



## Long-term follow-up of renal function in patients treated with migalastat for Fabry disease

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### ABSTRACT

The effect of migalastat on long-term renal outcomes in enzyme replacement therapy (ERT)-naïve and ERT-experienced patients with Fabry disease is not well defined. An integrated posthoc analysis of the phase 3 clinical trials and open-label extension studies was conducted to evaluate long-term changes in renal function in patients with Fabry disease and amenable *GLA* variants who were treated with migalastat for  $\geq 2$  years during these studies. The analysis included ERT-naïve ( $n = 36$  [23 females]; mean age 45 years; mean baseline estimated glomerular filtration rate (eGFR), 91.4 mL/min/1.73 m<sup>2</sup>) and ERT-experienced ( $n = 42$  [24 females]; mean age, 50 years; mean baseline eGFR, 89.2 mL/min/1.73 m<sup>2</sup>) patients with amenable variants who received migalastat 123 mg every other day for  $\geq 2$  years. The annualized rate of change from baseline to last observation in estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR<sub>CKD-EPI</sub>) was calculated by both simple linear regression and a random coefficient model. In ERT-naïve patients, mean annualized rates of change from baseline in eGFR<sub>CKD-EPI</sub> were  $-1.6$  mL/min/1.73 m<sup>2</sup> overall and  $-1.8$  mL/min/1.73 m<sup>2</sup> and  $-1.4$  mL/min/1.73 m<sup>2</sup> in male and female patients, respectively, as estimated by simple linear regression. In ERT-experienced patients, mean annualized rates of change from baseline in eGFR<sub>CKD-EPI</sub> were  $-1.6$  mL/min/1.73 m<sup>2</sup> overall and  $-2.6$  mL/min/1.73 m<sup>2</sup> and  $-0.8$  mL/min/1.73 m<sup>2</sup> in male and female patients, respectively. Mean annualized rate of change in eGFR<sub>CKD-EPI</sub> in ERT-naïve patients with the classic phenotype (defined by white blood cell alpha galactosidase A [ $\alpha$ -Gal A] activity of  $<3\%$  of normal and multiorgan system involvement) was  $-1.7$  mL/min/1.73 m<sup>2</sup>. When calculated using the random coefficient model, which adjusted for sex, age, and baseline renal function, the annualized eGFR<sub>CKD-EPI</sub> change was minimal (mean:  $-0.1$  and  $0.1$  mL/min/1.73 m<sup>2</sup> in ERT-naïve and ERT-experienced patients, respectively). In conclusion, patients with Fabry disease and amenable *GLA* variants receiving long-term migalastat treatment ( $\leq 8.6$  years) maintained renal function irrespective of treatment status, sex, or phenotype.

**Abbreviations:**  $\alpha$ -Gal A,  $\alpha$ -galactosidase A; Gb<sub>3</sub>, globotriaosylceramide; eGFR<sub>CKD-EPI</sub>, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; GLP-HEK, Good Laboratory Practice-validated human embryonic kidney; LVMI, left ventricular mass index; Q1, quartile 1; Q3, quartile 3; RI, renin inhibitor.

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1. Introduction

Fabry disease is a rare, multisystemic disorder caused by pathogenic *GLA* gene variants that result in functional deficiency of lysosomal enzyme  $\alpha$ -galactosidase A ( $\alpha$ -Gal A) and accumulation of globotriaosylceramide (Gb<sub>3</sub>) throughout the body [1,2].

In the kidney, glycosphingolipids accumulate in multiple kidney cell types, such as podocytes, endothelial cells, and tubular epithelial cells, causing proteinuria and a decline in glomerular filtration rate (GFR) [3]. Furthermore, the accumulation of Gb<sub>3</sub> activates inflammatory and

profibrotic processes that subsequently lead to glomerular injury [4,5].

Fabry disease is X-linked, and hemizygous males typically experience the most severe manifestations; however, heterozygous females can develop complications in major organs [1]. Renal manifestations are a significant cause of mortality and morbidity in Fabry disease [6,7], with renal disease being reported as the third most common cause of death after cardiac and cerebrovascular disease based on registry data [7]. Furthermore, decreased renal function and kidney failure have been associated with cardiovascular events and stroke, suggesting that renal and cardiac manifestations may be interrelated in Fabry disease [8,9].

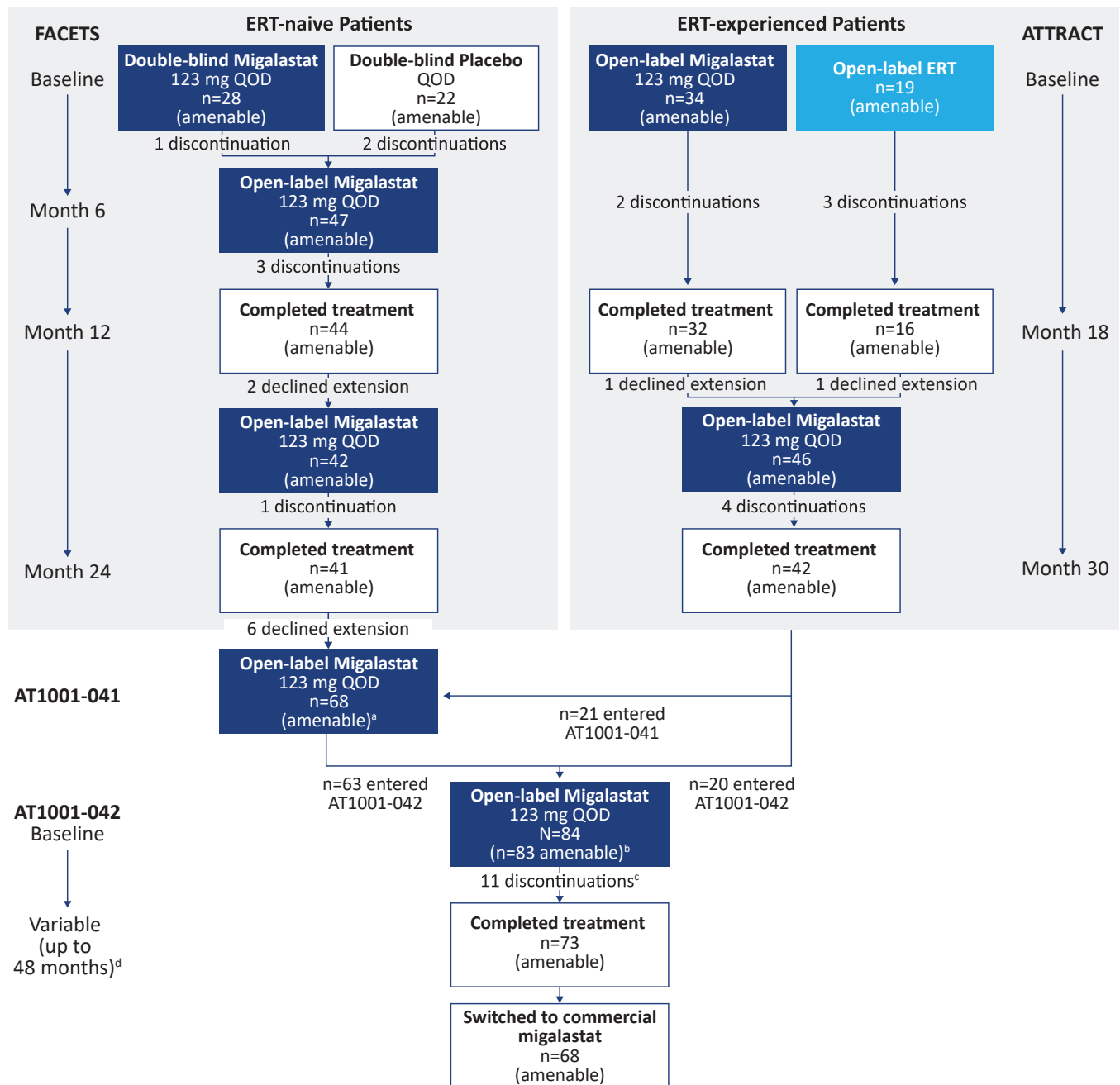


Fig. 1. Patient flow in phase 3 studies of migalastat.

<sup>a</sup>The AT1001-041 study also included 12 amenable patients from phase 2 studies.

<sup>b</sup>The AT1001-042 study also enrolled 1 patient from a phase 2 study, for a total of 84 patients, including 1 patient who had a nonamenable *GLA* variant.

<sup>c</sup>One patient discontinued due to an adverse event, 3 patients met protocol-defined stopping criteria (ie, estimated glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>), 1 patient was lost to follow-up, 4 patients discontinued per physician decision, and 2 patients chose to withdraw.

<sup>d</sup>Duration of the treatment varied among patients. Patients completed the study when they switched to commercial migalastat or had access to migalastat through an alternate source. ERT, enzyme replacement therapy; QOD, every other day.

Current treatments for Fabry disease include enzyme replacement therapy (ERT) with recombinant human  $\alpha$ -Gal A and the oral pharmacological chaperone migalastat [10–12]. As a small molecule pharmacological chaperone, migalastat binds to and stabilizes *amenable* mutant forms of  $\alpha$ -Gal A in the endoplasmic reticulum, facilitating trafficking of  $\alpha$ -Gal A to lysosomes and restoring endogenous enzyme activity [13,14]. Migalastat 123 mg every other day is approved for the treatment of Fabry disease in adult patients in the United States and in patients aged  $\geq 16$  years in the European Union who have an amenable *GLA* variant.

In phase 3 clinical trials, migalastat demonstrated efficacy in reducing Gb<sub>3</sub> in diverse renal cell types and in stabilizing renal function [15–17]. ERT-naïve patients demonstrated stable renal function for  $\leq 2$  years in the double-blind, placebo-controlled study FACETS, as calculated by simple linear regression [15]. In the open-label, active-controlled ATTRACT study, ERT-experienced patients who switched to migalastat experienced an annualized rate of change in GFR comparable to that of patients who continued ERT [16]. In ERT-naïve patients, the mean annualized rate of change from baseline to month 24 was  $-0.3$  mL/min/1.73 m<sup>2</sup> with migalastat [15]. In ERT-experienced patients, the mean annualized rate of change in estimated glomerular filtration rate (eGFR) from baseline to month 18 was  $-0.4$  mL/min/1.73 m<sup>2</sup> after switching to migalastat and  $-1.0$  mL/min/1.73 m<sup>2</sup> in patients continuing ERT [16].

Studies are ongoing to evaluate long-term renal outcomes in ERT-naïve and ERT-experienced patients treated with migalastat. Here, a post hoc analysis was conducted to evaluate long-term changes in renal function in 78 patients with Fabry disease and amenable *GLA* variants who were treated with migalastat for  $\geq 2$  years in the phase 3 FACETS and ATTRACT trials and long-term open-label extension (OLE) studies.

## 2. Materials and methods

### 2.1. Design

ERT-naïve and ERT-experienced patients enrolled in the phase 3 FACETS (AT1001–011; NCT00925301) or ATTRACT (AT1001–012; NCT01218659) clinical trials received migalastat 123 mg every other day for  $\geq 2$  years; details of these studies have been described previously [15,16]. Patients completing FACETS or ATTRACT were also allowed to enter an additional OLE study of  $\leq 5$  years (AT1001–041 [NCT01458119] and/or AT1001–042 [NCT02194985]).

We performed a post hoc analysis in which data collected during FACETS, ATTRACT, and the subsequent 5-year OLE studies (AT1001–041 and/or AT1001–042) (Fig. 1) were integrated across studies. The data cutoff date for the ongoing AT1001–042 study was March 11, 2020.

### 2.2. Participants

Selection criteria for patients enrolled in the FACETS and ATTRACT studies have been previously published [15,16]. Briefly, patients were ERT-naïve (FACETS; never received ERT or had not received ERT for  $\geq 6$  months) or ERT-experienced (ATTRACT; initiated ERT  $\geq 12$  months before study entry); aged 16–74 years; had genetically confirmed Fabry disease; and had *GLA* variants that met the amenability criteria. Patients had an eGFR of  $\geq 30$  mL/min/1.73 m<sup>2</sup> at enrollment, and those taking angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor blockers had to be on a stable dose for  $\geq 4$  weeks before the screening visit [15,16]. This post hoc analysis included all patients who received migalastat for  $\geq 2$  years and had migalastat-amenable *GLA* variants based on results from the good laboratory practice-validated assay using human embryonic kidney 293 cells (GLP-HEK assay) [18].

### 2.3. Study endpoints and assessments

Serum creatinine values were used to calculate the estimated

glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR<sub>CKD-EPI</sub>) [19]. eGFR<sub>CKD-EPI</sub> was determined at baseline and every 6 months through to the completion of each study, and annualized changes in eGFR<sub>CKD-EPI</sub> were calculated.

### 2.4. Statistical analyses

The annualized rate of change in eGFR<sub>CKD-EPI</sub> was calculated with two methods: by the slope of simple linear regression based on observed values and assessment times [15] and by a random coefficient model [20]. The simple linear regression was calculated individually for each patient using their longitudinal data. The random coefficient model comprised a mixed model that included eGFR as the dependent variable and study visit as a main effect, and the rate of eGFR decline was adjusted for the following baseline factors: sex, age, baseline eGFR<sub>CKD-EPI</sub>, baseline proteinuria, and time from Fabry diagnosis. Random coefficients were used for the intercept and visit. The beginning of migalastat treatment was the baseline and corresponded to month 6 of FACETS for patients in the placebo arm and month 18 of ATTRACT for patients in the ERT arm. One model was fitted on all data which resulted in obtaining a slope for each patient adjusted for the covariates. Then the slopes were grouped by sex, baseline eGFR<sub>CKD-EPI</sub> ( $>30$  to  $<60$ ,  $60$ – $90$ , and  $>90$  mL/min/1.73 m<sup>2</sup>), baseline urine protein ( $<300$ ,  $300$ – $1000$ , and  $>1000$  mg/24 h). For ERT-naïve patients, the slope was also grouped by phenotype (male patients with the classic phenotype vs others). ERT-naïve male patients were classified as having the classic phenotype if they had residual white blood cell  $\alpha$ -Gal A activity of  $<3\%$  of normal and multiorgan system involvement at baseline, defined as involvement of  $\geq 2$  of the following organ systems: renal, cardiac, central nervous system, peripheral nervous system, and gastrointestinal tract (Table A.1) [21]. The classification of “Other” included ERT-naïve male patients who did not meet the above criteria and all ERT-naïve female patients [21]. ERT-experienced male patients were not evaluated by phenotype because their baseline white blood cell  $\alpha$ -Gal A activity may have been confounded by previous ERT. Instead, we analyzed a subset of ERT-experienced male patients who had multiorgan involvement at baseline.

Descriptive statistics including mean, standard deviation (SD), median, range, and percent of total were used for efficacy analyses.

### 2.5. Ethics

FACETS, ATTRACT, AT1001–041, and AT1001–042 were designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. Clinical protocols for these studies were reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board at each study site. All patients provided written informed consent prior to initiation of the study.

## 3. Results

### 3.1. Demographics and baseline characteristics of the integrated analysis population

Demographic characteristics of the 78 patients who had  $\geq 2$  years of migalastat treatment are shown in Table 1. Of these, 36 were ERT-naïve (23 females), and 42 were ERT-experienced (24 females). The mean (SD) age of patients at treatment initiation was 45.1 (10.5) years in the ERT-naïve group and 50.1 (13.8) years in the ERT-experienced group. The mean (SD) time since Fabry diagnosis was 7.4 (8.0) years in ERT-naïve patients and 12.6 (12.4) years in ERT-experienced patients. Overall, 78% of patients had multiorgan involvement (81% of ERT-naïve patients and 76% of ERT-experienced patients). In particular, male patients with the classic phenotype comprised 27.8% of the ERT-naïve group and male patients with multiorgan involvement made up 35.7% of the ERT-

**Table 1**  
Baseline characteristics.

Variable	Overall (N = 78)	ERT-naive patients			ERT-experienced patients (n = 42)	Males (n = 31)	Females (n = 47)
		All (n = 36)	Classic phenotype <sup>a</sup> (n = 10)	Other (n = 26)			
Age (years)							
Mean (SD)	47.8 (12.6)	45.1 (10.5)	45.6 (12.0)	44.9 (10.2)	50.1 (13.8)	48.7 (12.2)	47.2 (12.9)
Median (range)	48.0 (18–70)	45.5 (25–68)	45.0 (25–62)	46.0 (27–68)	53.5 (18–70)	48.0 (20–67)	48.0 (18–70)
Sex, n (%)							
Male	19 (24.4)	13 (36.1)	10 (100)	2 (11.5)	18 (42.9)	31 (100)	0
Female	59 (75.6)	23 (63.9)	0	23 (88.5)	24 (57.1)	0	47 (100%)
Race, n(%)							
White	70 (89.7)	34 (94.4)	9 (90.0)	25 (96.2)	36 (85.7)	27 (87.1)	43 (91.5)
Asian	5 (6.4)	0	0	0	5 (11.9)	3 (9.7)	2 (4.3)
Multiple	1 (1.3)	0	0	0	1 (2.4)	0	1 (2.1)
Other	2 (2.6)	2 (5.6)	1 (10.0)	1 (2.8)	0	1 (3.2)	1 (3.2)
eGFR <sub>CKD-EPI</sub> (mL/min/1.73 m <sup>2</sup> )							
Mean (SD)	90.2 (21.0)	91.4 (22.4)	86.4 (27.5)	93.3 (20.4)	89.2 (19.9)	85.8 (22.1)	93.1 (19.9)
Median (range)	90.3 (41.4–131.3)	92.0 (41.4–125.6)	94.8 (41.4–119.0)	92.0 (44.6–125.6)	88.9 (51.4–131.3)	84.0 (41.4–131.3)	95.9 (44.6–125.6)
eGFR <sub>CKD-EPI</sub> category, n (%)							
>30–<60 mL/min/1.73 m <sup>2</sup>	5 (6.4)	3 (8.3)	2 (20.0)	1 (3.8)	2 (4.8)	4 (12.9)	1 (2.1)
60–90 mL/min/1.73 m <sup>2</sup>	33 (42.3)	14 (38.9)	3 (30.0)	11 (42.3)	19 (45.2)	15 (48.4)	18 (38.3)
>90 mL/min/1.73 m <sup>2</sup>	40 (51.3)	19 (52.8)	5 (50.0)	14 (53.8)	21 (50.0)	12 (38.7)	28 (59.6)
Urinary protein, mg/24 h, n (%)							
<300 mg/24 h	54 (69.2)	22 (61.1)	4 (40.0)	18 (69.2)	32 (76.2)	18 (58.1)	36 (76.6)
300–1000 mg/24 h	18 (23.1)	10 (27.8)	4 (40.0)	6 (23.1)	8 (19.0)	9 (29.0)	9 (19.1)
>1000 mg/24 h	6 (7.7)	4 (11.1)	2 (20.0)	2 (7.7)	2 (4.8)	4 (12.9)	2 (4.3)
Patients taking ACEI/ARB/RI, n (%)	32 (41.0)	10 (27.8)	4 (40.0)	6 (23.1)	22 (52.4)	13 (41.9)	19 (40.4)
Time since diagnosis (years)							
Mean (SD)	10.2 (10.9)	7.4 (8.0)	6.5 (4.4)	7.8 (9.1)	12.6 (12.4)	7.9 (8.6)	11.8 (11.9)
Median (range)	5.5 (1.0, 44.0)	5.0 (1.0, 34.0)	6.0 (1–14)	5.0 (1–34)	6.0 (3.0, 44.0)	5.0 (1.0, 39.0)	6.0 (1.0, 44.0)
LVMi (g/m <sup>2</sup> )							
Mean (SD)	95.7 (30.3)	99.2 (35.3)	120.5 (24.8)	89.9 (35.5)	92.9 (25.8)	116.4 <sup>b</sup> (35.3)	82.4 (16.3) <sup>b</sup>
Median (range)	88.8 (47.7, 234.4)	88.8 (61.0, 234.4)	115.4 (89.6–176.2)	81.2 (61.0–234.4)	87.9 (47.7, 165.7)	109.4 (69.9, 234.4)	77.6 (47.7, 121.8)

α-Gal A, alpha galactosidase; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; eGFR<sub>CKD-EPI</sub>, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; LVMi, left ventricular mass index; RI, renin inhibitor; SD, standard deviation.

<sup>a</sup> ERT-naive male patients who had residual white blood cell α-Gal A activity of <3% of normal and multiorgan system involvement, defined as involvement of ≥2 of the following organ systems: renal, cardiac, central nervous system, peripheral nerves, and gastrointestinal tract [21].

<sup>b</sup> LVMi data were not available for 2 male patients and 2 female patients.

experienced group. The median (range) migalastat treatment duration was 7.0 (2.0–8.6) years and 5.1 (2.1–7.2) years for ERT-naive and ERT-experienced patients, respectively.

### 3.2. Effects on renal function

During long-term follow-up, renal function was generally stable in both ERT-naive and ERT-experienced patients and in both male and female patients (Table 2). Using simple linear regression, the mean (SD) annualized rates of change in eGFR<sub>CKD-EPI</sub> were –1.6 (3.1) mL/min/1.73 m<sup>2</sup> and –1.6 (3.6) mL/min/1.73 m<sup>2</sup> in ERT-naive and ERT-experienced patients, respectively. eGFR<sub>CKD-EPI</sub> over time and annualized rate of change in eGFR<sub>CKD-EPI</sub> in individual patients are shown in Fig. 2 and Fig. A.1A, respectively. Using the random coefficient model, which adjusted for age, sex, baseline renal function, and time since Fabry diagnosis, the mean (SD) annualized rates of change in eGFR<sub>CKD-EPI</sub> were –0.1 (1.8) mL/min/1.73 m<sup>2</sup> and 0.1 (1.7) mL/min/1.73 m<sup>2</sup> in ERT-naive and ERT-experienced patients, respectively. When patients were analyzed by sex, the mean annualized rates of change in eGFR<sub>CKD-EPI</sub> were –0.5 mL/min/1.73 m<sup>2</sup> in (ERT-naive) and –0.4 mL/min/1.73 m<sup>2</sup> in (ERT-experienced) in males, and 0.1 mL/min/1.73 m<sup>2</sup> in (ERT-naive) and 0.5 mL/min/1.73 m<sup>2</sup> (ERT-experienced) in females

**Table 2**

Annualized rate of change in eGFR<sub>CKD-EPI</sub> in ERT-naive and ERT-experienced patients treated with migalastat for ≥2 years using simple linear regression.

	ERT-naive patients			ERT-experienced patients		
	Overall (n = 36)	Male (n = 13)	Female (n = 23)	Overall (n = 42)	Male (n = 18)	Female (n = 24)
Mean	–1.6	–1.8	–1.4	–1.6	–2.6	–0.8
(SD)	(3.1)	(2.7)	(3.3)	(3.6)	(4.8)	(2.1)
Median	–1.1	–1.0	–1.1	–1.3	–1.4	–1.1
(Q1, Q3)	(–2.4, –0.6)	(–3.8, –0.8)	(–1.7, –0.6)	(–2.2, –0.5)	(–2.6, –0.7)	(–2.1, –0.4)

eGFR<sub>CKD-EPI</sub>, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; SD, standard deviation; Q1, quartile 1; Q3, quartile 3.

(Table A.2).

eGFR<sub>CKD-EPI</sub>, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy.

Annualized rates of change from baseline in eGFR<sub>CKD-EPI</sub> by baseline renal function are provided in Table 3 (simple linear regression) and

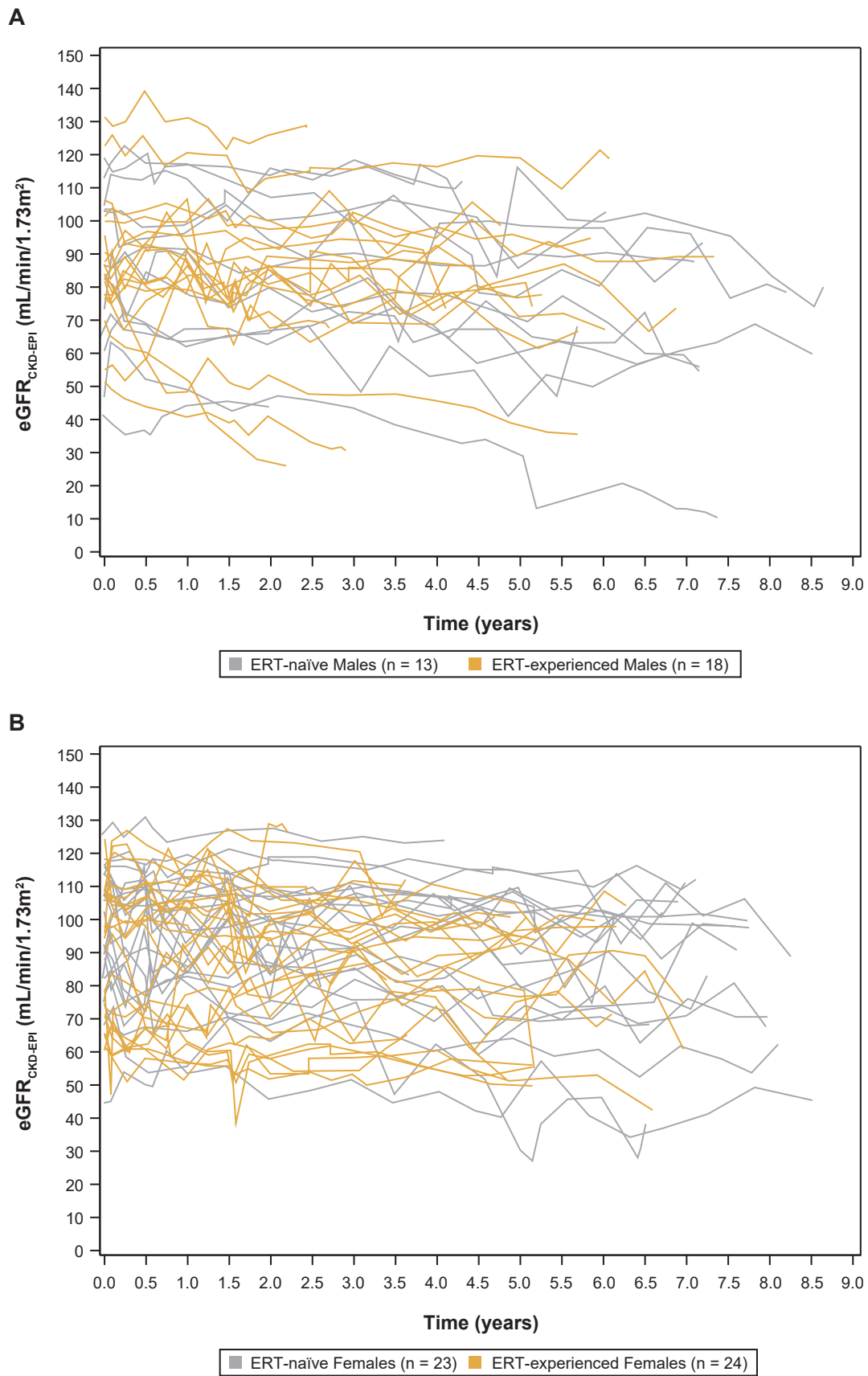


Fig. 2. Estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation over time in (A) male and (B) female patients receiving long-term migalastat treatment.

**Table 3**

Annualized rates of change in eGFR<sub>CKD-EPI</sub> in ERT-naive and ERT-experienced patients treated with migalastat for  $\geq 2$  years by baseline renal function using simple linear regression.

	ERT-naive patients			ERT-experienced patients		
	n = 36			n = 42		
	>90	60–90	>30–<60	>90	60–90	>30–<60
Baseline eGFR <sub>CKD-EPI</sub> , mL/min/1.73 m <sup>2</sup>	(n = 19)	(n = 14)	(n = 3)	(n = 21)	(n = 19)	(n = 2)
Mean (SD)	–2.2 (2.9)	–0.81 (2.9)	–1.2 (5.1)	–1.2 (1.5)	–1.6 (5.0)	–4.7 (2.1)
Median (Q1, Q3)	–1.0 (–2.3, –0.7)	–1.1 (–2.6, 0.1)	–1.2 (–6.3, 4.0)	–1.3 (–2.0, –0.8)	–0.9 (–2.2, –0.2)	–4.7 (–6.2, –3.2)
Baseline urinary protein, mg/24 h	<300 (n = 22)	300–1000 (n = 10)	>1000 (n = 4)	<300 (n = 32)	300–1000 (n = 8)	>1000 (n = 2)
Mean (SD)	–2.0 (3.0)	–0.1 (3.1)	–2.9 (2.6)	–0.8 (1.9)	–1.9 (0.8)	–13.3 (10.1)
Median (Q1, Q3)	–1.1 (–2.3, –0.7)	–0.8 (–1.7, 0.0)	–2.3 (–5.0, –0.8)	–1.0 (–1.7, –0.3)	–1.7 (–2.6, –1.3)	–13.3 (–20.5, –6.2)

eGFR<sub>CKD-EPI</sub>, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

Table A.3 (random coefficient model); Fig. A.1B shows individual patient data. We analyzed the influence of each covariate included in the analysis and found that baseline eGFR was significant in predicting further decline in renal function ( $p < 0.0001$ ), followed by age ( $p = 0.046$ ). Baseline urine protein was approaching statistical significance ( $p = 0.059$ ). Other covariates were not significant.

Annualized change in eGFR<sub>CKD-EPI</sub> up to 24 months has been reported for 16 male patients with the classic phenotype in FACETS [21]. Among them, 10 patients had received migalastat for  $\geq 2$  years and were included in the current post hoc analysis. The mean (SD) annualized rates of change in eGFR<sub>CKD-EPI</sub> were  $-1.7$  (3.0) mL/min/1.73 m<sup>2</sup> in this subset of male patients with the classic phenotype and  $-1.5$  (3.2) mL/min/1.73 m<sup>2</sup> in other patients in FACETS (simple regression) during long-term follow-up (Table 4). Using the random coefficient model, the mean (SD) annualized rates of change in eGFR<sub>CKD-EPI</sub> were  $-0.5$  (2.1) mL/min/1.73 m<sup>2</sup> in ERT-naive males with the classic phenotype and  $0.0$  (1.7) mL/min/1.73 m<sup>2</sup> in other patients in FACETS, respectively (Table A.4). Annualized rate of change in eGFR<sub>CKD-EPI</sub> in male patients with multiorgan involvement versus others have been similarly analyzed for ERT-experienced patients (Table A4 and Table A.4) The genotype, phenotype, and annualized rate of change in eGFR<sub>CKD-EPI</sub> of individual patients are presented in Table A.5. Multiorgan involvement for patients is listed in Table A.6. Individual eGFR<sub>CKD-EPI</sub> slopes are

**Table 4**

Annualized rates of change in eGFR<sub>CKD-EPI</sub> in ERT-naive and ERT-experienced patients treated with migalastat for  $\geq 2$  years by disease characteristics using simple linear regression.

	ERT-naive		ERT-experienced	
	Classic phenotype <sup>a</sup>	Others	Multiorgan involvement <sup>b</sup>	Others
	(n = 10)	(n = 26)	(n = 15)	(n = 27)
Mean (SD)	–1.7 (3.0)	–1.5 (3.2)	–2.5 (5.1)	–1.1 (2.3)
Median (Q1, Q3)	–0.9 (–4.0, 0.1)	–1.1 (–2.3, –0.7)	–1.3 (–2.6, –0.4)	–1.3 (–2.2, –0.5)

$\alpha$ -Gal A, alpha galactosidase; eGFR<sub>CKD-EPI</sub>, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; ERT, enzyme replacement therapy; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

<sup>a</sup> ERT-naive male patients with the classic phenotype had residual white blood cell  $\alpha$ -Gal A activity of  $<3\%$  of normal and multiorgan involvement, defined as involvement of  $\geq 2$  of the following organ systems: renal, cardiac, central nervous system, peripheral nerves, and gastrointestinal tract [21].

<sup>b</sup> Baseline white blood cell  $\alpha$ -Gal A activity in ERT-experienced patients was confounded by ERT and the same classic phenotype definition could not be applied. Instead, male patients with multiorgan involvement were compared with males without multiorgan involvement and females (specified above as “others”).

plotted against patient age in Fig. A.2.

#### 4. Discussion

This post hoc analysis assessed long-term renal measures associated with migalastat therapy in ERT-naive and ERT-experienced patients with Fabry disease and amenable GLA variants. With either the random coefficient model or simple linear regression, ERT-naive and ERT-experienced patients who received migalastat treatment for  $\geq 2$  and  $\leq 8.6$  years in the current study had a rate of eGFR decline that was slower than that in untreated historical cohorts [22,23] and similar to the normal rate of decline with age [24]. Renal function was also generally stable in patients receiving long-term migalastat treatment irrespective of treatment status, sex, or phenotype.

Although linear regression models have often been used to estimate rates of change in eGFR over time, this statistical method fails to consider the correlation among repeated measurements in the same patient. A subject-specific mixed model with random intercepts and slopes for each patient may be more suitable to the heterogeneous nature of Fabry disease and has been used to describe the natural history of Fabry nephropathy [22], which showed that untreated males and females (mean age 41 years at baseline) with a baseline eGFR<sub>MDRD</sub> of  $\geq 60$  mL/min/1.73 m<sup>2</sup> experienced an annual loss in eGFR of  $-3.0$  mL/min/1.73 m<sup>2</sup> and  $-0.9$  mL/min/1.73 m<sup>2</sup>, respectively; males and females with chronic kidney disease at baseline experienced an annual loss in eGFR of  $-6.8$  mL/min/1.73 m<sup>2</sup> and  $-2.1$  mL/min/1.73 m<sup>2</sup>, respectively [22]. Using a similar model, we found that eGFR<sub>CKD-EPI</sub> remained stable during median follow-ups of 7 years and 5 years in ERT-naive and ERT-experienced patients, respectively (mean annualized rate of change was  $-0.1$  mL/min/1.73 m<sup>2</sup> and  $0.1$  mL/min/1.73 m<sup>2</sup>, respectively).

A range of mean eGFR declines has been reported for ERT using different statistical methods [25–28]. In a 5-year follow-up of adult patients treated with agalsidase alfa or agalsidase beta, the mean annualized rates of change in eGFR were approximately  $-3$  mL/min/1.73 m<sup>2</sup> in males (mean age 38.9 years, mean baseline eGFR 88.5 mL/min/1.73 m<sup>2</sup>) and approximately  $-0.9$  mL/min/1.73 m<sup>2</sup> in females (mean age 46.8 years, mean eGFR 86.6 mL/min/1.73 m<sup>2</sup>) using a random coefficient model [25]. In another long-term study of patients (median age 33 years) receiving agalsidase alfa or agalsidase beta for a median of 7 years, the mean annualized rates of change in eGFR were  $-1.8$  mL/min/1.73 m<sup>2</sup> and  $-0.01$  mL/min/1.73 m<sup>2</sup> in males (mean baseline eGFR 121 mL/min/1.73 m<sup>2</sup>) and females (mean baseline eGFR 98 mL/min/1.73 m<sup>2</sup>), respectively, using a linear mixed model [29]. These rates of eGFR decline during ERT are generally similar to or greater than those reported here for migalastat.

It is known that baseline clinical status plays a critical role in renal outcomes with treatment [25–27]. In long-term studies, ERT did not stabilize renal function in patients with severe renal involvement (ie,

proteinuria  $>1$  g/24 h or eGFR  $<60$  mL/min/1.73 m<sup>2</sup>, or urinary protein:creatinine ratio  $\geq 1$  g/g) [30–32]. In our study, renal outcomes were similar across baseline renal function groups in ERT-naïve patients with the random coefficient model that adjusted for baseline factors. Unsurprisingly, with the simple linear regression method, larger annualized rates of change in eGFR were observed in ERT-experienced patients with low eGFR ( $> 30$  to  $<60$  mL/min/1.73 m<sup>2</sup>) or high urine protein ( $> 1000$  mg/24 h) at baseline in the current study compared with other analyzed subgroups. However, our results are severely limited by the small sample sizes of these 2 patient subgroups ( $n = 2$  each). Results were also distorted by one patient with an eGFR decline of  $>20$  mL/min/1.73 m<sup>2</sup>; however, it is likely that this patient had irreversible nephropathy prior to migalastat initiation, as evidenced by the large decline in renal function that also occurred during ERT treatment.

Long-term data are especially important when assessing annualized change in eGFR. A recent Delphi consensus has recommended at least 2 years of data for reliable eGFR analyses [33], and the current analysis provides data on patients who were treated with migalastat for at least 2 years (median exposure 5.9 years). Published real-world evidence can also be helpful in guiding treatment decisions. A recent 24-month real-world cohort publication from Lenders et al. in Germany provided further evidence of LVMi reduction in migalastat-treated patients with Fabry disease (primary outcome), especially in those with left ventricular hypertrophy at baseline [34]. That publication also examined annualized eGFR slopes over 24 months and found antihypertensive medication use was associated with greater annualized eGFR decline over time, and the authors posited that either this may have been causative of the larger decline in eGFR, or that these patients were more severely affected at baseline. When excluding the patients on inhibitors of angiotensin-converting enzyme, angiotensin II receptor 1, or aldosterone, eGFR was found to be stable over 24 months in migalastat-treated patients (mean change over 24 months:  $-3.0 \pm 10.9$  mL/min/1.73 m<sup>2</sup>;  $p = 0.4346$ ). These findings support the thinking that patient management decisions should be made holistically, and that treatment before irreversible damage has occurred may be beneficial.

The current study also extends findings from a previous analysis of male patients with the classic phenotype in the FACETS study [21], which reported a mean annualized rate of change in eGFR<sub>CKD-EPI</sub> of  $-0.3$  mL/min/1.73 m<sup>2</sup> over 2 years. The current study shows that renal function remained stable in ERT-naïve male patients with the classic phenotype for  $\leq 8.6$  years (median exposure: 6.6 years), supporting long-term efficacy in this patient population. In comparison, male patients with the classic phenotype (mean age 31 years, median baseline eGFR  $\sim 120$  mL/min/1.73 m<sup>2</sup>) who received agalsidase beta for 54 months had an eGFR decline of  $-2.2$  mL/min/1.73 m<sup>2</sup>, as estimated by a random coefficient model [21,30]. The current study also included male patients with the classic phenotype who had relatively high eGFR values at baseline (mean [SD]: 88.5 [22.5] mL/min/1.73 m<sup>2</sup>). Interestingly, one patient with the classic phenotype in our study had a *GLA* variant associated with the late-onset phenotype (p.I253T) according to the International Fabry Disease Genotype-Phenotype Database, which consolidates data in the literature as well as available biochemical data to set a reasonable expectation of phenotypic severity [35]. This supports the thinking that that genotype-phenotype correlation is complex and that environmental factors and genetic modifiers may be at work. This observation highlights the importance of evaluating each patient holistically, and of making individualized treatment decisions that account for the multiple organ systems affected by Fabry disease. It also highlights the fact that the GLP-HEK amenability assay should be used only to determine a patient's eligibility for treatment with migalastat and that the assay is not prognostic of clinical outcomes or disease course. Finally, some patients with the same variant had different severity of disease at study baseline, possibly related to entering the study at different stages during the progressive disease course [1], which highlights the importance of multisystemic monitoring and early treatment initiation when managing this disease.

There is a growing consensus that treatment should be initiated early to limit or prevent irreversible organ damage and improve treatment outcomes in patients with Fabry disease [31,37,38]. In this study, we defined the classic phenotype as multiorgan system involvement at baseline, and  $< 3\%$  enzyme activity for male patients (ERT-naïve only). We used this phenotypic definition in accordance with the definition used in the FACETS trial [15,21] in order to analyze patients with clinically advanced Fabry disease at study start. Fabry disease phenotypes and rates of disease progression are highly variable, even within families with the same variant [39]. A binary definition of “classic” versus “other” does not capture the true complexity of Fabry disease. We posit that Fabry disease is a continuum, dependent upon many factors, including genetic, epigenetic, environmental, and lifestyle, and that such binary classifications should be considered as only one factor in terms of guiding treatment decisions. Biopsy studies suggest that podocyte injury occurs in early childhood, progresses with increasing age, and may act as an early marker for renal damage in Fabry disease [40–42]. Therefore, treatment before substantial renal damage occurs is imperative because renal function may not be restored when podocyte loss and damage to glomeruli have occurred [43,44]. There is also evidence of a strong correlation between proteinuria and renal disease progression in patients with Fabry disease [45]. Therefore, stabilizing or slowing the decline in renal function requires strategies that control proteinuria (ie, angiotensin-converting-enzyme inhibitors and/or angiotensin II receptor blockers) [46]. Furthermore, inflammatory processes in podocytes have been linked to Fabry nephropathy, suggesting inflammatory pathways could potentially be therapeutic targets in Fabry disease [4]. Further studies are needed to investigate the impact of current therapies, including migalastat, on these pathophysiological processes in renal tissues and optimal time for treatment initiation.

Limitations of this study that should be considered when interpreting the results include its post hoc design, small sample sizes in some subgroups, and the lack of statistical comparisons with untreated or ERT-treated historical cohorts. Assessment of renal function using eGFR may also be a limitation, given that eGFR has been associated with pseudo-hyperfiltration in some patients with Fabry disease [36]. In addition, the heterogeneity of statistical methods used to estimate eGFR slopes in the literature limited direct comparisons.

In summary, the results of this post hoc analysis suggest that patients with Fabry disease and amenable *GLA* variants had stable renal function during long-term migalastat treatment ( $\leq 8.6$  years) irrespective of treatment status, sex or phenotype. Early treatment should be encouraged to stabilize or slow the decline in renal function in patients with Fabry disease.

#### Data availability statement

All relevant data, including deidentified participant data, are contained in this manuscript and its supplemental materials.

#### Author contributions

D.G.B., R.T., D.H., R.G., N.S., U.F.R. and K.N. contributed to conceptualization; D.H., N.S., U.F.R. and K.N. participated in data curation; R.T., D.H., R.G., N.S., U.F.R. and K.N. participated in investigation; R.T., R.G., N.S., E.K., U.F.R. and K.N. contributed to methodology; D.G.B. and D.H. participated in supervision; R.T. and D.H. contributed to validation; R.T. and E.W. contributed to visualization; N.S. and E.K. analyzed and interpreted the data; R.T. participated in writing the original draft; D.G.B., R.T., E.W., D.H., R.G., N.S., E.K., U.F.R., R.S. and K.N. participated in reviewing and editing the article.

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## Declaration of Competing Interest

D.G.B. served as a consultant and speaker for and received grants from Amicus, Sanofi Genzyme and Otsuka; and served as a board member for Amicus.

E.W. received grants and consulting fees from Sanofi Genzyme and received research and travel support from Protalix and Idorsia.

D.H. received consultant fees from Amicus, Sanofi Genzyme, Shire-Takeda, Protalix, Idorsia, and Freeline Therapeutics; and served as a speaker for Amicus, Shire-Takeda, and Sanofi Genzyme.

R.G. was a paid consultant for JCR Pharmaceuticals, REGENXBIO, and Sigilon; received grants from BioMarin, Novartis, Shire-Takeda, and Ultragenyx; was a paid speaker for Amicus, BioMarin, Chiesi, Janssen, PTC Therapeutics, Sanofi Genzyme, Shire-Takeda, and Ultragenyx; and served as a board member for Amicus, Abeona, Sobi, Sanofi Genzyme, and Shire-Takeda.

N.S. was an employee of Amicus at the time of this study.

E.K. served as a paid consultant for Amicus.

U.F.R. served as a board member and paid consultant for Amicus, Sanofi Genzyme, and Shire-Takeda, and received an unrestricted research grant from Sanofi Genzyme.

K.N. has served on advisory boards for Amicus Therapeutics, Sanofi Genzyme, and Shire; has served as a speaker for Amicus Therapeutics; and has received research funding from Sanofi Genzyme and Shire.

R.T. and R.S. have no conflicts to declare.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ymgmr.2021.100786>.

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