

Fabry Registry

Annual Report 2010

(This report covers data collected through 31 December 2009)





Table of Contents

I. FOREWORD	2
II. INTRODUCTION	3
III. SELECTED CURRENT DATA	4
WOMEN HAVE A SUBSTANTIAL BURDEN OF DISEASE	4
FEMALES RECEIVE ERT LESS FREQUENTLY THAN MALES	5
CHILDREN CAN EXPERIENCE LIFE-THREATENING COMPLICATIONS OF FABRY DISEASE	6
DEVELOPMENT OF MINIMUM RECOMMENDED SCHEDULE OF ASSESSMENTS FOR CHILDREN WITH FABRY DISEASE	7
IV. SUMMARY	8
ADVERSE EVENT REPORTING	8
APPENDIX 1	
2009 BOARDS OF ADVISORS AND REGISTRY COORDINATORS	9
APPENDIX 2	
NEW MINIMUM RECOMMENDED SCHEDULES OF ASSESSMENTS DEVELOPED IN 2009	11
APPENDIX 3	
ORIGINAL MINIMUM RECOMMENDED SCHEDULE OF ASSESSMENTS	13
APPENDIX 4	
FABRY REGISTRY PEER-REVIEWED PUBLICATIONS	14



2010 Annual Report

I. FOREWORD

On behalf of the Boards of Advisors for the Fabry Registry, we are pleased to present the Fabry Registry 2010 Annual Report summarizing the activities and accomplishments of the Fabry Registry during the past year.

The Fabry Registry has now enrolled more than 3,400 patients, including a growing number who have longitudinal clinical data available from both before and after the initiation of enzyme replacement therapy (ERT). This increasing body of data can be used to evaluate longitudinal disease progression and ERT outcomes in patients with Fabry disease. Over the past year, investigators were asked to update the Fabry Registry database with echocardiographic and electrocardiographic data from patients enrolled at their sites. We are pleased to report that this cardiac data collection effort was very successful; untreated and treated patient cohort sizes have grown considerably. For example, the number of treated patients with left ventricular mass data has increased 8-fold. This is an important step towards analyzing longitudinal cardiac disease progression and ERT outcomes—we are grateful to all who contributed to this major project.

Another important milestone achieved in 2009 was development of the new Pediatric Minimum Recommended Schedule of Assessments (Appendix 2). Increasing evidence indicates that young Fabry patients are at risk for life-threatening complications (Section III). The Fabry Registry Boards of Advisors accepted the Pediatric Workgroup's recommendations for guidelines designed to more closely monitor children with Fabry disease. Thus, there are now separate age-specific recommendations for assessing adults and children (Appendix 2).

We hope that you find this edition of the Fabry Registry Annual Report to be informative. 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.

David G. Warnock, MD
Fabry Registry North American Board of Advisors

Prof. Dr. Christoph Wanner
Fabry Registry European Board of Advisors

Juan Manuel Politei, MD
Fabry Registry International Board of Advisors

II. INTRODUCTION

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.

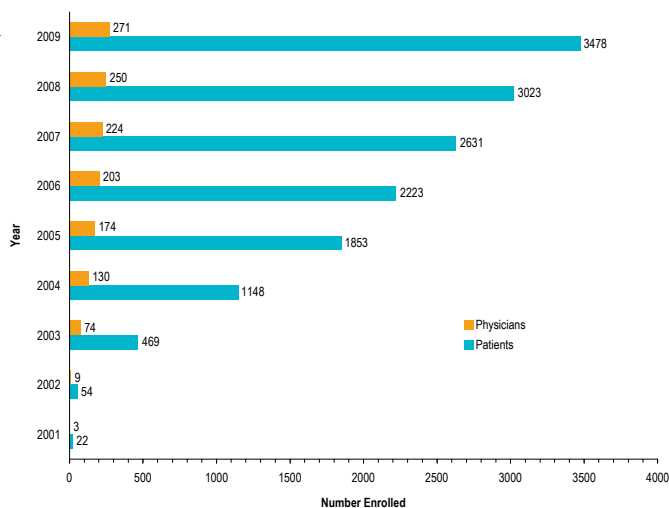
Regional Advisory Boards provide scientific oversight and direction to the Fabry Registry. Board members are physicians with expertise in Fabry disease who serve as liaisons between the Fabry Registry and the Fabry medical community within their respective geographic regions (**Appendix 1**).

The infrastructure of the Fabry Registry is sponsored by Genzyme, 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 & Regulatory Affairs 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 31 December 2009, a total of 271 physicians worldwide have enrolled 3,478 patients in the Fabry Registry, as shown in **Figure 1**.

The Fabry Registry population includes nearly equal numbers of males (1,730) and females (1,748) and most are from Europe and North America, as shown in **Table 1**. As of 31 December 2009, the median age of Fabry Registry participants was 40 years for males and 44 years for females. At that time, 13% of males and 9% of females enrolled were children (less than 18 years old). Males were diagnosed at a median age of 25 years, versus 33 years for females.

Figure 1
Cumulative Enrollment of Patients and Physicians in the Fabry Registry



The numbers of enrolled patients and participating physicians are shown by year, through 31 December 2009. Note that participating physicians are designated as those with 1 or more patients enrolled in the Fabry Registry.

Table 1
Summary of Patient Demographics

	Males	Females
Total Number of Patients Enrolled, N	1730	1748
Regional Enrollment, n (%)		
Europe	723 (41.8)	796 (45.5)
North America	670 (38.7)	714 (40.8)
Latin America	151 (8.7)	137 (7.8)
Japan-Asia Pacific	183 (10.6)	100 (5.7)
Current Age, All Patients (years)		
Mean (SD)	38 (16.6)	43 (17.8)
Median	40	44
Minimum, Maximum	<1, 85	<1, 89
Current Age Distribution, n (%)		
Age ≥18 years	1505 (87.0)	1583 (90.6)
Age <18 years	224 (12.9)	164 (9.4)
Age at Fabry Diagnosis (years)		
n	1707	1684
Mean (SD)	27 (16.8)	34 (18.0)
Median	25	33
Minimum, Maximum	0, 81	0, 82

Data reflect those available as of 31 December 2009. SD, standard deviation.

III. SELECTED CURRENT DATA

Women Have a Substantial Burden of Disease

Serious complications of Fabry disease do not occur exclusively in males. Of the 1,748 females enrolled in the Fabry Registry, 308 (18%) have reported experiencing at least one serious renal, cardiovascular, or stroke event. The average ages at which females initially experienced these events are shown in **Table 2**.

Seventy-one of 1,748 women in the Fabry Registry (4%) reported having a stroke, at an average age of 48 years (**Table 2**). This is much younger than the mean age at first stroke among women in the general US population, which is 81 years (Carandang et al. *JAMA* 2006; 296:2939-2946). The incidence rates of first strokes in all 1,748 females in the Fabry Registry and in the general US population are shown in **Figure 2**. Within each age category, women with Fabry disease exhibited a markedly higher incidence of stroke than women in the general US population.

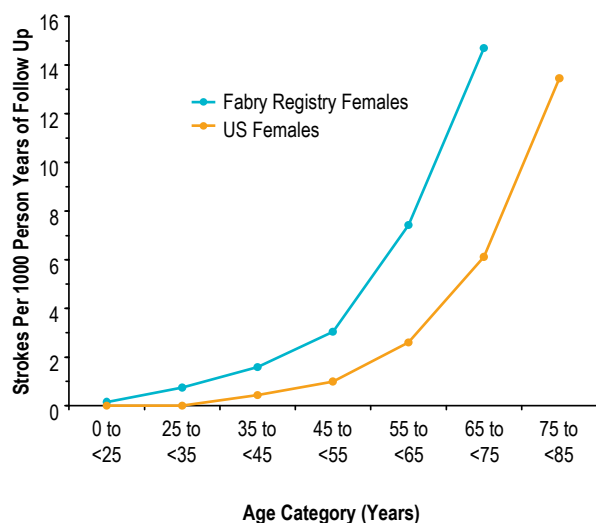
Women with Fabry disease also have a shorter life expectancy than women in the general US population. **Figure 3** shows life expectancy calculated at 5-year increments for women in the Fabry Registry and for women in the US general population. At birth, the life expectancy of Fabry Registry females was 75 years, compared to 80 years in the general population (Waldek, 2009). Across all age categories, the average life expectancy was 6.4 years less in Fabry females compared to the general population.

Table 2
Females Experience Serious Clinical Events

	Renal	Cardiovascular	Stroke
Females with Clinical Events, n (%)	33 (1.9)	243 (13.9)	71 (4.1)
Age at first event, (years)			
Mean (SD)	42 (12.8)	48 (13.8)	48 (14.6)
Median	41	49	47
Minimum, maximum	17, 78	4, 79	19, 75

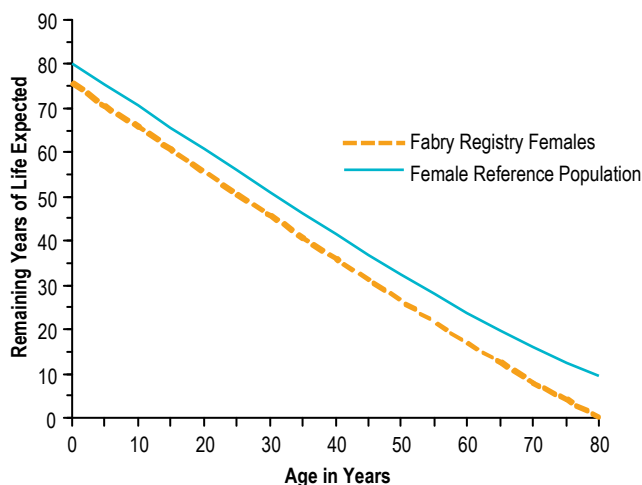
Data reflect those available as of 31 December 2009. Renal events were defined as chronic dialysis (≥40 days) or renal transplantation. Cardiovascular events were defined as myocardial infarction, significant cardiac procedures (e.g. pacemaker placement, coronary bypass, stent placement, valve replacement, etc.), arrhythmia, angina pectoris, or congestive heart failure. Patients may have experienced more than one type of clinical event.

Figure 2
Fabry Registry Females Have Elevated Incidence of Stroke



Fabry Registry data were obtained from untreated patients or from before any ERT was initiated, based on data available as of 31 December 2009. Stroke incidence rates in the general US population are from the Framingham Study and from the American Heart Association Statistics Committee and the Stroke Statistics Subcommittee (Wolfe et al. In: *Stroke: Pathophysiology, Diagnosis, and Management*, 3rd ed. New York, NY: Churchill Livingstone; 2004:3-13; Rosamond et al. *Circulation* 2007; 115:e69-e171).

Figure 3
Life Expectancy is Diminished in Women with Fabry Disease



The dashed line shows life expectancy of Fabry Registry females at birth, based on data available as of August 2, 2008. The solid line shows the life expectancy of females in the general US population (from Waldek, 2009).

Patients with Fabry disease frequently suffer from clinical depression and experience diminished health-related quality of life (HRQL). In untreated women with Fabry disease, HRQL has been reported to be similar to that of patients with rheumatoid arthritis or multiple sclerosis (Street et al. *Genet Med* 2006;8:346-353). The SF-36® Health Survey, which has been widely used to assess HRQL in various chronic diseases, was used to evaluate HRQL in women in the Fabry Registry. Because HRQL declines with age, comparisons are made between groups within the same age range. **Figure 4** shows SF-36 scores in Fabry Registry women ages 35 to <45 years and women in the general US population in the same age group. Compared to women in the general population, women in the Fabry Registry reported significantly lower SF-36 scores in the Physical Functioning, Role Physical, General Health, Vitality, and Social Functioning scales. Similar reductions in HRQL have been reported for Fabry women in other age categories (Wilcox, 2008).

Females Receive ERT Less Frequently Than Males

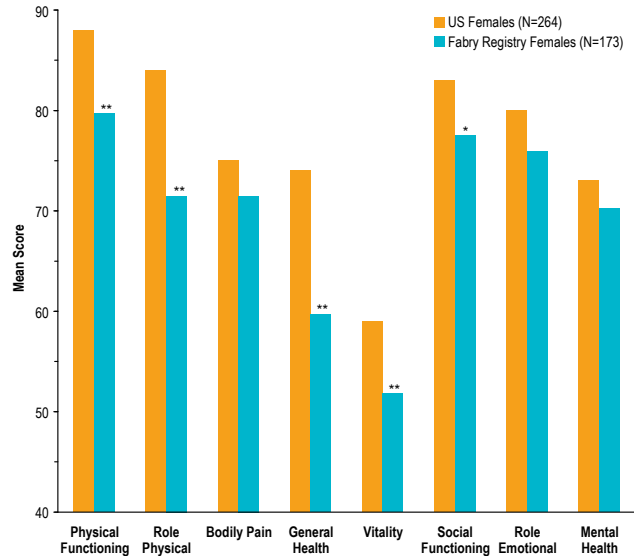
Women with Fabry disease continue to receive ERT less frequently than men. As shown in **Table 3**, only 40% of Fabry Registry adult females have ever received ERT, compared to 84% of adult males. Even women with serious cardiac or renal complications are less likely to receive ERT than men who have those complications. **Figure 5** shows that 56% of females with left ventricular hypertrophy (LVH) had received ERT at some time, compared to 88% of males with LVH. Similarly, 57% of females with chronic kidney disease (CKD) had been treated with ERT, compared to 88% of males with CKD.

Table 3
Treatment Status by Gender and Age

	Adults		Children	
	Males	Females	Males	Females
Total Number of Patients Enrolled, N	1505	1583	224	164
Treatment Status, n (%)				
Ever on ERT	1270 (84.4)	631 (39.9)	98 (43.8)	18 (11.0)
Never on ERT	215 (14.3)	935 (59.1)	126 (56.3)	144 (87.8)
Unknown Treatment Status	20 (1.3)	17 (1.1)	0	2 (1.2)

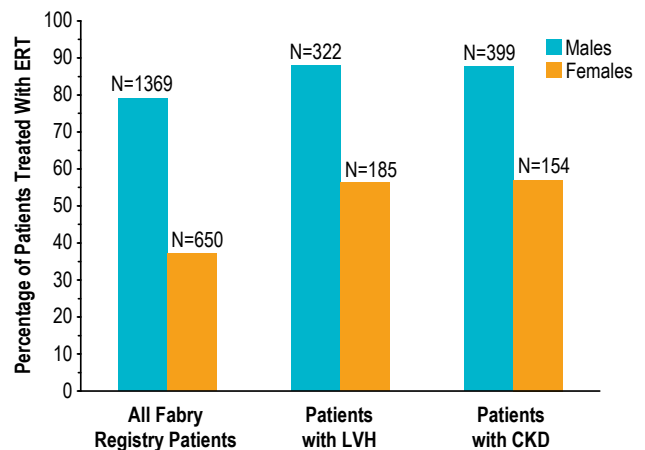
Data shown represent those available as of 31 December 2009. Patients were designated as children if they were <18 years old as of that date.

Figure 4
Fabry Registry Women Age 35 to <45 Have Diminished Health-Related Quality of Life



Data are expressed as average SF-36 scores in women age 35 to <45 years in the general US population (N=264, orange bars) and in the Fabry Registry (N=173, blue bars). All data were obtained from untreated patients or from before any enzyme replacement therapy was initiated. SF-36 scores are based on a 100-point scale, with a higher score indicating better HRQL. **p<0.005 by t-test; *p<0.05 by t-test. US norm data are from Ware et al, *SF-36 Health Survey Manual and Interpretation Guide*, New England Medical Center, The Health Institute, Boston, MA, 1993.

Figure 5
Females with Serious Renal or Cardiac Disease Receive ERT Less Often than Males



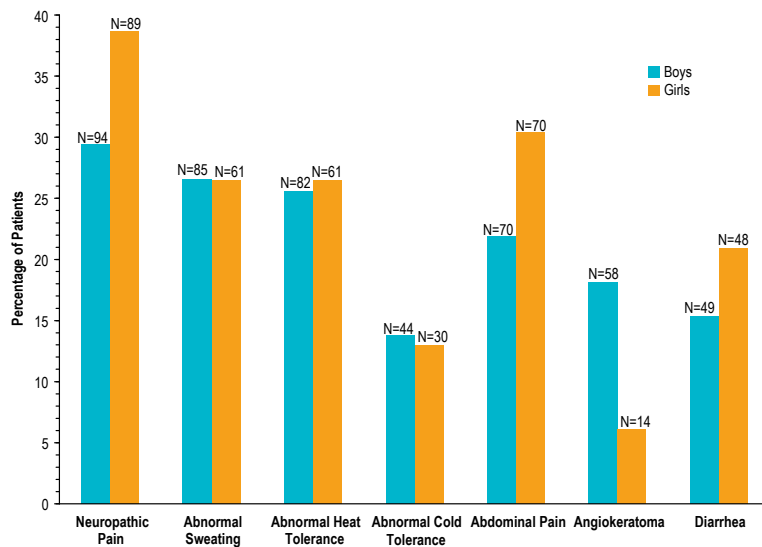
Data shown represent those available as of 31 December 2009. Percentages were calculated based on the number of patients for whom LVH (left ventricular hypertrophy) or chronic kidney disease (CKD) status were available. LVH was defined as left ventricular posterior wall thickness ≥12 mm. CKD was defined as a urinary protein:urinary creatinine ratio ≥0.3 or urinary protein levels ≥0.3g/day or estimated glomerular filtration rate <60 mL/min/1.73m² or renal transplant or chronic dialysis (≥40 days). The number of patients in each group is indicated above each bar.

Children Can Experience Life-Threatening Complications of Fabry Disease

A substantial number of Fabry Registry patients reported pain and other manifestations of Fabry disease during childhood (i.e., younger than 18 years old). As shown in **Figure 6**, 29% of boys and 39% of girls reported experiencing neuropathic pain. Abnormal sweating, abnormal heat tolerance, and abdominal pain were also reported by 20 to 30% of children. Abdominal pain and diarrhea were more frequently reported by girls, whereas angiokeratoma was more common among boys.

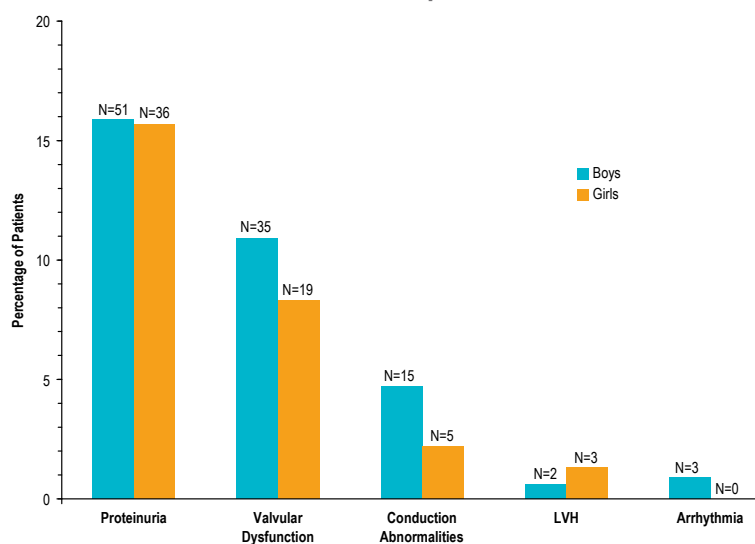
Renal and cardiovascular dysfunction are complications of Fabry disease typically considered to develop during adulthood. However, a considerable number of children in the Fabry Registry have experienced these complications, as shown in **Figure 7**. Approximately 15% of boys and girls exhibited significant proteinuria (i.e., urinary protein to urinary creatinine ratio ≥ 0.3 or urinary protein levels $\geq 0.3\text{g/day}$). A smaller proportion of children reported cardiac complications, including some with LVH or arrhythmias.

Figure 6
Children Exhibit Considerable Manifestations of Fabry Disease



Data shown represent those available as of 31 December 2009 for patients who were <18 years old at the time they enrolled in the Fabry Registry. Percentages were calculated based on the number of patients reporting signs or symptoms within key organ systems at the time of enrollment. The number of patients in each group is indicated above each bar.

Figure 7
Some Children with Fabry Disease Have Renal and Cardiac Complications



Data shown represent those available as of 31 December 2009, for patients who were <18 years old at the time they enrolled in the Fabry Registry. Percentages were calculated based on the number of pediatric patients for whom urinary protein or cardiac examination data were available. Proteinuria was defined as a urinary protein:urinary creatinine ratio ≥ 0.3 or urinary protein levels $\geq 0.3\text{g/day}$. The number of patients in each group is indicated above each bar.

Development of Minimum Recommended Schedule of Assessments for Children with Fabry Disease

Through 2009, the Fabry Registry had a single Minimum Recommended Schedule of Assessments that was used for patients of all ages (Appendix 3). Last year, in view of the growing body of evidence that many patients experience significant manifestations of Fabry disease during childhood, the Fabry Registry Pediatric Workgroup developed a set of guidelines for assessing Fabry disease in children. A summary of the general types of assessments recommended for children is shown in **Table 4** and the complete Pediatric Minimum Recommended Schedule of assessments is included in Appendix 2. These new guidelines recommend that children with a family history of early or severe disease receive complete evaluations at the time they are diagnosed and that all other children should be completely evaluated by the age of 5 years. The new Pediatric Minimum Recommended Schedule of Assessments, which will be implemented in 2010, will both increase the medical community’s awareness of the burden of Fabry disease in children and assist with monitoring these young patients.

Table 4
Summary of Recommended Pediatric Assessments

Medical-Family History	Patient Reported Outcomes	Other Studies
<ul style="list-style-type: none"> ▪ GI, pain, sweating ▪ Heat/cold intolerance 	<ul style="list-style-type: none"> ▪ Quality of life ▪ Fatigue, pain 	<ul style="list-style-type: none"> ▪ Audiologic evaluation ▪ Cranial MRI – T1, T2, FLAIR ▪ ECHO and ECG ▪ Ophthalmology – slit lamp exam
Diagnostic	Laboratory Tests	Specialized Laboratory Tests
<ul style="list-style-type: none"> ▪ Enzyme activity ▪ Genotype 	<ul style="list-style-type: none"> ▪ GFR ▪ Albuminuria/proteinuria 	<ul style="list-style-type: none"> ▪ Antibodies ▪ Plasma GL-3
Physical Exam	Treatment/Medications	
<ul style="list-style-type: none"> ▪ Vital signs, height, weight ▪ Blood pressure 	<ul style="list-style-type: none"> ▪ ERT status ▪ Concomitant medications 	

See Appendix 2 for complete Pediatric Minimum Recommended Schedule of Assessments.

IV. SUMMARY

- Now in its tenth year, the Fabry Registry continues to grow. As of 31 December 2009, the Fabry Registry had accrued clinical assessment and outcomes data from an international population of 3,478 patients.
- Serious complications of Fabry disease do not occur exclusively in males or in adults. The medical community should be aware that women and children carry a substantial burden of Fabry disease; they should be carefully and regularly monitored.
- The new Pediatric Minimum Recommended Schedule of Assessments (Appendix 2) provides specific guidance for physicians to evaluate children comprehensively. In addition, when the resulting data are reported to the Fabry Registry, more detailed analyses of pediatric Fabry disease can be undertaken.
- The cardiac data collection effort put forward in 2009 considerably increased the number of Fabry Registry patients who have longitudinal data. This will permit evaluation of cardiac disease progression and ERT outcomes in Fabry Registry patients.
- Three key manuscripts describing the natural history of Fabry disease were accepted for publication in 2009, as shown in Appendix 4. The first of these publications provides important new information about the life expectancy and cause of death of patients with Fabry disease (Waldek, 2009). The second characterizes Fabry patients who had progressed to end-stage renal disease (Ortiz, 2010). The third, published in Spanish, describes various natural history findings from the Fabry Registry and will increase awareness of Fabry disease in the Latin American region (Politei, 2009). To date, a total of 9 articles from the Fabry Registry have been published in peer-reviewed journals (Appendix 4).

Adverse Event Reporting

Life threatening anaphylactic and severe allergic reactions have been observed in patients during agalsidase beta infusions. The most serious adverse reactions reported with agalsidase beta are infusion-associated reactions, some of which can be severe or life-threatening. Adverse events, including all deaths, in patients treated with agalsidase beta should be reported promptly to Genzyme Global Patient Safety and Risk Management as shown below, even if the event does not appear to be related to this product. Refer to the Safety section of the Fabry Registry Protocol for specific reporting guidelines.

Genzyme Global Patient Safety and Risk Management

fax +1 617-761-8506

email pharmacovigilancesafety@genzyme.com

phone **United States & Non-European Countries:** +1(617)768-9000 option 2
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APPENDIX 1 2009 Boards of Advisors and Registry Coordinators

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Manesh Patel, M.D.	Duke University Medical Center	Durham, NC, USA
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European Board of Advisors

Advisor	Affiliation	Location
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Dr. A. Fouilhoux	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. P. Lee	National Hospital for Neurology and Neurosurgery	London, United Kingdom
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Dr. B. Vujkovic	General Hospital	Slovenj Gradec, Slovenia
Dr. S. Waldek	Hope Hospital	Manchester, United Kingdom

Japan Asia-Pacific Board of Advisors

Advisor	Advisor	Advisor
Prof. Nan Chen	Ruijin Hospital	Shanghai, China
Dr. Janice Fletcher	Women's and Children's Hospital	North Adelaide, Australia
Dr. Wuh-Liang Hwu	National Taiwan University Hospital	Taipei, Taiwan
Dr. Toya Ohashi	Tokyo Jikei University School of Medicine	Tokyo, Japan
Dr. Chih-Chao Yang	National Taiwan University Hospital	Taipei, Taiwan
Dr. Han-Wook Yoo	Asan Medical Center	Song Pa-ku, Korea

Latin American Fabry Registry Coordinators

Coordinator	Affiliation	Location
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Sandra Ospina, M.D.	Universidad del Rosario	Bogotá, Colombia
Juan Manuel Politei, M.D.	Juan Fernandez Hospital	Buenos Aires, Argentina
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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
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Prof. Dr. C. Wanner (European Representative)	Universitätsklinik Würzburg	Würzburg, Germany
Juan Manuel Politei, MD (Latin American Representative)	Hospital Juan Fernandez	Buenos Aires, Argentina

APPENDIX 2

New Minimum Recommended Schedules of Assessments Developed in 2009

Fabry Registry Minimum Recommended Schedule of Assessments for Patients Under 18 Years of Age*†

	Upon Enrollment	Every 6 – 12 months ^A	Every 24-36 months	At time of an event or therapy change
GENERAL				
Medical History, with particular focus on:				
Gastrointestinal Symptoms				
Pain	■	■		■
Sweating				
Heat & cold intolerance				
Family History	■		■	
Physical Exam	■	■		■
Vital Signs, Height and Weight	■	■		■
Blood Pressure ^B	■	■		■
Enzyme Activity and Genotype	■			
Enzyme Replacement Therapy Status	■	■		■
Concomitant Medication Assessment	■	■		■
Pediatric Quality of Life Assessment – PedsQL™ Pediatric Quality of Life Inventory	■	■		■
Pediatric Quality of Life Assessment – PedsQL™ Multidimensional Fatigue Scale	■	■		■
Pediatric Pain Assessment – PedsQL™ Pediatric Pain Questionnaire™	■	■		■
LABORATORY TESTS				
Glomerular Filtration Rate ^C	■		■	■
Albuminuria and Proteinuria ^D	■	■		■
OTHER STUDIES				
Audiologic Evaluation ^E	■		■	■
Cranial MRI – T1, T2 and FLAIR	■		■ ^F	■ ^{F1}
Electrocardiogram ^G	■		■	■
Echocardiogram ^H	■		■	■
Ophthalmology – Slit Lamp Exam ^I	■		■	
SPECIALIZED LABORATORY TESTS				
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 2 consecutive negative results are confirmed.			
ADVERSE EVENTS				
Adverse Event Reporting	Ongoing/continuous monitoring with reporting through Genzyme Global Patient Safety and Risk Management (GPS-RM). Refer to the Safety section of the protocol for specific reporting guidelines and instructions.			

* Physicians will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care. Abnormal findings may require more frequent assessment.

† Initiation of Laboratory Tests, Imaging, and Other Studies: There is variability in the clinical complications and progression of Fabry disease. Children are at risk for life threatening complications. There are no biomarkers available to discern mildly affected from severely affected patients. In children with a family history of early presenting or severe disease, complete evaluations should be done at the time of diagnosis. Other patients should be completely evaluated at no later than 5 years of age.

^A Patients receiving ERT are recommended to undergo these evaluations every 6 months; for those not on ERT or with milder disease, once per year may be sufficient

^B Blood pressure is an important determinant of disease severity in Fabry disease. Measurement should be carefully done by a standard procedure (NIH pub#05-5267). A common method is to have the patient sit quietly in a room for at least 5 minutes and then perform 3 measurements with an age specific BP cuff or instrument. The cuff must cover at least two-thirds of the upper arm from the elbow to the shoulder. Record only the last 2 measurements.

^C Glomerular Filtration Rate (GFR) should be measured or estimated every 24-36 months until age 15, and annually thereafter. More frequent monitoring may be appropriate if abnormalities are detected. GFR can be measured as described by Schwartz et al (Pediatr Nephrol 2007; 22:1839) or an equivalent procedure. A less reliable method is creatinine clearance performed on a 24hr collection and repeated on a separate day. 24 hour urinary creatinine standards can be used to determine adequacy of the collection. If measured GFR can not be performed, serum creatinine levels should be obtained at the recommended intervals for an estimation of GFR, a less sensitive method of detecting renal deterioration.

^D First morning voided urine for protein, albumin and creatinine in order to calculate a protein/creatinine ratio and albumin/creatinine ratio. Protein, albumin, and creatinine measurements can also be performed on timed samples (e.g. 24 hours).

^E Audiologic evaluation should be performed at the earliest age that is practical.

^F First MRI should be performed at 10 years then every 5 years until 15, every 3 years after age 15.

^{F1} At the time of an event, a cranial MRI should also include DWI/ADC.

^G Electrocardiogram should be performed starting at 10-15 years. If abnormal and/or clinical symptoms arise, Holter monitoring is recommended.

^H Echocardiogram should be performed starting at 10 - 15 years. Monitor yearly if retinal vessel tortuosity noted.

^I Monitor yearly if retinal vessel tortuosity noted.



Fabry Registry Minimum Recommended Schedule of Assessments for Patients 18 Years of Age and Over*

	Upon Enrollment	Every 6 months	Every 12 months	Every 24-36 months	At time of an event or therapy change
GENERAL					
Medical History	■	■			■
Family History	■			■	
Physical Exam	■	■			■
Vital Signs, Height and Weight	■	■			■
Enzyme Activity and Genotype	■				
Enzyme Replacement Therapy Status	■	■			■
Concomitant Medication Assessment	■	■			■
Quality of Life (SF-36®, BPI)	■	■			■
LABORATORY TESTS					
Serum Creatinine ^A and BUN	■	■			■
Urine Protein Excretion ^B	■	■			■
Lipid panel	■		■		
OTHER STUDIES					
Audiologic Evaluation	■			■	■
Cranial MRI – T1, T2 and FLAIR	■			■	■ ^C
Electrocardiogram ^D	■		■		■
Echocardiogram	■		■		■
24 Hour Holter Monitoring ^E	■		■		■
Respiratory – Spirometry Exam ^F	■			■	
Ophthalmology – Slit Lamp Exam ^G	■				
SPECIALIZED LABORATORY TESTS					
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 2 consecutive negative results are confirmed.				
ADVERSE EVENTS					
Adverse Event Reporting	Ongoing/continuous monitoring with reporting through Genzyme Global Patient Safety and Risk Management Department. Refer to the Safety section of the protocol for specific reporting guidelines and instructions.				

* Physicians will determine the actual frequency of necessary assessments according to a patient's individualized need for medical care. Abnormal findings may require more frequent assessment.

^A Directly measuring glomerular filtration rate (GFR) is recommended if a more precise evaluation is desired.

^B 24 hour or first morning void urine for protein, creatinine and albumin.

^C At the time of an event, a cranial MRI should also include DWI/ADC.

^D If electrocardiogram is abnormal and/or clinical symptoms arise, Holter monitoring is recommended.

^E Annual 24 hour holter monitoring is recommended for males 30 years of age or older and females 40 years of age or older.

^F If spirometry is abnormal, perform yearly.

^G Monitor yearly if retinal vessel tortuosity noted.

APPENDIX 3 Original 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
General						
Demographics	●					
Enzyme Activity	●					
Genotype	●					
Diagnosis	●					
Medical History	●	●		●		
Physical Examination	●					
Fabry Disease Clinical Assessment ^a						
Cerebrovascular - TIA, Stroke	●	●	●	●		●
Neurology - Sweating, Heat/Cold Intolerance, Pain	●	●		●		
Gastroenterology	●	●		●		
Cardiology - ECHO ^b , ECG ^b	● ^c	● ^c	●	●	● ^d	●
Renal - Dialysis, Transplant	●	●	●	●		●
Skin	●	●		●		
Respiratory - Spirometry	●	●	●	●		●
Ophthalmology	●	●	●		●	●
Vital Signs and Laboratory Tests						
Height/Weight	●	●	●	●		●
Blood Pressure	●	●	●	●		●
Serum Creatinine and BUN	●	●	●	●		●
Urinary Protein Excretion ^e	●	●	●	●		●
GFR ^f	●	●	●	●		●
Specialized Tests						
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.					
Pain/Quality of Life (QOL) ^g						
SF-36 ^h Health Survey	●	●		●		●
Brief Pain Inventory (Short Form)	●	●		●		●
PedsQL ^h 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.					

^a 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.

^b ECHO and ECG are recommended for patients ≥ 35 years of age every other year.

^c 24 hour or first morning void urine for urine protein, creatinine and microalbumin

^d GFR can be estimated using equations such as the MDRD equation for adults and Schwartz formula for children

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

APPENDIX 4 Fabry Registry Peer-Reviewed Publications

- Ortiz A, Cianciaruso B, Cizmarik M, Germain DP, Mignani R, Oliveira JP, Villalobos J, Vujkovic B, Waldek S, Wanner C, Warnock DG. End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry. *Nephrol Dial Transplant*. 2010;25:769-775. [published online 2009, 21 October].
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- Politei J.M., Cabello J.F , Villalobos J., Valadez G., Loaeza A., Linares L., Martins A.M. New concepts of the natural history, evolution and treatment, related to the findings of Fabry Registry. [Spanish]. *Revista de nefrología, diálisis y trasplante*. 2009; 29:145-152.
- 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.
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- 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.



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