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FollowME Fabry Pathfinders registry: renal effectiveness in a multi-national, multi-center cohort of patients on migalastat treatment for at least three years

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Introduction and objectives

- Fabry disease is an X-linked, multisystemic, progressive lysosomal storage disorder caused by *GLA* gene variants that leads to α-galactosidase A deficiency.[1,2]
- This enzyme deficiency leads to glycosphingolipid accumulation, multisystemic dysfunction and a wide variety of clinical symptoms and manifestations, including cardiovascular disease (CVD), stroke, end-stage renal disease and premature death.[3]
- The current leading cause of death in patients with Fabry disease is CVD, with males and females experiencing their first cardiac event at a median age of 42 and 50 years old, respectively[4]
  - Patients with Fabry disease are at higher risk for cardiac events than those with hypertrophic cardiomyopathy (HCM) or left ventricular hypertrophy (LVH) due to HCM[5]
  - If left untreated, cardiac involvement may reach a critical point at which symptoms cannot be reversed, leading to high morbidity and mortality, and lower-than-expected treatment efficacy.[6]
- The followME Fabry Pathfinders registry (EUPAS20599) is evaluating safety, effectiveness and patient-reported outcomes for current Fabry disease treatments in a real-world clinical setting.
- Here, we present the renal, cardiac and clinical event outcomes in a cohort of patients who had received migalastat for at least 3 years as of August 12, 2022. These patients represented a population with clinically significant Fabry disease in which to assess real-world migalastat use.[7]

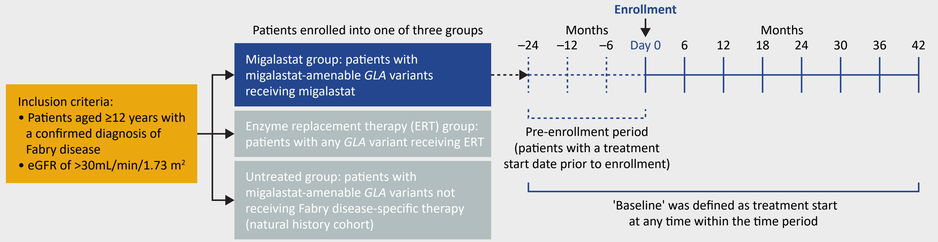
Conclusions

- The followME Pathfinders registry will provide ongoing real-world data as it continues to mature.
- Patients with Fabry disease and amenable mutations who were treated with migalastat exhibited stable renal function over an average of 3.9 years in a real-world clinical setting.
- Overall, these data support sustained and multisystemic migalastat effectiveness in an amenable Fabry population that is older and has a higher cardiac risk as reflected in the stable estimated glomerular filtration rate (eGFR) and observed Fabry-associated clinical events (FACEs) incidence in real-world clinical practice.

Methods

- After enrollment, patients will be followed-up for up to 5 years.
- Here, we report effectiveness and safety outcomes which include renal and cardiac measures, and incidence and occurrence of FACEs: predefined cardiac, cerebrovascular and renal events.[8] Occurrence and incidence of serious adverse events is also being collected.
- Patients are eligible to enter the registry if they have a treatment start date within 24 months prior to enrollment or if they did not receive treatment in the last 24 months
  - For longitudinal assessments, data are anchored at enrollment (day 0):
    - For patients with a treatment start date prior to enrollment, the pre-enrollment period is defined in 6-month intervals prior to enrollment going back to the treatment start date
    - For patients who did not have a treatment start date prior to enrollment, all retrospective data in the prior 24 months are included, but no pre-enrollment period is defined
    - To prevent undercounting, events without a date were attributed to the migalastat treatment period.

FollowME study design and analyses to account for patients starting migalastat treatment at different timepoints prior to their enrollment into the registry



Results

Patient demographics and characteristics at enrollment

A total of 125 patients had at least 3 years of migalastat exposure[7] with a total exposure to migalastat of 493 patient-years*

Migalastat group	Overall	Males	Females
n (%)	125 (100)	75 (60.0)	50 (40.0)
Age (years)			
Median (range)	58.0 (16.0–77.0)	57.0 (16.0–75.0)	60.0 (18.0–77.0)
>40 years, n (%)	102 (81.6)	59 (78.6)	43 (86.0)
≤40 years, n (%)	23 (18.4)	16 (21.3)	7 (14.0)
Race, n (%)			
Caucasian	124 (99.2)	74 (98.7)	50 (100)
Asian	1 (0.8)	1 (1.3)	0 (0)
Ethnicity, n (%)			
Hispanic or Latino	23 (18.4)	12 (16.0)	11 (22.0)
Not Hispanic or Latino	80 (64.0)	52 (69.3)	28 (56.0)
Not reported	22 (17.6)	11 (14.7)	11 (22.0)

*Based on the sum of all patients' treatment duration starting at 2 years prior to enrollment until the end of treatment or the last available treatment date.

Reported pregnancies in Table S1

- In total, 60.0% of patients were male and the median age was 58.0 years; 102 patients (81.6%) were over 40 years of age.
- The mean migalastat exposure for the 125 patients was 3.9 years
  - Prior to enrollment in the registry, 116 patients had received a mean of 1.0 years of migalastat exposure.
- The most common amenable variants were p.N215S, which was seen in 30.4% of patients and was most frequently represented in males compared with females, as well as p.S238N (8.0%) and p.F113L (7.2%).

GLA gene variants in Table S2

- Hearing loss was the most frequent sign/symptom of Fabry disease reported by patients at enrollment (36.8%), with over a third of patients also reporting acroparesthesia and gastrointestinal symptoms.
- 33/50 (66.0%) of females and 46/75 (61.3%) of males reported multi-organ involvement.

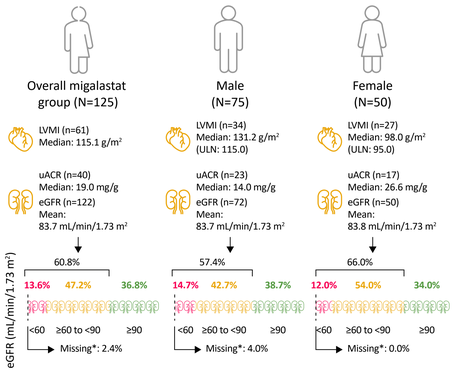
Signs/symptoms in Table S3

Renal and cardiac function at enrollment

- Nearly 14% of patients had renal impairment with an eGFR <60 mL/min/1.73 m².
- Although sample size was small, females had a higher median urine albumin creatinine ratio (uACR) than males at enrollment.

uACR by categories in Figure S1

A meaningful proportion of patients had renal involvement at enrollment, as well as significant cardiac involvement with median left ventricular mass index (LVMI) above the cutoff for LVH in both sexes



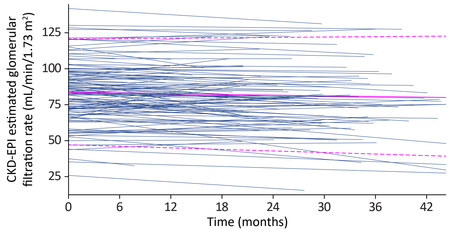
*Values >150 or <20 mL/min/1.73 m² are set to 'missing', which resulted in 4 patients with excluded eGFR values; 3 patients had values <20 mL/min/1.73 m², one of which had an eGFR value of 0.02 mL/min/1.73 m², and 1 patient had an eGFR value of 202.0 mL/min/1.73 m². ULN, upper limit of normal.

LVMI, eGFR and uACR data in Table S1

Renal effectiveness

- These results are consistent with long-term renal data from clinical trials where mean annualized eGFR Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) change from baseline was –1.6 mL/min/1.73 m² for both ERT-naïve and ERT-experienced patients.[9]

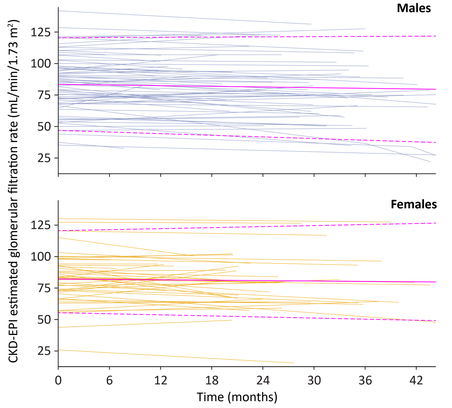
The median eGFR CKD-EPI annualized rate of change for all patients was –1.2 (Q1 –3.7, Q3 1.0) mL/min/1.73 m²/year



Solid magenta line indicates the mean eGFR CKD-EPI annualized rate of change; dashed magenta line indicates the 5th and 95th percentiles, respectively, of the eGFR CKD-EPI annualized rate of change. Annualized rate of eGFR change was calculated using three or more data points for 91/116 patients and two data points for 25/116 patients.

eGFR over time in Figure S2

A similar median rate of change was observed for males (–1.4 [Q1 –3.7, Q3 1.1]) and females (–1.1 [Q1 –3.4, Q3 1.0])



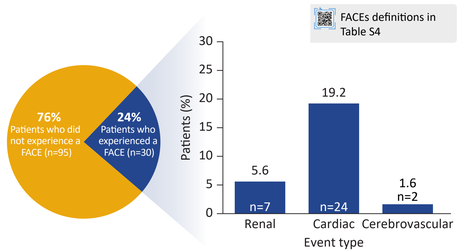
Solid magenta line indicates the mean eGFR CKD-EPI annualized rate of change; dashed magenta line indicates the 5th and 95th percentiles, respectively, of the eGFR CKD-EPI annualized rate of change.

eGFR over time by sex in Figure S2

Incidence of FACEs

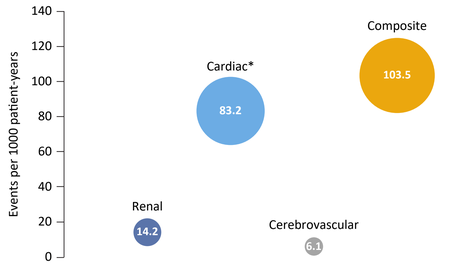
- The 24% of patients experiencing FACEs in this study was similar to clinical trial reports in which 17.5% of migalastat-treated patients and 27% of ERT-treated patients experienced FACEs over a median 5-year follow-up.[8]
- One death occurred due to a cardiac event in a male patient at 30 months post-enrollment. The patient was 66 years old at enrollment, was diagnosed with Parkinson's disease in 2009 and Fabry disease in 2018, and had the p.N215S variant. This patient had no history of FACEs documented at enrollment.

During the mean 3.9 years of migalastat exposure, 76% of patients did not experience a FACE



FACEs definitions in Table S4

A higher incidence of cardiac events was observed in this patient cohort compared to other FACEs



*Includes one death due to a cardiac event.

- Incidence rates are comparable to reports in ERT-treated patients from clinical trials where 61 events per 1000 patient-years were reported over a 5-year follow-up period, with 96 events per 1000 patient-years observed in patients ≥40 years old at ERT initiation.[8,10]

Study limitations

- It should be noted that when considering the low patient numbers for uACR and LVMI, and the rate of proteinuria and LVH, there may have been ascertainment bias in collecting and reporting these parameters in patients with more severe disease. Data validation is currently ongoing.
- followME is a registry reflective of real-world treatment practices, and data prior to enrollment have been collected retrospectively so may not be complete.
- Events were captured as reported by the study center according to the registry criteria; analysis did not include central review.

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