (Table 1)
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NR
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	15-17
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	16-17
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	144-145
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	17
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	18-19
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	18-19
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	19
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	20-21
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	22-38
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	149-150
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 6 to 35
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	141
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	142
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	143
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX 2: PubMed Search

Appendix Figure 1 summarizes results from a PubMed search completed by DEPI to complement a Technical Report from a *Systematic Literature Review of Fabrazyme for the Treatment of Fabry Disease*. This search identified three additional articles with information about agalsidase beta and an outcome of interest [117-119]. Missing information about the type of ERT (agalsidase alfa or agalsidase beta) accounted for 9 of 14 articles excluded upon examination of full text.



Appendix Figure 1: Information flow diagram. FOOTNOTE: English-language articles, published in 2016 or later, identified by PubMed query on July 2, 2020: (Fabry) AND (((ERT OR "enzyme replacement") OR (agalsidase)) OR ("alpha-galactosidase/therapeutic use"[MeSH Terms])).

Listing of articles excluded after examination of full text:

1. (b) (4)
2.
3.
4.

(b) (4)

5.

6.

7.

8.

9.

10.

11.

12.

13.

14.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
10/30/2020 08:51:17 AM

CATHERINE L CALLAHAN
10/30/2020 08:52:49 AM

WEI HUA
10/30/2020 09:07:02 AM

JIE J LI
10/30/2020 09:28:41 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Real-World Evidence (RWE) Review

Date:	October 30, 2020
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology I
Acting Team Leader:	Catherine Callahan, PhD MA Division of Epidemiology I
Associate Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology I
Associate Director for RWE	Jie (Jenni) Li, PhD Office of Pharmacovigilance and Epidemiology
Drug Name:	Agalsidase beta (Fabrazyme®)
Subject:	Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01)
Application Type/Number:	BLA 103979 Efficacy Supplement-5309 (eCTD 0415)
Applicant/sponsor:	Sanofi Genzyme
OSE RCM #:	2020-438

TABLE OF CONTENTS

EXECUTIVE SUMMARY

To assist decision-making in the Division of Rare Disease and Medical Genetics (DRDMG), the Division of Epidemiology I (DEPI) assessed data quality and integrity for *Fabry Registry/Natural History Matched Analysis* (DIREGC07006/AGAL-014-01), a source of real-world evidence (RWE) included in an efficacy supplement for agalsidase beta (Fabrazyme®).

The efficacy supplement concerns agalsidase beta, an intravenous enzyme replacement therapy (ERT) for Fabry disease, a heterogeneous X-linked lysosomal storage disorder caused by galactosidase alpha gene (*GLA*) mutation and resultant galactosidase alpha enzyme (αGAL) deficiency. Fabry disease classically presents with symptoms in childhood, proteinuria in early adulthood, and death during the fourth decade of life from renal failure, heart failure, cardiac arrhythmia, or stroke (Fabry-associated clinical events).

Fabrazyme® BLA 103979 used results from a Phase 3 placebo-controlled clinical trial with surrogate endpoint to obtain accelerated FDA-approval in April 2003. (b) (4) The current application for traditional approval includes RWE from *Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis* (DIREGC07006/AGAL-014-01).

DEPI summarized sponsor-submitted documents to comprehend real-world data sources used for Matched Analysis. DEPI analyzed sponsor-submitted datasets to assess data quality and integrity.

Matched Analysis used prospectively and retrospectively collected data from the *Fabry Disease Registry* (DIREGC07006) to identify Fabry disease patients treated with agalsidase beta and retrospectively collected data from the *Epidemiologic Study of Natural History of Fabry Disease* (AGAL-014-01) to identify Fabry disease patients (the non-contemporaneous external comparison group) not treated with agalsidase beta or other ERT.

One analysis matched on sex, age, and derived Fabry phenotype to measure association between agalsidase beta and change in kidney function (primary efficacy endpoint). Using data for 1,138 treated and 124 untreated patients (untreated patients matched more than once), a linear mixed model showed kidney function declining less rapidly in treated than untreated patients (change in estimated glomerular filtration rate,-1.7 *vs.* -3.0 mL/min/1.73 m^2/y; p<.001).

Another analysis matched on sex, age, and derived Fabry phenotype to measure association between agalsidase beta and clinical events of interest (secondary efficacy endpoint defined as a composite of death and Fabry-associated clinical events). Using data for 1,754 treated and 233 untreated patients (untreated patients matched more than once), this analysis showed a first (post-index) clinical event occurring less often in treated than untreated patients (49 *vs.* 69 per 1,000 patient-years; hazard ratio 0.67, 95% confidence interval 0.49-0.90, p=0.008).

DEPI concluded that:

- Sponsor-submitted documents and datasets described results from additional analyses requested by an unfulfilled Post-Marketing Commitment (PMC 2421-2).

- The Sponsor conducted reasonably transparent analyses that withstood DEPI scrutiny for integrity (a conclusion supported by independent DEPI review and analysis of sponsor-submitted documents and datasets).

- The Sponsor's approach to analysis complied with FDA advice offered during pre-submission meetings.

- The results from analyses using a non-contemporaneous (historical) external comparison group provided low-level evidence for possible treatment benefit from agalsidase beta.

- Additional threats to proper interpretation of results included high patient attrition, limiting sample size, and missing data for critical covariates (study limitations disclosed by the Sponsor during pre-submission meetings with FDA).

DEPI recommended that DRDMG:

- Accept the Study Report from DIREGC07006/AGAL-014-01 as fulfillment for PMC 2421-2.

- Assess results from Matched Analysis (DIREGC07006/AGAL-014-01) as low-level evidence for possible clinical benefit from treatment with agalsidase beta.

- (b) (4)

- Request pre-submission RWE Subcommittee review of future RWE applications to DRDMG.

1 INTRODUCTION

1.1 Background

To assist decision-making in the Division of Rare Disease and Medical Genetics (DRDMG), the Division of Epidemiology I (DEPI) assessed data quality and integrity for *Fabry Registry/Natural History Matched Analysis* (DIREGC07006/AGAL-014-01), a source of real-world evidence (RWE) included in an efficacy supplement for agalsidase beta (Fabrazyme®).

The efficacy supplement concerns agalsidase beta, an intravenous enzyme replacement therapy (ERT) for Fabry disease, a rare heterogeneous X-linked lysosomal storage disorder caused by galactosidase alpha gene (*GLA*) mutation and resultant galactosidase alpha enzyme (αGAL) deficiency. Fabry disease classically presents with symptoms in childhood, proteinuria in early adulthood, and death during the fourth decade of life from renal failure, heart failure, cardiac arrhythmia, or stroke. Depending on genotype and pattern of X-chromosome inactivation, severe illness can occur in women.

The Sponsor (Sanofi) submitted a Study Report from DIREGC07006/AGAL-014-01 and results from systematic reviews of medical literature to support its application for traditional approval (full approval) for agalsidase beta. (See Section 1.2, below, for references to other Sponsor-conducted efficacy studies of agalsidase beta.)

1.2 Regulatory History for BLA 103979

BLA 103979 used a Phase 3 placebo-controlled clinical trial (AGAL-1-002-98) with a surrogate endpoint (globotriaosylceramide inclusions in capillary endothelium on kidney biopsy) to obtain accelerated FDA-approval in April 2003.

(b) (4)

To guide development of the current application for traditional approval (Efficacy Supplement-5309, submitted on February 14, 2020), Sanofi and FDA agreed to two Post-Marketing Commitments (PMCs):

- PMC 2421-1 (fulfilled), committing to additional analyses in the Epidemiologic Study of the

Natural History of Fabry Disease (AGAL-014-01).[1]

- PMC 2421-2 (not yet fulfilled), committing to additional analyses in the Fabry Disease Registry (DIREGC07006; NCT00196742).

On four occasions, DRDMG advised Sanofi about evidence required from the Fabry Disease Registry.

- On November 29, 2017, DRDMG advised that analyses in the Fabry Disease Registry "could potentially provide additional evidence of [agalsidase beta] effectiveness." DRDMG recommended analyses with a suitably matched comparator group, possibly from the Epidemiologic Study of the Natural History of Fabry Disease (AGAL-014-01).[2]

- On July 24, 2018, DRDMG advised that a long-term observational study might support an efficacy claim for agalsidase beta "if appropriate comparisons are made between comparable populations of treated and untreated patients to minimize bias in data interpretation."[3]

- On January 18, 2019, DRDMG identified "critically important [baseline] confounders," including Fabry phenotype, estimated glomerular filtration rate (eGFR), proteinuria, and use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[4]

- On May 21, 2019, DRDMG recommended separate data presentations by sex and Fabry phenotype, with a classic phenotype defined by pathogenic *GLA* variant or reduced αGAL activity.[5]

2 REVIEW METHODS AND MATERIALS

2.1 Documents Reviewed

DEPI reviewed documents pertaining to the *Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis* (DIREGC07006/AGAL-014-01).

1. Case Report Forms: Epidemiologic Study of the Natural History of Fabry Disease, March 12, 2001, submitted to BLA 103979 (eCTD 0159) on February 1, 2011.

---

[1] See, Fulfillment of Post-Marketing Commitment, filed under BLA 130979 on May 15, 2014 (DARRTS Reference ID: 3507214).

[2] Meeting Minutes, filed under BLA 103979 on December 12, 2017 (DARRTS Reference ID: 4193821).

[3] Meeting Minutes, filed under BLA 103979 on July 30, 2018 (DARRTS Reference ID: 4299344).

[4] Meeting Request – Written Responses, filed under BLA 103979 on January 18, 2019 (DARRTS Reference ID: 4378266).

[5] Meeting Minutes, filed under BLA 103979 on June 3, 2019 (DARRTS Reference ID: 4442233).

2. Protocol: Epidemiologic Study of the Natural History of Fabry Disease, March 22, 2001, submitted to BLA 103979 (eCTD 0376) on July 9, 2018.
3. Addendum to Final Clinical Study Report: Epidemiologic Study of the Natural History of Fabry Disease, January 11, 2011, submitted to BLA 103979 (eCTD 0159) on February 1, 2011.
4. Fabry Disease Registry Protocol (Amendment 5), July 9, 2014, submitted to IND 007616 (eCTD 0360) on September 16, 2014.
5. Case Report Form (CRF) for the Fabry Registry, December 20, 2016, submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
6. Study Report: Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis, January 9, 2020, submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
7. Statistical Analysis Plan: Fabry Registry/Natural History Matched Data, January 13, 2020, submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

2.2 Criteria Applied to Review

DEPI summarized sponsor-submitted documents (listed in Section 2.1) to comprehend the real-world data sources (Fabry Disease Registry and Natural History) used for matched analysis.

DEPI analyzed sponsor-submitted datasets to assess data quality and integrity (*i.e.*, accuracy of Sanofi's narrative descriptions of analytic methods).

3 REVIEW RESULTS

3.1 Epidemiologic Study of the Natural History of Fabry Disease (AGAL-014-01)

3.1.1 Study Overview

The *Epidemiologic Study of the Natural History of Fabry Disease* (AGAL-014-01) used data abstracted from the medical charts of 447 patients to define the natural history of Fabry disease (disease course in the absence of ERT). See **APPENDIX 1** for a tabular summary of AGAL-014-01.

3.1.2 Study Objective

AGAL-014-01 sought to characterize the natural history of Fabry disease.

3.1.3 Study Methods

3.1.3.1 Study Setting

Employees of a contract research organization ((b) (4)) abstracted patient charts at 27 clinical sites (five countries) with access to patients with Fabry disease.

3.1.3.2 Eligibility Criteria
Patient eligibility required a diagnosis of Fabry disease without other major illness (*e.g.*, cancer or HIV/AIDS) or investigator-determined renal disease that might "confound assessment of Fabry disease symptoms."[6]

3.1.3.3 Exposure and Outcome Variables
Natural history analyses truncated follow-up upon first exposure to a disease-specific therapy.[7]

Outcome variables included:

- Renal disease progression – eGFR slope, proteinuria, chronic renal insufficiency (serum creatinine ≥1.5 mg/dL).
- Renal events – kidney transplantation, chronic dialysis (≥40 days).
- Cardiac events – myocardial infarction, change in cardiac status (defined by percutaneous transluminal coronary angioplasty, intra-aortic balloon pump placement, coronary artery bypass graft surgery, valve replacement for ischemic heart disease, or hospitalization for heart disease), arrhythmia, angina, cardiac failure.
- Cerebrovascular events – ischemic or hemorrhagic stroke, transient ischemic attack (TIA).
- Death.

3.1.3.3 Other Variables
Other variables available for analysis included sex, race, *GLA* genotype, αGAL enzyme activity, family history of Fabry disease, body weight, height, blood pressure, and concomitant use of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

3.1.3.4 Sample Size and Power
AGAL-014-01 abstracted the medical charts for 447 Fabry disease patients (58.5% men, mean age at last contact 38.5 years).

3.1.3.5 Statistical Analysis
See Section 3.3 (below).

---

[6] Genzyme, Case Report Forms (12/MAR/2001 Version 1), Protocol No. AGAL-014-01, Epidemiologic Study of the Natural History of Fabry Disease, submitted to BLA 103979 (eCTD 0159) on February 1, 2011, p. 4.1.

[7] AGAL-014-01 collected information about enzyme replacement therapy (ERT). However, the study period for AGAL-014-01 preceded regulatory approvals for ERT (last patient chart abstracted in 2002 for AGAL-014-01 and agalsidase beta approved by FDA in April 2003.) AGAL-014-01 recorded investigational or compassionate use of ERT in 119 of 447 (26.6%) patients. The first exposure to agalsidase beta in AGAL-014-01 occurred on June 9, 1998.

3.1.3.6 Quality Controls

Each clinical site maintained a logbook that recorded the enrollment status of patients considered for AGAL-014-01. To obtain patient consent, AGAL-014-01 hired a tracing firm to locate patients lost to clinical contact. Supervisors re-abstracted a 10% sample of patient charts as a quality check. (b) (4) double-entered abstracted data into an Oracle database.

3.1.4 Results

3.1.4.1 Clinical Site Information

AGAL-014-01 enrolled 447 patients from 27 clinical sites (16.7 patients per site) in five countries (Table 1). The six largest clinical sites screened 592 patient charts to enroll 331 eligible patients (74.0% of all patients in AGAL-014-01).[8]

Table 1: Patient enrollment, by country (AGAL-014-01).

Country	Number of Clinical Sites	Number of Patients Enrolled
USA	19	327
Czech Republic	1	43
Canada	5	34
The Netherlands	1	24
Denmark	1	19
Total	27	447

SOURCE: Table prepared by DEPI from General Study Information - Study Sites and Investigators, Epidemiologic Study of the Natural History of Fabry Disease (AGAL-014-01), February 11, 2020, submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

3.1.4.2 Enrolled Population

AGAL-014-01 enrolled 447 patients (including 23 with clinical history ending in death), 62.4% men and mean age 38.5 years at last contact. The clinical record for 286 patients (64.0% of total) ended in 2001 or 2002 (Table 2).

[8] Mount Sinai School of Medicine (New York; N=109 enrolled), National Institute of Neurological Disorders and Stroke (Bethesda; N=88), Children's Hospital (Denver; N=45), University Hospital (Prague; N=43), Academisch Medisch Centrum (Amsterdam; N=24), and University of California (San Francisco; N=22).

Table 2: Patient characteristics, by vital status (AGAL-014-01).

Characteristic	Vital Status, N		Total N	Percent of Total
	Alive	Dead		
N	453	24	447	100.0
Country				
USA	306	21	327	73.2
Czech Republic	43	0	43	9.6
Canada	33	1	34	7.6
The Netherlands	24	0	24	5.4
Denmark	18	1	19	4.3
Sex				
men	259	20	279	62.4
women	165	3	168	37.6
Age (years) at last contact				
<5	2	0	2	0.4
5-9	8	0	8	1.8
10-4	19	0	19	4.3
15-19	34	0	34	7.6
20-29	55	0	55	12.3
30-39	99	2	101	22.6
40-49	123	8	131	29.3
50-59	58	13	71	15.9
60-69	20	0	20	4.5
70-79	6	0	6	1.3
Year of last contact				
1965-1990	13	2	15	3.4
1991-1995	19	3	22	4.9
1996-2000	110	14	124	27.7
2001	230	2	232	51.9
2002	52	2	54	12.1

SOURCE: Table prepared by DEPI from tabulation datasets (DEMOG_1, SNAME_0, DEATH_0, CHRON_0, TRANS_0, CARDI 1, CHSTAT_2, CEREBR_0, LABS_0, LABS_1, AND WTHT_0) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

FOOTNOTE: Date of last contact determined by date of death (if known) or latest non-missing date for (1) Fabry disease symptom onset, (2) Fabry disease diagnosis, (3) clinical events, (4) blood draws, or (5) body weight or height measurements.

3.1.4.3 Outcomes

AGAL-014-01 documented death or ≥1 event (renal, cardiac, or cerebrovascular) in 161 men

(57.7% of 279) and 73 women (43.5% of 168). Supporting Table 1 tabulates patients by sex, age, vital status, occurrence of ≥1 event, and timing of last event in relation to the initial diagnosis of Fabry disease.

3.2 Fabry Disease Registry (DIREGC07006; NCT00196742)

3.2.1 Study Overview

The *Fabry Disease Registry* (DIREGC07006) constructed patient cohorts with data provided by investigators at clinical sites with access to patients with Fabry disease. See **APPENDIX 2** for a tabular summary of DIREGC07006.

3.2.2 Study Objective

DIREGC07006 sought to understand the natural history of Fabry disease and the long-term safety and effectiveness of agalsidase beta (Fabrazyme®).

3.2.3 Study Methods

3.2.3.1 Study Setting

DIREGC07006 obtained data about 6,099 patients (enrolled in April 2001 through December 2017) from investigators at 204 clinical sites in 42 countries. At enrollment (posthumous enrollment permitted), investigators transferred historical data to case report forms (CRFs). Investigators performed follow-up assessments at "regular intervals" with guidance provided by separate Recommended Schedules of Assessments for adult (≥18-year-old) and pediatric (<18-year-old) patients.[9]

3.2.3.2 Eligibility Criteria

Patient eligibility required Fabry disease confirmed by *GLA* mutation or αGAL deficiency.

3.2.3.3 Exposure and Outcome Variables

DIREGC07006 collected patient data about Primary Fabry Therapy, defined as treatment with an enzyme replacement or oral therapy for Fabry disease. The CRF instructed investigators to submit Primary Fabry Therapy data "every six months or at the time of any treatment regimen changes."[10]

Outcome variables included:

---

[9] Fabry Disease Registry Protocol (Amendment 5), Recommended Schedules of Assessments, Section 17.1, pp. 20-23.

[10] Fabry Registry, Case Report Form (Version 20-Dec-2016), submitted to BLA 103979 (eCTD 0415) on February 14, 2020 p. 22.

- Renal disease progression – eGFR slope, proteinuria.
- Renal events – kidney transplantation, chronic dialysis.
- Cardiac events – myocardial infarction, significant cardiac procedure, arrhythmia, angina pectoris, cardiac failure, cardiac syncope.[11]
- Cerebrovascular events – ischemic or hemorrhagic stroke.
- Death.

3.2.3.3 Other Variables
Other variables available for analysis included sex, race, *GLA* genotype, αGAL enzyme activity, family history of Fabry disease, body weight, height, blood pressure, secondary Fabry disease therapy (*i.e.*, concomitant medication, including ACEI and ARB).

3.2.3.4 Sample Size and Power
DIREGC07006 enrolled 6,099 patients with Fabry disease.

3.2.3.5 Statistical Analysis
See Section 3.3 (below).

3.2.3.6 Quality Controls
Quality controls included training for physicians and data entry personnel at clinical sites and data checks for missing data points, incomplete information, and data discrepancies.

3.2.4 Results

3.2.4.1 Clinical Site Information
DIREGC07006 enrolled 6,099 patients from 204 clinical sites (29.9 patients per site) in 42 countries. Clinical sites in 13 countries enrolled 5,487 patients (90.0% of total; Table 3).

Table 3: Patient enrollment, by country, sorted in descending order by the number of patients enrolled (DIREGC07006).

Country	Number of Sites	Number of Patients
United States	85	2,457
United Kingdom	5	674
Germany	4	492
Canada	10	356

[11] Significant cardiac procedures include angioplasty, balloon pump, stent, bypass graft, valvular replacement, implantable cardioverter defibrillator (ICD), pacemaker, other, and unknown.

Country	Number of Sites	Number of Patients
France	3	317
Italy	8	291
Brazil	9	254
Australia	5	184
Czech Republic	1	128
Taiwan	11	102
Finland	1	91
Denmark	1	72
Chile	6	69
Other countries	55	612
All countries	204	6,099

SOURCE: Table prepared by DEPI from the DM tabulation dataset and General Study Information - Study Sites and Investigators, Fabry Disease Registry (DIREGC07006), January 24, 2020, submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

3.2.4.2 Enrolled Population

DIREGC07006 enrolled 6,099 patients (43.9% men and mean age 37.6 years). Nearly all patients (99.2%) entered DIREGC07006 in 2003 or later (Table 4). (FDA approved agalsidase beta in 2003.)

Table 4: Patient characteristics at enrollment, by sex (DIREGC07006).

Characteristic	Sex, N		Total N	Percent of Total
	Women	Men		
Region				
North America	1,581	1,232	2,813	46.1
Europe	1,408	1,070	2,478	40.6
Asia/Australia	202	217	419	6.9
South America	233	156	389	6.4
Year				
2001-2002	15	33	48	0.8
2003-2007	1,106	1,059	2,165	35.5
2008-2012	889	618	1,507	24.7
2013-2017	1,414	965	2,379	39.0
Age (years)				
<5	56	99	155	2.5
5-9	116	111	227	3.7
10-4	175	182	357	5.9
15-19	217	228	445	7.3

Characteristic	Sex, N		Total N	Percent of Total
	Women	Men		
20-29	529	419	948	15.5
30-39	618	520	1,138	18.7
40-49	661	542	1,203	19.7
50-59	605	369	974	16.0
60-69	328	163	491	8.1
70-85	119	42	161	2.6
Duration since Fabry disease diagnosis				
unknown	322	184	506	8.3
<1 year	1,139	834	1,973	32.3
≥1 year, <2 years	524	355	879	14.4
≥2 year, <3 years	358	207	565	9.3
≥3 years, <4 years	186	143	329	5.4
≥4 years, <5 years	123	103	226	3.7
≥5 years, <10 years	356	317	673	11.0
≥10 years	416	532	948	15.5

SOURCE: Table prepared by DEPI from tabulation datasets (DM, DS, and DX) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
FOOTNOTE: Date of Fabry disease diagnosis replaced by (1) date of birth, if date of diagnosis earlier than date of birth (N=20) and (2) date of enrollment, if date of diagnosis later than date of enrollment (N=25).

3.2.4.3 Exposure

DIREGC07006 documented use of agalsidase beta as the initial Primary Fabry Therapy in 1,524 men (57.0% of all men) and 1,118 women (32.7% of all women). Among these patients choosing agalsidase beta as the initial Primary Fabry Therapy, 394 men and 531 women started therapy after enrolling in the Fabry Disease Registry.

3.2.4.4 Outcomes

DIREGC07006 documented death or ≥1 event (renal, cardiac, or cerebrovascular) with non-missing start date (before or after date of enrollment to the Fabry Disease Registry) in 1,068 men (39.9% of 2,675) and 786 women (23.0% of 3,424). As shown in Table 5, 265 men and 241 women first experienced a renal, cardiac, or cerebrovascular event after enrolling in the Fabry Disease Registry.

Table 5: Patients with at least one renal, cardiac, or cerebrovascular event, by sex and event start date in relation to date of enrollment (DIREGC07006).

Vital Status	Event Status	Women	Men	Total
Dead	No events	16	23	39
Alive	No events	2,638	1,607	4,245
Dead or Alive	≥1 event before enrollment (with or without events after enrollment)	529	780	1,309
Dead or Alive	No events before enrollment, ≥1 event after enrollment	241	265	506

SOURCE: Table prepared by DEPI from tabulation datasets (DM, DS, RE, CE, and SE) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
FOOTNOTE: DIREGC07006 enrolled 7 women and 19 men posthumously.

3.3 Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01)

3.3.1 Patient Selection

Matched analysis used the following criteria to identify treated patients in the Fabry Disease Registry (DIREGC07006):

- Criteria for inclusion (all required):
  - non-missing value for sex.
  - non-missing value for date of birth.
  - age ≥16 years when agalsidase beta initiated as first Primary Fabry Therapy.
- Criteria for exclusion:
  - *GLA* mutation classified as neutral allelic variant.[12]
  - missing value for phenotype.[13]
  - dialysis or kidney transplantation before starting treatment with agalsidase beta.

These criteria selected 2,079 treated patients (34.1% of 6,099; Table 6).

[12] Neutral allelic variants: A143T, P60L, D313Y, R118C, T385A, IVS0-10 C>T, or complex haplotype: IVS0-10 C>T/IVS4-16A>G/IVS6-22C>T).

[13] Patient not found in ADPHENO analysis dataset.

Table 6: Patient loss from Fabry Registry (N=6,099) after sequential application of eligibility criteria for matched analysis.

Reason excluded	Number Excluded	Number Remaining
Sex missing	0	6,099
Date of birth missing	0	6,099
Neutral *GLA* variant	246	5,853
Phenotype missing	24	5,829
Not treated with AGAL as 1° therapy	3,250	2,579
AGAL treatment dates missing	5	2,574
AGAL started before age 16 years	310	2,264
AGAL started after renal event	185	2,079

SOURCE: Table prepared by DEPI from tabulation (DM, EX, and RE) and analysis datasets (ADPHENO) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: AGAL – agalsidase beta (Fabrazyme®); *GLA* – galactosidase alpha.
FOOTNOTE: DEPI identified 24 missing patient records in ADPHENO.

Matched analysis used the following criteria to select untreated patients from the Natural History study (AGAL-014-01):

- Criteria for inclusion (all required):
  - non-missing value for sex.
  - non-missing value for date of birth.
  - non-missing value for date of symptom onset.
  - non-missing value for phenotype.

These criteria selected 264 untreated patients (59.1% of 447; Table 7).

Table 7: Patient loss from Natural History (N=447) after sequential application of eligibility criteria for matched analysis.

Reason excluded	Number Excluded	Number Remaining
Sex missing	0	447
Date of birth missing	0	447
Phenotype missing	0	447
Symptom onset date missing	183	264

SOURCE: Table prepared by DEPI from tabulation (DEMOG_1) and analysis datasets (ADPHE014) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

3.3.2 Primary Efficacy Endpoint

3.3.2.1 Outcome Definition

Matched analysis assessed the primary efficacy endpoint of eGFR (expressed in units of mL/min/1.73 m^2) as calculated by the CKD-EPI formula from variable values for serum creatinine concentration (measured in local laboratories), sex, age, and black race.

3.3.2.2 Matching Procedure

The matching algorithm for eGFR analysis identified treated patients with a baseline assessment of kidney function. To establish baseline kidney function, the matching algorithm used the result from an index eGFR determined (1) within six months before or after the treatment start date for agalsidase beta and (2) before patient switch to a Primary Fabry Therapy other than agalsidase beta. To permit assessment of change in kidney function, the matching algorithm also required results from one or more post-index eGFRs determined in the 6-month through 5-year post-index period (truncated by switch to a Primary Fabry Therapy other than agalsidase beta, such as agalsidase alfa, or first renal event, such as kidney transplantation or chronic dialysis). These criteria excluded 724 (34.8% of 2,079; Table 8) patients from the treated group (Table 6), thereby leaving 1,355 patients for matching.

Table 8: Loss of treated patients from Fabry Registry (N=2,079) after sequential application of eligibility criteria pertaining to the primary efficacy endpoint (change in kidney function).

Reason excluded	Number Excluded	Number Remaining
No usable eGFR results available	59	2,020
Usable eGFR result not available for assessment of baseline kidney function	462	1,558
Usable eGFR result not available for assessing change in kidney function	203	1,355

SOURCE: Table prepared by DEPI using SAS code (adgfrfz.sas and adgfall.sas), tabulation datasets (DM, EX, and RE), and analysis datasets (ADPOP, ADLB, ADSL) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATION: eGFR – estimated glomerular filtration rate.

To identify natural history patients suitable for assessment of the primary efficacy endpoint, the matching algorithm required untreated patients with results from at least two useable eGFRs determined more than six months, but less than five years apart. The matching algorithm restricted analysis to eGFRs (index eGFR or otherwise) determined (1) after age 16 years, (2) after onset of Fabry disease symptoms, (3) before Primary Fabry Therapy, and (4) before first renal event (kidney transplantation or dialysis ≥40 days). These criteria excluded 140 (53.0% of 264; Table 7) patients from the untreated group (Table 6), thereby leaving 124 patients for matching (Table 9).

Table 9: Loss of untreated patients from Natural History (N=264) after

sequential application of eligibility criteria pertaining to the primary efficacy endpoint (change in kidney function).

Reason excluded	Number Excluded	Number Remaining
Fabry treatment history not known	1	263
No eGFR results available	18	245
All available eGFR results unusable	26	219
Only one usable eGFR result available	57	162
More than one usable eGFR result available, but no two results 183 to 1,825 days apart	38	124

SOURCE: Table prepared by DEPI using tabulation (DEMOG_1, CLINTR_2, CHRON_0, and TRANS_0) and analysis datasets (ADLB014) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATION: eGFR – estimated glomerular filtration rate.
FOOTNOTE: Using eGFRs determined (1) after age 16 years, (2) after onset of Fabry disease symptoms, (3) before Primary Fabry Therapy, and (4) before first renal event (kidney transplantation or dialysis ≥40 days).

The matching algorithm used three factors (sex, phenotype, and age) to pair (if possible) each treated patient with a randomly selected untreated patient. For each treated patient, the matching algorithm matched an untreated patient with same sex, same phenotype, and eGFR assessed at an age approximating the treated patient's index age (±5 years).[14]

An algorithm used data available for *GLA* genotype and diagnostic αGAL activity to categorize patients according to the following 3-level phenotype hierarchy:

- Classic Fabry phenotype – *GLA* genotype classified as classic by the International Fabry Disease Genotype-Phenotype Database (dbFGP; August 2018) or leukocyte αGAL activity ≤4 nmol/hr/mg protein or plasma αGAL activity ≤1.5 nmol/hr/mL plasma (if leukocyte αGAL activity not known).

- Late-Onset Fabry phenotype – *GLA* genotype classified as late-onset by dbFGP.

- Other/Unclassified/Missing Fabry phenotype.

3.3.2.3 Matched Population

The matching algorithm found an untreated-patient match for 1,138 (84.0%) of 1,355 match-eligible Fabry Registry patients (Table 8). The matching algorithm found matches for 973 (93.4%) of 1,042 patients with Classic phenotype and 570 (95.5%) of 597 male patients with

[14] Index age for matching defined by the treated patient's age (baseline age) on a date determined by an eGFR assessed six months before or after the start date for agalsidase beta treatment.

Classic phenotype (Supporting Table 2).

Each match-eligible Natural History patient (N=124; Table 9) found one or more matches in the Fabry Registry. Table 10 distributes Natural History patients by the number of times matched to patients in the Fabry Registry. For example, the algorithm selected one Natural History as a match for 20 different patients in the Fabry Registry.

Table 10: Natural History patients (N=124), by number of matches in Fabry Registry (for analysis of primary efficacy endpoint).

Number of Fabry Registry matches	N
4	1
5	5
6	21
7	50
8	8
9	4
10	7
11	2
12	2
14	1
16	4
17	7
18	9
19	2
20	1

SOURCE: Table prepared by DEPI using SAS code (adgfall.sas) and analysis dataset (ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

Treated-untreated matched pairs (56.6% men, 85.5% Classic phenotype) differed on baseline age by mean 3.1 years.[15]

Table 11 summarizes fixed characteristics in treated and untreated groups. Differences between groups included (1) geographic region (USA and Canada) – 53.4% (treated) *vs.* 88.5% (weighted

[15] With 823 treated patients older than untreated match by mean 3.3 years and 315 treated patients younger than untreated match by mean 2.5 years.

percent in untreated) and (2) age at Fabry disease diagnosis (≥33 years) – 49.2% (treated) *vs.* 31.1% (weighted percent in untreated). The difference with respect to age at diagnosis appeared similarly extreme in the subgroup of men with Classic phenotype, age at diagnosis (≥33 years) – 41.1% (treated) *vs.* 23.9% (weighted percent in untreated; Supporting Table 3).

Table 11: Fixed characteristics (matched population for primary efficacy endpoint).

	Fabry Registry (N=1,138)		**Natural History (N=124)**		
Characteristic	**N**	**%**	**N**	**%**	**%***
Sex					
Men	644	56.6	89	71.8	56.6
Women	494	43.4	35	28.2	43.4
Phenotype					
Classic	973	85.5	104	83.9	85.5
Other/Unclassified/Missing	165	14.5	20	16.1	14.5
Region					
USA and Canada	608	53.4	111	89.5	88.5
Europe	430	37.8	13	10.5	11.5
Other	100	8.8	0	0.0	0.0
Age at symptom onset (years)					
UNKNOWN	(263)				
0-7	243	27.8	47	37.9	31.2
8-11	213	24.3	40	32.3	31.1
12-24	199	22.7	21	16.9	20.4
25-63	220	25.1	16	12.9	17.3
Age at Fabry disease diagnosis (years)					
UNKNOWN	(19)		(5)		
0-20	286	25.6	43	36.1	33.6
21-32	282	25.2	43	36.1	35.3
33-43	264	23.6	23	19.3	19.2
44-63	287	25.6	10	8.4	11.9
ACEI/ARB use any time during follow-up					
No/UNKNOWN	483	42.4	89	71.8	72.1
Yes	655	57.6	35	28.2	27.9
Urine protein sample source					
NONE	276	24.3	52	41.9	42.2
24-hour urine protein	460	40.4	39	31.5	31.1
Spot urine protein	348	30.6	0	0.0	0.0
24-hour urine albumin	12	1.0	0	0.0	0.0
Spot urine albumin	42	3.7	0	0.0	0.0
Dipstick urine protein	0	0.0	33	26.6	26.7

SOURCE: Table prepared by DEPI using analysis dataset (ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: eGFR – estimated glomerular filtration rate; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

FOOTNOTES:

1. Column indicated by asterisk provides results weighted by matched design (each Natural History patient weighted by 124*i*/1138, *i*=number of times used as a Fabry Registry match). Values in parentheses indicate counts excluded from calculation of column percentages.
2. On June 5, 2020, Sanofi disclosed (BLA 103979, eCTD 0426) a programming error expected to impact results shown for urine protein sample source in the Natural History population.

Table 12 summarizes baseline characteristics for treated patients (N=1,138) and N=1,138 matches to N=124 untreated patients. Differences according to treatment included (1) baseline year (a difference intrinsic to study designs that use historical controls), (2) baseline age (≥40 years) – 49.0% (treated) *vs.* 43.9% (untreated), and (3) baseline eGFR (<90 mL/min/1.73 m^2) – 44.7% (treated) *vs.* 58.3% (untreated). The difference with respect to baseline eGFR appeared less extreme in the subgroup of men with Classic phenotype, baseline eGFR (<90 mL/1.73 min/m^2) – 43.0% (treated) *vs.* 47.4% (untreated; Supporting Table 4).

Table 12: Baseline characteristics (age and year), duration of follow-up, and number of times eGFR assessed during follow-up (matched population for primary efficacy endpoint).

	Fabry Registry (N=1,138)		**Natural History**
Characteristic	**N**	**%**	**%***
Baseline age (years)			
16-29	285	25.0	25.7
30-39	295	25.9	30.3
40-49	297	26.1	28.2
50-82	261	22.9	15.7
Baseline year			
1971-1992	0	0.0	18.5
1993-1997	0	0.0	38.0
1998-2001	110	9.7	43.5
2002-2005	451	39.6	0.0
2006-2017	577	50.7	0.0
Baseline eGFR (mL/min/1.73 m^2)			
≥90 (Stage 1)	629	55.3	41.7
60-89 (Stage 2)	326	28.6	38.8
30-59 (Stage 3)	135	11.9	13.1
15-29 (Stage 4)	43	3.8	5.7
<15 (Stage 5)	5	0.4	0.7
Duration of follow-up (years)			
0.5-1.9	257	22.6	47.4
2.0-3.4	267	23.5	28.0
3.5-4.4	271	23.8	16.4
4.5-5.0	343	30.1	8.2

Characteristic	Fabry Registry (N=1,138)		Natural History
	N	%	%*
Number of follow-up eGFR assessments			
1	149	13.1	29.3
2-3	289	25.4	29.8
4-8	429	37.7	32.5
≥9	271	23.8	8.4

SOURCE: Table prepared by DEPI using analysis datasets (ADGFMXX and ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATION: eGFR – estimated glomerular filtration rate.
FOOTNOTES: Column indicated by asterisk provides results for 1,138 matches – 124 Natural History patients individually matched (with possibly different baseline ages) to between 4 and 20 patients in the Fabry Registry (Table 10).

Matched analysis assessed change in kidney function (Table 12):

- With a single follow-up eGFR in 13.1% of 1,138 patients from the Fabry Registry population and in 29.3% of 1,138 matches from the Natural History population.

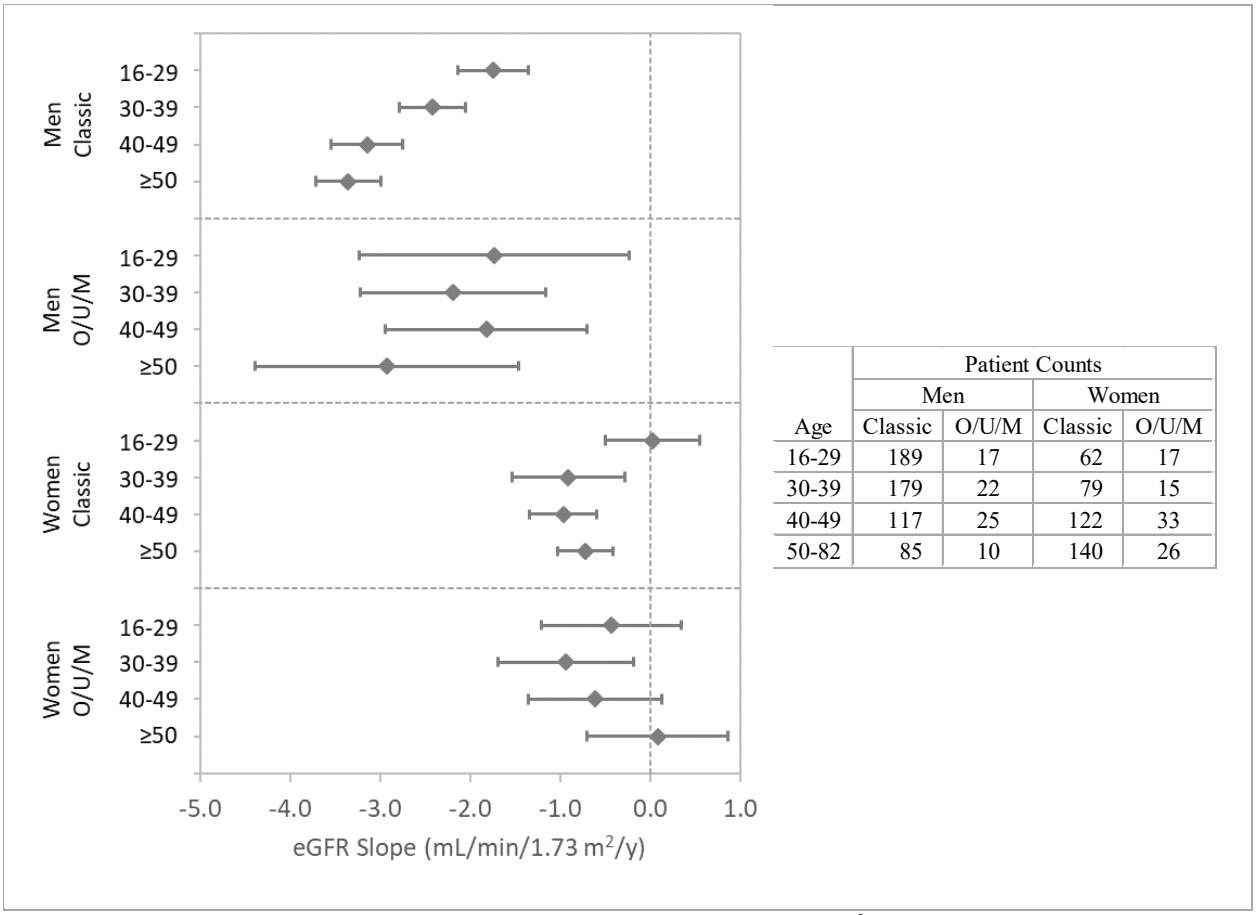
- Over a follow-up duration less than two years in 22.6% of 1,138 patients from the Fabry Registry population and in 47.4% of 1,138 matches from the Natural History population.

3.3.2.4 Results

Linear mixed models estimated annual change in eGFR (expressed in units of mL/min/1.73 m^2/y).[16] Model inputs included the baseline eGFR and subsequent eGFRs determined between six months and five years post baseline.

As shown in Figure 1 for treated patients in the Fabry Registry, kidney function appeared to decline more rapidly in men than women, particularly older men with Classic phenotype.

[16] Linear mixed (random-intercept random-slope) model of eGFR over time with intercept and time specified as random effects (covariance unstructured), intercept and time specified as fixed effects, and untreated patients inverse weighted by frequency (for designs that match untreated patient more than once; Table 10).



	Patient Counts			
	Men		Women	
Age	Classic	O/U/M	Classic	O/U/M
16-29	189	17	62	17
30-39	179	22	79	15
40-49	117	25	122	33
50-82	85	10	140	26

Figure 1: Annual change in estimated glomerular filtration rate (mL/min/1.73 m^2/y), estimates (diamonds) and standard errors (error bars), in treated patients from Fabry Registry (N=1,138), by sex, phenotype (Classic or O/U/M – Other / Unclassified / Missing), and baseline age (years). Plot prepared by DEPI using linear mixed models and analysis datasets (ADGFMXX and ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

Overall, kidney function declined less rapidly in treated (-1.7 mL/min/1.73 m^2/y) than untreated patients (-3.0 mL/min/1.73 m^2/y; p<.001; Table 13). Kidney function also declined less rapidly in treated than untreated men with Classic phenotype (a subgroup of interest; -2.5 *vs.* -3.8 mL/min/1.73 m^2/y; p-value 0.012).

Table 13: Results from linear mixed models for eGFR change in treated and untreated patients matched on sex, phenotype, and baseline age.

				eGFR change — mL/min/1.73 m^2/y				
				Treated		**Untreated**		
Sex	**Phenotype**	**N_1**	**N_0**	**EST**	**95% CI**	**EST**	**95% CI**	**p-value**
All	ALL	1,138	124	-1.7	-2.0, -1.4	-3.0	-3.4, -2.6	<.001
	Classic	973	104	-1.8	-2.1, -1.5	-2.6	-3.1, -2.1	0.018
Men	ALL	644	89	-2.4	-2.8, -2.0	-4.6	-5.1, -4.0	<.001
	Classic	570	81	-2.5	-2.9, -2.1	-3.8	-4.4, -3.2	0.012
Women	ALL	494	35	-0.7	-1.1, -0.3	-0.5	-1.0, 0.1	0.799
	Classic	403	23	-0.8	-1.2, -0.3	0.0	-0.6, 0.7	0.290

SOURCE: Table prepared by DEPI using analysis datasets (ADGFMXX and ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: eGFR – estimated glomerular filtration rate; N_1 – number of treated patients; N_0 – number of unique untreated patients; EST – model estimate; CI – confidence interval; P-value – statistical significance of difference between treated and untreated groups.
FOOTNOTE: Reproducing results presented as Table 8 (p. 60) and Table 13 (pp. 70-71) in the Study Report for Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01).

The treated *vs.* untreated difference in kidney function decline appeared robust to sensitivity analyses summarized in Table 14.

Table 14: Results from linear mixed models (main analysis and selected sensitivity analyses) for eGFR change (mL/min/1.73 m^2/y) in treated (Fabry Registry, FR) and untreated (Natural History, NH) patients.

Linear mixed model	N_1	N_0	eGFR change		p-value
			FR	NH	
Treated and untreated patients matched on sex, phenotype, and baseline age	1,138	124	-1.7	-3.0	<.001
With statistical control for baseline age (continuous) and eGFR (continuous)	1,138	124	-1.7	-3.0	<.001
With statistical control for proteinuria category [1,2]	1,138	124	-1.7	-3.0	<.001
With statistical control for ACEI/ARB use during follow-up	1,138	124	-1.7	-3.0	<.001
In matched pairs concordant on ACEI/ARB use during follow-up	318	35	-1.9	-4.0	<.001
In matched pairs concordant on ACEI/ARB non-use (or unknown use) during follow-up	808	87	-1.6	-2.5	0.038
Treated and untreated patients uniquely matched on sex, phenotype, and baseline age	124	124	-1.5	-2.8	0.020
Treated and untreated patients matched on sex, phenotype, baseline age, and baseline eGFR (±5 mL/min/1.73 m^2)	950	122	-1.6	-3.3	<.001
In matched pairs concordant on baseline eGFR ≥60 mL/min/1.73 m^2	850	102	-1.3	-2.9	<.001

SOURCE: Table prepared by DEPI from Table 8 (p. 60), Table 11 (p. 67), and Table 12 (p. 69) in the Study Report for Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01).
ABBREVIATIONS: eGFR – estimated glomerular filtration rate; N_1 – number of treated patients; N_0 – number of unique untreated patients; P-value – statistical significance of difference between treated and untreated groups.
FOOTNOTES:
1. Five baseline proteinuria categories defined by values for 24-hour urine protein, spot urine protein, 24-hour urine albumin, spot urine albumin, and dipstick urine protein: urine protein (1) <30 mg/dL or dipstick negative, (2) 30 to <100 mg/dL or dipstick 1+, (3) 100 to <300 mg/dL or dipstick 2+, (4) ≥300 mg/dL or dipstick 3+, and (5) Missing.
2. On June 5, 2020, Sanofi disclosed (BLA 103979, eCTD 0426) a programming error expected to impact results from statistical control for proteinuria category.

3.3.3 Secondary Efficacy Endpoint

3.3.3.1 Outcome Definition
Matched analysis assessed a secondary outcome defined as a composite of four clinical event categories:

- Renal Events – kidney transplantation or chronic dialysis.
- Cardiovascular Events – congestive heart failure, atrial fibrillation, ventricular tachycardia, or significant cardiac procedure (pacemaker, bypass graft, angioplasty, balloon pump, stent, or implantable cardioverter defibrillator).
- Cerebrovascular Events – hemorrhagic or ischemic stroke.
- Death from Any Cause.

3.3.3.2 Matching Procedure
An algorithm attempted to match a follow-up interval for every treated patient (N=2,079; Table 6) to a follow-up interval for an untreated patient (N=264; Table 7) with same sex and phenotype (Classic or Other/Unclassified/Missing). This algorithm defined match-eligible follow-up intervals by excluding follow-up time occurring (1) before age 16 years, (2) before symptom onset (untreated group only), (3) after switch to a Primary Fabry Therapy other than agalsidase beta (treated group) or initiation of ERT (untreated group), (4) after a renal event (kidney transplantation or chronic dialysis), and (5) after an event, if subsequently followed by the same event.[17]

As a first step, the algorithm determined the age (index age) when a Fabry Registry patient started agalsidase beta. As a next step, the algorithm randomly selected (as an age match) a Natural History interval covering an age range that spanned the index age determined for the corresponding Fabry Registry patient.

The observation period for clinical events in treated and untreated patients began on the index age and ended on first post-index clinical event.

3.3.3.3 Matched Population
The algorithm matched follow-up intervals (with possibly different index ages) for 233 Natural History patients (88.3% of 264; Table 7) to 1,754 Fabry Registry patients (84.4% of 2,079; Table 6).

Table 15 distributes Natural History patients by the number of times matched to patients in the Fabry Registry. For example, the algorithm selected one Natural History patient as a match for

[17] Specific to type (*e.g.*, atrial fibrillation in Cardiovascular Event category); an interpretation by DEPI of adev014.sas and adevtfz.sas, SAS code submitted to BLA 103979, eCTD 0415, on February 14, 2020.

21 different patients in the Fabry Registry.

Table 15: Natural History patients (N=233), by number of matches in Fabry Registry (for analysis of secondary efficacy endpoint).

Number of Fabry Registry matches	N
1	6
2	2
3	1
4	16
5	89
6	28
7	8
8	9
9	4
10	16
11	29
12	2
13	2
14	1
16	5
17	7
18	1
19	1
20	5
21	1

SOURCE: Table prepared by DEPI using an analysis dataset (ADEVIDXX) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

The algorithm produced 1,754 matches (54.4% men, 83.0% Classic phenotype, and mean index age 38.3 years).

The algorithm produced matches without regard to kidney function. DEPI assessed the 1,754 matches to identify pairs with eGFR available in both members (465 and 735 matched pairs with eGFR available ±0.5 and ±1.0 years of index age, respectively; Table 16). On average, the Natural History group started follow-up with worse kidney function. When assessed within 0.5 years of index age, for example, 3.7 and 2.8 percent in the Natural History and Fabry History

groups started follow-up in advanced kidney disease (eGFR <15 mL/min/1.73 m^2).

Table 16: Fabry Registry and Natural History intervals (for analysis of secondary efficacy endpoint; N=1,754 matched pairs) with kidney function determined (in both members of pair) by eGFR closest to index age (±0.5 and ±1.0 years).

	Fabry Registry		Natural History	
eGFR (mL/min/1.73 m^2)	**N**	**%**	**N**	**%**
eGFR ±0.5 years of index age	465	100.0	465	100.0
≥90 (Stage 1)	241	51.8	220	47.3
60-89 (Stage 2)	132	28.4	124	26.7
30-59 (Stage 3)	57	12.3	76	16.3
15-29 (Stage 4)	22	4.7	28	6.0
<15 (Stage 5)	13	2.8	17	3.7
eGFR ±1.0 year of index age	735	100.0	735	100.0
≥90 (Stage 1)	408	55.5	355	48.3
60-89 (Stage 2)	198	26.9	200	27.2
30-59 (Stage 3)	80	10.9	109	14.8
15-29 (Stage 4)	30	4.1	41	5.6
<15 (Stage 5)	19	2.6	30	4.1

SOURCE: Table prepared by DEPI using analysis datasets (ADEVIDXX, ADSL, ADLB, and ADLB014) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATION: eGFR – estimated glomerular filtration rate.

3.3.3.4 Results

A clinical event occurred during 437 Fabry Registry and 371 Natural History intervals (incidence 49 *vs.* 69 per 1,000 patient-years; rate ratio, RR, 0.71; Table 1). Of note, renal events accounted for 193 of 371 (52%) total events during untreated follow-up in Natural History patients, but only 135 of 437 (31%) total events during treatment follow-up in Fabry Registry patients. Moreover, matched analysis followed Fabry Registry intervals for median 4.1 years (interquartile range, IQR, 1.9-7.4 years), but Natural History intervals for median 1.9 years (IQR 0.8-4.1 years).

Because of these marked differences in clinical event profile and follow-up duration, DEPI assessed event rates in subgroups defined by sex, Fabry phenotype, and eGFR near index age (Table 17). These sensitivity analyses showed RRs varying between 0.55 and 0.90 (*e.g.*, men with eGFR ≥15 mL/min/1.73 m^2 – determined ±0.5 year of index age – Fabry Registry *vs.* Natural History incidence, 65 *vs.* 95 per 1,000 patient-years, RR 0.69). (See Supporting Table 5 for results from analyses that used a Natural History patient for matching no more than once.)

Table 17: Follow-up intervals with a clinical event, counts (n) and incidence rates (per 1,000 patient-years), by exposure (Fabry Registry or Natural History), study group (all matched pairs, pairs with eGFR

≥15 mL/min/1.73 m^2 – determined ±1.0 year of index age, and eGFR ≥15 mL/min/1.73 m^2 – determined ±0.5 year of index age), sex, and Fabry phenotype.

Study Group	Sex and Phenotype	N	Fabry Registry				Natural History			
			PY	n	Rate	Event Types	PY	n	Rate	Event Types
ALL	ALL	1,754	8,884	437	49	193/75/135/34	5,363	371	69	98/50/193/30
	Men	954	5,208	290	56	97/50/119/24	2,821	284	101	68/39/158/19
	Men Classic	810	4,488	255	57	89/45/100/21	1,954	172	88	54/32/71/15
eGFR ±1.0 y	ALL	686	3,430	188	55	87/32/50/19	1,103	94	85	40/3/45/6
	Men	390	2,081	126	61	44/22/46/14	693	65	94	24/3/32/6
	Men Classic	358	1,948	117	60	40/21/44/12	573	39	68	18/0/15/6
eGFR ±0.5 y	ALL	435	2,286	137	60	59/23/41/14	611	60	98	24/2/32/2
	Men	263	1,472	96	65	28/16/39/13	411	39	95	13/2/22/2
	Men Classic	247	1,403	89	63	25/16/37/11	369	26	71	11/0/13/2

SOURCE: Table prepared by DEPI using analysis datasets (ADEVXTOX, ADEVIDXX, ADSL, ADLB, and ADLB014) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: eGFR – estimated glomerular filtration rate.; N – number of matched interval pairs; PY – patient-years.
FOOTNOTE: Events counts by type presented in the following order: Cardiovascular Events / Cerebrovascular Events / Renal Events / Death.

3.4 Supplemental Pediatric Analyses in the Fabrazyme Disease Registry

Supplemental analyses in the Fabry Disease Registry assessed changes in eGFR and plasma GL-3 (globotriaosylceramide-3, a Fabry disease biomarker) in 2- to <16-year-old children (N=309) exposed to agalsidase beta as first Primary Fabry Therapy. These analyses excluded patients with (1) missing values for date of birth or sex, (2) dialysis or kidney transplantation before first exposure to agalsidase beta, or (3) *GLA* mutation classified as neutral allelic variant. Analyses excluded eGFR and GL-3 values measured after patients (1) switched to a Primary Fabry Therapy other than agalsidase beta or (2) turned 16 years of age.

In children (N=90) with index eGFR (Bedside Schwartz formula) measured within 6 months before or after the agalsidase beta start date and ≥1 eGFR measured between 0.5 and 5.0 years post index, linear mixed models estimated eGFR change at (1) 0.84 mL/min/1.73 m^2/y (95% CI -3.11, 4.80 mL/min/1.73 m^2/y) in 2- to <8-year-old children (N=17) and (2) -0.89 mL/min/1.73 m^2/y (95% CI -2.80, 1.01 mL/min/1.73 m^2/y) in 8- to <16-year-old children (N=73).[18]

Table 18 summarizes results for children (N=101; 70.3% male, 71.3% 8 to ≤16 years in age) with a baseline and ≥1 post-baseline GL-3 value (measured by Sanofi Genzyme LC/MS/MS). Baseline measurements showed high GL-3 (>7.03 µg/mL) in 60 of 101 (59.4%) children. Follow-up measurements 6, 12, and 24 months later (when available) showed high GL-3 in 4 of

[18] Study Report, Table 23, p. 99.

77 (5.2%), 2 of 69 (2.9%), and 1 of 38 (2.6%) children, respectively.

Table 18: Number and percentage of children with normal GL-3 plasma concentration (≤7.03 μg/mL), by sex, age, and time after baseline.

		Baseline			6 Months			12 Months			24 Months		
			GL-3 ≤7.03			GL-3 ≤7.03			GL-3 ≤7.03			GL-3 ≤7.03	
Sex	Age (years)	N	n	%	N	n	%	N	n	%	N	n	%
Male	2 to <8	27	24	88.9	22	2	9.1	21	1	4.8	13	1	7.7
	8 to <l6	44	35	79.5	36	2	5.6	31	1	3.2	14	0	0.0
	ALL	71	59	83.1	58	4	6.9	52	2	3.8	27	1	3.7
Female	2 to <8	2	0	0.0	2	0	0.0	1	0	0.0	2	0	0.0
	8 to <l6	28	1	3.6	17	0	0.0	16	0	0.0	9	0	0.0
	ALL	30	1	3.3	19	0	0.0	17	0	0.0	11	0	0.0
All	2 to <8	29	24	82.8	24	2	8.3	22	1	4.5	15	1	6.7
	8 to <l6	72	36	50.0	53	2	3.8	47	1	2.1	23	0	0.0
	ALL	101	60	59.4	77	4	5.2	69	2	2.9	38	1	2.6

SOURCE: Table prepared by DEPI using analysis datasets (ADPOP, ADSL, and ADGL3) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBEVIATION: GL-3 – globotriaosylceramide-3.
FOOTNOTES:
1. Baseline GL-3 identified by closest measurement to agalsidase beta start date (in window starting 6 months before and ending 4 weeks after agalsidase beta start date).
2. Post-baseline GL-3 identified by measurements closest (±3-month window) to 6-, 12-, and 24-month timepoints.
3. Partly reproducing results presented as Table 26 (p. 105) and Table 27 (p. 106) in the Study Report for Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01). Study Report Table 26 shows 43, 35, 30, and 13 instead of 44, 36, 31, and 14 ≥8- to <l6-year-old boys with GL-3 measured at baseline, 6 months, 12 months, and 24 months, respectively.

3.5 Prescribing Information for Fabrazyme®: Changes Proposed by Sanofi

BLA 103979 Efficacy Supplement-5309 proposes changes to Prescribing Information for Fabrazyme®. New claims possibly supported by Matched Analysis include:

- Indication statement expanded from "use in patients with Fabry disease" to "treatment of patients with Fabry disease" (SECTION 1 : INDICATIONS AND USAGE).
- (b) (4)

An addition to Section 8.4 asserts that (b) (4)

(b) (4)

(b) (4)

- (b) (4)
-
-

4 DISCUSSION

Matched Analysis used the Fabry Disease Registry (DIREGC07006) to identify Fabry disease patients treated with agalsidase beta and a non-contemporaneous Epidemiologic Study of Natural History (AGAL-014-01) to identify Fabry disease patients not treated with agalsidase beta or other ERT.

One analysis matched on sex, age, and Fabry phenotype to measure association between agalsidase beta and change in kidney function (primary efficacy endpoint). Using data for 1,138 treated and 124 untreated patients (untreated patients matched more than once), a linear mixed model showed kidney function declining less rapidly in treated than untreated patients (change in eGFR, -1.7 *vs.* -3.0 mL/min/1.73 m^2/y; p<.001; Table 13).

Another analysis matched on sex, age, and Fabry phenotype to measure association between agalsidase beta and clinical events (secondary efficacy endpoint). Using data for 1,754 treated and 233 untreated patients (untreated patients matched more than once), this analysis showed a first (post-index) clinical event occurring less often in treated than untreated patients (49 *vs.* 69 per 1,000 patient-years; HR 0.67, 95% CI 0.49-0.90, p=0.008; Table 17 and Supporting Table 6).

Sensitivity analyses (restricting to men with Classic Fabry phenotype, controlling for baseline eGFR, baseline proteinuria, or ACEI/ARB use during follow-up, or using untreated patients no more than once) all showed kidney function declining less rapidly in treated than untreated patients (Table 13 and Table 14).

Specific therapeutic benefit from agalsidase beta might wholly or partly explain the slower rates of eGFR decline and lower event rates observed in treated *vs.* untreated patients. Alternatively, treated patients from the Fabry Disease Registry and untreated patients from the Epidemiologic Study of Natural History might differ too much for valid comparison. In this context, FDA

---

[19] Study Report, Figure 2, p. 61.

[20] Study Report, Figure 4, p. 65.

[21] Study Report, Table 25, p. 103.

Guidance for Rare Diseases advises that "a well-designed and conducted natural history study" might provide (in special circumstances) external control for a single-arm clinical (interventional) trial of treatment efficacy (when a two-arm randomized controlled trial is "impractical or unethical").[22] However, the Framework for FDA's Real-World Evidence Program emphasizes the limitation to this approach (*i.e.*, single-arm trial with external historical control) as a difficulty in "reliably selecting a comparable population" because of (1) changes (temporal and geographic variability) in medical practice, (2) non-standardized diagnostic criteria for determining outcomes of therapeutic interest, and (3) variable procedures for clinical follow-up.[23] Matched Analysis extends FDA Guidance by replacing a single-arm clinical trial with real-world evidence (Fabry Disease Registry).

The following paragraphs use selection and information bias as guiding principles for assessment of the comparability (or non-comparability) of treated patients from the Fabry Disease Registry and untreated patients from the Epidemiology Study of Natural History.

Selection Bias. Matched Analysis used a non-contemporaneous (historical) external comparison group, a study design expected to produce (at best) low-level evidence for treatment efficacy because of major inferential threats related to possible non-comparability of treated and untreated groups (despite matching on important determinants of outcome). Non-comparability due to selection bias occurs if factors associated with efficacy endpoints differently determine patient enrollment to the prospective registry (Fabry Disease Registry) and retrospective chart review (Natural History) studies used for matched analysis. Indicators of non-comparability (in addition to understandable discordance between matched groups with respect to clinical site location and calendar time; Table 11 and Table 12) might include the younger age of diagnosis in untreated patients (a possible marker of more aggressive Fabry phenotype; Table 11).

FDA Guidance suggests conditions that might impart credibility to efficacy results from historically controlled studies.[24] Applicable conditions according to Guidance include (1) "well-documented, highly predictable disease course that can be objectively measured and verified" and (2) "drug effect that is large, self-evident, and temporally closely associated with the intervention." These conditions might not apply to Fabry disease, a heterogeneous condition with beneficial effects from treatment possibly delayed by years. With respect to temporality, for example, Matched Analyses assessed drug effects over timeframes that FDA might not regard as temporally close to intervention (eGFR change assessed in treated patients over median 3.8 years, IQR 2.1-4.6 years, N=1,138; clinical events assessed in treated patients over median 4.1 years, IQR 1.9-7.4 years, N=1,754). Matched Analysis estimated clinically meaningful, but not large differences between treated and untreated patients (*i.e.*, eGFR change, -1.7 *vs.* -3.0

---

[22] FDA Guidance for Industry, January 2019, Rare Diseases: Common Issues in Drug Development, accessed at https://www fda.gov/media/119757/download on June 2, 2020, p. 4.

[23] FDA, Framework for FDA's Real-World Evidence Program, December 2018, accessed at https://www fda.gov/media/120060/download on July 15, 2020, p. 20.

[24] Rare Disease Guidance, *op. cit.*, p. 14.

mL/min/1.73 m^2/y; clinical event incidence, 49 *vs.* 69 per 1,000 patient-years). Factors other than the direct pharmacologic action of agalsidase beta might explain these differences.

Information Bias. Despite reliance on information recorded to Case Report Forms (CRFs) with similar data elements, Matched Analysis used possibly non-equivalent methods to collect information (including information about the efficacy endpoints) concerning treated and untreated patients.

- Independent investigators at 204 clinical sites (in 42 countries; Table 3) for the Fabry Disease Registry (data source for treated patients) used both a retrospective and prospective method to collect data about the treatment exposures and efficacy endpoints of interest. Investigators used a retrospective method to transfer pre-enrollment data (obtained by medical record review or patient interview) to CRFs. Investigators also used a prospective method to collect post-enrollment data, subsequently recorded to CRFs at intervals guided by Recommended Schedules of Assessments.

- By comparison, a solitary contract research organization coordinated with 27 clinical sites (in five countries; Table 1) to obtain patient charts and extract historical (retrospective) data about untreated patients (Epidemiologic Study of Natural History).

DEPI regards as speculative and unverified any statement regarding the relative completeness or accuracy of information acquired through these prospective and retrospective methods. Acquisition of complete and accurate information under the prospective method presumes uniform commitment to study protocols and associated data collection procedures. Acquisition of complete and accurate information under the retrospective method presumes dependable access to patient records from all sources, including primary and referral physicians.

Other threats to proper interpretation of results from Matched Analysis include:

- High patient attrition (primarily due to criteria for study inclusion; Table 6, Table 7, Table 8, and Table 9).

- Analysis for efficacy endpoints without regard to patients possibly discontinuing primary treatment with agalsidase beta.

- Imperfect control for Fabry phenotype (*i.e.*, Classic phenotype defined broadly according to data available for *GLA* genotype and αGAL activity as opposed to αGAL activity alone).

- Imperfect control for baseline eGFR despite matching (Table 12).

- Missing data for critical covariates (*e.g.*, baseline proteinuria; Table 11).

- A relatively small number of untreated patients matched with variable frequency to a much larger number of treated patients (*e.g.*, 124 untreated patients selected as matches for 1,138

treated patients in eGFR analysis matching on sex, phenotype, and baseline age; Table 10).[25]

- Limiting sample size, particularly for tightly controlled sensitivity analyses (*e.g.*, clinical event analysis in men with Classic phenotype and eGFR (near baseline, ±0.5 years) ≥15 mL/min/1.73 m^2; Table 17).

On June 5, 2020, Sanofi disclosed (in BLA 103979, eCTD 0426) a programming error impacting one sensitivity analysis presented in the Study Report from Matched Analysis. The sensitivity analysis concerns statistical control for proteinuria category (Table 14). However, any possible result from a corrected sensitivity analysis would not change DEPI's overall assessment of Matched Analysis. The sensitivity analysis merits correction only if relevant to labeling decisions.

BLA 103979 Efficacy Supplement-5309 proposes to add results from Matched Analysis to Prescribing Information (PI) for Fabrazyme®. The results selected for addition suggest beneficial effects from agalsidase beta treatment on kidney function decline (b) (4) (b) (4)). These results, though subject to interpretation, might support traditional approval. (b) (4)

(b) (4)

See **APPENDIX 5** for a summary analysis (RWE Review Framework) formatted for the RWE Subcommittee to the Medical Policy and Program Review Council (MPPRC). CDER recently established the multidisciplinary RWE Subcommittee (in part) because real-world data sources permit a wide range of research designs and analytic methods for controlled comparison.

Sanofi presented and DEPI assessed an approach that individually matched treated and untreated patients from different real-world data sources. One possible alternative might have restricted analysis to data derived solely from the Fabry Disease Registry. The Fabry Disease Registry collected longitudinal data from patients not treated with agalsidase beta and patients treated with an ERT other than agalsidase beta (*i.e.*, agalsidase alfa), in addition to patients treated with agalsidase beta. In principle, this situation provides opportunity for controlled analysis internal to the Fabry Disease Registry. A thoughtfully designed analysis internal to the Fabry Disease Registry might overcome some of the challenges presented to Matched Analysis. Because of

[25] A small number of non-representative patients in the untreated group might exert undue influence on final results.

data limitations that might prohibit effective confounder control by means of propensity-score adjustment or similar method, however, an internal analysis might still not provide satisfactory evidence about the efficacy of agalsidase beta. Regardless, pre-submission review by the RWE Subcommittee might improve future RWE submissions to DRDMG.

5 CONCLUSIONS

Sponsor-submitted documents and datasets described results from additional analyses in the Epidemiologic Study of the Natural History of Fabry Disease (PMC 2421-1) and Fabry Disease Registry (PMC 2421-2).

The Sponsor conducted reasonably transparent analyses that withstood DEPI scrutiny for integrity (a conclusion supported by independent DEPI review and analysis of sponsor-submitted documents and datasets).

The Sponsor's approach to analysis complied with FDA advice offered during pre-submission meetings (*i.e.*, matched study design comparing treated and untreated patients with design and statistical controls for sex, age, Fabry phenotype, and other critical covariates).

The results from analyses using a non-contemporaneous (historical) external comparison group provided low-level evidence for possible treatment benefit from agalsidase beta.

Additional threats to proper interpretation of results included high patient attrition, limiting sample size, and missing data for critical covariates (study limitations disclosed by the Sponsor during pre-submission meetings with FDA).

6 RECOMMENDATIONS FOR DRDMG

DEPI recommends that DRDMG:

- Accept the Study Report from DIREGC07006/AGAL-014-01 as fulfillment for PMC 2421-2.
- Assess results from Matched Analysis (DIREGC07006/AGAL-014-01) as low-level evidence for possible clinical benefit from treatment with agalsidase beta.
- (b) (4)
- Request pre-submission RWE Subcommittee review of future RWE applications to DRDMG.

CC: Dal Pan G / Ball R / Blum M / Li J / Pinheiro S / Sandhu S / Hua W / Callahan C / Lerro C / Booth B / Dunson A / Sun S / Calloway P (OSE)

Wang Y / Usher T (DB-IV)

Joffe H / Smpokou P / Zaidi A / Kong N (DRDMG)

APPENDIX 1: Epidemiologic Study of the Natural History of Fabry Disease

Domain	Description
1.1 Objectives/Aims/Scope	To characterize the natural history of Fabry disease
1.2.1 Design for the Primary Analysis	
1.2.1.2 Data Sources	Clinical records (patient charts)
1.2.1.3 Time Period	Final patient chart abstracted in 2002
1.2.1.4 Criterion (Selection) Standards	Diagnosis of Fabry disease without other major illness (*e.g.*, cancer or HIV/AIDS) or investigator-determined renal disease that might "confound assessment of Fabry disease symptoms"
1.2.1.5 Protected Health Information	Informed consent for release of medical records obtained from patient, guardian, or next of kin
1.2.2 Setting	Clinical sites (27 internationally) with access to clinical records for Fabry disease patients
1.2.3 Exposure/Intervention	None
1.2.4 Outcome(s)	• Renal disease progression – eGFR slope, proteinuria, chronic renal insufficiency (serum creatinine ≥1.5 mg/dL) • Renal events – kidney transplantation, chronic dialysis (≥40 days) • Cardiac events – myocardial infarction, change in cardiac status, arrhythmia, angina, cardiac failure • Cerebrovascular events – ischemic or hemorrhagic stroke, transient ischemic attack (TIA) • Death
1.2.5 Covariates	sex, race, *GLA* genotype, αGAL enzyme activity, family history of Fabry disease, body weight, height, blood pressure, concomitant medication (ACEI or ARB)
1.2.6 Sample Size	N=447 (62.4% men, mean age at last contact 38.5 years)
1.2.7 Statistical Analyses	Descriptive
1.2.8 Study Results	Death or ≥1 event (renal, cardiac, or cerebrovascular) in 161 men (57.7% of 279) and 73 women (43.5% of 168)

ABBREVIATIONS: *GLA* – galactosidase alpha gene; αGAL –galactosidase alpha enzyme; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; eGFR – estimated glomerular filtration rate

APPENDIX 2: Fabry Disease Registry

Domain	Description
1.1 Objectives/Aims/Scope	To understand the natural history of Fabry disease and the long-term safety and effectiveness of agalsidase beta (Fabrazyme®)
1.2.1 Design for the Primary Analysis	
1.2.1.1 Type	Prospective cohort (registry) with periodic clinical assessments guided by recommended schedule
1.2.1.2 Data Sources	Retrospectively (posthumous enrollment permitted) and prospectively collected clinical data transferred at enrollment and "regular intervals" to case report forms by study site investigators
1.2.1.3 Time Period	Patient enrollment April 19, 2001 to December 27, 2017
1.2.1.4 Criterion (Selection) Standards	Fabry disease confirmed by *GLA* mutation or αGAL deficiency
1.2.1.5 Protected Health Information	Informed consent requirements governed by local Institutional Review Boards
1.2.2 Setting	Clinical sites (international) with access to Fabry disease patients
1.2.3 Exposure/Intervention	Primary Fabry Therapy status
1.2.4 Outcome(s)	• Renal disease progression – eGFR slope, proteinuria • Renal events – kidney transplantation, chronic dialysis • Cardiac events – myocardial infarction, significant cardiac procedure, arrhythmia, angina pectoris, congestive heart failure, cardiac syncope • Cerebrovascular events –ischemic or hemorrhagic stroke • Death
1.2.5 Covariates	sex, race, *GLA* genotype, αGAL enzyme activity, family history of Fabry disease, body weight, height, blood pressure, secondary Fabry disease therapy (*i.e.*, concomitant medications, including ACEI and ARB)
1.2.6 Sample Size	N=6,099 (43.9% men, mean age 37.6 years)
1.2.7 Statistical Analyses	Descriptive
1.2.8 Study Results	One or more clinical events (renal, cardiac, cerebro-vascular, or death) with non-missing start date (before or after Fabry Disease Registry enrollment): 1,068 of 2,675 (39.9%) men and 786 of 3,424 (23.0%) women

ABBREVIATIONS: *GLA* – galactosidase alpha gene; αGAL –galactosidase alpha protein; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; eGFR – estimated glomerular filtration rate

APPENDIX 3: Supporting Tables

Supporting Table 1: Patients with and without a study outcome (death or at least one renal, cardiac, or cerebrovascular event), by sex and age at Fabry disease diagnosis (AGAL-014-01).

Sex and age (years) at Fabry disease diagnosis	Alive				Dead
	No Events	At least one clinical event			
		Timing of last event in relation to diagnosis of Fabry disease			
		UNK	Before	After	
Women					
UNK	13	9	0	0	0
<5	5	0	0	1	0
5-9	9	0	0	2	0
10-14	13	0	0	4	0
15-19	9	0	0	3	1
20-29	15	0	1	12	0
30-39	12	0	3	15	0
40-49	13	0	5	8	2
50-59	4	0	0	3	0
60-69	1	0	2	1	0
70-79	1	0	1	0	0
All women	95	9	12	49	3
Men					
UNK	11	9	0	0	1
<5	14	0	0	7	0
10-14	12	0	0	12	0
15-19	19	0	4	11	2
15-19	18	0	1	10	3
20-29	19	0	1	31	5
30-39	14	0	3	29	7
40-49	6	0	2	15	2
50-59	5	0	0	4	0
60-69	0	0	2	0	0
All men	118	9	13	119	20

SOURCE: Table prepared by DEPI from tabulation datasets (demog_1, death_0, chron_0, trans_0, cardi_1, chstat_2, and cerebr_0) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

FOOTNOTE: Clinical events include renal (kidney transplantation or chronic dialysis), cardiac (myocardial infarction, significant cardiac procedure, arrhythmia, angina pectoris, or congestive heart failure), and cerebrovascular events (stroke or transient ischemic attack).

Supporting Table 2: Treated patients matched to an untreated patient (for assessment of primary efficacy endpoint), by matching factors (phenotype, sex, and baseline age).

Phenotype	Sex	Baseline Age (years)	ALL	Matched		
				No	Yes	
			N	N	N	%
Classic	Men	16-29	192	3	189	98.4
		30-39	187	8	179	95.7
		40-49	124	7	117	94.4
		50-82	94	9	85	90.4
	Women	16-29	63	1	62	98.4
		30-39	82	3	79	96.3
		40-49	126	4	122	96.8
		50-82	174	34	140	80.5
Late onset	Men	16-29	5	5	0	0.0
		30-39	7	7	0	0.0
		40-49	15	15	0	0.0
		50-82	26	26	0	0.0
	Women	16-29	9	9	0	0.0
		30-39	15	15	0	0.0
		40-49	15	15	0	0.0
		50-82	22	22	0	0.0
Other/Unclassified/Missing	Men	16-29	18	1	17	94.4
		30-39	23	1	22	95.7
		40-49	26	1	25	96.2
		50-82	16	6	10	62.5
	Women	16-29	17	0	17	100.0
		30-39	15	0	15	100.0
		40-49	33	0	33	100.0
		50-82	51	25	26	51.0
Classic	Men	ALL	597	27	570	95.5
	Women	ALL	445	42	403	90.6
Late onset	Men	ALL	53	53	0	0.0
	Women	ALL	61	61	0	0.0
Other/Unclassified/Missing	Men	ALL	83	9	74	89.2
	Women	ALL	116	25	91	78.4
Classic	ALL	ALL	1,042	69	973	93.4
Late onset	ALL	ALL	114	114	0	0.0
Other/Unclassified/Missing	ALL	ALL	199	34	165	82.9
ALL	ALL	ALL	1,355	217	1,138	84.0

SOURCE: Table prepared by DEPI using SAS code (adgfall.sas) and an analysis dataset (ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.

Supporting Table 3: Fixed characteristics (men with Classic phenotype from matched population for primary efficacy endpoint).

Characteristic	Fabry Registry (N=570)		Natural History (N=81)		
	N	%	N	%	%*
Sex					
men	570	100.0	81	100.0	100.0
Phenotype					
Classic	570	100.0	81	100.0	100
Region					
USA and Canada	295	51.8	73	90.1	90.9
Europe	223	39.1	8	9.9	9.1
Other	42	7.4	0	0.0	0.0
Age at symptom onset (years)					
UNKNOWN	(97)				
0-7	162	34.2	38	46.9	47.7
8-11	129	27.3	27	33.3	31.8
12-24	94	19.9	12	14.8	13.9
25-63	88	18.6	4	4.9	6.7
Age at Fabry disease diagnosis (years)					
UNKNOWN	(5)		(1)		
0-20	180	31.9	31	38.8	36.6
21-32	153	27.1	31	38.8	39.4
33-43	134	23.7	14	17.5	17.9
44-63	98	17.3	4	5.0	6.0
ACEI/ARB use any time during follow-up					
No/UNKOWN	228	40.0	57	70.4	70.9
Yes	342	60.0	24	29.6	29.1
Urine protein sample source					
NONE	126	22.1	33	40.7	40.2
24-hour urine protein	239	41.9	28	34.6	35.1
Spot urine protein	181	31.8	0	0.0	0.0
24-hour urine albumin	7	1.2	0	0.0	0.0
Spot urine albumin	17	3.0	0	0.0	0.0
Dipstick urine protein	0	0.0	20	24.7	24.7

SOURCE: Table prepared by DEPI using analysis dataset (ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: eGFR – estimated glomerular filtration rate; ACEI/ARB – angiotensin converting enzyme inhibitor or angiotensin receptor blocker.
FOOTNOTES: Column indicated by asterisk provides results weighted by matched design (each Natural History patient weighted by 124*i*/1138, *i*=number of times used as a Fabry Registry match). Values in parentheses indicate counts excluded from calculation of column percentages.

Supporting Table 4: Baseline characteristics (age and year), duration of follow-up, and number of times eGFR assessed during follow-up (men with Classic phenotype from matched population for primary efficacy endpoint).

	Fabry Registry (N=570)		Natural History
Characteristic	**N**	**%**	**%***
Baseline age (years)			
16-29	189	33.2	33.0
30-39	179	31.4	37.5
40-49	117	20.5	20.2
50-82	85	14.9	9.3
Baseline year			
1971-1992	0	0.0	21.8
1993-1997	0	0.0	43.9
1998-2001	87	15.3	34.4
2002-2005	253	44.4	0.0
2006-2017	230	40.4	0.0
Baseline eGFR (mL/min/1.73 m^2)			
≥90 (Stage 1)	325	57.0	52.6
60-89 (Stage 2)	131	23.0	25.1
30-59 (Stage 3)	80	14.0	14.4
15-29 (Stage 4)	30	5.3	6.7
<15 (Stage 5)	4	0.7	1.2
Number of follow-up eGFR assessments			
1	60	10.5	21.8
2-3	130	22.8	28.9
4-8	209	36.7	40.0
≥9	171	30.0	9.3
Duration of follow-up (years)			
0.5-1.9	116	20.4	47.9
2.0-3.4	124	21.8	25.8
3.5-4.4	139	24.4	17.9
4.5-5.0	191	33.5	8.4

SOURCE: Table prepared by DEPI using analysis datasets (ADGFMXX and ADXXGFR) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATION: eGFR – estimated glomerular filtration rate.
FOOTNOTES: Column indicated by asterisk provides results for 1,138 matches (124 Natural History patients individually matched (with possibly different baseline ages) to between 4 and 20 patients in the Fabry Registry; Table 10).

Supporting Table 5: Follow-up intervals with a clinical event (Natural History patients matched only once), counts (n) and incidence rates (per 1,000 patient-years), by exposure (Fabry Registry or Natural History), study group (all matched pairs, pairs with eGFR ≥15 mL/min/1.73 m^2 – determined ±1.0 year of index age, and eGFR ≥15 mL/min/1.73 m^2 – determined ±0.5 year of index age), sex, and Fabry phenotype.

Study Group	Sex and Phenotype	N	Fabry Registry				Natural History			
			PY	n	Rate	Event Types	PY	n	Rate	Event Types
ALL	ALL	233	1,354	53	39	22/10/17/4	606	49	81	11/7/28/3
	Men	164	1,006	45	45	18/7/16/4	381	41	108	9/6/24/2
	Men Classic	149	908	44	48	17/7/16/4	317	29	92	8/5/14/2
eGFR ±1.0 y	ALL	106	593	25	42	9/4/9/3	210	11	52	4/0/6/1
	Men	76	438	22	50	7/3/9/3	142	8	56	3/0/4/1
	Men Classic	73	426	21	49	6/3/9/3	133	6	45	3/0/2/1
eGFR ±0.5 y	ALL	69	408	16	39	5/2/6/3	118	7	59	2/0/4/1
	Men	50	307	15	49	4/2/6/3	88	5	57	2/0/2/1
	Men Classic	50	307	15	49	4/2/6/3	88	5	57	2/0/2/1

SOURCE: Table prepared by DEPI using analysis datasets (ADEV1TO1, ADEVIDXX, ADSL, ADLB, and ADLB014) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: eGFR – estimated glomerular filtration rate.; N – number of matched interval pairs; PY – patient-years.
FOOTNOTE: Events counts by type presented in the following order: Cardiovascular Events / Cerebrovascular Events / Renal Events / Death.

Supporting Table 6: Follow-up interval pairs (N), composite clinical event incidence rates (per 1,000 patient-years) for Fabry Registry (FR) and Natural History (NH) intervals and hazard ratios, by study group (all matched pairs, pairs with eGFR ≥15 mL/min/1.73 m^2 – determined ±1.0 year of index age, and eGFR ≥15 mL/min/1.73 m^2 – determined ±0.5 year of index age), sex, and Fabry phenotype.

Part A: Natural History patients possibly matched more than once.

Study Group	Sex and Phenotype	N	Rates (FR/NH)	HR	95% CI	p-value
ALL	ALL	1,754	49/69	0.67	0.49,0.90	0.008
	Men	954	56/101	0.63	0.45,0.88	0.006
	Men Classic	810	57/88	0.76	0.51,1.12	0.167
eGFR ±1.0 y	ALL	686	55/85	0.76	0.47,1.23	0.257
	Men	390	61/94	0.77	0.45,1.32	0.332
	Men Classic	358	60/68	1.14	0.59,2.18	0.690
eGFR ±0.5 y	ALL	435	60/98	0.65	0.39,1.09	0.097
	Men	263	65/95	0.65	0.36,1.17	0.140
	Men Classic	247	63/71	0.96	0.47,1.96	0.887

Part B: Natural History patients matched only once.

Study Group	Sex and Phenotype	N	Rates (FR/NH)	HR	95% CI	p-value
ALL	ALL	233	39/81	0.41	0.22,0.74	0.003
	Men	164	45/108	0.43	0.23,0.83	0.012
	Men Classic	149	48/92	0.57	0.29,1.12	0.100
eGFR ±1.0 y	ALL	106	42/52	0.67	0.24,1.87	0.442
	Men	76	50/56	1.00	0.32,3.10	1.000
	Men Classic	73	49/45	1.20	0.37,3.93	0.763
eGFR ±0.5 y	ALL	69	39/59	0.43	0.11,1.66	0.220
	Men	50	49/57	0.60	0.14,2.51	0.484
	Men Classic	50	49/57	0.60	0.14,2.51	0.484

SOURCE: Tables prepared by DEPI using analysis datasets (ADEVXTOX, ADEV1TO1, ADEVIDXX, ADSL, ADLB, and ADLB014) submitted to BLA 103979 (eCTD 0415) on February 14, 2020.
ABBREVIATIONS: eGFR – estimated glomerular filtration rate.; N – number of matched interval pairs; HR – hazard ratio; CI – confidence interval.
FOOTNOTES: Hazard ratios estimated by Cox regression, weighted frailty model for clustered data (Part A) or stratified model for 1:1-matched data (Part B). For a partial presentation by Sanofi of results from Cox regression, see Table 9 (p. 63) and Table 15 (pp. 73-74) in the Study Report for Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01).

APPENDIX 4: Addition Proposed by Sanofi to Fabrazyme® Label

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX 5: RWE REVIEW TEMPLATE

Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis (DIREGC07006/AGAL-014-01)

Background: FDA currently indicates agalsidase beta (Fabrazyme® BLA 103979) "for use in patients with Fabry disease," an X-linked lysosomal storage disorder caused by alpha galactosidase A (α-Gal A) enzyme deficiency.[26] In April 2003, BLA 103979 obtained accelerated FDA-approval based on results from a Phase 3 placebo-controlled clinical trial with surrogate endpoint (globotriaosylceramide inclusions in renal capillary endothelium). (b) (4) (b) (4) On February 14, 2020, the BLA Sponsor submitted Efficacy Supplement-5309, which included Real World Evidence (RWE) in the form of a Study Report from *Effectiveness of Fabrazyme: Fabry Registry/Natural History Matched Analysis*. Supplement-5309 seeks traditional FDA approval based on "the totality of evidence for clinical effectiveness of agalsidase beta."[27]

The totality of evidence included RWE in addition to evidence from AGAL-008-00, a completed Phase 4 placebo-controlled randomized clinical trial of agalsidase beta for advanced Fabry disease. Between February 2001 and January 2004, AGAL-008-00 enrolled (from 41 centers in 9 countries) ≥16-year-old treatment-naïve patients with clinical evidence of Fabry disease, low α-Gal A activity, and evidence of kidney disease (serum creatinine 1.2-2.9 mg/dL or serum creatinine <1.2 mg/dL and estimated glomerular filtration rate <80 mL/min). AGAL-008-00 excluded patients with transient ischemic attack (TIA), ischemic stroke, unstable angina, or myocardial infarction (MI) in the 3 months before enrollment. AGAL-008-00 randomized patients (2:1) to receive biweekly intravenous agalsidase beta 1 mg/kg or placebo for up to 35 months (median, 18.5 months). Death or a renal, cardiac, or cerebrovascular event (primary efficacy endpoint) occurred in 14 of 51 (27.5%) and 13 of 31 (41.9%) patients during active and placebo treatment, respectively. Cox regression models estimated treatment benefit with (1) hazard ratio (HR) 0.57 (unadjusted), 95% confidence interval (CI) 0.27-1.22, p-value 0.14 and (2) HR 0.47 (adjusted for baseline proteinuria), 95% CI 0.21-1.03, p-value 0.06.

Study design: Single Arm Registry with External RWD Control

Data source: Fabry Disease Registry (DIREGC07006) / Epidemiologic Study of Natural History of Fabry Disease (AGAL-014-01)

Study population: ≥16-year-old patients with Fabry disease and functioning native kidneys

Exposure: agalsidase beta as first Fabry-disease-specific treatment (Fabry Disease Registry)

Comparator: untreated (natural history) control

Outcome: Primary efficacy endpoint – estimated glomerular filtration rate (eGFR); Secondary efficacy endpoint – clinical event composite (renal, cardiovascular, cerebrovascular, or death)

---

[26] Prescribing Information for FABRAZYME (agalsidase beta),revised 12/2018, accessed at Drugs@FDA on August 19, 2020.

[27] Sanofi, Clinical Overview (Fabry Disease), submitted to BLA 103979 (eCTD 0415) on February 14, 2020, p 26.

Section I. Considerations for questions ought to be addressed in the review of RWE submission

a. What is the regulatory purpose?			
☐	Approval of new indication	☒	For effectiveness only
☒	Fulfillment of PMC 2421-2	☐	For safety only
☐	Labeling change	☐	For both effectiveness and safety
☒	Other: Convert accelerated approval (indicated for use) to traditional approval (indicated for treatment)		Will this be considered as pivotal evidence or supportive evidence?

b. What is the study design using RWD to generate RWE?					
☐	Randomized design (pragmatic trial)				
☐	Non-randomized single arm trial with external RWD control (check all that apply)				
	External RWD control:	☐	Prospective	☐	Primary data
		☐	Retrospective	☐	Secondary data
☒	Observational study (check all that apply) Exposure groups from ☐ Same data source ☒ Different data sources				
	☒ Cohort design (See FOOTNOTE)	☒	Prospective	☒	Primary data
	☐ Case-control design	☒	Retrospective	☒	Secondary data
	☐ Cross-sectional design				
	☐ Self-controlled design (please specify)				

c. What is the relevant clinical question?

- Both FDA and the Sponsor seek an answer to the following clinical question. Does treatment with agalsidase beta (as opposed to no treatment) slow the progression of Fabry disease in adults? Measures of disease progression include decline in kidney function, occurrence of a renal, cardiovascular, or cerebrovascular clinical event, and death.

d. What data are needed to address the clinical question?

- FDA needs additional data about disease progression in adults treated with agalsidase beta for Fabry disease.
- Clinicians recognize Fabry disease as a slowly progressive disease with highly variable natural history. Useful predictors of unfavorable outcome in untreated patients include (1) male sex and (2) classic phenotype as defined by extreme galactosidase alpha enzyme deficiency and symptom onset at young age. Studies in untreated patients identify proteinuria as a major risk factor for subsequent loss of kidney function. (Wanner C, Oliveira JP, Ortiz A et al. Prognostic indicators of renal disease progression in adults with Fabry disease: Natural history data from the Fabry Registry. Clin J Am Soc Nephrol 2010; 5: 2220–2228.)
- Therefore, measuring the impact of agalsidase beta on disease progression demands sufficiently long duration follow-up (≥18 months) in patients well characterized at baseline with respect to major risk factors for disease progression, e.g., sex, age at symptom onset, Fabry disease phenotype, and (baseline) disease status at treatment initiation.

e. Was the study designed to address the clinical question of interest?
• RWE in Supplement-5309 addressed the clinical question of interest.

f. What are the threats to study validity and what is the overall impact?

• Supplement-5309 presented RWE from analyses that matched agalsidase beta treated patients from the *Fabry Disease Registry* (DIREGC07006) to non-contemporaneous untreated patients from the *Epidemiologic Study of Natural History of Fabry Disease* (AGAL-014-01).
• Selection Bias. Matched analyses used a non-contemporaneous (historical) external comparison group, a study design expected to produce (at best) low-level evidence for treatment efficacy because of inferential threats related to possible non-comparability of treated and untreated groups (despite matching on important determinants of outcome). Non-comparability due to selection bias might occur if factors associated with efficacy endpoints differently determined patient enrollment to the prospective registry (Fabry Disease Registry) and retrospective chart review (Natural History) studies used for matching treated and untreated patients, respectively. Indicators of non-comparability included younger age of diagnosis in untreated patients (a possible marker of more aggressive Fabry disease phenotype) and understandable discordance between matched groups with respect to clinical site location and calendar time.
• Information Bias. Despite reliance on information recorded to Case Report Forms with similar data elements, matched analyses used non-equivalent methods to collect information (including information about the efficacy endpoints) in treated and untreated patients. Investigators at 204 clinical sites (in 42 countries) for the Fabry Disease Registry (data source for treated patients) actively (prospectively) sought and recorded information at intervals guided by Recommended Schedules of Assessments. By comparison, a solitary contract research organization extracted historical (retrospective) information from patient charts (data source for untreated patients) at 27 clinical sites (in five countries). Confidence in the quality of information produced by the prospective method presumes investigator commitments to data collection protocols and procedures. Confidence in the quality of information produced by the retrospective method presumes dependable study access to complete and accurate patient records from all sources, including primary and referral physicians.
• Other identified threats to study validity from matched analyses included:
  • High patient attrition (primarily due to criteria for study inclusion).
  • Analysis for efficacy endpoints without regard to patients possibly discontinuing primary treatment with agalsidase beta.
  • Imperfect control for Fabry phenotype (i.e., Classic phenotype defined broadly according to data available for genotype and enzyme activity as opposed to enzyme activity alone).
  • Missing data for critical covariates (e.g., baseline proteinuria).
  • A relatively small number of untreated patients matched with variable frequency to a much larger number of treated patients.
  • Limiting sample size, particularly for tightly controlled sensitivity analyses (e.g., clinical event analysis in men with Classic phenotype and eGFR (near baseline, ±0.5 years) ≥15 mL/min/1.73 m^2).
• One analysis matched on sex, age, and Fabry phenotype to measure association between agalsidase beta and change in kidney function (primary efficacy endpoint). Using data for 1,138 treated and 124 untreated patients (untreated patients matched more than once), a

linear mixed model showed kidney function declining less rapidly in treated than untreated patients (change in eGFR, -1.7 vs. -3.0 mL/min/1.73 m^2/y; p<.001).

- Another analysis matched on sex, age, and Fabry phenotype to measure association between agalsidase beta and clinical events (secondary efficacy endpoint). Using data for 1,754 treated and 233 untreated patients (untreated patients matched more than once), this analysis showed a first (post-index) clinical event occurring less often in treated than untreated patients (49 vs. 69 per 1,000 patient-years; HR 0.67, 95% CI 0.49-0.90, p=0.008).
- The review team considered the plausible sources of selection and information bias as major threats to study validity. The review team assessed these threats as sufficient in magnitude to completely explain differences observed between treated and untreated patients with respect to Fabry disease progression.

g. Is there any existing evidence from other sources?	
☒	Non-clinical study
☒	Clinical trial AGAL-008-00
☐	Observational study
☒	Others (please specify) Systematic Literature Review (SLR)

h. What is the regulatory context, need, and gap for using RWE?

- FDA seeks RWE to supplement (support) clinically beneficial effects suggested by AGAL-008-00, a completed Phase 4 placebo-controlled clinical trial of agalsidase beta in patients with Fabry disease.

i. Does the completed RWE study provide adequate scientific evidence to address the regulatory need?

- Because of questionable comparability between treated (Fabry Registry) and untreated (Natural History) patients, the completed RWE study alone does not provide adequate scientific evidence to address the regulatory need.
- However, the completed RWE study provides supplementary (supporting) evidence that aligns with results from AGAL-008-00, a completed Phase 4 placebo-controlled clinical trial of agalsidase beta in patients with Fabry disease.

j. Is RWE study acceptable for the defined regulatory purpose?	
☒	Yes . The RWE study is acceptable for the defined regulatory purpose because: • Matched Analysis provides information about change in kidney function over time (primary efficacy endpoint) and clinical events or death (secondary efficacy endpoint) in Fabry disease patients receiving agalsidase beta. • The Sponsor conducted reasonably transparent analyses that withstood DEPI scrutiny for integrity. • The direction of clinical benefit indicated by Matched Analysis and suggested by AGAL-008-00 agree with respect to clinical outcomes valued by patients and important to medical providers.
☐	No
☐	Pending

FOOTNOTE: The RWE Subcommittee of the Medical Policy and Program Review Council (meeting date September

21, 2020) received a different version of this RWE Template. The RWE Subcommittee version presented Matched Analysis as a cohort study of retrospectively collected data derived from secondary sources. The version provided as **APPENDIX 5** more accurately captures the study design as a cohort study of prospectively and retrospectively collected data derived from primary and secondary sources.

Section II. Study Synopsis and Appraisal by Study Design Using RWD to Support Effectiveness or Safety

Table 1. Study Synopsis

Product, therapeutic area, indication	agalsidase beta, rare diseases, Fabry disease	
Regulatory purpose	Convert accelerated approval (indicated for use) to traditional approval (indicated for treatment)	
Existing evidence from other sources	Clinical trial AGAL-008-00	
Regulatory need and gap	To supplement (support) clinically beneficial effects suggested by AGAL-008-00	
Study objective	Assess progression of Fabry disease in adults treated with agalsidase beta	
Study design	RWD: Treated group selected from Fabry Disease Registry	RWD: Untreated group selected from external historical comparator
Studied period	Patient enrollment April 19, 2001 to December 27, 2017	Final patient chart abstracted in 2002
Design	Prospective patient enrollment with data captured by clinical-site investigator	Data extracted from medical charts by contract research organization
Data source	Fabry Disease Registry: Case Report Forms submitted by 204 clinical sites in 42 countries	Natural History Study: Clinical records (patient charts) at 27 clinical sites in five countries
Patient selection	Fabry disease confirmed by *GLA* mutation or αGAL deficiency Adults: Age ≥16 years at agalsidase beta treatment initiation	Diagnosis of Fabry disease without other major illness (e.g., cancer or HIV/AIDS) or investigator-determined renal disease that might confound assessment of Fabry disease symptoms
Exposure	agalsidase beta initiated as first Fabry-disease-specific treatment	not applicable (untreated natural history comparator)

Outcomes	• Primary Efficacy Endpoint: eGFR rate of decline
	• Secondary Efficacy Endpoint: composite of four clinical event categories
	  • Renal Events – kidney transplantation or chronic dialysis
	  • Cardiovascular Events – congestive heart failure, atrial fibrillation, ventricular tachycardia, or significant cardiac procedure (pacemaker, bypass graft, angioplasty, balloon pump, stent, or implantable cardioverter defibrillator)
	  • Cerebrovascular Events – hemorrhagic or ischemic stroke	

		• Death from Any Cause	
Covariates (available)		sex, race, *GLA* genotype, αGAL enzyme activity, family history of Fabry disease, body weight, height, blood pressure, secondary Fabry disease therapy (i.e., concomitant medications, including ACEI and ARB)	sex, race, *GLA* genotype, αGAL enzyme activity, family history of Fabry disease, body weight, height, blood pressure, concomitant medication (ACEI or ARB)
Index time		Primary Efficacy Endpoint: index timepoint (baseline age) determined by eGFR assessed six months before or after start date for agalsidase beta treatment Secondary Efficacy Endpoint: index timepoint (baseline age) determined by start date for agalsidase beta treatment	Primary Efficacy Endpoint: index timepoint determined by age match, i.e., eGFR determined at same age as treated-patient match (±5 years) Secondary Efficacy Endpoint: index timepoint determined by age match
Follow-up		Primary Efficacy Endpoint: post-index eGFRs determined in the 6-month through 5-year post-index period (truncated by switch to a primary Fabry therapy other than agalsidase beta, such as agalsidase alfa, or first renal event, such as kidney transplantation or chronic dialysis) Secondary Efficacy Endpoint: post-index follow-up censored on switch to a Primary Fabry Therapy other than agalsidase beta (treated group) or initiation of ERT (untreated group)	
Statistical method		Primary Efficacy Endpoint: Linear mixed (random-intercept random-slope) model of eGFR over time with intercept and time specified as random effects (covariance unstructured), intercept and time specified as fixed effects, and untreated patients inverse weighted by frequency Secondary Efficacy Endpoint: Cox proportional hazards regression shared frailty models with matched pair cluster added as a random effect and untreated patients inverse weighted by frequency	
Sample size	Primary Efficacy Endpoint	N=1,138 (unique patients)	N=124 (unique patients)
	Secondary Efficacy Endpoint	N=1,754 (unique patients)	N=233 (unique patients)
Methods to handle confounding		Primary and Secondary Efficacy Endpoints: index dates for treated and untreated patients matched on sex, age, and Fabry disease phenotype with other covariates (e.g., baseline proteinuria) addressed by subgroup or sensitivity analysis	

Methods to handle missing data	missing data (e.g., baseline proteinuria) handled as separate category in statistical analysis

ABBREVIATIONS: ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; eGFR – estimated glomerular filtration rate; ERT – enzyme replacement therapy; *GLA* – galactosidase alpha gene; αGAL– galactosidase alpha enzyme

Table 2: Study Appraisal

Threats to study validity	External RWD control	Single-Arm Registry	Comparability	Direction of bias	Impact of limitation	Approaches to bias mitigation
Selection bias	Historical untreated patients identified at selected clinical centers	Present-day patients identified by industry-sponsored disease registry with broad reach	Questionable	Prognosis possibly worse for historical untreated patients (See Footnote)	Major	Retrieve or impute missing data for enzyme activity and baseline proteinuria
Information bias (ascertainment of efficacy endpoint)	Data recorded to Case Report Forms	Data abstracted from patient charts	Questionable	Unpredictable, ascertainment of clinical events possibly better for untreated patients (See Section 1, Part f)	Major for secondary efficacy endpoint (clinical events); possibly minor for primary efficacy endpoint (eGFR decline)	Audit (validate) outcome for Fabry Disease Registry

FOOTNOTE: Instead of therapeutic benefit from agalsidase beta, the appearance of a better disease outcome in treated patients from the Fabry Disease Registry might indicate (partly or entirely) a worse underlying disease prognosis in historical untreated patients.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOEL L WEISSFELD
10/30/2020 08:51:31 AM

CATHERINE L CALLAHAN
10/30/2020 08:53:52 AM

WEI HUA
10/30/2020 09:07:55 AM

JIE J LI
10/30/2020 09:38:33 AM