Received: 22 December 2023 | Revised: 3 June 2024 | Accepted: 19 June 2024

DOI: 10.1002/jimd.12773

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Clinical outcomes in patients switching from agalsidase beta to migalastat: A Fabry Registry analysis

Antonio Pisani[1] | **Kathryn M. Wilson**[2] | **Julie L. Batista**[3] | **Ilkka Kantola**[4] | **Alberto Ortiz**[5,6] | **Juan Politei**[7] | **Laila Al-Shaar**[3] | **Manish Maski**[3] | **Ana Crespo**[3] | **Elvira Ponce**[3] | **Aleš Linhart**[8,9]

[1]Department of Public Health, University of Naples Federico II, Naples, Italy

[2]Navitas Data Sciences, Pottstown, Pennsylvania, USA

[3]Sanofi, Cambridge, Massachusetts, USA

[4]Division of Medicine, Turku University Hospital, Turku University, Turku, Finland

[5]Jiménez Díaz Foundation University Hospital and IIS-Fundación Jiménez Díaz UAM, Madrid, Spain

[6]Department of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

[7]Neurology Department, Fundación SPINE, Buenos Aires, Argentina

[8]Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic

[9]General University Hospital, Prague, Czech Republic

Correspondence
Antonio Pisani, Department of Public Health, University of Naples Federico II, Via S. Pansini 5, Naples 80131, Italy.
Email: antonio.pisani13@gmail.com

Funding information
Sanofi

Communicating Editor: Areeg El-Gharbawy

Abstract

Fabry Registry data were analyzed among 83 agalsidase beta-treated patients with Fabry disease who switched to migalastat. Outcomes (estimated glomerular filtration rate [eGFR], urine protein-creatinine ratio [UPCR], plasma globotriaosylceramide [GL-3], plasma globotriaosylsphingosine [lyso-GL-3], interventricular septal wall thickness [IVST], left posterior wall thickness [LPWT], left ventricular mass index [LVMI]) were assessed using linear mixed models to estimate annual change over time in the pre- and postswitch periods. eGFR decreased throughout both periods (preswitch: −0.85 mL/min/1.73 m^2/year; postswitch: −1.96 mL/min/1.73 m^2/year; both $p < 0.0001$), with steeper decline postswitch ($p_{pre/post} = 0.01$) in both classic and late-onset patients. UPCR increased significantly postswitch ($p_{pre/post} = 0.003$) among classic patients and was stable in both periods among late-onset patients. GL-3 trajectories worsened postswitch across phenotypes ($p_{pre/post} = 0.0005$ classic, 0.02 late-onset). LPWT was stable preswitch (0.07 mm/year, $p = 0.25$) and decreased postswitch (−0.51 mm/year, $p = 0.0005$; $p_{pre/post} = 0.0009$), primarily among late-onset patients. IVST and LVMI slopes varied significantly by phenotype. Among classic patients, IVST and LVMI were stable and decreasing, respectively preswitch and increasing postswitch ($p_{pre/post} = 0.02$ IVST,

Article Guarantor: Manish Maski

0.01 LVMI). Among late-onset patients, IVST significantly decreased postswitch ($p_{pre/post} = 0.0003$); LVMI was stable over time ($p_{pre/post} = 0.89$). Ultimately, eGFR and GL-3 trajectories worsened postswitch across phenotypes, while UPCR and cardiac measures worsened among classic and stabilized/improved among late-onset patients. These findings indicate variability in long-term outcomes after switching from ERT to migalastat, underscoring the importance of careful monitoring.

KEYWORDS

agalsidase beta, chaperone, enzyme replacement therapy (ERT), Fabry disease, migalastat

1 | INTRODUCTION

Fabry disease (OMIM #301500) is a rare, X-linked lysosomal storage disorder caused by pathogenic variants in the gene encoding α-Galactosidase A (α-Gal A), leading to deficiency in α-Gal A activity and accumulation of globotriaosylceramide (GL-3), globotriaosylsphingosine (lyso-GL-3), and other substrates in various tissues, causing progressive tissue damage and organ impairment.[1,2] Fabry disease is typically categorized as classical, with little or no residual α-Gal A activity usually due to missense and nonsense *GLA* variants, or late-onset, often characterized by predominant cardiac involvement, in which many patients have a higher level of residual enzyme activity frequently due to missense variants or *GLA* gene splicing site variants, although enzyme activity and presentation can be variable, particularly in females due to lyonization.[3–6]

Reversal of symptoms or prevention of disease progression is the goal for most parameters associated with Fabry disease.[7] Since 2001, standard of care in Fabry disease has been enzyme replacement therapy (ERT); there are several ERT therapies available that differ in dosing and indication.[1,4,8–11] The ability of ERT to reduce GL-3 accumulation and slow or halt disease progression is well-documented, although differences in efficacy have been observed between different types and doses of ERT.[4,12–14] The oral small-molecule therapy migalastat (Galafold®/Amicus Therapeutics; 123 mg once every other day at the same time of day), approved in 2016 for use in patients with amenable *GLA* variants, has been evaluated in trials of ERT-naïve and ERT-experienced patients as well as real-world studies.[15–19] Migalastat is a competitive inhibitor of α-Gal A that can, at lower concentrations, act as a chaperone and is thought to stabilize the endogenous α-Gal A enzyme in patients with amenable variants, mediating movement from the endoplasmic reticulum into the lysosome, where it exerts its activity.[16,20,21]

Migalastat product labeling references in vitro amenability, based on activity in human embryonic kidney (HEK-293) cells transfected with *GLA* mutants and incubated with migalastat, not on evidence of clinical improvement.[16,20] In amenable variants, α-Gal A activity in HEK-293 cells increases ≥1.2-fold with an absolute increase of ≥3% over wild-type α-Gal A activity in the presence of 10 μmol/L migalastat.[22] Currently, there are >1300 amenable variants identified, with regional variations in amenability definitions and product labeling.[23] Some amenable variants are of unknown clinical significance or are known to be benign. Amenability assays have reproducibility challenges; one published assay of 59 *GLA* variants listed as amenable found discordant results for 6 variants.[24]

Although clinical and real-world data demonstrate favorable responses to migalastat in many patients, there are reports indicating that some patients do not respond well or may experience worsening conditions after switching from ERT to migalastat.[15,17,18,25–30] In order to help identify these patients in clinical practice, the current analysis uses data from the Fabry Registry to formally explore this possibility. The objective of this study was to analyze within-patient clinical outcomes, including renal and cardiac measures, biomarkers, and Fabry symptoms, among those who switched their primary Fabry therapy from agalsidase beta to migalastat. Within-patient clinical outcomes were compared during the preswitch (agalsidase beta-treated) and postswitch (migalastat-treated) time periods.

2 | METHODS

2.1 | Study design and participants

The Fabry Registry (NCT00196742, sponsored by Sanofi) is an ongoing observational program tracking clinical outcomes for patients with Fabry disease, regardless of

treatment status or treatment type.[31] Patients undergo clinical assessments and receive care at the discretion of their treating physician.

Fabry Registry data collected up to April 7, 2023, were analyzed. Included patients (Figure 1) had known disease-causing *GLA* variants, were treated with agalsidase beta as their first primary therapy and with migalastat as their second primary therapy for Fabry disease, had ≥1 year of uninterrupted agalsidase beta treatment immediately prior to the switch, ≥6 months of uninterrupted migalastat treatment immediately following the switch, and ≤1 month interruption between the two periods. Five patients who switched back to agalsidase beta within 6 months of initial migalastat treatment were excluded. Patients were required to be ≥16 years at first treatment (aligning with ATTRACT[17] and FACETS[15]), have no renal events (dialysis or transplant; migalastat is not recommended in patients who have eGFR <30 mL/min/1.73 m^2)[16] prior to 6 months after the migalastat switch date, and at least one Registry record on an outcome of interest after treatment initiation.

Outcomes were measured during the *preswitch period*, from the date of agalsidase beta initiation until the date of migalastat initiation (*switch date*); and the *postswitch period*, the migalastat-treated period from the date of migalastat initiation until the end of follow-up (Figure 2). The end of migalastat follow-up was the earliest of a treatment change, >3-month interruption in migalastat treatment, or a renal event, death, or the most recent Registry follow-up assessment.

2.2 | Outcome assessments

eGFR was assessed using the creatinine-based 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[32] Assessments reflecting acute kidney injury were excluded (see Table 2 footnote for details). Urine protein-creatinine ratio (UPCR) was based on 24-h urine collection when possible and spot urine assessments otherwise. Proteinuria was defined using UPCR when possible and urine albumin-creatinine ratio (UACR) otherwise; values of UPCR >0.5 mg/mg and UACR >0.3 mg/mg were considered proteinuric.

Fabry biomarker outcomes included plasma GL-3 and plasma lyso-GL-3, measured by Genzyme or LabCorp/Covance (considered comparable based on previous internal validation).

Echocardiogram measures included interventricular septal wall thickness (IVST), left posterior wall thickness (LPWT), and left ventricular mass index (LVMI). LVMI was calculated as left ventricular mass (LVM) divided by body surface area (BSA), with LVM calculated using reported values for left ventricular end-diastolic diameter, IVST, and LPWT,[33] and BSA calculated using the Mosteller formula.[34] Because few patients had MRI results in the Registry, only echocardiogram measures were used. Fabry symptoms of abdominal pain, diarrhea, peripheral pain and acute pain crisis were all assessed using binary yes/no responses. The frequency and timing of assessments varied across patients.

2.3 | Clinical characteristics

Patients were classified as having classic, late-onset, or other/unclassified/missing Fabry disease phenotypes using the International Fabry Disease Genotype–Phenotype database[35] (version August 15, 2018; on file). Patients were classified as having an amenable *GLA* variant for migalastat if their variant was on any approved amenable variant list compiled across countries, including historical lists when possible.

2.4 | Statistical analysis

Throughout this analysis, results are presented for the overall study population and separately for males, females, classic phenotype, late-onset phenotype (including the p.N215S variant), and for patients with the p.N215S variant alone, when sample sizes were ≥5. Descriptive analysis of demographic and clinical information was conducted overall and for subgroups. Third party consultation and review of statistical analyses were obtained.

2.4.1 | Comparison of last pre- versus last postswitch assessments

Among patients with at least one assessment in each time period, the last preswitch assessment was compared to the last (i.e., most recent) postswitch assessment. For continuous measures, mean and median paired differences (i.e., within- or intrapatient differences) were calculated with bootstrap 95% confidence intervals (CIs). CIs that do not include zero indicate statistical significance. The last pre- and last postswitch assessments for the binary outcomes were compared using McNemar's exact test.

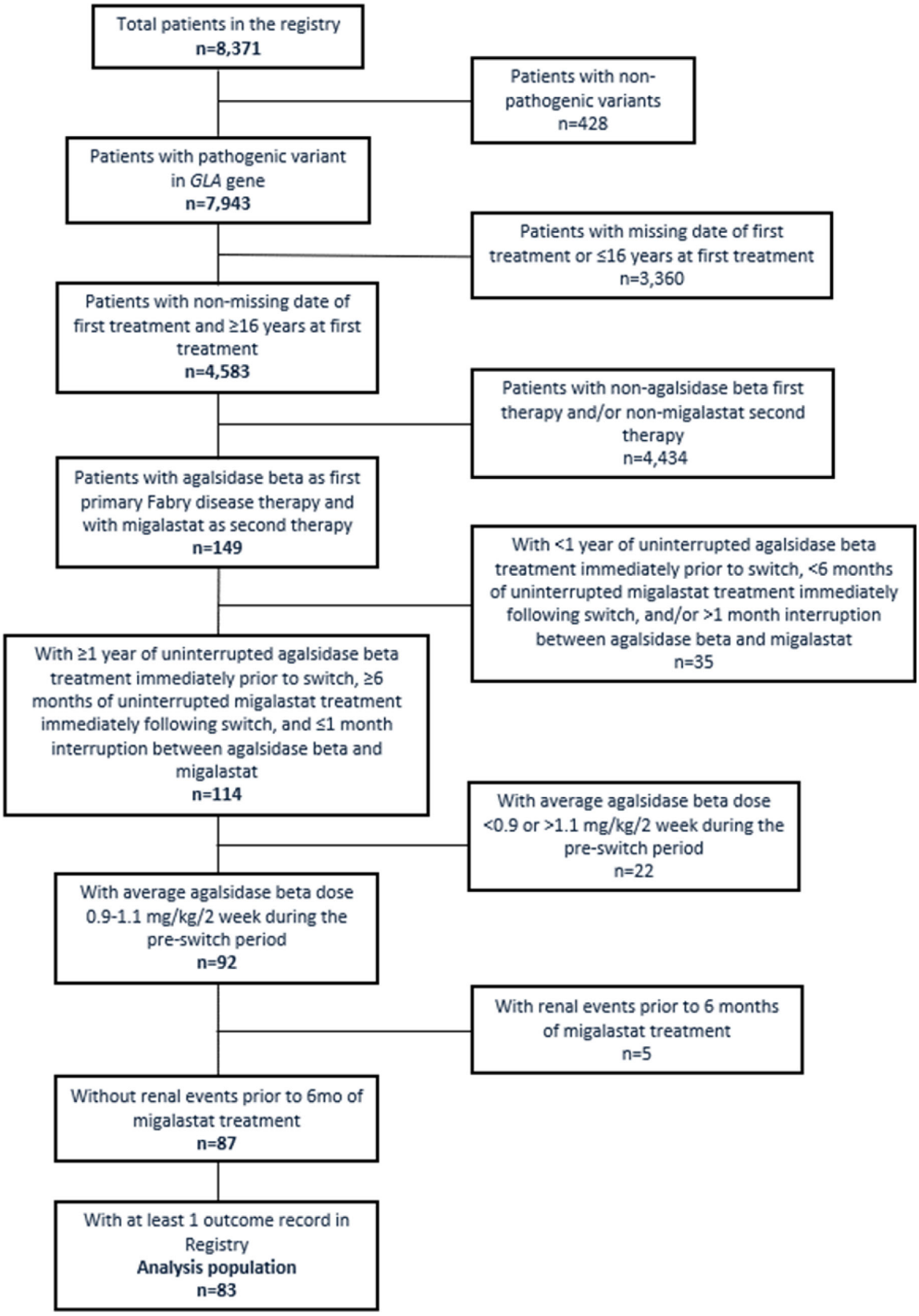

FIGURE 1 Derivation of study population. *Note*: Renal events included kidney transplant or chronic dialysis (>40 days).

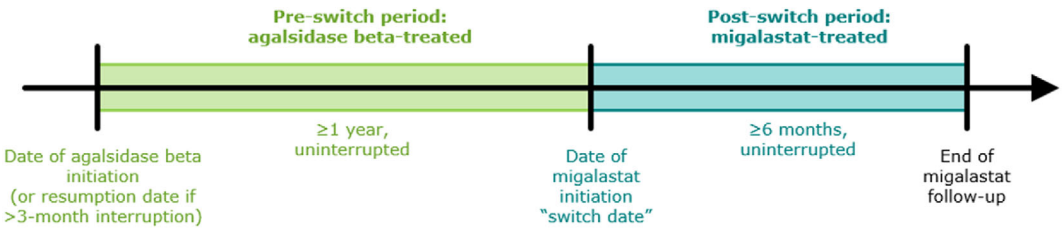

FIGURE 2 Study design and observation periods. *Note*: For patients with interruptions of >3 months during agalsidase beta treatment, the *preswitch* period began after the interruption, on the date of resumption of agalsidase beta treatment, and observations prior to or during the >3-month interruption were not included.

2.4.2 | Pre- and postswitch outcome trajectories

Trajectories for continuous outcomes were estimated using linear mixed models, with slopes representing the estimated annual change in the outcome during the pre- and postswitch time periods. Fixed effects included intercept, time relative to switch date, time by time–period interaction (to allow different pre- and postswitch slopes), age at switch date (continuous), sex, and phenotype (classic/late-onset/other). A random intercept was included. *p*-Values were generated to assess the difference from 0 of the pre- and postswitch slopes ($p_{\text{from 0}}$, i.e., stability over time) and to assess the difference between pre- and postswitch slopes ($p_{\text{pre vs. post}}$); $p_{\text{pre vs. post}} < 0.05$ indicates a significant difference in outcome trajectories in the two periods. Models were fit using restricted maximum likelihood (REML) estimation and an unstructured covariance matrix. UPCR was natural log-transformed in all models to improve model fit; as a result, slopes for UPCR are presented as percent change/year rather than units/year. Model fit was assessed by visual inspection of QQ plots of scaled marginal residuals and scatter plots of scaled residuals versus predicted values. For all models, fixed effects for age, sex, and phenotype were included based on improved model fit (lower Akaike information criterion) for most outcomes.

The probability of experiencing proteinuria or Fabry symptoms over time was estimated using logistic mixed models (generalized linear mixed models with a logit link function and binomial distribution). Results are presented as odds ratios (ORs) for the risk of experiencing symptoms per one-year increment; OR <1 indicates decreasing risk over time and OR >1 indicates increasing risk. Fixed and random effects were as for the continuous outcome models. Models were fit using maximum likelihood estimation based on a 50-point adaptive Gaussian quadrature and an unstructured covariance matrix.

The primary mixed model analyses included patients with at least one preswitch and one postswitch assessment for a given outcome. "Overall" models were fit for the full study population to estimate pre- and postswitch slopes across all patients (i.e., all phenotypes and both sexes). Models were also fit allowing separate slopes by (1) phenotype (classic vs. late-onset), and (2) sex. In models with separate slopes by phenotype, patients with other/unknown/unclassified phenotypes were excluded. The statistical significance of differences in slopes by phenotype or sex was tested using likelihood ratio tests (LRT) comparing models with and without separate slopes by subgroup (using maximum likelihood rather than REML estimation). An LRT *p*-value <0.05 indicates that trajectories vary significantly between subgroups ($p_{\text{diff by pheno}}$).

We performed a number of sensitivity analyses to assess the stability of our results, including models (1) restricted to patients with at least 2 records in each period, (2) restricted to patients with at least one record in each period and a postswitch record ≥12 months after the switch date, (3) restricted to assessments done at age ≥40 years (to assess the impact of age), and (4) restricted to patients with ≤5 years of agalsidase beta treatment prior to the switch date (to assess the impact of treatment duration). Finally, analyses were repeated excluding patients who switched back to agalsidase beta from migalastat after ≥6 months, to examine whether findings were driven by a small number of patients who responded poorly to migalastat.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Table 1 summarizes baseline demographics and clinical characteristics. There were 44 (53%) males, 39 (47%) females, 34 (41%) classic, 38 (46%) late-onset, and 11 (13%) other/unclassified/missing phenotype patients. Approximately one-quarter of the population ($n = 22$,

TABLE 1 Demographic and baseline clinical characteristics.

Parameters	Total ($N = 83$)	Classic phenotype ($N = 34$)	Late-onset phenotype ($N = 38$)	Male ($N = 44$)	Female ($N = 39$)	p.N215S ($N = 22$)
Sex						
Male, *n* (%)	44 (53.0)	17 (50.0)	22 (57.9)	44 (100.0)	—	16 (72.7)
Female, *n* (%)	39 (47.0)	17 (50.0)	16 (42.1)	—	39 (100.0)	6 (27.3)
Country/Region, *N*	83	34	38	44	39	22
EMA-regulated,[a] *n* (%)	23 (27.7)	9 (26.5)	10 (26.3)	13 (29.5)	10 (25.6)	6 (27.3)
The United States, *n* (%)	47 (56.6)	20 (58.8)	21 (55.3)	21 (47.7)	26 (66.7)	12 (54.5)
Other,[b] *n* (%)	13 (15.7)	5 (14.7)	7 (18.4)	10 (22.7)	3 (7.7)	4 (18.2)
Fabry phenotype						
Classic, *n* (%)	34 (41.0)	34 (100.0)	0	17 (38.6)	17 (43.6)	0
Late-onset, *n* (%)	38 (45.8)	0	38 (100.0)	22 (50.0)	16 (41.0)	22 (100.0)
Other/Unclassified/ Missing, *n* (%)	11 (13.3)	0	0	5 (11.4)	6 (15.4)	0
p.N215S *GLA* variant, *n* (%)	22 (26.5)	0	22 (57.9)	16 (36.4)	6 (15.4)	22 (100.0)
Nonamenable Migalastat *GLA* variants, *n* (%)	1 (1.3)	1 (2.9)	0	1 (2.3)	0	0
Age at Fabry diagnosis in years, median (25th, 75th)	41.6 (31.1, 54.1)	35.1 (22.4, 45.0)	47.1 (33.3, 59.0)	37.6 (28.5, 51.5)	41.7 (33.4, 55.1)	49.4 (32.4, 61.4)
Age at start of preswitch period in years, median (25th, 75th)	44.2 (34.3, 55.0)	38.0 (31.8, 47.2)	49.5 (35.0, 62.2)	42.8 (32.9, 51.6)	47.2 (35.6, 60.0)	49.9 (33.5, 62.2)
Duration of preswitch period in years, median (25th, 75th)	3.7 (2.1, 6.4)	3.8 (2.6, 12.3)	3.5 (2.0, 6.0)	3.8 (2.1, 7.1)	3.5 (2.1, 6.2)	3.1 (1.7, 5.2)
Age at start of postswitch period in years, median (25th, 75th)	50.2 (37.7, 59.7)	46.7 (36.2, 57.5)	52.1 (43.6, 63.4)	49.1 (37.6, 56.9)	53.0 (43.7, 62.4)	51.4 (40.8, 63.4)
Duration of postswitch period, years in years, median (25th, 75th)	2.6 (1.5, 3.7)	2.2 (1.0, 3.4)	2.9 (2.0, 3.9)	2.4 (1.5, 3.7)	2.8 (1.5, 3.7)	2.8 (2.0, 3.9)
Reason for end of postswitch follow-up						
End of Registry follow-up, *n* (%)	74 (89.2)	28 (82.4)	36 (94.7)	40 (90.9)	34 (87.2)	21 (95.5)
>3 month interruption in migalastat, *n* (%)	1 (1.2)	1 (2.9)	0	0	1 (2.6)	0
Resumption of agalsidase beta treatment, *n* (%)	8 (9.6)	5 (14.7)	2 (5.3)	4 (9.1)	4 (10.3)	1 (4.5)

[a]Includes EU countries and European countries that follow EMA guidance.
[b]Includes Australia, Canada, the United Kingdom, Republic of Korea, and Argentina.

27%) had the p.N215S variant. Among patients with known genotype ($n = 79$), all but one had a migalastat-amenable *GLA* variant. Eight patients (10%) discontinued migalastat and switched back to agalsidase beta during the observation period. The median duration of the preswitch (agalsidase beta-treated) period was 3.7 years, compared with 2.6 years for the postswitch (migalastat-treated) period. Median age at switch was 50.2 years.

TABLE 2 Last preswitch to last postswitch comparison.

	Total		Classic phenotype		Late-onset phenotype	
Parameter/Statistic	**Preswitch**	**Postswitch**	**Preswitch**	**Postswitch**	**Preswitch**	**Postswitch**
eGFR (mL/min/1.73 m^2), *n*	**58**		**24**		**26**	
Median (25th, 75th)	86.7 (75.9, 105.1)	89.2 (73.4, 99.7)	88.2 (77.5, 106.0)	89.7 (78.8, 107.6)	84.8 (73.7, 110.2)	79.5 (68.1, 96.7)
Mean within-patient difference (95% CI)	**−3.19 (−6.27, −0.11)**		−1.59 (−6.27, 3.08)		**−7.03 (−11.53, −2.54)**	
Median within-patient difference (95% CI)	−1.89 (−5.18, 1.69)		−1.88 (−7.17, 2.61)		−4.74 (−10.24, 1.44)	
UPCR (mg/mg), *n*	**35**		**11**		**15**	
Median (25th, 75th)	0.14 (0.10, 0.37)	0.18 (0.09, 0.32)	0.22 (0.12, 1.08)	0.20 (0.10, 0.73)	0.12 (0.07, 0.40)	0.17 (0.08, 0.31)
Mean within-patient difference (95% CI)	0.09 (−0.10, 0.29)		0.34 (−0.21, 0.89)		−0.04 (−0.19, 0.12)	
Median within-patient difference (95% CI)	0.02 (−0.02, 0.07)		0.03 (−0.33, 0.36)		0.02 (−0.06, 0.10)	
Plasma GL-3 (μg/mL), *n*	**27**		**12**		**11**	
Median (25th, 75th)	2.2 (1.9, 2.8)	2.9 (2.4, 3.8)	2.2 (1.0, 2.8)	3.0 (2.3, 5.3)	2.2 (2.0, 2.4)	2.8 (1.9, 3.2)
Mean within-patient difference (95% CI)	**1.25 (0.61, 1.88)**		**1.96 (1.06, 2.87)**		0.25 (−0.56, 1.05)	
Median within-patient difference (95% CI)	**1.22 (0.38, 2.15)**		**1.99 (1.07, 3.00)**		0.36 (−0.45, 1.09)	
Lyso-GL-3 (ng/mL), *n*	**22**		**9**		**9**	
Median (25th, 75th)	0.2 (0.2, 5.9)	3.0 (0.6, 6.3)	2.1 (0.2, 9.2)	6.3 (3.6, 67.0)	0.2 (0.2, 0.2)	0.5 (0.3, 0.8)
Mean within-patient difference (95% CI)	**10.95 (1.11, 20.78)**		**25.23 (4.77, 45.69)**		−0.01 (−1.20, 1.18)	
Median within-patient difference (95% CI)	1.50 (−1.41, 3.80)		6.15 (−31.99, 31.83)		0.32 (−0.28, 0.87)	
IVST (mm), *n*	**36**		**14**		**17**	
Median (25th, 75th)	12.8 (10.0, 16.0)	12.4 (9.9, 17.0)	13.5 (11.0, 15.0)	14.0 (12.3, 17.0)	12.0 (9.0, 21.0)	12.0 (9.0, 18.4)
Mean within-patient difference (95% CI)	−0.38 (−1.40, 0.64)		1.01 (−0.46, 2.48)		−1.32 (−2.84, 0.19)	
Median within-patient difference (95% CI)	0.00 (−0.62, 0.76)		0.95 (−0.03, 2.50)		0.00 (−0.60, 1.20)	
LPWT (mm), *n*	**36**		**16**		**16**	
Median (25th, 75th)	11.9 (9.0, 14.0)	11.0 (9.0, 12.9)	11.9 (10.5, 13.5)	11.7 (9.5, 15.5)	11.0 (8.5, 13.5)	10.0 (8.3, 12.0)
Mean within-patient difference (95% CI)	−0.55 (−1.79, 0.70)		0.37 (−0.93, 1.67)		−1.16 (−3.61, 1.28)	
Median within-patient difference (95% CI)	−0.55 (−1.54, 0.36)		0.15 (−0.88, 1.02)		**−1.00 (−2.29, −0.24)**	
LVMI (g/m^2), *n*	**26**		**12**		**10**	
Median (25th, 75th)	96.4 (74.5, 134.7)	90.3 (76.4, 125.9)	98.9 (75.3, 122.2)	97.5 (81.9, 139.2)	94.6 (65.5, 117.3)	83.0 (62.1, 125.9)
Mean within-patient difference (95% CI)	−4.26 (−14.36, 5.83)		5.59 (−10.39, 21.57)		−7.96 (−18.68, 2.75)	
Median within-patient difference (95% CI)	0.52 (−5.37, 7.62)		4.78 (−6.57, 14.54)		−2.66 (−14.70, 12.39)	

Note: Bold text indicates statistical significance ($p < 0.05$). Late-onset phenotype includes N215S patients. Within-patient differences were calculated by subtracting the preswitch from the postswitch measurement. eGFR records reflecting acute kidney injury were excluded from the analysis (defined as a ≥30% decline in eGFR compared to the previous record and within ≤1 year of the previous record, or ≥30% decline in eGFR compared to the previous record and within >1 and ≤2 years of the previous record, if a subsequent record then showed a regain of at least 50% of the loss in eGFR).

3.2 | Outcomes

3.2.1 | Last preswitch and last postswitch assessment comparisons

Table 2 presents results of the last preswitch and last postswitch assessment comparison overall and among classic and late-onset patients (results by sex and for p.N215S patients alone are in Table S1). eGFR decreased significantly in the last post- versus last preswitch assessment, overall and in late-onset patients (overall mean within-patient difference: −3.19 mL/min/1.73 m^2 [95% CI: −6.27, −0.11]). However, the median within-patient difference was smaller and not statistically significant (−1.89 mL/min/1.73 m^2 [95% CI: −5.18, 1.69]). The difference between the mean and median changes indicates variability in patient responses, with a subset experiencing large increases in eGFR in the postswitch period. There were no significant within-patient differences in UPCR or risk of proteinuria (Table S2) at the last pre- versus last postswitch assessments, overall or by phenotype. However, the mean within-patient difference in classic patients was 0.34 mg/mg, while the median difference was 0.03, again suggesting wide variability in responses.

A significant increase in plasma GL-3 after switching to migalastat was reflected by both the mean (1.25 μg/mL [95% CI: 0.61, 1.88]) and median (1.22 μg/mL [95% CI: 0.38, 2.15]) within-patient differences, overall and in classic patients. While both pre- and postswitch mean and median values remained within the normal range, several patients had values markedly outside of the normal range (Figure S4), and 5 patients (18.5%) had levels changing from normal to abnormal. Some overlap between healthy controls and Fabry patients can be observed in plasma GL-3 values, unlike for lyso-GL-3.[36] No significant changes were seen in late-onset patients.

Lyso-GL-3 increased significantly postswitch based on the mean within-patient difference (10.95 ng/mL [95% CI: 1.11, 20.78]); however, the median within-patient difference was smaller and not significant (1.50 ng/mL [95% CI: −1.41, 3.80]); a significant mean increase was seen in classic, but not late-onset patients. The lyso-GL-3 response varied widely, as seen in Figure 3. A subset of patients experienced very large increases in lyso-GL-3 postswitch, while others experienced moderate increases or stability over time. In a sensitivity analysis excluding patients who switched back to agalsidase beta from migalastat after ≥6 months, a similar, though not significant, mean increase in lyso-GL-3 was observed postswitch (mean within-patient difference: 6.22 ng/mL [95% CI: −1.52, 13.96]), and the median difference was also consistent with the main analysis (1.05 ng/mL [95% CI: −1.56, 2.80]).

Overall, there were no significant mean or median within-patient differences among the echocardiogram measures (IVST, LPWT, and LVMI; Table 2). The subgroup of p.N215S patients experienced a significant mean within-patient decrease for IVST (−2.44 mm [95% CI: −4.75, −0.13], $n = 10$) but the median within-patient difference was smaller and not significant (−1.00 mm [95% CI: −3.16, 1.66]) (Table S1). A significant median within-patient decrease in LPWT was observed in late-onset patients (−1.00 mm [95% CI: −2.29, −0.24]); however, the mean within patient difference was not significant.

Fabry symptoms did not differ significantly between the preswitch and postswitch periods, although the proportion of patients reporting abdominal pain was greater after the switch (17% preswitch vs. 27% postswitch). Additional results for symptoms are shown in Table S2 and Figure S1.

3.2.2 | Linear mixed models of pre- and postswitch trajectories (estimated annual change)

Spaghetti plots showing individual patients' outcome data over time are shown in Figures S2–S7 and Figure 3. In mixed model analysis, there were significant differences in trajectories by phenotype for most outcomes, so results by phenotype are presented (Figure 4) alongside the overall models (Table S3). Results with separate slopes by sex are shown in Table S4.

Results for eGFR did not vary significantly by phenotype ($p_{\text{diff by pheno}} = 0.63$). Overall, eGFR declined significantly during both the pre- and postswitch periods (pre: −0.854 units/year [95% CI −1.142, −0.566], $p_{\text{from 0}} < 0.0001$; post: −1.957 units/year [95% CI −2.704, −1.211], $p_{\text{from 0}} < 0.0001$; Table S3), but the decline was significantly steeper after switching to migalastat ($p_{\text{pre vs. post}} = 0.01$). This pattern was seen in both classic and late-onset patients in the model with separate slopes by phenotype (Figure 4A); the differences in the pre- versus postswitch slopes were borderline significant in this model ($p_{\text{pre vs. post}} = 0.049$ for classic, 0.055 for late-onset).

UPCR slopes increased significantly postswitch ($p_{\text{pre vs. post}} = 0.02$; Table S3); this pattern was seen only in classic patients, although the difference by phenotype was not statistically significant ($p_{\text{diff by pheno}} = 0.21$). Classic patients had a significant decrease in UPCR preswitch followed by a significant increase postswitch (pre: −6.3%/year [95% CI −9.7, −2.8], $p_{\text{from 0}} = 0.0006$; post: 15.2%/year [95% CI 1.6, 30.5], $p_{\text{from 0}} = 0.03$; $p_{\text{pre vs. post}} = 0.003$; Figure 4B), while UPCR was stable in both periods for late-onset patients.

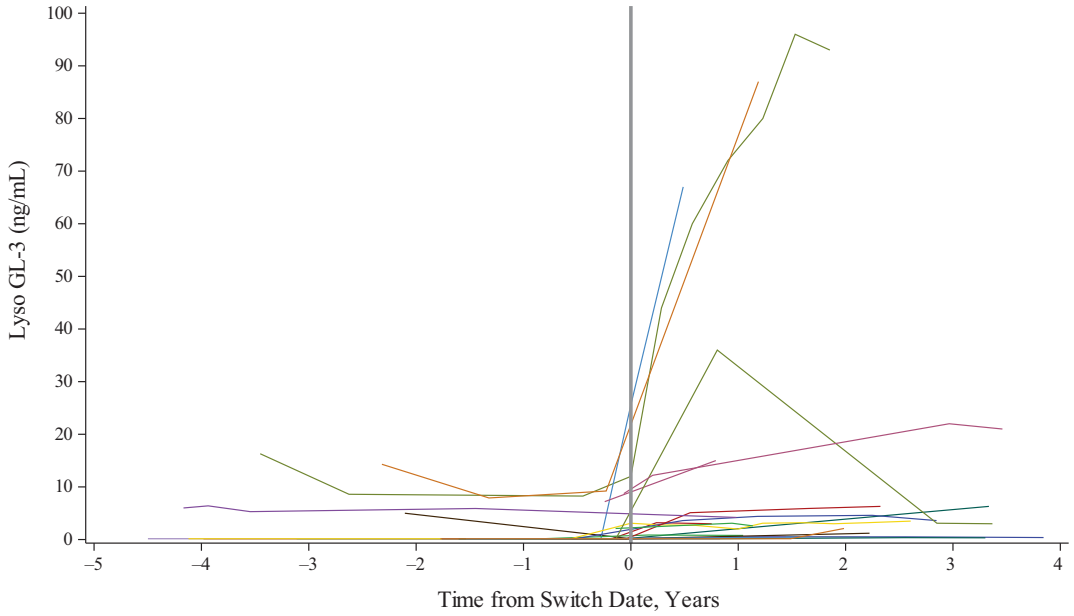

FIGURE 3 Lyso-GL-3 over time among patients with both pre- and postswitch measurements ($n = 22$). *Note*: Measurements below the limit of quantitation are set to half the value of the lowest limit of quantitation across labs.

Plasma GL-3 trajectories varied significantly by phenotype ($p_{\text{diff by pheno}} = 0.0002$), though postswitch slopes were significantly worse than preswitch slopes in both classic and late-onset patients ($p_{\text{pre vs. post}} = 0.0005$ and 0.02, respectively). Classic patients had a stable plasma GL-3 trajectory preswitch, and a significant increase over time postswitch, while late-onset patients had significantly decreasing plasma GL-3 levels preswitch, followed by stability in the postswitch period (Figure 4C).

A mixed model analysis of lyso-GL-3 was not feasible due to data heterogeneity and small sample size (Figure 3).

IVST trajectories differed significantly by phenotype ($p_{\text{diff by pheno}} < 0.0001$). Classic patients showed stability preswitch followed by a significant increase over time postswitch ($p_{\text{pre vs. post}} = 0.02$). In contrast, late-onset patients had a significant increase over time preswitch followed by a significant decrease postswitch ($p_{\text{pre vs. post}} = 0.0003$; Figure 4D).

The difference between phenotypes was not statistically significant for LPWT ($p_{\text{diff by pheno}} = 0.11$); the overall model found stability preswitch followed by a significant decrease over time postswitch ($p_{\text{pre vs. post}} = 0.0009$). In the model by phenotype, this pattern was seen only in late-onset patients ($p_{\text{pre vs. post}} = 0.03$), while classic patients were stable over both periods ($p_{\text{pre vs. post}} = 0.46$; Figure 4E).

LVMI trajectories differed significantly by phenotype ($p_{\text{diff by pheno}} = 0.02$). Classic patients showed a significant decrease over time preswitch followed by a significant increase postswitch ($p_{\text{pre vs. post}} = 0.01$), while late-onset patients had nonsignificant decreases across both periods ($p_{\text{pre vs. post}} = 0.89$; Figure 4F).

3.2.3 | Logistic mixed models of risk of proteinuria and Fabry symptoms over time

The risk of proteinuria over time in the pre- and postswitch periods was significantly different by phenotype ($p_{\text{diff by pheno}} = 0.0492$; Table S5), and results were consistent with those for UPCR as a continuous outcome above. Classic patients had significantly decreasing risk of proteinuria over time preswitch (OR = 0.83 [95% CI: 0.72, 0.96]), followed by significantly increasing risk postswitch (OR = 2.12 [95% CI: 1.01, 4.44]; $p_{\text{pre vs. post}} = 0.02$). Late-onset patients had borderline significant decreasing risk preswitch (OR = 0.62 [95% CI: 0.38, 1.01]) and stable risk postswitch, with no significant difference between the periods ($p_{\text{pre vs. post}} = 0.43$).

In the analysis of Fabry symptoms (Table S5), risk of abdominal pain was not significantly different by phenotype ($p_{\text{diff by pheno}} = 0.55$); risk was stable over time during the preswitch period and increased significantly during the postswitch period. The difference between the

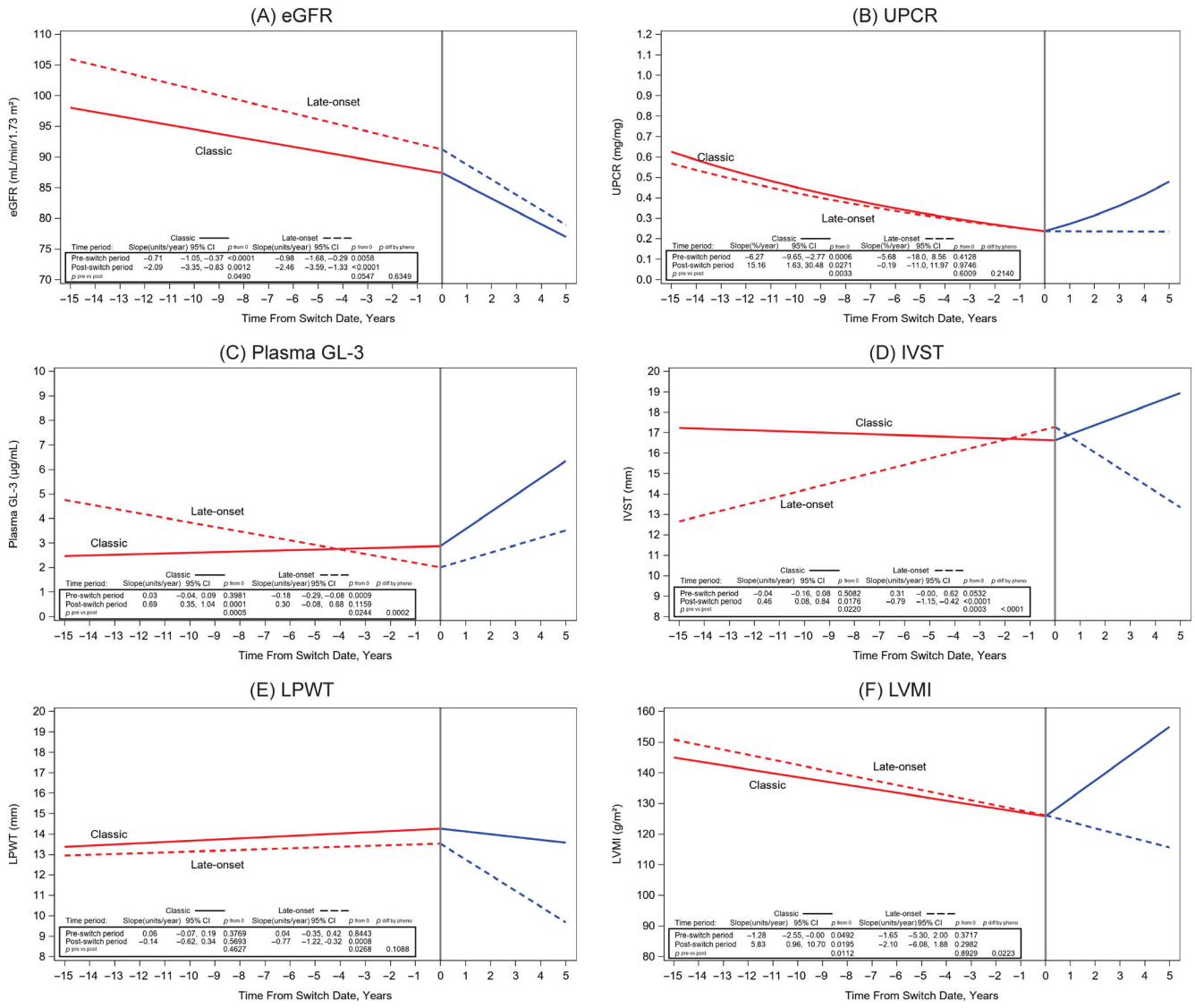

FIGURE 4 Pre- and postswitch outcome trajectories by phenotype.

two periods was borderline significant ($p_{\text{pre vs. post}} = 0.06$). The risk of diarrhea varied significantly by phenotype ($p_{\text{diff by pheno}} = 0.04$); however, the difference between the periods was not statistically significant in either classic or late-onset patients, and ORs were not significantly different from 1.

The risk of peripheral pain also varied by phenotype ($p_{\text{diff by pheno}} = 0.005$; Table S5). Classic patients had a significantly decreasing risk of peripheral pain in the preswitch period, with stable risk postswitch, though the pre–post difference was not significant ($p_{\text{pre vs. post}} = 0.61$). Late-onset patients had a borderline significant increase in risk preswitch and stable risk postswitch; this difference between periods was borderline significant ($p_{\text{pre vs. post}} = 0.07$). A logistic mixed model of acute pain crisis was not feasible due to the infrequency of this symptom.

3.2.4 | Sensitivity analyses

In addition to the main analyses, several sensitivity analyses were performed (Table S3). In sensitivity analyses of patients with ≥2 records in each time period, results were largely consistent with the main analyses. In sensitivity analysis restricted to patients with a record >12 months postswitch, the results for all outcomes except UPCR were very similar to the main analysis. Results for UPCR were no longer statistically significant, though the magnitude of the slopes was only mildly attenuated (decrease of 4.2%/year preswitch, increase of 4.2%/year postswitch). Results of a sensitivity analysis restricted to patients with ≤5 years of agalsidase beta treatment prior to the switch were also similar to the main analysis: eGFR declined significantly during the postswitch period, but not during the preswitch period. UPCR slopes in both

periods were similar to those in the main models but lost statistical significance. Plasma GL-3 decreased significantly in the preswitch period but increased significantly postswitch. LPWT decreased significantly postswitch, but the between-period difference was no longer statistically significant. As in the main analysis, there were no significant differences in IVST or LVMI.

An analysis restricted to assessments performed at age ≥40 years done for outcomes known to change with age, that is, eGFR and cardiac dimensions, were consistent with the main analysis (Table S3): eGFR declined significantly in both periods, with a significantly steeper decline postswitch, and LPWT decreased postswitch following stability over time in the preswitch period.

To address whether the main results were driven by poor treatment responses of those who discontinued migalastat, another sensitivity analysis was conducted excluding those patients ($n = 8$), with results very similar to the main analysis across all outcomes (results not shown).

4 | DISCUSSION

While migalastat efficacy and safety in patients with amenable variants have been demonstrated in clinical trials, some real-world evidence suggests the potential for variability in outcomes.[15,17,18,25–30] This Fabry Registry analysis formally explored this possibility by comparing clinical outcomes within patients treated with agalsidase beta as their first primary Fabry therapy who then switched to migalastat. Renal and cardiac measures, biomarkers, and Fabry symptoms were compared during the preswitch (agalsidase beta-treated) and postswitch (migalastat-treated) time periods.

In line with recently published guidance, the findings of the present study support careful monitoring after switching patients from ERT to migalastat.[23] In some patients with one of the >1300 *GLA* variants deemed to be amenable by product labeling, switching from agalsidase beta to migalastat resulted in changes in eGFR and plasma GL-3 that are suggestive of postswitch disease progression in both the comparison of last post- to last preswitch assessments and in linear mixed models. These results were consistent across phenotype and sex, and in an analysis excluding the 10% of patients who had switched back to agalsidase beta from migalastat after ≥6 months, suggesting that the results were not driven by patients who discontinued migalastat. UPCR assessments also indicated disease progression postswitch among classic patients in linear mixed models, although no significant within-patient differences were observed between the last post- to last preswitch assessments. The mean postswitch increase in lyso-GL-3 observed in this study contrasts with the European consensus recommendation that lyso-GL-3 should be reduced as much as possible.[7]

Linear mixed models found that LPWT decreased significantly during the postswitch period, while there were no differences in IVST and LVMI. Notably, there were several significant differences between classic and late-onset patients in cardiac outcome trajectories before and after the switch. After switching to migalastat, IVST increased and LPWT remained stable in classic patients, but both parameters decreased in late-onset patients. Consequently, LVMI also increased postswitch among classic patients; however, there was no change in late-onset patients. This may reflect some degree of LV remodeling or may in part be a result of the smaller sample size for LVMI as well as the greater potential for measurement error with this outcome given its multiple inputs.

While the comparison of last post- to last preswitch assessments found little evidence of change in echocardiogram parameters, a significant mean within-person decrease in IVST was observed in a subgroup of patients with the p.N215S variant, confirming that this late-onset variant, associated with considerable residual enzyme activity, responds well to migalastat.[37–39] Whether these results suggest a phenotype-dependent effect of migalastat on cardiac outcomes or reflect limitations associated with echocardiographic measurements is unclear and requires further study. While improvements in LVMI with migalastat treatment were demonstrated using transthoracic echocardiography in the ATTRACT and FACETS trials, more recent studies using cardiac MRI did not replicate these results.[15,17,40,41] Previous research suggests that transthoracic echocardiography may not be preferred for quantifying LVMI because of its pronounced inter- and intraobserver variability, although this may be mitigated in clinical trials through central blinded reading.[42,43] Moreover, as discussed in the FAMOUS publication, cardiac parameters such as LVMI may be influenced by ongoing disease progression leading to left ventricular posterior wall thinning in patients with progressive fibrosis, mimicking cardiac mass improvements.[18,44,45]

Both real-world and clinical trial data have demonstrated favorable responses to migalastat among patients with amenable variants. In the FAMOUS trial, which included 24 ERT-pretreated patients (57.6% of the study population) at 12 months and 33 (61.1%) at 24 months, migalastat demonstrated decreases in LVMI in the overall sample as well as in male and female subgroups at both follow-up points, and α-Gal A activity increased significantly among male patients at 12 months.[18,25]

Additionally, a post-hoc analysis of patients from the phase 3 ATTRACT and FACETS trials and subsequent open-label extension studies observed stable renal function as measured by eGFR in both ERT-naive and ERT-experienced patients treated with migalastat for up to 8.6 years.[19]

Although many patients respond well after initiating treatment with migalastat, evidence suggests a group of patients who, despite having amenable variants, do not achieve the desired clinical outcomes from migalastat therapy and/or display differing responses between organ systems.[18,25,28,29] In FAMOUS, kidney function measured by eGFR significantly declined in males and females at 12 and 24 months, and lyso-GL-3 levels were heterogeneous at 12 months, leading to a group of male patients switching back to ERT.[18,25] At 24 months, no significant changes in α-Gal A activity were observed, and a cohort of males again presented with significantly increased lyso-GL-3 levels.[18] A study evaluating amenability to migalastat using a patient-specific and mutation-specific cell model found similar results.[27] Lyso-GL-3 significantly improved among patients carrying the p.N215S variant but significantly worsened among p.L294S carriers, two of whom developed severe albuminuria after switching from ERT.[27] Of note, all patients in our analysis switched from ERT with agalsidase beta to migalastat, whereas in most previous reports, some or all of the patients switched from agalsidase alfa, which is administered at a lower dose than agalsidase beta, to migalastat. In this regard, a negative clinical impact of switching from agalsidase beta to agalsidase alfa has previously been previously observed, as has a positive impact of switching back to agalsidase beta.[13]

While the reasons for worsening outcomes among a select group of migalastat-treated patients have not yet been established, one preliminary theory involves the question of whether in vitro amenability to migalastat reliably reflects in vivo amenability, as discussed by Lenders et al. (2020), among others.[37,46] Lenders et al.[37] theorize that in some patients with variants classified as amenable based on in vitro assays, migalastat actually has an inhibitory effect, leading to adverse clinical outcomes. Although migalastat, a competitive inhibitor of *GLA*, typically increases enzymatic α-Gal A activity at subinhibitory doses, multiple factors may impact its concentration across tissue types and result in the drug becoming inhibitory at the administered dose.[37] This theory by Lenders et al. may be further explained by preclinical migalastat studies which have reported considerable variability in concentrations among different organs, with high concentrations found in kidney tissues.[47,48] Considering relatively low inhibitory concentration of migalastat to human α-Gal A (0.07 μM), these high concentrations of migalastat in kidney tissues could theoretically contribute to an inhibitory effect resulting in decreasing eGFR.[47] Research in other lysosomal storage disorders is supportive of the potential for an inhibitory effect of chaperones; clinically relevant target enzyme inhibition by chaperones has been previously observed in Pompe disease.[49] Further research is needed to confirm whether a similar effect may be observed in Fabry disease.

Renal function is an important consideration when selecting patients for migalastat, as its use is not recommended by product labeling in patients with eGFR ≤30 mL/min per 1.73 m^2 due to increased exposure to migalastat among patients with greater renal impairment; issues with GFR overestimation should be noted as creatinine-based eGFR may differ from measured GFR (mGFR) by ±30%.[16,50,51]

Female Fabry patients may have significant residual enzyme activity, which, while reducing the rate of disease progression, also has implications for treatment: if treatment has an unanticipated effect of enzyme inhibition as discussed above, residual enzyme activity may be reduced, and substrate may accumulate.[52] Thus, decreasing α-Gal A activity in a female patient, as observed in the FAMOUS trial, may be suggestive of high migalastat plasma concentrations leading to inhibition of α-Gal A.[18] Interpatient variability in α-Gal A activity in migalastat-treated patients was also observed in the previously mentioned study by Müntze et al.[38] More research is needed to determine whether different responses to migalastat might be seen among families with the same *GLA* variants, depending on enzyme concentration.

Due to the uncertainties of predicting clinical activity, it has been proposed that a patient's in vivo amenability be confirmed by measuring changes in α-Gal A activity and lyso-GL-3 from the start of migalastat treatment and after 6 months of treatment.[18] This suggestion, would, however, be less helpful in patients with low/normal baseline enzyme activity as well as in patients with target organ disease and normal lyso-GL-3 levels associated with atypical variants. Furthermore, there is disagreement among Fabry disease experts on the role of α-Gal A as a marker of in vivo amenability. A 2023 Delphi panel not only recommended measuring α-Gal A activity in leukocytes before starting migalastat and during routine follow-up but also recommended continuation of migalastat in patients with stable or improved organ function regardless of changes in α-Gal A activity.[23]

This study has several limitations. First, the "switch" study design, while selected to deal with confounding and possible noncomparability between treatment groups, allows for confounding by age and/or time on treatment, as all patients were older during the

migalastat-treated period than during the agalsidase beta-treated period. This makes interpretation of the comparison of last preswitch and last postswitch assessments difficult for outcomes that are known to worsen with age, that is, eGFR and some echocardiographic measures.[53] Confounding by age or time on treatment is less likely to explain differences in slopes between the two time periods if the underlying rate of change in these outcomes is linear over time. As the migalastat treatment period in the present study lasted a median of 2.6 years, it is unlikely that a large age-related change would be observed.

We addressed possible confounding by age and time with several sensitivity analyses. Given the possibility that eGFR and the cardiac measures may change more rapidly due to age and/or time on treatment/disease progression, we modeled the pre- and postswitch trajectories based only on assessments done at age 40 years or older, and among patients with 5 years or less of agalsidase beta treatment prior to the switch date. Reassuringly, these results were largely similar to the main analysis, although there was greater variability in LVMI results likely due to multiple inputs used in the calculation, introducing greater potential for random error. Although the overall assessment populations in this study were relatively large for a rare disease, an additional limitation includes the low patient numbers in the subgroup analyses, particularly for lyso-GL-3 and LVMI. Further, the last preswitch/last postswitch assessment comparison used a single record in each time period, introducing the potential for random variation and measurement error. Finally, the Registry has limited data from cardiac MRIs, so analysis of cardiac outcomes was limited to data from echocardiograms. In addition, the Registry does not collect information on the reason for treatment changes. It should be noted that long-term prospective outcome studies are needed to confirm the findings of this study. Monitoring of biomarkers and renal and cardiac function, as well as the collection of data on quality of life, are essential for patients on both therapies to inform decisions and optimize care in relation to individual treatment responses.

Despite the limitations of this analysis, several key attributes support its value and relevance to the greater body of literature. First, the switch design used in this study provides a within-patient comparison, which controls for possible confounding, including unknown and unmeasured factors that do not change within a patient over time. The study sample included male and female Fabry patients with both phenotypes, thus adding generalizability to the findings. Multiple records per patient were used over time in both the pre- and postswitch periods, reducing the impact of random within-person measurement error. The findings of this study are relatively consistent across different analytic approaches and are generally robust across sensitivity analyses. Finally, our findings are in line with hypothesized biological effects of both treatments, although future studies to determine the biological effects of both treatments on target organs in Fabry disease are recommended.

5 | CONCLUSION

These real-world findings of patients who switched from treatment with the ERT agalsidase beta to migalastat indicate variability in long-term outcomes with migalastat treatment, building upon a growing body of research that underscores the importance of careful monitoring after changes in treatment for Fabry disease.

AUTHOR CONTRIBUTIONS

MM conceived of the study concept, participated in the study design and the interpretation of the results, contributed to the writing of the manuscript, and supervised its development from a medical perspective. AC conceived of the study concept, participated in the study design and the interpretation of the results, and contributed to the writing of the manuscript. KMW, JLB, and LAS contributed to the design and implementation of the research, performed the statistical analyses, interpreted the results, and contributed to the writing of the manuscript. AP, IK, AO, JP, and AL participated in generating the study concept, provided important contributions to the interpretation of data, and were involved in drafting and revising the manuscript. EP participated in the interpretation of the results and contributed to the writing of the manuscript.

ACKNOWLEDGEMENTS

Editorial support was provided by Katherine O'Ruanaidh of Evidera. Statistical programming support was provided by Badari Gudivada of Sanofi, Steve Willhoite of Navitas Data Sciences, and Radhika Kollu of Navitas Data Sciences. Carlota Garcia of Sanofi assisted with the study concept and initial compilation of scientific evidence. Hans Ebels and Chase Lee, both of Sanofi, reviewed the manuscript and provided key insights.

FUNDING INFORMATION

This work was supported by Sanofi, the sponsor of the Fabry Registry, including the medical writing/editing support in the preparation of this manuscript from Evidera, and statistical programming support from Navitas Data Sciences. The authors are responsible for the content of this manuscript and the decision to submit the

manuscript for publication. Furthermore, AP, JP, AO, IK, and AL confirm independence from the sponsor and relevance of the content.

CONFLICT OF INTEREST STATEMENT

Antonio Pisani has provided expert opinion for AIFA 2023, has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events for EDTA 2023 and SIN 2023, and has received travel support for meetings. Kathryn M. Wilson is a paid contractor for Sanofi. Julie L. Batista is an employee of Sanofi and holds stock or stock options in Sanofi. Laila Al-Shaar is an employee of Sanofi and holds stock or stock options in Sanofi. Manish Maski is an employee of Sanofi and holds stock or stock options in Sanofi. Ana Crespo is an employee of Sanofi and holds stock or stock options in Sanofi. Elvira Ponce is an employee of Sanofi and holds stock or stock options in Sanofi. Ilkka Kantola has received consulting fees, payment, or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, support for attending meetings and/or travel, and participated on a data safety monitoring or advisory board for Sanofi, Amicus, and Chiesi, has received payment for expert testimony from Chiesi, holds a leadership or fiduciary role at the Finnish Society of Hypertension, and has received medical writing support from Sanofi. Alberto Ortiz has received grants from Sanofi and consultancy or speaker fees or travel support from Advicenne, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Idorsia, Chiesi, Otsuka, Novo-Nordisk, and Vifor Fresenius Medical Care Renal Pharma, is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra AstraZeneca-UAM of chronic kidney disease and electrolytes, and holds a leadership or fiduciary role on the SOMANE and ERA Councils. Juan Politei has received consulting fees, payment, or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, support for attending meetings and/or travel, and has participated on a Data Safety Monitoring Board or Advisory Board for Sanofi, Amicus, Pint Pharma, GADOR, Biomarin, Acelink, and Biosidus. Aleš Linhart has received grants or contracts from Sanofi, has received consulting fees, payment, or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Sanofi, Takeda, Amicus, and Chiesi, has received payment for expert testimony from Chiesi and Amicus Therapeutics, has received support for attending meetings and/or travel from Sanofi, has participated on a Data Safety Monitoring Board or Advisory Board for Sanofi and Amicus, and has held a leadership or fiduciary role at the Czech Society of Cardiology. Additionally, Aleš Linhart has received medical equipment from Takeda.

DATA AVAILABILITY STATEMENT

Data archiving is not mandated but data will be made available on reasonable request.

ETHICS APPROVAL

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

DECLARATION

Real-world findings from the Fabry Registry indicate variability in long-term outcomes in patients with amenable variants who switched from treatment with agalsidase beta to treatment with migalastat, highlighting the importance of careful monitoring in these patients.

INFORMED CONSENT

For each participating site, the Fabry Registry protocol, informed consent form, and any locally required authorization documents are reviewed and approved by the local fully constituted Institutional Review Board or Independent Ethics Committee.

PATIENT CONSENT STATEMENT

All patients within the Fabry Registry have provided informed consent for the use and publication of their data.

APPROVAL FOR THE USE OF LABORATORY ANIMALS

No animals were studies in this analysis.

REFERENCES

1. Germain DP. Fabry disease. *Orphanet J Rare Dis*. 2010;5:30. doi:10.1186/1750-1172-5-30
2. Svarstad E, Marti HP. The changing landscape of Fabry disease. *Clin J Am Soc Nephrol*. 2020;15(4):569-576. doi:10.2215/cjn.09480819
3. Arends M, Wanner C, Hughes D, et al. Characterization of classical and nonclassical Fabry disease: a multicenter study. *J Am Soc Nephrol*. 2017;28(5):1631-1641. doi:10.1681/asn.2016090964
4. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metab*. 2018;123(4):416-427. doi:10.1016/j.ymgme.2018.02.014
5. Pieroni M, Moon JC, Arbustini E, et al. Cardiac involvement in Fabry disease: JACC review topic of the week. *J Am Coll Cardiol*. 2021;77(7):922-936. doi:10.1016/j.jacc.2020.12.024

6. Izhar R, Borriello M, La Russa A, et al. Fabry disease in women: genetic basis, available biomarkers, and clinical manifestations. *Genes*. 2023;15(1):37. doi:10.3390/genes15010037
7. Wanner C, Arad M, Baron R, et al. European Expert Consensus Statement on therapeutic goals in Fabry disease. *Mol Genet Metab*. 2018;124(3):189-203. doi:10.1016/j.ymgme.2018.06.004
8. Genzyme Corporation. Fabrazyme (agalsidase beta) summary of product characteristics. Accessed November 3, 2023. https://www.ema.europa.eu/en/documents/product-information/fabrazyme-epar-product-information_en.pdf
9. JCR and Sumitomo Dainippon pharma enter into marketing alliance for agalsidase beta BS I.V. infusion [JCR], for treatment of Fabry disease in Japan March 1, 2022. Accessed November 3, 2023. https://ssl4.eir-parts.net/doc/4552/tdnet/2091921/00.pdf
10. Takeda Pharmaceuticals. Replagal (agalsidase alfa) summary of product characteristics. Accessed November 3, 2023. https://www.ema.europa.eu/en/documents/product-information/replagal-epar-product-information_en.pdf
11. Chiesi Farmaceutici. Elfabrio (pegunigalsidase alfa) summary of product characteristics. Accessed November 3, 2023. https://www.ema.europa.eu/en/documents/product-information/elfabrio-epar-product-information_en.pdf
12. Riccio E, Pisani A. New insights in efficacy of different enzyme replacement therapy dosages in Fabry disease: switch studies data following agalsidase beta shortage. *Clin Genet*. 2023;103(3):371-376. doi:10.1111/cge.14266
13. Krämer J, Lenders M, Canaan-Kühl S, et al. Fabry disease under enzyme replacement therapy-new insights in efficacy of different dosages. *Nephrol Dial Transplant*. 2018;33(8):1362-1372. doi:10.1093/ndt/gfx319
14. Arends M, Biegstraaten M, Wanner C, et al. Agalsidase alfa versus agalsidase beta for the treatment of Fabry disease: an international cohort study. *J Med Genet*. 2018;55(5):351-358. doi:10.1136/jmedgenet-2017-104863
15. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. *N Engl J Med*. 2016;375(6):545-555. doi:10.1056/NEJMoa1510198
16. Amicus Therapeutics Europe Limited. Galafold (migalastat) summary of product characteristics. Accessed November 3, 2023. https://www.ema.europa.eu/en/documents/product-information/galafold-epar-product-information_en.pdf
17. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet*. 2017;54(4):288-296. doi:10.1136/jmedgenet-2016-104178
18. Lenders M, Nordbeck P, Kurschat C, et al. Treatment of Fabry disease management with migalastat-outcome from a prospective 24 months observational multicenter study (FAMOUS). *Eur Heart J Cardiovasc Pharmacother*. 2022;8(3):272-281. doi:10.1093/ehjcvp/pvab025
19. Bichet DG, Torra R, Wallace E, et al. Long-term follow-up of renal function in patients treated with migalastat for Fabry disease. *Mol Genet Metab Rep*. 2021;28:100786. doi:10.1016/j.ymgmr.2021.100786
20. Amicus Therapeutics. Galafold (migalastat) US prescribing information. Accessed October 29, 2023. https://www.amicusrx.com/pi/galafold.pdf
21. Fan J-Q, Ishii S, Asano N, Suzuki Y. Accelerated transport and maturation of lysosomal α–galactosidase A in Fabry lymphoblasts by an enzyme inhibitor. *Nat Med*. 1999;5(1):112-115. doi:10.1038/4801
22. Benjamin ER, Della Valle MC, Wu X, et al. The validation of pharmacogenetics for the identification of Fabry patients to be treated with migalastat. *Genet Med*. 2017;19(4):430-438. doi:10.1038/gim.2016.122
23. Bichet DG, Hopkin RJ, Aguiar P, et al. Consensus recommendations for the treatment and management of patients with Fabry disease on migalastat: a modified Delphi study. *Front Med*. 2023;10:1220637. doi:10.3389/fmed.2023.1220637
24. Oommen S, Zhou Y, Meiyappan M, Gurevich A, Qiu Y. Inter-assay variability influences migalastat amenability assessments among Fabry disease variants. *Mol Genet Metab*. 2019;127(1):74-85. doi:10.1016/j.ymgme.2019.04.005
25. Lenders M, Nordbeck P, Kurschat C, et al. Treatment of Fabry's disease with migalastat: outcome from a prospective observational multicenter study (FAMOUS). *Clin Pharmacol Ther*. 2020;108(2):326-337. doi:10.1002/cpt.1832
26. Vanyo T, Pillai N, Ahmed A, Whitley CB. Comparison of therapeutic potential of ERT to chaperone therapy in I270T related Fabry disease. *Mol Genet Metab*. 2022;135(2):S123. doi:10.1016/j.ymgme.2021.11.327
27. Lenders M, Stappers F, Niemietz C, et al. Mutation-specific Fabry disease patient-derived cell model to evaluate the amenability to chaperone therapy. *J Med Genet*. 2019;56(8):548-556. doi:10.1136/jmedgenet-2019-106005
28. Nowak A, Huynh-Do U, Krayenbuehl PA, Beuschlein F, Schiffmann R, Barbey F. Fabry disease genotype, phenotype, and migalastat amenability: insights from a national cohort. *J Inherit Metab Dis*. 2020;43(2):326-333. doi:10.1002/jimd.12167
29. Fernandes RM, Bento D, Marques N, et al. Challenges in Fabry disease: the combination of two individually amenable GLA variants may be nonamenable to migalastat. *Future Cardiol*. 2023;19(1):39-43. doi:10.2217/fca-2022-0080
30. Riccio E, Zanfardino M, Ferreri L, et al. Switch from enzyme replacement therapy to oral chaperone migalastat for treating Fabry disease: real-life data. *Eur J Hum Genet*. 2020;28(12):1662-1668. doi:10.1038/s41431-020-0677-x
31. Wanner C, Ortiz A, Wilcox WR, et al. Global reach of over 20 years of experience in the patient-centered Fabry Registry: advancement of Fabry disease expertise and dissemination of real-world evidence to the Fabry community. *Mol Genet Metab*. 2023;139(3):107603. doi:10.1016/j.ymgme.2023.107603
32. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006
33. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. doi:10.1016/j.echo.2014.10.003

34. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317(17):1098. doi:10.1056/nejm198710223171717
35. Desnick RJ, Chen R, Srinivasan R, Doheny DO, Bishop D. The Fabry disease genotype-phenotype database (dbFGP): an international expert consortium. *Mol Genet Metab*. 2017;120(1):S41-S42. doi:10.1016/j.ymgme.2016.11.082
36. Rombach SM, Dekker N, Bouwman MG, et al. Plasma globotriaosylsphingosine: diagnostic value and relation to clinical manifestations of Fabry disease. *Biochim Biophys Acta*. 2010;1802(9):741-748. doi:10.1016/j.bbadis.2010.05.003
37. Lenders M, Stappers F, Brand E. In vitro and in vivo amenability to migalastat in Fabry disease. *Mol Ther Methods Clin Dev*. 2020;19:24-34. doi:10.1016/j.omtm.2020.08.012
38. Müntze J, Gensler D, Maniuc O, et al. Oral chaperone therapy migalastat for treating Fabry disease: enzymatic response and serum biomarker changes after 1 year. *Clin Pharmacol Ther*. 2019;105(5):1224-1233. doi:10.1002/cpt.1321
39. Germain DP, Brand E, Burlina A, et al. Phenotypic characteristics of the p.Asn215Ser (p.N215S) GLA mutation in male and female patients with Fabry disease: a multicenter Fabry Registry study. *Mol Genet Genomic Med*. 2018;6(4):492-503. doi:10.1002/mgg3.389
40. Gatterer C, Beitzke D, Graf S, et al. Long-term monitoring of cardiac involvement under migalastat treatment using magnetic resonance tomography in Fabry disease. *Life*. 2023;13(5):1213. doi:10.3390/life13051213
41. Camporeale A, Bandera F, Pieroni M, et al. Effect of migalastat on cArdiac InvOlvement in FabRry DiseAse: MAIORA study. *J Med Genet*. 2023;60(9):850-858. doi:10.1136/jmg-2022-108768
42. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90(1):29-34. doi:10.1016/s0002-9149(02)02381-0
43. Bottini PB, Carr AA, Prisant LM, Flickinger FW, Allison JD, Gottdiener JS. Magnetic resonance imaging compared to echocardiography to assess left ventricular mass in the hypertensive patient. *Am J Hypertens*. 1995;8(3):221-228. doi:10.1016/0895-7061(94)00178-e
44. Yousef Z, Elliott PM, Cecchi F, et al. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. *Eur Heart J*. 2013;34(11):802-808. doi:10.1093/eurheartj/ehs166
45. Ambale Venkatesh B, Volpe GJ, Donekal S, et al. Association of longitudinal changes in left ventricular structure and function with myocardial fibrosis: the Multi-Ethnic Study of Atherosclerosis study. *Hypertension*. 2014;64(3):508-515. doi:10.1161/hypertensionaha.114.03697
46. Weidemann F, Jovanovic A, Herrmann K, Vardarli I. Chaperone therapy in Fabry disease. *Int J Mol Sci*. 2022;23(3):1887.
47. Wu YS, Khanna R, Schmith V, et al. Migalastat tissue distribution: extrapolation from mice to humans using pharmacokinetic modeling and comparison with agalsidase beta tissue distribution in mice. *Clin Pharmacol Drug Dev*. 2021;10(9):1075-1088. doi:10.1002/cpdd.941
48. Ishii S, Chang HH, Yoshioka H, et al. Preclinical efficacy and safety of 1-deoxygalactonojirimycin in mice for Fabry disease. *J Pharmacol Exp Ther*. 2009;328(3):723-731. doi:10.1124/jpet.108.149054
49. Parenti G, Andria G, Valenzano KJ. Pharmacological chaperone therapy: preclinical development, clinical translation, and prospects for the treatment of lysosomal storage disorders. *Mol Ther*. 2015;23(7):1138-1148. doi:10.1038/mt.2015.62
50. Porrini E, Ruggenenti P, Luis-Lima S, et al. Estimated GFR: time for a critical appraisal. *Nat Rev Nephrol*. 2019;15(3):177-190. doi:10.1038/s41581-018-0080-9
51. Aakre KM, Tøndel C, Brun A, Svarstad E. The MDRD equation may mask decline of glomerular filtration rate in Fabry patients with normal or nearly normal kidney function. *Clin Nephrol*. 2009;71(2):118-124. doi:10.5414/cnp71118
52. Echevarria L, Benistan K, Toussaint A, et al. X-chromosome inactivation in female patients with Fabry disease. *Clin Genet*. 2016;89(1):44-54. doi:10.1111/cge.12613
53. Madsen CV, Granqvist H, Petersen JH, et al. Age-related renal function decline in Fabry disease patients on enzyme replacement therapy: a longitudinal cohort study. *Nephrol Dial Transplant*. 2019;34(9):1525-1533. doi:10.1093/ndt/gfy357

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pisani A, Wilson KM, Batista JL, et al. Clinical outcomes in patients switching from agalsidase beta to migalastat: A Fabry Registry analysis. *J Inherit Metab Dis*. 2024; 1-16. doi:10.1002/jimd.12773