SUPPLEMENT

METHODS

The association between baseline characteristics and the risk of FACE was assessed using a Cox proportional hazards model that treated time to the first FACE (either a composite FACE or each event category) as a dependent variable. The group assignment ERT naïve versus ERT experienced, classic versus others (ERT naïve), multiorgan involvement versus others (ERT experienced), or age ≤40 years versus age >40 years was an independent variable. Furthermore, the following baseline variables were used in each model as covariates: age, time since Fabry diagnosis, previous clinical event, urine protein at baseline, LVMI at baseline and $eGFR_{CKD\text{-}EPI}$ at baseline. Prior clinical events were events that occurred before the initiation of migalastat therapy and were identified from patients' medical history using preferred terms in MedDRA version 16.1: microalbuminuria, proteinuria, renal failure, renal failure chronic, renal impairment, nephropathy, myocardial infarction, unstable cardiac angina, congestive heart failure, any major cardiac medical procedure, stroke and transient ischaemic attack. Prior cardiac events also include new symptomatic arrhythmia requiring a medication, direct current cardioversion, pacemaker, or defibrillator implantation, as evaluated by a physician. In addition to covariates, an independent binary variable (ERT naïve versus ERT experienced, classic versus others [ERT naïve], multiorgan involvement versus others [ERT experienced], or age ≤40 years versus age >40 years) was always kept in the model and its significance was tested to see if there was a difference in the time of the first FACE adjusted by covariates. The impact of each covariate on the time to the first FACE was evaluated individually. The impact of each covariate was evaluated in three sets of data (ERT naïve, ERT experienced and all data). Patients who discontinued from the studies or had not experienced any events at data cut-off were right censored.

Search strategy for historical Fabry publications reporting FACE incidence

Relevant publications reporting on FACE incidence, definitions and outcomes in Fabry disease were identified via PubMed using the following search strategy:

- (Agalsidase beta) AND (events)
- (Agalsidase beta) AND (composite)
- (Agalsidase alfa) AND (events)
- (Agalsidase alfa) AND (composite)
- (migalastat) AND (composite)
- (migalastat) AND (events)

Publications including paediatric data and reviews were excluded. Abstracts for publications identified in the search were screened for relevance; full papers were analysed if the abstract met the relevance criteria. Searches were carried out in February 2022.

RESULTS

Supplemental Table 1. Genotypes of patients with classic and multiorgan phenotypes

Classic males *FACETS: <3% enzyme activity; multiorgan involvement at baseline*				**Multiorgan males** *ATTRACT: multiorgan involvement at baseline*			
Patient number	**Age range (years)**	**Sex**	**Genotype**	**Patient number**	**Age range (years)**	**Sex**	**Genotype**
1	21–30	M	G183D	**15**	61–70	M	R363H
2	31–40	M	L243F	**16**	51–60	M	G35R
3	61–70	M	I253T	**17**	21–30	M	P205T
4	61–70	M	I253T	**18**	51–60	M	N215S
5	21–30	M	C174R	**19**	41–50	M	D322E
6	21–30	M	D55V/Q57L	**20**	16–20	M	D322E
7	31–40	M	G144V	**21**	51–60	M	N215S
8	51–60	M	R301Q	**22**	51–60	M	N215S
9	41–50	M	G373S	**23**	51–60	M	N215S
10	61–70	M	D322E	**24**	61–70	M	N215S
11	16–20	M	G325R	**25**	31–40	M	M284T
12	31–40	M	Y216C	**26**	41–50	M	R112G
13	41–50	M	P259R	**27**	51–60	M	L403S
14	41–50	M	P259R	**28**	41–50	M	M96I
				29	16–20	M	G85D
				30	41–50	M	A156T

M, male.

Enzyme Replacement Therapy (ERT)-naïve patients were stratified by phenotype. Male patients were classified as having the classic phenotype if they had residual white blood cell (WBC) α-Galactosidase A (α-Gal A) activity <3% of normal and multiorgan involvement, which was defined as involvement of ≥2 of the following organ systems: renal, cardiac, central nervous system, peripheral nervous system and gastrointestinal system. A subset of ERT-experienced male patients who had multiorgan involvement at baseline were analysed and were not evaluated by phenotype because their baseline WBC α-Gal A activity may have been confounded by previous ERT.

Supplemental Table 2. Baseline patient demographics and disease characteristics by treatment group

	ERT-treated patients n=15	**Migalastat-treated patients n=49**
Sex, n (%)		
Male	5 (33.3)	19 (38.8)
Female	10 (66.7)	30 (61.2)
Age, years		
Mean (SD)	45.5 (15.89)	50.0 (13.98)
Median (Q1, Q3)	48.0 (35.0, 57.0)	54.0 (43.0, 59.0)
Time since Fabry diagnosis, years		
Mean (SD)	16.93 (13.56)	12.45 (11.93)
Median (Q1, Q3)	10.0 (6.0, 27.0)	6.0 (5.0, 18.0)
$eGFR_{CKD-EPI}$, mean (SD), mL/min/1.73 m^2	95.81 (21.04)	88.96 (20.39)
$eGFR_{CKD-EPI}$ category, n (%)		
>90 mL/min/1.73 m^2	10 (66.7)	24 (49.0)
60–90 mL/min/1.73 m^2	4 (26.7)	22 (44.9)
>30–<60 mL/min/1.73 m^2	1 (6.7)	3 (6.1)
Urinary protein, median (Q1, Q3), mg/24h	108.0 (0.0, 279.0)	116.0 (0.0, 265.0)
LVMI, mean (SD), g/m^2	88.51 (25.64)	91.48 (26.32)
Patients taking ACEI/ARB/RI, n (%)	8 (53.3)	26 (53.1)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; $eGFR_{CKD-EPI}$, 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.

Supplemental Table 3. Associations between baseline variables and the risk of FACEs (composite events)

	ERT naïve (N=43)	**ERT experienced (N=48)**	**Total (N=91)**
HR (95% CI)*			
eGFR at baseline (per 10 mL/min/1.73m^2)	**0.41 (0.25, 0.66)**	0.65 (0.37, 1.14)	**0.68 (0.55, 0.85)**
Baseline LVMi (per 5 g/m^2)	1.05 (0.99, 1.11)	1.09 (0.94, 1.27)	1.04 (0.98, 1.10)
24-h urine proteinuria at baseline (per 1000 mg/24 h)	0.61 (0.22, 1.73)	1.42 (0.92, 2.19)	1.34 (0.93, 1.95)
Previous events	**3.81 (1.07, 13.56)**	0.48 (0.07, 3.14)	1.15 (0.51, 2.61)
Time from Fabry diagnosis (per 5 years)	1.46 (0.99, 2.17)	0.91 (0.63, 1.32)	1.00 (0.81, 1.24)
Age (per 5 years)	0.72 (0.47, 1.11)	1.20 (0.76, 1.90)	1.05 (0.83, 1.33)

CI, confidence interval; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; FACEs, Fabry-associated clinical events; LVMI, left ventricular mass index.

Composite events is the total of all events that included all cardiac, cerebrovascular and renal events (as previously defined) and death due to FACE. Hazard ratio <1 indicates ERT-naïve patients fared better and hazard ratio >1 indicates ERT-experienced patients fared better. Data set in bold indicates a statistically significant outcome. *Calculated through three separate Cox proportional regression models for ERT naïve, ERT experienced and overall.

Supplemental Table 4. FACE definitions and outcomes across various Fabry studies

Treatment	Migalastat N=97	Agalsidase beta N=52	Agalsidase beta N=40	Agalsidase alfa or beta N=178	Agalsidase alfa or beta N=387	Agalsidase beta N=1411	Migalastat N=31	Agalsidase beta N=51	MigalastatN=36	Agalsidase beta N=1044
Author, Year	**Current Analysis**	**Germain, 2015**	**Weidemann, 2013**	**Sirrs, 2014**	**Arends, 2018**	**Hopkin, 2016**	**Feldt-Rasmussen, 2020**	**Banikazemi, 2007**	**Hughes, 2017**	**Ortiz, 2016**
Patient population	Pts with amenable mutations (37 M; 60 F)	Adult pts with classic FD (50 M; 2 F)	Adult pts with advanced FD (31 M; 9 F)	Pts with FD meeting Canadian ERT criteria (100 M; 78 F)	Pts with FD (195 M; 192 F)	Pts in the Fabry Registry (969 M; 442 F)	ERT-experienced pts with amenable mutations (16 M; 17 F)*	Adult pts with advanced FD (45 M; 6 F)	ERT-experienced pts with amenable mutations (16 M; 20 F)	Pts in the Fabry Registry (641 M; 403 F)
Length of follow-up, median	5 y	10 y	6 y	5 y	5 y	M: 4 y F: 3 y	2.5 y	1.5 y	1.5 y	NR¶
Events Overall, % of patients	18%	19%	33%	27%	27%	M: 21%; F: 13%	32%	28%	29%	17%
Renal Events, % of patients	2%	7.7%	10%	3%†	3%†	M: 7%; F: 2%	29%	20%	24%	6%
End-stage renal disease	**X**		**X**	**X**	**X**			**X**		
Dialysis	**X**	**X**	**X**		**X**	**X**		**X**		**X**
Transplant	**X**	**X**			**X**	**X**		**X**		**X**
Serum creatinine (predefined increase)	**X**							**X**		
Increased urinary protein							**X**		**X**	

(predefined)										
GFR decrease (predefined rate)				**X**			**X**		**X**	
Cardiac Events, % of patients	12%	4%	15%	17%	14%	M: 9%; F: 7%	3%	6%	6%	7%
Cardiac-related death						**X**				
Myocardial infarction	**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**
Chronic heart failure	**X**	**X**		**X**		**X**	**X**	**X**	**X**	**X**
Atrial fibrillation	**X**					**X**				**X**
Ventricular tachy-arrhythmia			**X**	**X**		**X**				**X**
Symptomatic arrhythmia requiring medication or intervention	**X**						**X**	**X**	**X**	
Heart disease progressive enough to require pacemaker	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Bypass surgery (CABG)		**X**		**X**		**X**				**X**
Coronary artery dilation						**X**				**X**
Implantation of cardioverter or	**X**	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**

defibrillator										
Direct cardioversion	**X**			**X**			**X**	**X**	**X**	
Unstable angina	**X**			**X**			**X**	**X**	**X**	
Percutaneous transluminal coronary angioplasty				**X**						
Valve replacement surgery	**X**			**X**						
Stent	**X**			**X**						
Acute coronary syndrome				**X**						
Heart block				**X**						
Cardiac arrest				**X**						
Cardiac ablation	**X**									
Cerebrovascular Events, % of patients	5%	10%	10%	8%	7%	M: 5%; F: 3%	0%	0%	0%	3%
Stroke	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Transient Ischemic Attack	**X**		**X**	**X**	**X**		**X**	**X**	**X**	
Acute hearing loss				**X**						
Death, % of patients	0%		18%	5%	3%	M: 4%; F: 1%	0%	2%	0%	1%

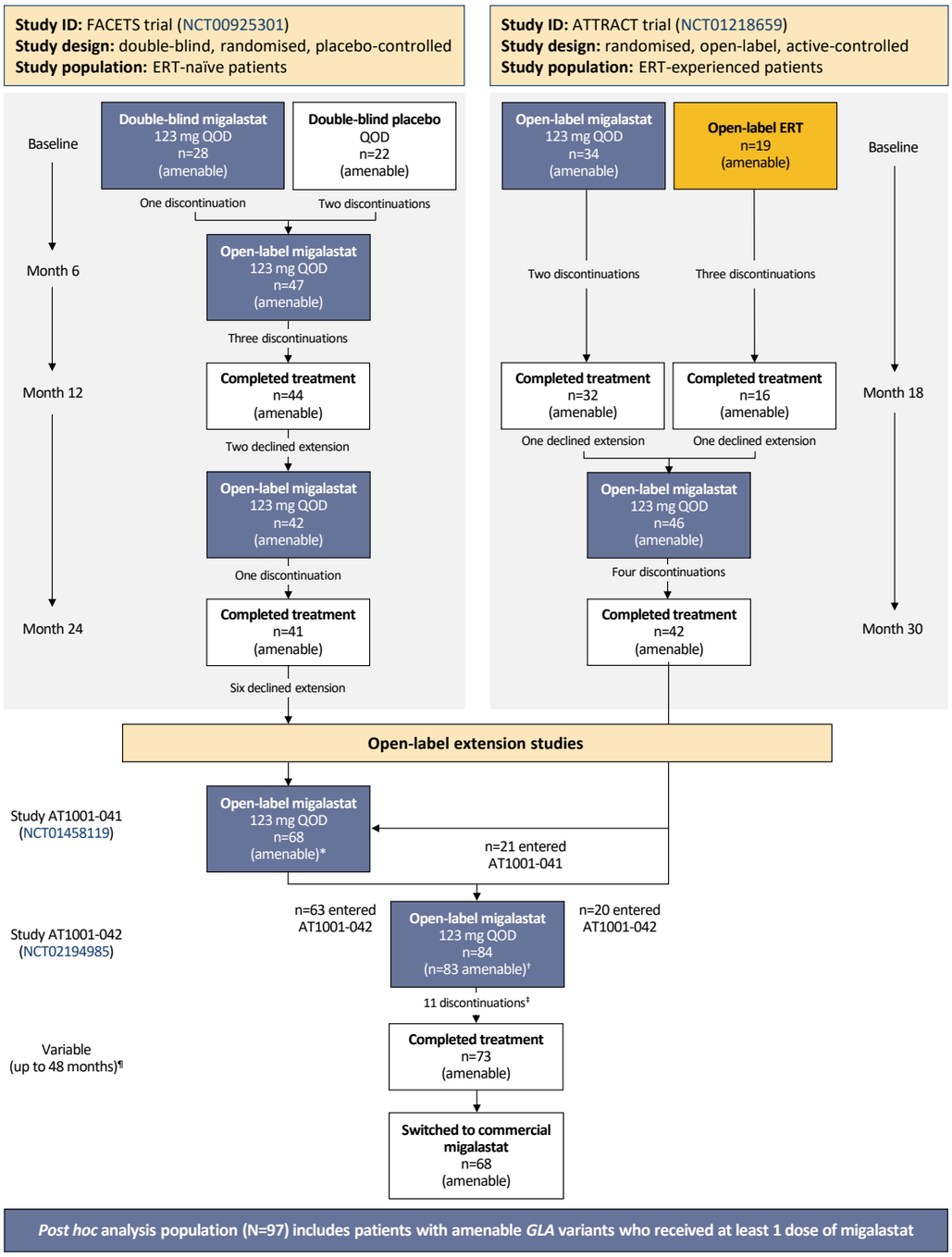
Due to any cause			X	X	X	X‡		X	X	X
Due to Fabry disease	X						X			

CABG, coronary artery bypass grafting; ERT, enzyme replacement therapy; F, females; FACEs, Fabry-associated clinical events; FD, Fabry Disease; GFR, Glomerular Filtration Rate; M, males; NR, not reported; Pts, Patients; y, years.

FACEs are defined as renal, cardiac and cerebrovascular events. The specific renal, cardiac or cerebrovascular events that are included within these definitions for each Fabry study, which are marked by 'X', are provided.

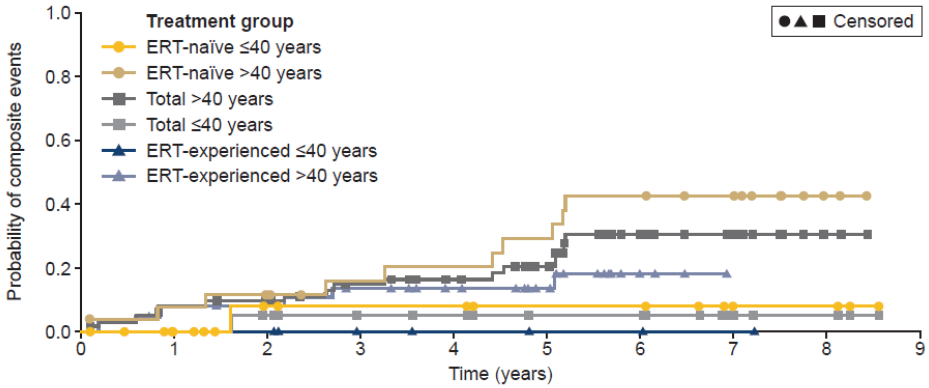
*33 patients were originally included in the open-label population; 2 patients were subsequently found to have non-amenable variants by Good Laboratory Practice-validated migalastat amenability assay and were excluded from the efficacy analyses. †Patients needing renal replacement therapy; excludes patients who had end-stage renal disease at study entry. ‡Non-cardiac death. ¶Median follow-up duration was not reported. Maximum follow-up was 5 years.

Supplemental Figure 1. Study design for the FACET and ATTRACT studies and their open-label extensions



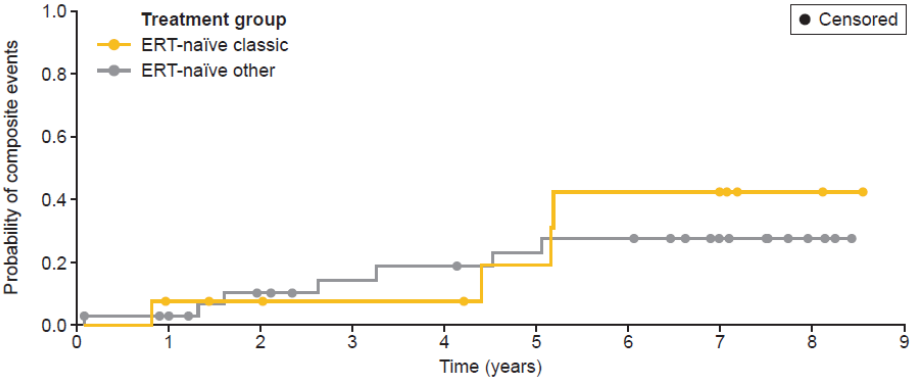
Supplemental Figure 2. Kaplan–Meier analysis of time to first composite event by (A) age, (B) phenotype in ERT-naïve patients and (C) multiorgan involvement in ERT-experienced patients

A.



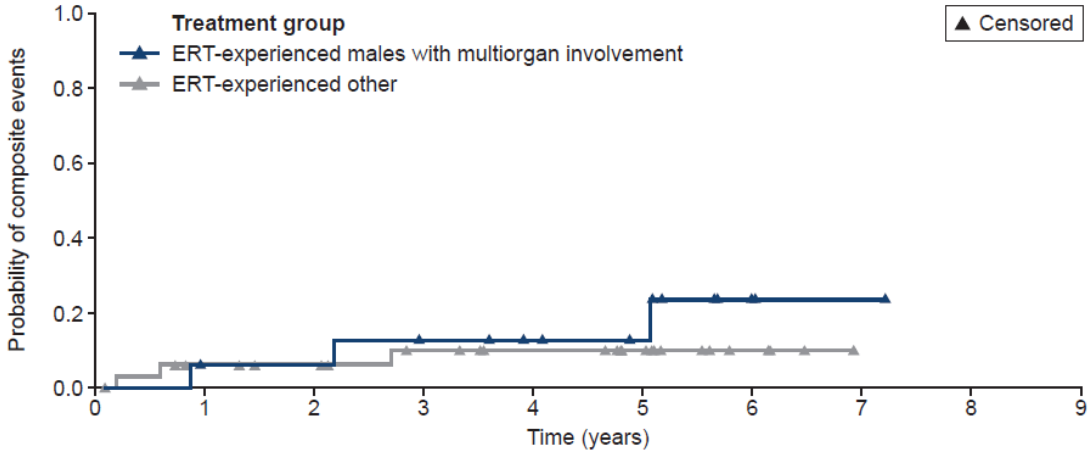
Comparison groups	*P* value by log rank test
ERT-naïve ≤40 vs ERT-naïve >40	0.06
ERT-experienced ≤40 vs ERT-experienced >40	0.29
Total ≤40 vs total >40	0.06

B.



Comparison groups	*P* value by log rank test
ERT-naïve classic males vs ERT-naïve others	0.60

C.



Comparison groups	*P* value by log rank test
ERT-experienced males with multiorgan involvement vs ERT-experienced others	0.46

ERT, enzyme replacement therapy; FACEs, Fabry-associated clinical events.

Time to first composite event by A) age (≤40 years or >40 years), of which was further analysed according to ERT status (ERT-naïve and ERT-experienced patients), B) phenotype (classic or other) of ERT-naïve patients or C) multiorgan involvement in ERT-experienced patients. ERT-naïve classic males was defined as males with multiorgan involvement (ie at least 2 organs of the renal system, cardiac system, central nervous system, peripheral nervous system and gastrointestinal system are affected) and baseline white blood cell α-Galactosidase A <3% of wild type. ERT-naïve 'other' patients include non-classic males and all females. ERT-naïve is defined as never having received ERT or not having received ERT for >6 months; ERT experienced is defined as having initiated ERT >12 months prior to the study. Composite event included cardiac, cerebrovascular and renal events (as previously defined) and death due to FACE. Number of subjects with events at time 0 is 0.