Fabry Registry

Annual Report 2011

(This report covers data collected through 31 December 2010)

FABRY REGISTRY

FMRB-0009-02

FABRY REGISTRY

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FABRY REGISTRY

2011 Annual Report

FOREWORD

On behalf of the Boards of Advisors for the Fabry Registry, we are pleased to present the Fabry Registry 2011 Annual Report. This year's report highlights key findings published from the Fabry Registry during the past year.

First, we would like to recognize the many challenges that Fabry physicians and their patients have faced during the past year, due to interruption in the manufacturing of agalsidase beta. Amidst this difficult situation, we sincerely thank all of the participating sites who have reported their patients' changes in treatment status and other clinical data during this difficult period. The clinical status of Fabry Registry patients on lowered doses is regularly reported to Health Authorities and we urge all participating sites to continue to submit these data. It is essential that the Fabry Registry collects these data, in order to better understand the clinical impact of these treatment changes for patients.

Publication of clinical data continues to be a major emphasis of the Fabry Registry. We are pleased to let you know that four manuscripts were published or accepted for publication in peer-reviewed journals during the past year, including the first to report longitudinal renal data in Fabry Registry patients (Wanner, 2010) and the first to describe agalsidase beta outcomes in Fabry Registry patients (Watt, 2010).

Another achievement of 2010 was that Elsevier designated a Fabry Registry publication as one of the top 10 most-cited articles in *Molecular Genetics and Metabolism* over the past 3 years (Wilcox, 2008). This article, entitled "Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry", was also the most-cited article on Fabry disease published in any journal during the past 3 years! We congratulate the authors as well as you and your patients on this remarkable accomplishment. This would not have been possible without the continued dedication of all our participating sites.

We hope that you find this edition of the Fabry Registry Annual Report to be informative. We also thank you for your continued active participation in the Fabry Registry.

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

Christoph Wanner, MD
Fabry Registry European Board of Advisors

Juan Manuel Politei, MD
Fabry Registry International Board of Advisors

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. Publication of these data in peer-reviewed biomedical journals is a major emphasis of the Fabry Registry. In addition, such data 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.

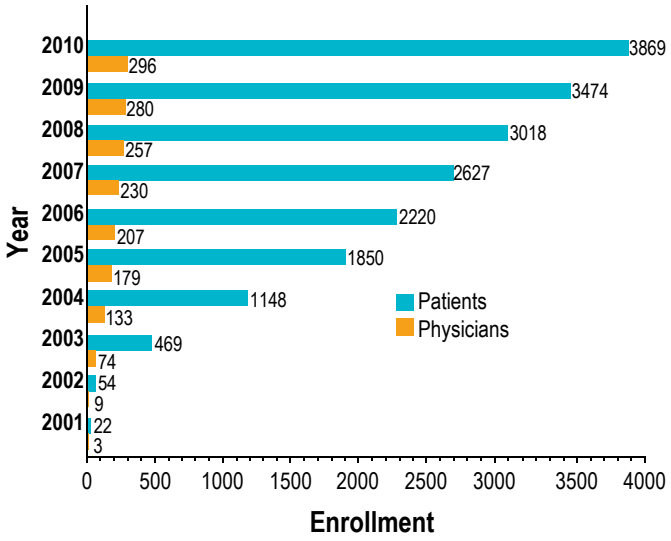
Regional Advisory Boards provide scientific oversight and direction to the Fabry Registry. Board members are physicians with expertise in Fabry disease who serve as liaisons between the Fabry Registry and the Fabry medical community within their respective geographic regions (Appendix 1).

The infrastructure of the Fabry Registry is sponsored by Genzyme, which underwrites a third party to maintain the 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 Clinical Development & Medical 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 2010, a total of 296 physicians worldwide have enrolled 3,869 patients in the Fabry Registry, as shown in **Figure 1**.

The Fabry Registry population includes nearly equal numbers of males (1,896) and females (1,973) and most are from Europe and North America, as shown in **Table 1**. As of 31 December 2010, the median age of Fabry Registry participants was 41 years for males and 44 years for females. At that time, 12% of males and 9% of females enrolled were children (below the age of 18 years). Males were diagnosed at a median age of 26 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 2010. Note that participating physicians are designated as those with 1 or more patients enrolled in the Fabry Registry.

Table 1.
Patient Demographics

	Males	Females
Total Number of Patients Enrolled, N	1896	1973
Regional Enrollment, n (%)		
North America	732 (38.6)	777 (39.4)
Europe	792 (41.8)	900 (45.6)
Latin America	176 (9.3)	178 (9.0)
Asia Pacific	196 (10.3)	118 (6.0)
Current Age*, All Patients (years)		
n	1895	1972
Mean (SD)	39.0 (16.59)	43.2 (17.94)
Median	40.7	44.1
25th, 75th	(27.3, 51.4)	(29.4,56.8)
Minimum, Maximum	(1.2,85.0)	(1.7,90.2)
Current Age* Distribution, n (%)		
Age ≥18 years	1663 (87.7)	1791 (90.8)
Age <18 years	232 (12.2)	181 (9.2)
Age at Fabry Diagnosis (n)		
n	1875	1902
Mean (SD)	27.5 (16.98)	33.5 (18.03)
Median	25.8	32.7
25th, 75th	(13.9,40.0)	(18.9,47.3)
Minimum, Maximum	(0.0,81.1)	(0.0,82.4)

*indicates age as of 31 December 2010.
SD, standard deviation; 25th, 25th percentile; 75th, 75th percentile

Selected Recent Analyses

Patients Treated with Agalsidase Beta Report Improved Health-Related Quality of Life

Patients with Fabry disease frequently suffer from pain crises, clinical depression, and other complications associated with diminished health-related quality of life (HRQL). In untreated men with Fabry disease, HRQL has been reported to be similar to that of patients undergoing renal dialysis and patients affected with acquired immune deficiency syndrome (Gold, 2002). Health-related quality of life in untreated women with Fabry disease has been reported to be similar to that of patients with rheumatoid arthritis or multiple sclerosis (Street, 2006). Fabry Registry data were recently analyzed to evaluate the effect of agalsidase beta on HRQL outcomes (Watt, 2010).

The SF-36® Health Survey is a validated instrument that has been extensively used to evaluate HRQL in patients with chronic diseases. As shown in **Table 2**, the SF-36 includes 8 scales that relate to various self-reported aspects of physical, mental, and social well-being and functioning.

The SF-36 was used to evaluate HRQL in 71 Fabry Registry men prior to the start of agalsidase beta treatment and during 3 or more years of treatment (Watt, 2010). These analyses were based on data collected through 05 June 2009, from patients who received the recommended licensed dose of agalsidase beta during the period of SF-36 data collection (averaged dose 1 mg/kg every other week).

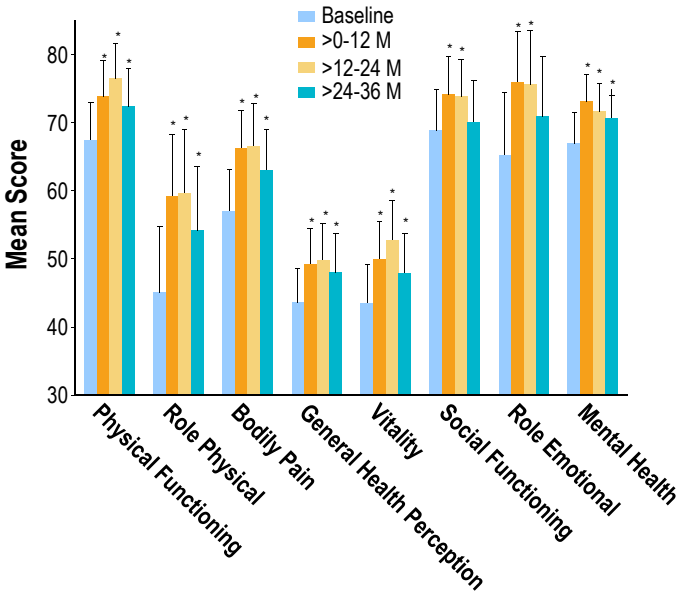
As shown in **Figure 2**, HRQL was significantly improved in men after the first 2 years of treatment with agalsidase beta in all eight SF-36 scales. The greatest improvements were reported in the Role Physical and Role Emotional scales, which measure the impact of physical and mental health on the ability to perform work and daily activities. Men reported sustained improvements during the third year of treatment, except for the Social Functioning and Role Emotional scales. Women reported improvements in 6 of the 8 SF-36 scales during 2 years of agalsidase beta treatment (Watt, 2010).

Table 2.
Summary of SF-36® Health Survey Scales

Physical Functioning	Limitations in performing various physical activities
Role Physical	Impact of physical health on completion of work or other daily activities
Bodily Pain	Pain magnitude and its effect on daily activities
General Health	Overall health perception
Vitality	Perceived energy levels
Social Functioning	Impact of physical and mental health on the ability to engage in normal social activities
Role Emotional	Impact of emotional health on work or other daily activities
Mental Health	Self-reported mood levels

All scores have a 100-point scale, with a higher score indicting better HRQL (Ware, 1993).

Figure 2.
Health-Related Quality of Life in Men Treated with Agalsidase Beta



Data represent that available in the Fabry Registry as of 05 June 2009. Data are expressed as average SF-36 scores at baseline (light blue bars), after 0–12 months of treatment (orange bars), >12–24 months of treatment (yellow bars), and >24–36 months of treatment (dark blue bars). Error bars represent the upper limit of 95% confidence intervals.
*p <0.05; significantly different from baseline value by repeated measures model, using age at baseline as a covariate. Reproduced with permission from Watt et al., Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. *Genet Med*, 2010;12:703-712.

Hypertension and LVH are Key Risk Factors for Cardiovascular Events

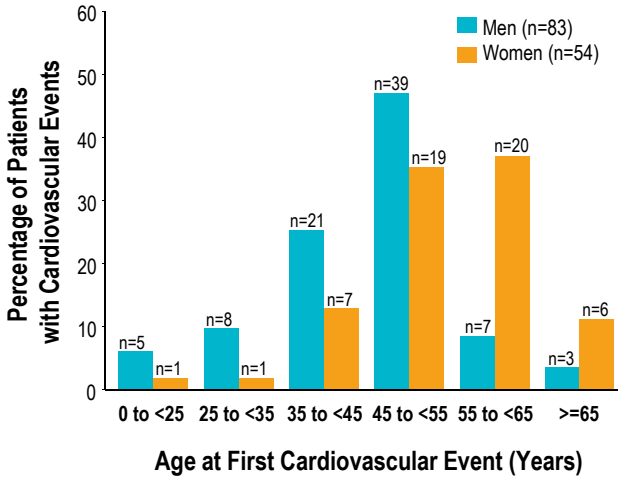
Fabry disease is associated with various cardiovascular complications, including hypertension, left ventricular hypertrophy (LVH), rhythm and conduction abnormalities, increased intima-media thickness, valvular insufficiency, and ischemic heart disease. Over time, these cardiovascular complications can progress to heart failure, myocardial infarction, and life-threatening arrhythmias.

Data from the Fabry Registry were recently analyzed to determine whether specific risk factors are associated with major cardiovascular events in untreated patients (i.e., before ERT or among patients who never received therapy) (Patel, 2011)

As of 03 October 2008, 137 of 2,869 untreated Fabry Registry patients (5%) had experienced a major cardiovascular event (defined as heart failure, myocardial infarction, or cardiac-related death), including 83 males and 54 females. As shown in **Figure 3**, most males experienced their first cardiovascular event between the ages of 35 to <55 years (median 47 years) and most females experienced their first cardiovascular event between the ages of 45 to <65 years (median 55 years) (Patel, 2011). Thirteen of 83 males (16%) and 2 of 54 females (4%) experienced a cardiovascular event before age 35.

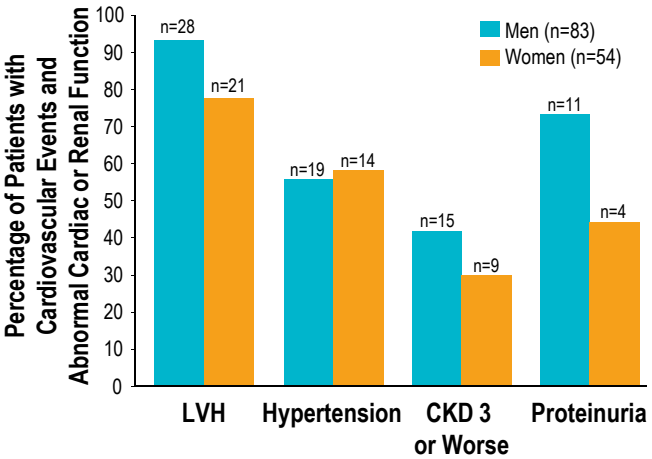
Multivariate analyses indicated that hypertension and LVH are the 2 risk factors most strongly associated with the occurrence of cardiovascular events, in both men and women with Fabry disease (Patel, 2011). In fact, 86% of patients had LVH and 57% of patients had hypertension at the time of their first cardiovascular event, among those for whom such data were available (**Figure 4**). Thus, cardiac function and risk factors for cardiovascular events should be closely monitored in patients with Fabry disease.

Figure 3.
Untreated Fabry Registry Patients Can Have Major Cardiovascular Events at Young Ages



Data represent that available in the Fabry Registry as of 03 October 2008. Percentages of patients experiencing their first major cardiovascular event (heart failure, myocardial infarction, or cardiac-related death) during 6 age categories are shown. Numbers above the bars indicate the number of patients in each category. All data are from patients who had not been treated with ERT at the time of their first cardiovascular event. Reproduced with permission from Patel et al. Cardiovascular events in patients with Fabry disease: natural history data from the Fabry Registry. *J Am Coll Cardiol*. 2011;57:1093-1099.

Figure 4.
Most Untreated Fabry Registry Patients who had Major Cardiovascular Events had Left Ventricular Hypertrophy and/or Hypertension



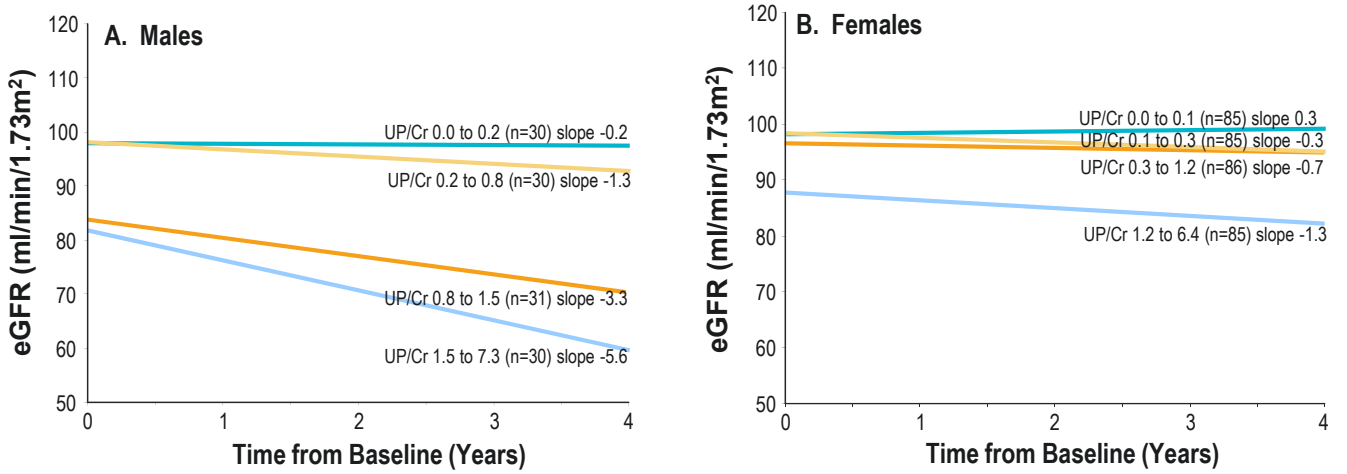
Data represent that available in the Fabry Registry as of 03 October 2008. Percentages were calculated based on the number of patients who had cardiac or renal data available within ±12 months of the date of their first cardiovascular event. Clinical assessments designated as "abnormal" included: LVH, left ventricular posterior wall thickness ≥12 mm; Hypertension, systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg; CKD (chronic kidney disease) Stage 3 or worse, estimated glomerular filtration rate <60 mL/min/1.73m^2; Proteinuria, urinary protein:urinary creatinine ratio ≥1 g/g. Numbers above the bars show the number of patients with abnormal cardiac or renal values in each group. Reproduced with permission from Patel et al. Cardiovascular events in patients with Fabry disease: natural history data from the Fabry Registry. *J Am Coll Cardiol*. 2011;57:1093-1099.

Proteinuria is a Major Risk Factor for Renal Disease Progression

Most men and some women with Fabry disease exhibit progressive loss of renal function, and many eventually develop kidney failure (Schiffmann, 2009; Ortiz, 2010). Longitudinal data from the Fabry Registry were analyzed to characterize changes in kidney function over time before the initiation of ERT (Wanner, 2010).

Renal function was assessed by change in estimated glomerular filtration rate (eGFR) over time in 462 untreated adults (121 men and 341 women) who were included in the analyses. Renal function declined most rapidly in patients who had the highest urinary protein:creatinine ratios (UP/Cr) (**Figure 5**). The average rate of renal decline was –5.6 mL/min/1.73m^2/year among the 30 men with the highest UP/Cr levels (**Figure 5**, upper panel), whereas the expected loss of renal function in healthy adults is approximately –1 mL/min/1.73m^2/year. Renal function was more stable for females, but women with the highest levels of proteinuria also had the most rapid declines in renal function (**Figure 5**, lower panel). Regression models indicated that proteinuria (UP/Cr) is the most important indicator of renal disease progression in adults with Fabry disease (Wanner, 2010).

Figure 5.
Patients with Proteinuria have the Most Rapid Renal Disease Progression



Data represent mean estimated glomerular filtration rate (eGFR) in patients who had not received ERT or prior to the initiation of ERT, as of 03 July 2009. Baseline represents the first eGFR value reported to the Fabry Registry. To be included in these analyses, patients were required to have 2 or more eGFR values over a span of ≥12 months prior to receiving any ERT and 1 or more corresponding urinary protein:creatinine ratio (UP/Cr) values reported. Patients were grouped into quartiles with approximately equal numbers of patients, based on averaged UP/Cr levels. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Reproduced with permission from Wanner et al. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. *Clin J Am Soc Nephrol.* 2010;5:2220-2228.

SUMMARY

- HRQL improved among both men and women who were treated with agalsidase beta (Watt, 2010).
- Patients with Fabry disease have a high risk for experiencing major cardiovascular events (i.e., heart failure and myocardial infarction) at a relatively young age. Hypertension and LVH are strongly associated with the occurrence of these events in untreated patients. Earlier diagnosis, before the onset of these risk factors, will allow for prompt initiation of appropriate treatment. The medical community in general, especially cardiologists, should be aware of Fabry disease as a possible cause of cardiac dysfunction (Patel, 2011).
- Proteinuria is a key prognostic indicator of renal disease progression in untreated patients. Higher levels of urinary protein excretion are associated with more rapid renal disease progression, particularly in men (Wanner, 2010). In clinical trials of agalsidase beta, patients who had proteinuria before starting treatment had poorer clinical outcomes (Banikazemi, 2007; Germain, 2007). Therefore, it is critical to closely monitor and aggressively manage proteinuria in all patients with Fabry disease, regardless of other signs or symptoms.
- Continued growth and future directions: The Fabry Registry continues to grow, with 3,869 patients enrolled as of 31 December 2010. A substantial body of longitudinal clinical data has now been collected. Analyses of renal and cardiac outcomes among patients treated with agalsidase beta are currently in progress.

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	**In Europe:** +31(0)35 699 1299

LITERATURE CITED

Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med*. 2007;146:77-86.

Germain D, Waldek S, Banikazemi M, et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. *J Am Soc Nephrol*. 2007;18:1547-1557.

Gold KF, Pastores GM, Botteman MF, et al. Quality of life of patients with Fabry disease. *Qual Life Res*. 2002;11:317–327.

Ortiz A, Cianciaruso B, Cizmarik M, et al. End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry. *Nephrol Dial Transplant*. 2010;25:769-775.

Patel MR, Cecchi F, Cizmarik M, et al. Cardiovascular events in patients with Fabry disease: natural history data from the Fabry registry. *J Am Coll Cardiol*. 2011;57:1093-1099.

Schiffmann R, Warnock DG, Banikazemi M, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol Dial Transplant*. 2009;24:2102-2111.

Street NJ, Yi MS, Bailey LA, et al. Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease. *Genet Med*. 2006;8:346-353.

Wanner C, Oliveira JP, Ortiz A, et al. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. *Clin J Am Soc Nephrol*. 2010;5:2220-2228.

Ware JE, Snow KK, Kosinski M, et al. SF-36® Health Survey Manual and Interpretation Guide. Boston, MA: New England Medical Center, The Health Institute, 1993.

Watt T, Burlina AP, Cazzorla C, et al. Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. *Genet Med*. 2010;12:703-712.

Wilcox WR, Oliveira JP, Hopkin et al. Females with Fabry disease frequently have major organ involvement: Lessons from the Fabry Registry. *Mol Genet Metab*. 2008;93:112-128.

APPENDIX 1. 2010 Boards of Advisors and Registry Coordinators

North American Board of Advisors

Advisor	Affiliation	Location
David G. Warnock, M.D. (chair)	University of Alabama at Birmingham	Birmingham, AL, 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
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
Katherine Sims, M.D.	Massachusetts General Hospital	Boston, MA, USA
William Wilcox, M.D., Ph.D.	Cedars Sinai Medical Center	Los Angeles, CA, USA

European Board of Advisors

Advisor	Affiliation	Location
Prof. Dr. C. Wanner (Chair)	Universitätsklinik Würzburg	Würzburg, Germany
Dr. A. Burlina	San Bassiano Hospital	Bassano del Grappa, Italy
Prof. Dr. U. Feldt-Rasmussen	National University Hospital	Copenhagen, Denmark
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
Dr. G. Linthorst	Academisch Medisch Centrum	Amsterdam, Netherlands
Prof. 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
Prof. Dr. J. Strotmann	I. Medizinische Klinik	Kiel, Germany
Prof. Dr. A. Tylki-Szymanska	Children's Memorial Health Institute	Warsaw, Poland
Dr. B. Vujkovac	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
Prof. Ana Maria Martins, M.D., Ph.D.	Universidade Federal de São Paulo	São Paulo, Brazil
Sandra Ospina, M.D.	Universidad del Rosario	Bogotá, Colombia
Juan Manuel Politei, M.D.	Juan Fernandez Hospital	Buenos Aires, Argentina
Gustavo Cabrera*	Grupo Médico Del Viso	Buenos Aires, Argentina
Carmen Varas, M.D.	Hospital San Pablo	Coquimbo, Chile
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
Katherine Sims, M.D. (North American Representative)	Massachusetts General Hospital	Boston, MA
Prof. Dr. C. Wanner (European Representative)	Universitätsklinik Würzburg	Würzburg, Germany
Juan Manuel Politei, MD (Latin American Representative)	Hospital Juan Fernandez	Buenos Aires, Argentina

* new member since July 2010

APPENDIX 2. Fabry Registry Abstracts Presented in 2010

Patel MR, Cecchi F, Cizmarik M, et al. Cardiovascular Events in Patients with Fabry Disease: Natural History Data from the Fabry Registry. Presented 09 March, 2010 at the American College of Cardiology conference, Atlanta, Georgia, United States.

Watt T, Feldt-Rasmussen U, Burlina A, et al. Agalsidase Beta Treatment Improves Quality of Life in Patients with Fabry Disease: Findings from the Fabry Registry. Presented 27 March, 2010 at the American College of Medical Genetics conference, Albuquerque, New Mexico, United States.

Wanner C, Beitner-Johnson D, Germain DP, et al. Prognostic Indicators of Renal Disease Progression in Fabry Disease. Presented 26 June 2010 at the XLVII EDTA-ERA Congress, Munich, Germany.

Hopkin RJ, Banikazemi M, Germain DP, et al. Guidelines for the evaluation and management of children with Fabry disease. Presented 04 November 2010 at the American Society for Human Genetics conference, Washington DC, United States.

Wilcox WR, Gruskin DJ, Warnock DG. Few females develop anti-α-galactosidase A IgG antibodies in response to agalsidase beta treatment: data from the Fabry Registry. Presented 04 November 2010 at the American Society for Human Genetics conference, Washington DC, United States.

Wanner C, Warnock DG. Prognostic Indicators of Renal Disease Progression in Fabry Disease: Natural History Data from the Fabry Registry. Presented 19 November 2010 at the American Society for Nephrology conference, Denver, Colorado, United States.

Villalobos J, Politei J, Valádez G, Martíns A, Ospina S, Varas C. Análisis Longitudinal del Compromiso Renal de la Enfermedad de Fabry. Datos Obtenidos del Registro Fabry. XI Congress of Nephrology, Maracaibo, Venezuela.

Martins AM, Ospina S, Villalobos J, Politei J, Varas C on behalf of the Latin America Registry Coordinators. Fabry Disease in Latin America: a Report from the Fabry Registry. 11th European Round Table on Fabry decease. Istanbul, Turkey.

Politei J, Cabrera G, Martins AM, Ospina S, Varas C, Villalobos J. Compromiso neurológico en niños y mujeres con Enfermedad de Fabry. Datos del Registro Fabry. Argentinean Neurologic Congress, Mar del Plata, Argentina.

APPENDIX 3. Fabry Registry Peer-Reviewed Publications

Patel MR, Cecchi F, Cizmarik M, et al. Cardiovascular events in patients with Fabry disease: natural history data from the Fabry registry. *J Am Coll Cardiol*. 2011;57:1093-1099.

Wanner C, Oliveira JP, Ortiz A, et al. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. *Clin J Am Soc Nephrol*. 2010;5:2220-2228.

Watt T, Burlina AP, Cazzorla C, et al. Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry. *Genet Med*. 2010;12:703-712.

Ortiz A, Cianciaruso B, Cizmarik M, Germain DP, Mignani R, Oliveira JP, Villalobos J, Vujkovac 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.

Waldek S, Patel M, Banikazemi M, Lemay R, Lee P. Life Expectancy and Cause of Death in Males and Females with Fabry Disease: Findings from the Fabry Registry. *Genet Med*. 2009;11:790-796.

Politei JM, Cabello JF, Villalobos J, Valadez G, Loaeza A, Linares L, Martins AM. 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.

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.

APPENDIX 4. Minimum Recommended Schedules of Assessments

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

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.
Directly measuring glomerular filtration rate (GFR) is recommended if a more precise evaluation is desired.
24 hour or first morning void urine for protein, creatinine and albumin.
At the time of an event, a cranial MRI should also include DWI/ADC.
If electrocardiogram is abnormal and/or clinical symptoms arise, Holter monitoring is recommended.
Annual 24 hour holter monitoring is recommended for males 30 years of age or older and females 40 years of age or older.
If spirometry is abnormal, perform yearly.
Monitor yearly if retinal vessel tortuosity noted.

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