Minireview

The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease – A systematic literature review by a European panel of experts

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ABSTRACT

Background: Heterozygous females with Fabry disease have a wide range of clinical phenotypes depending on the nature of their mutation and their X-chromosome inactivation pattern; it is therefore important to examine outcomes of enzyme replacement therapy (ERT) in the female patient population specifically. This paper presents the findings of a systematic literature review of treatment outcomes with ERT in adult female patients.
Methods: A comprehensive systematic literature review was conducted through January 2017 to retrieve published papers with original data on ERT in the treatment of Fabry disease. The review included all original articles that presented ERT outcomes data on patients with Fabry disease, irrespective of the study type.
Results: Clinical evidence for the efficacy of ERT in female patients was available from 67 publications including six clinical trial publications, and indicates significant reductions in plasma and urine globotriaosylceramide (GL-3) accumulation (in female patients with elevated pre-treatment levels) and improvements in cardiac parameters and quality of life (QoL). To date, data are insufficient to conclude on the effects of ERT on the nervous system, gastrointestinal manifestations, and pain in female patients with Fabry disease.
Conclusions: This review of available literature data demonstrates that ERT in adult female patients with Fabry disease has a beneficial effect on GL-3 levels and cardiac outcomes. The current evidence also suggests that ERT may improve QoL in this patient population, though further studies are needed to examine these results.

1. Introduction

Fabry disease (OMIM #301500) is an X-linked lysosomal disease caused by a mutation in the *GLA* gene (OMIM #300644; HGNC 4296) encoding the acid hydrolase α-galactosidase [1]. This leads to the accumulation of globotriaosylceramide (GL-3) and its deacylated product globotriaosylsphingosine (lyso-GL-3) in plasma and urine as well as in a wide range of cell types, particularly the kidney, heart, and nervous system, resulting in progressive organ damage [1,2]. Fabry disease can be treated with enzyme replacement therapy (ERT) with recombinant α-galactosidase, available for more than a decade.

There are two preparations available: agalsidase alfa (Replagal®) administered at the licensed dose of 0.2 mg/kg body weight; and agalsidase beta (Fabrazyme®) administered at the licensed dose of 1.0 mg/kg body weight. Both preparations are administered intravenously every other week (EOW) [3,4]. ERT with recombinant α-galactosidase was approved in Europe in 2001. Agalsidase alfa and agalsidase beta are available in most European countries, and in Asia, Australia, and Canada. Agalsidase beta was approved by the US Food and Drug Administration in 2003.

Clinical evidence suggests that ERT can slow or delay organ damage and improve clinical signs and symptoms of Fabry disease, such as kidney dysfunction, neuropathic pain, gastrointestinal (GI) outcomes, and cardiac manifestations [1,4,5]. Literature reviews have been conducted to consolidate and report the efficacy and safety of ERT in Fabry disease [6,7]. However, much of the available literature focused on reporting outcomes in male patients. Females are heterozygotes for the *GLA* mutation [8,9], experience X-chromosome inactivation, are much harder to diagnose as they can be asymptomatic or have only mild symptoms, often have plasma α-galactosidase activity within the normal range, and typically present with symptoms later than males. Data on the effect of ERT in females can be deduced from publications that either included a large proportion of female patients in their study population, or reported the effects in males and females separately. However, to our knowledge, no previous systematic review has attempted to summarize all the published evidence regarding the effect of any type of ERT regimen on all Fabry-related outcomes specifically in female Fabry patients.

We conducted a comprehensive systematic literature review of all original articles investigating the effect of ERT in the treatment of Fabry disease published through January 2017 [10]. In this paper, we present the findings specifically in female patients with Fabry disease.

2. Methods

The full methodology for the systematic literature searches and analysis that were performed has been published in this issue [10]. The literature search included articles published up to and including January 2017. The results of the systematic literature analysis for the female population are described in this article; publications summarizing the findings of the literature analysis for the male [11] and paediatric populations [12], as well as a position statement on therapeutic goals in Fabry disease based on the outcomes of an expert consensus panel [13] are also published in this issue.

The outcomes that were selected for analysis included plasma and urine (lyso-)GL-3 levels, GL-3 histology, measures of kidney and heart function as well as heart morphology. Other outcomes included autonomic, peripheral, and central nervous system parameters in addition to GI outcomes, pain, and quality of life (QoL).

Results are described for the approved dose regimens of agalsidase alfa (0.2 mg/kg EOW) and agalsidase beta (1.0 mg/kg EOW) unless specified otherwise. Publications describing results of studies in which data from patients treated with agalsidase alfa and agalsidase beta were combined or in which the ERT type was not specified are referred to in the analysis as 'mixed-ERT' publications.

3. Results

3.1. Female population and publication overview

Publications that were included in the systematic literature analysis presenting ERT outcomes data for female patients specifically are listed in Supplementary Table 1a. Overall, for agalsidase alfa there were five publications from clinical trials (CT) (one from a Grade 1a randomized controlled trial [RCT] and four from Grade 1c single-arm clinical trials), ten publications from observational studies (OS) (of which three covered Grade 2 prospective OS publications and seven Grade 3 retrospective OS publications), and one case series (Grade 4 evidence). For agalsidase beta, there were no CT publications, seven OS publications (two from Grade 2 prospective OS publications and five from Grade 3 retrospective OS publications), four case series (Grade 4 evidence), and 10 case reports (CRs). There were no CT publications, 18 OS publications (seven Grade 2 prospective OS publications and 11 Grade 3 retrospective OS publications), four case series (Grade 4 evidence), and one CR describing mixed-ERT clinical outcomes.

Supplementary Table 1b lists the publications included in this analysis that presented ERT outcomes data for mixed-gender (MG) populations including ≥50% female patients. For agalsidase alfa there were no CT publications, four OS publications (one Grade 2 prospective OS publication and three Grade 3 retrospective OS publications), and no CRs. For agalsidase beta there were no CT publications, one publication from a Grade 2 prospective OS publication, and no CRs. There was one Grade 1c single-arm clinical trial publication, seven OS publications (five Grade 2 prospective OS publications and two Grade 3 retrospective OS publications), and no CRs presenting outcomes from mixed-ERT in MG populations.

The main findings regarding clinical outcomes of treatment with approved doses of agalsidase beta or agalsidase alfa in female patients with Fabry disease are summarized in Table 1.

3.2. GL-3 accumulation

3.2.1. Plasma GL-3

3.2.1.1. *Agalsidase alfa 0.2 mg/kg EOW.* One RCT [18] and three single-arm CT publications [14,16,17] reported plasma GL-3 outcomes data after treatment with agalsidase alfa in female patients. One single-arm open-label CT publication described no changes in plasma GL-3 levels when patients who were either ERT-naïve (*n* = 15) or previously exposed to agalsidase beta (*n* = 31) received agalsidase alfa [17]. In the ERT-naïve group, 14 patients had data at baseline and three patients had data available after 24 months of treatment; in the switch group, data were available for 29 and 19 patients at baseline and 2-year follow-up, respectively [17]. A significant decrease in mean plasma GL-3 semi-quantitative scores was reported in a prospective single-arm, open-label CT of 36 female patients (mean age 47 [range 14–76] years) who completed 4 years of treatment with agalsidase alfa; in this trial, 72% of patients had elevated GL-3 levels before treatment [16]. The use of scores, instead of actual concentrations, is a limitation of this study. In one RCT in which baseline and 1-year post-ERT treatment data were reported for six patients [18] and another single-arm CT (which included 15 patients at baseline, mean age 45 [range 20–66] years and had data for 11 patients after 13 months of treatment) [14], the female patients had normal or only slightly elevated plasma GL-3 levels before starting ERT and no significant changes were observed. An OS publication reported no significant change in plasma GL-3 in female patients who generally had normal levels before starting ERT (seven patients with baseline and post-12 months of agalsidase alfa data) [50] (Table 2). A CR of a 62-year-old female patient who switched from agalsidase beta (1.0 mg/kg for 3 years and 5 months; 0.7 mg/kg EOW for 10 months) to 0.2 mg/kg EOW agalsidase alfa showed an increase in plasma GL-3 levels in the first 12 months after the switch. However, after 12 months, these levels decreased to levels lower than those seen

Table 1

Summary of outcomes with agalsidase beta 1.0 mg/kg EOW or agalsidase alfa 0.2 mg/kg EOW from clinical and observational studies of adult female patients with Fabry disease.

Outcome		Agalsidase alfa 0.2 mg/kg EOW	Agalsidase beta 1.0 mg/kg EOW
3.1 GL-3 accumulation			
3.1.1.	**Plasma GL-3**	↓ Significant (Whybra et al. 2009 [16])	No data from patients with elevated baseline levels
	[in patients with elevated pre-treatment levels]	↓ Non-significant (Baehner et al., 2003 [14]) — No change (Goker-Alpan et al. 2015 [17])	— No change from normal baseline levels (Bénichou et al., 2009 [30])
3.1.2.	**Plasma lyso-GL-3**	↓ Significant (Goker-Alpan et al. 2015 [17 (treatment-naïve patients)]	No data from clinical or observational studies with approved dose of agalsidase beta
	[in patients with elevated pre-treatment levels]	— No change (Goker-Alpan et al. 2015 [17 (after switch)]	
3.1.3.	**Urinary GL-3**	↓ Significant (Whybra et al. 2009 [16]; Baehner et al., 2003 [14])	No data from clinical or observational studies with approved dose of agalsidase beta
	[in patients with elevated pre-treatment levels]	↓ Significance unknown (Whitfield et al. 2005 [19]) — No significant change (Goker-Alpan et al. 2015 [17])	
	Urinary lyso-GL-3 [in patients with elevated pre-treatment levels]	No data from clinical or observational studies with approved dose of agalsidase alfa	No data from clinical or observational studies with approved dose of agalsidase beta
3.1.4.	**GL-3 histology**	No data from clinical or observational studies with approved dose of agalsidase alfa	No data from clinical or observational studies with approved dose of agalsidase beta
3.2 Renal outcomes			
3.2.1.	**eGFR** [compared with decline as with natural history]	— No change (Whybra et al. 2009 [16]; Baehner et al. 2003 [14]; Feriozzi et al. 2012 [24]; Hughes et al. 2011 [26]; Feriozzi et al. 2009 [23]; Beck et al. 2015 [27]; Kampmann et al. 2015 [28])	— No change (Warnock et al. 2012 [33]; Kim et al. 2016 [34])
3.2.2.	**Proteinuria/Albuminuria**	↓ Significant in a subgroup of patients with baseline proteinuria levels > 300 mg/day (Whybra et al. 2009 [16]) — No change (Hughes et al. 2011 [26]; Feriozzi et al. 2009 [23]; Kampmann et al. 2015 [28])	— No change (Kim et al. 2016 [34])
3.3. Cardiac outcomes			
3.3.1.	**LVM/LVMi**	↑ Significant (Beck et al. 2015 [27]) ↓ Significant in LVM (Tsuboi et al. 2012 [51]; Whybra et al. 2009 [16]; Baehner et al. 2003 [14]; Hughes et al. 2011 [26]; Kampmann et al. 2015 (first 3 years [28]) — Stable LVMi (Goláň et al. 2015 [18]; Kampmann et al. 2015 [28 (after 10 years)])	↓ Significant in LVM (Motwani et al. 2012 [32]) — No change (Kim et al. 2016 [34])
3.3.2.	**LVWT**	↓ Non-significant (Tsuboi et al. 2012 [51]) — Stable (Kampmann et al. 2015 [28])	↓ Significant (Motwani et al. 2012 [32])
3.3.3.	**LVEF**	↓ Significant (Kampmann et al. 2015 [28])	— No change (Motwani et al. 2012 [32])
3.3.4.	**ECG measures**	↓ Significant [QRS duration] (Baehner et al., 2003 [14])	↓ Significant, QTc interval (Motwani et al. 2012 [32]) ↑ Significant, P wave duration, PQ interval (Motwani et al. 2012 [32])
3.3.5.	**Exercise testing**	↓ Significant, NYHA classification (Whybra et al. 2009 [16])	No data from clinical or observational studies with approved dose of agalsidase beta
3.4.	**Nervous system outcomes [sweat function, heat intolerance, auditory impairment]**	— No change, hearing function (Sergi et al. 2010 [25]) ↑ Significant, vestibular function (Palla et al. 2007 [20]) ↑ Non-significant, vestibular function (Palla et al. 2003 [15])	No data from clinical or observational studies with approved dose of agalsidase beta
3.4.1.	**Brain MRI findings**	No data from clinical or observational studies with approved dose of agalsidase alfa	No data from clinical or observational studies with approved dose of agalsidase beta
3.4.2.	**TIA/Stroke**	No data from clinical or observational studies with approved dose of agalsidase alfa	No data from clinical or observational studies with approved dose of agalsidase beta
3.5.	**Pain**	↓ Significant, BPI (Whybra et al. 2009 [16]) ↓ Significant, pain average/right now (Hoffmann et al. 2007 [22]) ↓ Non-significant, pain worst/least (Hoffmann et al. 2007 [22]) — No change (Whitfield et al. 2005 [19]; Sergi et al. 2010 [25]; Hughes et al. 2011 [26])	No data from clinical or observational studies with approved dose of agalsidase beta
3.6.	**GI outcomes**	↓ Non-significant, constipation and diarrhoea (Hughes et al. 2011 [26])	No data from clinical or observational studies with approved dose of agalsidase beta
3.7.	**QoL**	↑ Significant for SF-36 physical function, role-physical score, and general health (Baehner et al. 2003 [14]) ↓ Significant for SF-36 general health and vitality (Smid et al. 2011 [49 (switch)]) — No change in EQ-5D/VAS (Hughes et al. 2011 [26]) — No change, energy levels (Ghali et al. 2012 [56])	↑ Significant, SF-36 mental and overall score (Watt et al. 2010 [31]) — No change in SF-36 physical component summary (Watt et al. 2010 [31])

Results are summarized as increase [↑], decrease [↓] or no change from baseline to follow-up after ERT initiation. Significance refers to statistical significance. Results are not adjusted for differences in study designs, patient characteristics, or disease stage. Case series, case reports, mixed-ERT, non-approved dose regimens, and mixed-gender studies are not included.

BPI, Brief Pain Inventory; ECG, electrocardiogram; EOW, every other week; eGFR, estimated glomerular filtration rate; EQ-5D, 5-dimension EuroQol questionnaire; GI, gastrointestinal; GL-3, globotriaosylceramide; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, left ventricular mass index; lyso-GL-3, globotriaosylsphingosine; MRI, magnetic resonance imaging; NYHA, New York Heart Association; QoL, quality of life; QTc, corrected QT interval; SF-36, 36-item Short Form Health Survey; EQ-VAS, EuroQol-Visual Analogue Scale.

Table 2
Plasma GL-3 level outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients.

	Study, year [reference] (number of patients[a]) Evidence grade[b]	Female, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	Endpoint (number of patients[e])	Overall result (p value/95% CI)
Alfa	Goláň et al. 2015 [18] (N = 44) Grade 1a	18 (41)	12	nmol/mL	Mean: 3.5 (n = 6)	Mean: 3.5 (n = 6)	NC (95% CI: −0.95, 0.93)
	Whybra et al. 2009 [16] (N = 40) Grade 1c	40 (100)	48	Plasma GL-3 score[6] (times above ULN[7]) Patients, n (%)	1.81 [0.58] (n = 36) Prevalence stratified by GL-3 score[6]: 1: 7 (19.4) 2: 26 (72.2) 3: 3 (8.3) (n = 36)	1.31 [0.47] (n = 36) Prevalence stratified by GL-3 score[6]: 1: 25 (69.4) 2: 11 (30.6) 3: 0 (0.0) (n = 36)	↓ (p < 0.001)
	Baehner et al. 2003 [14] (N = 15) Grade 1c	15 (100)	13	nmol/mL (range)	3.04–17.59 (n = 15)	6 months: decreased (NR) (n = 11)	↓ (NS from BL)
	Goker-Alpan et al. 2015 [17] (N = 100) Pre-treatment with agalsidase beta (1 mg/kg EOW; n = 71): 55 months (4–146) Grade 1c	46 (46) ERT-naïve: 15 (52) Switch: 31 (44)	24	nmol/mL (normal 4.55 ± 3.90)	ERT-naïve: 13.76 ± 2.32 (n = 14) Switch:11.46 ± 0.96 (n = 29)	ERT-naïve: NR (n = 3) Switch:NR (n = 19)	NC NC NC
Beta	Bénichou et al. 2009 [30] (N = 134) Grade 3	12 (9)	Range: 1.9–60.7	µg/mL (normal > 7.03)	Above normal in 17% (2 patients) (n = 12)	NC	NC (NR)
Alfa Beta	Van Breemen et al. 2011 [50] (N = 43) Grade 3	21 (49)	12	µM (normal < 3.18)	Alfa 0.2: 2.82 (2.45–3.28) (n = 7) Beta 1.0: 2.53 (1.20–6.76) (n = 9)	Alfa 0.2: 2.44 (2.02–3.60) (n = 7) Beta 1.0: 1.76 (0.79–3.65) (n = 8)	NC (NR) NC (NR)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included. Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.

↓, decrease in levels; ↑, increase in levels; BL, baseline; CI, confidence interval; EOW, every other week; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; NC, no change; NR, not reported; NS, not significant; SD, standard deviation; SE, standard error; ULN, upper limit of normal range.

[a] Total number of patients included in the study who were treated with ERT.

[b] Study grades defined as follows: Grade 1a randomized controlled trial; Grade 1c single-arm clinical trial; Grade 1a/c randomized controlled trial with single-arm open-label extension; Grade 2 prospective observational study; Grade 3 retrospective observational study; Grade 4 case series; Grade 5 case report.

[c] Number of female patients who were treated with ERT.

[d] Number of female, ERT-treated patients with data for the outcome at baseline.

[e] Number of female, ERT-treated patients with data for the outcome at endpoint; [6]GL-3 values were converted to a 3-point scale as follows: (1) in the normal range; (2) > normal, but ≤2 x ULN; and (3) > 2 x ULN; [7]ULN < 3.3 µmol/L or < 4 µg/mL.

when the patient was receiving agalsidase beta [52].

In a small Japanese MG study, 11 patients (seven females; mean age 52 years, age at switch 23–68 years) were switched from agalsidase beta (pre-switch treatment duration 15–77 months) to agalsidase alfa. Pre-switch plasma GL-3 levels were near the normal range for the female patients but increased 12 months after switching to agalsidase alfa [51]. However, a follow-up publication from the same study showed that plasma GL-3 levels had returned to pre-switch levels 24 months after switching, and this reduction was sustained at 36 months [74].

3.2.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, two OS publications reported plasma GL-3 outcome data; in both publications, the majority of female patients had GL-3 levels within the normal range at the start of treatment and no significant changes in plasma GL-3 were reported [data in 12 patients 30, 50] (Table 2). In one publication, data were available for nine patients at baseline and eight patients after 1 year of agalsidase beta treatment [50]. A CR that included six female patients treated with agalsidase beta reported a decrease in plasma GL-3 in one 35-year-old female patient [37]. A CR of a 62-year-old female patient who first received agalsidase beta 1.0 mg/kg EOW for 3 years

and 5 months, then a reduced dose of 0.7 mg/kg EOW for 10 months, and eventually switched to agalsidase alfa showed that the patient had stable GL-3 levels during treatment with the approved dose of agalsidase beta [52].

3.2.1.3. Mixed ERT. An OS publication, including data from 28 females treated for at least 1 year, reported mean plasma GL-3 levels within normal range at baseline that decreased and remained decreased after 6 years [60].

3.2.2. Plasma lyso-GL-3
3.2.2.1. Agalsidase alfa 0.2 mg/kg EOW. Plasma lyso-GL-3 was reported as an outcome in female patients in one single-arm open-label CT with agalsidase alfa [17]. In the ERT-naïve group baseline lyso-GL-3 data were available for 14 patients and 24-month follow-up data in three patients. In three ERT-naïve patients with elevated baseline lyso-GL-3, ERT resulted in a significant reduction, albeit very small, in plasma lyso-GL-3 levels at 18 and 24 months [17]. Lyso-GL-3 levels in female patients who switched from agalsidase beta to agalsidase alfa were reported in one CT publication (baseline data in 29 patients), which

found no significant change after 24 months in 19 patients [17]. One OS publication showed a decrease in plasma lyso-GL-3 levels in seven patients treated for 12 months [50] (Supplementary Table 2). Further, a CR of a 62-year-old female patient who switched from agalsidase beta (1.0 mg/kg for 3 years and 5 months; 0.7 mg/kg EOW for 10 months) to agalsidase alfa also described that plasma lyso-GL-3 levels were increased slightly 12 months after switching but gradually decreased to below pre-switch levels [52].

A Japanese, observational MG study including seven female patients also showed no significant change in plasma lyso-GL-3 levels 36 months after switching from agalsidase beta 1.0 mg/kg EOW (pre-switch treatment duration 15–77 months; age at switch 23–68 years) to agalsidase alfa 0.2 mg/kg EOW [74].

3.2.2.2. Agalsidase beta 1.0 mg/kg EOW. One OS publication showed a decrease in plasma lyso-GL-3 levels in nine patients treated for 12 months [50] (Supplementary Table 2).

3.2.2.3. Mixed ERT. Two publications from a retrospective mixed-ERT OS also reported significant reductions in plasma lyso-GL-3 over a median period of 16 months compared with pre-treatment levels in female patients with the classical or the cardiac variant of Fabry disease. This reduction in lyso-GL-3, however, was not sustained with increases in lyso-GL-3 observed during long-term follow-up especially in the female patients with a cardiac-type *GLA* mutation [six patients, age at ERT initiation 44–67 years, treatment duration 8–24 months [62], and seven patients 64 [64]. One OS publication reported no statistical difference in lyso-GL-3 levels before and a median of 1.3 years after the global shortage of agalsidase beta in 3 female patients who either switched from agalsidase beta to agalsidase alfa or reduced the dose of agalsidase beta [49].

In MG populations, one mixed-ERT OS reported a slight decrease in plasma lyso-GL-3 during ERT (median treatment duration 5.7 years) in 21 classically affected female patients who had elevated pre-treatment lyso-GL-3 levels [77]. One OS publication in 27 female patients with elevated pre-treatment lyso-GL-3 levels also reported a significant reduction in lyso-GL-3 levels after 12 months, which was sustained at 6 years' follow-up [60].

3.2.3. Urinary GL-3 and lyso-GL-3
3.2.3.1. Agalsidase alfa 0.2 mg/kg EOW. Three single-arm CT publications presented urinary GL-3 outcomes with agalsidase alfa in female patients [14,16,17]. A significant reduction in urinary GL-3 scores was reported after 12 months of ERT in a prospective single-arm open-label trial in 36 female patients (mean age 47 [range 14–76] years); urinary GL-3 scores decreased during 4 years of follow-up, and at the end of the study only one female patient had a score above the normal range [16]. An open-label single-arm trial of ERT with agalsidase alfa in 15 female patients (mean age 45 [range 20–66] years) with severe Fabry disease symptoms reported that patients had a wide range of urinary GL-3 levels before ERT, with the largest reductions in urinary GL-3 occurring in patients with the highest pre-treatment levels, but no significant overall differences after 6 months of treatment (n = 11) [14]. One single-arm open-label CT reported no change in urinary GL-3 levels from baseline to 24 months in treatment-naïve patients (baseline data for 14 patients, follow-up data for three patients) or in patients who switched to agalsidase alfa (data available for 28 and 18 patients at baseline and follow-up, respectively) [17]. A small OS publication described decreases in urinary GL-3 after 1 year of agalsidase alfa in the two female patients included (aged 27 and 41 years) [19] (Supplementary Table 3).

One OS publication reported data from a single 35-year-old female patient during ERT showing a reduction in urinary lyso-GL-3 at 9 months after agalsidase alfa [58].

3.2.3.2. Agalsidase beta 1.0 mg/kg EOW. There was no literature

published regarding the impact of agalsidase beta on urinary GL-3 or urinary lyso-GL-3 levels in female patients.

3.2.3.3. Mixed ERT. Data from an observational mixed-ERT study described reductions in urinary GL-3 in female patients during treatment [60].

3.2.4. Kidney, heart, and other organ GL-3
There were no publications from CTs or OS that reported GL-3 histology data in the kidneys, heart, or other organs after ERT.

3.2.4.1. Agalsidase alfa 0.2 mg/kg EOW. There were no publications available that described changes in GL-3 levels in the kidneys, heart, or other organs with agalsidase alfa.

3.2.4.2. Agalsidase beta 1.0 mg/kg EOW. In one case series there was a 10-fold reduction in GL-3 levels in heart tissue after 6 months of agalsidase beta treatment in a 46-year-old female patient [36] who was originally treated in a multicentre, randomized, placebo-controlled study [79]. In addition, there were two case reports that provided histopathological evidence of GL-3 inclusions in placental tissue of mothers, one pregnant with a boy and the other with a girl, treated with agalsidase beta during pregnancy, but it remains unclear if treatment had an effect on the placental tissue [41 (24-year-old patient who started ERT at the age of 21 years), 43 (37-year-old, with 2-years prior ERT experience before the pregnancy)].

3.2.4.3. Mixed ERT. There were no publications available that described changes in GL-3 levels in the kidneys, heart, or other organs with mixed-ERT regimens.

3.3. Renal outcomes

3.3.1. Estimated glomerular filtration rate (eGFR)
3.3.1.1. Agalsidase alfa 0.2 mg/kg EOW. Two publications from open-label single-arm CTs of agalsidase alfa reported no decline in eGFR during treatment in female patients [14,16]. One included 15 severely affected female patients (mean age 45 [range 20–66] years) treated for 13 months [14]. In the other, 36 female patients with an average age of 47 (range 14–76) years reported stabilization of eGFR during 4 years of ERT [16]. Four observational registry data publications also reported a minimal loss of eGFR over time with agalsidase alfa [change in eGFR < 1 to −2 mL/min/1.73 m^2/year] [50 female patients with an average age of 50 years and duration of treatment of 36 months (23), 74 females with an average age of 46 years and mean duration treatment of 7.4 years (24), 78 females who started ERT at age 49 years and were treated for 4 years [26], and 317 females with a median follow-up of 5 years [27]]. In one of these publications, long-term data from the Fabry Outcome Survey (FOS) registry on outcomes with agalsidase alfa showed a trend toward improved mean annualized eGFR slopes in patients without proteinuria at baseline, although the annual changes in glomerular filtration rate (GFR) in female patients were within the normal age-expected range [27]. One OS publication reported stabilization in eGFR in 24 female patients (average age 39 years) treated with agalsidase alfa for 10 years [28] (Supplementary Table 4).

The main findings from MG studies with ≥50% female patients are summarized as follows: a small OS, which studied the effects of agalsidase alfa in subjects from an extended single family group (including 11 females with ages ranging from 21 to 56 years), reported a significant improvement in eGFR after 6 months of ERT [72]. Two papers from the same OS, in which seven of 11 patients were female (mean age 52 years), showed that eGFR remained stable during 36 months of follow-up after switching from agalsidase beta to agalsidase alfa [51,74]. Another CR with a 62-year-old female patient showed that after switching from agalsidase beta (1.0 mg/kg for 3 years and 5 months; 0.7 mg/kg EOW for 10 months) to agalsidase alfa eGFR

remained stable at the decreased level (2-year post-switch follow-up) [52]. It is important to note when reviewing this evidence that the inclusion of male patient data in the eGFR outcomes will impact the results, as male patients typically have more renal involvement than females [80].

3.3.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one Fabry Registry publication reported a decrease in eGFR in 62 female patients treated with ERT although no statistics were provided [33]. ERT was started at a median of age 43 years and patients were followed for a mean of 4 years [33]. One OS publication reported no change in eGFR in four female patients (age at treatment 22, 39, 48, and 48 years) with normal eGFR levels at baseline who received agalsidase beta (for a range of 7–10 years). In these patients, dose reduction of agalsidase beta to 0.25 and 0.5 mg/kg EOW did not have an effect on eGFR [34] (Supplementary Table 4). Three CRs also note that eGFR was stable in female patients during agalsidase beta treatment [one 29-year-old patient, 10 months after ERT initiation [39], one 37-year-old patient treated for over 2 years [42], 46], with one CR of a 62-year-old female patient with up to 12 years of follow-up [46]. In one case study, eGFR increased slightly in two female patients (26 and 29 years old) treated with agalsidase beta throughout pregnancy (an increase in eGFR is a normal feature of pregnancy) [35]. Another CR with one 62-year-old female patient showed a decrease in eGFR after 2 years on agalsidase beta [52]. One CR of a 29-year-old patient with marked proteinuria at baseline noted resolution of renal dysfunction after 1 year of agalsidase beta treatment [45].

3.3.1.3. Mixed ERT. Publications of data from mixed-ERT studies also show that ERT is associated with stable eGFR in female patients, reporting no or minimal declines in eGFR in line with normal age-related changes in renal function [one 71-year-old female patient treated for 12 months [57], 17 women, 11 with classic and 6 cardiac phenotypes who started ERT aged 33–79 years and were treated for 6–26 months (62), 65, 52 ERT-naïve females, mean age 52 years (66)]; one study reported an improvement in eGFR in 103 female ERT-treated patients without proteinuria at baseline [63]. One retrospective OS publication with 28 female patients (average age at baseline 52 years) showed that eGFR significantly declined over time, with evidence of greater renal involvement at baseline (mean treatment duration was 80 months) [78]. One OS publication in 18 female patients showed no significant change in the slope of eGFR loss a median of 1.3 years after switching from agalsidase beta to agalsidase alfa or to reduced-dose agalsidase beta [49]; the slope of eGFR loss in both ERT treatment periods (pre- and post-switch) was within the range found in age-related GFR loss in the general population. Data from two CRs further support the findings that ERT is associated with eGFR improvement or stabilization in female ERT-treated patients [four patients with age at ERT initiation of 21–52 years and duration of ERT 2.8–11 years (53), and one 42-year–old [70]].

3.3.2. Albuminuria/Proteinuria
3.3.2.1. Agalsidase alfa 0.2 mg/kg EOW. One prospective single-arm open-label CT publication of agalsidase alfa in 36 females (mean age 47 [range 14–76] years) reported stable proteinuria levels in 33 females, and a significant improvement in proteinuria after 4 years of treatment in a subgroup of 11 patients with baseline proteinuria > 300 mg/24 h [16]. In this study, the seven women who received angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARBs) during the whole study duration, and had proteinuria levels of 1349 ± 1760 mg/24 h at baseline, experienced a 3-fold decline in proteinuria [16]. Three observational registry studies reported no overall change in proteinuria outcomes with agalsidase alfa [50 female patients, average age 50 years, duration of treatment 36 months [23], 74 females, average age 46 years, mean duration of treatment 7.4 years [24], 78 females, started ERT age 49 years, treated

for 4 years [26]], and another OS publication also reported no change in proteinuria in 24 female patients (average age 39 years) with or without baseline proteinuria after 10 years of treatment [28] (Supplementary Table 5).

In MG populations, one OS publication of agalsidase alfa noted a significant decrease in albuminuria in 11 females (ages ranging from 21 to 56 years treated for 6–12 months) [72], while another study including 46 female patients with proteinuria data showed minimal changes during treatment of up to 5 years [24]. Another OS publication showed no change in proteinuria levels in seven female patients over 3 years of follow-up when patients were switched from agalsidase beta to agalsidase alfa [74]; urinary protein levels were within the normal physiological range before the switch in ERT regimen [74].

3.3.2.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one OS publication reported no change in proteinuria in four female patients with normal proteinuria levels at baseline (age at treatment initiation ranged from 22 to 48 years, duration of treatment 7–10 years). In these patients, dose reduction of agalsidase beta to 0.25 and 0.5 mg/kg EOW did not have an effect on proteinuria [34] (Supplementary Table 5). One CR in a woman who started ERT aged 52 years showed worsening of proteinuria despite treatment with agalsidase beta for 7 years [44]. In female patients treated with agalsidase beta during pregnancy, one publication noted stable proteinuria levels in a 21-year-old [48] and another described improvement in proteinuria levels in two pregnant (aged 26 and 29 years) patients [35].

3.3.2.3. Mixed ERT. Publications reporting proteinuria outcomes from mixed-ERT OS in 17 female patients (age at ERT 33–79 years) described an improvement in albuminuria during ERT treatment (duration 6–26 months) [62], a non-significant inverse association between time on ERT and the likelihood of developing proteinuria (analysis in 158 females) [63], and significant improvements in proteinuria during treatment (13 patients, mean age 45 years, 6-years follow-up) compared with a worsening of proteinuria in the 4 untreated patients (mean age 34 years, 4-years follow-up) [65]. One CR showed that, in four female patients (age at ERT initiation 21–52 years; duration of ERT 2.8–11 years), ERT resulted in a small increase, decrease, or stabilization of proteinuria levels [53]. One study showed that proteinuria during ERT was not affected by the use of ACEi/ARBs [65].

3.4. Cardiac outcomes

3.4.1. Left ventricular mass (LVM)/left ventricular mass index (LVMi)
3.4.1.1. Agalsidase alfa 0.2 mg/kg EOW. LVM was reported as an outcome in three CT publications, all of which used echocardiography to determine LVM. A randomized, multicentre, open-label study including 18 female patients treated for 12 months with one of three different regimens of agalsidase alfa (0.2 mg/kg EOW, 0.2 mg/kg weekly, or 0.4 mg/kg weekly) reported that treatment with agalsidase alfa 0.2 mg/kg EOW was associated with a stable LVMi [18]. A prospective single-arm open-label study of 36 women (average age 47 [range 14–76] years) treated with agalsidase alfa for 4 years reported decreases in LVM; 25 [69%] women in this trial had left ventricular hypertrophy (LVH) at baseline. Decreases in LVM > 20% were reported in 13 of these 25 patients with seven patients demonstrating decreases of 10–20% [16]. An open-label single-arm clinical trial of 15 female patients (mean age 45 [range 20–66] years) treated with agalsidase alfa for up to 13 months reported a progressive decrease in LVM that was statistically significant after 9 months of treatment ($n = 7$) [14]. Two registry study publications from the FOS reported LVMi outcomes, determined by echocardiography, after treatment with agalsidase alfa in 24 [26, treatment duration 4 years] and 93 female patients [27, median follow-up 5 years]. One of these registry studies reported a significant decrease in LVMi after 4 years of agalsidase alfa in 12 women with LVH at baseline [26], and the other registry study showed

that LVH progression significantly increased, and the rate of increase in LVH was slower with ERT compared with untreated patients [27]. The annualized rate of LVMi significantly increased in female patients in this study [27]. An OS publication including 24 ERT-treated females (average age 39 years) reported no change in LVMi after 10 years of treatment with agalsidase alfa, although there was an initial significant improvement between the first and fourth year of treatment [28]. Another OS study including seven females (mean age 52 years) found that patients switching from agalsidase beta to agalsidase alfa showed significant reductions in LVMi 12 months after switching [51] (Supplementary Table 6). One CR of a 62-year-old female who had previously received agalsidase beta (1.0 mg/kg for 3 years and 5 months; 0.7 mg/kg EOW for 10 months) reported stabilization of LVMi 6 months after switching to agalsidase alfa [52].

In MG studies with ≥ 50% female patients, one OS publication of 17 Fabry patients (of whom 11 were female, with ages ranging from 21 to 56 years) found that agalsidase alfa treatment resulted in an improvement in LVMi after 6 months of treatment [72]. Another OS publication, which assessed 7 female patients (mean age 52 years) switching to agalsidase alfa, reported that the reduction in LVMi (method of assessment not stated) 12 months after switching [51] was maintained during 36 months of follow-up [74]. The patients in this study had been treated with agalsidase beta 1.0 mg/kg EOW for 1.2–6.5 years before switching [51]. In contrast, another observational MG study that included LVM data for nine female patients did not report any significant changes in LVMi, assessed using cardiac ultrasound, a median of 1.3 years after switching from agalsidase beta to agalsidase alfa or to reduced dose agalsidase beta [49].

3.4.1.2. Agalsidase beta 1.0 mg/kg EOW. LVMi outcomes were reported in one OS publication in a cohort of 22 female patients with a mean age of 44 years who were treated with agalsidase beta for a median of 36 months. 12 patients had LVH at baseline. Treatment resulted in a significant reduction in LVMi from baseline, as assessed using echocardiography [32]. One OS publication on four patients (age at ERT initiation 22–48 years) treated for 7–10 years reported no change in LVMi [34] (Supplementary Table 6). Similarly, two CRs of female Fabry patients showed that both patients had stabilized LVH and LVMi values during 18–27 months of agalsidase beta treatment [40 (44-year-old), (52) (62-year-old)]. One CR also showed that a 62-year-old female patient had increased LVMi values after 10 months of treatment with a reduced dose of agalsidase beta (0.7 mg/kg EOW) [52]. One CR of a 29-year-old patient demonstrated an improvement in cardiomegaly after 12 months of agalsidase beta [45], although two other CRs in two female patients found that these patients either developed LVH or showed LVH progression after agalsidase beta initiation [38 (51-year-old),44 (52-year-old, 5 years post-ERT follow-up)].

3.4.1.3. Mixed ERT. Echocardiography data on LVMi outcomes from mixed-ERT OS publications indicate a reduction in LVM and LVMi during ERT in females with classical Fabry disease [one 71-year-old female and a 45-year-old female treated for 12 months [57], 59, eleven patients with age at ERT start 33–79 years and treatment duration 6–26 months (62),and another reference in eleven patients [64]. A publication from a mixed-ERT OS (the Canadian Fabry Disease Initiative) that included 55 women (mean age 52 years) newly starting on ERT described a reduction in LVMi, measured by echocardiography, in female patients with proteinuria > 0.5 g/day at baseline, but an increase in LVMi in females with proteinuria ≤ 0.5 g/day [66]. One of the publications (reporting LVMi data on 26 females aged 47 years) also reported subgroup data showing a slightly greater improvement in LVM in patients with LVH at baseline [59]. Another publication from a mixed-ERT study showed that patients with an abnormal baseline electrocardiogram (ECG) had a significant increase in LVMi, whereas in patients with a normal ECG there was no change in LVMi; this report included 12 females with mean age 34 years at

baseline and 41 years at follow-up (median duration of follow-up of 6.4 years) [68]. One CR publication in four females who started ERT age 21–52 years and were treated for 2.8–11 years also supports these findings [53].

3.4.2. Left ventricular wall thickness (LVWT)
3.4.2.1. Agalsidase alfa 0.2 mg/kg EOW. An OS publication including 24 females (average age 39 years) reported no significant change in wall thickness after 10 years of treatment with agalsidase alfa, although there was a significant improvement after 1 year of treatment [28]. One small OS publication previously described non-significant improvements in LVWT variables in the seven female patients (mean age 52 years) who switched from agalsidase beta to agalsidase alfa [51] (Supplementary Table 7).

A CR of a 62-year-old showed that wall thickness increased when the patient treated with agalsidase beta (treatment duration 3 years 5 months) was switched to reduced-dose agalsidase beta (treatment duration 10 months) and maintained in the subsequent period on agalsidase alfa [52].

3.4.2.2. Agalsidase beta 1.0 mg/kg EOW. Wall thickness was assessed using cardiac echocardiography in an OS publication of agalsidase beta in 22 female patients (mean age 44 years), 12 of whom had LVH before starting ERT. After a median duration of 36 months, there was a significant reduction in maximal wall thickness [32] (Supplementary Table 7). Two CRs observed increases in LVWT in females receiving agalsidase beta; in both cases the women had lung or cardiac manifestations of Fabry disease before initiation of ERT in their fourth or fifth decade [one 51-year–old (38), and another 44-year–old [40]]. A CR in a 62-year-old female showed that wall thickness variables increased when the dose of agalsidase beta was reduced from 1.0 mg/kg EOW (treatment duration 3 years and 5 months) to 0.7 mg/kg EOW (10 months) [52]. A CR reported worsening of LVH in a cardiac-type 52-year-old female patient treated with agalsidase beta for 5 years [44].

3.4.2.3. Mixed ERT. One mixed-ERT publication reported that six female patients (started ERT aged 44–67 years) with a mutation leading to the late-onset cardiac variant of Fabry disease had reductions in the thicknesses of the intraventricular septum and the left posterior wall throughout 6–39 months of ERT as determined by echocardiography [62]. One mixed-ERT OS publication showed no change in posterior wall thickness (data available for 12 females, mean age 34 years at baseline with a median duration of follow-up of 6.4 years) [68].

3.4.3. Left ventricular ejection fraction (LVEF)
3.4.3.1. Agalsidase alfa 0.2 mg/kg EOW. An OS publication including 24 females (average age 39 years) reported a small but significant decrease in ejection fraction (EF) after 10 years of treatment with agalsidase alfa, although mean values remained within normal limits [28] (Supplementary Table 8).

3.4.3.2. Agalsidase beta 1.0 mg/kg EOW. LVEF was analysed as an outcome in one prospective OS publication of ERT with agalsidase beta; no changes were observed (EF was 63% at baseline) after a median of 36 months treatment [32 (22 females, mean age 44 years)] (Supplementary Table 8). Three CRs described an increase in EF in patients receiving agalsidase beta [46-year–old with improvement seen after 2-years of treatment (36), one 44-year-old treated for up to 18 months [40], and one 29-year-old patient treated for 12 months (45)].

3.4.3.3. Mixed ERT. One MG, mixed-ERT OS publication including 12 females (age 34 years at baseline) showed no change in LVEF after a median follow-up duration of 6.4 years [68].

3.4.4. Electrocardiogram (ECG) measures

3.4.4.1. Agalsidase alfa 0.2 mg/kg EOW. An open-label single-arm CT that assessed treatment with agalsidase alfa in 15 severely affected female patients (mean age 45 years [range 20–66] years) reported that the mean QRS duration decreased progressively but non-significantly from baseline to 9 months (*n* = 5) [14] (Supplementary Table 9).

3.4.4.2. Agalsidase beta 1.0 mg/kg EOW. An OS publication of agalsidase beta in 22 female patients (mean age 44 years) demonstrated significant improvement in P wave duration, PQ interval, and corrected QT interval a after median of 36 months of agalsidase beta treatment [32] (Supplementary Table 9). These findings are supported by two CRs, one in which a 65-year-old patient reported resolution of ST segment abnormalities after 1 year of agalsidase beta [47] and another in which a 46-year-old patient experienced normalization of PR interval after 6 months of agalsidase beta [36].

3.4.4.3. Mixed ERT. A mixed-ERT OS publication in 12 females (mean age at baseline of 34 years) reported no changes in ECG findings after a follow-up duration of 6.4 years [68].

3.4.5. Exercise testing

3.4.5.1. Agalsidase alfa 0.2 mg/kg EOW. One prospective single-arm open-label CT publication in 36 female patients (mean age 47 [range 14–76] years) reported a significant improvement in exercise capacity, measured using the New York Heart Association (NYHA) classification, after 4 years of agalsidase alfa treatment [16] (Supplementary Table 10), and one MG OS publication including 24 females (average age 39 years) described an improvement in NYHA heart failure classification following 10 years of agalsidase alfa [28].

3.4.5.2. Agalsidase beta 1.0 mg/kg EOW. One CR of a 62-year-old female noted a decline in exercise tolerance after at least 3 years of agalsidase beta [46].

3.4.5.3. Mixed ERT. There were no publications for mixed ERT describing changes in exercise testing or cardiac function following treatment.

3.5. Nervous system outcomes

3.5.1. Agalsidase alfa 0.2 mg/kg EOW

For hearing loss and vestibular function, one single-arm CT publication (21 patients, 8 females with data at baseline, three females with data after 12-months follow-up) [15], and one OS publication (nine females, treated for 51.5 months) of agalsidase alfa [25] found no significant improvement/stabilization of hearing acuity during ERT (Supplementary Table 11). However, one OS publication found that 12 months of treatment with agalsidase alfa significantly improved vestibular function in a MG group including 14 ERT-treated females, although auditory function did not improve during a 5-year follow-up period [20]. One CR of a 54-year-old female patient treated with agalsidase alfa in combination with omeprazole observed stabilization of hearing after 30 months of ERT [29].

3.5.1.1. Agalsidase beta 1.0 mg/kg EOW. One CR mentioned the development of hypohidrosis after ERT initiation in a 51-year-old patient [38].

3.5.1.2. Mixed ERT. Similarly, two OS publications on mixed ERT [61,67] found no significant improvement/stabilization of hearing acuity during ERT. One publication included nine females, with an average age of 39 years and average follow-up of 47 months [61], and the other 38 females (36 classic phenotype with a median age 48 [range 19–81] years and two non-classic with a median age of 39 [range 31–65] years) who were followed for a median of 7 (range 0–11) years

[67]. In addition, a MG OS publication that included 17 female patients (median age 51 [range 22–73] years) treated with ERT of unspecified type for a median of 3.6 years reported no overall change in autonomic symptom profile scores during ERT [76].

3.5.2. Brain magnetic resonance imaging (MRI) findings (chronic white matter hyperintensities [WMH])

3.5.2.1. Agalsidase alfa 0.2 mg/kg EOW. No publications reported WMHs with agalsidase alfa in females or MG populations.

3.5.2.2. Agalsidase beta 1.0 mg/kg EOW. One 62-year-old female, with small WMHs at baseline, received 12 years of agalsidase beta. After 3 years of therapy she received a pacemaker and did not develop any new WMHs in the following years [46].

3.5.2.3. Mixed ERT. Several mixed-ERT publications reported the incidence of WMHs in female patients [54,59,60]. In one publication, seven female patients with a mean age of 53 years were treated with ERT for 2 years [56] and in another, 25 females (aged 47 years) had follow-up MRIs [59]. However, these publications did not describe the effect of ERT on the pathology. One case series specifically investigated the impact of ERT on brain structure/function/pathology in 20 patients (age range 15–66 years). Most patients on agalsidase beta were switched to agalsidase alfa during shortage. At baseline, five of 20 treated female patients had WMHs, five patients had moderate WMHs, and one had severe WMHs. During follow-up positron emission tomography/MRI scans, five patients experienced progressive pathology [69]. A CR described an ERT-treated 55-year-old female patient with WMHs who had no increase in WMHs burden after up to 2 years' follow-up [71].

3.5.3. Transient ischaemic attack (TIA)/stroke

There have been no publications that show the effect of ERT on the incidence of TIA or ischaemic or haemorrhagic stroke in females with Fabry disease.

3.6. Pain outcomes

3.6.1.1. Agalsidase alfa 0.2 mg/kg EOW. A prospective, open-label single-arm CT showed significant decreases in Brief Pain Inventory (BPI) 'pain at its worst' scores in 36 female patients (mean age 47 [range 14–76] years) who completed 48 months of treatment with agalsidase alfa [16]. In addition, three OS publications showed no change or non-significant improvements in patient-reported pain scores during treatment with agalsidase alfa [19,25,26]. In one publication, nine female patients were followed for 51.5 months [25], another included a 27-year-old and a 41-year-old woman who were treated for up to 1 year [19], and the last publication reported data in 78 females who started ERT at 49 years and received treatment for up to 4 years [26] (Supplementary Table 12).

In a MG OS publication including 11 female patients (aged 21–56 years), acroparaesthesiae decreased after 6 months' treatment with agalsidase alfa [72]. Another MG OS publication, including a total of 752 patients (of whom 393 were female), showed that 36 months of treatment with agalsidase alfa resulted in significantly decreased pain severity, though the measurements for 'pain at its worst' and 'pain at its least' remained unchanged [22]. Three publications from two OS publications in MG populations did not identify any changes in BPI when patients were switched from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [49 (18 patients, a median of 1.3 years after switch/dose reduction),[74] (seven female patients, mean age 52 years, pain data reported 12 months after switching),[51]]. One CR reported stable pain outcomes in the two female patients who received agalsidase alfa (age at start of ERT 21 and 52 years, ERT duration 3.1 and 2.8 years, respectively) [53].

3.6.1.2. Agalsidase beta 1.0 mg/kg EOW. One CR reported the development of peripheral neuropathy (tingling in hands/feet, temperature intolerance) when the 51-year-old patient was treated with agalsidase beta [38]. A CR reported improved pain outcomes in two female patients treated with agalsidase beta (age at ERT initiation 46 and 50 years, duration of ERT 10.3 and 11 years, respectively) [53].

3.6.1.3. Mixed ERT. One open-label, MG study in 18 patients, aged 8–51 years and mostly females, showed that 10 months of treatment with ERT resulted in significant decreases in neuropathic pain scales scores (Douleur Neuropathique 4 and the Leeds Assessment of Neuropathic Symptoms and Signs) in 13 treated patients [74]. One OS publication of mixed ERT described reduction in pain in three out of 14 female patients on ERT and reported no change in intra-epidermal nerve fibre density in the two females on ERT who agreed to undergo a biopsy [55].

3.7. Gastrointestinal (GI) outcomes

3.7.1.1. Agalsidase alfa 0.2 mg/kg EOW. GI outcomes were reported in female patients in two OS publications with agalsidase alfa [21,26]. The first of these studies reported data from 25 female patients, including paediatric patients, showing that abdominal pain was reduced after 24 months of ERT, although the incidence of diarrhoea in female patients had increased at this time point compared with baseline levels [21]. The other OS publication reported non-significant improvements in constipation and diarrhoea after 4 years of treatment, compared with baseline in 78 females (age at ERT initiation 49 years) [26] (Supplementary Table 13). In addition, one CR of a 54-year-old female patient treated with agalsidase alfa in combination with omeprazole also observed an improvement in GI outcomes during 30 months of ERT [29].

3.7.1.2. Agalsidase beta 1.0 mg/kg EOW. There were no publications reporting changes in GI outcomes with agalsidase beta in female or MG populations.

3.7.1.3. Mixed ERT. There were no publications reporting changes in GI outcomes with mixed-ERT regimens.

3.8. Quality of life (QoL)

3.8.1.1. Agalsidase alfa 0.2 mg/kg EOW. QoL measures were reported in two publications with agalsidase alfa, one from a single-arm open-label CT [14], and one from a registry study [26]. The single-arm CT presented QoL data after 27 weeks of ERT in 10 female patients (mean age 45 [range 20–66] years) using the 36-item Short-Form Health Survey (SF-36) [14]. Significant improvements were shown in the overall summary component for physical functioning, as well as the role-physical, and general health components of the SF-36 [14]. However, the OS publication did not report any significant changes in 5-dimension EuroQol questionnaire and visual analogue health scores in 78 female patients during 4 years of ERT (age at ERT initiation 49 years) [26]. An OS publication described no change in self-reported energy levels in the three female patients who received agalsidase alfa [56] (Supplementary Table 14).

The two papers from the MG, long-term OS of the impact of switching ERT regimen from agalsidase beta to agalsidase alfa reported no changes in QoL (EuroQol dimensions; baseline mean [standard error (SE)]: 1.0 [0.0]; 12 months after switch mean [SE]: 0.9 [0.1]), but did not report the data for females separately or show data beyond 12 months [51,74].

3.8.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one Fabry

Registry study publication in 59 female patients (who started ERT at a median age of 48 [range 16–71] years) treated for an average of 41 months reported significant improvements in overall QoL, including bodily pain, but with no consistent difference between the older and younger female patients, and SF-36 mental summary score, but no change in physical summary score [31] (Supplementary Table 14). Another OS publication described no change in self-reported energy levels in five patients who received reduced doses (0.5 mg/kg EOW, 0.3 mg/kg EOW) of agalsidase beta (patients had been treated with the approved 1.0 mg/kg EOW dose for 74 months before the dose reduction) [56]. Also, a published case series of patients treated with agalsidase beta reported that three female patients (aged 35, 64, and 67 years) had an improved ability to perform everyday tasks [37].

There was one MG OS publication describing significant improvements in the SF-36 score with agalsidase beta. The study included 18 patients (nine females, age range 21–64 years) of whom 10 received treatment (but the number of females receiving treatment was not specified) [73].

3.8.1.3. Mixed ERT. One MG, open-label study of 18 patients, mostly females, found that ERT treatment improved depression symptoms, as measured by the Beck Depression Scale, Fatigue Severity Scale, and the Pittsburgh Sleep Quality Index, after 10 months of treatment (patients aged 8–51 years) [75]. Similarly, one prospective MG OS publication, including 14 females receiving treatment, found that patients who had GFR levels > 60 mL/min/1.73m^2 at baseline generally showed lower depression scores (as measured by the Center for Epidemiologic Studies Depression Scale questionnaire) throughout the study period of 4 years. Females with GFR scores < 60 mL/min/1.73m^2 at baseline tended to show low depression scores in the first 2 years of follow-up, but these scores increased during the third year of follow-up [55]. One OS publication reported significant decreases in the SF-36 subscale scores of general health and vitality but no change in SF-36 physical functioning, role-physical, bodily pain, social functioning, role-emotional, or mental health scores in 16 female patients who switched from agalsidase beta to agalsidase alfa or to reduced-dose agalsidase beta (median duration of treatment post-switch/dose reduction was 1.3 years) [49].

4. Discussion

For many years, heterozygous females with Fabry disease were thought to be only carriers of the disease. More recently, increasing evidence has emerged that females with Fabry disease manifest clinical symptoms and have a reduced life expectancy compared with healthy subjects [1,2,16,81]; but they differ from classic male patients. First of all, females with Fabry disease have a wider spectrum of disease severity ranging from asymptomatic to severely affected phenotype (rare). The pattern and severity of the organ involvement depends on the *GLA* mutation [1,2,82] and the X-chromosome inactivation pattern [80,83]. Secondly, females sometimes present with symptoms in a single organ, rather than the multisystemic manifestations observed in classic males [1,16,80,84]. Furthermore, contrary to males, females may develop myocardial fibrosis before LVH, suggesting that LVH may not be the only driver of cardiac disease burden in females.

Nevertheless, regardless of phenotype and clinical symptomatology, female patients are not mere carriers of Fabry disease and may benefit from receiving treatment. However, the scope of the literature regarding the effect of ERT specifically in female patients only has not been previously explored or published. Therefore, this systematic literature review was conducted to analyse the effect of ERT on Fabry-related outcomes specifically in female patients. We included all types of publication with original data, any type of ERT regimen, and all Fabry disease-related outcomes in the population of female Fabry patients over the past 16 years. The current article summarizes the outcomes data available in females or MG studies in which > 50% of the

study population was female.

Our analysis covered 67 publications including six CTs. The data suggest that ERT results in significant reductions in plasma and urine GL-3 accumulation in women with elevated pre-treatment levels, and improvements in cardiac parameters and QoL. These findings are similar to trends identified in the male population [11]. In males, there was improvement in some outcomes when the higher dose (1.0 mg/kg EOW agalsidase beta) was administered and benefits to starting ERT early [11]. In females, further studies are needed to clarify the relevance of ERT dose in female patients. With regard to timing of treatment initiation, there is one observational registry study publication which showed that initiation of agalsidase beta earlier resulted in a lower risk of clinical events in females [85]. Another analysis of the Fabry Registry in over 400 females reported that the severe clinical event rate was 14% and that the incidence of severe clinical events was highest for the first 6 months of agalsidase beta and declined thereafter [86].

Our methodology does have limitations that are reviewed in detail elsewhere [10]. Our analysis highlights the difference in the levels of evidence between male and female patients with Fabry disease, however, we acknowledge that, due to the rare nature of Fabry disease, patient populations are small and the amount of level 1/grade A evidence from CTs is limited. For example, data in females were often derived from small OS or CRs. Another limitation may result from the likelihood of individual patients included in multiple studies. For example, when registry data were reported in different publications, it is likely that patient data were reported more than once. Also, there was limited information available on certain outcomes (nervous system, GI, and pain), and short-term studies did not always capture changes in female patients with mild disease progression. In fact, for GI symptoms, a recent analysis of the Fabry Registry reported data for abdominal pain and diarrhoea at baseline and following 2.5 years of agalsidase beta therapy in 168 female Fabry patients. They reported that 45% had abdominal pain and 39% had diarrhoea at baseline, which decreased significantly following treatment, to 31% and 27%, respectively ($p < 0.01$ for both) [87]. Based on natural history observations in female patients, kidney variables such as proteinuria, albuminuria, and eGFR are unlikely to deteriorate significantly over 1–3 years of follow-up) [11,88]. Therefore, to fully understand the effect of ERT in female Fabry patients, there is a need to perform clinical studies and examine a broad range of relevant outcomes for an extended duration of time. Furthermore, we urge researchers collating and publishing data on MG populations to include a breakdown of outcomes for males and females separately, so that readers and prescribers can determine any sex-specific effects.

Few publications described the nature of the genetic variants or the underlying disease severity for all female patients studied. In particular, no paper included data on X-chromosome inactivation patterns. Differences in X-chromosome inactivation patterns may have resulted in heterogeneous female study populations. A skewed X-chromosome inactivation pattern with a predominant expression of the mutant allele is associated with a more severe disease phenotype [80] and as a consequence may also impact on the responses that can be expected following treatment with ERT. X-chromosome inactivation patterns can be determined by analysing the methylation status at the HUMARA locus using two biological samples, preferably peripheral leukocytes and buccal smear cells [80,89]. For future research, we encourage reporting of the *GLA* variant and the pattern of X-chromosome inactivation in order to provide context for ERT-treatment effects.

In conclusion, female patients with Fabry disease often have clinical manifestations but can only benefit from receiving treatment if the disease has been diagnosed. Similar to male patients, ERT has a positive effect on GL-3 levels and cardiac outcomes. However, as Fabry disease manifestations in females are more heterogeneous compared with classic males, there is a need to develop gender-specific therapeutic guidelines and goals of ERT. Furthermore, reporting information

regarding the nature of the Fabry *GLA* variant and the X-chromosome inactivation profile (random or skewed) will help the interpretation of ERT treatment effects in female patients with classic and later-onset Fabry disease.

Conflicts of interest

- Dominique P. Germain is a consultant for Amicus Therapeutics, Sanofi Genzyme and Shire; has received research support from Sanofi Genzyme and Shire; has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire.
- Michael Arad has received travel support from Sanofi Genzyme and Shire.
- Alessandro Burlina has received speaker honoraria and travel support from Amicus Therapeutics, Biomarin, Nutricia, and Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.
- Perry M. Elliott has received speaker honoraria from Shire; has received consultant and speaker honoraria from Gilead Sciences, MyoKardia, Pfizer, and Sanofi Genzyme.
- Bruno Falissard has been a consultant for Actelion, Allergan, Almirall, Astellas, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Gilead Sciences, GlaxoSmithKline, Grünenthal, HRA Pharma, Janssen, Lundbeck, MSD, Novartis, Otsuka, Pierre Fabre, Roche, Sanofi, Sanofi Genzyme, Servier, Stallergene**,** UCB Pharmaceuticals, and ViiV Healthcare.
- Ulla Feldt-Rasmussen has received speaker and advisory board honoraria from Amicus Therapeutics, Sanofi, Sanofi Genzyme, and Shire; has received unrestricted research grants from Sanofi Genzyme and Shire; is a member of the European Advisory Board of the Fabry Registry and the Nordic and International Advisory Boards of Amicus Therapeutics.
- Max J. Hilz has received research/grant support from Bayer Health Care and Novartis Pharma; has received speaker honoraria and travel support from Sanofi Genzyme.
- Derralynn A. Hughes has received speaker and advisory board honoraria, travel support and research support from Amicus Therapeutics, Protalix, Sanofi Genzyme and Shire.
- Alberto Ortiz has received speaker honoraria from Amicus Therapeutics, Sanofi Genzyme and Shire; has received consulting honoraria, and conference and travel support from Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.
- Christoph Wanner has received research support from Sanofi

Genzyme; is a consultant for Actelion Pharmaceuticals, Protalix, Boehringer Ingelheim, and Sanofi Genzyme; is a member of the European Advisory Board of the Fabry Registry.

- Frank Weidemann has received speaker honoraria and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire; has received research support from Sanofi Genzyme and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Marco Spada has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme and Shire.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2018.09.007.

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