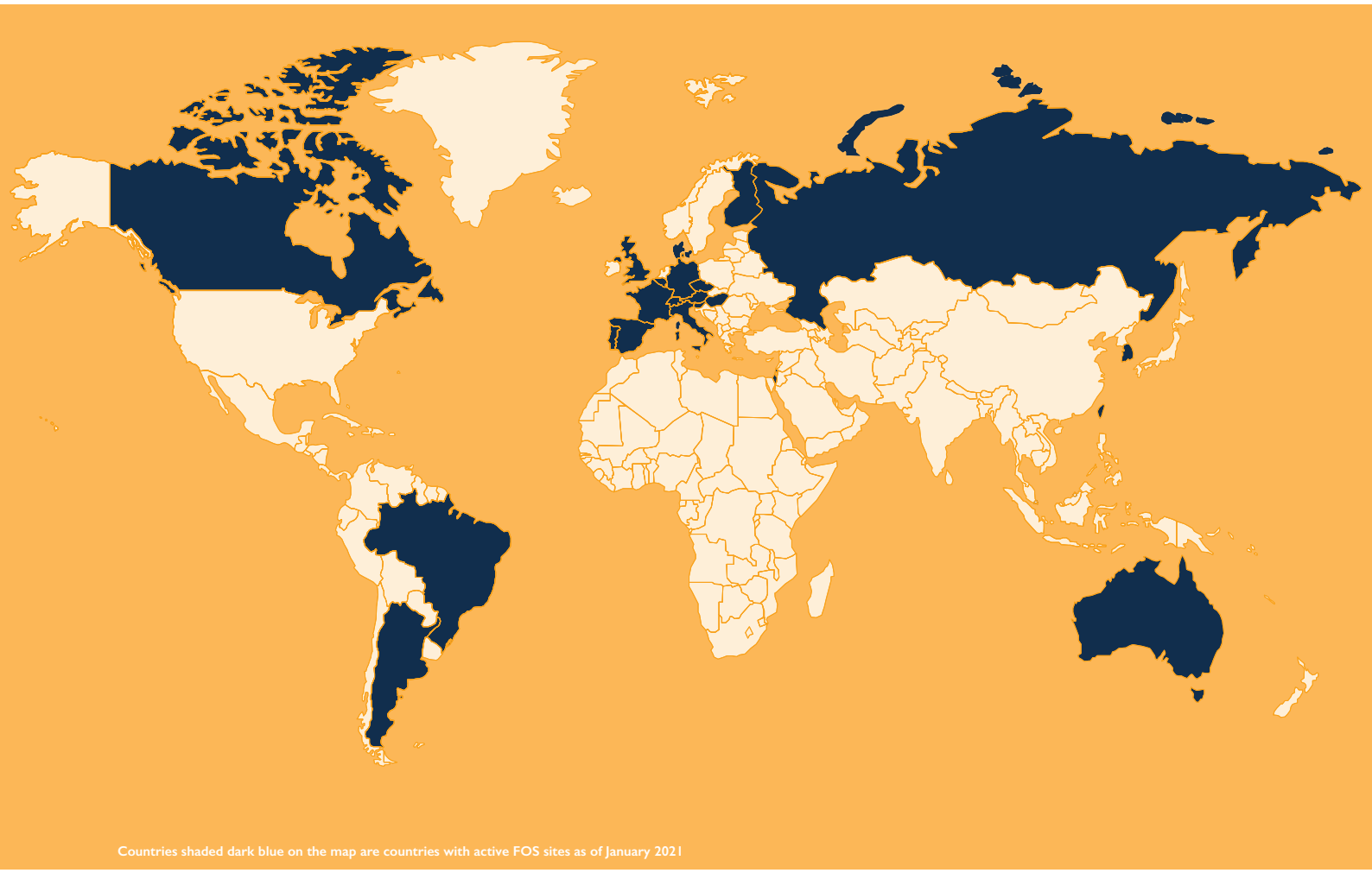
Fabry Outcome Survey



Countries shaded dark blue on the map are countries with active FOS sites as of January 2021

2020 annual update for patient organizations

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: July 2021
Item code: VV-MEDMAT-41546

FOS
FABRY OUTCOME SURVEY

Welcome

I am very pleased to welcome you to the 2020 update on the Fabry Outcome Survey (FOS). The role of this disease registry, which is sponsored by Takeda, is to collect information on patients with Fabry disease across the world. Since FOS began in 2001, it has collected information from enrolled patients about symptoms, disease progression and treatment and, as of January 2021, there are 4484 patients enrolled in the registry. The information is collected with the aim of improving our understanding of Fabry disease, which will help healthcare professionals to provide the best care possible for their patients.

We hope that this report will help patients and caregivers who are involved with FOS to understand better the role of the registry and what has been achieved so far. The 2020 report provides an update on the information collected in FOS up to January 2021, a summary of published articles from the registry (which you can download from the journal publisher's website) and answers to commonly asked questions about FOS.

Throughout 2020, the COVID-19 pandemic posed many challenges for both FOS and the wider Fabry disease community. The members of the FOS Steering Committee and I would like to thank all patients and caregivers involved in the registry for their extremely valuable contributions and for their continued commitment to FOS during these challenging times. As we collect more information on Fabry disease, we can improve our understanding of this disease and aim to improve the care of patients in the future.

MARY PAVLOU
Patient organization representative on the FOS Steering Committee

This report is for information 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:

MARY PAVLOU (Secretary of the Fabry International Network, Patient organization representative on the FOS Steering Committee)
Email: secretary@fabrynetwork.org
www.fabrynetwork.org

CHRISTINA ANAGNOSTOPOULOU (Global Medical Lead, Takeda)
Email: christina.anagnostopoulou@takeda.com

DALIA JAZUKEVICIENE (FOS Registry Lead, Takeda)
Email: dalia.jazukeviciene@takeda.com

What is FOS and what can it help us to investigate?

Who can take part in FOS?

- All patients with diagnosed Fabry disease.
  - Patients may be of any age or sex.
  - Patients may be untreated or may have previously received or currently be receiving any approved treatment for Fabry disease.[a]
- Patients continue to be assessed and treated as determined by their own healthcare professionals.

What information is collected?

- Information is collected from patients at their regular visits to their physician and is entered into the registry. The information collected includes:

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

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

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

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

genetic data (under a separate informed consent form).

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

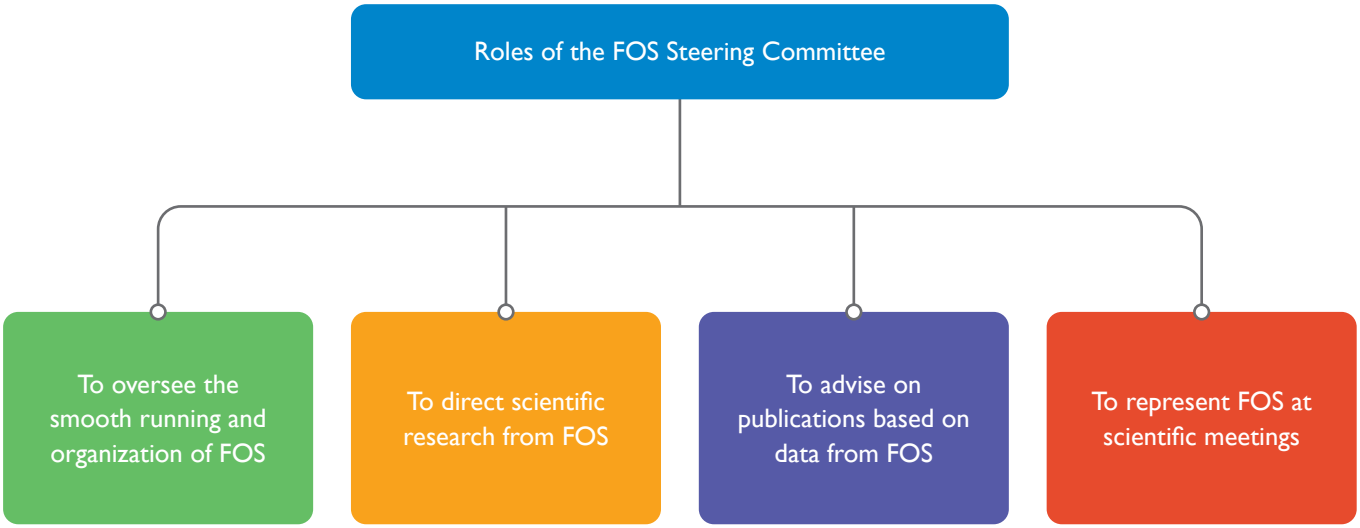
FOS
FABRY OUTCOME SURVEY

FOS has made important contributions to our understanding of Fabry disease and its treatment

Information collected in FOS can be used to improve our understanding of Fabry disease. Some findings from FOS are communicated in publications. A list of published findings from FOS in the past 10 years is provided in the 'FOS publications' section (pages 9–11).

The FOS Steering Committee: who are they and what do they do?

Members of the FOS Steering Committee meet regularly and help to ensure that FOS is run in an effective way.



The FOS Steering Committee currently includes:

Ten Fabry disease experts from around the world

- **Roberto Giugliani (Chair)**, Porto Alegre, Brazil
- **Michael Beck**, Mainz, Germany
- **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

Five Takeda representatives

- **Christina Anagnostopoulou**, Global Medical Lead
- **Jaco Botha**, FOS Lead Biostatistician
- **Elizabeth (Beth) Daro-Kaftan**, Publications Lead
- **Dalia Jazukeviciene**, FOS Registry Lead
- **Jörn Schenk**, Global Medical Unit Head

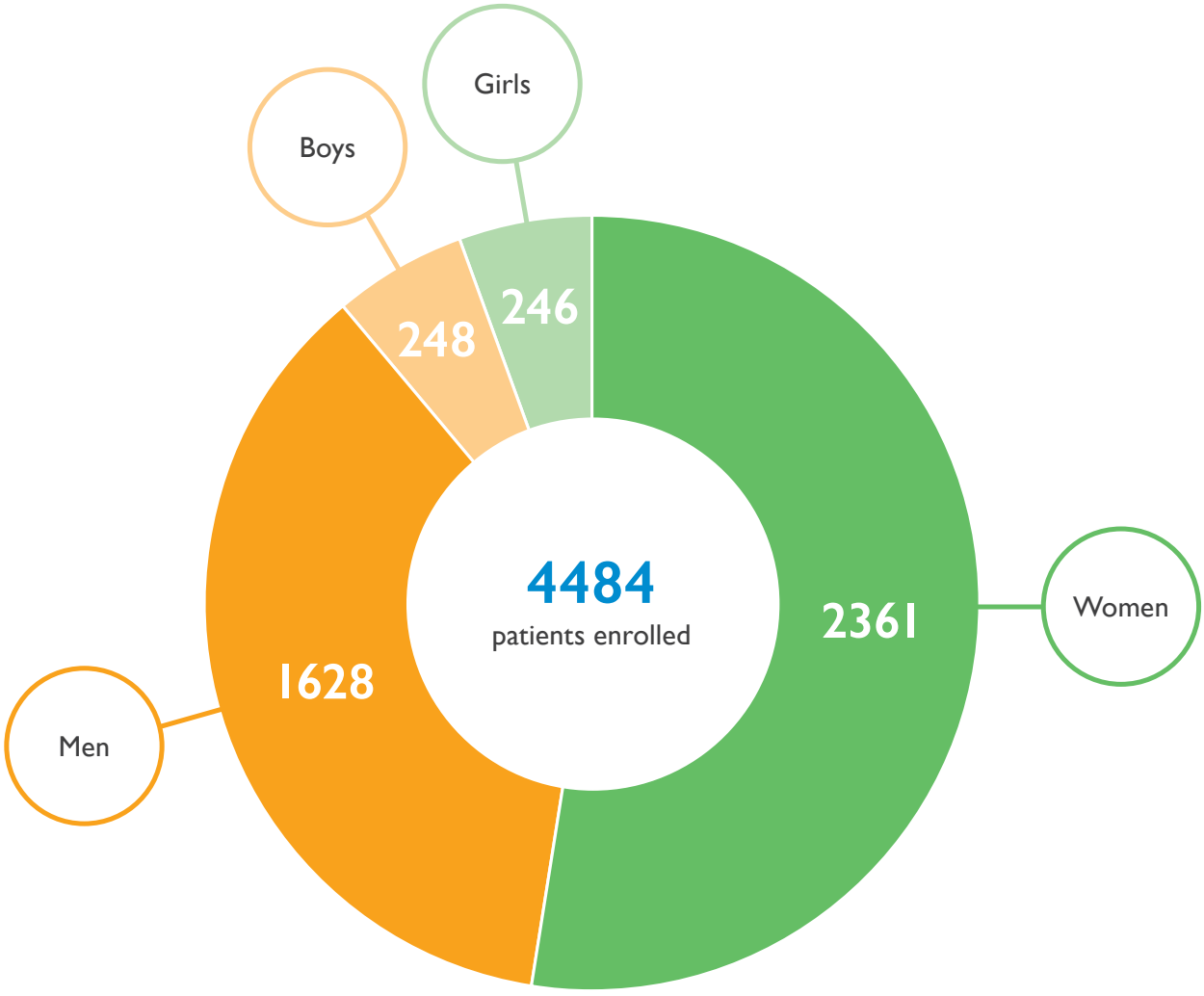
One patient organization representative

- **Mary Pavlou**, Fabry International Network, Athens, Greece

What are the characteristics of patients enrolled in FOS?

Update as of January 2021

Number of patients in FOS by sex and age at enrolment



The number of men, women, boys and girls does not match the total number of enrolled patients because the age at enrolment in FOS was missing for one patient.

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.

FOS FABRY OUTCOME SURVEY

Patients enrolled in FOS come from across the world

Total number of countries: 26

Total number of study sites: 144

Total number of patients: 4484

Country	Number of study sites	Number of patients
Germany	12	807
UK	8	675
Taiwan	4	515
Japan	1	462
Canada	10	351
Italy	14	237
Spain	35	180
France	32	163
Australia	1	159
Czech Republic	1	149
Netherlands	1	137
Argentina	2	102
Finland	1	100

Country	Number of study sites	Number of patients
Switzerland	2	88
Austria	2	59
Brazil	1	55
Russia	1	53
Slovenia	2	41
Portugal	2	37
Belgium	3	26
Sweden	1	23
Hungary	1	19
Israel	1	19
USA	2	14
South Korea	3	8
Denmark	1	5

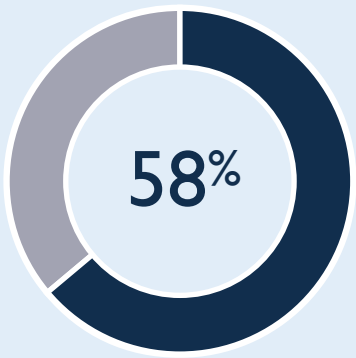
FOS FABRY OUTCOME SURVEY

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**
♂ Males	12 years	31 years	6 years
♀ Females	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 have received disease-specific treatment for Fabry disease

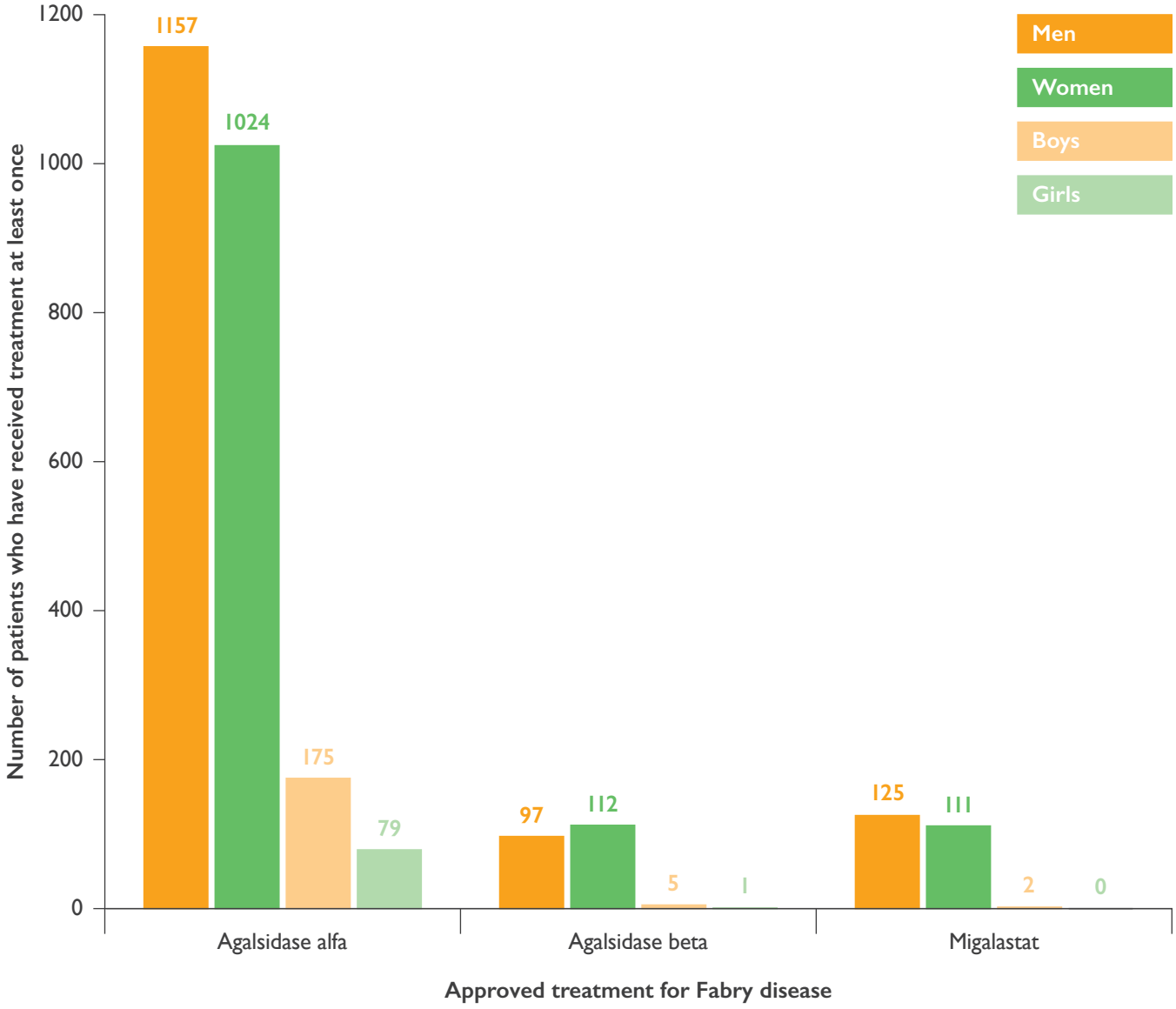


Over **5** out of **10**

patients have received at least one approved treatment for Fabry disease.

FOS FABRY OUTCOME SURVEY

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



FOS also contains information on whether patients have switched treatment since enrolment.

258 patients have changed treatment once.

8 patients have changed treatment multiple times.

FOS publications

It is important to share the findings from FOS with other doctors and researchers by publishing research in scientific journals and presenting it at medical conferences. This helps to raise awareness of Fabry disease and to make sure that it is possible for everyone to learn from the registry. FOS publications can be used to inform future research and to help to facilitate care around the world.

FOS poster presentations

- Owing to the COVID-19 pandemic, many conferences planned for 2020 were either cancelled or rescheduled.
- However, **three** posters using information from FOS were presented at an international scientific congress in 2020.
- Topics covered by these posters include:
  - diagnosis of Fabry disease[1]
  - effects on the heart and kidneys of promptly starting agalsidase alfa treatment[2]
  - use of agalsidase alfa in older patients[3].

[1]Ramaswami U and co-authors. *Mol Genet Metab* 2020;**2**:S134.
[2]Hughes D and co-authors. *Mol Genet Metab* 2020;**2**:S77.
[3]Nowak A and co-authors. Presented at Lysosomal Disease Network, 16th WORLD*Symposium* 2020, 10–13 February 2020, Orlando, FL, USA.

FOS manuscripts

In total, 57 articles containing information from FOS have been published in scientific journals,* including two in 2020 (Feriozzi and co-authors 2020, and Parini and co-authors 2020)

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.

*As of January 2021.

Journal article (main topic in **bold**)	Link to journal website
FOS overview	
Giugliani R and co-authors. **A 15-year perspective** of the Fabry Outcome Survey. *J Inborn Errors Metab Screen* 2016;4:1–12.	
Clarke JTR and co-authors. Impact of measures to enhance the **value of observational surveys** in rare diseases: the Fabry Outcome Survey (FOS). *Value Health* 2011;14:862–6.	

Journal article (main topic in **bold**)	Link to journal website
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.	
Barba-Romero M-Á and co-authors. **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.	
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**)	Link to journal website
Disease progression and outcomes	
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 Rep* 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 Rep* 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.	
Hughes DA and co-authors. **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 and co-authors. **Safety of agalsidase alfa** in patients with Fabry disease **under 7 years**. *Acta Paediatr* 2011;100:605–11.	

Summary of FOS journal articles published in 2020

Feriozzi S, Linhart A, Ramaswami U 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.e0.

Background

Heart and kidney conditions are common complications in patients with Fabry disease.[1] In this study, data from FOS were analysed **to investigate how the presence of particular heart or kidney conditions in patients receiving ERT[a] for up to 10 years affected the patients' risk of complications.**

Key results

In total, 560 patients had information available for analysis of heart size at the start of treatment

Of these, 306 patients had an enlarged heart and 254 patients did not have an enlarged heart at the start of treatment.

Patients with an enlarged heart at the start of treatment had a higher risk of developing heart or kidney conditions during follow-up than those with normal heart size.

- The risk of developing a heart condition was 57% higher in patients with an enlarged heart at the start of treatment than in those without.

In total, 1093 patients had information available for the analysis of kidney function at the start of treatment

Of these, 433 patients had poor kidney function and 660 patients had healthy kidney function at the start of treatment.

Patients with poor kidney function at the start of treatment had a higher risk of developing heart or kidney conditions during follow-up than those with healthy kidney function.

- The risk of developing a heart condition was 33% higher in patients with poor kidney function at treatment start than in those with healthy kidney function.
- The risk of developing a kidney condition was more than five times higher in those with poor kidney function than in those with healthy kidney function.

Things to consider

Owing to the observational nature of the FOS study, the results of this analysis of FOS data have some limitations. These results should be considered in the context of other study results regarding treatment of patients with Fabry disease. The full article with more detail is available via Open Access from the journal's website here: *Clin Ther* 2020;42:2321–30.e0. For questions or further discussion, it may be helpful to consult your healthcare team.

[a]ERT stands for enzyme replacement therapy. In this study, it was agalsidase alfa.
[1]Mehta A and co-authors. *Eur J Clin Invest* 2004;**34**:236e242.

FOS FABRY OUTCOME SURVEY

Parini R, Pintos-Morell G, Hennermann JB 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.

Background

Patients with Fabry disease often develop heart and kidney conditions, and these complications can reduce lifespan.[1–4] Once Fabry disease is at an advanced stage, ERT has not been shown to prevent further disease progression and recommendations support early treatment initiation to maximize benefit.[5–7] Using data from FOS, **this study compared kidney and heart health in 560 male patients who started ERT[a] in three different age groups.**

Key results

Group 1 started ERT at the age of 18 years or younger

- 151 patients (27%)
- Average time on ERT: 6.3 years

Group 2 started ERT between the ages of 18 and 30 years

- 155 patients (28%)
- Average time on ERT: 8.6 years

Group 3 started ERT after the age of 30 years

- 254 patients (45%)
- Average time on ERT: 7.9 years

Patients in Group 3, who started ERT after 30 years of age, had poorer kidney health[b] than patients in Groups 1 or 2, who started treatment earlier.

Kidney function worsened each year in patients in Group 3, declined slightly in patients in Group 2 and was stable in patients in Group 1.

Patients in Group 3 also had poorer heart health[c] than patients in Groups 1 or 2, and heart health worsened each year in this group.

Things to consider

Owing to the observational nature of the FOS study, the results of this analysis of FOS data have some limitations. These results should be considered in the context of other study results regarding the treatment of patients with Fabry disease. The full article with more detail is available via Open Access from the journal's website here: *Drug Des Devel Ther* 2020;14:2149–58. For questions or further discussion, it may be helpful to consult your healthcare team.

[a]Agalsidase alfa.
[b]Based on average values for estimated glomerular filtration rate [eGFR] and proteinuria. eGFR is an estimate of how much blood passes through the filters in the kidney that separate waste from the blood; eGFR is reduced if kidneys are not functioning well. Proteinuria is the leakage of protein into the urine; it is a sign that the kidneys are not working properly.
[c]Based on average values for left ventricular mass indexed to height [LVMI]. LVMI is a measurement of heart enlargement; increased LVMI, indicating an enlarged heart, can be associated with heart failure.

[1]Branton MH and co-authors. *Medicine* 2002;**81**:122–38.
[2]Mehta A and co-authors. *Eur J Clin Invest* 2004;**34**:236–42.
[3]Kampmann C and co-authors. *J Am Coll Cardiol* 2002;**40**:1668–74.
[4]Linhart A and co-authors. *Eur Heart J* 2007;**28**:1228–35.
[5]Germain DP and co-authors. *J Med Genet* 2015;**52**:353–8.
[6]Weidemann F and co-authors. *J Intern Med* 2013;**274**:331–41.
[7]Biegstraaten M and co-authors. *Orphanet J Rare Dis* 2015;10:36.

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.