

# Fabry Registry

## Annual Report 2009

(This report covers data collected through 31 December 2008)







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## 2009 Annual Report

### I. FOREWORD

On behalf of the Boards of Advisors for the Fabry Registry, we are pleased to present the Fabry Registry 2009 Annual Report summarizing Fabry Registry data collected and/or published during the past year. This report is being provided only to Fabry Registry participants, in recognition of their continued support of the Fabry Registry.

Two key manuscripts describing the natural history of Fabry disease were accepted for publication in 2008. These investigations provide important information about the characteristics of Fabry disease in children and in patients who experience strokes. A brief overview of the 4 articles published or accepted for publication during the past year is included in this year's report. The report also presents various new analyses from renal, cardiac, and cause of death data that were compiled during the past year.

The Fabry Registry now includes more than 3,000 patients, including a growing number who have reported longitudinal clinical data obtained both before and after the initiation of enzyme replacement therapy (ERT). A high priority for the Registry in upcoming years is to analyze ERT outcomes based on this growing body of longitudinal data. With your continued participation, and that of your patients, we are steadily moving closer to achieving this goal. We hope that you find this edition of the Fabry Registry Annual Report to be an informative summary of the data and activities of the Fabry Registry in 2008. Finally, please do not hesitate to contact any one of us with your insights and research proposals so that we may support you and collaborate where appropriate in advancing our understanding of Fabry disease.

**Katherine Sims, MD**  
Fabry Registry North American Board of Advisors

**Dr. Philip Lee**  
Fabry Registry European Board of Advisors

**William Wilcox, MD, PhD**  
Fabry Registry International Board of Advisors

**Prof. Dr. Christoph Wanner**  
Fabry Registry International Board of Advisors

**Prof. Ana Maria Martins, MD, PhD**  
Fabry Registry International Board of Advisors

## II. INTRODUCTION

Fabry disease is an inherited lysosomal storage disease caused by deficient activity of the lysosomal hydrolase,  $\alpha$ -galactosidase A. Mutations in the X-linked gene that encodes the  $\alpha$ -galactosidase A protein cause progressive accumulation of globotriaosylceramide (GL-3) and related glycolipids in various tissues. The early symptoms of Fabry disease include neuropathic pain, hypohidrosis, heat- and cold-intolerance, and gastrointestinal distress. As the disease progresses, more serious complications typically develop, including renal insufficiency, cardiac disease, and stroke.

The Fabry Registry is a global, observational, and voluntary program designed to collect clinical data related to the onset, progression, and treated course of Fabry disease. Data from the Registry are also used to fulfill various global regulatory commitments. All patients with Fabry disease are eligible to participate in the Fabry Registry, regardless of whether they are receiving enzyme replacement therapy (ERT) and irrespective of the commercial product with which they are being treated.

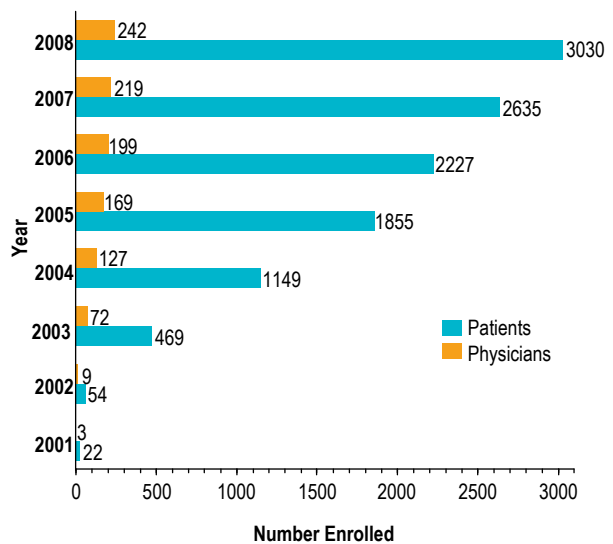
Three Advisory Boards provide scientific oversight and direction to the Fabry Registry, including a North American Board, a European Board, and an International Board. Board members are physicians with expertise in Fabry disease who serve as liaisons between the Fabry Registry and the Fabry medical community within their respective geographic regions ([Appendix 1](#)). In addition, the Latin American Registry Coordinators oversee Registry programs, including outcomes analyses and data entry for the Latin American region ([Appendix 1](#)). The Boards of Advisors developed the Fabry Registry's Minimum Recommended Schedule of Assessments ([Appendix 2](#)) in conjunction with Genzyme. This schedule recommends key clinical and laboratory parameters for monitoring patients with Fabry disease, and forms the basis of the clinical data and the frequency at which they are collected for the Fabry Registry. Because the Registry is voluntary, assessments and their frequency for individual patients are determined by their treating physicians.

It is important to recognize certain limitations associated with this type of voluntary, observational data collection. For example, registry patients are not randomized to treated and untreated groups. Furthermore, treated patients frequently have more severe disease than untreated patients, which can result in inherent bias. These and other factors must be considered when registry data are evaluated.

The infrastructure of the Fabry Registry is sponsored by Genzyme Corporation, which underwrites a third party to maintain the electronic data capture application and clinical database. Genzyme also provides financial support for data collection at some participating sites. Personnel who manage and administer the Fabry Registry programs operate within the Biomedical Data Sciences and Informatics Division and Global Registry Programs at Genzyme.

The Fabry Registry began enrolling patients in April 2001 and is currently the largest registry that tracks clinical data for patients with Fabry disease. As of December 31, 2008, a total of 242 physicians worldwide have enrolled 3,030 patients in the Fabry Registry, as shown in [Figure 1](#).

**Figure 1.**  
Cumulative Enrollment of Patients and Physicians in the Fabry Registry through December 2008



The numbers of enrolled patients and participating physicians are shown by year. Note that participating physicians are defined as those physicians with 1 or more patients enrolled in the Fabry Registry.

### Fabry Registry Publications in 2008

Now in its ninth year, the Fabry Registry has accrued a large and diverse set of clinical data from patients with Fabry disease. During 2008, 4 articles based on data from the Fabry Registry were published or accepted for publication in peer-reviewed journals. A summary of these publications is provided below.

Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, Sims K, Waldek S, Pastores GM, Lee P, Eng CM, Marodi L, Stanford KE, Breunig F, Wanner C, Warnock DG, Lemay RM, Germain DP

Females with Fabry disease frequently have major organ involvement:  
Lessons from the Fabry Registry

*Molecular Genetics and Metabolism 2008 93:112-128*

This article presents detailed data from 2,236 untreated patients enrolled in the Fabry Registry as of January 2007. The article reported that a considerable percentage of females suffer from serious complications of Fabry disease, including renal, cardiac, and cerebrovascular manifestations. Cardiac involvement, particularly left ventricular hypertrophy and arrhythmia, were the most common serious complications exhibited by females. It was also reported that many females exhibited substantial levels of proteinuria across a wide range of ages. Estimated glomerular filtration rate (eGFR) declined with age in both genders. Females reported dramatically worsened quality of life from the third decade onward. The article concludes that both males and females with Fabry disease should undergo comprehensive regular monitoring of the disease burden and progression. Findings from these analyses add to the growing body of evidence that females are not merely “carriers” of Fabry disease, but that they also experience substantial signs and symptoms.

Ortiz A, Oliveira JP, Waldek S, Warnock DG, Cianciaruso B, Wanner C; on behalf of the Fabry Registry  
Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment  
with enzyme replacement therapy

*Nephrology Dialysis Transplantation 2008 23:1600-1607*

This article reports comprehensive analyses of renal data from untreated Fabry Registry patients who had renal assessment data available as of April 2007. This cohort included 1,262 patients (585 males and 677 females). Among these patients, 28% of males and 13% of females had chronic kidney disease (CKD) stage 3 or worse (i.e., eGFR <60 ml/min/1.73 m<sup>2</sup>). Albuminuria and proteinuria were more prevalent among females than previously thought. The data also suggest that albuminuria may precede overt proteinuria and may be an even more sensitive marker of renal disease progression. In addition, a large proportion of patients with CKD stage 1-2 had inadequately controlled blood pressure. Elevated blood pressure is a major concern in these patients, as higher proteinuria values were significantly correlated with elevated systolic blood pressure in both genders. This investigation represents an important contribution to the literature and to the medical community, as it further characterizes the nature of renal dysfunction in Fabry disease and demonstrates that a significant proportion of females with Fabry disease suffer from moderate to severe kidney disease.

Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, Lemay R,  
Tylki-Szymanska A, Wilcox WR

Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry

*Pediatric Research 2008 64:550-555*

This investigation analyzed reported signs and symptoms, cardiac abnormalities, and renal function in 352 untreated pediatric patients with Fabry disease (age <18 years at the time of enrollment, as of November 2007). Boys generally experienced a higher frequency of symptoms at an earlier age than girls. However, females also reported considerable symptoms and some serious manifestations of Fabry disease during childhood. Brief Pain Inventory scores indicated that 53% of males and 15% of females had experienced moderate or severe pain during the previous 24 hours. However, most patients had not received any treatment for pain, underscoring the importance of better pain management in children with Fabry disease, regardless of other associated signs or symptoms. A surprising number of serious cardiac abnormalities were identified among both boys and girls, including 9 children with arrhythmias and 3 children with left ventricular hypertrophy. Three pediatric patients exhibited overt renal disease (i.e., stage 2 or 3 CKD) and 13 patients exhibited proteinuria or microalbuminuria, indicating some level of renal dysfunction. Mean and median eGFR values were >140 ml/min/1.73m<sup>2</sup> among both genders and 22% of those with available data exhibited eGFR >170 ml/min/1.73m<sup>2</sup>, suggesting possible renal hyperfiltration. In summary, children clearly experience substantial signs and symptoms of Fabry disease and a small percentage of children with Fabry disease experience serious cardiac and renal manifestations during childhood.

Sims K, Politei J, Banikazemi M, Lee P

Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events: Natural History Data from the Fabry Registry

*Stroke, 2009; 40:788-794 (accepted for publication August 2008)*

This article describes clinical characteristics of untreated patients with Fabry disease who experienced a stroke. Among 2,446 patients enrolled in the Fabry Registry as of October 2007, a total of 138 patients (86 males and 52 females) had experienced strokes during the natural history period. The incidence rate of stroke was markedly higher and the age at first stroke was much younger in Fabry Registry patients than among the general US population. Fifty percent of males and 38% of females experienced their first stroke before being diagnosed with Fabry disease. Most patients had not experienced renal or cardiac events before their first stroke. Thirty patients had strokes at young ages (<30 years), including 2 patients who had strokes in their teen years. Most patients had ischemic strokes, but 16 patients (13 males and 3 females) had hemorrhagic strokes, among those for whom stroke type was reported. Thus, physicians should be aware that stroke can occur in the absence of other key clinical signs of the disease.

### III. PROGRESS TOWARDS 2008 GOALS

The following sections summarize progress that has been made over the past year towards 2008 goals set by the Fabry Registry.

#### Analysis of Renal Disease Progression

The first goal for the Fabry Registry in 2008 was to analyze renal disease progression using available longitudinal data. As the severity of Fabry disease varies considerably among individuals, analyses of disease progression over time require a sufficient number of patients with multiple renal assessments. As of April 2008, a total of 380 adult Registry patients (131 males and 249 females) were identified who had 3 or more eGFR values over a span of 2 or more years during the natural history period (i.e., prior to any ERT) and prior to any chronic dialysis or renal transplant. At the

time of their first renal assessment, 64 of 131 males (49%) and 147 of 249 females (59%) exhibited Stage 2 or worse CKD, as shown in **Figure 2**. The percentages of males and females who exhibited Stage 3 or worse CKD were similar in both genders: 16 of 131 males [12%] and 32 of 249 females [13%].

As longitudinal renal data are accrued for more patients, further analyses of renal function will be possible. Preliminary analyses of change in eGFR over time indicate that patients with Fabry disease who initially exhibited low eGFR levels and/or proteinuria were generally reported to lose renal function more quickly than those with better renal function and little or no urinary protein excretion (data not shown). In view of these and previous findings, eGFR and urinary protein excretion should be closely monitored in all Fabry patients, regardless of other signs or symptoms.

### Analysis of Cardiac Disease Progression

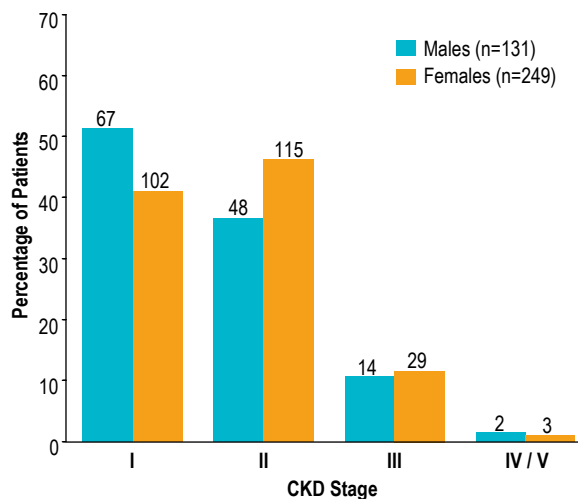
Cardiovascular dysfunction is another common and serious manifestation of Fabry disease. A second goal set by the Fabry Registry for 2008 was to analyze available longitudinal cardiac data. Such data may provide valuable information about the progression of cardiac complications in individual patients over time as well as response to ERT. However, in order to perform these analyses, it was determined that the Registry needed to collect additional cardiac parameters. Therefore, the Fabry Registry Boards of Advisors accepted the recommendation of the Cardiology Work Group to revise the cardiac electronic case report form (eCRF). In response to these eCRF changes, the Fabry Registry has encouraged sites to capture at least 3 longitudinal echocardiograms and electrocardiograms for each patient, and to provide more detailed cardiac medical history data related to cardiac events. Acquisition of these data in 2009 will make it possible to better analyze cardiac disease progression in Fabry Registry patients. In 2008, the Registry analyzed cross-sectional cardiac data, to better understand general cardiac manifestations in both genders. Some of these data are presented in the Current Data section of this report ([Section IV](#)).

### Genotype Standardization and Reconciliation

One important aspect of Fabry disease that remains largely unknown is the relationship between genotype and phenotype, i.e., what specific genetic mutation a patient carries and how that may affect the clinical manifestations of the disease. This is a particularly challenging issue for Fabry disease, both because of the complexity of the disease and the relative rarity of each mutation. Over 400 mutations in the gene that encodes  $\alpha$ -galactosidase A have been described to date, and many are unique to single families.

A third goal that the Registry set for 2008 was to establish a standard format for genotype data recorded in the Registry. Because various molecular laboratories describe genetic mutations in different ways, genotype data has been entered into the Registry in various formats. A formal genotype review and reconciliation process has been developed and the Fabry Registry has begun to identify and re-classify genotypes submitted to the Fabry Registry database according to standardized nomenclature. Moving forward, newly entered genotypes will undergo biannual expert review, and any genotype that is not in the standard nomenclature will be converted. Once this process is completed, the Fabry Registry database will provide a valuable tool for analyzing potential relationships between genotype and phenotype.

**Figure 2.**  
Summary of Initial CKD Stage Among Untreated Fabry Registry Patients for whom Longitudinal Renal Data are Available



Data are expressed as percentages of patients in CKD Stage I (eGFR  $\geq$  90 mL/min/1.72m<sup>2</sup>), Stage II (eGFR 60 to <90 mL/min/1.73 m<sup>2</sup>), Stage III (eGFR 30 to <60 mL/min/1.72m<sup>2</sup>), and Stage IV/V (eGFR <30 mL/min/1.73 m<sup>2</sup>) at the time of their initial eGFR assessments, among patients who had 3 or more eGFR assessments available. The numbers above each bar show the number of male and female patients in each CKD stage, as of April 4, 2008. All data are from patients who had not been treated with ERT at the time of these assessments.



## IV. CURRENT DATA

### Demographics

At the end of 2008, the Fabry Registry had collected data from 3,030 patients, including nearly equal numbers of males and females, as shown in **Table 1**. Among the global Fabry Registry population, 89% of males and 90% of female patients were classified as adults (18 years of age or older). The majority of patients within both genders were Caucasian and most patients reported having a family member diagnosed with Fabry disease, among the global population. Demographic data are also shown for specific geographic regions in **Table 1**. The majority of patients enrolled in the Registry are from Europe (45%) and North America (41%), followed by Latin America (8%) and the Asia Pacific region (5%). Across all geographic regions, males were diagnosed at a younger age than females. Among the global population, males were diagnosed at a median age of 25 years, versus 32 years in females.

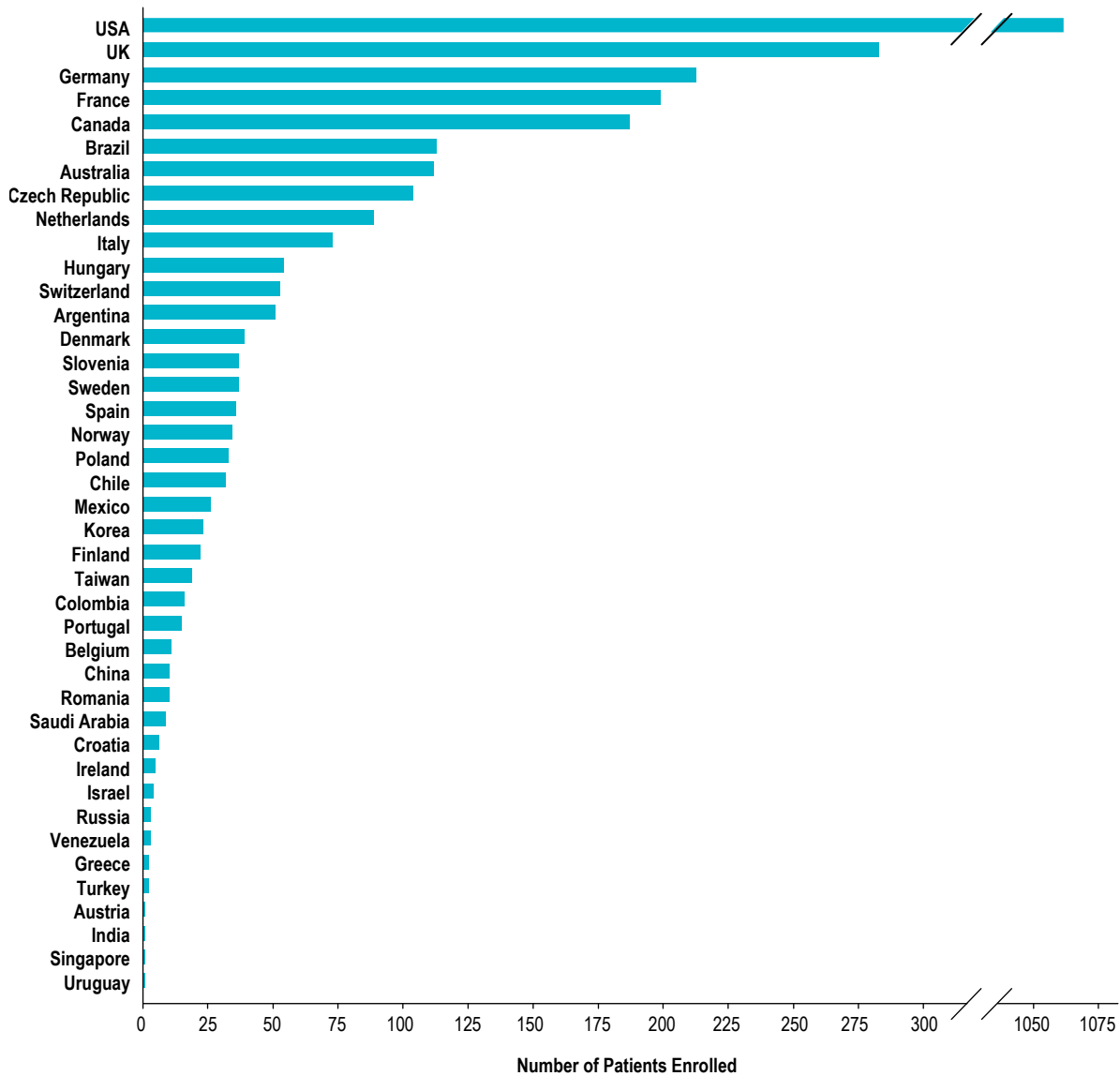
**Table 1.**  
Demographic Profile of Fabry Registry Patients

	Global Total		North America		Europe		Latin America		Asia Pacific	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
<b>Number Enrolled, N</b>	1509	1521	618	630	663	712	127	115	101	64
<b>Current Age (yr)</b>										
n	1508	1520	617	629	663	712	127	115	101	64
Mean (SD)	38.2 (15.31)	42.2 (17.50)	37.6 (16.05)	42.4 (17.62)	39.9 (14.95)	42.5 (17.39)	35.1 (13.54)	39.5 (17.39)	35.5 (13.88)	41.3 (17.63)
Median	39.0	43.0	40.0	44.0	41.0	43.0	34.0	40.0	37.0	43.5
Range	(2.0,84.0)	(0.0,88.0)	(2.0,83.0)	(1.0,84.0)	(5.0,84.0)	(3.0,88.0)	(7.0,75.0)	(5.0,83.0)	(8.0,68.0)	(0.0,81.0)
<b>Current Age Distribution, n (%)</b>										
Age ≥ 18 years	1347 (89)	1374 (90)	536 (87)	564 (90)	607 (92)	653 (92)	113 (89)	100 (87)	91 (90)	57 (89)
Age < 18 years	161 (11)	146 (10)	81 (13)	65 (10)	56 (8)	59 (8)	14 (11)	15 (13)	10 (10)	7 (11)
<b>Age at Diagnosis (yr)</b>										
n	1486	1460	609	595	654	695	122	108	101	62
Mean (SD)	26.9 (16.01)	33.0 (17.89)	24.8 (16.15)	31.5 (18.18)	28.5 (16.46)	34.3 (17.60)	28.7 (13.39)	33.8 (17.51)	25.9 (13.61)	32.2 (18.20)
Median	25.0	32.0	23.0	31.0	27.5	33.0	27.5	34.5	23.0	31.5
Range	(0.0,81.0)	(0.0,80.0)	(0.0,79.0)	(0.0,78.0)	(0.0,81.0)	(0.0,80.0)	(2.0,62.0)	(0.0,77.0)	(1.0,61.0)	(0.0,68.0)
<b>Ethnicity, n (%)</b>										
Caucasian	1145 (76)	1210 (80)	470 (76)	481 (76)	591 (89)	642 (90)	31 (24)	39 (34)	53 (52)	48 (75)
Black	31 (2)	23 (2)	22 (4)	19 (3)	5 (0.8)	2 (0.3)	4 (3)	2 (2)	0	0
Hispanic	117 (8)	100 (7)	49 (8)	50 (8)	2 (0.3)	0	66 (52)	50 (43)	0	0
Asian	56 (4)	19 (1)	2 (0.3)	2 (0.3)	12 (2)	7 (1.0)	0	0	42 (42)	10 (16)
Other	53 (4)	35 (2)	19 (3)	19 (3)	14 (2)	7 (1.0)	19 (15)	7 (6)	1 (1.0)	2 (3)
Unknown/Not Reported	107 (7)	134 (9)	56 (9)	59 (9)	39 (6)	54 (8)	7 (6)	17 (15)	5 (5)	4 (6)
<b>Fabry in Family?</b>										
Yes	1166 (77)	1306 (86)	496 (80)	551 (87)	500 (75)	603 (85)	104 (82)	98 (85)	66 (65)	54 (84)
No	169 (11)	48 (3)	55 (9)	20 (3)	81 (12)	26 (4)	11 (9)	0	22 (22)	2 (3)
Unknown/Not reported	174 (12)	167 (11)	67 (11)	59 (9)	82 (12)	83 (12)	12 (9)	17 (15)	13 (13)	8 (13)

Data reflect data available as of December 31, 2008.

The Fabry Registry includes patients enrolled in 41 countries, as shown in Figure 3. The largest numbers of patients are enrolled in the United States (1,060), the United Kingdom (283), Germany (213), France (199), and Canada (187).

Figure 3.  
Countries of Origin of Fabry Registry Patients



Data shown reflect enrollment as of December 31, 2008. Data from the United States (USA) are shown with a break in the x-axis, to better visualize enrollment data for countries with fewer patients.

## ERT Treatment and Dosing Status Among Fabry Registry Patients

Two licensed ERT products are commercially available to treat Fabry disease: agalsidase beta (Genzyme Corporation) and agalsidase alfa (Shire, plc). Agalsidase alfa is not currently approved for use in the United States. The Fabry Registry is open to all patients with Fabry disease, irrespective of whether they have received ERT and irrespective of the commercial product with which they are being treated (if any). As of December 31, 2008, 1,790 of 3,030 Fabry Registry patients (59%) were reported to have received ERT, as shown in **Table 2**. Among those for whom the source of ERT was specified, 1519 of 1702 (89%) had received agalsidase beta at some point. Among the global population, 84% of adult males have received ERT, as compared to 40% of adult females. This gender difference is also seen among pediatric patients and across all geographic regions.

**Table 2.**  
ERT status for Patients in the Fabry Registry

	Global Total		North America		Europe		Latin America		Asia Pacific	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
<b>Number Enrolled, N</b>	1509	1521	618	630	663	712	127	115	101	64
<b>ERT Status, n (%)</b>										
<b>Currently Adult (≥18 yr)</b>	1347 (89)	1374 (90)	536 (87)	564 (90)	607 (92)	653 (92)	113 (89)	100 (87)	91 (90)	57 (89)
Never On ERT	189 (14)	808 (59)	69 (13)	322 (57)	73 (12)	376 (58)	25 (22)	74 (74)	22 (24)	36 (63)
Ever On ERT	1137 (84)	549 (40)	455 (85)	229 (41)	532 (88)	274 (42)	81 (72)	25 (25)	69 (76)	21 (37)
Unknown	21 (2)	17 (1)	12 (2)	13 (2)	2 (0)	3 (0)	7 (6)	1 (1)	0	0
Only on agalsidase beta as ERT	924 (69)	430 (31)	384 (72)	202 (36)	415 (68)	189 (29)	74 (65)	25 (25)	51 (56)	14 (25)
Ever on agalsidase beta as ERT	988 (73)	444 (32)	408 (76)	203 (36)	452 (74)	202 (31)	74 (65)	25 (25)	54 (59)	14 (25)
ERT source not specified	53 (4)	30 (2)	18 (3)	11 (2)	25 (4)	18 (3)	7 (6)	0	3 (3)	1 (2)
<b>Currently Pediatric (&lt;18 yr)</b>	161 (11)	146 (10)	81 (13)	65 (10)	56 (8)	59 (8)	14 (11)	15 (13)	10 (10)	7 (11)
Never On ERT	73 (45)	127 (87)	31 (38)	54 (83)	30 (54)	51 (86)	7 (50)	15 (100)	5 (50)	7 (100)
Ever On ERT	87 (54)	17 (12)	50 (62)	11 (17)	25 (45)	6 (10)	7 (50)	0	5 (50)	0
Unknown	1 (1)	2 (1)	0	0	1 (2)	2 (3)	0	0	0	0
Only on agalsidase beta as ERT	71 (44)	16 (11)	42 (52)	11 (17)	18 (32)	5 (8)	7 (50)	0	4 (40)	0
Ever on agalsidase beta as ERT	71 (44)	16 (11)	42 (52)	11 (17)	18 (32)	5 (8)	7 (50)	0	4 (40)	0
ERT source not specified	4 (2)	1 (1)	2 (2)	0	1 (2)	1 (2)	0	0	1 (10)	0

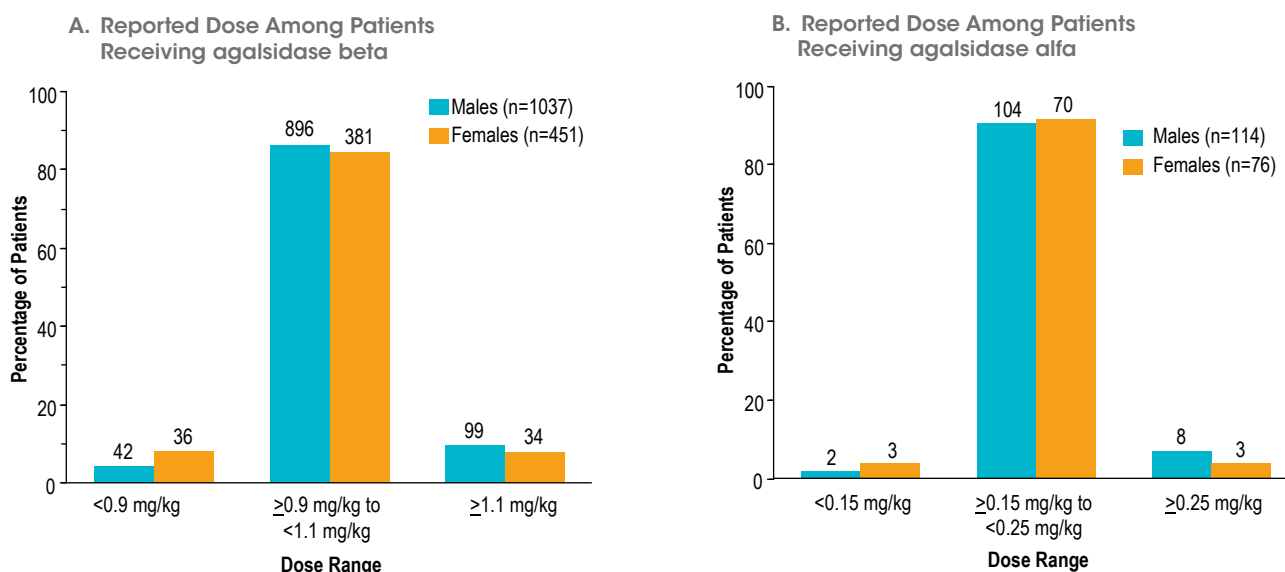
Data reflect data available as of December 31, 2008.

\*ERT source not specified" indicates that the patient reported that ERT was received, but the source (agalsidase beta or agalsidase alfa) was not specified.

Note that percentages may not total to exactly 100% due to rounding.

The Fabry Registry collects ERT dosing data from patients who receive ERT. As of December 31, 2008, dosing data were available for 1,037 males and 451 females who had been treated with agalsidase beta. As shown in **Figure 4**, panel A, 86% of males and 84% of females were receiving agalsidase beta at or near the labeled recommended dose (1 mg/kg biweekly), at the time of the last reported dose. A higher percentage of females who were treated with agalsidase beta were receiving doses in the lower range (< 0.9 mg/kg biweekly), as compared to males (8% of females versus 4% of males). A smaller number of patients (114 males and 76 females) had been treated with agalsidase alfa at the time of their last reported dose, as shown in **Figure 4**, panel B. At that time, nearly all patients treated with agalsidase alfa (91% of males and 92% of females) were receiving agalsidase alfa at or near the labeled recommended dose for that product (0.2 mg/kg biweekly).

**Figure 4.**  
Distribution of Patients on ERT by Product and Dose Category



Data are expressed as a percentage of patients in each dosing category and represent the most recently reported dose and commercial product used. The labeled recommended dose for agalsidase beta is 1.0 mg/kg biweekly and the labeled recommended dose for agalsidase alfa is 0.2 mg/kg biweekly. Numbers above the bars indicate the number of patients in each category.

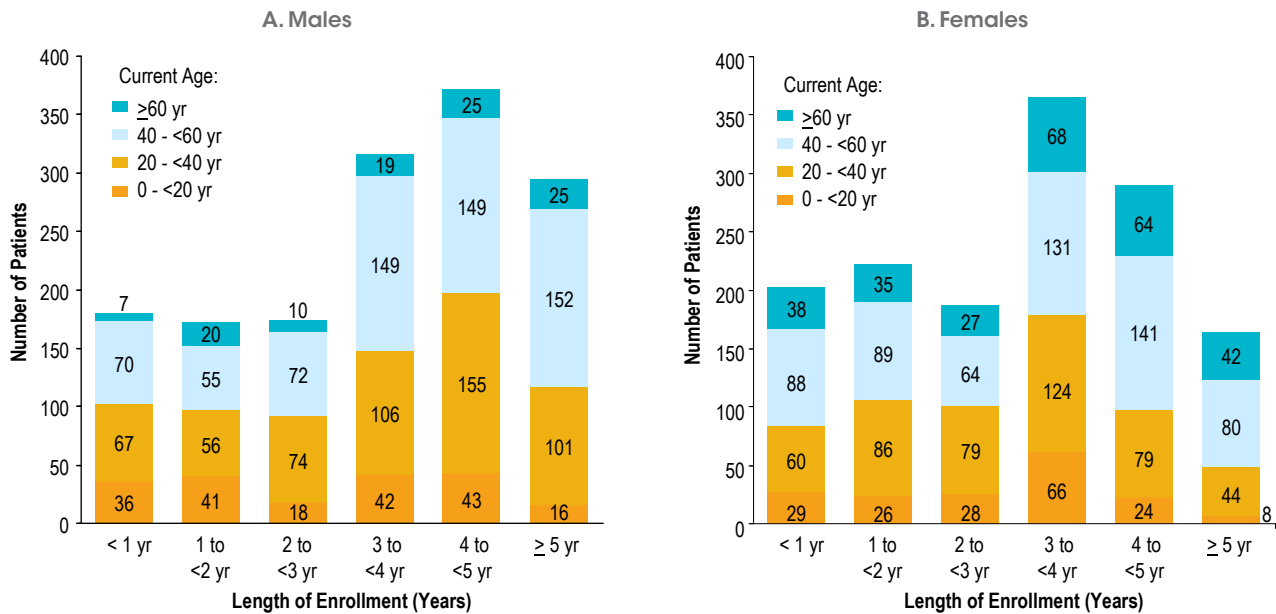
### Growth in Number of Patients with Longitudinal Data

The patient population within the Fabry Registry continues to increase, as does the length of time over which data are available for individual patients. To date, 2,635 patients in the Fabry Registry (87%) have been participating in the Registry for 1 year or more and 469 patients (15%) have now been participating for 5 years or more, as shown in **Figure 5**. Among patients who have been enrolled in the Registry for 3 or more years, the largest percentage are between the ages of 40 to <60 years (802 of 1855, 43%). Thus, the Registry is positioned to provide increasingly detailed longitudinal data, which may be used to further describe disease progression as well as the long-term effects of treatment.

In accordance with the growing number of patients who have been enrolled in the Registry over long periods of time, the number of patients with multiple important clinical assessments has also increased. In terms of renal data, for example, **Figure 6** shows how the amount of longitudinal renal data has progressively increased over the past year, both among patients who have been treated with ERT (panel A) as well as among patients who have never received ERT (panel B). This type of longitudinal data may be used to describe the progression of renal disease and the effect of ERT on renal outcomes.

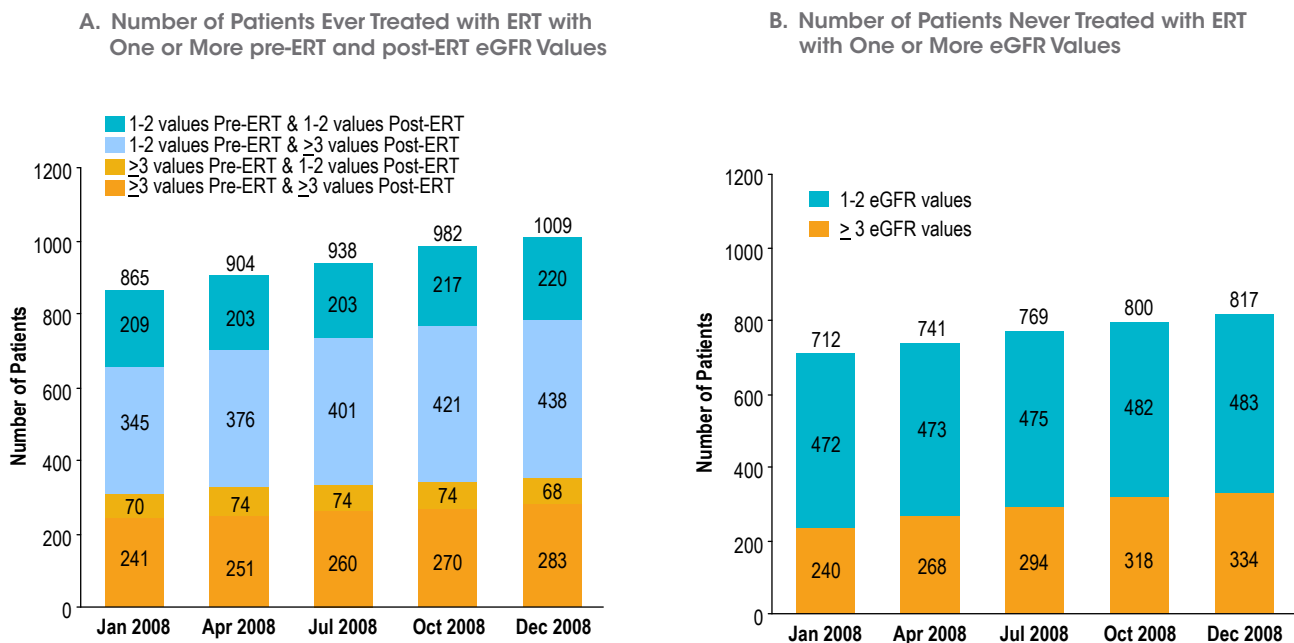
Various analyses of Fabry Registry data performed during the course of 2008 are presented below. Note that because these analyses were performed at different times during the past year, the number of patients enrolled differs slightly from that shown in [Table 1](#), which reports total enrollment as of December 31, 2008.

**Figure 5.**  
Length of Time Patients have been Enrolled in the Fabry Registry



Data shown represent the number of patients who have been enrolled in the Fabry Registry for the indicated time periods, as of December 31, 2008. For each time period, the number of patients enrolled is broken down into 4 age categories, as indicated. Note that 1 male and 1 female patient for whom length of enrollment was available but current age was unknown are not represented in the graph.

**Figure 6.**  
Growth in Number of Fabry Registry Patients with Longitudinal Renal Data

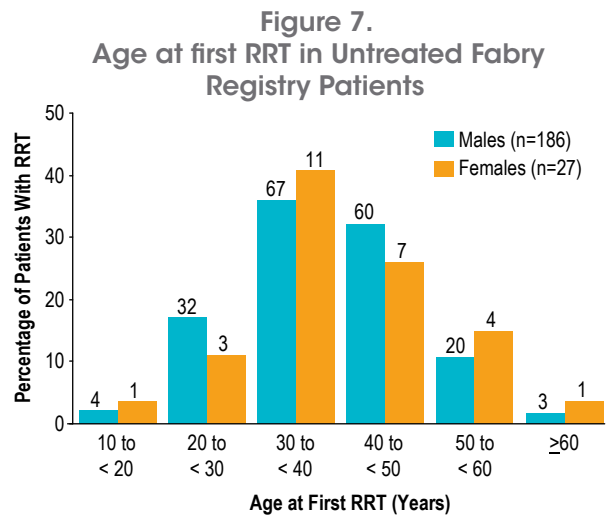


Data are expressed as the number of patients within the indicated categories at the end of each month. The number of patients in each category is shown within the bars, with the total number of patients with eGFR data available at that month shown above each bar. eGFR values were calculated from serum creatinine levels, using the Modification of Diet in Renal Disease (MDRD) equation for patients ≥18 years old and the Schwartz equation for patients <18 years old at the time of the serum creatinine collection.

## Characterization of Fabry Registry patients who Experience Renal Failure

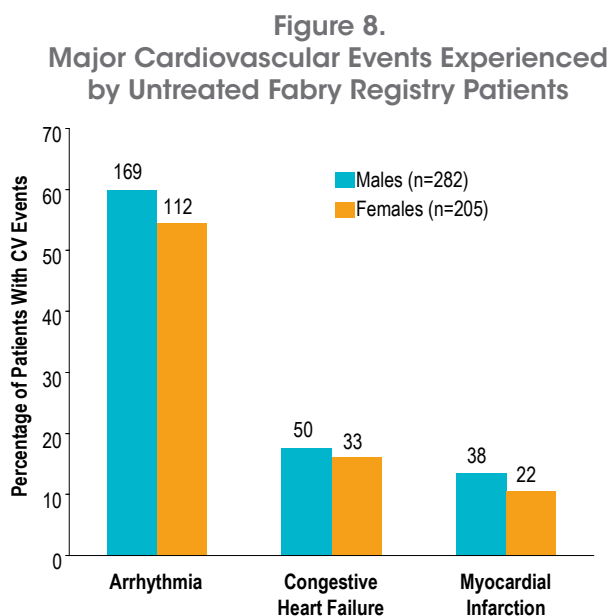
Progressive renal dysfunction is a common and life-threatening manifestation of Fabry disease, among both genders. Many Fabry patients eventually require renal replacement therapy (RRT), either in the form of chronic dialysis or a kidney transplant. The large, international cohort of patients enrolled in the Fabry Registry provides a unique resource to study progression of renal disease in these patients. As of May 2008, 186 of 1359 males (14%) and 27 of 1353 females (2%) in the Fabry Registry had received RRT during the natural history period (i.e., prior to any treatment with ERT). The median age at first RRT was 38 years, among both genders. As shown in **Figure 7**, most patients received their first RRT between the ages of 30 and 50 years.

The median age at diagnosis was much older among the cohort of patients who required RRT, compared to that of the overall Registry population. Both males and females who received RRT were diagnosed at a median age of 35 years, compared to 24 years in males and 31 years in females in the overall Fabry Registry population [[Wilcox 2008](#)]. Moreover, a substantial proportion of these patients were not diagnosed with Fabry disease until after they had received RRT (33% of males and 37% of females). The late age at which these patients were diagnosed likely played a major role in their progression to end stage renal disease.



Percentages of patients experiencing their first RRT during each of 6 age categories are shown. The numbers above each bar indicate the number of patients in each age category. All data are from patients not treated with ERT at the time of their first RRT. Data shown reflect data available as of May 2, 2008.

## Characterization of Cardiovascular Events Among Fabry Registry Patients



Data are expressed as the percentages of males and females who experienced arrhythmias, myocardial infarctions, or congestive heart failure as of October 3, 2008. The number of patients in each age category shown above each bar. CV=cardiovascular.

The cardiovascular manifestations of Fabry disease include left ventricular hypertrophy, conduction abnormalities, and ischemic heart disease. Over time, these cardiac complications can progress to congestive heart failure, myocardial infarction, and life-threatening arrhythmias. A better understanding of the natural history of cardiovascular manifestations of Fabry disease may provide valuable information about which patients may be at greatest risk for cardiac problems.

As of October, 2008, 487 Fabry Registry patients had experienced 1 or more cardiovascular events during the natural history period, with cardiovascular events defined as arrhythmia, myocardial infarction, congestive heart failure, angina pectoris, or significant cardiac procedures (e.g. pacemaker placement, coronary bypass, stent placement, valve replacement, transplantation). A total of 282 of 1424 males (20%) and 205 of 1445 females (14%) reported a cardiovascular event. The median age at patients' first cardiovascular event was 42.8 years in males and 49.1 years in females. Arrhythmia was the most common type of cardiovascular event among both genders, reported

by 169 of 282 males (60%) and 112 of 205 females (55%), as shown in **Figure 8**. The percentages of patients who experienced each type of cardiovascular event were generally similar between males and females. Among both genders, patients who reported cardiovascular events were diagnosed at a much later age than patients who did not experience these events (median 37 years versus 23 years in males and 46 versus 31 years in females).

### Cause of Death Among Fabry Registry Patients

As of August 2, 2008, 75 of 1422 males and 12 of 1426 females in the Fabry Registry had died. These analyses included all patients, regardless of ERT status. The median age at death was 54.3 years in males and 62.0 years in females. The reported cause of death was known for 56 males and 10 females, as shown in **Table 3**. Cardiovascular disease was the most common cause of death among both genders; 30 of 75 males (40.0%) and 5 of 12 females (41.7%) had their deaths classified as being due to cardiovascular disease. The median age at death due to cardiovascular disease was 55.5 years in males and 66.0 years in females. Most of the deceased patients (81.3% of males and 41.7% of females) had received ERT, which became commercially available in 2001 (agalsidase alfa and agalsidase beta in the European Union) and 2003 (agalsidase beta in the United States). However, these patients were untreated for the majority of their lives, as the median duration of ERT was 12 months in males (range 0.1 to 7.3 years) and 4 months in females (range 0.1 to 2.8 years). Deceased patients were diagnosed at much older median ages than living patients (age 40 versus age 24 years in males and age 55 versus age 33 years in females).

**Table 3**  
Cause of Death Among Fabry Registry Patients

Cause of Death	Deceased Males (N=75)		Deceased Females (N=12)	
	Number of Deaths, n%	Median Age at Death (years)	Number of Deaths, n%	Median Age at Death (years)
Cardiovascular	30 (40.0)	55.5	5 (41.7)	66.0
Unknown or Not Reported	19 (25.3)	53.8	2 (16.7)	56.0
Cerebrovascular	7 (9.3)	49.3	1 (8.3)	56.7
Renal	6 (8.0)	55.5	1 (8.3)	74.3
Infection	5 (6.7)	42.2	0	-
Gastrointestinal	3 (4.0)	44.9	0	-
Cancer	2 (2.7)	61.1	3 (25.0)	63.3
Respiratory	1 (1.3)	71.5	0	-
Suicide	1 (1.3)	31.2	0	-
Other*	1 (1.3)	47.9	0	-

Two male and 1 female Fabry Registry patients who were deceased, but who did not have a date of death reported were excluded from the dataset.

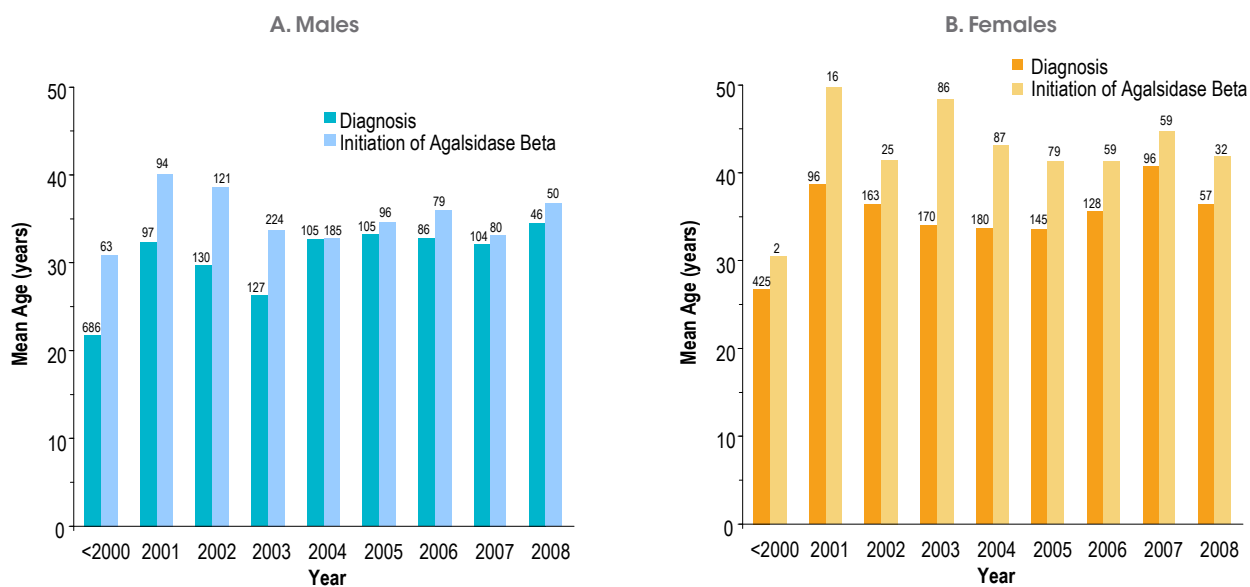
\*One male died after suffering multi-organ failure during hip surgery (sepsis, hepatic insufficiency, and cardiorespiratory failure).

Data shown reflect data available as of August 2, 2008.

### Age at Diagnosis and Initiation of agalsidase beta Treatment

Older age at diagnosis was a common factor among patients who experienced end-stage renal failure, patients who experienced cardiovascular events, and patients who died, compared to Fabry Registry patients who did not experience these complications. **Figure 9** shows the annual average age at diagnosis and the average age at initiation of agalsidase beta treatment, among males and females in the Fabry Registry. Overall, the age gap between diagnosis and initiation of treatment has narrowed considerably since 2001, particularly among males. However, average age at diagnosis still lags far behind the average age at which symptoms first appear [[Eng 2007](#); [Wilcox 2008](#)].

**Figure 9.**  
Age at Diagnosis and Age at Initiation of agalsidase beta Treatment



Data shown in dark blue (left panel, males) or dark orange (right panel, females) represent mean age at diagnosis among all Fabry Registry patients reported to be newly diagnosed in each indicated year. Data shown in light blue (left panel, males) or light orange (right panel, females) represent mean age at initiation of agalsidase beta treatment, among the population of patients who began treatment during each indicated year and who had received only agalsidase beta as a source of ERT. The numbers above the bars indicate the number of patients (n) in each category.



## V. SUMMARY

As of December 2008, the Fabry Registry has accrued clinical assessment and outcomes data from 3,030 patients in 41 countries. The major points summarized in the Fabry Registry 2009 Annual Report are:

- Two key manuscripts describing the natural history of Fabry disease were accepted for publication in 2008 [[Hopkin, 2008](#); [Sims, 2009](#)]. These investigations provide important information about the characteristics of Fabry disease in children and in patients who experience strokes. To date, a total of 6 articles from the Fabry Registry have been published in peer-reviewed journals.
- Various analyses of renal disease among Fabry Registry patients were performed over the past year. Among untreated patients who had sufficient renal data available, 49% of males and 59% of females exhibited Stage 2 or worse CKD, at the time of their initial assessment. This includes 12% of males and 13% of females who exhibited Stage 3 or worse CKD at that time.
- Analyses of natural history cardiovascular data revealed that arrhythmia was the most common type of cardiovascular event experienced by both genders. The median age at patients first cardiovascular event was 42.8 years in males and 49.1 years in females.
- Cardiovascular disease was the most common reported cause of death among deceased Fabry Registry patients. The median age at death due to cardiovascular disease was 55.5 years in males and 66.0 years in females.
- Delayed diagnosis was a reported common factor among patients who reached end-stage renal failure, patients who experienced cardiovascular events, and patients who died.

## VI. GOALS FOR 2009

- Collect more longitudinal cardiac data. A focused cardiac data collection effort will continue in 2009. Acquisition of at least 3 longitudinal echocardiograms and ECGs for each patient, as well as more detailed cardiac medical history data related to cardiac events will facilitate analyses of cardiac disease progression.
- Collect more key baseline and longitudinal data, from both treated and untreated patients. In addition to the cardiac data mentioned above, clinical event, serum creatinine, urinalysis, and concomitant medication data are needed for upcoming analyses of ERT outcomes.
- Initiate renal ERT outcome analyses. Once sufficient pre-ERT and post-ERT renal data become available, ERT renal outcomes will be analyzed.
- Collect additional pregnancy and neonatal outcomes data. The Fabry Registry requests information regarding pregnancy course and neonatal outcomes, regardless of exposure to ERT.
- Establish a Fabry Registry Asia Pacific Board of Advisors. The number of Fabry Registry patients and physicians in the Asia Pacific region continues to grow, and a Board of Advisors for this region will be established in 2009.

## ADVERSE EVENT REPORTING

Adverse events, including all deaths, in patients treated with agalsidase beta should be reported promptly to the appropriate Genzyme Pharmacovigilance Office, even if the event does not appear to be related to this product, as follows: Within the United States, 800-745-4447 (option 2); within Europe, +31-35-699-1299; within Latin America, +55-21-2156-9970; within other parts of the world, +617-768-9000 (option 2). Refer to the Safety section of the Fabry Registry Protocol for specific reporting guidelines.

## APPENDIX 1 – 2008 BOARDS OF ADVISORS AND REGISTRY COORDINATORS

### North American Board of Advisors

Advisor	Affiliation	Location
Katherine Sims, M.D. (Chair)	Massachusetts General Hospital	Boston, MA, USA
Ademola Abiose, M.D.	Iowa University Health Center	Iowa City, IA, USA
Maryam Banikazemi, M.D.	Columbia University College of Physicians and Surgeons	New York, NY, USA
John Barranger, M.D., Ph.D.	Consultant for Genzyme Corporation	Cambridge, MA, USA
Daniel Bichet, M.D.	Hôpital du Sacré-Coeur de Montréal	Montréal, QC, Canada
Joel Charrow, M.D.	Children's Memorial Hospital	Chicago, IL, USA
Lorne Clarke, M.D.	British Columbia Research Institute for Child & Family Health	Vancouver, BC, Canada
Christine Eng, M.D.	Baylor College of Medicine	Houston, TX, USA
Robert Hopkin, M.D.	Cincinnati Children's Hospital Medical Center	Cincinnati, OH, USA
Michael Mauer, M.D.	University of Minnesota	Minneapolis, MN, USA
Manesh Patel, M.D.	Duke University Medical Center	Durham, NC, USA
C. Ronald Scott, M.D.	University of Washington	Seattle, WA, USA
David G. Warnock, M.D.	University of Alabama at Birmingham	Birmingham, AL, USA
William Wilcox, M.D., Ph.D.	Cedars Sinai Medical Center	Los Angeles, CA, USA

### European Board of Advisors

Advisor	Affiliation	Location
Dr. P. Lee (Co-Chair)	National Hospital for Neurology and Neurosurgery	London, United Kingdom
Prof. Dr. C. Wanner (Co-Chair)	Universitätsklinik Würzburg	Würzburg, Germany
Dr. A. Burlina	San Bassiano Hospital	Bassano del Grappa, Italy
Dr. U. Feldt-Rasmussen	National University Hospital	Copenhagen, Denmark
Dr. A. Foulhoux	Hôpital Edouard Herriot	Lyon, France
Prof. D. P. Germain	Hôpital Raymond Poincaré	Garches, France
Dr. L. Golan	General Hospital Charles University	Prague, Czech Republic
Dr. G. Linthorst	Academisch Medisch Centrum	Amsterdam, Netherlands
Dr. J-E. Mansson	Shalgren's University Hospital	Molndal, Sweden
Dr. J.P. Oliveira	Médica Faculdade de Medicina da Universidade Do Porto	Porto, Portugal
Dr. A. Ortiz	Fundacion Jiménez Díaz	Madrid, Spain
Dr. J. Strotmann	I. Medizinische Klinik	Kiel, Germany
Prof. Dr. A. Tytki-Szymanska	Children's Memorial Health Institute	Warsaw, Poland
Dr. B. Vujkovic	General Hospital	Slovenj Gradec, Slovenia
Dr. S. Waldek	Hope Hospital	Manchester, United Kingdom

## Latin American Fabry Registry Coordinators

Coordinator	Affiliation	Location
Juan Fransisco Cabello, M.D.	Universidad de Chile, Instituto de Nutrición y Tecnología de los Alimentos	Santiago de Chile, Chile
Alexandra Carnevale, M.D.	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado	Cd Mexico, Mexico
Adriana Linares, M.D.	Universidad Nacional de Colombia, Hospital La Misericordia	Bogotá, Colombia
Prof. Ana Maria Martins, M.D., Ph.D.	Universidade Federal de São Paulo	São Paulo, Brazil
Juan Manuel Polifei, M.D.	Juan Fernandez Hospital	Buenos Aires, Argentina
Guillermo Valadez Javera, M.D.	Clinica San Jose	Cd Obregón, Mexico
Jacobo Villalobos, M.D.	Universidad Central de Venezuela. Escuela de Medicina Luis Razetti. Cátedra de Fisiología	Caracas, Venezuela

## International Board of Advisors

Advisor	Affiliation	Location
William Wilcox, M.D., Ph.D. (North American Representative)	Cedars Sinai Medical Center	Los Angeles, CA, USA
Prof. Dr. C. Wanner (European Representative)	Universitätsklinik Würzburg	Würzburg, Germany
Prof. Ana Maria Martins, M.D., Ph.D. (Latin American Representative)	Inatos do Metabolismo - CREIM	São Paulo, Brazil

## APPENDIX 2 - MINIMUM RECOMMENDED SCHEDULE OF ASSESSMENTS

### Minimum Recommended Schedule of Assessments for Monitoring Patients with Fabry Disease

	All Patients	Patients not on Enzyme Therapy		Patients on Enzyme Therapy		
	Upon Enrollment	Every 12 months	At time of an event	Baseline and every 6 months	Baseline and every 12 - 24 months	At time of an event or therapy change
<b>General</b>						
Demographics	●					
Enzyme Activity	●					
Genotype	●					
Diagnosis	●					
Medical History	●	●		●		
Physical Examination	●					
<b>Fabry Disease Clinical Assessment <sup>a</sup></b>						
Cerebrovascular - TIA, Stroke	●	●	●	●		●
Neurology - Sweating, Heat/Cold Intolerance, Pain	●	●		●		
Gastroenterology	●	●		●		
Cardiology - ECHO <sup>b</sup> , ECG <sup>b</sup>	● <sup>a</sup>	● <sup>a</sup>	●	●	● <sup>a</sup>	●
Renal - Dialysis, Transplant	●	●	●	●		●
Skin	●	●		●		
Respiratory - Spirometry	●	●	●	●		●
Ophthalmology	●	●	●		●	●
<b>Vital Signs and Laboratory Tests</b>						
Height/Weight	●	●	●	●		●
Blood Pressure	●	●	●	●		●
Serum Creatinine and BUN	●	●	●	●		●
Urinary Protein Excretion <sup>c</sup>	●	●	●	●		●
GFR <sup>d</sup>	●	●	●	●		●
<b>Specialized Tests</b>						
Plasma GL-3	Plasma samples for GL-3 testing should be drawn prior to the first infusion, then every 3 months for the first 18 months of treatment, then every 6 months thereafter.					
Antibody Testing	Serum samples for IgG testing should be drawn prior to the first infusion, then every 3 months for the first 18 months of treatment, then every 6 months until a negative result is confirmed, and annually thereafter.					
Immune Complex Testing	If signs and symptoms of immune complex are evident, appropriate laboratory assessments for circulating immune complexes, such as Raji and C1q binding methods, will be undertaken in consultation with the Genzyme Safety Officer.					
<b>Pain/Quality of Life (QOL) <sup>e</sup></b>						
SF-36 <sup>®</sup> Health Survey	●	●		●		●
Brief Pain Inventory (Short Form)	●	●		●		●
PedsQL <sup>™</sup> Measurement Model	●	●		●		●
Enzyme Replacement Therapy Status	●			●		●
Adverse Event Reporting	Ongoing/continuous monitoring with reporting through Genzyme Pharmacovigilance Department. Refer to Safety section of Protocol and Manual for specific reporting guidelines and instructions.					

<sup>a</sup> Relates to a series of questions of Fabry specific symptoms that are delineated in the CRFs attached. The Clinical Assessments represent the core Fabry-related disease manifestations that are assessed to stage disease progression over the life-long course of the disease. Physicians will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care and routine follow-up.

<sup>b</sup> ECHO and ECG are recommended for patients  $\geq 35$  years of age every other year.

<sup>c</sup> 24 hour or first morning void urine for urine protein, creatinine and microalbumin

<sup>d</sup> GFR can be estimated using equations such as the MDRD equation for adults and Schwartz formula for children

<sup>e</sup> Ideally, pain, Quality of Life and Health-Related assessments should be measured at Baseline and every 6 months.

## APPENDIX 3 - 2008 KEY PRESENTATIONS OF FABRY REGISTRY DATA

## Abstracts Presented at Scientific Conferences

Giannini EH

**Progress in Development and Testing of Reliability and Validity of a Disease Severity Scoring System (DS3) for Anderson-Fabry Disease**

Presented at the 2008 meeting of the American College of Medical Genetics

**Introduction:** A DS3 is a method of quantifying burden of disease in a given patient and allows for the comparison with other patients with the same disease. A DS3 for Anderson-Fabry Disease (AFD-DS3) is needed to monitor disease progression and treatment response in individuals, and to compare disease status among patient cohorts in clinical studies, both at baseline and follow-up.

**Objective:** To develop and test the reliability and validity of a DS3 which can be completed quickly during routine clinic visits, is easy to interpret and does not require placing the patient at increased risk for its assessment.

**Methods:** We used a combination of consensus formation (N = 88 AFD experts) and statistical techniques to develop the provisional AFD-DS3. Feasible and reliable methods of assessment and weighting of each item has been completed in accord with standard methodological approaches. Several aspects of validity have been completed.

**Results:** The provisional AFD-DS3 incorporates 4 *clinical* and 2 *Observer-reported* domains. Clinical domains are renal, cardiac, peripheral- and central nervous system, each containing 3 items. The 2 observer-reported domains contain 1 item each; patient assessment of overall-well being, and physician's global assessment, each scored on Likert-like scales. Face (clinical sensibility), content, and feasibility were established by 80% consensus by experts. Quantitative content validity (a measure of how comprehensive the instrument is rated by experts in measuring the most crucial components of disease severity) yielded a content validity index of 100%. Inter-physician reliability when scoring disease severity yielded kappa values of > 0.8. Regression analysis showed that the renal and cardiac domains should have more weight than the PNS and CNS domains. The most sensitive method of overall instrument scoring is to sum the weights in all domains, rather than using an average or maximum domain score. Minimal clinically important difference (MCID) estimates for each domain are shown in the table. (MCID is the amount of absolute change in a domain score which patients and physicians perceive as beneficial or detrimental and which typically mandate a change in therapeutic management or a change in prognosis).

**Table: Domains, domain score ranges, minimal clinically important difference**

Domain	Domain Score Range	Minimal clinically important improvement	Minimal clinically important worsening
Cardiac	0 – 30	-2	+2
CNS	0 – 26	-2	+2
PNS	0 – 15	to be determined	to be determined
Renal	0 – 30	-2	+2
Patient reported	0 – 10	to be determined	+2
Physician reported	0 – 10	-2	+2

**Conclusions:** At this point the provisional AFD-DS3 appears to provide reliable and valid assessment and monitoring of disease status. This instrument is likely to find use as a therapeutic endpoint in clinical studies assessing change in domain-specific, or the overall DS3 score. Further testing of reliability and validity will continue during the coming year and prior to implementation in to clinical studies

Hopkin RH, Wilcox, WR, Eng CM, Bissler J.

### Characterization of Fabry Disease in 283 Pediatric Patients in the Fabry Registry

Presented at the 2008 World Organization of Research on Lysosomal Diseases (WORLD) meeting

The Fabry Registry made a directed effort to enroll pediatric patients, regardless of their symptomatology. Only data collected prior to the initiation of enzyme replacement therapy (ERT) are reported. A total of 283 patients age <18 at enrollment were identified. Median age at enrollment was 12 years for both males and females. The median age at symptom onset was 6 years in males and 9 years in females. Neurologic pain was often the first symptom (reported by 48.8% of children at enrollment) with a median age at onset at 8 years. Gastrointestinal symptoms were reported by 17.3% of children with a median age at onset of 6 years. Males age 14-18 years reported substantially impaired quality of life (QOL), as measured with the SF-36® health survey and females reported moderately impaired QOL. Among males, height and weight were below the US 50th percentile (median 25th centile  $p=0.005$  and  $p=0.003$ , respectively) for males. Height and weight were > 50th centile for females (median 75th centile  $p=0.014$  and  $p=0.0001$ , respectively). Among both males and females, estimated GFR was substantially higher than the mean eGFR in healthy children. The elevated eGFR levels did not correlate with patients' height, weight, or BMI. In summary, children clearly experience substantial symptoms of Fabry disease, including pain, gastrointestinal symptoms, and impaired QOL. In addition, there are early effects of Fabry disease on eGFR in both sexes and growth appears to be impaired in males.

Eng, CM, on behalf of the Fabry Registry Investigators.

### Characterization of symptom onset and clinical events in patients with Fabry disease: findings from the Fabry Registry

Presented at the 2008 World Organization of Research on Lysosomal Diseases (WORLD) meeting

The Fabry Registry is a voluntary observational database that tracks the natural history and outcomes of patients with Fabry disease. We analyzed natural history data from patients in the Fabry Registry to evaluate the age at symptom onset and diagnosis, and the incidence of clinical events between genders (i.e., prior to treatment with enzyme replacement therapy [ERT]). Among 949 adult female Fabry Registry patients, the median age of symptom onset was 14 years, as compared to 10 years in 1,035 adult males. However, diagnosis occurred much later, at a median age of 27 years in adult males and 38 years in adult females. Many fewer female Fabry patients experienced major clinical events, i.e., renal, cardiac, or cerebrovascular events. However, among patients who did experience such events, the ages at which clinical events occurred were similar in males and females, although males tended to experience their first cardiac event at an earlier median age than females (42 years in males versus 48 years in females). Overall, among all patients in the Fabry Registry (i.e., both adult and pediatric patients), 80% of males have ever received ERT, whereas only 33% of females have ever received ERT. In summary, both males and females with Fabry disease experience substantial symptoms, with males typically experiencing symptom onset earlier than females. All Fabry patients should be regularly monitored for signs and symptoms and should be considered for ERT.

Eng, CM on behalf of the Fabry Registry Renal Working Group: Ortiz A, Olivera JP, Waldek S, Warnock DG, Cianciaruso B, Wanner C.

### **Nephropathy In Fabry Disease: Baseline Characteristics Of 1,262 Patients In The Fabry Registry**

Presented at the 2008 World Organization of Research on Lysosomal Diseases (WORLD) meeting

**Background:** The spectrum of kidney involvement in Fabry disease has not yet been well defined, especially in female patients who may also be considerably burdened with disease manifestations.

**Methods:** We performed a cross-sectional retrospective analysis of natural history data from the Fabry Registry (estimated glomerular filtration rate (eGFR), proteinuria, albuminuria, blood pressure) from 677 female and 585 male patients.

**Results:** Chronic kidney disease (CKD) with eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$  was reported in 13% of females (age 20-82 years) and 28% of males (20-79 years). Proteinuria  $>300\text{mg}/24\text{hr}$  was seen both in females (26%) and in males (43%) with CKD stage 1, and median values were higher with more severe kidney dysfunction. 28% of females and 11% of males with eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$  had proteinuria  $<300\text{mg}/24\text{hr}$ . Among patients with eGFR  $\geq 60\text{ml}/\text{min}/1.73\text{m}^2$  without overt proteinuria (n=93), albuminuria  $>30\text{mg}/24\text{hr}$  was found in 35% of the females and 55% of the males. Systemic blood pressure was  $\geq 130/80\text{mmHg}$  in 48% and 67% of patients with eGFR  $\geq$  and  $<60\text{ml}/\text{min}/1.73\text{m}^2$ , respectively. Proteinuria values were significantly correlated with systolic blood pressure in both sexes.

**Conclusions:** Kidney injury in Fabry disease is more prevalent and heterogeneous than previously reported. Albuminuria and proteinuria are common early elements in both sexes and may reach nephrotic range. Blood pressure is often above recommended values for patients with CKD suggesting inadequate blood pressure control. Our analysis confirms that a significant proportion of females with Fabry disease suffer moderate to severe kidney involvement.

## APPENDIX 4 – ALL FABRY REGISTRY PUBLICATIONS TO DATE

### Peer-Reviewed Publications:

- Sims K, Politei J, Banikazemi M, Lee P. Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events: Natural History Data from the Fabry Registry. *Stroke*. 2009; 40:788-794.
- Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, Sims K, Waldek S, Pastores GM, Lee P, Eng CM, Marodi L, Stanford KE, Breunig F, Wanner C, Warnock DG, Lemay RM, Germain DP. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. *Mol Genet Metab*. 2008; 93:112-128.
- Ortiz A, Oliveira JP, Waldek S, Warnock DG, Cianciaruso B, Wanner C; on behalf of the Fabry Registry. Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. *Nephrol Dial Transpl*. 2008; 23:1600-1607.
- Hopkin RJ, Bissler J, Banikazemi M, Clarke L, Eng CM, Germain DP, Lemay R, Tylki-Szymanska A, Wilcox WR. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatr Res*. 2008; 64:550-555.
- Eng CM, Fletcher J, Wilcox WR, Waldek S, Scott CR, Sillence DO, Breunig F, Charrow J, Germain DP, Nicholls K, Banikazemi M. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J Inherit Metab Dis*. 2007; 30:184-192.
- Eng CM, Germain DP, Banikazemi M, Warnock DG, Wanner C, Hopkin RJ, Bultas J, Lee P, Sims K, Brodie SE, Pastores GM, Strotmann JM, Wilcox WR. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet Med*. 2006; 8:539-548.

### Abstracts Presented at Scientific Conferences:

- Hopkin R, Wilcox W, Eng C, Bissler J. Characterization of Fabry disease in 283 pediatric patients in the Fabry Registry [abstract]. *Mol Genet Metab* 2008;93:S24.
- Giannini E. Progress in development and testing of reliability and validity of a disease severity scoring system for Anderson-Fabry disease [abstract]. Presented at the 15th Annual Clinical Genetics Meeting of the American College of Medical Genetics; Mar 12-16, 2008; Phoenix, AZ. p. 198.
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- Eng C. Characterization of symptom onset and clinical events in patients with Fabry disease: findings from the Fabry registry [abstract]. *Mol Genet Metab* 2008;93:S21.
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# APPENDIX 5 - AGALSIDASE BETA US PACKAGE INSERT

**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
 These highlights do not include all of the information needed to use Fabrazyme safely and effectively. See full prescribing information for Fabrazyme.  
 Fabrazyme (agalsidase beta)  
 Injection, Powder, for Solution for Intravenous Use  
 United States Approval: 2009

**RECENT MAJOR CHANGES**  
 Warnings and Precautions, Anaphylaxis and Allergic Reactions (5.1), 12/2008  
**INDICATIONS AND USAGE**  
 Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces glycosaminoglycan (GAG) deposition in capillary endothelium of the kidney and certain other cell types (1).  
**DOSE AND ADMINISTRATION**  
 1 mg/kg body weight given every two weeks as an IV infusion. Patients should receive antiepileptics prior to infusion (2).



For intravenous infusion

5031 (01/09)



**CONTRAINDICATIONS**  
 None (4).  
**WARNINGS AND PRECAUTIONS**  
 Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediate discontinuation of Fabrazyme and prompt emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion reactions (5.1).  
 Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions, and these patients should be monitored more closely (5.2).  
**DRUG INTERACTIONS**  
 No drug interaction studies were performed (7).  
**USE IN SPECIFIC POPULATIONS**  
 Pregnancy: Registry available (8.3).  
 Nursing Mothers: Registry available (8.3).  
**See 17 for PATIENT COUNSELING INFORMATION**

**ADVERSE REACTIONS**  
 The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring (≥5% incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, pruritus, rash, facial edema, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, paresthesia, arthralgia, hypotension, chest pain, and somnolence (6).  
**TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT GENENTEC AT 1-800-745-4447 OR FDA AT 1-800-FDA-1088 OR WWW.FDA.GOV/medwatch**

**DRUG INTERACTIONS**  
 No drug interaction studies were performed (7).  
**USE IN SPECIFIC POPULATIONS**  
 Pregnancy: Registry available (8.3).  
 Nursing Mothers: Registry available (8.3).  
**See 17 for PATIENT COUNSELING INFORMATION**

**ADVERSE REACTIONS**  
 The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring (≥5% incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, pruritus, rash, facial edema, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, paresthesia, arthralgia, hypotension, chest pain, and somnolence (6).  
**TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT GENENTEC AT 1-800-745-4447 OR FDA AT 1-800-FDA-1088 OR WWW.FDA.GOV/medwatch**

**DRUG INTERACTIONS**  
 No drug interaction studies were performed (7).  
**USE IN SPECIFIC POPULATIONS**  
 Pregnancy: Registry available (8.3).  
 Nursing Mothers: Registry available (8.3).  
**See 17 for PATIENT COUNSELING INFORMATION**

**ADVERSE REACTIONS**  
 The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring (≥5% incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, pruritus, rash, facial edema, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, paresthesia, arthralgia, hypotension, chest pain, and somnolence (6).  
**TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT GENENTEC AT 1-800-745-4447 OR FDA AT 1-800-FDA-1088 OR WWW.FDA.GOV/medwatch**

**DRUG INTERACTIONS**  
 No drug interaction studies were performed (7).  
**USE IN SPECIFIC POPULATIONS**  
 Pregnancy: Registry available (8.3).  
 Nursing Mothers: Registry available (8.3).  
**See 17 for PATIENT COUNSELING INFORMATION**

**ADVERSE REACTIONS**  
 The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring (≥5% incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, pruritus, rash, facial edema, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, paresthesia, arthralgia, hypotension, chest pain, and somnolence (6).  
**TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT GENENTEC AT 1-800-745-4447 OR FDA AT 1-800-FDA-1088 OR WWW.FDA.GOV/medwatch**

**DRUG INTERACTIONS**  
 No drug interaction studies were performed (7).  
**USE IN SPECIFIC POPULATIONS**  
 Pregnancy: Registry available (8.3).  
 Nursing Mothers: Registry available (8.3).  
**See 17 for PATIENT COUNSELING INFORMATION**

**ADVERSE REACTIONS**  
 The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring (≥5% incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, pruritus, rash, facial edema, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, paresthesia, arthralgia, hypotension, chest pain, and somnolence (6).  
**TO REPORT SUSPECTED ADVERSE REACTIONS, CONTACT GENENTEC AT 1-800-745-4447 OR FDA AT 1-800-FDA-1088 OR WWW.FDA.GOV/medwatch**

**DRUG INTERACTIONS**  
 No drug interaction studies were performed (7).  
**USE IN SPECIFIC POPULATIONS**  
 Pregnancy: Registry available (8.3).  
 Nursing Mothers: Registry available (8.3).  
**See 17 for PATIENT COUNSELING INFORMATION**

**FULL PRESCRIBING INFORMATION**  
**INDICATIONS AND USAGE**  
 Fabrazyme (agalsidase beta) is indicated for use in patients with Fabry disease. Fabrazyme reduces glycosaminoglycan (GAG) deposition in capillary endothelium of the kidney and certain other cell types.  
**DOSE AND ADMINISTRATION**  
**Recommended Dose**  
 The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every 2 weeks as an intravenous (IV) infusion. Patients should receive antiepileptics prior to infusion (see Warnings and Precautions (5.2)).  
 The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of a severe allergic reaction. Increments of 0.25 mg/min (15 mg/hr) may be used for subsequent infusions. For patients weighing <30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing >30 kg, the administration duration should not be less than 1.5 hours based on individual patient tolerability.  
 Patients who have had a positive skin test to Fabrazyme or who have tested positive for Fabrazyme-specific IgE may be administered Fabrazyme at a reduced infusion rate. The infusion rate should be increased to 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/min (15 mg/hr)) if tolerated (5.1).  
**Warnings and Precautions**  
 Fabrazyme does not contain any preservatives. Vials are for single use only. Discard any unused portion.  
 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).  
 2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).  
 3. Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 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).  
 4. 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.  
 5. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to 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 for Injection, USP from the infusion bag.  
**Table 1**

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

Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the total number of mg in the total volume of the infusion. For example, a 35 mg vial and a 5 mg vial will yield 40 mg of Fabrazyme in 100 mL of solution. The total extractable amount per vial is 35 mg, 7 mL.  
 Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 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).  
 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.  
 The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to 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 for Injection, USP from the infusion bag.  
**Table 1**

**CONTRAINDICATIONS**  
 None.  
**WARNINGS AND PRECAUTIONS**  
**5.1 Anaphylaxis and Allergic Reactions**  
 Life-threatening anaphylactic and severe allergic reactions have been observed in patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediate discontinuation of Fabrazyme and prompt emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion reactions (5.1).  
 Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions, and these patients should be monitored more closely (5.2).  
**DRUG FORMS AND STRENGTHS**  
 Fabrazyme is available as 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the total volume of the infusion. For example, a 35 mg vial and a 5 mg vial will yield 40 mg of Fabrazyme in 100 mL of solution. The total extractable amount per vial is 35 mg, 7 mL.  
 Single-use vials are available in 35 mg and 5 mg doses.

**CONTRAINDICATIONS**  
 None.  
**WARNINGS AND PRECAUTIONS**  
**5.1 Anaphylaxis and Allergic Reactions**  
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**WARNINGS AND PRECAUTIONS**  
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 None.  
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**WARNINGS AND PRECAUTIONS**  
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 Single-use vials are available in 35 mg and 5 mg doses.

**CONTRAINDICATIONS**  
 None.  
**WARNINGS AND PRECAUTIONS**  
**5.1 Anaphylaxis and Allergic Reactions**  
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 Single-use vials are available in 35 mg and 5 mg doses.

**5.4 Immunogenicity and Re-challenge**  
 In clinical trials with Fabrazyme, a few patients developed IgE antibodies or skin test reactivity specific to Fabrazyme. Two of six patients in the re-challenge study discontinued treatment with Fabrazyme prematurely due to recurrent infusion reactions. Four serious infusion reactions occurred during Fabrazyme infusions, including anaphylaxis, severe allergic reactions, and severe allergic reactions. One patient experienced severe allergic reactions occurring in more than one patient during the study including rigors, hypertension, nausea, vomiting, and pruritus. Physicians should consider testing for IgE antibodies in patients who experienced severe allergic reactions and consider the risks to the patient of continuing treatment with Fabrazyme. Patients with anti-Fabrazyme IgE antibodies who have had a positive skin test to Fabrazyme or who have tested positive for Fabrazyme-specific IgE antibody have been re-challenged with Fabrazyme using a re-challenge protocol (see Clinical Studies (14)). Re-challenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.  
**5.5 Immunogenicity and Re-challenge**  
 There are no known interactions between Fabrazyme and antibodies against Fabrazyme. If testing is warranted, contact your local Genentec representative at Genentec Corporation at (800) 745-4447.

**6 ADVERSE REACTIONS**  
 The most serious adverse reactions reported with Fabrazyme treatment during clinical trials were anaphylactic and allergic reactions (see Warnings and Precautions (5.1)). Fabrazyme infusions reactions, some of which were severe (see Warnings and Precautions (5.1) and (5.2)). Serious and/or frequently occurring (≥5% incidence) related adverse reactions consisted of one or more of the following: chills, pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, pruritus, rash, facial edema, nasal congestion, diarrhea, edema peripheral, arthralgia, hypotension, chest pain, back pain, paresthesia, myalgia, back pain, paresthesia, arthralgia, hypotension, chest pain, and somnolence. The occurrence of somnolence can be attributed to clinical trial specific pretreatment with antihistamines. Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of other medical therapies, such as steroids, inhaled beta<sub>2</sub> agonists, antihistamines, cardiac arrhythmia, cardiac arrest, decreased cardiac output, vertigo, hypotension, and nephrotic syndrome. These adverse events also occur as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.  
 The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1 mg/kg Fabrazyme every two weeks for 15.5 months. All 59 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 antiepileptics and antihistamines prior to the infusions.  
 Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials are not necessarily predictive of rates in the clinical use of another drug and may not reflect the rates observed in patients in clinical practice.  
**Table 2** enumerates treatment-emergent adverse reactions (regardless of relationship) that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2) (see Clinical Studies (14)). Reported adverse reactions have been classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology System Organ Class and Preferred Term.

**Table 2**  
**Summary of Adverse Reactions (regardless of relationship) Occurring in Fabrazyme Treated Patients at an Incidence Greater than 2.5% Compared to Placebo Treated Patients**

MedDRA System Organ Class/Preferred Term	Fabrazyme n=60 (%)	Placebo n=60 (%)
<b>Cardiac Disorders</b>		
Tachycardia	2 (8)	2 (3)
Ventricular wall thickening	4 (5)	1 (2)
<b>Ear and Labyrinth Disorders</b>		
Tinnitus	6 (8)	2 (3)
Hypacusis	4 (5)	0
<b>Gastrointestinal Disorders</b>		
Toothache	5 (6)	2 (3)
Dry mouth	3 (4)	0
<b>General Disorders and Administration Site Conditions</b>		
Chills	34 (43)	7 (12)
Pyrexia	31 (39)	13 (22)
Fatigue	19 (24)	10 (17)
Edema peripheral	17 (21)	4 (7)
Pain	15 (16)	8 (13)
Feeling cold	9 (11)	1 (2)
Adverse event	8 (10)	3 (5)
Chest discomfort	4 (5)	1 (2)
<b>Infections and Infestations</b>		
Upper respiratory tract infection	35 (44)	18 (30)
Lower respiratory tract infection	14 (18)	4 (7)
Sinusitis	7 (9)	2 (3)
Pharyngitis	5 (6)	1 (2)
Fungal infection	4 (5)	0
Viral infection	4 (5)	0
Localizer infection	3 (4)	0
<b>Injury, Poisoning and Procedural Complications</b>		
Procedural pain	20 (25)	12 (20)
Post procedural complication	8 (10)	1 (2)
Exorcitation	7 (9)	1 (2)
Fall	5 (6)	2 (3)
Contusion	3 (4)	0
Thermal burn	3 (4)	0
<b>Investigations</b>		
Blood creatine increased	7 (8)	3 (5)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Pain in extremity	15 (19)	5 (8)
Back pain	12 (16)	6 (10)
Myalgia	11 (14)	3 (5)
Muscle spasms	4 (5)	1 (2)

