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Review

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

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ABSTRACT

Background: Fabry disease is caused by a deficiency of the lysosomal enzyme α-galactosidase, resulting in progressive accumulation of globotriaosylceramide (GL-3). The disease can manifest early during childhood and adolescence. Enzyme replacement therapy (ERT) with recombinant human α-galactosidase is the first specific treatment for Fabry disease and has been available in Europe since 2001. This paper presents the findings of a systematic literature review of clinical outcomes with ERT in paediatric patients with Fabry disease.

Methods: A comprehensive systematic review of published literature on ERT in Fabry disease was conducted in January 2017. The literature analysis included all original articles reporting outcomes of ERT in paediatric patients.

Results: Treatment-related outcomes in the paediatric population were reported in six publications derived from open-label clinical trials and in 10 publications derived from observational or registry-based studies. ERT was shown to significantly reduce plasma and urine GL-3 levels in paediatric patients with Fabry disease. The effect of ERT on GL-3 clearance from renal podocytes appeared to be agalsidase dose-dependent. ERT relieved pain and improved gastrointestinal symptoms and quality of life.

Conclusions: Based on the published literature, the use of ERT in paediatric patients can significantly clear GL-3 accumulation, ameliorate the early symptoms of Fabry disease, and improve quality of life. Treatment with ERT in paediatric patients with Fabry disease may be important to prevent further disease progression and overt organ damage.

List of abbreviations

BPI	Brief Pain Inventory
BRIEF	Behaviour Rating Inventory of Executive Function
CHQ-P50	Child Health Questionnaire Parent Form 50
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOW	every other week
ERT	enzyme replacement therapy
FOS	Fabry Outcome Survey
GFR	glomerular filtration rate
GI	gastrointestinal
GL-3	globotriaosylceramide
HRV	heart rate variability
HUI2/3	Health Utility Index 2/3

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LNR	laboratory normal range
LVH	left ventricular hypertrophy
LVM	left ventricular mass
LVMi	left ventricular mass index
lyso-GL-3	globotriaosylsphingosine
mGFR	measured glomerular filtration rate
PedsQL™-CFS	PedsQL™ Cognitive Functioning Scale
pNN50	percentage of successive normal sinus RR intervals > 50 ms
QoL	quality of life
QSART	quantitative sudomotor axon reflex testing
QTc	heart rate-corrected QT interval
r-MSSD	root mean square of the successive differences
SDNN	standard deviation of the normal-to-normal interval
VAS	visual analogue scale

1. Introduction

Fabry disease (OMIM #301500), an X-linked lysosomal storage disorder, is caused by mutations in the *GLA* gene (OMIM #300644; HGNC 4296) encoding the lysosomal enzyme α-galactosidase resulting in the accumulation of glycosphingolipids, such as globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-GL-3), in a wide range of cell types [1]. The accumulation of glycosphingolipids triggers a cascade of events causing cellular dysfunction and progressive damage to multiple vital organ systems including the heart, nervous system, and kidneys [1]. Individuals with mutations associated with the classic phenotype generally experience symptoms from early childhood onwards. The earliest symptoms seen in affected paediatric patients typically include neuropathic pain, hypohidrosis, heat intolerance, and gastrointestinal (GI) complaints such as nausea, abdominal cramps, and diarrhoea. In adults, there are manifestations of progressive disease in multiple organ systems including albuminuria/proteinuria, decline in glomerular filtration rate (GFR), end-stage kidney disease, left ventricular hypertrophy (LVH), cardiac arrhythmia, heart failure, transient ischaemic attack, and stroke [1–11].

Two forms of human α-galactosidase enzyme replacement therapy (ERT) are available for the treatment of Fabry disease: agalsidase alfa (Replagal®), administered at a dose of 0.2 mg/kg every other week (EOW); and agalsidase beta (Fabrazyme®) administered at a dose of 1.0 mg/kg EOW. Agalsidase alfa and agalsidase beta are both available in most European and Asian countries, and in Australia and Canada, but only agalsidase beta is approved by the US Food and Drug Administration (FDA) (in 2003) [12].

Previous literature reviews reporting on the efficacy and safety of ERT in Fabry disease have analysed data derived from randomized controlled clinical trials only [13–15]. To our knowledge, there is no comprehensive report covering all types of original publications, and the whole range of treatment outcomes across all organ systems.

In 2017, a comprehensive systematic literature review of all published original articles on ERT in the treatment of Fabry disease was conducted. This paper summarizes the findings of the literature review with respect to treatment outcomes in paediatric patients.

2. Methods

A full description of the methodology used in the systematic literature search and analysis also appears in a related article in this issue [16]. The findings of the literature analysis for male [17] and female [18] populations, as well as a position statement on therapeutic goals in Fabry disease based on the outcomes of an expert consensus panel [19] also appear in this issue. This article reviews publications retrieved in the literature search that describe ERT outcomes in the paediatric population (patients ≤ 18 years of age) published up to 31 January 2017.

The outcomes that were selected for analysis included plasma and urine GL-3 and lyso-GL-3, tissue histology, measures of kidney and cardiac function, and cardiac morphology. Other outcomes included nervous system parameters as well as pain, GI outcomes, and quality of life (QoL). Regarding GL-3 values, if GL-3 was reduced by ERT treatment, the values are reported as described in the publication. Normalization is only reported if it is described as such in the publication, due to differences in assays and cut-off levels for GL-3.

Results are described for the approved dose regimens: agalsidase alfa 0.2 mg/kg EOW and agalsidase beta 1.0 mg/kg EOW, unless otherwise specified. Publications describing the 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

A total of 34 publications included in the systematic literature analysis reported ERT outcomes data in paediatric patients (Table 1). Publications were available from clinical trials (CT), observational studies (OS), and case reports (CR). Studies describing both treatments (i.e. mixed-ERT studies), or when treatment was not specified (i.e. ERT NS), were also included.

For agalsidase alfa, there were 5 CT publications (all of which were Grade 1c single-arm clinical trials), four OS publications (all of which were Grade 3 retrospective observational studies), and 6 CR publications (two grade 4 case series, and four Grade 5 case reports). Two CT publications [22,23] were extension trials of study [21]. Patients lost to follow-up in the first extension study were due to study site closures and differences in treatment duration due to staggered study entries [22]. The second extension study only included patients who had participated in two separate phases of the study, prior to (phase 1) and after (phase 2) manufacturing changes in agalsidase alfa [23].

For agalsidase beta, 1 CT publication of a Grade 1c single-arm clinical trial was included, as well as 2 OS publications (both Grade 3 retrospective observational studies), and 8 CR publications (one Grade 4 case series, seven Grade 5 case reports).

No clinical trial studies were performed with mixed or unspecified ERT regimens; 4 OS publications were included (two Grade 2 prospective observational studies and two Grade 3 retrospective observational studies), as well as 4 CR publications (two Grade 4 case series and two Grade 5 case reports).

The main findings regarding clinical outcomes of treatment with approved doses of agalsidase beta or agalsidase alfa in paediatric patients with Fabry disease are summarized in Table 2.

3.1. GL-3 accumulation

3.1.1. Plasma GL-3

3.1.1.1. Agalsidase alfa 0.2 mg/kg EOW. Treatment with agalsidase alfa was associated with plasma GL-3 reductions in five single-arm CT publications (Table 3) [20–24]. Of these, one CT followed 24 paediatric patients for 6 months [21], of which 17 were then followed for 48 months [22] and 11 followed for 78 months [23] in extension trials. The first publication showed that agalsidase alfa was associated with significant reductions after 6 months in plasma GL-3 levels, which were elevated at baseline in males [21]; these reductions were sustained for up to 48 months [22]. In the 78-month follow-up report of this CT [23], plasma GL-3 levels did not decrease further. In contrast, no change was observed in the females, the majority of whom did not have abnormally elevated GL-3 levels at baseline [21,22]. In a report of a single-arm CT involving 13 paediatric patients [20], male patients had slightly elevated GL-3 levels at baseline, which were reduced after 5.3 months of treatment, whereas female patients did not have elevated plasma GL-3 levels at baseline. In another single-arm CT publication including 14 paediatric patients treated for 12.6 months, plasma GL-3

Table 1
Publications reporting clinical outcomes of ERT in paediatric patients with Fabry disease.

Treatment	Study, year [reference]	Study type and evidence grade	Dose	Duration (months)[a]	ERT-treated paediatric patients, n (% male)	Clinical outcomes reported
Agalsidase alfa	Ramaswami et al. [20]	Clinical; Grade 1c single-arm study	0.2 mg/kg EOW	5.4	13 (69)	Plasma GL-3, urinary GL-3, eGFR, proteinuria, ECG, sweat function, heat intolerance, hearing impairment, pain, GI outcomes
	Ries et al. [21]	Clinical; Grade 1c single-arm study	0.2 mg/kg EOW	6	24 (79)	Plasma GL-3, urinary GL-3, eGFR, proteinuria, albuminuria, LVM, ECG, ejection fraction, HRV, sweat function, pain, QoL
	Schiffmann et al. [22]	Clinical; Grade 1c single-arm study	0.2 mg/kg EOW	48	17 (94)	Plasma GL-3, urinary GL-3, eGFR, albuminuria, LVM, ECG, sweat function, pain
	Schiffmann et al. [23]	Clinical; Grade 1c single-arm study	0.2 mg/kg EOW	78	11 (91)	Plasma GL-3, urinary GL-3, eGFR, proteinuria, LVM, HRV
	Goker-Alpan et al. [24]	Clinical; Grade 1c single-arm study	0.2 mg/kg EOW	12.6	14 (36)	Plasma GL-3, urinary GL-3, eGFR, proteinuria, albuminuria, LVM, mid-wall fractional shortening, HRV, pain, QoL
	Hoffmann et al. [25]	Observational; Grade 3 retrospective study	0.2 mg/kg EOW	< 24	127 (45)	GI outcomes
	Ramaswami et al. [26]	Observational; Grade 3 retrospective study	0.2 mg/kg EOW	14–80	8 (88)	eGFR, LVM
	Ramaswami et al. [27]	Observational; Grade 3 retrospective study	0.2 mg/kg EOW	24	98 (65)	eGFR, proteinuria, albuminuria, LVM, heat intolerance, pain, hearing impairment, GI outcomes, QoL
	Havranek et al. [28]	Observational; Grade 3 retrospective study	0.2 mg/kg EOW	NR	7 (71)	ECG, LVH
	Tøndel et al. [29]	Case; Grade 4 case series	0.2 mg/kg EOW	24	2 (100)	Renal GL-3 (incl. Podocyte GL-3)
	Martin-Suarez et al. [30]	Case; Grade 5 case report	0.2 mg/kg EOW	64	1 (100)	eGFR, heat intolerance, pain, GI outcomes
	Nishida et al. [31]	Case; Grade 5 case report	Dose NR	9	1 (100)	Proteinuria
	Illsinger et al. [32]	Case; Grade 5 case report	0.2 mg/kg EOW	20	1 (100)	Pain, sweat function, heat intolerance
	Furujo et al. [33]	Case; Grade 5 case report	0.2 mg/kg EOW	60	2 (100)	Plasma GL-3, urinary GL-3, eGFR, proteinuria, LVM, sweat function, pain
	Tøndel et al. [34]	Case; Grade 4 case series	0.2 mg/kg EOW	76	1 (0)	Renal GL-3 (incl. Podocyte GL-3)
Agalsidase beta	Wraith et al. [35]	Clinical; Grade 1c single-arm study	1 mg/kg EOW	11	16 (87.5)	Plasma GL-3, dermal GL-3, eGFR, proteinuria, ECG, GI outcomes, QoL
	Borgwardt et al. [36]	Observational; Grade 3 retrospective study	1 mg/kg EOW[b]	12–96	10 (60)	Plasma GL-3, urinary GL-3, eGFR, albuminuria, ECG sweat function, pain, GI outcomes, QoL
	Kim et al. [37]	Observational; Grade 3 retrospective study	1 mg/kg EOW	65–126	4 (100)	eGFR, proteinuria, LVMi
	Mills et al. [38]	Case; Grade 4 case series	1 mg/kg EOW	24	3 (100)	Plasma GL-3, urinary GL-3, echocardiography, pain
	Tümer et al. [39]	Case; Grade 5 case report	Dose NR	4	1 (0)	Proteinuria
	Phadke et al. [40]	Case; Grade 5 case report	1 mg/kg EOW	24	1 (100)	Pain
	Park et al. [41]	Case; Grade 5 case report	1 mg/kg EOW	8	1 (100)	Pain
	Kanai et al. [42]	Case; Grade 5 case report	1 mg/kg EOW	14	1 (100)	Plasma GL-3, pain
	Ito et al. [43]	Case; Grade 5 case report	1 mg/kg EOW	36	1 (100)	Renal GL-3, eGFR, pain
	Kanai et al. [44]	Case; Grade 5 case report	1 mg/kg EOW	66	1 (100)	Plasma GL-3, renal GL-3, proteinuria, pain
	Politei et al. [45]	Case; Grade 5 case report	1 mg/kg EOW	12	1 (100)	Sweat function, pain, GI symptoms

(*continued on next page*)

Table 1 (*continued*)

Treatment	Study, year [reference]	Study type and evidence grade	Dose	Duration (months)[a]	ERT-treated paediatric patients, n (% male)	Clinical outcomes reported
Mixed ERT: treatment not specified or combination of agalsidase alfa and agalsidase beta	Manwaring et al. [46]	Observational; Grade 2 prospective study	ERT NS	12	10 (100)	Plasma GL-3, urinary GL-3
	Tøndel et al. [47]	Observational; Grade 2 prospective study	Different regimens:[c] Alfa 0.2 mg/kg EOW or weekly, 0.4 mg/kg EOW Beta 0.2 mg/kg EOW, 1.0 mg/kg EOW	13–94	9 (89)	Plasma GL-3, urinary GL-3, renal GL-3 (incl. Podocyte GL-3), mGFR, albuminuria, ECG, pain
	Anderson et al. [48]	Observational; Grade 3 retrospective study	Both, dose NR	0–50	7 (57)	eGFR, LVM
	Bugescu et al. [49]	Observational; Grade 2 prospective study	ERT NS	NR	7 (NR)	Cognitive function
	Skrunes et al. [50]	Case; Grade 4 case series	Different regimens:[d] Alfa 0.2 mg/kg EOW Beta 0.5 mg/kg EOW or 1.0 mg/kg EOW	120	3 (67)	Renal GL-3 (incl. Podocyte GL-3), GFR, albuminuria, hearing, pain, GI outcomes
	Zarate et al. [51]	Case; Grade 5 case report	ERT NS	NR	1 (100)	Proteinuria
	Lynch et al. [52]	Case; Grade 5 case report	ERT NS	NR	1 (0)	Pain
	Iemolo et al. [53]	Case; Grade 4 case series	ERT NS	NR	1 (0)	Pain, GI outcomes, heat intolerance

ECG, electrocardiography; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; GI, gastrointestinal; GL-3, globotriaosylceramide; HRV, heart rate variability; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; mGFR, measured glomerular filtration rate; NR, not reported; NS, not specified; QoL, quality of life.

[a] Duration as reported in the publication.

[b] Six of 10 patients received agalsidase alfa (dose not reported) at the end of the study because of a temporary shortage of agalsidase beta

[c] The low-dose group received (1) agalsidase alfa 0.2 mg/kg EOW (n = 5) or (2) agalsidase beta 0.2 mg/kg EOW (n = 1) throughout the study. The high-dose group received (1) agalsidase beta 1 mg/kg EOW (n = 3) for the entire study period or (2) agalsidase beta 1 mg/kg EOW after 4 years of agalsidase alfa 0.4 mg/kg EOW (n = 1), agalsidase alfa 0.4 mg/kg EOW (n = 1), or agalsidase alfa 0.2 mg/kg, on a weekly basis (n = 1) for the entire study period.

[d] Case 1 received 5 years of agalsidase beta 1.0 mg/kg EOW, 3 years of agalsidase alfa 0.2 mg/kg EOW, and 2 years of agalsidase beta 1.0 mg/kg EOW. Case 2 was treated with 5 years of agalsidase beta 1.0 mg/kg EOW, had a 7-month treatment hiatus, received agalsidase alfa 0.2 mg/kg EOW for 2 years and 5 months, and then was switched to agalsidase beta 1.0 mg/kg EOW. The regimen for Case 3 was as follows: 5 years of agalsidase beta 1.0 mg/kg EOW, 13 months of agalsidase beta 0.5 mg/kg EOW, 2 years of agalsidase alfa 0.2 mg/kg EOW and was then switched back to agalsidase beta 1.0 mg/kg EOW.

Table 2
Summary of outcomes with agalsidase beta 1.0 mg/kg EOW or agalsidase alfa 0.2 mg/kg EOW from clinical and observational studies[a] of paediatric 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, male patients (Ries et al. [21]; Schiffmann et al. [22]) No change, no elevated levels in female patients (Ries et al. [21]; Schiffmann et al. [22]; Goker-Alpan et al. [24]) ↓ Significance unknown, male and female patients (Ramaswami et al. [20]) ↓ Not significant, overall (Schiffmann et al. [23]; Goker-Alpan et al. [24])	↓ Towards normal range (male patients) and normalization (female patients), significance unknown (Borgwardt et al. [36] ↓ Significant (normalization), male patients (Wraith et al. [35]) No change, no elevated levels in female patients (Wraith et al. [35])
3.1.2	Urinary GL-3	↓ Significant, male patients (Schiffmann et al. [22]) ↓ Significant, female patients (Goker-Alpan et al. [24]) ↓ Not significant, male and female patients (Ries et al. [21]; Schiffmann et al. [23]) ↓ Not significant, male patient (Goker-Alpan et al. [24]) ↓ Significance unknown, male and female patients (Ramaswami et al. 2007 [20])	↓ Towards normal range (male patients), normalization (female patients), significance unknown (Borgwardt et al. [36])
3.1.3	GL-3 histology	↓ Clearance of GL-3 from renal mesangial and epithelial cells and from podocytes (Tøndel et al. [34]); evidence of dose dependence (Tøndel et al. [34])[1]	↓ Complete GL-3 clearance from dermal endothelial cells (Wraith et al. [35]) ↓ GL-3 clearance from renal podocytes (Ito et al. [43]; Kanai et al. [44])[1]
		↓ GL-3 clearance from renal mesangial and epithelial cells[1] and clearance of GL-3 from podocytes (Tøndel et al. [47]); evidence of dose dependence (Tøndel et al. [47])[1]	
3.2 Renal outcomes			
3.2.1	GFR	↓ Significance unknown, all patients, normal levels (Ramaswami et al. [20]) No change, normal levels, all patients (Ries et al. [21]; Schiffmann et al. [22]; Schiffmann et al. [23]; Goker-Alpan et al. [24]; Ramaswami et al. [26]; Ramaswami et al. [27])	No change, normal levels, all patients (Wraith et al. [35]; Borgwardt et al. [36]; Kim et al. [37])
3.2.2	Albuminuria	↑ Significance unknown, all patients (Schiffmann et al. [22]) ↓ Normalized, male patients with microalbuminuria (Schiffmann et al. [22]) No change, normal levels, all patients (Ries et al. [21]; Goker-Alpan et al. [24]; Ramaswami et al. [27]) ↓ Significance unknown, all patients with microalbuminuria (Ries et al. [21])	No change, normal levels, all patients (Borgwardt et al. [36])
3.2.3	Proteinuria	↑ Significance unknown, all patients (Ramaswami et al. [27]) No change, all patients with microalbuminuria (Goker-Alpan et al. [24]) No change, all patients (Schiffmann et al. [23]) No change, normal levels, all patients (Ramaswami et al. [20]; Ries et al. [21])	↓ Significance unknown (Wraith et al. [35]) No change, normal levels, male patients (Kim et al. [37])
3.3 Cardiac outcomes			
3.3.1	LVM/LVMi	↓ Not significant, all patients (Ries et al. [21]; Schiffmann et al. [23]) ↓ Significance unknown, all patients (Ramaswami et al. [26]; Ramaswami et al. [27]) ↑ Significance unknown, male patients (Havranek et al. [28]) No change, all patients (Schiffmann et al. [22]; Goker-Alpan et al. [24]) (LVMi and MFS)	No change, male patients (Kim et al. [37])
3.3.3	ECG measures	↑ Significant, male patients (Ries et al. [21]) ↑ Significance unknown, male patients (Havranek et al. [28]) No change, all patients (Ramaswami et al. [20]; Schiffmann et al. [22]) No change, female patients at normal levels (Ries et al. [21])	No change, all patients (Wraith et al. [35]; Borgwardt et al. [36])
3.3.3	Heart rate variability	↑ Significance unknown, male patients (Ries et al. [21]) ↓ Not significant, all patients (Schiffmann et al. [23]) No change, female patients (Ries et al. [21]); all patients (Goker-Alpan et al. [24])	N/A
3.4 Nervous system outcomes			
3.4.1	Sweat function	↑ Not significant, 6 months, all patients (Ries et al. [21]) ↑ Significance unknown, 6 months, all patients (Ramaswami et al. [20]; Schiffmann et al. [22]) ↓ Significance unknown, 3.5 years, all patients (Schiffmann et al. [22])	↑ Significance unknown, year 1, all patients (Borgwardt et al. [36]) ↓ and ↑ Significance unknown, years 2–6, all patients (Borgwardt et al. [36])
3.4.2	Heat intolerance	No change, all patients (Ramaswami et al. [20]) ↓ Significance unknown, all patients (Ramaswami et al. [27])	N/A
3.4.3	Hearing function	No change, all patients with hearing impairment (Ramaswami et al. [20])	N/A
3.4.4	Cognitive function	N/A	N/A
3.5	Pain outcomes	↓ Significant, BPI worst/average, male patients (Schiffmann et al. [22]) ↓ Significance unknown, BPI worst/average, all patients (Ramaswami et al. [20]; Ries et al. [21]; Goker-Alpan et al. [24]) ↓ Significance unknown, neuropathic pain, all patients (Ramaswami et al. [20]) ↓ Significance unknown, pain crises, all patients (Ramaswami et al. [27])	↓ Significance unknown, VAS scores, all patients (Borgwardt et al. [36])
3.6	GI outcomes	↑ Significance unknown, some patients (Ramaswami et al. [20]) ↓ Significant, 12 months, all patients (Hoffmann et al. [25]) ↓ Not significant, all patients (Ramaswami et al. [27]) ↓ Significance unknown, 24 months, all patients (Hoffmann et al. [25]; Ramaswami et al. [27]) ↓ Significance unknown, some patients (Ramaswami et al. [20])	↓ Significant, postprandial pain and vomiting, all patients (Wraith et al. [35]) No change, nausea, all patients (Wraith et al. [35]) ↓ Significance unknown, VAS score abdominal pain, all patients (Borgwardt et al. [36])
3.7	QoL		

(*continued on next page*)

Table 2 (*continued*)

Outcome	Agalsidase alfa 0.2 mg/kg EOW	Agalsidase beta 1.0 mg/kg EOW
	No change, normal HUI2/3 score, all patients (Ries et al. [21]; Goker-Alpan et al. [24]) ↓ Fatigue, significance unknown, 24 months, 7 patients (Ramaswami et al. [27])	↓ Significant, absence from school, difficulty with low-energy activities (Wraith et al. [35]) ↑ Not significant, good general health, all patients (Wraith et al. [35]), energy levels and physical exercise, all patients (Borgwardt et al. [36]) ↓ Not significant, difficulty with mid/high-energy activities, all patients (Wraith et al. [35])

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included. 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. BPI, Brief Pain Inventory; ECG, electrocardiogram; EOW, every other week; ERT, enzyme replacement therapy; GFR, glomerular filtration rate; GL-3, globotriaosylceramide; HUI2/3, Health Utility Index 2/3; LVM, left ventricular mass; LVMi, left ventricular mass index; N/A, not available; QoL, quality of life; VAS, visual analogue scale.

[a] As an exception, renal GL-3 histology results from case series, case reports, and mixed-ERT publications have provided the only evidence.

levels were elevated at baseline in both male and female patients. A significant decrease was observed in male patients only [24]. One CR supported reduction of elevated plasma GL-3 at baseline levels with ERT [33].

3.1.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one single-arm CT publication reported plasma GL-3 levels in paediatric males and females (Table 3). In males, the levels were elevated at baseline, normalized by week 4, and remained normal thereafter. Levels in females were normal at baseline and remained unchanged during

Table 3
Plasma GL-3 outcomes for approved doses of agalsidase beta and agalsidase alfa in paediatric patients.[a]

	Study, year [reference] (number of patients[b]) *Evidence grade*[c]	Male, n (%)[d]	Duration, months	Units	Baseline (number of patients[e])	End-point (number of patients[f])	Overall result (*p* value/ 95% CI)
Alfa	Goker-Alpan et al. [24] (N = 14) *Grade 1c*	5 (36)	12.6	nmol/mL (normal < 5.26)	Male: 28.2 (11.36) (n = 5) Females: 7.34 (1.92) (n = 9)	Mean change from baseline Males: −15.2 (*n* = 5) Females: −0.5 (*n* = 9)	Mean: Males: ↓ (95% CI − 25.9, −4.5) Females: NC (95% CI –1.4, 0.5)
	Ramaswami et al. [20] (N = 13) *Grade 1c*	9 (69)	5.4	μmol/L (LNR 1.6–3.3)	Males: range 4.3–10.8 (n = 9) Females: range 2.3–3.3 (*n* = 4)	Males: decrease (n = 9) Females: decrease (n = 2), increase (*n* = 2) (graphs by gender and individual patients)	Males: ↓ (NR) Females: ↓↑ (NR)
	Ries et al. [21] (N = 24) *Grade 1c*	19 (79)	6	nmol/mL (normal < 3.0)	Males: 7.91 (0.71) (*n* = 19) Females: 2.54 (0.25) (n = 5)	Males: reduced (n = 19) Females: no change (n = 5)	Males: ↓ (*p* < 0.001) Females: NC (NR)
	Schiffmann et al. [22] (N = 17) *Grade 1c*	16 (94)	48	nmol/mL (normal < 3.0)	Males: 7.91 (3.09) (n = 19)[g] Females: not elevated	Males: 4.03 (0.89) (n = 9) Females: NR	Males: ↓ (*p* < 0.05) Females: NR
	Schiffmann et al. [23] (N = 11) *Grade 1c*	10 (91)	78	nmol/mL (LNR NR)	3.61 (1.60) (n = 11)	Annualized slope −0.01/year (*n* = 8)	NC (95% CI −0.14, 0.12)
Beta	Wraith et al. [35] (N = 16) *Grade 1c*	14 (87.5)	11	μg/mL (normal < 7)	Males: median 15.9 (n = 14) Females: ≤5 (n = 2)	Males: median 6.3 (n = 14) Females: ≤5 (n = 2)	Males: ↓ (*p* = 0.001) normalization Females: NC (NR)
	Borgwardt et al. [36] (N = 10) *Grade 3*	6 (60)	12–96	μmol/L (LNR 1.6–3.3)	Males: 7.6–9.7 (n = 5) Female: 3.9 (n = 1)	Plasma levels decreased to normal range after 2–33 months	↓ (NR) normalization

Red font indicates statistically significant changes. CI, confidence interval; GL-3, globotriaosylceramide; LNR, laboratory normal range; NC, no change; NR, not reported; SD, standard deviation.

[a] Other clinical parameters are detailed in the supplementary tables.

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

[c] Evidence grade 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.

[d] Number of paediatric male patients who were treated with ERT.

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

[f] Number of paediatric, ERT-treated patients with data for the outcome at endpoint.

[g] 17 children of the original 24 children were included in this extension study [22] of the clinical trial [21]. The baseline data for plasma GL-3 in [22] however are presented for the total group of 24 patients from the original RCT [21] of which 19 were male. Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included. Results are summarized as increase (↑), decrease (↓), or no change from baseline to follow-up after ERT initiation. Data are means (SD) or means ± SE or medians (range), unless otherwise indicated.

treatment [35]. An OS publication of agalsidase beta in 10 paediatric patients showed that elevated plasma GL-3 levels decreased towards the normal range in male patients, and normalized in female patients after 2–33 months of treatment (Table 3) [36]. Three CRs also reported normalization of plasma GL-3 levels with agalsidase beta [38,42,44].

3.1.1.3. Mixed ERT. Two OS publications showed that elevated plasma GL-3 levels were reduced in 9 or 10 paediatric patients after 12–60 months of treatment with ERT [46,47].

3.1.1.4. Plasma lyso-GL-3. No publications reporting on the change in plasma lyso-GL-3 levels in paediatric patients following agalsidase treatment were retrieved.

3.1.2. Urinary GL-3

3.1.2.1. Agalsidase alfa 0.2 mg/kg EOW. Five single-arm CT publications of paediatric patients receiving agalsidase alfa reported a reduction in the level of urinary GL-3 [20–24] (Supplementary Table 1). Of these, two single-arm CT extension trials of study [21] showed significant reductions from baseline levels at 18 months in males [22], and were sustained for up to 78 months [23]. Two other CT publications reported higher baseline urinary GL-3 levels in males than in females; decreases from baseline were observed in both male and female patients [20,24]. One CR showed a decline in urinary GL-3 [33].

3.1.2.2. Agalsidase beta 1.0 mg/kg EOW. One OS publication on agalsidase beta reported that, in the three paediatric males with elevated urinary GL-3:sphingomyelin ratios at baseline, levels declined towards normal values after 5–27 months of treatment. In one female, a slightly elevated urinary GL-3:creatinine ratio at baseline normalized during follow-up (Supplementary Table 1) [36]. One CR also described normalization of urinary GL-3 levels [38].

3.1.2.3. Mixed ERT. Two OS publications showed that elevated urinary GL-3 levels were reduced in 9 or 10 paediatric patients after 12–60 months of treatment with mixed ERT [46,47].

3.1.2.4. Urinary lyso-GL-3. No publications reporting on the change in urinary lyso-GL-3 levels in paediatric patients following agalsidase treatment were found.

3.1.3. Histological assessment of dermal and renal GL-3 accumulation

3.1.3.1. Dermal GL-3

3.1.3.1.1. Agalsidase alfa 0.2 mg/kg EOW. No publications describing the effect of agalsidase alfa on dermal GL-3 levels in paediatric patients were retrieved.

3.1.3.1.2. Agalsidase beta 1.0 mg/kg EOW. In a single-arm CT study of 16 paediatric patients (14 males), agalsidase beta for 11 months resulted in complete GL-3 clearance from dermal capillary endothelium. Furthermore, in 12 male patients with moderate-to-severe GL-3 accumulation in superficial dermal capillary endothelial cells at baseline, complete GL-3 clearance was observed from 6 months of ERT (Supplementary Table 2) [35].

3.1.3.1.3. Mixed ERT. No publications describing the effect of mixed ERT on dermal GL-3 levels were found.

3.1.3.2. Renal GL-3

3.1.3.2.1. Agalsidase alfa 0.2 mg/kg EOW. A CR describing nine paediatric patients (seven males) showed that all patients had GL-3 inclusions in renal cells. Seven patients did not receive ERT prior to renal biopsy, whereas two patients (both male) received agalsidase alfa for 2 years prior to renal biopsy, and were the only patients with no GL-3 inclusions in endothelial cells of the kidney [29]. Additionally, another CR examining pre-treatment renal GL-3 accumulation and pathology in eight paediatric patients reported data from one patient who had renal GL-3 levels re-assessed after initiation of ERT. This patient had an unchanged, high podocyte GL-3 accumulation score after 3 years of agalsidase alfa [34].

3.1.3.2.2. Agalsidase beta 1.0 mg/kg EOW. Two CR publications of agalsidase beta with accumulation of GL-3 in podocytes at baseline showed normalization of podocyte appearance and almost complete GL-3 clearance in podocytes after 3 years [43] or 5 years of agalsidase beta treatment [44].

3.1.3.2.3. Mixed ERT. One OS of 12 young classic Fabry patients (nine of whom were ≤18 years of age) investigated kidney GL-3 accumulation during ERT with either agalsidase alfa 0.2 or 0.4 mg/kg EOW or agalsidase beta 0.2 or 1.0 mg/kg EOW [47]. After 65 months of treatment, complete clearance of GL-3 from glomerular epithelial and mesangial cells was reported in all patients. In podocytes, the clearance of GL-3 was ERT dose-dependent: patients who received agalsidase 0.2 mg/kg EOW did not achieve significant GL-3 clearance from podocytes, whereas patients receiving agalsidase beta 1.0 mg/kg EOW showed significant clearance [47].

In a CR, composite podocyte scores decreased in three patients as compared with baseline after 5 years of agalsidase beta 1.0 mg/kg EOW, and increased again after switching to 3 years of agalsidase alfa 0.2 mg/kg EOW [50]. The GL-3 clearance from podocytes was most notable in the patient who started ERT at a younger age (7 years), compared with the patient who started ERT later (18 years) [50].

3.2. Renal outcomes

3.2.1. Glomerular filtration rate (GFR)

3.2.1.1. Agalsidase alfa 0.2 mg/kg EOW. Four single-arm CT publications of agalsidase alfa, including two extension studies [22,23], reported that estimated GFR (eGFR) values, which were normal at baseline, did not change after 6–78 months of ERT [21–23], which was further supported by the fourth CT study [24]. Another single-arm CT, however, reported a reduction in eGFR from baseline after 6 months of ERT in all 11 paediatric patients studied, four of whom (3 males, 1 female) had eGFR levels > 120 mL/min/1.73 m^2 at baseline [20]. Two OS publications using Fabry Outcome Survey (FOS) data (Supplementary Table 3) [26,27] and two case reports [30,33] reported no overall change in eGFR.

3.2.1.2. Agalsidase beta 1.0 mg/kg EOW. One 11-month single-arm CT publication of 16 paediatric patients [35], one OS of 10 patients with 12–96-month data [36] and one CR (3 years of treatment [43]) reported no change in eGFR values, which were normal at baseline. One OS publication reported normal eGFR at baseline, which remained normal after over 60 months of agalsidase beta treatment (Supplementary Table 3) [37].

3.2.1.3. Mixed ERT. An OS mixed-ERT publication examining iohexol clearance (measured GFR [mGFR]) found no change in GFR [47]. Similarly, another OS study found that mixed-ERT treatment did not result in significant eGFR changes [48]. One CR reported that in one male patient treated with agalsidase beta 1.0 mg/kg EOW for five years, mGFR values decreased on switching to agalsidase alfa 0.2 mg/kg EOW [50].

3.2.2. Albuminuria

3.2.2.1. Agalsidase alfa 0.2 mg/kg EOW. One single-arm CT publication reported normal albuminuria following 6 months agalsidase alfa treatment in the 16 of 24 patients who had normal albuminuria at baseline [21]. The single-arm CT extension phase of this study reported a slight increase in albuminuria levels up to 48 months of treatment in 10 paediatric patients [22]. Another single-arm CT publication in which all patients had microalbuminuria at baseline reported no changes in microalbuminuria after 12.6 months of ERT [24]. An OS FOS registry publication reported no change in the number of patients with

microalbuminuria during 24 months of treatment (12 patients at baseline, 11 patients at 24 months) (Supplementary Table 4) [27].

3.2.2.2. Agalsidase beta 1.0 mg/kg EOW. In one single-arm CT publication, urinary albumin:creatinine ratio, which was normal at baseline, did not change after up to 96 months' follow-up in 10 paediatric patients (6 males) [36].

3.2.2.3. Mixed ERT. The impact of ERT on the albumin:creatinine ratio might be dose-related. An OS reported significantly decreased albumin:creatinine ratios with agalsidase beta (1.0 mg/kg EOW), but not with agalsidase alfa (0.2 mg/kg EOW) [47]. In one CR, the normal albumin excretion levels at baseline generally remained stable during ERT [50].

3.2.3. Proteinuria

3.2.3.1. Agalsidase alfa 0.2 mg/kg EOW. Two single-arm CT publications reported normal proteinuria levels in patients without proteinuria at baseline [20,21]. An extension CT publication reported that none of the eleven paediatric patients who were normoproteinuric at baseline developed proteinuria at the last follow-up at 78 months [23]. Another single-arm CT publication in which all patients had microalbuminuria at baseline reported no changes in proteinuria levels after 12.6 months of treatment [24]. In a FOS registry study, proteinuria was observed in one patient at baseline and after 12 months; three other patients also developed proteinuria after 24 months of treatment (Supplementary Table 4) [27]. Two case reports noted stable proteinuria levels in the normal range during agalsidase alfa treatment [31,33].

3.2.3.2. Agalsidase beta 1.0 mg/kg EOW. One single-arm CT publication including 16 paediatric patients (14 males) reported a slight reduction in mean urinary protein excretion after 11 months of treatment with agalsidase beta [35]. Mild proteinuria ($> 100\,mg/m^2/24\,h$) was present in 8 of 15 evaluable patients before treatment, but in only three patients at the end of follow-up [35]. An OS publication reported that proteinuria remained within the normal range in 4 males during 65–126 months of follow-up (Supplementary Table 4) [37]. One CR stated no change in proteinuria [39], but another showed temporary increases in proteinuria when the agalsidase beta dose was reduced from 1.0 mg/kg EOW to 0.7 mg/kg once a month or 0.6 mg/kg EOW [44].

3.2.3.3. Mixed ERT. One CR described a 16-year old boy with severe proteinuria which decreased to normal levels after 1 year of ERT and adjuvant therapy [51]. Another CR of an 11-year old girl with early signs of renal involvement as demonstrated by the presence of proteinuria described that proteinuria levels improved after starting ERT (no follow-up specified) [53].

3.3. Cardiac outcomes

3.3.1. Left ventricular mass (LVM) and other cardiac echocardiography and magnetic resonance imaging outcomes

3.3.1.1. Agalsidase alfa 0.2 mg/kg EOW. Three clinical trial publications of a paediatric population followed for 6, 48, and 78 months reported normal LVM or LVM index (LVMi) at baseline and stable LVM/LVMi during ERT [21–23], an effect that was also observed in another single-arm CT after 12.6 months of treatment [24]. An OS FOS registry publication reported that five of the six paediatric patients with echocardiography assessments had LVMi above the 75th percentile for their age. Mean LVMi decreased during treatment [26]. Another OS FOS registry publication reported normal LVMi in 40 children at baseline, which remained normal and stable in the 17 children followed for 24 months (Supplementary Table 5) [27]. One OS described three males who developed LVH during treatment (Supplementary Table 5) [28]. LVM measurements were stable and normal in one CR [33].

3.3.1.2. Agalsidase beta 1.0 mg/kg EOW. One OS publication noted that cardiac structure (as measured by LVMi) remained normal and stable during 65–126 months of agalsidase beta treatment (four males) (Supplemental Table 5) [37].

3.3.2. Other cardiac outcomes

3.3.2.1. Agalsidase alfa 0.2 mg/kg EOW. One single-arm CT publication reported no change in mid-wall fractional shortening after 12.6 months of agalsidase alfa [24]. Effects of ERT on ventricular wall thickness were not described in this population and left ventricular ejection fraction data were reported in only one single-arm CT publication, where normal ejection fraction value at baseline and during 6 months of ERT was observed [21].

3.3.2.2. Agalsidase beta 1.0 mg/kg EOW and mixed ERT. A case report noted normal and stable echocardiography findings during agalsidase beta treatment [38]. One mixed-ERT OS publication described normal and stable echocardiography findings during agalsidase treatment [48].

3.3.3. Electrocardiogram (ECG) measures

3.3.3.1. Agalsidase alfa 0.2 mg/kg EOW. Two single-arm CT publications including a 6 month study and a 48 month extension study of paediatric patients reported no overall change from normal baseline values in ECG parameters of heart rate, PR interval, QRS duration, and heart rate-corrected QT interval (QTc) (Supplementary Table 5) [21,22]. This effect was also observed in another single-arm CT publication [20]. One OS publication including 22 treated and 44 untreated patients reported the appearance of frequent ventricular premature beats in two treated patients during the third year of agalsidase alfa treatment and supraventricular premature beats with T-wave inversion in one treated patient during the second year of treatment [28].

One single-arm CT publication described that at baseline, heart rate variability (HRV) was generally lower in males compared with females. After 6 months of agalsidase alfa treatment, HRV increased significantly in males and remained normal in females [21]. An extension study including 11 patients showed that HRV improvements remained stable after 78 months of treatment [23]. One single-arm CT publication reported no changes in HRV, which was normal in most cases at baseline, measured using three different parameters after 12.6 months of agalsidase alfa treatment (Supplementary Table 5) [24].

3.3.3.2. Agalsidase beta 1.0 mg/kg EOW. Published data from two single-arm CT studies of agalsidase beta reported normal ECG findings at baseline and no significant overall changes in ECG parameters after up to 96 months of treatment (Supplementary Table 5) [35,36].

3.3.3.3. Mixed ERT. One OS publication reported the occurrence of significant bradyarrhythmia that required implantation of a pacemaker in one patient despite 5.5 years of ERT, comprising 26 months of agalsidase alfa 0.2 mg/kg EOW and 41 months of agalsidase alfa 0.4 mg/kg EOW. After implantation, the patient received agalsidase beta 1.0 mg/kg EOW [47].

3.4. Nervous system outcomes

3.4.1. Sweat function

3.4.1.1. Agalsidase alfa 0.2 mg/kg EOW. One single-arm CT publication reported an increase in sweat volume after 6–12 months of agalsidase alfa as measured by quantitative sudomotor axon reflex testing (QSART) or with a Macroduct® sweat collector [20]. This effect was also observed in two CT publications examining paediatric patients

after 6 months [21] and after 6 and 12 months [22] of treatment. The single-arm extension CT publication, however, reported decreased sweat volume after 3.5 years of treatment. There were only six paediatric patients with data available at this time-point (Supplementary Table 6) [22]. Two CR publications report treatment with agalsidase alfa also described improved sweating in paediatric patients with ERT [32,33].

3.4.1.2. Agalsidase beta 1.0 mg/kg EOW. One OS examining treatment with agalsidase beta in 10 paediatric patients reported increased sweat function in the majority of male patients after 1 year of treatment, which was sustained throughout the treatment period (up to 96 months) [36]. In two female patients, sweat function decreased (Supplementary Table 6) [36]. One CR reported normalization of sweating after 1 year of agalsidase beta [45].

3.4.1.3. Mixed ERT. No publications describing sweat function outcomes in paediatric patients were identified.

3.4.2. Heat and cold intolerance

3.4.2.1. Agalsidase alfa 0.2 mg/kg EOW. In a single-arm CT publication including 13 paediatric patients, there was no change in heat intolerance after almost 6 months of agalsidase alfa treatment [20]. An OS FOS registry publication of 98 paediatric patients reported heat intolerance in 11 patients at baseline and in seven patients after 24 months of treatment, and cold intolerance in eight patients at baseline and in five patients after 24 months of treatment (Supplementary Table 6) [27]. One CR described a rapid improvement in heat intolerance in a male patient after initiation of treatment [30], and another noted that the ability to sense heat and cold improved during treatment in one male patient [32].

3.4.2.2. Agalsidase beta 1.0 mg/kg EOW. No publications describing the effect of agalsidase beta on heat intolerance in the paediatric population were identified.

3.4.2.3. Mixed ERT. One CR described heat intolerance in a female patient, which improved with ERT treatment [53].

3.4.3. Hearing function

3.4.3.1. Agalsidase alfa 0.2 mg/kg EOW. One single-arm CT publication in 13 paediatric patients reported a hearing impairment in three patients that did not improve during agalsidase alfa treatment [20].

An OS FOS registry publication reported the hearing function at baseline and after 24 months of treatment in 39 paediatric patients: hearing impairment was reported in 7 patients at baseline and in 4 patients after 24 months of treatment, and tinnitus in 14 patients at baseline and in 11 patients after 24 months of treatment (Supplemental Table 6) [27].

3.4.3.2. Agalsidase beta 1.0 mg/kg EOW. No publications were identified that describe the effect of agalsidase beta on hearing outcomes.

3.4.3.3. Mixed ERT. One patient from a CR experienced sudden deafness in one ear after 3.5 years of agalsidase beta 1.0 mg/kg EOW [50].

3.4.4. Cognitive function

3.4.4.1. Agalsidase alfa and Agalsidase beta. No publications describing the effect of agalsidase alfa or agalsidase beta treatment on cognitive function in paediatric patients were retrieved.

3.4.4.2. Mixed ERT. One OS publication reported significantly higher cognitive functioning in paediatric patients treated with ERT compared with those who did not receive treatment with ERT. Cognitive function was assessed using the Behaviour Rating Inventory of Executive Function (BRIEF) and PedsQL™ Cognitive Function Scale (PedsQL™ CFS), but, as a limitation of the study, the treated group was not assessed at baseline [49].

3.5. Pain outcomes

3.5.1. Agalsidase alfa 0.2 mg/kg EOW

Pain outcomes assessed using Brief Pain Inventory (BPI) scores were reported in two single-arm CT studies [20,24], as well as two CT single-arm studies following a paediatric population for 48 months after an initial six month trial [21,22]. One of these did not report significant decreases in BPI "pain at its worst" scores in both male and female paediatric patients after 6 months of treatment, but in the same study 6 out of 11 patients were able to reduce or stop the use of neuropathic pain medications [21]. The publication that reported 12-month pain outcomes in the same cohort did show significant decreases in both "average pain" and "pain at its worst" BPI scores in males [22]. One single-arm CT publication (13 patients) reported a reduction in the number of patients with neuropathic pain after 5.4 months of treatment [20] and an OS FOS registry publication reported a reduced incidence of pain crises in female paediatric patients during 24 months of treatment [27]. This publication also reported chronic pain in nine patients at baseline and in four patients after 24 months of treatment (Supplementary Table 7) [27]. The effects on pain from CRs were variable, with one showing a decrease in pain following treatment [30], while another reported a dose reduction of neuropathic pain medication with carbamazepine (from 750 to 300 mg daily) following ERT [32], and another an increase in pain [33].

3.5.2. Agalsidase beta 1.0 mg/kg EOW

One OS publication assessed pain outcomes using visual analogue scale (VAS) scoring in patients treated with agalsidase beta 1.0 mg/kg EOW [36]. All patients reported acroparaesthesia at baseline. After 12–96 months of ERT, neuropathic pain was ameliorated as indicated by reduced VAS scores from 6.5 and 6.6 to 1.0 and 2.5 in male and female paediatric patients, respectively (Supplementary Table 7) [36]. The effects of agalsidase beta on pain outcomes were variable in CRs: one reported an increase in pain [44] whereas most described a decrease in pain [38,40,42,43,45] and one reported a reduction of neuropathic pain medication with phenytoin (from 200 mg/day to 100 mg/day) and carbamazepine (from 400 mg/day to 200 mg/day) after enzyme treatment [41].

3.5.3. Mixed ERT

A five-year follow-up OS publication showed a substantial reduction in Fabry disease severity score of the peripheral nervous system (DS3-PNS score) of which pain is an integral factor, in eight of the nine ERT-treated children studied [47]. Two CRs noted an improvement in pain outcomes [52,53]. Another CR reported that acral pain decreased during 5 years of treatment with agalsidase beta 1.0 mg/kg EOW, and increased again with treatment discontinuation, agalsidase beta dose reduction (0.5 mg/kg EOW), or when patients were switched to agalsidase alfa 0.2 mg/kg EOW [50].

3.6. Gastrointestinal (GI) outcomes

3.6.1. Agalsidase alfa 0.2 mg/kg EOW

A cohort of 13 patients reported variable effects of treatment on GI outcomes in one single-arm CT study [20]. Two OS FOS registry publications reported improvements in abdominal pain and diarrhoea in children treated for up to 24 months of treatment [25,27]: one of these publications, which included 127 paediatric patients (14 with available GI data at 12 months, 10 with available data at 24 months), showed a decline in GI pain from 80% to 50% of patients after 24 months of treatment (Supplementary Table 8) [25]. A CR described improvements

in GI events [30].

3.6.2. Agalsidase beta 1.0 mg/kg EOW

A single-arm CT of 16 paediatric patients treated with agalsidase beta reported a significant improvement in postprandial pain and vomiting, and a non-significant decline in nausea [35]. In another OS publication, VAS scores for abdominal pain were reduced in both male and female patients following 12–96 months of treatment [36] (Supplementary Table 8) [36]. In one CR, diarrhoea resolved after 1 year of agalsidase beta treatment [45].

3.6.3. Mixed ERT

One CR noted improvements in GI events after ERT initiation [53]. In another CR, GI outcomes (abdominal pain, diarrhoea) decreased with 5 years of agalsidase beta (1.0 mg/kg EOW), but increased when treatment was stopped, the dose was reduced, or the regimen was changed to agalsidase alfa (0.2 mg/kg EOW) [50].

3.7. Quality of life (QoL)

3.7.1. Agalsidase alfa 0.2 mg/kg EOW

In a single-arm CT study including 24 paediatric patients, QoL was assessed using the Health Utility Index (HUI) 2 or 3 questionnaires [21]. Near-normal QoL scores were observed at baseline and during 6 months of treatment [21]. In another single-arm CT study, there was little change in QoL scores (HUI2/HUI3 and Childhood Health Questionnaire physical and psychosocial scores) after 12.6 months of treatment (Supplementary Table 9) [24]. An OS FOS registry publication (98 paediatric patients) described fatigue in 14 patients at baseline and in seven patients after 24 months of treatment [27].

3.7.2. Agalsidase beta 1.0 mg/kg EOW

In a single-arm CT study of agalsidase beta, 48 months of treatment in 16 paediatric patients (14 males) was associated with improvement in a range of QoL parameters including significantly reduced proportion of days absent from school due to illness, increased proportion of days where patients could report good general health, and a decrease in the number of days when the patients experienced difficulty in performing low, medium, and high-energy activities [35]. An increase in energy levels and the ability to perform physical exercise in 10 paediatric patients (six males) was also reported in another OS publication (Supplementary Table 9) [36].

3.7.3. Mixed ERT

No publications describing the change in QoL following treatment were identified.

4. Discussion

This systematic literature review investigates the effect of ERT on clinical outcomes in paediatric patients with Fabry disease as reported in six publications derived from clinical trials, and in 10 publications derived from observational studies. ERT significantly reduced or normalized plasma GL-3 levels, relieved pain, improved gastrointestinal symptoms, and increased quality of life [20–22,25,27,35,36,47]. Some patients were able to reduce or discontinue the use of pain medication [21,32,40,41,50]. The management of pain is particularly important in children [36] as pain relief – or decrease in use of symptomatic neuropathic pain-control medications –can reduce sedation, improve concentration, and lessen school absences [35].

In one publication, the youngest patient to receive agalsidase beta treatment had almost complete clearance of podocyte GL-3, suggesting a potential relationship between age of ERT initiation and extent of podocyte GL-3 clearance [47]. Considering that the podocyte's integrity is important to prevent proteinuria, the timely initiation of treatment – before the onset of irreversible pathological changes – may contribute to the long-term positive prognosis for patients with Fabry disease. These data are supported by studies in adults in which ERT has limited ability to prevent end-stage organ damage when therapy is started in adulthood [54], and where ERT is most effective in patients who initiated treatment at a younger age with less renal involvement (10-year follow-up) [55].

Furthermore, whilst the clearance of glomerular endothelial cell inclusions and mesangial cell inclusions was observed in paediatric patients who underwent ERT irrespective of treatment regimen, the clearance of GL-3 from podocytes may be dose-dependent [47,50] as demonstrated by a significant correlation between cumulative agalsidase dose and GL-3 clearance in podocytes [47]. Patients receiving agalsidase 0.2 mg/kg EOW did not achieve GL-3 clearance from podocytes, whereas all patients receiving agalsidase beta 1.0 mg/kg EOW showed significant clearance [47]. Additionally, when agalsidase beta 1.0 mg/kg EOW was switched to agalsidase alfa 0.2 mg/kg EOW podocyte GL-3 scores increased [50]. Moreover, urine albumin levels seemed sensitive to ERT dose, with greater reductions observed with agalsidase 1.0 mg/kg EOW compared with agalsidase 0.2 mg/kg EOW [44,47]. The potential importance of ERT dose was further demonstrated by a reduction in GI outcomes and pain with agalsidase beta (1.0 mg/kg EOW), but increasing abdominal and neuropathic pain when the treatment was stopped, the dose of agalsidase beta was reduced, or when ERT was switched to agalsidase alfa (0.2 mg/kg EOW) [50].

Limitations of this systematic literature review are described elsewhere [16]. The analysis of published literature on ERT in paediatric patients with Fabry disease must take into account the heterogeneity of the patient population and the limited clinical evidence available for various outcomes. Larger studies, with age-matched healthy or untreated children would be needed to demonstrate any effects of ERT on delay to Fabry disease progression. Furthermore, it may be interesting to investigate the usefulness of urinary GL-3 and lyso-GL-3 as a non-invasive, easily measurable biomarker for monitoring paediatric patients with Fabry disease [35,56–58].

In conclusion, ERT has a beneficial clinical impact in paediatric patients with Fabry disease, as it can relieve neuropathic pain, ameliorate gastrointestinal symptoms and improve quality of life. Moreover, ERT has been shown to normalize plasma GL-3 levels and to clear GL-3 inclusions from renal cells, with a dose-dependent mechanism in podocytes. The evidence of a clinical and of a metabolic response following treatment in young patients suffering from Fabry disease indicate that ERT may be important to prevent disease progression and end-stage organ damage.

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Conflicts of interest

- Marco Spada has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme and Shire.
- Ralf Baron has received speaker honoraria from Astellas, Bayer-Schering, Boehringer Ingelheim Pharma, Desitin, Eisai, Grünenthal, Lilly, Medtronic. Neuro-modulation, MSD, Mundipharma, Pfizer, Sanofi Genzyme, Sanofi Pasteur, Seqirus, and Teva Pharma; has been a consultant for AbbVie, Allergan, Astellas, AstraZeneca, Biogen Idec, Boehringer Ingelheim Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Galapagos, Genentech, Glenmark Pharmaceuticals, Grünenthal, Lilly, Medtronic, Merck, Mundipharma, Novartis, Pfizer, Sanofi Genzyme, Sanofi Pasteur, Seqirus, and Teva Pharma; has received research/grant support from AbbVie, Grünenthal, Mundipharma, Pfizer, and Sanofi Genzyme; is a member of the EU Project No 633491: DOLORisk; is a member of the IMI “Europain” collaboration, industry members of which are: AstraZeneca, Boehringer Ingelheim Pharma, Esteve, Eli Lilly, Grünenthal, Pfizer, Sanofi Aventis, and UCB-Pharma; German Federal Ministry of Education and Research (BMBF); Member of the ERA_NET NEURON/IM-PAIN Project (01EW1503), German Research Network on Neuropathic Pain (01EM0903), NoPain system biology (0316177C), and German Research Foundation (DFG).
- 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.
- 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.
- Lorenzo Monserrat has received speaker honoraria and travel support from Sanofi Genzyme and Shire; is a shareholder of Health in Code SL.
- Camilla Tøndel has received speaker honoraria and travel support from Sanofi Genzyme and Shire; has participated in studies supported by Protalix, Sanofi Genzyme, and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Anna Tylki-Szymańska has received speaker honoraria from Sanofi Genzyme and Shire; 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.
- 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2018.04.007.

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