STARTING TREATMENT AT THE RIGHT TIME

MANAGEMENT OF FABRY DISEASE IN WOMEN, CHILDREN, AND MEN

Fabrazyme®
agalsidase beta

INDICATION AND USAGE

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

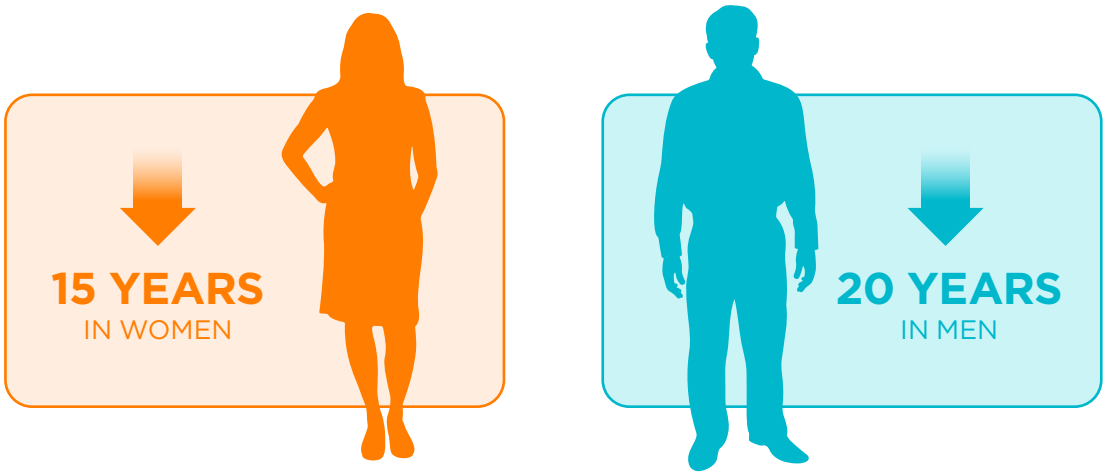
SANOFI GENZYME

FABRY DISEASE: PROGRESSIVE. OFTEN LIFE THREATENING.[1-5]

Time is of the essence for diagnosing Fabry disease.[6]

- A multisystemic disease that impacts essential organs, such as the kidney, heart and skin[7,8]
- An X-linked disorder that affects men, women, and children[1,2]

Undiagnosed and unmanaged, Fabry disease can reduce life expectancy by approximately[9,10]:



Fabry disease is classified into 2 main phenotypes.[2]

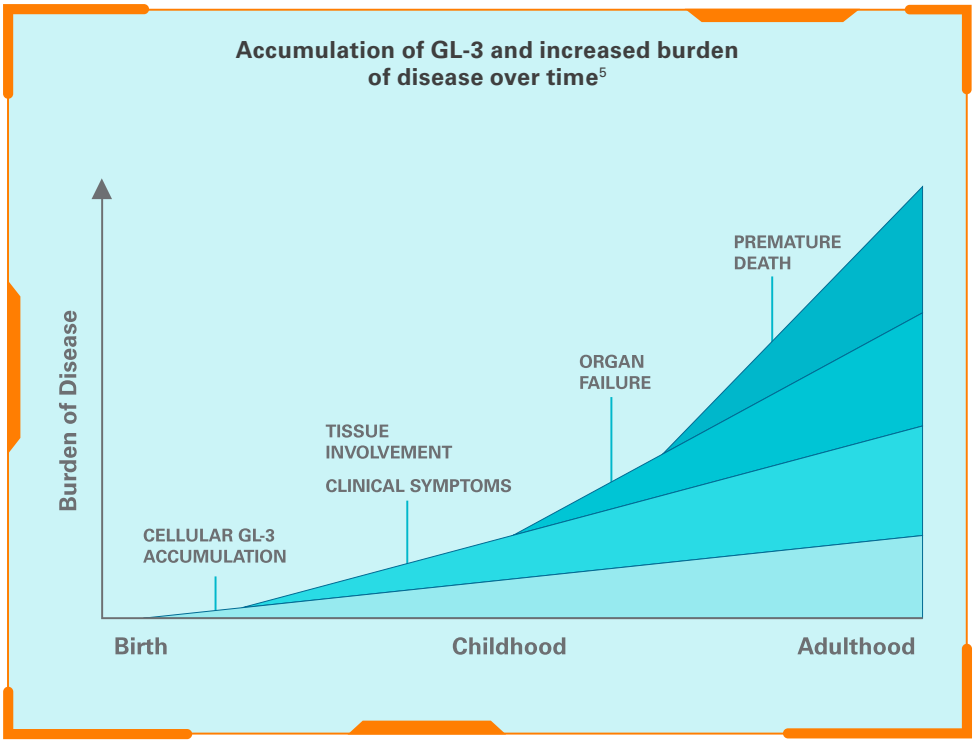
Classic	**No or very low α galactosidase A (α-GAL A) activity** Patients present with characteristic Fabry disease symptoms, which usually begin in childhood or adolescence[2,11]
Nonclassic	**Residual α-GAL A activity** Patients do not have the early major manifestations of classic Fabry disease but instead a more variable disease course[12]

- **Both types can lead to organ failure, serious complications in adulthood, and reduction in life expectancy[9,10]**

THE HALLMARK OF FABRY DISEASE IS GL-3 ACCUMULATION.[13]

Globotriaosylceramide (GL-3) buildup starts in utero and continues throughout life.[2,14-18]

- In healthy individuals, GL-3 is metabolized by the lysosomal enzyme α-galactosidase A (α-GAL A)[2]
- In Fabry disease, variants in the *galactosidase alpha* (*GLA*) gene cause complete or partial deficiency of α-GAL A[2]
- This deficiency leads to lifelong GL-3 accumulation in the lysosomes[2]
- Over time, this buildup of GL-3 may cause irreversible damage in important organs such as the kidney, heart, and brain and even premature death[16-18]



Adapted from Schiffmann R, Hughes DA, Linthorst GE, et al. *Kidney Int*. 2017;91(2):284-293.

LIFE-THREATENING EVENTS MAY INCLUDE[7-10]:	LIFE-ALTERING SYMPTOMS MAY INCLUDE[19]:
• Kidney failure	• GI issues
• Heart failure	• Pain
• Early stroke	• Angiokeratomas
• Premature death	• Heat and cold intolerance

Identifying Fabry disease early can enable improved patient outcomes[6]

FABRY DISEASE CAN PROGRESS SILENTLY FOR YEARS BEFORE CLINICAL SYMPTOMS APPEAR.[17]

Fabry disease affects males and females of all ages. Symptoms can vary, even among family members with the same genetic variant.[1,2]

Women

Women with Fabry disease have a significant risk of major organ involvement and debilitating symptoms[19]

In the Fabry Registry:

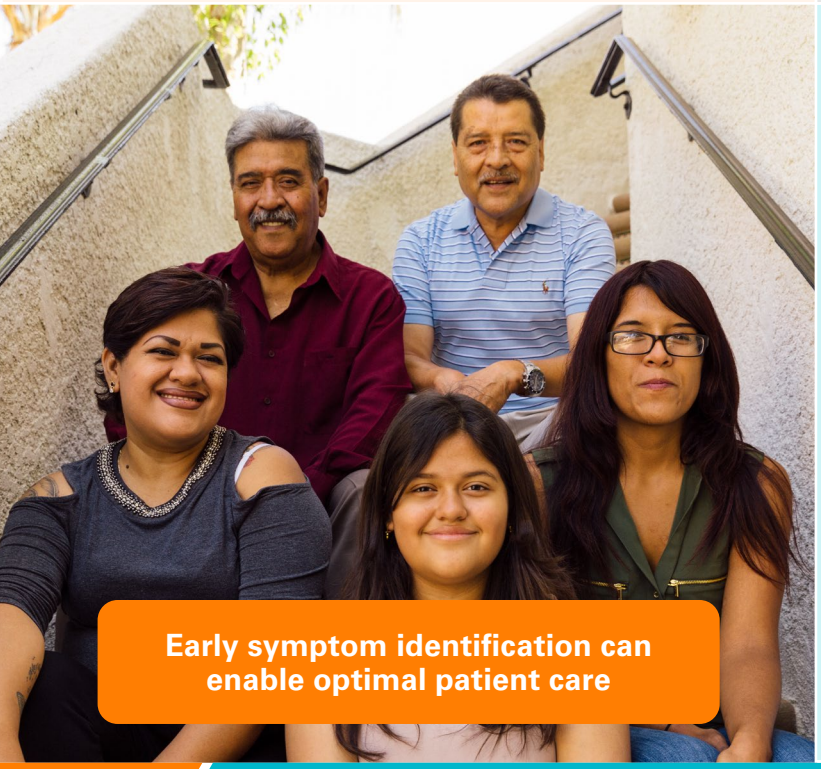
- Nearly **70%** of women reported having signs and symptoms (N=1077)[19]
- Only **53%** of females with LVH are on treatment versus **85%** of males with LVH, and only **47%** of females with CKD ≥ Stage 3 are treated versus **88%** of males[19]

Children

Many children with Fabry disease exhibit a wide range of symptoms that can progress to life-threatening complications over time[11,20]

In the Fabry Registry:

- **77%** of boys and **51%** of girls reported symptoms (N=352)[11]
- Median ages of symptom onset were **6 and 9 years** in boys and girls, respectively (N=352)[11]
- **53%** of boys and **87%** of girls with symptoms that warrant treatment remain untreated[11]



Early symptom identification can enable optimal patient care

Men

Men with Fabry disease are at a significantly increased risk of morbidity and mortality[9]

In the Fabry Registry:

- Male patients experienced a higher frequency of symptoms at an early age[17]
- The median age at the time of diagnosis was **24 years**[19]
- Men experienced a mean delay of **14 years** from symptom onset to diagnosis[19]
- **67%** of male patients had symptom onset prior to diagnosis (N=1159)[19]

WOMEN

Cindy and Amanda, *Fabry patients*

WOMEN CAN HAVE SIGNIFICANT DISEASE MANIFESTATIONS AND ARE NOT JUST CARRIERS.[19]

Women with Fabry disease can experience serious symptoms.[19]

43% Neuropathic pain

70% Corneal pattern in the eye[21]

39% Proteinuria

21% Abdominal pain

19% Diarrhea

18% Angiokeratomas

Women with Fabry disease have a higher occurrence of serious complications than women in the general population:

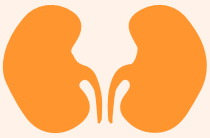
- LVH **2x higher**[22,23]
- ESRD **11x higher**[19,24]
- Stroke/TIA **4x higher**[10,25]
- White matter lesions **7x higher**[26,27]

LVH=left ventricular hypertrophy; ESRD=end-stage renal disease.

FEMALES WHO APPEAR ASYMPTOMATIC SHOULD BE MONITORED FOR SYMPTOM DEVELOPMENT.[6]

A considerable percentage of females can experience major complications, and should be monitored.[6,19]

Vital organ involvement in female patients in the Fabry Registry was noted as early as the following ages:



KIDNEY: 14.4 YEARS[19]

(mean age 30.9 ± 16.5 years, n=87)

CARDIOVASCULAR: 14.0 YEARS[19]

(mean age 33.4 ± 19.4 years, n=106)

CEREBROVASCULAR: 12.6 YEARS[19]

(mean age 31.2 ± 18.6 years, n=44)

Fabry disease is progressive: monitor patients closely for early identification of potentially life-threatening complications[1-4]

ERT SHOULD BE CONSIDERED UPON EARLY SIGNS OF FABRY DISEASE IN WOMEN.[6,12]

ERT should be considered upon early signs of renal, cardiac, CNS complications, pain, and GI issues.[6,12]

International Panel Consensus Guidelines[6,12]

	Classic Symptomatic Signs/symptoms suggesting major organ involvement	**Classic Asymptomatic OR Nonclassic*** Lab/histological/imaging evidence of injury to kidney, heart, or CNS
RENAL	Proteinuria/albuminuria not attributable to other causes, evidence of renal impairment	GFR <90 mL/min/1.73m^2, adjusted for age >40 years, persistent albuminuria >30 mg/g, podocyte foot process effacement on renal biopsy Moderate or severe GL-3 inclusions in a range of renal cell types
CARDIAC	Symptomatic cardiac disease not due to other causes (dyspnea, palpitation, syncope, chest pain)	Asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI)
CNS	Stroke/TIA	Silent strokes, cerebral white matter lesions (on brain MRI)
PAIN	Neuropathic pain, pain crises, Fabry disease neuropathy	
GI	Recurrent diarrhea; chronic, disabling GI dysfunction (excluding alternative causes)	
OTHER	Exercise intolerance and impaired sweating	

ERT=enzyme replacement therapy; GFR=glomerular filtration rate; TIA=transient ischemic attack.

*Nonclassic or missense *GLA* variants of unknown significance (VUS) have the same recommendation for males and females.

CHILDREN

Heather and Charles, *Fabry patients*

CHILDREN WITH FABRY DISEASE BEGIN DEVELOPING SYMPTOMS AT AN EARLY AGE, WHICH PROGRESS OVER TIME.[11,18]

Children with Fabry disease exhibit a wide range of symptoms[11]:

BOYS	SYMPTOMS	GIRLS
58.8% (114/194)	Neuropathic pain	40.5% (64/158)
23.2% (45/194)	Gastrointestinal symptoms*	11.4% (18/158)
28.4% (55/194)	Abnormal sweating	22.2% (35/158)
28.9% (56/194)	Abnormal heat tolerance	24.7% (39/158)
18% (35/194)	Abnormal cold tolerance	10.1% (16/158)
19.6% (98/194)	Angiokeratomas	7.6% (12/158)
10% (4/42)	Proteinuria†	11% (5/44)
23% (21/93)	Valvular dysfunction	14% (11/79)
7% (9/93)	Conduction abnormalities	4% (3/79)
1% (1/93)	Left ventricular hypertrophy	3% (2/79)
7% (7/96)	Arrhythmia	3% (2/79)

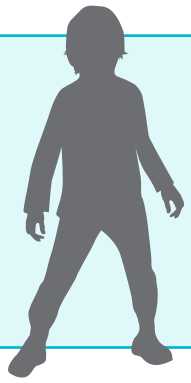
*Abdominal pain and diarrhea.
†Proteinuria defined as total protein > 150mg/24hr

GUIDELINES RECOMMEND THAT CHILDREN SHOULD BE MONITORED CLOSELY.[29]

- Children may experience serious cardiac and renal manifestations during childhood, and careful monitoring for disease progression is essential to detect symptoms before irreversible damage occurs[11]
- Pediatric patients who appear asymptomatic should be monitored closely for symptom development[29]

Treatment should be considered in asymptomatic patients when appropriate.

Physicians should consider initiating treatment at approximately 8–10 years of age in asymptomatic boys with classic Fabry variants[29]



In asymptomatic male patients with classic variants, timing of treatment should be based on individual cases, weighing the risks and benefits[29]

In asymptomatic female patients and asymptomatic male patients with nonclassic variants, a decision to defer treatment should be based on comprehensive longitudinal monitoring for the development of symptoms; family history should also be considered[29]

ERT SHOULD BE CONSIDERED IN SYMPTOMATIC PEDIATRIC PATIENTS.[29]

Signs and symptoms warranting treatment[29]

NEUROLOGIC	• Neuropathic pain crises • Fabry neuropathy
RENAL	• Decline in eGFR • Pathological albuminuria • Pathological proteinuria • Creatinine elevation • Cellular GL-3 accumulation • Evidence of tissue damage such as podocyte effacement
CARDIAC	• Cardiomyopathy • Arrhythmia, including sinus bradycardia attributable to Fabry disease
GI	• Recurrent abdominal pain and diarrhea (excluding alternative causes)
OTHER	• Exercise intolerance and impaired sweating

eGFR=estimated glomerular filtration rate.

MEN

Mario and Braulio, *Fabry patients*

ERT SHOULD BE CONSIDERED FOR MEN AT TIME OF DIAGNOSIS.[6]

Classic Fabry variant (symptomatic or asymptomatic)[6]

- ERT should be considered and is appropriate
- Treatment decisions may be influenced by advanced, elderly age of the patient and severe comorbidity

Nonclassic Fabry variant or missense *GLA* VUS[6*]

- ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS, even in the absence of typical Fabry symptoms
- The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL-3 accumulation
- The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS

*Nonclassic or missense *GLA* VUS have the same recommendation for males and females.

THE IMPORTANCE OF STARTING AND STAYING ON TREATMENT.

Men with Fabry disease can be reluctant to start treatment because of concerns about time, commitment, and clinical benefit. Continued follow-up can provide support for men as they learn to live with Fabry disease and recognize the importance of adhering to treatment.

Your recommendation could help provide male Fabry patients with the information they need to make an appropriate treatment decision.

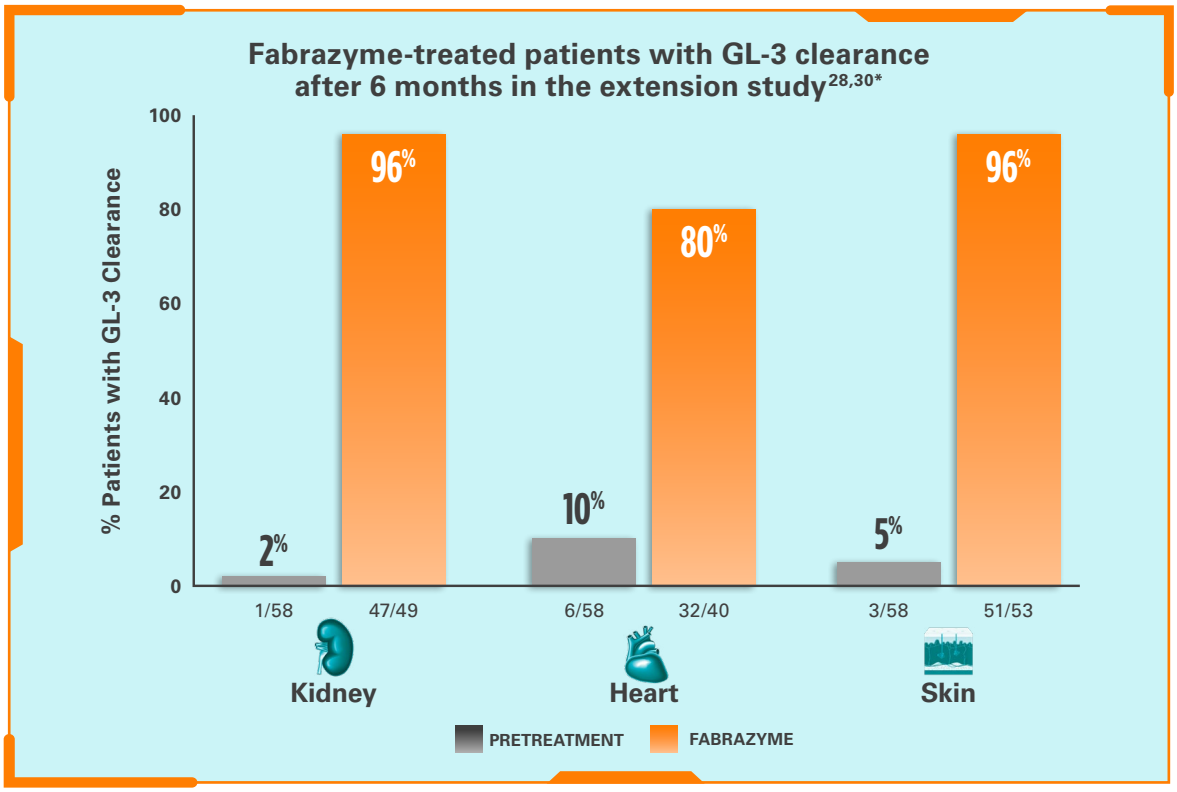
Randal and Roland, *Fabry patients*

COUNT ON FABRAZYME.

Fabrazyme® agalsidase beta

FABRAZYME was proven to clear GL-3 in as quickly as 5 months in the capillary endothelium of the kidney, heart, and skin.[28]

- **Study 1:** At 5 months, a GL-3 inclusion score of 0 was achieved in the capillary endothelium of the: **Kidney:** 20/29 (69%) Fabrazyme patients compared with 0/29 (0%) placebo patients; **Heart:** 21/29 (72%) Fabrazyme patients compared with 1/29 (3%) placebo patient; **Skin:** 29/29 (100%) Fabrazyme patients compared with 1/29 (3%) placebo patient[28]
- **Study 1 open-label extension:** After 6 months, the majority of patients treated with Fabrazyme had a GL-3 inclusion score of 0 in the capillary endothelium of the kidney, heart, and skin[28]



*Study 1: Randomized, 1:1, double-blind, placebo-controlled study. 58 patients with Fabry disease (56 males, 2 females), 16 to 61 years, all naive to ERT. Patients received either 1 mg/kg of Fabrazyme or placebo every 2 weeks for 5 months. GL-3 inclusions were graded on a scale of 0 (trace or nearly none) to 3 (severe). All 58 patients in Study 1 participated in the Study 1 extension, a 54-month, open-label extension trial.[28]

Placebo patients began Fabrazyme treatment at entry into the open-label extension. This graph represents pooled results from all patients in the study (Fz/Fz and Pl/Fz).[28]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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 infusions. Life-threatening anaphylactic and severe hypersensitivity reactions have been observed in patients during Fabrazyme infusions.

COUNT ON FABRAZYME.

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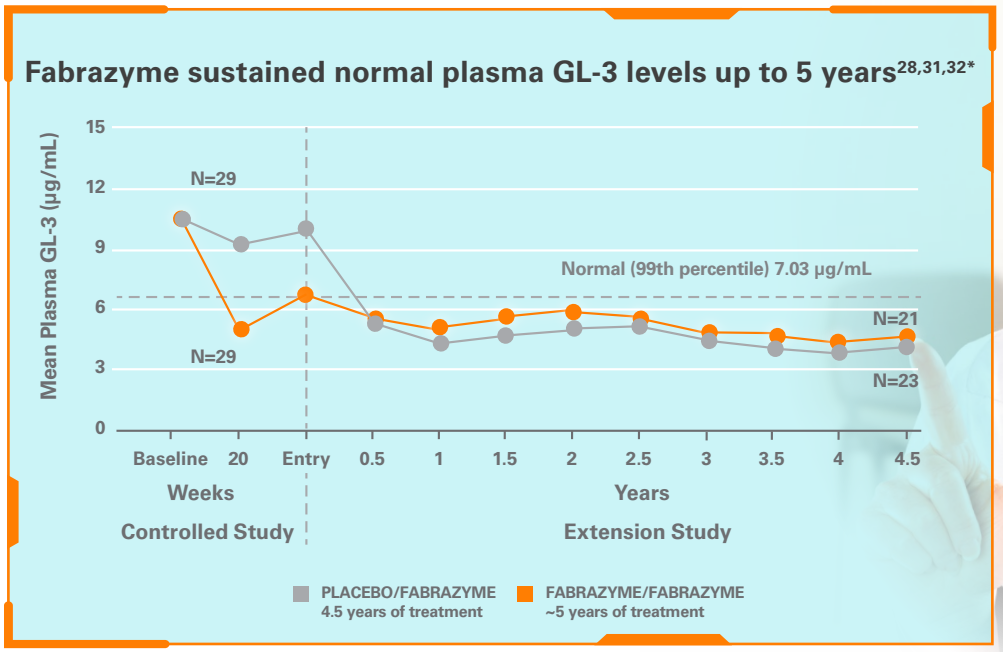
FABRAZYME rapidly normalized plasma GL-3 and maintained it for up to 5 years.[28,31]



*Study 1: Randomized, 1:1, double-blind, placebo-controlled study. 58 patients with Fabry disease (56 males, 2 females), 16 to 61 years, all naive to enzyme replacement therapy. Patients received either 1 mg/kg of Fabrazyme or placebo every 2 weeks for 5 months. GL-3 inclusions were graded on a scale of 0 (trace or nearly none) to 3 (severe). All 58 patients in Study 1 participated in the Study 1 extension, a 54-month, open-label extension trial.[28]

- Similar long-term responses were seen in a majority of patients, with sustained GL-3 clearance in the capillary endothelium of the kidney (8/8) and heart (6/8) at 4.5 years[28]

IMPORTANT SAFETY INFORMATION

- 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, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, antihistamines, epinephrine, and IV corticosteroids.

FABRAZYME WAS EVALUATED FOR OUTCOMES IN CLINICALLY SIGNIFICANT EVENTS.[28*]

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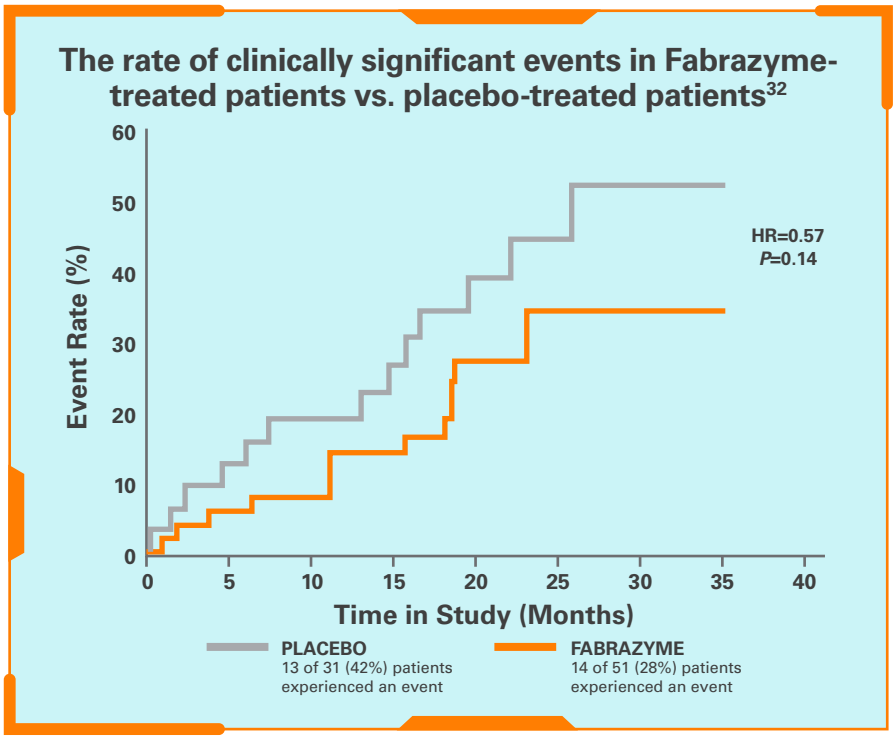
A smaller percentage of patients in the FABRAZYME treatment group experienced a clinically significant event.[28]



VS

HAD RENAL, CARDIAC, CEREBROVASCULAR EVENTS, OR DEATH*

28% (14 of 51) of Fabrazyme-treated patients versus 42% (13 of 31) of placebo-treated patients experienced a clinically significant event (HR† 0.57, 95% CI: 0.27, 1.22, *P*=0.14)[28]

- The primary efficacy endpoint was the time to first occurrence of a clinically significant event (renal, cardiac, or cerebrovascular event, or death)[28]

The study included patients aged 20 to 72 years (median age: 45), with a baseline median plasma αGAL level of 1.5 nmol/hour/mL (range: 0 to 1.5). Patients included had advanced Fabry disease with mild-to-moderate kidney dysfunction at baseline (median eGFR=52 mL/min/1.73m^2 [range: 25 to 113]).[28]

Study 2 design: A randomized, double-blind, placebo-controlled, multinational, multicenter study of 82 patients (72 males and 10 females) with Fabry disease, all naive to enzyme replacement therapy. Patients were randomly assigned to Fabrazyme 1 mg/kg or placebo every 2 weeks for up to 35 months (median follow-up 18.5 months).[28]

eGFR=estimated glomerular filtration rate.

*Clinically significant event is defined as renal, cardiac, or cerebrovascular event or death.

†The hazard ratio is a comparison between the probability of events in a treatment group, compared to the probability of events in a control group.

IMPORTANT SAFETY INFORMATION

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

FABRAZYME IN PEDIATRIC POPULATIONS.

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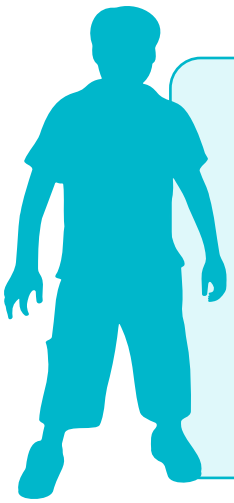
The overall efficacy and safety profile of FABRAZYME in pediatric patients was consistent with that seen in adults.[28]



- This pediatric study evaluated 16 pediatric patients with Fabry disease (14 males, 2 females), aged 8 to 16 years (median 12 years)[28]
- In 14 male patients, Fabrazyme normalized plasma GL-3 levels at 24 weeks and sustained levels at 48 weeks[28]
- The two female patients' plasma GL-3 levels remained normal through week 48[28]
- 12 of the 14 males had GL-3 inclusions at baseline, and all 12 male patients achieved GL-3 inclusion scores of 0 at 24 and 48 weeks of treatment[28]

Study Design: 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). Histological evaluation of the capillary endothelium, 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 (defined as none) to 3 (severe).[28]

Study Dose: Fabrazyme 1 mg/kg every 2 weeks for up to 48 weeks. Female patients (n=2) had no measurable GL-3 inclusions and had normal plasma GL-3 levels at baseline, which remained normal through 48 weeks.[28]

Baseline Characteristics: All 14 males had elevated plasma GL-3 levels (ie, >7.03 µg/mL), whereas the two female patients had normal plasma GL-3 levels. 12 of the 14 males had GL-3 inclusions present on skin biopsy (scores 1, 2, or 3), whereas the two females had no GL-3 inclusions at baseline.[28]

Safety: The most common adverse reactions (>20%) were headache, abdominal pain, pharyngitis, fever, nausea, vomiting, rhinitis, diarrhea, arthralgia, and dizziness.[28]

IMPORTANT SAFETY INFORMATION

In clinical trials with Fabrazyme, some patients developed IgE antibodies or skin test reactivity specific to Fabrazyme.

- 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.
- 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. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.

FABRAZYME AND PEDIATRIC POPULATIONS.

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FABRAZYME is THE ONLY ENZYME REPLACEMENT THERAPY indicated for patients ages 2 years of age and older.[28]

- In an analysis of 24 Fabrazyme-treated pediatric patients with Fabry disease aged 2 to <8 years, plasma GL-3 levels were normalized[28]
- At baseline, all patients had elevated plasma GL-3 (ie, >7.03 µg/mL)[28]
- After treatment, plasma GL-3 levels fell within the normal range (ie, ≤7.03 µg/mL) in 91% (20/22), 95% (18/19), and 92% (12/13) of patients at 6, 12, and 24 months, respectively[28]

IMPORTANT SAFETY INFORMATION

Infusion-Associated Reactions: In clinical trials with Fabrazyme, 59% of patients experienced infusion-associated reactions, 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.

THE RATE OF KIDNEY FUNCTION DECLINE WAS STUDIED IN FABRAZYME-TREATED PATIENTS.

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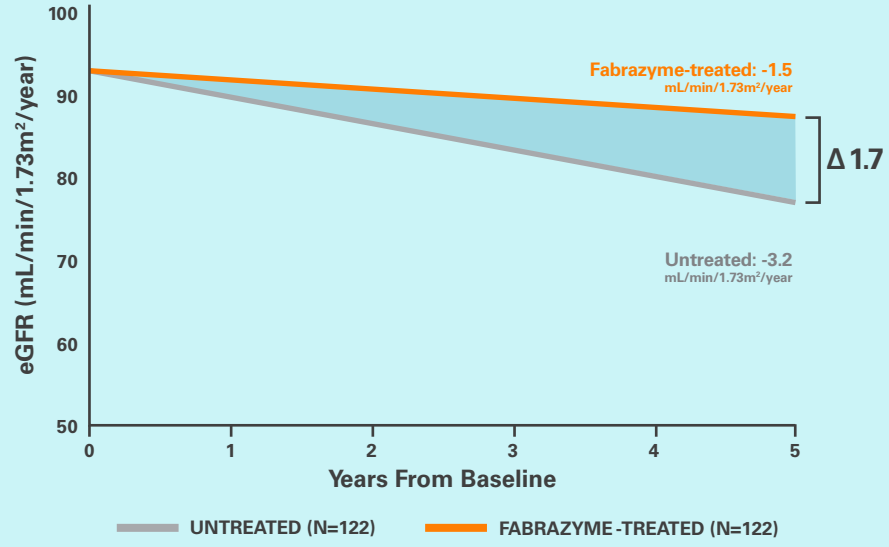
Long-term observational study results show a difference in the mean eGFR slope between the FABRAZYME-treated and untreated patients.*

Five-year observational study comparing eGFR slopes[28]

1:1 matching based on age at Fabrazyme initiation, sex, phenotype, and baseline eGFR



1.7 mL/MIN/1.73M²/YEAR

ESTIMATED DIFFERENCE IN MEAN SLOPE OF eGFR

- Estimated difference in mean slope of eGFR was 1.7 mL/min/1.73m²/year (95% CI: 0.5, 3.0)[28]
- The mean slopes of eGFR of the 2 groups were[28]:
  - Fabrazyme-treated group: -1.5 mL/min/1.73m²/year
  - Untreated group: -3.2 mL/min/1.73m²/year

- The median follow-up time was 3 years in the untreated group and 4.5 years in the treated group (maximum follow-up time was 5 years in both groups)[28]

Study design: In a long-term observational study, the rate of decline in renal function (eGFR slope) was assessed in Fabry disease patients aged ≥16 years, treated with Fabrazyme (n=122) and matched to a historical cohort of untreated patients (n=122).[28]

Patient Baseline Characteristics[28]:

- The median age at Fabrazyme initiation was 35 years. Proportion of male patients=72%. The proportion of patients with a classic phenotype=84%
- The median baseline eGFR was 93 mL/min/1.73m²
- The median age at symptom onset was 10 years and median age at diagnosis was 26 years

*eGFR slope is a measurement of kidney function over time.

IMPORTANT SAFETY INFORMATION

- In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion-associated reactions occurred in some patients after receiving pretreatment.
- If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms.

COUNT ON THE WELL-ESTABLISHED SAFETY PROFILE OF FABRAZYME®.

Fabrazyme® agalsidase beta

The safety of FABRAZYME has been assessed in **4 clinical trials** involving **162 patients** with over **473 patient-years** of experience.[28,32]

- 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, 59% of patients experienced infusion-associated reactions, some of which were severe. Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion
- In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion-associated reactions occurred in some patients after receiving pretreatment
- 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
- 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. These patients should be monitored closely if Fabrazyme is administered

Sophia and Blanca, *Fabry patients*

SUMMARY OF COMMON ADVERSE REACTIONS IN CLINICAL TRIALS (STUDIES 1 AND 2).

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Reported at rate of at least 5% in FABRAZYME-treated patients and >2.5% compared with placebo-treated patients.[28]

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

Adverse Reaction	Fabrazyme (n=80) %	Placebo (n=60) %
Pruritus	10	3
Tachycardia	9	3
Excoriation	9	2
Increased blood creatinine	9	5
Tinnitus	8	3
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

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.

COUNT ON OPTIONS.

FABRAZYME® can be administered in multiple treatment settings.

Fabrazyme® agalsidase beta

PHYSICIAN OFFICES

INFUSION CENTERS

HOME

- Choice of treatment setting is at the discretion of the physician
- Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available

Visit Fabrazyme.com/HCP to learn more

IMPORTANT SAFETY INFORMATION

- If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated. 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, appropriate medical support measures should be readily available when Fabrazyme is administered.

COUNT ON FABRAZYME. COUNT ON EXPERIENCE.

Fabrazyme® agalsidase beta

FABRAZYME is the longest-studied Fabry disease therapy.[32]

Over **17 years** of real-world experience[28]

Chosen for more than **5000 patients** worldwide[32]

Can be used for patients regardless of genotype or disease severity[28]

IMPORTANT SAFETY INFORMATION

- 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.

INDICATION AND USAGE

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

Fabrazyme® agalsidase beta

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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. 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, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, antihistamines, epinephrine, and IV corticosteroids.
- If anaphylactic or severe hypersensitivity reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Because of the potential for severe hypersensitivity reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

In clinical trials with Fabrazyme, some patients developed IgE antibodies or skin test reactivity specific to Fabrazyme.

- 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.
- 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. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.

Infusion-Associated Reactions

In clinical trials with Fabrazyme, 59% of patients experienced infusion-associated reactions, 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.

- In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion-associated reactions occurred in some patients after receiving pretreatment.
- If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms.

- If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated. 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, appropriate medical support measures should be readily available when Fabrazyme is administered.
- 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.

ADVERSE REACTIONS

- Common adverse reactions reported (≥20% and >2.5% compared to placebo) were upper respiratory tract infection (53% vs 42%), chills (49% vs 13%), pyrexia (39% vs 22%), headache (39% vs 28%), cough (33% vs 25%), paresthesia (31% vs 18%), fatigue (24% vs 17%), peripheral edema (21% vs 7%), dizziness (21% vs 8%), and rash (20% vs 10%).

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TIME IS OF THE ESSENCE FOR MANAGING FABRY DISEASE.[6]

Fabrazyme® agalsidase beta

The hallmark of Fabry disease is GL-3 accumulation, which starts in utero and continues throughout life.[13,15,18]

- Fabry disease can silently progress for many years before the appearance of clinical symptoms[17]
- The buildup of GL-3 may cause irreversible damage in essential organs such as the kidney, heart, and brain,and even premature death[16-18]
- Fabry disease is heterogeneous and can affect males and females of all ages[1,2]

ERT SHOULD BE CONSIDERED IN:

Women upon early signs of organ involvement or significant symptoms[6,12]

Children at the onset of clinically significant symptoms[29]

Classic males at diagnosis, and nonclassic males with early organ involvement[6]

CHOOSE THE PROVEN THERAPY FOR FABRY DISEASE WITH OVER 17 YEARS OF REAL-WORLD EXPERIENCE.

- Long-term observational study (maximum follow-up time of 5 years) results show a difference in the mean eGFR slope between the Fabrazyme-treated and untreated patients. The mean slope of eGFR 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 difference in mean slope of 1.7 mL/min/1.73m^2/year (95% CI: 0.5, 3.0)[28]
- A smaller percentage of Fabrazyme-treated patients experienced a renal, cardiac, or cerebrovascular event, or death. In a randomized, placebo-controlled trial over 35 months (median follow-up 18.5 months), a total of 14/51 (28%) Fabrazyme-treated patients and 13/31 (42%) placebo-treated patients experienced a clinically significant event. The estimated hazard ratio for the risk of clinically significant events was 0.57 (95% CI: 0.27, 1.22)[28]
- Can be used in patients regardless of genotype or disease severity
- Has a well-established safety profile

FABRAZYME IS THE ONLY ERT INDICATED FOR PATIENTS 2 YEARS OF AGE AND OLDER AND HAS PROVEN LONG-TERM EFFICACY AND SAFETY

IMPORTANT SAFETY INFORMATION

- 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, 59% of patients experienced infusion-associated reactions, some of which were severe.
- Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

INDICATION AND USAGE

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

SANOFI GENZYME

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