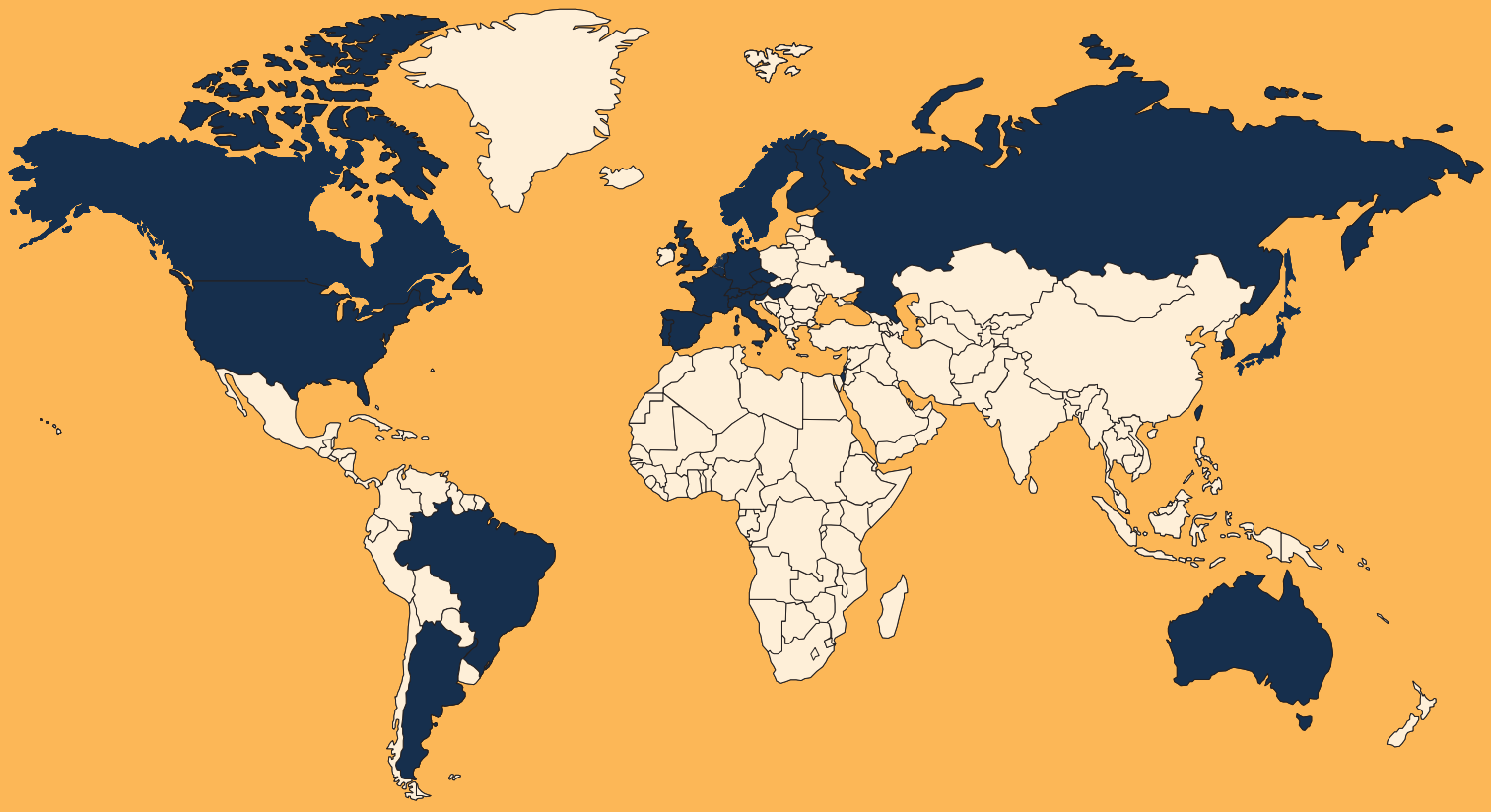
Fabry Outcome Survey



Countries shaded dark blue on the map are countries that participated in FOS

Final annual update for patients and caregivers

To provide information upon request to individuals involved in the registry

FABRY OUTCOME SURVEY

This report has been prepared by Takeda on behalf of the FOS Steering Committee

Date of preparation: May 2023
Item code: VV-MEDMAT-84964

FOS
FABRY OUTCOME SURVEY

Welcome

I am pleased to introduce the final Fabry Outcome Survey (FOS) report for patients and caregivers, which is based on data collected within FOS from 5 October 2001 to 30 September 2022. The aim of this registry, funded by Takeda, was to collect information on patients with Fabry disease. Since initiation in 2001 by Shire (now part of Takeda), FOS has collected a large amount of information on the clinical symptoms, natural progression and treatment outcomes of patients with Fabry disease. As of September 2022, FOS contained data available for analyses from 4480 patients across 24 countries worldwide. After 21 years of operation, FOS has now fulfilled its regulatory objectives, and database closure was completed in September 2022.

The data collected by FOS over the past two decades have contributed vastly to the better understanding of Fabry disease pathophysiology and management; in total, 61 articles based on FOS data have been published in scientific journals. Registry data have also informed several national, European and international guideline and recommendation documents for the management of Fabry disease.

The support and contributions from patients and their caregivers over the past 21 years have an immeasurable value and, on behalf of the FOS Steering Committee, I would like to thank everyone who was involved in the registry over the years. We hope that insights into the disease stemming from these contributions will continue to lead to improvements in patient care in the future.

MARY PAVLOU
Patient organization representative on the FOS Steering Committee

This report is for informational purposes only; it should not be used for diagnosing or treating a health problem or disease. It is not intended to substitute for consultation with a healthcare provider. Please consult your healthcare provider for further advice.

Any questions?

If so, please get in touch with one of the following contacts.

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What was FOS and what has it helped us to study?

FOS was a patient registry that was initiated in 2001 and used observational study methods and collected long-term information from patients with Fabry disease across different countries around the world.
Data collected in FOS over the past 21 years have increased our understanding of Fabry disease by finding answers to the following questions.

Who was eligible to take part in FOS?

- All patients (adults and children) with a diagnosis of Fabry disease who:
  - were untreated
  - were receiving or had previously received any approved treatment for Fabry disease.[a]
- Patients continued to be assessed and treated as determined by their own healthcare provider while enrolled in FOS.

What information was collected?

- During a patient's regular visit to their physician, information was collected and entered into the registry. This information included:

basic information (e.g. height, weight, age)

medical history (e.g. age at which the first symptoms of Fabry disease were experienced, age at diagnosis, other medical events)

results of medical tests (e.g. blood and urine tests, genetic tests, heart and kidney function tests)

any treatment(s) received and details of any side effects experienced.

Mehta A and co-authors, 2004

[a]When it was first set up, FOS included only untreated patients and those treated with agalsidase alfa. However, from 2016 onwards, FOS was open to all patients with Fabry disease.

FOS
FABRY OUTCOME SURVEY

Data collected in FOS have facilitated important contributions to our understanding of Fabry disease and its treatment[a]

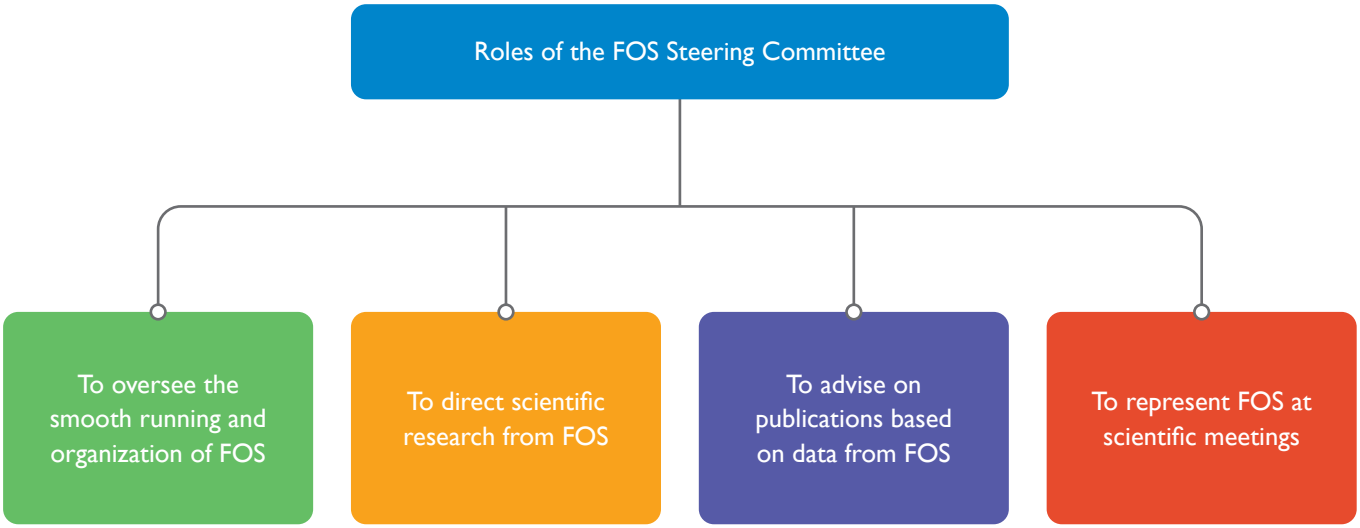
- Over the past 21 years, FOS has substantially improved our knowledge of patient management and has expanded our understanding of Fabry disease (Beck M and co-authors, 2022).
- For example, information from FOS suggests that prompt treatment initiation may slow down kidney damage related to Fabry disease over time in patients who have no renal impairment (Cybulla M and co-authors, 2022).

[a]Please see full reference details for these and all other published FOS journal articles on pages 9–11.

FOS FABRY OUTCOME SURVEY

The FOS Steering Committee: who were they and what did they do?

Members of the FOS Steering Committee met regularly, helping to ensure that FOS was running efficiently.



The FOS Steering Committee included the individuals below.

Ten Fabry disease experts from around the world

- **Roberto Giugliani (Chair)**, Porto Alegre, Brazil
- **Michael Beck**, Mainz, Germany[a]
- **Derralynn Hughes**, London, UK
- **Christoph Kampmann**, Mainz, Germany
- **Kathy Nicholls**, Melbourne, VIC, Australia
- **Dau-Ming Niu**, Taipei, Taiwan
- **Guillem Pintos-Morell**, Barcelona, Spain
- **Uma Ramaswami**, London, UK
- **Ricardo Reisin**, Buenos Aires, Argentina
- **Michael West**, Halifax, NS, Canada

[a]Professor Michael Beck sadly died in September 2022. He was a valued member of the FOS Steering Committee and a pioneer in the field. His vast contributions to the study of LSDs have been greatly appreciated and have benefited many patients. Professor Beck will be deeply missed.

Five Takeda representatives

- **Siddharth Jain**, Global Medical Lead for LSDs
- **Jaco Botha**, FOS Biostatistician Lead
- **Jamie L Weiss**, Publications Lead
- **Neil Yadav**, Senior Clinical Operations Manager
- **Ashley Yegin**, Medical Unit Head, Hereditary Angioedema and LSDs, Global Medical Affairs

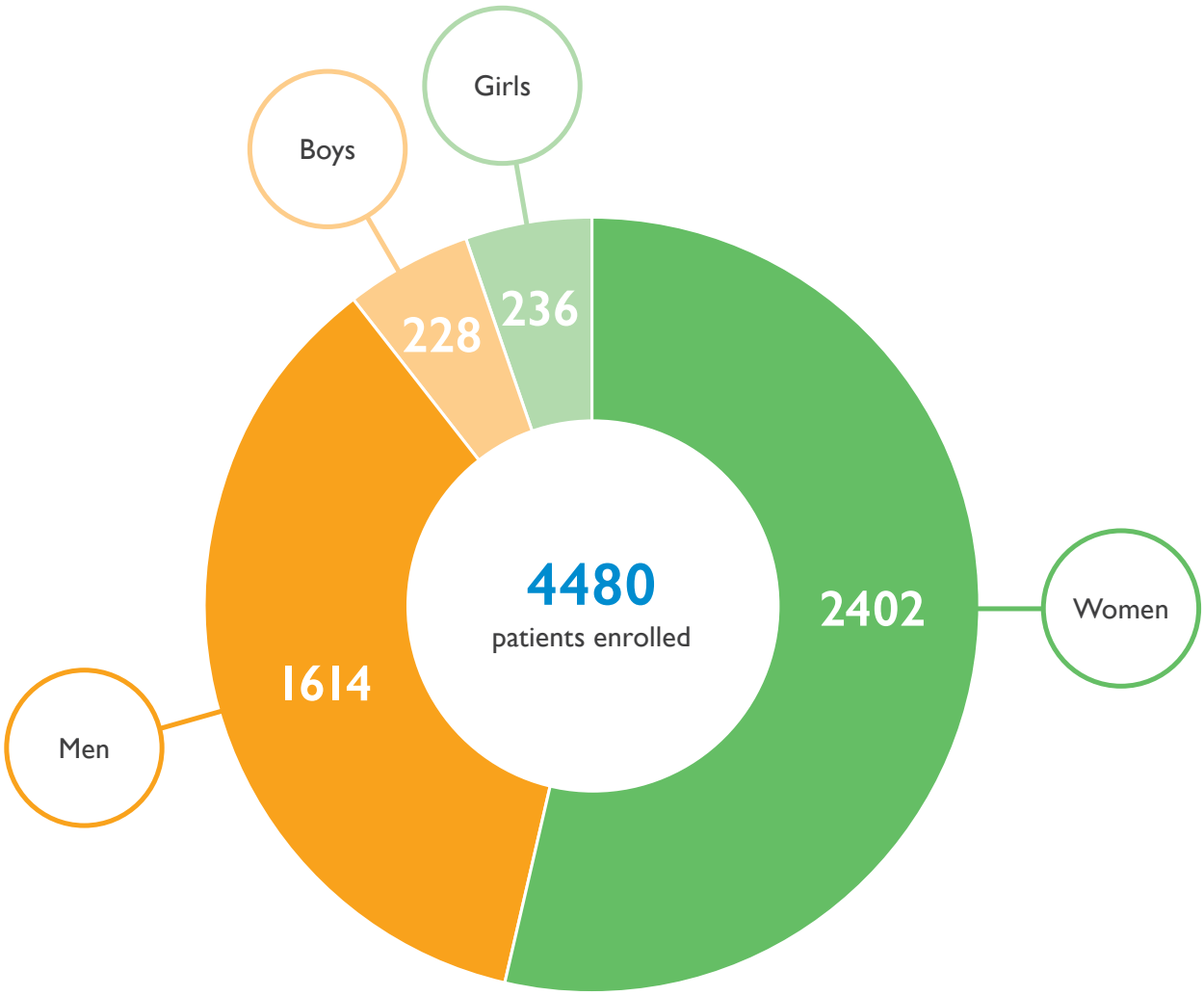
One patient organization representative

- **Mary Pavlou**, President of the Fabry International Network, Athens, Greece

What were the characteristics of patients in FOS?

Update as of September 2022

Number of patients in FOS by sex and age group at time of enrolment



Here, boys are defined as male patients who were younger than 18 years old when they joined FOS, and men are defined as male patients who were 18 years old or older when they joined FOS.

Girls are defined as female patients who were younger than 18 years old when they joined FOS, and women are defined as female patients who were 18 years old or older when they joined FOS.

Patients who did not have a signed informed consent form by FOS closure were removed from the database, thus explaining why the number of patients is lower than in the previous report.

FOS
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Patients who participated in FOS came from across the world

Total number of countries: 24

Total number of study sites: 109

Total number of patients: 4480

Country	Number of study sites	Number of patients
Germany	10	798
UK	7	653
Taiwan	4	566
Japan	1	462
Canada	9	350
Italy	11	233
Spain	27	164
Australia	1	163
Czech Republic	1	158
Netherlands	1	136
France	17	128
Finland	1	103

Country	Number of study sites	Number of patients
Argentina	2	102
Switzerland	1	101
Russia	1	76
Austria	2	66
Portugal	2	60
Brazil	1	57
Slovenia	1	40
Belgium	3	27
Hungary	1	19
South Korea	3	8
Denmark	1	5
Israel	1	5

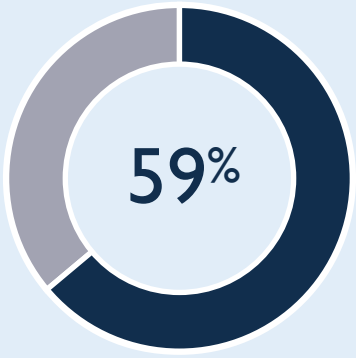
FOS FABRY OUTCOME SURVEY

Age at symptom onset and diagnosis for patients in FOS

	Average **age at onset** of signs and symptoms	Average **age at diagnosis**	Average **delay from onset to diagnosis**
♂ Male patients	12 years	32 years	7 years
♀ Female patients	20 years	37 years	5 years

Averages presented are median values (the median is the middle number in a list of numbers that are arranged by value).

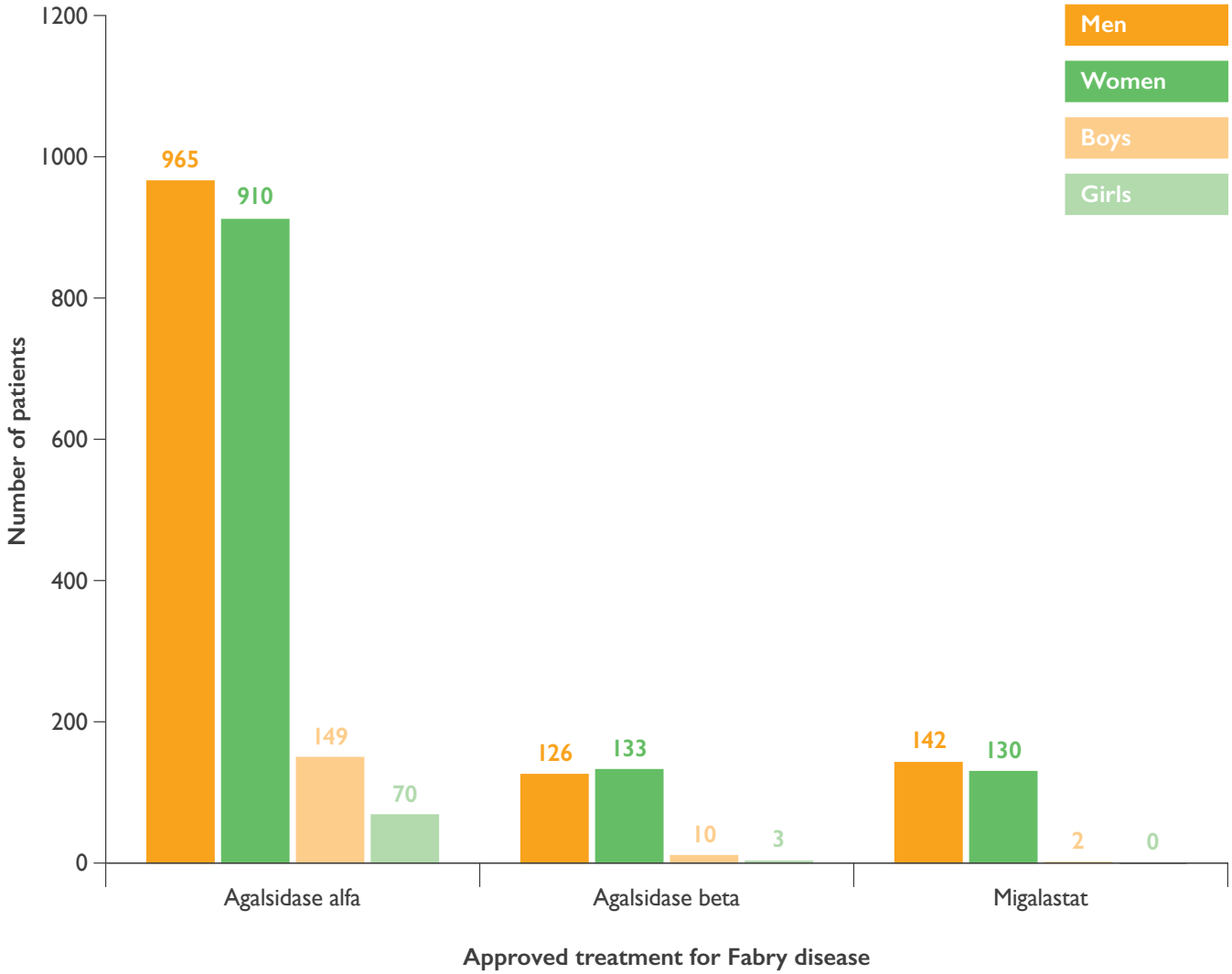
Patients in FOS who received treatment for Fabry disease



More than half of patients received at least one approved treatment for Fabry disease.

FOS FABRY OUTCOME SURVEY

Number of patients in FOS who received at least one dose of disease-specific treatment



Boys are defined as male patients who were younger than 18 years old when they joined FOS, and men are defined as male patients who were 18 years old or older when they joined FOS.

Girls are defined as female patients who were younger than 18 years old when they joined FOS, and women are defined as female patients who were 18 years old or older when they joined FOS.

FOS also collected information on whether patients switched treatment after enrolment.

319 patients changed treatment once.

10 patients changed treatment multiple times.

FOS medical publications

It is important to keep the Fabry disease community up to date by sharing findings from FOS in scientific journal articles and medical conference presentations. Over the past 21 years, the data collected by the FOS registry have contributed to the better understanding of Fabry disease and have informed several national, European and international guideline and recommendation documents for the management of Fabry disease. These include the recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease by the European Fabry Working Group,[1] the European expert consensus statement on therapeutic goals in Fabry disease,[2] consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients[3] and an expert consensus document on the management of cardiovascular manifestations of Fabry disease.[4]

1. Biegstraaten M and co-authors. *Orphanet J Rare Dis* 2015;10:36
2. Wanner C and co-authors. *Mol Genet Metab* 2018;124:189–203
3. Germain DP and co-authors. *Clin Genet* 2019;96:107–17
4. Linhart A and co-authors. *Eur J Heart Fail* 2020;22:1076–96

FOS medical conference poster presentations

- **Four** posters based on FOS data were presented at international scientific congresses in 2022 and early 2023.
- The posters covered a variety of topics. Their titles were:
  - Early initiation of agalsidase alfa treatment improves clinical outcomes in male patients with classical Fabry disease: a Fabry Outcome Survey (FOS) analysis (Pintos-Morell G and co-authors, 2023)
  - Long-term outcomes in patients with Fabry disease who were treated with agalsidase alfa for more than 19 years: the Fabry Outcome Survey (Giugliani R and co-authors, 2023)
  - Lasting impact of the COVID-19 pandemic on LSD patient care: results from a large multinational survey of healthcare professionals (Elstein D and co-authors, 2023)
  - Lyso-Gb_3 as a biomarker for renal and cardiac involvement in Fabry disease: an analysis from the Fabry Outcome Survey (FOS) (Ramaswami U and co-authors, 2022).

FOS manuscripts

As of September 2022, a total of 61 articles containing information from FOS have been published in scientific journals, including two in 2022 (Cybulla M and co-authors, and Beck M and co-authors).

Articles published in the past 10 years are arranged by topic in the table below and on the following pages. Links provide access to the articles via Open Access from the journal website.

Journal article (main topic in **bold**)	Click here to see full article
FOS overview	
Cybulla M and co-authors. **Renoprotective effect of agalsidase alfa**: a long-term follow-up of patients with Fabry disease. *J Clin Med* 2022;11:4810	
Beck M and co-authors. **Twenty years of the Fabry Outcome Survey (FOS)**: insights, achievements, and lessons learned from a global patient registry. *Orphanet J Rare Dis* 2022;17:238	

Journal article (main topic in **bold**)	Click here to see full article
Giugliani R and co-authors. **A 15-year perspective** of the Fabry Outcome Survey. *J Inborn Errors Metab Screen* 2016;4:1–12.	
COVID-19 pandemic	
Elstein D and co-authors. **Impact of the COVID-19 pandemic on the standard of care** for patients with lysosomal storage diseases: a survey of healthcare professionals in the Fabry, Gaucher, and Hunter Outcome Survey registries. *Mol Genet Metab Rep* 2021;28:100788.	
Patient and disease characteristics	
Lee H-J and co-authors. **A comparison of central nervous system involvement** in patients with classical Fabry disease or the later-onset subtype with the IVS4+919G>A mutation. *BMC Neurol* 2017;17:25.	
Hsu T-R and co-authors. Correlations between endomyocardial biopsies and **cardiac manifestations in Taiwanese patients** with the Chinese hotspot IVS4+919G>A mutation: data from the Fabry Outcome Survey. *Int J Mol Sci* 2017;18:119.	
Lidove O and co-authors. **Fabry in the older patient**: clinical consequences and possibilities for treatment. *Mol Genet Metab* 2016;118:319–25.	
Liu H-C and co-authors. **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.	
Terryn W and co-authors. 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 M-Á and co-authors. **Comparison of patients** from a Spanish registry of Fabry disease **in two periods**. *Med Clin (Barc)* 2012;139: 379–84 [written in Spanish].	
Ramaswami U and co-authors. Measuring **patient experiences** in Fabry disease: validation of the Fabry-specific Paediatric Health and Pain Questionnaire (FPHPQ). *Health Qual Life Outcomes* 2012;10:116.	
Diagnosis and predicting disease severity	
Reisin R and co-authors. Time **delays in the diagnosis and treatment** of Fabry disease. *Int J Clin Pract* 2017;71:e12914.	
Kalkum G and co-authors. **Paediatric Fabry disease: prognostic significance of ocular changes for disease severity**. *BMC Ophthalmol* 2016;16:202–8.	
Pitz S and co-authors. **Ocular signs** correlate well with **disease severity** and genotype in Fabry disease. *PLoS One* 2015;10:e0120814.	
Hughes DA and co-authors. Fabry International Prognostic Index: a **predictive severity score** for Anderson-Fabry disease. *J Med Genet* 2012;49:212–20.	

Journal article (main topic in **bold**)	Click here to see full article
Disease progression and outcomes	
Hughes D and co-authors. **Prompt agalsidase alfa therapy initiation** is associated with **improved renal and cardiovascular outcomes** in a Fabry Outcome Survey analysis. *Drug Des Devel Ther* 2021;15:3561–72.	
Feriozzi S and co-authors. Effects of baseline left ventricular hypertrophy and decreased renal function on **cardiovascular and renal outcomes** in patients with Fabry disease treated with agalsidase alfa: a Fabry Outcome Survey study. *Clin Ther* 2020;42:2321–30.	
Parini R and co-authors. Analysis of renal and cardiac **outcomes** in male participants in the Fabry Outcome Survey **starting agalsidase alfa enzyme replacement therapy before and after 18 years of age**. *Drug Des Devel Ther* 2020;14:2149–58.	
Ramaswami U and co-authors. **Cardio-renal outcomes with long-term agalsidase alfa** enzyme replacement therapy: a 10-year Fabry Outcome Survey (FOS) analysis. *Drug Des Devel Ther* 2019;13:3705–15.	
Beck M and co-authors. **Long-term outcomes with agalsidase alfa** enzyme replacement therapy: analysis using deconstructed composite events. *Mol Genet Metab Reports* 2018;14:31–5.	
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.	
Kampmann C and co-authors. Effectiveness of **agalsidase alfa** enzyme replacement in Fabry disease: **cardiac outcomes** after 10 years' treatment. *Orphanet J Rare Dis* 2015;10:125.	
Beck M and co-authors. **Long-term effectiveness of agalsidase alfa** enzyme replacement in Fabry disease: a Fabry Outcome Survey analysis. *Mol Genet Metab Reports* 2015;3:21–7.	
Ramaswami U and co-authors. **Fabry disease in children and response to enzyme replacement therapy**: results from the Fabry Outcome Survey. *Clin Genet* 2012;81:485–90.	
Feriozzi S and co-authors. The **effectiveness of long-term agalsidase alfa** therapy in the treatment of Fabry **nephropathy**. *Clin J Am Soc Nephrol* 2012;7:60–9.	

Thank you for reading this annual FOS update.
If you have any questions, please get in touch with one of the contacts listed on page 1.