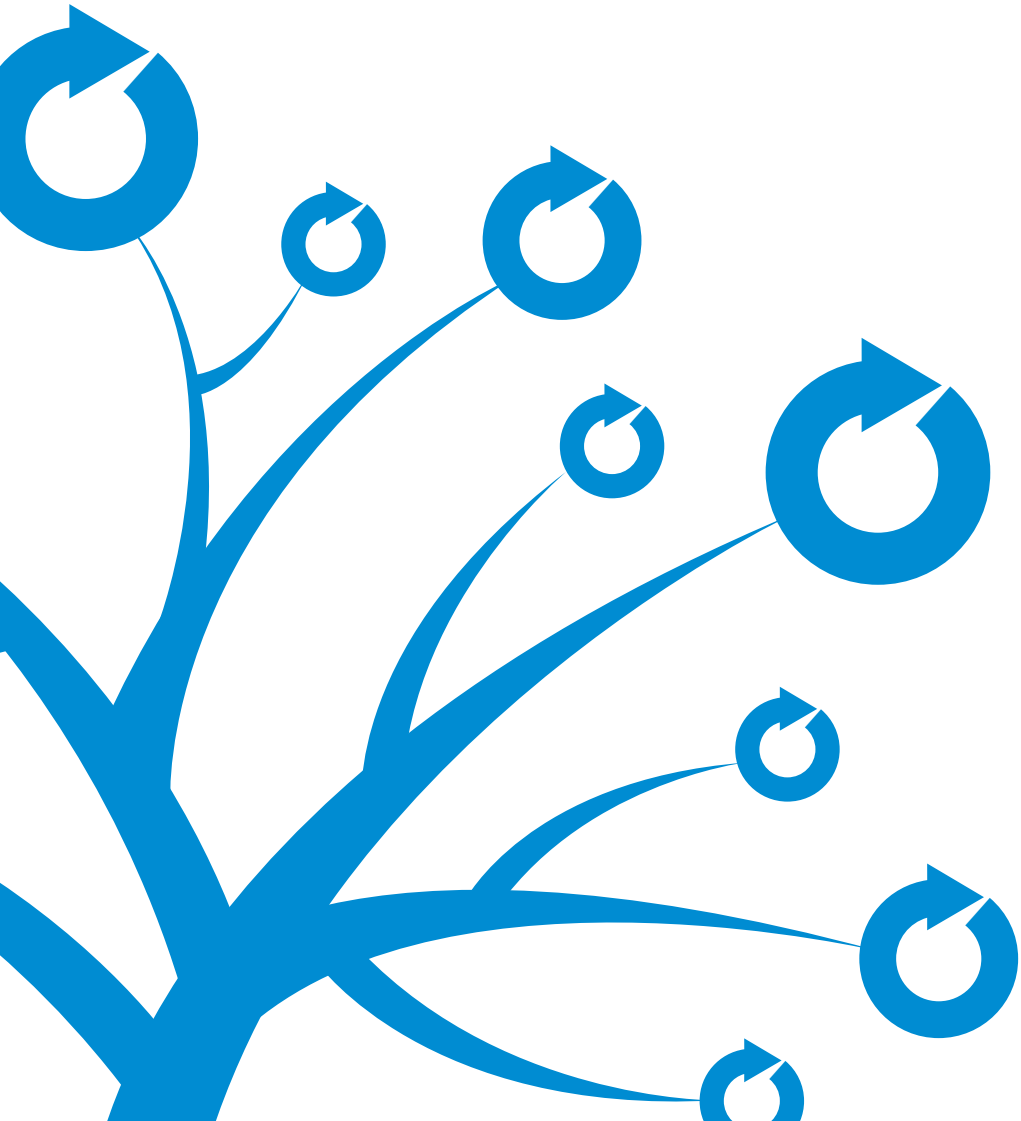
Fabry Outcome Survey

Annual Report 2016

Reporting Period: 17-04-2001 to 05-01-2017



FOS
FABRY OUTCOME SURVEY

This report has been prepared by Shire Outcome Surveys,
on behalf of the FOS Steering Committee

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Contents

Data in this report are from the 5 January 2017 datacut.

FOS management, administration and infrastructure are funded by Shire.
Data collection and analysis in FOS are also supported by Shire.
Data review and analysis are conducted by Shire under the direction of the clinical expert members of the FOS Steering Committee and Task Forces. Meetings of the FOS Steering Committee and Task Forces are organized and supported by Shire.

All publications containing FOS data are prepared in compliance with the applicable Shire policies and procedures.

FOS
FABRY OUTCOME SURVEY

Outcome Survey

Annual Report 2016

Executive summary

Welcome to the 2016 Fabry Outcome Survey (FOS) Annual Report, which provides an overview of FOS as of 5 January 2017.

FOS is a large, global, multicentre, observational registry, sponsored by Shire, for patients with Fabry disease. The registry was established in 2001 with the aim of collecting real-world data on the long-term safety and effectiveness of enzyme replacement therapy (ERT) with agalsidase alfa and the natural history of the disease. This report includes details of the FOS Steering Committee as well as a summary of patient demographics and the publications that have been developed on the basis of data collected in the registry.

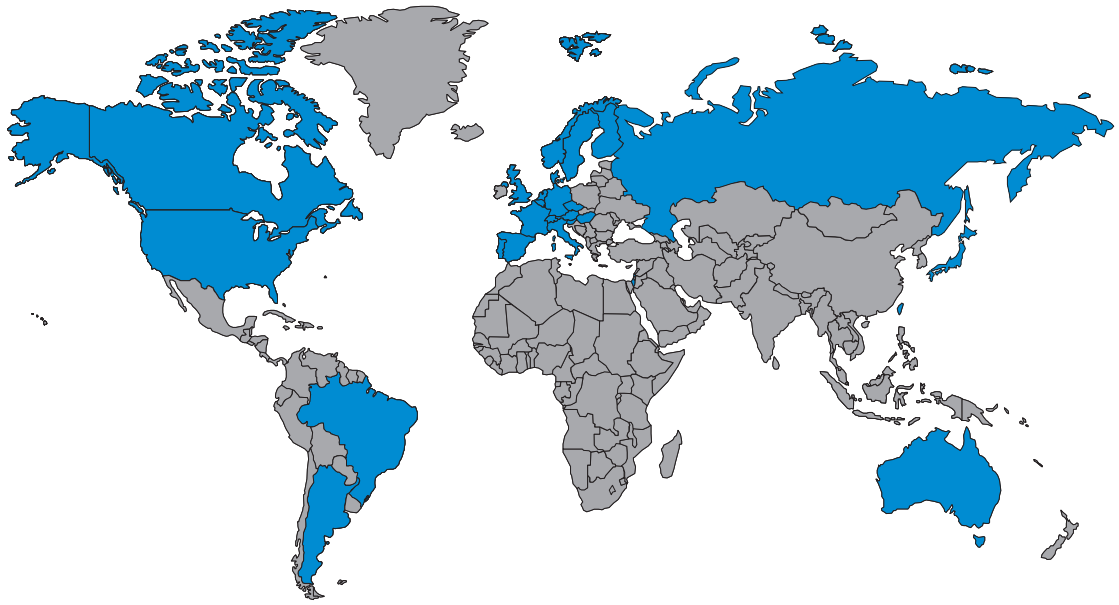

Figure 1. Map highlighting (in blue) the countries in which patients with Fabry disease are enrolled in FOS.

Key highlights from FOS, as of January 2017

- A total of 3112 patients from 133 clinics in 24 countries have been enrolled in FOS. Just over half of all patients are female (56%), and the proportion of children (defined as < 18 years old at FOS entry) is 12%. More than 60% of patients have received treatment with agalsidase alfa at some point during the management of their disease.
- The key contributions of the registry during its first 15 years were detailed in a review in 2016 (Giugliani R *et al.* A 15-year perspective of the Fabry Outcome Survey. *Journal of Inborn Errors of Metabolism and Screening* 2016; 4: 1–12).
- Three other manuscripts based on FOS data were published in peer-reviewed journals in 2016, and by June 2017 the total number of FOS publications had increased to 53.
- In 2016, six posters based on information collected in FOS were presented by participating physicians at two international scientific conferences in Europe and North America.

Shire would like to take this opportunity to thank all of the patients and their families, and the physicians and their staff, who have participated in FOS and contributed data to the registry.

Background to the FOS registry

Registry design

FOS is designed to collect information on various aspects of Fabry disease, based on data obtained during routine patient visits and assessments. The registry is open to individuals with confirmed diagnosis of Fabry disease. At its initiation, FOS was set up as a drug registry (for patients currently untreated or treated with agalsidase alfa, or previously treated with any ERT), but at the start of 2017 it became a disease registry, and it is open to all patients with Fabry disease irrespective of their treatment in countries where Protocol Amendment 4 has been approved by institutional review boards.

Registry objectives

A broad range of disease- and treatment-related information is captured in the registry with the overall aim of collecting and disseminating information about the long-term course of Fabry disease. The objectives of the registry are to: monitor the long-term safety and effectiveness of agalsidase alfa; characterize the population of patients with Fabry disease and provide data on the clinical course of the disease in untreated patients and those receiving approved therapies; and enhance the understanding of the natural history of the disease, including intra- and inter-familial variation. Patients can also complete questionnaires on issues such as health-related quality of life. It is hoped that the data collected will help to form a basis for further development of clinical management recommendations for the disease.

Achievements of FOS

The data recorded in FOS can be used to research specific topics of interest within the field of Fabry disease, such as the effect of treatment on particular organ systems or in specific populations such as children. Since the registry's initiation more than 15 years ago, publications based on FOS data have helped to establish disease severity scores, describe disease manifestations in different patient populations, and report the long-term effects of ERT with agalsidase alfa on kidney and heart function, mortality and morbidity. The continued collection of data in FOS should help to ensure that further important contributions can be made to the knowledge of this rare disease.

FOS Scientific Boards

The FOS registry is committed to increasing the knowledge of Fabry disease and its treatment. With this in mind, FOS scientific boards enable the smooth operation of the registry and ensure the scientific accuracy and appropriateness of all research concepts and proposals for data analyses and publications. The scientific boards comprise the FOS Steering Committee (SC), the Shire FOS team and the FOS Task Forces.

The FOS SC, consisting of 10 FOS experts in the area of Fabry disease, plus representatives of Shire, provides overall direction for the FOS registry and represents FOS at scientific meetings. As well as providing input on operational changes, members of the SC review data reports, endorse proposed data analyses and topics for publication, and oversee the functioning and activities of the Task Forces.

The SC met most recently at the Lysosomal Disease Network (LDN) WORLD Symposium in February 2017 in San Diego, CA, USA. Currently, members of the SC are investigating the factors influencing treatment decisions in patients in FOS and their alignment with European criteria for treatment initiation.

The FOS Steering Committee

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Medical genetics

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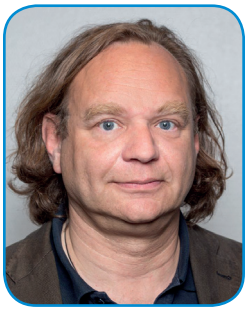

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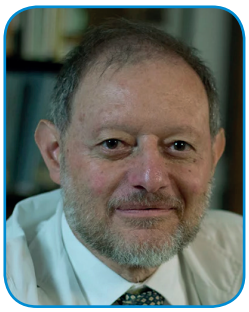

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Global Medical Franchise Lead
Fabry/Gaucher/MLD
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FOS Task Forces

There are currently five FOS Task Forces, each relating to an organ system manifestation or patient subgroup: Cardiac, Female, Neurology (created in 2016), Paediatric and Renal. Task Force members are physicians or researchers with particular expertise and interest in the relevant area, and they are responsible for all activities related to conducting and publishing in-depth analyses of FOS data in their field of interest.

Update on demographic data as reported in FOS

Patient enrolment

As of January 2017, there were 3112 patients in FOS. Compared with January 2016, the number of patients increased by 6%, which is similar to the increases in rates of enrolment seen in recent years (Figure 2).

As in previous years, the number of females enrolled in FOS exceeds the number of males: 1749 (56%) were female and 1363 (44%) were male. The number of children (defined as < 18 years old at FOS entry; n = 382) also increased compared with January 2016, and the proportion of paediatric patients (12%) remains the same as in previous years.

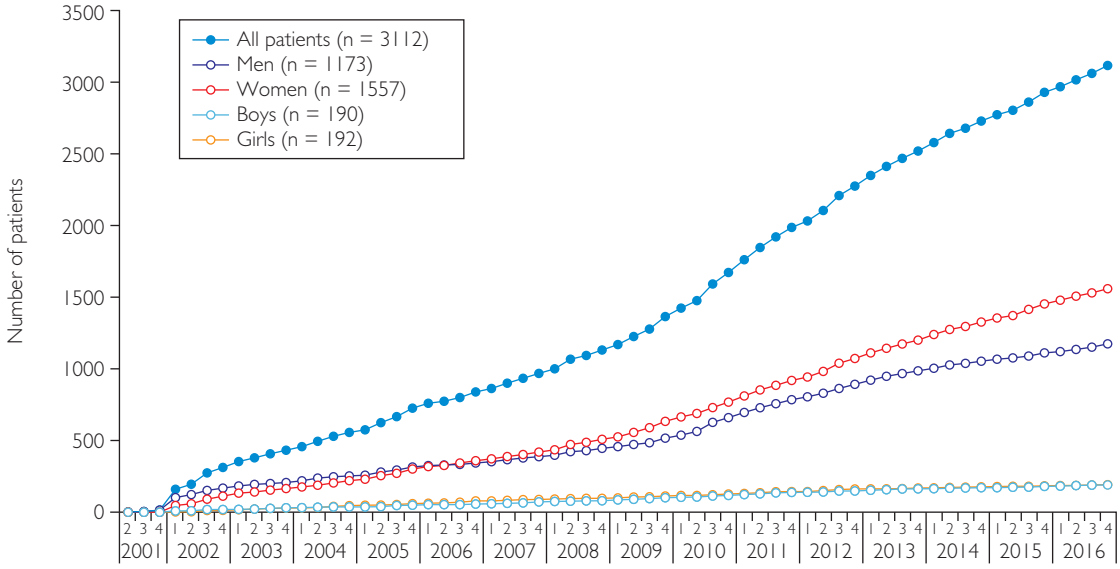

Figure 2. Cumulative number of patients since 2001 (n = 3112). Men and women defined as patients ≥ 18 years old at FOS entry; boys and girls defined as patients < 18 years old at FOS entry.

Global reach of FOS

As of January 2017, patients were enrolled at 133 FOS centres in 24 countries (Figure 3), and during 2016, patients were enrolled for the first time in Israel and Russia. Most patients have been enrolled in Europe, Asia or North America (62%, 20% and 10%, respectively), with large proportions of patients in Germany, Japan, the UK and Canada (18%, 15%, 13% and 9%, respectively; Figure 4).

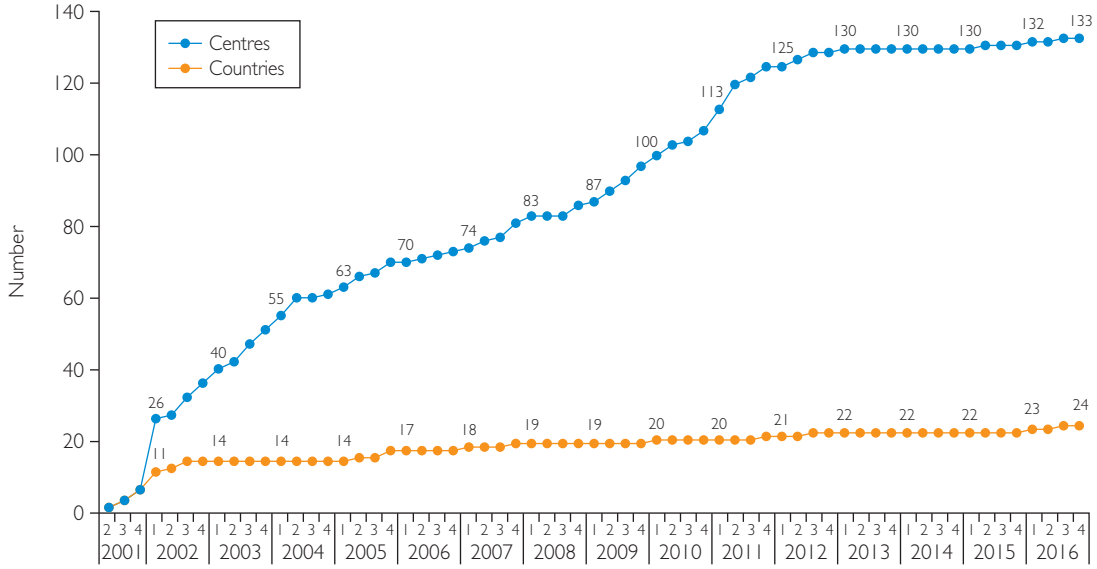

Figure 3. Cumulative number of centres (n = 133) and countries (n = 24) in which patients have been enrolled since 2001.

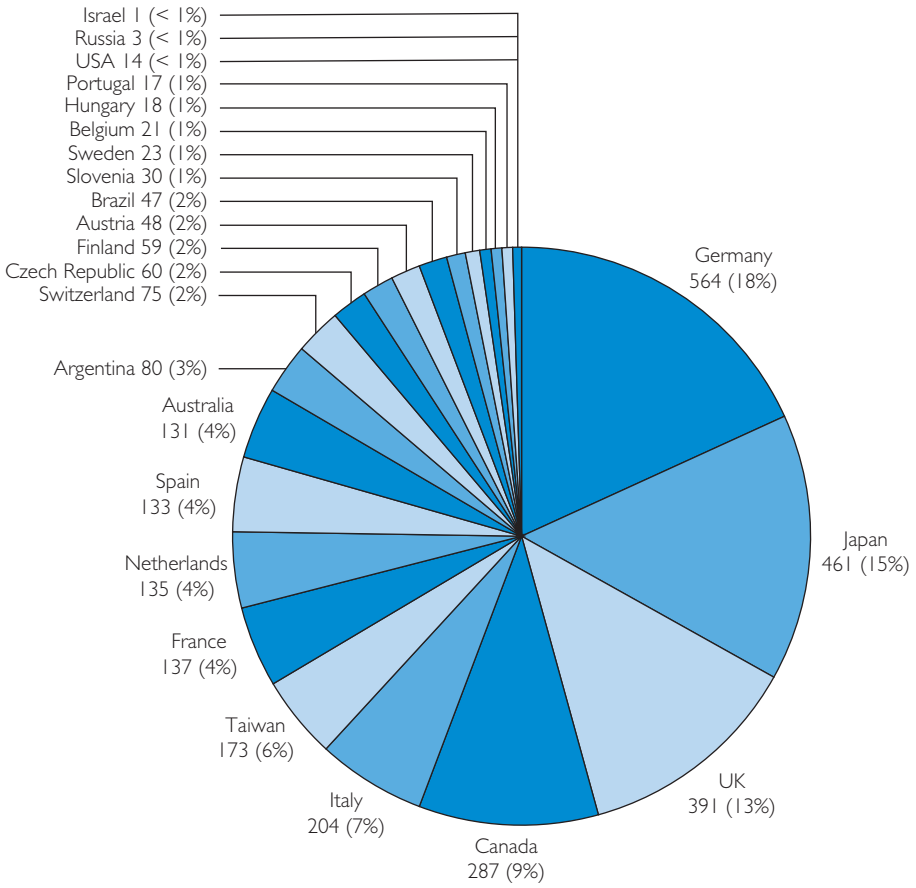

Figure 4. Geographical distribution of patients (n = 3112). The number and proportion (%) of patients enrolled are given for each country.

Symptom onset and diagnosis

First symptoms of Fabry disease were reported earlier in males (median age [Q1–Q3]: 11.0 [7.0–26.0] years) than in females (19.0 [10.0–38.0] years) (Figure 5). The age at diagnosis was also earlier in males (29.0 [15.0–44.0] years) than in females (36.0 [22.0–50.0] years). In patients with data available for both age at symptom onset and age at diagnosis, the delay between onset of symptoms and diagnosis was about the same in males and females (6.0 [0.3–20.0] years and 6.0 [0.0–20.0] years, respectively).

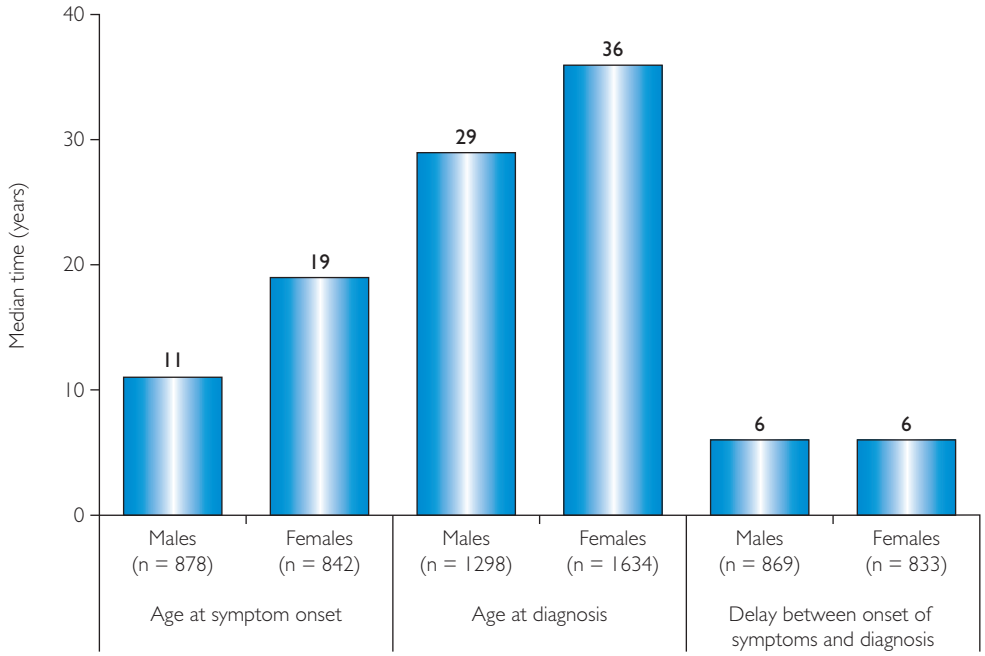

Figure 5. Median age at symptom onset and at diagnosis and median delay between onset of symptoms and diagnosis for male and females.

Patients receiving agalsidase alfa

Of the 3112 patients in FOS, 1975 (63%) had received one or more doses of enzyme replacement therapy (ERT) with agalsidase alfa (at any point in time). As well as untreated patients and those receiving agalsidase alfa, the FOS registry has started to enrol those receiving Fabry treatment other than agalsidase alfa to reflect that it is becoming a disease registry and to ensure that FOS reflects the wider population of individuals with Fabry disease.

The median duration of treatment was 6.9 (5.5–11.3) years. The proportion of men who had received treatment was greater than that of women (82% vs 52%, respectively). In children, 75% of boys and 32% of girls had started agalsidase alfa treatment (age range, 1.9–18.0 years; Figure 6).*

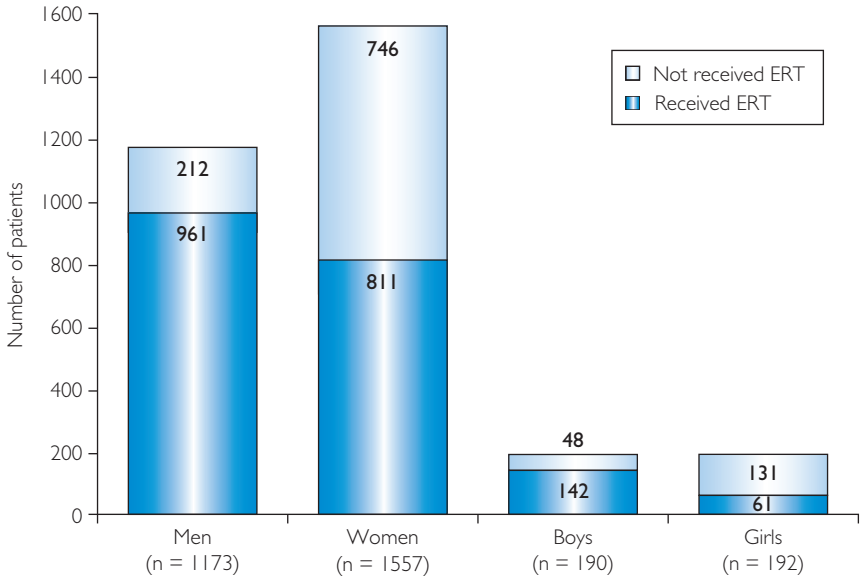

Figure 6. Number of patients who had received ERT with agalsidase alfa (at any point in time) compared with those who had not.

*Summary of Product Characteristics for agalsidase alfa is available here: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000369/WC500053612.pdf. Accessed March 2017.

Home therapy with agalsidase alfa

As of January 2017, 823 patients had received home therapy with agalsidase alfa, equating to 42% of treated patients. The median duration of treatment in these patients was 8.6 (6.3–12.5) years. Most individuals receiving home therapy were from Europe (77%) (Figure 7). The largest numbers of treated patients receiving home therapy were recorded in the UK, Germany and Canada (n = 211, 187 and 127, respectively).

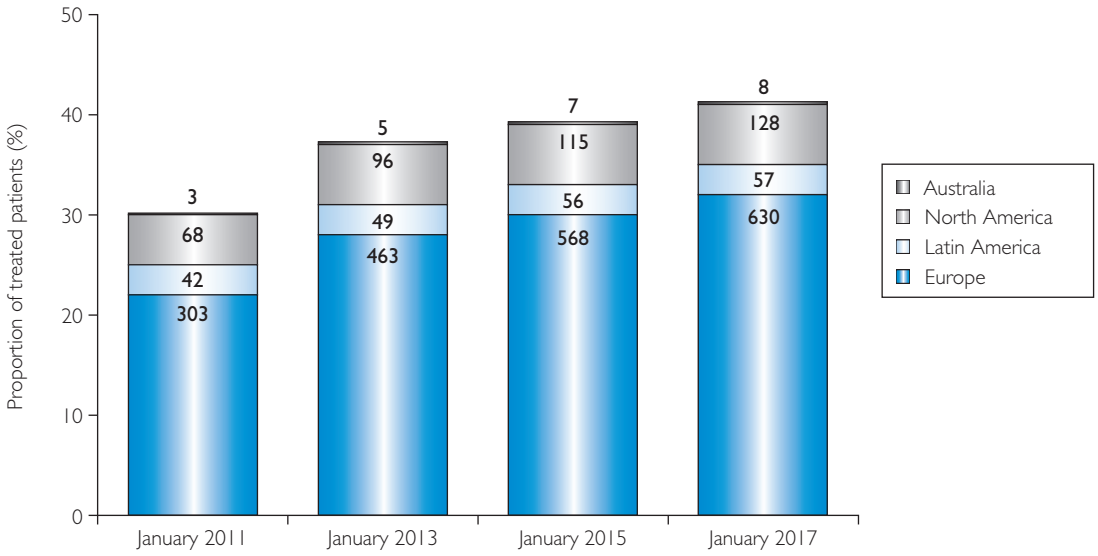

Figure 7. Proportions of treated patients who have received home therapy with agalsidase alfa in recent years. Patients were considered to have received home therapy if at least one infusion was recorded as 'home infusion' in the FOS database; no patients from Asia (Japan and Taiwan) had received home therapy with agalsidase alfa. The numbers of patients who had received therapy with agalsidase alfa as of January 2011, 2013, 2015 and 2017 were 1355, 1683, 1887 and 1975, respectively.

FOS publications and congress activity

The FOS registry disseminates the results of data analyses in peer-reviewed journals and at congresses. Since the initiation of the registry in 2001, FOS publications have covered various topics of interest in Fabry disease, including measures of disease severity, signs and symptoms in specific populations and the long-term effects of ERT on kidney and heart function, mortality and morbidity. A full list of completed FOS publications (2001–2016) can be found on pages 13–16. These articles have been cited more than 2900 times in total, providing an indication of the value of the data collected in FOS.

To mark 15 years of the FOS registry being in operation in 2016, the members of FOS SC co-authored a review article (Giugliani R *et al.* A 15-year perspective of the Fabry Outcome Survey. *Journal of Inborn Errors of Metabolism & Screening* 2016; 4: 1–12). The review detailed the key contributions of the registry, not only in describing various aspects of the natural history of Fabry disease and clinical manifestations in specific populations, but also in generating tools for diagnosis and management.

The FOS Task Forces also continue to progress analyses based on FOS data and ensure that these are published. In 2016, three original research articles were published in peer-reviewed journals. In addition, three original articles have been published so far in 2017, and there are now 53 publications based on FOS data. During 2016, six posters were presented at two international scientific conferences in Europe and North America.

Currently, several FOS manuscripts are being developed. These include analyses of data from FOS on long-term cardio-renal morbidity in patients receiving agalsidase alfa over a 10-year period, a sub-analysis of separate cerebrovascular, cardiac and renal outcomes in patients receiving agalsidase alfa, and an investigation of the impact of prompt treatment initiation after diagnosis and symptom onset on cardiac and renal outcomes. The FOS Task Forces are also developing a number of analyses that may lead to publications. It is hoped that the continued publication of data in FOS will help to ensure that further important contributions can be made to the knowledge of Fabry disease.

FOS publication archive (2001–2016)

Author	Title	Reference
Barba-Romero M-Á and Pintos-Morell G	Gender differences in the application of Spanish criteria for initiation of enzyme replacement therapy for Fabry disease in the Fabry Outcome Survey	*Int J Mol Sci* 2016; **17**: 1965
Kalkum G *et al.*	Paediatric Fabry disease: prognostic significance of ocular changes for disease severity	*BMC Ophthalmol* 2016; **16**: 202–8
Giugliani R *et al.*	A 15-year perspective of the Fabry Outcome Survey	*J Inborn Errors Metab Screen* 2016; **4**: 1–12
Lidove O *et al.*	Fabry in the older patient: clinical consequences and possibilities for treatment	*Mol Genet Metab* 2016; **118**: 319–25
Kampmann C *et al.*	Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment	*Orphanet J Rare Dis* 2015; **10**: 125
Pitz S *et al.*	Ocular signs correlate well with disease severity and genotype in Fabry disease	*PLoS One* 2015; **10**: e0120814
Liu H-C *et al.*	Age at first cardiac symptoms in Fabry disease: association with a Chinese hotspot Fabry mutation (IVS4+919G>A), classical Fabry mutations, and sex in a Taiwanese population from the Fabry Outcome Survey (FOS)	*JIMD Rep* 2015; **22**: 107–13
Beck M *et al.*	Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: a Fabry Outcome Survey analysis	*Mol Genet Metab Rep* 2015; **3**: 21–7
Terryn W *et al.*	Questioning the pathogenic role of the GLA p.Ala143Thr "mutation" in Fabry disease: implications for screening studies and ERT	*JIMD Rep* 2013; **8**: 101–8
Barba-Romero MÁ *et al.*	Comparison of patients from a Spanish registry of Fabry disease in two periods	*Med Clin (Barc)* 2012; **139**: 379–84 (in Spanish)
Ramaswami U *et al.*	Measuring patient experiences in Fabry disease: validation of the Fabry-specific Paediatric Health and Pain Questionnaire (FPHPQ)	*Health Qual Life Outcomes* 2012; **10**: 116
Ramaswami U *et al.*	Fabry disease in children and response to enzyme replacement therapy: results from the Fabry Outcome Survey	*Clin Genet* 2012; **81**: 485–90
Hughes DA *et al.*	Fabry International Prognostic Index: a predictive severity score for Anderson–Fabry disease	*J Med Genet* 2012; **49**: 212–20
Feriozzi S *et al.*	The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy	*Clin J Am Soc Nephrol* 2012; **7**: 60–9
Barba-Romero MÁ *et al.*	Fabry disease in Spain: description of Spanish patients and a comparison with other European countries using data from the Fabry Outcome Survey (FOS)	*Int J Clin Pract* 2011; **65**: 903–10

Author	Title	Reference
Clarke JTR *et al.*	Impact of measures to enhance the value of observational surveys in rare diseases: the Fabry Outcome Survey (FOS)	*Value Health* 2011; **14**: 862–6
Hughes DA *et al.*	Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS – the Fabry Outcome Survey	*Mol Genet Metab* 2011; **103**: 207–14
Ramaswami U *et al.*	Safety of agalsidase alfa in Fabry disease patients under 7 years	*Acta Paediatr* 2011; **100**: 605–11
Hughes DA *et al.*	Age adjusting severity scores for Anderson–Fabry disease	*Mol Genet Metab* 2010; **101**: 219–27
Barba-Romero M-Á *et al.*	Does geographical location influence the phenotype of Fabry disease in women in Europe?	*Clin Genet* 2010; **77**: 131–40
Mehta A *et al.*	Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data	*Lancet* 2009; **374**: 1986–96. Erratum *Lancet* 2010; 375: 200
Keilmann A *et al.*	Ear symptoms in children with Fabry disease: data from the Fabry Outcome Survey	*J Inherit Metab Dis* 2009; **32**: 739–44
Mehta A *et al.*	Natural course of Fabry disease: changing pattern of causes of death in FOS – Fabry Outcome Survey	*J Med Genet* 2009; **46**: 548–52
Malmenäs M *et al.*	Analysis of effectiveness in patient registry data	*ISPOR Connections* 2009; **15**: 9–10
Feriozzi S *et al.*	Agalsidase alfa slows the decline in renal function in patients with Fabry disease	*Am J Nephrol* 2009; **29**: 353–61
Cybulla M *et al.*	Kidney transplantation in patients with Fabry disease	*Transplant Int* 2009; **22**: 475–81
Sodi A *et al.*	Ocular manifestations of Fabry's disease: data from the Fabry Outcome Survey	*Br J Ophthalmol* 2007; **91**: 210–14
Cybulla M *et al.*	Fabry disease: demographic data since introduction of enzyme replacement therapy	*Dtsch Med Wochenschr* 2007; **132**: 1505–9
Orteu CH *et al.*	Fabry disease and the skin: data from FOS, the Fabry Outcome Survey	*Br J Dermatol* 2007; **157**: 331–7
Hoffmann B *et al.*	Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy	*Clin Gastroenterol Hepatol* 2007; **5**: 1447–53
Linhart A *et al.*	Cardiac manifestations of Anderson–Fabry disease: results from the international Fabry Outcome Survey	*Eur Heart J* 2007; **28**: 1228–35

Author	Title	Reference
Hoffmann B *et al.*	Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy – a retrospective analysis from the Fabry Outcome Survey	*Clin J Pain* 2007; **23**: 535–42
Hoffmann B and Keshav S	Gastrointestinal symptoms in Fabry disease: everything is possible, including treatment	*Acta Paediatr Suppl* 2007; **96 (455)**: 84–6
Schwarting A *et al.*	Enzyme replacement therapy and renal function in 201 patients with Fabry disease	*Clin Nephrol* 2006; **66**: 77–84
Rivera-Gallego A *et al.*	Fabry disease in Spain: first analysis of the response to enzyme replacement therapy	*Med Clin (Barc)* 2006; **127**: 481–4 (in Spanish)
Lidove O *et al.*	Hyperhidrosis: a new and often early symptom in Fabry disease. International experience and data from the Fabry Outcome Survey	*Int J Clin Pract* 2006; **60**: 1053–9
Hajioff D *et al.*	Agalsidase alfa and hearing in Fabry disease: data from the Fabry Outcome Survey	*Eur J Clin Invest* 2006; **36**: 663–7. Erratum *Eur J Clin Invest* 2007; **37**: 828
Hegemann S *et al.*	Hearing loss in Fabry disease: data from the Fabry Outcome Survey	*Eur J Clin Invest* 2006; **36**: 654–62. Erratum *Eur J Clin Invest* 2007; **37**: 828
Kleinert J *et al.*	Prevalence of uncontrolled hypertension in patients with Fabry disease	*Am J Hypertens* 2006; **19**: 782–7
Ginsberg L *et al.*	Magnetic resonance imaging changes in Fabry disease	*Acta Paediatr Suppl* 2006; **95 (451)**: 57–62
Deegan PB *et al.*	Natural history of Fabry disease in females in the Fabry Outcome Survey	*J Med Genet* 2006; **43**: 347–52
Ramaswami U *et al.*	Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey	*Acta Paediatr* 2006; **95**: 86–92
Kleinert J *et al.*	Anaemia is a new complication in Fabry disease: data from the Fabry Outcome Survey	*Kidney Int* 2005; **67**: 1955–60
Schaefer E *et al.*	Genotype and phenotype in Fabry disease: analysis of the Fabry Outcome Survey	*Acta Paediatr Suppl* 2005; **94 (447)**: 87–92
Mehta A and Ginsberg L	Natural history of the cerebrovascular complications of Fabry disease	*Acta Paediatr Suppl* 2005; **94 (447)**: 24–7
Hoffmann B *et al.*	Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey)	*J Med Genet* 2005; **42**: 247–52
Beck M *et al.*	Fabry disease: overall effects of agalsidase alfa treatment	*Eur J Clin Invest* 2004; **34**: 838–44

Author	Title	Reference
Barba-Romero M-Á *et al.*	Fabry's disease in Spain. Study of 24 cases	*Med Clin (Barc)* 2004; **123**: 57–60 (in Spanish)
Mehta A *et al.*	Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey	*Eur J Clin Invest* 2004; **34**: 236–42
Dehout F *et al.*	Effects of enzyme replacement therapy with agalsidase alfa on glomerular filtration rate in patients with Fabry disease: preliminary data	*Acta Paediatr Suppl* 2003; **92 (443)**: 14–15

Appendix: useful contacts

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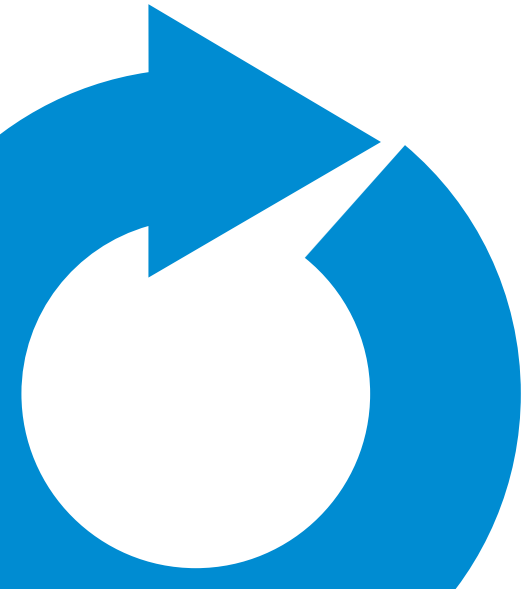

Outcome Surveys

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