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Fabry RADAR 2005

The Fabry Registry
Aggregate Data
Annual Report



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Executive Summary

It is our pleasure on behalf of the Boards of Advisors for the Fabry Registry to introduce the 2005 Registry Aggregate Data and Annual Report (RADAR). The objective of this report is to continue to advance the mission of the Fabry Registry to raise awareness of Fabry disease and to support the development of clinical knowledge among health care providers and investigators around the world. Fabry disease is an often life-threatening lysosomal storage disorder with a highly variable clinical presentation. It is also a rare disease - the incidence is estimated to be 1 in 40,000 males. For these reasons, the diagnosis of Fabry disease is often overlooked or delayed, which can result in progressive organ involvement leading to cardiac, renal, and cerebrovascular complications. As the largest global outcomes database on Fabry disease, the Fabry Registry can provide unique insight into the natural course of Fabry disease in patients worldwide. The data collected by the Fabry Registry through your efforts has already provided substantial insight into the progression of Fabry disease, the presentation in children, manifestations in females, and is poised to provide meaningful outcome information on enzyme replacement therapy (ERT) and other therapies in the year ahead. The Registry has collected considerable data from patients when they first enrolled; however, there is a relative lack of data from follow-up evaluations. This information is essential for measuring the outcomes of ERT and adjunctive therapies. We hope you find this report helpful and informative, and look forward to hearing your comments and feedback so that we may continue to improve our communications to you in the future. Above all, we thank you for all of your effort in assembling the data required to make this collaboration successful.

William Wilcox, MD, PhD

Fabry Registry North American Board of Advisors

Prof. Christoph Wanner

Fabry Registry European Board of Advisors

Introduction

Fabry disease is caused by an X-linked deficiency in lysosomal α -galactosidase A. The absence of this enzyme causes progressive accumulation of globotriaosylceramide and related glycolipids, which can severely impact the renal, cardiac, and cerebrovascular systems. The Fabry Registry is a global, observational, and voluntary program designed to collect clinical data related to the onset and progression of Fabry disease. All patients with Fabry disease are eligible to participate in the Fabry Registry, regardless of whether they are receiving ERT and irrespective of the commercial product with which they are being treated. Introduced in 2001, the year 2005 marks the fifth anniversary of the Fabry Registry. The following key objectives were addressed by the Fabry Registry between 2001-2005:

To enhance our understanding of the natural course of Fabry disease

- By developing a model of the progression of Fabry Disease, from early symptoms to late complications, to better characterize disease severity

To provide recommendations to the international medical community for diagnosing and monitoring Fabry patients

- By creating individual patient reports supporting the optimization of patient care

To evaluate the long-term effectiveness and safety of treatment options

- By capturing the clinical experience of patients being treated with ERT and those remaining off therapy

The Boards of Advisors provide scientific oversight and direction to the Fabry Registry. Board members are physicians with expertise in Fabry disease who serve as links between the Fabry Registry and the Fabry medical community within their respective geographic regions (Appendix 1). The Boards of Advisors developed the Fabry Registry's Minimum Recommended Schedule of Assessments (Appendix 2). This schedule recommends key clinical and laboratory parameters for monitoring patients with Fabry disease, and forms the basis of the clinical data collected in the Fabry Registry. Specific assessments and their frequency in individual patients are determined by their treating physicians.

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 participating sites. Personnel to manage and administer the Fabry Registry programs operate within the Biomedical Research Division and Global Registry Programs at Genzyme.

Goals for 2005

The first edition of the Fabry Registry Aggregate Data Annual Report was issued last year. In that report, the following goals were established for the Fabry Registry in 2005:

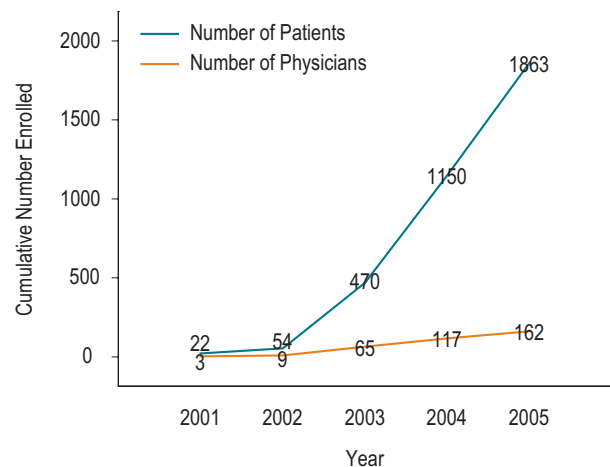
- Increase Patient Enrollment
- Complete Data Entry Forms
- Introduce Revised Protocol and Data Collection Forms
- Characterize Pediatric and Female Subpopulations
- Achieve Publication Objectives
- Improve Communication
- Extend the Boards of Advisors

The following section summarizes the progress that has been made towards these goals.

Increase Patient Enrollment

Since April 2001, the Fabry Registry has enrolled 1863 patients and 162 physicians, as shown in Figure 1. The number of patients and physicians participating in the Fabry Registry increased considerably in 2005. During the past year, the number of patients enrolled in the Fabry Registry grew by 62% and the number of participating physicians grew by 38%. The Fabry Registry is the largest outcomes assessment program in the world that monitors patients with Fabry disease.

Figure 1
Cumulative enrollment of patients and physicians in the Fabry Registry from 2001 to 2005

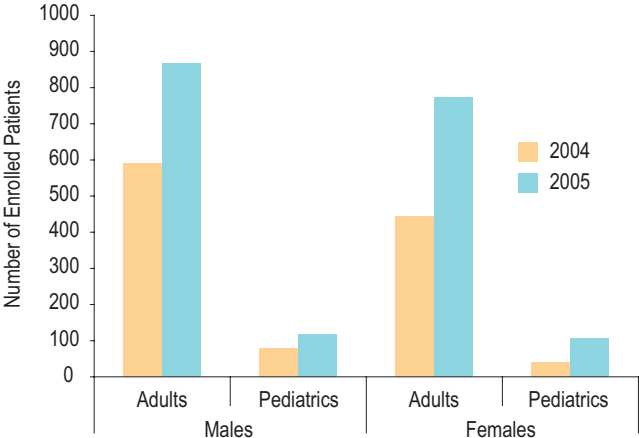


The number of female and pediatric patients enrolled in the Fabry Registry increased in 2005. As shown in Figure 2, the number of adult female patients enrolled in the Fabry Registry increased by 48% and the number of pediatric patients enrolled (both genders) increased by 86% in 2005 as compared to 2004. These increases are attributed to the efforts of participating physicians responding to “call to action letters” sent by both the Female and Pediatric Working Groups in early 2005 encouraging physicians to enroll their female and pediatric patients with Fabry disease into the Fabry Registry. At the same time, each Working Group requested that participating physicians submit needed patient follow-up data into the Fabry Registry’s data entry forms.

Complete Data Entry Forms

Further analyses of the natural course of Fabry disease and of outcomes of patients on ERT within the Fabry Registry are needed. To facilitate this, one of the goals set for 2005 was to increase the quantity of patient follow-up data submitted by participating physicians with emphasis on female and pediatric patients. As discussed above, the number of female and pediatric patients enrolled in the Fabry Registry has increased substantially. To supplement the efforts of participating physicians and the Female and Pediatric Working Groups, Fabry Registry Representatives conducted two semi-annual Registry reviews with active sites in 2005. These individual site reviews are designed to support patient enrollment, data collection and emphasize needed Registry data for planned analyses and publications. In 2005, these focused, scheduled meetings supplemented routine contact between a site and their local Registry Representative.

Figure 2
Increased numbers of female and pediatric patients enrolled in the Fabry Registry in 2005, as compared to 2004



Introduce Revised Protocol and Data Collection Forms

The Fabry Registry protocol was amended in 2005 in order to address the requests by regulatory agencies for reports of pregnancy outcomes and infant follow-up for patients enrolled in the Fabry Registry. This information is now being collected in the revised CRF. Another protocol change is designed to strengthen the characterization of health-related quality of life and pain in pediatric patients. This change was made in response to requests from physicians participating in the Fabry Registry. These and other changes that were made to the Fabry Registry CRF in 2005 are summarized in Table 1.

Table 1
Summary of major changes to Fabry Registry Protocol and Case Report Forms in 2005

Changes to Fabry Registry Protocol	Changes to CRF
Collect information regarding pregnancy course and outcome, including infant follow-up	Collect information regarding pregnancy course and outcome, including infant follow-up (paper CRF only)
PedsQL™ questionnaire (measures pediatric health-related quality of life, pain, and fatigue)	Electronic PedsQL™ questionnaire has been added to eCRF to better characterize health-related quality of life and pain in children
SF-36® Health Survey and Brief Pain Inventory Short Form will be administered more frequently (every 6 months) to capture additional quality of life and pain endpoints for patients on ERT	No change in CRF; appropriate modification made in the minimum recommended schedule of assessments
	Diabetes Diagnosis has been added to the eCRF, to record whether patients enrolled in the Fabry Registry have been diagnosed with diabetes
	Chronic Medication capture has been added to the eCRF to characterize chronic medication use by patients
	Four additional gastrointestinal (GI) questions have been added to the eCRF, to capture new GI signs and symptoms
	Two new methods to measure glomerular filtration rate (GFR) have been added to the eCRF

Characterize Pediatric and Female Subpopulations

Together with participating physicians, the Fabry Registry developed several new analyses that specifically focused on pediatric and female patients with Fabry disease. These findings were presented at various international conferences in 2005. Data from these analyses suggest that pain, angiokeratoma, and gastrointestinal symptoms are common in pediatric patients and that the severity of Fabry disease in the pediatric population has been underestimated (Clarke et al., 2005, *American College of Medical Genetics* abstract, Appendix 3). Among adults, females experienced cardiac and cerebrovascular events at rates similar to males, and some female patients exhibit disease complications that are as serious as those exhibited by male patients (Waldek et al., 2005, *Society for the Study of Inborn Errors of Metabolism* abstract, Appendix 3). However, females with Fabry disease are generally diagnosed at a later age than males with Fabry disease (Eng et al., 2005, *American Society of Human Genetics* abstract, Appendix 3). These findings demonstrate that it will be important to continue to increase awareness of the course of Fabry disease, particularly in pediatric and female subpopulations.

Achieve Publication Objectives

As mentioned above, analyses of data within the Fabry Registry were presented at various international conferences during 2005, including the annual meeting of the American Society for Human Genetics and the Society for the Study of Inborn Errors of Metabolism (see Appendix 3). In 2005, two scientific manuscripts were also submitted for publication by physicians participating in the Fabry Registry. One used data from the Fabry Registry to characterize the natural history of Fabry disease, and the other described guidelines for the evaluation of Fabry Disease and management of Fabry patients.

Improve Communication

The semi-annual registry reviews described previously improve communication by providing additional contact between sites and their local Registry Representatives. These meetings may also include a review of Registry reports, such as the Annual Report, which will help sites understand the use and importance of data entered into the Fabry Registry. This process was expanded to sites internationally in 2005.

The Fabry Registry also maintains a Data Request Program, which enables participating physicians and healthcare associates to obtain de-identified aggregate information about the entire Registry population or a defined subpopulation. In response to these requests, Fabry Registry programmers and biostatisticians issue Data Request analysis reports. In 2005, substantially more Data Requests were submitted, as compared to previous years. A total of 62 Fabry Data Request reports were completed in 2005, whereas 24 were completed in 2004.

The Fabry Registry encourages participants to present and publish information obtained from such reports. A sample data request form is included in Appendix 4.

Genzyme maintains a website at www.fabryregistry.com where health care professionals can obtain current information from the Fabry Registry and where patients and their families can learn more about participating in the Fabry Registry and can access various international resources and support groups. The website was updated in 2005 so that physicians can access the Fabry Registry's protocol, patient health surveys, the minimum recommended schedule of assessments, data request forms, and other Registry materials and documents online. Completed Fabry Registry Data Reports are also now securely posted at www.fabryregistry.com to facilitate dissemination of the most current information to participating physicians. The Fabry Registry Newsletter, an integrated part of the Lysosomal Storage Disease (LSD) eNewsletter, is another way that the Fabry Registry communicates with participating physicians, nurses, and genetic practitioners.

Extend the Boards of Advisors

Until 2005, there were two Fabry Registry Boards of Advisors, a North American Board and a European Board. In 2005, Dr. L. Pinderski was added to the North American Board of Advisors, while Dr. N. Leech resigned from the European counterpart. Due to the increasing participation of physicians and patients in Latin American and Asia-Pacific countries, a separate International Board of Advisors has been established. The new International Board of Advisors currently has three representatives: Dr. D. Germain was elected to the International Board of Advisors to represent the European Board, Dr. C. Eng was elected to represent the North American Board, and Prof. Dr. A.M. Martins will represent the Latin American Region. All members of the Boards of Advisors are listed in Appendix 1.

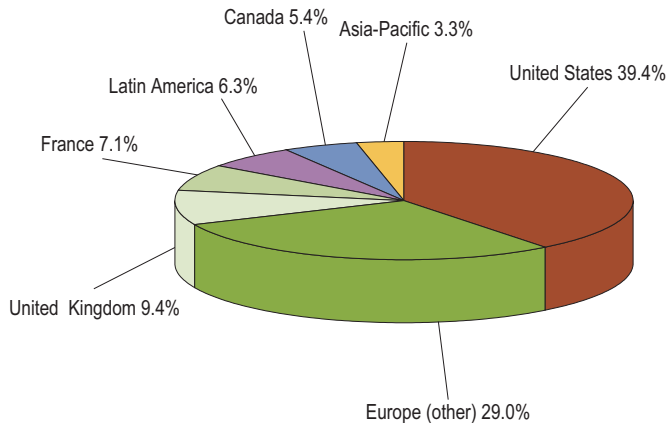
Current Data

Demographics

Of the 1863 patients enrolled in the Fabry Registry at the end of 2005, 53% were male and 47% were female, as shown in Table 2. This represents a substantial increase in the percentage of female patients enrolled in the Fabry Registry, as compared to previous years. Among both male and female patients, 88% of patients were classified as adults (18 years of age or older) and 12% were classified as pediatric patients (younger than 18 years of age). As mentioned previously, this reflects a considerable increase in the number of pediatric patients enrolled in the Fabry Registry, as compared to previous years. Similar to previous observations, within both genders the majority of patients with Fabry disease were Caucasian and most patients reported having a family member diagnosed with Fabry disease.

As of December 31st, 2005, patients from 34 countries participate in the Fabry Registry, as shown in Table 3. Overall, the largest numbers of patients are enrolled in Europe and the United States, as shown in Figure 3.

Figure 3
Global distribution of patients' enrollment



Individual countries that have ≥ 100 patients enrolled are shown. Countries with < 100 patients enrolled are grouped together by geographical region.

Over 61% of the patients in the Fabry Registry have been participating in the Registry for one year or more, as shown in Figure 4. This Figure also illustrates the increased numbers of female patients enrolled in the Fabry Registry during 2005 (shown as 0-12 months in Figure 4).

Figure 4
Length of time patients were enrolled as of December 31st, 2005

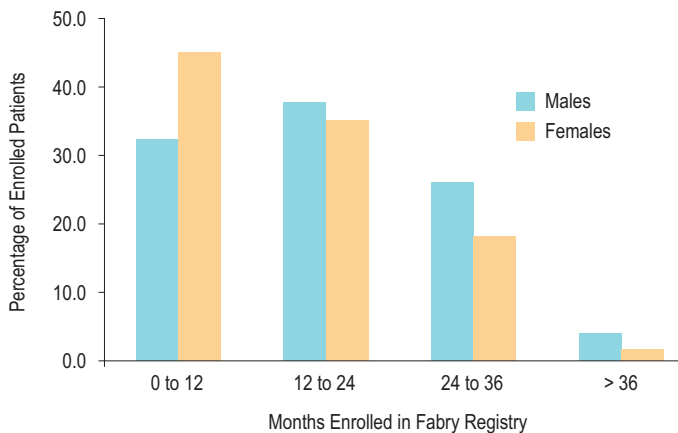


Table 2
Demographic profile of Fabry Registry patients as of December 31st, 2005

	Statistic	Males	Females
Number Enrolled	n (%)	985 (53%)	878 (47%)
Current Age	n	985	878
	Mean (SD)	37 (15)	40 (18)
	Median	38	42
	Min, Max	1, 84	0, 85
Age Distribution			
Age ≥ 18 yrs	n (%)	866 (88%)	772 (88%)
Age < 18 yrs	n (%)	119 (12%)	106 (12%)
Ethnicity	n	873	732
Caucasian	n (%)	715 (82%)	624 (85%)
Hispanic	n (%)	72 (8%)	61 (8%)
Black	n (%)	13 (1%)	10 (1%)
Asian	n (%)	34 (4%)	12 (2%)
Other	n (%)	39 (4%)	25 (3%)
Fabry in Family ?	n	985	878
Yes	n (%)	746 (76%)	688 (78%)
No	n (%)	94 (10%)	27 (3%)
Unknown/Not Reported	n (%)	145 (15%)	163 (19%)

Note: Percentages may not total to 100% due to rounding.

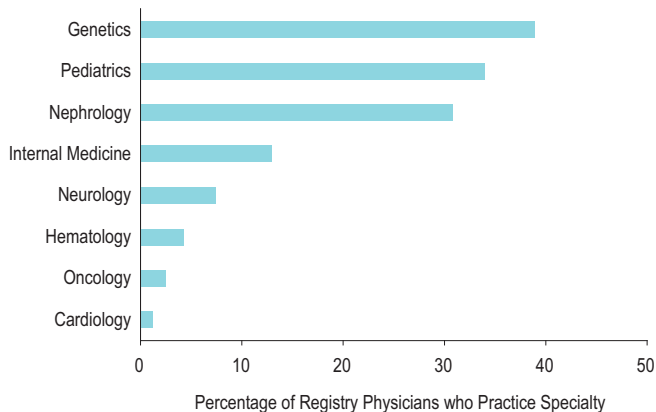
Table 3
Countries of origin of Fabry Registry patients

Argentina 23	Colombia 12	Hungary 27	P. R. China 10	Switzerland 20
Australia 33	Czech Republic 97	Israel 14	Poland 14	Taiwan 7
Austria 1	Denmark 39	Italy 49	Portugal 13	Turkey 1
Belgium 5	Finland 12	Korea 11	Singapore 1	United Kingdom 176
Brazil 47	France 133	Mexico 13	Slovenia 24	United States 734
Canada 100	Germany 75	Netherlands 71	Spain 22	Venezuela 2
Chile 21	Greece 2	Norway 34	Sweden 30	

The number of patients enrolled is shown for each country.

As of the end of 2005, 162 physicians had contributed data from at least one, and up to 116 patients. The most common specialty of physicians participating in the Fabry Registry is genetics. However, increasing numbers of participating physicians are specialized in internal medicine, neurology, hematology-oncology, and cardiology, as shown in Figure 5.

Figure 5
Medical specialties of the 162 participating physicians



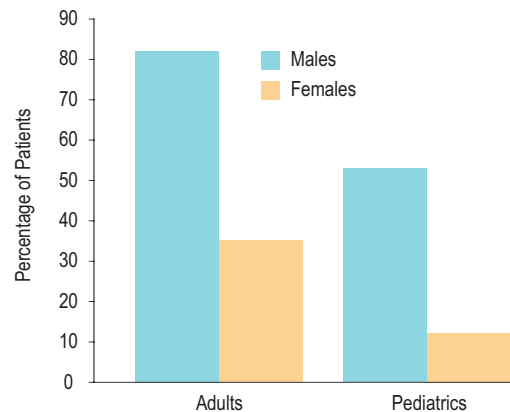
Each physician may have selected more than one specialty.

The percentages of patients in the Fabry Registry who were undergoing ERT as of December 31st, 2005 are summarized in Figure 6. Because Fabry disease is an X-linked genetic disorder, male patients are expected to be more profoundly affected than female patients. However, it has recently become clear that manifestations in female patients are more common than previously thought. As of 2005, a much higher percentage of adult males (82%), compared to adult females (35%) were undergoing ERT. Similarly, among pediatric patients, 53% of males were being treated with ERT as compared to 12% of females. In 2005, Genzyme worked closely with Fabry Registry Board members and selected experts in Fabry disease to develop analyses to better characterize Fabry disease in females and in pediatric patients. These initiatives will be useful for understanding the natural course of the disease and the efficacy of ERT in these subpopulations of patients.

Disease Onset and Progression

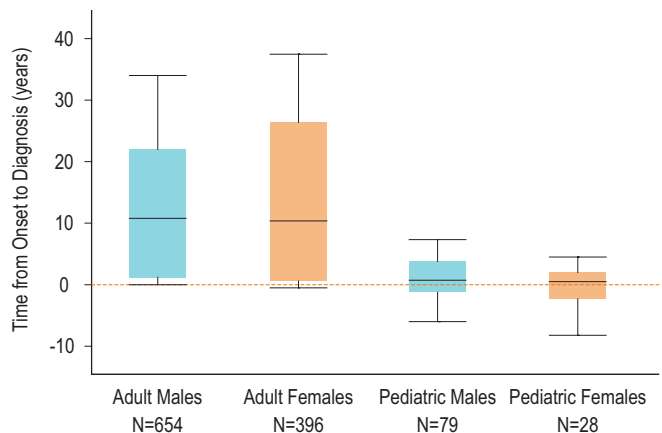
The signs and symptoms of Fabry disease can vary widely and, as a result, the disease is frequently not diagnosed until it has progressed to the point of organ dysfunction or failure. Analysis of data within the Fabry Registry showed that a similar duration of time elapsed between the onset of symptoms to diagnosis in male and female adult patients (median 10.8 years in males and 10.4 years in females), as shown in Figure 7. Pediatric patients were diagnosed much more quickly, with a median of 0.7 years in males and 0.5 years in females. Patients with Fabry disease will benefit from earlier diagnosis. Further analysis of data in the Fabry Registry is aimed at providing practical information that may help to reduce the time from onset of symptoms to diagnosis.

Figure 6
Percentage of Fabry Registry patients undergoing ERT by age category and gender



Adult patients were ≥ 18 years of age and pediatric patients were <18 years of age on December 31st, 2005. The total number of patients in each age and gender category is shown in Table 2.

Figure 7
Time from onset of symptoms to diagnosis



The horizontal line within each box is the median. Data are shown for patients who had both date of onset and date of diagnosis in the Fabry Registry. Bottom and top of box represent the 25th and 75th percentiles, respectively, while the error bars span the 10th and 90th percentiles. Data shown are as of December 31st, 2005.

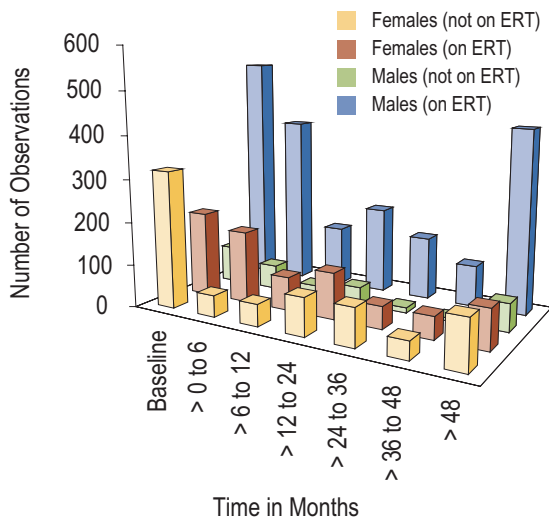
Increased Data Collection in 2005

Since its inception in 2001, an extensive amount of clinical data has been entered in the Fabry Registry. Figure 8 shows examples of some of the types of data that are available in the Fabry Registry as of December 31st, 2005. As shown in Figure 8a, substantial amounts of renal data (i.e., number of serum creatinine observations) have now been entered in the Fabry Registry. The largest proportion of data is available for patients who are receiving ERT, although there are also growing levels of renal data for patients who are not on ERT. The availability of this more extensive set of data will facilitate further characterization of the effects of Fabry disease on renal function, which are among the most devastating aspects of the disease, as well as the long-term effects of ERT on renal function.

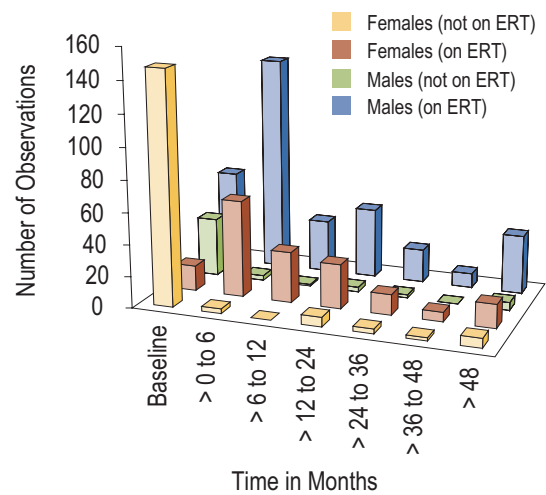
Despite this progress, additional data are still needed to perform longitudinal analyses that evaluate other aspects of Fabry disease, including the cardiac and cerebrovascular systems, as well as pain and quality of life. Follow-up data for those patients who are on ERT, as well as patients who are not on ERT are needed for these comparative analyses. Cardiac symptoms are evaluated by echocardiography, cerebrovascular symptoms are evaluated by echocardiography, cerebrovascular symptoms are evaluated by brain imaging observations, and health-related quality of life is evaluated by the SF-36[®] Health Survey. As shown in Figures 8b-8d, more data from both males and female patients who are and who are not on ERT will be needed to fully characterize the effect of ERT on these aspects of Fabry disease.

Figure 8
Examples of detailed data that are available in the Fabry Registry

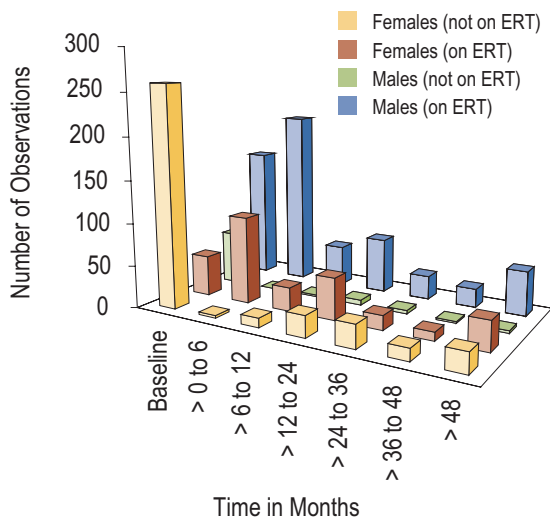
a. Number of serum creatinine observations by time period



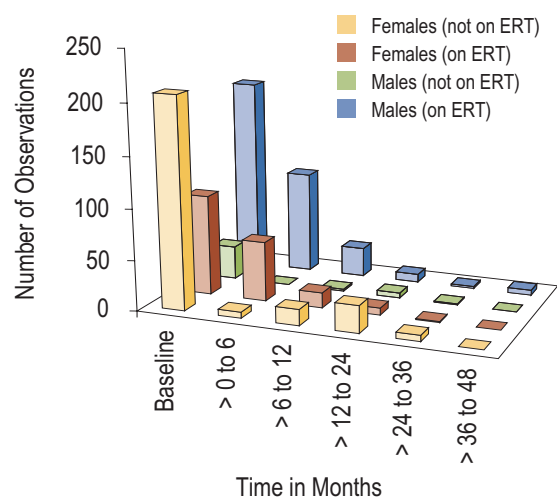
c. Brain imaging observations by time period



b. Number of echocardiogram observations by time period



d. SF-36[®] observations by time period



Baseline refers to the number of observations at the time of enrollment.
Time periods indicate the number of months patients have been enrolled in the Fabry Registry.

Onset and Severity of Fabry Disease in Males versus Females

Because Fabry disease is an X-linked genetic disorder, the disease, by definition, should primarily affect male patients. However, female patients with Fabry disease can also experience considerable manifestations, and recent studies indicate that the symptoms of Fabry disease in these female patients are much more prevalent than previously believed.^{1,2} Data in the Fabry Registry were analyzed to compare the age at symptom onset, diagnosis, clinical events, and the initiation of ERT in adult male and female patients who received ERT. The definitions of cardiac, cerebrovascular, and renal clinical events are summarized in Box 1.

Box 1	
Definitions of cardiac, cerebrovascular, and renal clinical events	
Cardiac	
	Arrhythmia
	Myocardial infarction
	Angina pectoris
	Congestive heart failure
	Significant cardiac procedure
Cerebrovascular	
	Stroke
Renal	
	Dialysis
	Transplantation

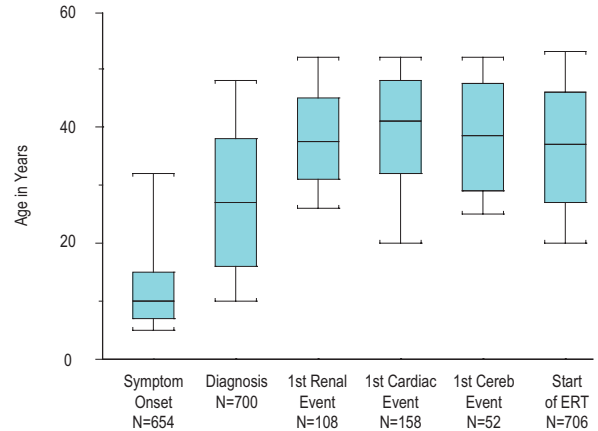
In this patient population, there was a 3-year difference in the median ages at onset of symptoms in males and females (10 years in male patients and 13 years in female patients), as shown in Figure 9. However, there was an 11-year difference in the median ages at diagnosis (27 years in males and 38 years in females). This highlights the importance of better characterizing the natural course of Fabry disease in adult females to facilitate earlier diagnosis in female patients. Among patients who experienced renal, cardiac, and cerebrovascular events, the ages at first onset of events were similar in males and females, although males tended to experience their first cardiac event at an earlier age than females (41 years in males versus 49 years in females).

¹Deegan P., Baehner, A.F., Barba-Romero, M.A., Hughes, D., Kampmann, C., Beck, M. Natural history of Fabry disease in females in the Fabry Outcome Survey. *J Med Genet.* 2005 (published online October 14, 2005).

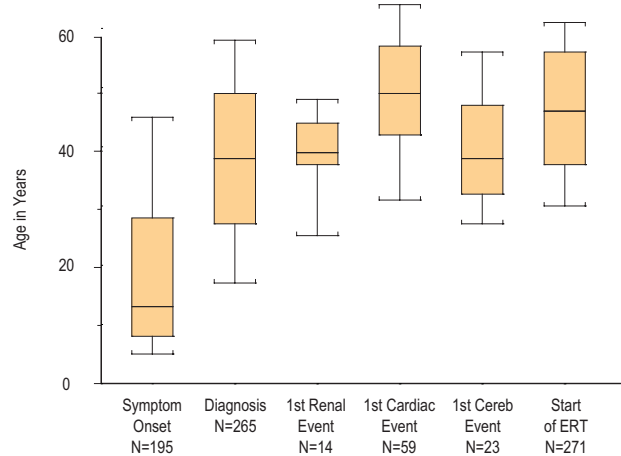
²Gupta, S, Ries, M., Kotsopoulos, S., Schiffmann, R. The relationship of vascular glycolipid storage to clinical manifestations of Fabry disease: a cross-sectional study of a large cohort of clinically affected heterozygous women. *Medicine* 2005, 84:261-268.

Figure 9
Age at symptom onset, diagnosis, first event, and start of ERT

9a. Adult males



9b. Adult females



Data shown represent natural history data (i.e., prior to the start of ERT) in 706 adult male and 271 adult female patients who eventually received ERT. Note that dates of symptom onset diagnosis were not available for all patients.

Analysis of data from the Fabry Registry shows that female patients self-report depression at a considerably higher rate than do male patients (31% in females versus 21% in males, see Figure 10). Depression is also more frequently reported by females than by males in the general population, and it cannot be concluded that these data reflect true differences in the effects of Fabry disease in female versus male patients. Nevertheless, depression clearly affects a patient's quality of life, and it will be valuable to continue to monitor the percentage of patients of each gender that experience depression. Depression is frequently under-reported and is something that needs to be specifically elicited during the medical history.

Characterization of Natural Course of Fabry Disease Prior to ERT

Analysis of data within the Fabry Registry has permitted a better characterization of the severity of Fabry disease in patients who undergo ERT as compared to those who do not. Figure 11a shows qualitative measures of disease severity in patients who have not undergone ERT (never on ERT), as compared to patients who initiated ERT (pre-ERT, or just prior to treatment). Patients who began ERT reported more severe symptoms in all categories, including heat and cold intolerance, abnormal sweating, and various pain measures prior to the initiation of their therapy, than did those who have remained untreated. However, it is important to note that a considerable proportion of the patients who did not undergo ERT (never on ERT), also reported these qualitative symptoms (36% reported heat intolerance, 35% reported abnormal sweating, and 40% reported chronic pain). Thus, even patients who do not undergo ERT experience a considerable spectrum of symptoms of Fabry disease.

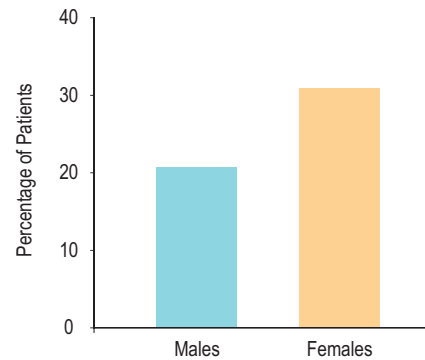
A similar picture emerges when the percentage of patients who experience cardiac, renal, or cerebrovascular events (as defined in Box 1) is analyzed. Figure 11b shows that a higher percentage of patients who eventually began ERT (pre-ERT) experienced one or more clinical events. However, 3 to 10% of patients who did not undergo ERT (never on ERT) still experienced cardiac, renal, or cerebrovascular events.

Progress Towards Stratifying Patients into Subpopulations to Analyze ERT Outcomes and to Predict Disease Severity

Findings from the Fabry Registry demonstrate that the severity of proteinuria can vary across different cohorts of Fabry patients, depending on gender, age, and other variables. Therefore, it is useful to stratify patients into various subpopulations in order to make practical predictions about disease severity. Figure 12 shows an example of this approach. The relationship between proteinuria and estimated glomerular filtration rate (GFR) in male and female patients is shown in Figure 12a and 12b, respectively. These data show that proteinuria is a good indicator of renal dysfunction in both genders. It can also be seen that more males than females exhibited estimated GFR values below 60 mL/min/1.73 m², indicating that male patients have more impaired renal function than female patients. To further stratify patients into subpopulations, patients were separated by gender, age (≥ 40), level of proteinuria (>300 mg protein per 24 hr period), the presence of hypertension, and stage of chronic kidney disease, where a glomerular filtration rate (GFR) > 60 corresponds to Stages 1 and 2 of kidney disease and GFR < 60 corresponds to Stages 3, 4, and 5, as shown in Figures 12c and 12d.

Figure 10

Differences between males and females in self-reported depression



Data are from adult natural history patients (prior to ERT) and are based only on patients who had depression assessments (unknown responses are not included). Among these patients, 27 of 130 males and 25 of 81 females who had depression assessments reported depression.

Figure 11a

Qualitative measures of disease severity: percentage of Fabry patients with various symptoms in their natural history by ERT status

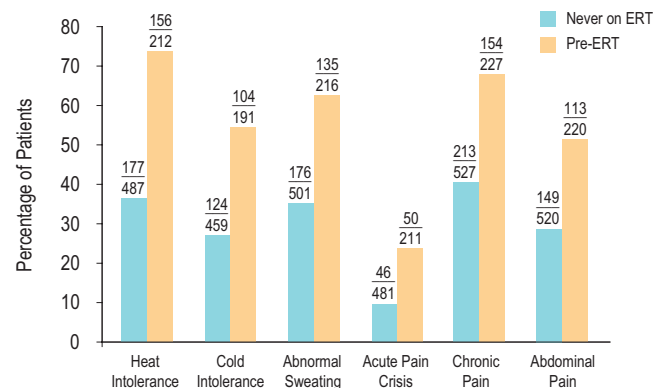
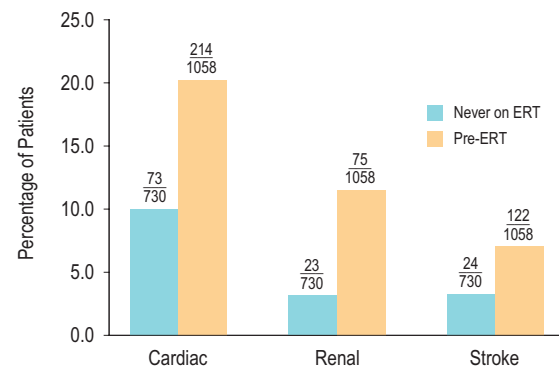


Figure 11b

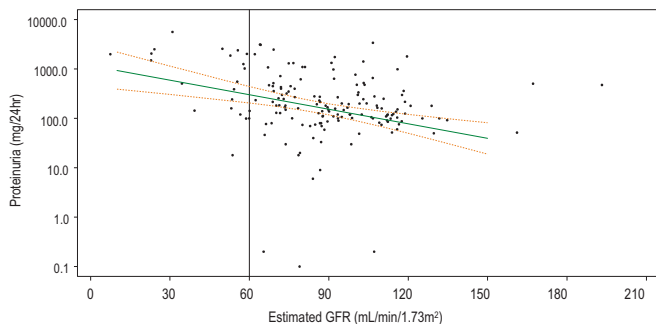
Percentage of patients in Fabry Registry with clinical events in their natural history by ERT status



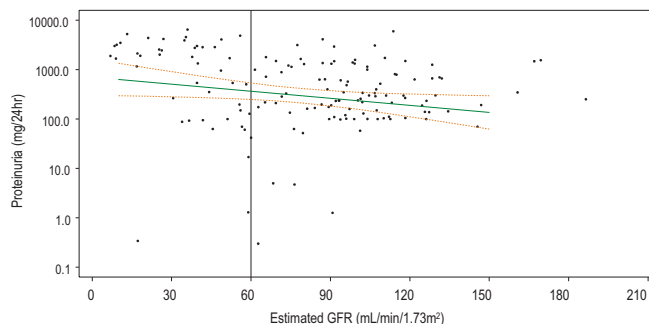
The bars show the percentage of patients who experienced these events (n) relative to the total number of patients in each group (N), as indicated by the numbers shown above each bar (n/N). Data shown are as of December 31st, 2005.

Figure 12
Estimated GFR versus proteinuria in male and female Fabry patients and stratification of patients by age, proteinuria levels, hypertension status, and gender

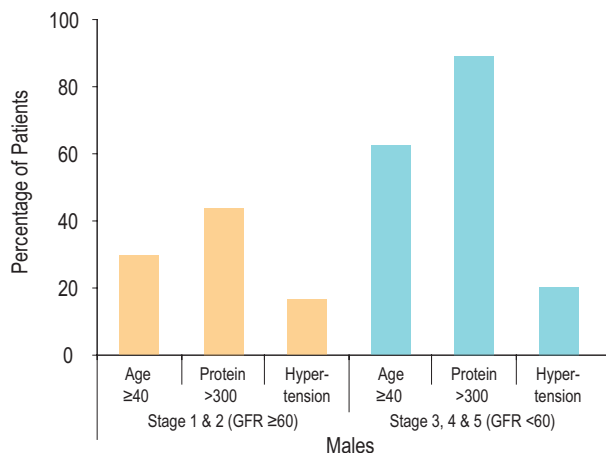
a. Estimated GFR versus proteinuria in males



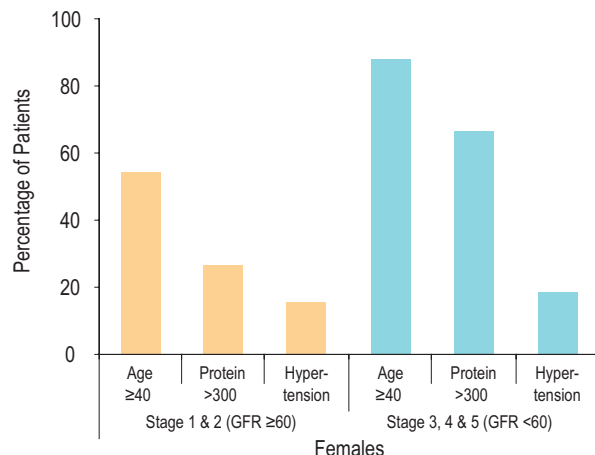
b. Estimated GFR versus proteinuria in females



c. Percentage of male Fabry patients in age, proteinuria, and hypertension categories by GFR stage



d. Percentage of female Fabry patients in age, proteinuria, and hypertension categories by GFR stage



Data are from adult natural history patients (prior to ERT). GFR = glomerular filtration rate. In Panels A and B, the green lines represent the least squares regression and the orange lines indicate 95% confidence bands around the least squares regression lines. The most recent estimated GFR and proteinuria values in the natural history are displayed. Proteinuria values are the closest proteinuria values within a window of ± 3 months of the estimated GFR value. In Panels C and D, Protein > 300 indicates >300 mg proteinuria in a 24-hr period.

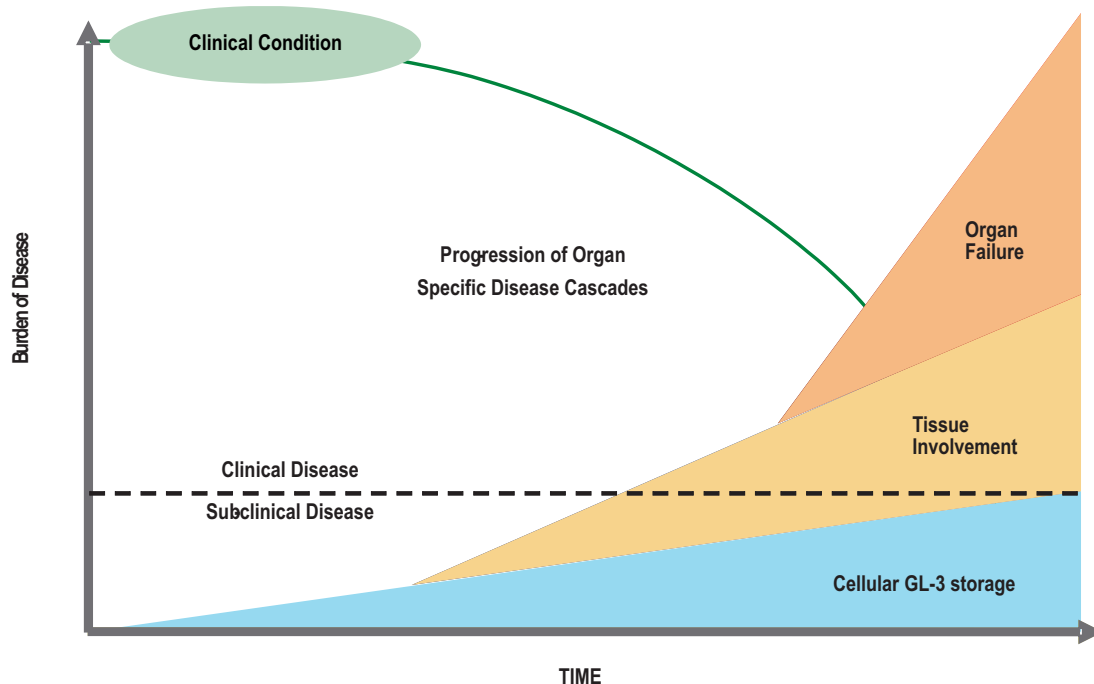
From these figures, it can be seen that as kidney disease progresses, a higher percentage of patients exhibit proteinuria and a higher percentage of patients are aged 40 or older. Also, males progress to severe kidney disease more quickly than females; 38% of males in Stage 3-5 kidney disease are less than 40 years old, whereas only 12% of female patients in Stage 3-5 kidney disease are less than 40 years old.

In addition, a higher percentage of males in Stages 1-2 exhibit proteinuria (44%), as compared to females in Stages 1-2 (27%). In both genders, the percentage of patients with hypertension was slightly higher in patients with more advanced stages of kidney disease, but far less than usually seen in other patients with renal disease. Further development of this type of stratification approach will facilitate assessing the severity of Fabry disease in individual patients and analyzing ERT outcomes.

Development of a Model for Fabry Disease Progression

One of the most valuable aspects of a registry is to delineate the natural course of a disease. Analysis of data from the Fabry Registry has led to the development of an organ-specific model of disease progression, as shown in Figure 13. Fabry disease is a genetic disorder that becomes progressively more severe over a period of years or decades and affects multiple organ systems. The primary disease process is driven by the deficiency of alpha-galactosidase A, leading to excessive lysosomal storage of globotriaosylceramide (GL-3), which initially causes cellular dysfunction and subclinical disease. As the disease progresses, secondary disease processes such as tissue responses to cellular signals lead to organ dysfunction or damage. Early symptoms of disease progression reflect involvement of the peripheral and autonomic nervous systems and manifest as neuropathic pain, gastrointestinal symptoms, and hypohidrosis. Ultimately, disease progression results in end organ dysfunction and failure. These late complications involve the cerebrovascular system, the heart, and kidney. These late complications are the major drivers of morbidity and mortality in the disease. The progression of Fabry disease is organ-specific and does not clearly follow a typical pattern or sequence in individual patients or cohorts of patients. This model highlights the importance of monitoring patients in each organ compartment, and of detecting progression before irreversible organ damage has occurred.

Figure 13
Schematic model of the progression of Fabry disease



Summary

Through 2005, the Fabry Registry has accrued clinical assessment and outcomes data from 1863 patients. The major points summarized in RADAR 2005 are:

- Increased enrollment of female and pediatric patients has helped facilitate a better understanding of the natural course of Fabry disease in these subpopulations.
- Extensive data are now available for patients that have received ERT treatment; more data on patients not undergoing ERT will be useful for further longitudinal analyses.
- Female patients are diagnosed at a later age than male patients, although among patients that eventually undergo ERT, females experience their first cerebrovascular and renal events at similar ages as male patients.
- Female patients self-report depression at higher rates than male patients.
- The symptoms of Fabry disease are more severe in patients who eventually go on to receive ERT, but patients who do not receive ERT still experience a significant disease burden.
- As Fabry disease progresses, accumulation of GL-3 increasingly affects the peripheral and autonomic nervous systems, the cerebrovascular system, the kidneys, and the heart.
- Further analysis of data from the Fabry Registry, particularly in subcategories of patients, will enable delineation of specific parameters that are most useful for assessing disease severity and predicting disease progression.

Goals for 2006

Improve the Collection of Cardiac Assessment Data

Cardiac dysfunction is a common and serious complication of Fabry disease. As Fabry disease progresses, increasing levels of GL-3 accumulate within the heart, leading to hypertrophy, fibrosis, and, in some cases, myocardial infarction. Furthermore, left ventricular hypertrophy can occur before any symptoms of Fabry disease are noticed. Collection of higher quality cardiac data in the Fabry Registry will enable physicians to better identify the early stages of cardiac decline in patients with Fabry disease, before irreversible cardiac damage or sudden death has occurred. The prevalence of life-threatening arrhythmias may be underappreciated.

Identify Clinically Defined Subpopulations within the Fabry Registry to Characterize and Report Longitudinal Outcomes

The Fabry Registry has collected an extensive amount of data over the past 5 years. However, the overall population that participates in the Fabry Registry is highly diverse, in terms of age, gender, state of disease progression, and other factors. As we identify prognostic factors in the disease, it will be useful to segregate patients into cohorts in order to more accurately describe disease severity and to collect more longitudinal data. This will enable us to make clinically useful predictions about the course of disease progression in individual patients.

Publish the Natural Course of Disease in Fabry Registry Patients

Natural history data from the Fabry Registry will continue to be published in 2006. Two manuscripts that focus on the pediatric and female subpopulations are currently being developed. These manuscripts will create awareness of Fabry disease in pediatric and female patients. Participating physicians will also present findings from the analysis of Fabry Registry data at various international meetings in 2006.

Questions and Adverse Event Reporting

Any queries about agalsidase beta (Fabryzyme®) or adverse events associated with its administration should be reported promptly to Genzyme Pharmacovigilance/Medical Affairs: within the United States, 800-745-4447 (option 2); within Europe, +31-35-699-1431; outside the United States and Europe, +617-252-7500 (option 2). Refer to the Safety section of the Fabry Registry Protocol for specific reporting guidelines.

Appendix 1

European and North American Boards of Advisors

North American Board of Advisors

Advisor	Affiliation	Location
William Wilcox, M.D., Ph.D. (Chair)	Cedars Sinai Medical Center	Los Angeles, CA
Maryam Banikazemi*, M.D.	Mount Sinai School of Medicine	New York, NY
John Barranger, M.D., Ph.D.	University of Pittsburgh Medical Center	Pittsburgh, PA
Joel Charrow, M.D.	Children's Memorial Hospital	Chicago, IL
Lorne Clarke, M.D.	British Columbia Research Institute for Child & Family Health	Vancouver, BC
Christine Eng, M.D.	Baylor College of Medicine	Houston, TX
Robert Hopkin, M.D.	Cincinnati Children's Hospital Medical Center	Cincinnati, OH
Gregory M. Pastores, M.D.	New York University School of Medicine	New York, NY
Laura J. Pinderski, M.D.	University of California, San Diego	San Diego, CA
C. Ronald Scott, M.D.	University of Washington	Seattle, WA
Katherine Sims, M.D.	Massachusetts General Hospital	Boston, MA
David G. Warnock, M.D.	University of Alabama	Birmingham, AL

European Board of Advisors

Advisor	Affiliation	Location
Prof. Dr. J Bultas	Charles University	Prague, Czech Republic
Dr. U. Feldt-Rasmussen	Rigshospitalet	Copenhagen, Denmark
Dr. D. P. Germain	Hôpital Européen Georges Pompidou	Paris, France
Dr. N. Guffon	Hôpital Debrousse	Lyon, France
Dr. P. Lee	National Hospital for Neurology and Neurosurgery	London, United Kingdom
Dr. N. Leech#	Royal Victoria Infirmary	Newcastle, United Kingdom
Dr. J-E. Mansson	Shalgren's University Hospital	Molndal, Sweden
Dr. J.P. Oliveira	Médica Faculdade de Medicina	Porto, Portugal
Dr. A. Ortiz	Fundacion Jiménez Díaz	Madrid, Spain
Dr. M. Spada	Hospital Azienda Ospedaliera Regina, Margherita Day Hospital	Torino, Italy
Prof. Dr. A. Tylki-Szymanska	Children's Memorial Helath Institute	Warsaw, Poland
Dr. A. Vedder	Academisch Medisch Centrum	Amsterdam, The Netherlands
Prof. Dr. C. Wanner	Medizinische Universitätsklinik	Würzburg, Germany

International Board of Advisors

Advisor	Affiliation	Location
Christine Eng, M.D. (North American Representative)	Baylor College of Medicine	Houston, TX
Dr. D.P. Germain (European Representative)	Hôpital Européen Georges Pompidou	Paris, France
Dr. Ana Maria Martins, M.D., Ph.D. (Latin American Representative)	Inatos do Metabolismo - CREIM	São Paulo, Brazil

* Note that Dr. Maryam Banikazemi was at the Mt. Sinai School of Medicine during the year 2005 ; however, she has since moved to the New York University School of Medicine.

Note that Dr. N. Leech served on the European Board of Advisors during the period covered by this report (1st January, 2005 through 31st December, 2005). However, she has since resigned from the European Board of Advisors.

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
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	● ^B	● ^B	●	●	● ^B	●
Renal - Dialysis, Transplant	●	●	●	●		●
Skin	●	●		●		
Respiratory - Spirometry	●	●	●	●		●
Ophthalmology	●	●	●		●	●
Vital Signs and Laboratory Tests						
Height/Weight	●	●	●	●		●
Blood Pressure	●	●	●	●		●
Serum Creatinine and BUN	●	●	●	●		●
Urinary Protein Excretion ^C	●	●	●	●		●
GFR ^D	●	●	●	●		●
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) ^E						
SF-36 [®] Health Survey	●	●		●		●
Brief Pain Inventory (Short Form)	●	●		●		●
PedsQL [™] 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 3

2005 Presentations of Fabry Registry Data

2005 Conference	Abstract Citation
American College of Medical Genetics	Clarke, L.A., Barranger, J., Hopkin, R., Banikazemi, M., Charrow, J., Eng, C.M., Pastores, G., Scott, C.R., Sims, K., Warnock, D., Wilcox, W. Fabry disease presenting in the pediatric age group: clinical and ethical concerns.
American Society of Human Genetics	Eng, C.M., Wilcox, W.R., Waldek, S., Linhorst, G., Germain, D., Charrow, J., Scott, C.R., Breunig, F., Banikazemi, M. Fabry disease: Early clinical manifestations and age at clinical events in a cohort of 1214 males and females.
European Society of Cardiology	Strotmann, J. Early intervention in Fabry disease - cardiac impact.
6 th European Round Table on Fabry Disease Meeting	Hayoz, D. Early intervention in Fabry disease - can we modify stroke risk?
6 th European Round Table on Fabry Disease Meeting	Ries, M., Gupta, S., Moore, D.F., Sachdev, V., Quirk, J.M., Murray, G.J., Rosing, D.R., Robinson, C., Schaefer, E., Gal, A., Dambrosia, J.M., Garman, S.C., Brady, R.O., Schiffman, R. Quantitative assessment of Fabry disease in children.
6 th European Round Table on Fabry Disease Meeting	Strotmann, J. Early intervention in Fabry disease - cardiac impact.
6 th European Round Table on Fabry Disease Meeting	Waldek, S. Early intervention in Fabry disease - preserving renal function.
6 th European Round Table on Fabry Disease Meeting	Wanner, C. Fabry is a progressive, multi-systemic disease.
Latin American Lysosomal Storage Disease Symposium	Martins, A.M., Kyosen, S.O., Gomes, J.G., Norato, D., Sobral Neto, J.O., Biagini, G., Azevedo, D.J., Aranda, P.C., Sousa, A.F., Bastos, R.V. The FABRY Registry: a comparative profile of reported symptom onset among Brazilian, Latin American, European and North American patients.
Pediatric Academic Societies	Clarke, L.A., Barranger, J., Hopkin, R., Banikazemi, M., Charrow, J., Eng, C.M., Pastores, G., Scott, C.R., Sims, K., Warnock, D., Wilcox, W. Fabry disease presenting in the pediatric age group: clinical and ethical concerns.
Society for the Study of Inborn Errors of Metabolism	Waldek, S. Germain, D. Burden of Fabry disease in females and the importance of early therapy: an analysis of Fabry registry data.

Fabry Data Request Form

Requested By: _____ **Date:** ____/____/____
Phone Number: _____ **Fax Number:** _____
Email Address: _____

FABRY REGISTRY

Tracking #: _____
(For Internal purposes only)

Fabry Registry Data Request Form

To assist with your data request, please see "Data Available for Request" on page 2 for a summary of key patient data collected for the Fabry Registry. If a data request pertains to a specific patient comparison, please list all relevant patient information to match. (e.g., gender, age, patient type, etc.)

Hypothesis or Question: _____

Purpose *(Please check one):*
 Abstract *(specify meeting and submission deadline)* _____
 Manuscript Clinical Care/Patient Education Site Status Report
 Presentation/Lecture *(specify audience and submission deadline)* _____
 Other *(please be specific)* _____

Request: _____

Please indicate the patient population for your data request (check desired selection criteria below).

Demographics Information
 Age: All < 18 years ≥ 18 years
 Gender: Both Male Female
 If Other, Specify: _____

Enzyme Replacement Therapy Information
 ERT Status: All patients Patients on ERT Patients not on ERT
 If Other, Specify: _____

Renal Information
 Kidney Status: Exclude Chronic Dialysis Patients (On dialysis > 40 days) Exclude Transplant Patients
 If Other, Specify: _____

United States and Non-Europe:
 Fax to: 617-374-7339
 Tel: 1-800-745-4447 x15500
 Email: help@fabryregistry.com

Europe:
 Fax to: +31-35-694-8688
 Tel: +31-35-699-1232
 Email: fabryregistryeurope@genzyme.com

Date Received: ____/____/____ Date Completed: ____/____/____

For Internal Use Only

Data Available for Request

Demography
 Gender
 Date of Birth (Age)
 Genotype
 Ethnicity
 Family Members
 • Screened
 • Diagnosed

Fabry Disease Medical History
 Neurology
 Cerebrovascular
 Renal
 Cardiovascular
 Ophthalmology
 Respiratory
 Gastroenterology
 Skin
 Smoking
 Additional Medical History

Vital Signs and Laboratory Tests
 Height, Weight, BP
 Cholesterol, Lipids
 Serum Creatinine
 Urinary Creatinine
 BUN
 Urinary Protein
 Microalbumin
 24 HR Urinary Protein
 Plasma GL-3
 GFR and Method

Enzyme Replacement Therapy
 Date of First Infusion
 Enzyme, Dose, Frequency and Infusion Time
 Reason for Dose Change or Treatment Interruption

Clinical Follow-Up Assessments and Events / Exams

Neurology
 Sweating
 Heat/Cold Tolerance
 Acute/Chronic Pain and Therapy
 Clinical Depression

Ophthalmology
 Ophthalmology Exam
 Visual Acuity and Slit Lamp

Respiratory
 Pulmonary Involvement
 Spirometry Results

Gastroenterology
 Abdominal Pain
 Diarrhea

Skin
 Angiokeratoma

Smoking
 Status and History

Additional Medical History
 Disease, Description, Status, Onset and Resolution Date

Quality of Life
 The SF-36[®] Health Survey

Pain
 Brief Pain Inventory / Short Form

Renal
 Proteinuria
 Dialysis and Type
 Transplant and Date Received

Cardiovascular
 ECHO / ECG Testing
 Hypertension
 Cardiovascular Event Type
 • Myocardial Infarction
 • Significant Cardiac Procedure
 • Arrhythmia
 • Angina Pectoris
 • Congestive Heart Failure
 Medication Required