Molecular Genetics and Metabolism Reports 19 (2019) 100454

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

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

Dominique P. Germain[a,*], Perry M. Elliott[b], Bruno Falissard[c], Victor V. Fomin[d], Max J. Hilz[e], Ana Jovanovic[f], Ilkka Kantola[g], Aleš Linhart[h], Renzo Mignani[i], Mehdi Namdar[j], Albina Nowak[k], João-Paulo Oliveira[l], Maurizio Pieroni[m], Miguel Viana-Baptista[n], Christoph Wanner[o], Marco Spada[p]

[a] French Referral Center for Fabry disease, Division of Medical Genetics and INSERM U1179, University of Versailles, Paris-Saclay University, Montigny, France
[b] University College London and Barts Heart Centre, London, United Kingdom
[c] INSERM U1018, University of Paris-Sud, University of Paris-Descartes, Paris, France
[d] Department of Internal Diseases No.1, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
[e] Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany
[f] Mark Holland Metabolic Unit, Salford Royal NHS Foundation Trust, Salford, United Kingdom
[g] Division of Medicine, Turku University Hospital, University of Turku, Turku, Finland
[h] Second Department of Medicine – Department of Cardiovascular Medicine, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic
[i] Department of Nephrology, Infermi Hospital, Rimini, Italy
[j] Service de Cardiologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland
[k] Department of Internal Medicine, University Hospital of Zurich and University of Zurich, Zurich, Switzerland
[l] Department of Genetics, São João Hospital Centre and Faculty of Medicine and "Instituto de Investigação e Inovação em Saúde (iS3)", University of Porto, Porto, Portugal
[m] Cardiovascular Department, San Donato Hospital, Arezzo, Italy
[n] Serviço de Neurologia, Hospital Egas Moniz, Centro Hospitalar de Lisboa Ocidental; CEDOC Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal
[o] Division of Nephrology, University Clinic, University of Würzburg, Würzburg, Germany
[p] Department of Paediatrics, University of Torino, Torino, Italy

ARTICLE INFO

Keywords:
Fabry disease
agalsidase alfa
agalsidase beta
systematic literature review
enzyme replacement therapy
adult male patients

ABSTRACT

Background: Enzyme replacement therapy (ERT) with recombinant human α-galactosidase has been available for the treatment of Fabry disease since 2001 in Europe and 2003 in the USA. Treatment outcomes with ERT are dependent on baseline patient characteristics, and published data are derived from heterogeneous study populations.

Methods: We conducted a comprehensive systematic literature review of all original articles on ERT in the treatment of Fabry disease published up until January 2017. This article presents the findings in adult male patients.

Results: Clinical evidence for the efficacy of ERT in adult male patients was available from 166 publications including 36 clinical trial publications. ERT significantly decreases globotriaosylceramide levels in plasma, urine, and in different kidney, heart, and skin cell types, slows the decline in estimated glomerular filtration rate,

Abbreviations: ANS, autonomic nervous system; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BPI, Brief Pain Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CNS, central nervous system; CR, case report; CT, clinical trial; ECG, electrocardiogram/electrocardiography; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; GFR, glomerular filtration rate; GI, gastrointestinal; GL-3, globotriaosylceramide; IVST, intraventricular septum thickness; IENFD, intra-epidermal nerve fibre density; LPWT, left posterior wall thickness; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; LVWT, left ventricular wall thickness; lyso-GL-3, globotriaosylsphingosine; MG, mixed gender; MRI, magnetic resonance imaging; MWT, maximal wall thickness; NYHA, New York Heart Association; OS, observational study; PNS, peripheral nervous system; QoL, quality of life; RCT, randomized controlled trial; SF-36, 36-item Short Form Health Survey; TIA, transient ischaemic attack; WMH, white matter hyperintensities.

* Corresponding author.
E-mail address: dominique.germain@uvsq.fr (D.P. Germain).

https://doi.org/10.1016/j.ymgmr.2019.100454
Received 23 January 2019; Accepted 23 January 2019
Available online 06 February 2019
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and reduces/stabilizes left ventricular mass and cardiac wall thickness. ERT also improves nervous system, gastrointestinal, pain, and quality of life outcomes.

Conclusions: ERT is a disease-specific treatment for patients with Fabry disease that may provide clinical benefits on several outcomes and organ systems. Better outcomes may be observed when treatment is started at an early age prior to the development of organ damage such as chronic kidney disease or cardiac fibrosis. Consolidated evidence suggests a dose effect. Data described in male patients, together with female and paediatric data, informs clinical practice and therapeutic goals for individualized treatment.

1. Introduction

Fabry disease (OMIM #301500) is an X-linked lysosomal storage disorder caused by pathogenic variants in the *GLA* gene (OMIM #300644; HGNC 4296) encoding the lysosomal enzyme α-galactosidase [1]. Subsequent accumulation of the glycosphingolipid globotriaosylceramide (GL-3) and its derivative globotriaosylsphingosine (lyso-GL-3) in cells, plasma, and urine causes progressive tissue damage in affected organs, resulting in multisystemic disease, life-threatening complications, and a reduced life expectancy in both males and females [2].

Fabry disease has a wide range of clinical presentations ranging from the early-onset 'classic' severe phenotype in patients with absent or severely decreased α-galactosidase activity, to later-onset 'non-classic' phenotypes often affecting a single organ system in patients with higher levels of residual α-galactosidase activity [1,3,4]. Patients with the classic phenotype, who are mostly males, generally experience signs and symptoms from early childhood onwards such as neuropathic pain, gastrointestinal (GI) disturbance, and hypohidrosis (all likely due to peripheral and autonomic nervous system [PNS, ANS] involvement), progressing to multi-organ failure involving the kidneys (albuminuria, proteinuria, decline in glomerular filtration rate [GFR], kidney failure), heart (left ventricular hypertrophy [LVH], heart failure, conduct abnormalities, and arrhythmias), auditory/vestibular system (hearing loss), and central nervous system (CNS) (stroke) in adulthood [1,5–15].

Enzyme replacement therapy (ERT) with recombinant α-galactosidase was approved in Europe in 2001. There are two preparations available: agalsidase alfa (Replagal®) administered at the licensed dose of 0.2 mg/kg; and agalsidase beta (Fabrazyme®) administered at the licensed dose of 1 mg/kg body weight. Both preparations are administered intravenously every other week (EOW) [16,17]. 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.

Although ERT has been in clinical use since 2001, many questions remain regarding treatment initiation timing, optimal dose, and treatment goals [1,17]. This is important as ERT in Fabry disease is expensive and is a lifelong commitment for patients. Traditionally used methods for analysing pooled data such as meta-analysis and meta-syntheses are difficult to apply in rare disease settings [18–20] and a systematic literature analysis including real-life experiences may be the best tool with which to provide a comprehensive overview of published clinical evidence.

We conducted a comprehensive systematic literature review of all original articles on ERT in the treatment of Fabry disease published up until January 2017 [21]. This article presents an analysis of treatment outcomes in adult male patients.

2. Methods

The full methodology for the systematic literature searches that were performed has been published in this issue [21], together with papers summarizing the findings of the literature review in female [22] and paediatric patients [23], and a position statement on therapeutic goals in Fabry disease based on the conclusions of an expert consensus panel [24]. The original searches included articles published up to and including January 2017.

The outcomes that were selected for analysis included plasma and urine GL-3 and lyso-GL-3 levels, GL-3 histology, measures of renal and cardiac function and of cardiac morphology. Other outcomes included ANS, PNS, and CNS parameters, GI symptoms, pain, and quality of life (QoL). GL-3 levels were described as 'normalized' if they were higher than reference values at baseline and decreased to within reference values during treatment, and if they were described as being normalized in the publication; note that the reference values varied in each publication.

Results are described for the approved dose regimens agalsidase alfa 0.2 mg/kg EOW and agalsidase beta 1.0 mg/kg EOW. Specific note has been made of altered dose regimens due to the temporary shortage of agalsidase beta to examine the efficacy of reduced-dose ERT [198]. Publications describing 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. Adult male population and publication overview

The publications that reported ERT outcomes data specific for adult male patients and that were included in the systematic literature analysis are summarized in Supplementary Table 1a. Publications were available from clinical trials (CT), observational study (OS) publications, studies describing both treatments, a combination of treatments, or when treatment was not specified (i.e. mixed-ERT studies), studies including both genders but with at least 50% male patients (i.e. mixed-gender [MG] studies), and case reports (CR).

For agalsidase alfa there were 16 CT publications (including five publications derived from Grade 1a randomized controlled trials [RCTs], nine publications from Grade 1c single-arm CTs and two from Grade 1a/c studies; four were placebo-controlled studies), 15 OS publications (of which six covered Grade 2 prospective OS publications, and nine Grade 3 retrospective OS publications) and 13 CRs (three Grade 4 case series and 10 Grade 5 CRs). For agalsidase beta, there were five CT publications (all Grade 1c single-arm CTs), 11 OS publications (four Grade 2 prospective OS publications, and seven Grade 3 retrospective OS publications) and 17 CRs (four Grade 4 case series and 13 Grade 5 CRs). There were no CT publications, 18 OS publications (seven Grade 2 prospective OS publications, and 11 Grade 3 retrospective OS publications), and 19 CRs (five Grade 4 case series and 12 publications which were either Grade 5 CRs or reported baseline and follow-up data on a single patient) describing mixed ERT, a comparison between agalsidase alfa and agalsidase beta, or not specifying the type of ERT.

The publications that reported ERT outcomes data for MG publications are summarized in Supplementary Table 1b. For agalsidase alfa there were five CT publications (two from Grade 1a RCTs, two from Grade 1c single-arm CTs and one from a Grade 1a/c study [1a portion was placebo-controlled]), 11 OS publications (five from Grade 2 prospective OS publications, and six from Grade 3 retrospective OS publications), and no CRs. For agalsidase beta, there were ten CT publications (one placebo-controlled Grade 1a RCT, seven Grade 1c single-arm CTs [including four open-label extension studies of the RCT] and

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 male patients with Fabry disease

Outcome		Agalsidase alfa 0.2 mg/kg EOW	Agalsidase beta 1.0 mg/kg EOW
3.2. GL-3 and lyso-GL-3 accumulation			
3.2.1.	Plasma GL-3	↓ Significant (Clarke et al. 2007 [25]; Pastores et al. 2007 [35]; Schiffmann et al. 2006 [39]; Schiffmann et al. 2007 [52]; van Breemen et al. 2011 [102]) ↓ Significance unknown (Goker-Alpan et al. 2015 [26]; Goláň et al. 2015 [27]; Hughes et al. 2008 [29]; Schiffmann et al. 2001 [36]; Rombach et al. 2012 [101]) – No change (Goker-Alpan et al. 2015 [26 (switch study)])	↓ Significant (Eto et al. 2005 [70]; Goker-Alpan et al. 2016 [71 (switch study)]; Lubanda et al. 2009 [72]; Elliott et al. 2006 [76]; van Breemen et al. 2011 [102]) ↓ Non-significant (Bénichou et al. 2009 [75]; Mignani et al. 2004 [80]) ↓ Unknown significance (Eng et al. 2001 [69]; Rombach et al. 2012 [101])
3.2.2.	Plasma lyso-GL-3	↓ Significant (Goker-Alpan et al. 2015 [26 (switch study)]) ↓ Unknown significance (Rombach et al. 2012 [101]; van Breemen et al. 2011 [102]) ↑ Significant (Smid et al. 2011 [54 (switch study)])	↓ Significant (Goker-Alpan et al. 2016 [71 (switch study)]) ↓ Unknown significance (Rombach et al. 2012 [101]; van Breemen et al. 2011 [102])
3.2.3.	Urinary GL-3	↓ Significant (Goker-Alpan et al. 2015 [26 (12 months)]; Hughes et al. 2008 [29 (6 months)]; Schiffmann et al. 2001 [36]; Schiffmann et al. 2006 [38]; Schiffmann et al. 2007 [52]) ↓ Unknown significance (Pastores et al. 2007 [35 (1/12 pts)]; Whitfield et al. 2005 [55]; Rombach et al. 2012 [101]) ↑ Non-significant (Goker-Alpan et al. 2015 [26 (switch study)])	↓ Significant (Lubanda et al. 2009 [72]) ↓ Non-significant (Eto et al. 2005 [70]; Goker-Alpan et al. 2016 [71 (switch study)]) ↓ Unknown significance (Rombach et al. 2012 [101]) – No change (Mignani et al. 2004 [80])
3.2.4.	Urinary lyso-GL-3	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
3.2.5. GL-3 accumulation: histology			
3.2.5.1.	Renal cells	↓ Non-significant (Schiffmann et al. 2001 [36])	↓Significant (Lubanda et al. 2009 [72]; Najafian et al. 2016 [73 (proportion of podocytes without GL-3 inclusions)]) ↓ Non-significant (Eng et al. 2001 [69]; Najafian et al. 2016 [73 (volume of GL-3 inclusions/podocyte and podocyte GL-3 score)])
3.2.5.2.	Cardiac cells	↓ Significance unknown (Hughes et al. 2008 [29])	↓ Significance unknown (Eng et al. 2001 [69])
3.2.5.3.	Other cell types	No data from clinical or observational studies with approved dose of agalsidase alfa	↓ Significance unknown (Eng et al. 2001 [69]; Lubanda et al. 2009 [72]; Bénichou et al. 2009 [75])
3.3. Renal outcomes			
3.3.1.	eGFR	↑ Significant (Hughes et al. 2008 [29]) Significantly slower decline (vs placebo, creatinine clearance (Schiffmann et al. 2001 [36]) ↓ Significant (Schiffmann et al. 2006 [39]; Feriozzi et al. 2009 [43]; Feriozzi et al. 2012 [44]; Hughes et al. 2011 [48]; Schiffmann et al. 2007 [52]) ↓ Non-significant (Schiffmann et al. 2006 [38]; Smid et al. 2011 [54 (switch study)]) ↓ Unknown significance (Beck et al. 2015 [41]) – No change (Kampmann et al. 2015 [49])	↓ Non-significant (Eto et al. 2005 [70]) ↓ Significance unknown, reduced decline (Warnock et al. 2012 [82]) ↓ Significance unknown (Kim et al. 2016 [79]) – No change (Lubanda et al. 2009 [72])
3.3.2.	Albuminuria/ Proteinuria	↑ Significant, CKD1 pts (Feriozzi et al. 2012 [44]; Kampmann et al. 2015 [49 (pts with baseline proteinuria)]) ↑ Unknown significance (Schiffmann et al. 2006 [39]) ↓ Non-significant (Bongiorno et al. 2003 [42]) – No change, stabilization (Schiffmann et al. 2001 [36]; Feriozzi et al. 2009 [43]; Feriozzi et al. 2012 [44 (CKD2/3)]; Hughes et al. 2011 [48]; Kampmann et al. 2015 [49 (pts without baseline proteinuria)]; Schiffmann et al. 2007 [52])	– No change (Lubanda et al. 2009 [72]; Kim et al. 2016 [79]) ↓ Non-significant (Najafian et al. 2016 [73])
3.4. Cardiac outcomes			
3.4.1.	LVM/LVMi	↓ Significant improvement (Hughes et al. 2008 [29]; Hughes et al. 2011 [48 (pts with baseline LVH]); Kampmann et al. 2015 [49 (pts with baseline LVH)]) ↓ Improvement of unknown significance (Tsuboi et al. 2012 [189]) ↑ Significant (Beck et al. 2015 [41 (slowed progression)]) ↑ Non-significant (Goláň et al. 2015 [27]) – No change (Kampmann et al. 2015 [49 (pts without baseline LVH)])	↓ Significant improvement (Germain et al. 2013 [7]; Motwani et al. 2012 [81]) — No change (Elliott et al. 2006 [76]; Kim et al. 2016 [79]; Mignani et al. 2004 [80])
3.4.2.	LVWT	↓ Significant (Kampmann et al. 2015 [49]) ↓ Improvement of unknown significance (Tsuboi et al. 2012 [189])	↓ Significant (Motwani et al. 2012 [81]) ↓ Non-significant (Mignani et al. 2004 [80 (2/3 patients)]) ↑ Non-significant (Mignani et al. 2004 [80 (1/3 patients)]) — No change (Elliott et al. 2006 [76])
3.4.3.	LVEF	– No change (Hughes et al. 2008 [29]; Kampmann et al. 2015 [49])	↑ Significant (Motwani et al. 2012 [81]) ↑ Non-significant improvement (Mignani et al. 2004 [80 (1/3 patients)])
3.4.4.	ECG measures	↓ Significant improvement in QRS duration (Schiffmann et al. 2001 [36]) ↓ Non-significant improvement in QRS duration (Hughes et al. 2008 [29]) – Conduction abnormality (Kampmann et al. 2015 [49 (1/21 pts)])	↑ Significant improvement in PQ interval, P-wave duration (Motwani et al. 2012 [81]) ↑ Significant improvement (Eng et al. 2001 [69]) ↓ Significant improvement of QTc interval (Motwani et al. 2012 [81]) – No change (Mignani et al. 2004 [80])
3.4.5.	Exercise testing	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

(*continued on next page*)

Table 1 (*continued*)

Outcome		Agalsidase alfa 0.2 mg/kg EOW	Agalsidase beta 1.0 mg/kg EOW
3.5. Nervous system outcomes			
3.5.1.	Sweat function	↑ Significant improvement, short-term (Schiffmann et al. 2003 [37]) ↑ Non-significant improvement (Bongiorno et al. 2003 [42]) ↑ Significance unknown (Hughes et al. 2011 [48]) — No change (Gupta et al. 2008 [45]; Schiffmann et al. 2007 [52])	↑ Subjective improvement (Eng et al. 2001 [69]; Hilz et al. 2004 [77])
3.5.2.	PNS nerve sensitivity	↓ Significant improvement IENFD (Schiffmann et al. 2006 [38]) ↓ Significant improvement cold/warm threshold (Schiffmann et al. 2003 [37]) — No change in cold/warm sensation (Schiffmann et al. 2006 [38]) — No change in neurological examination score (Jardim et al. 2004 [30]; Jardim et al. 2006 [31])	↓ Significant improvement (Hilz et al. 2004 [77])
3.5.3.	Vestibular/auditory and other CNS outcomes	↑ Significant improvement hearing loss (Hajioff et al. 2003 [28]) ↑ Non-significant improvement peripheral vestibular function (Palla et al. 2003 [34]) — Stabilization of hearing (Sergi et al. 2010 [53]) — No change, neurological examination (Jardim et al. 2004 [30]) ↓ Significant improvement in cerebral blood flow (Moore et al. 2001 [32]) ↓ Improvement of unknown significance in cerebral blood flow (Moore et al. 2002 [33])	— No change, neurological examination (Hilz et al. 2004 [77])
3.5.4.	White matter hyperintensities	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
3.6.	Pain outcomes	↓ Significant improvement (Schiffmann et al. 2001 [36]; Schiffmann et al. 2003 [37]; Hoffmann et al. 2007 [47]) ↓ Non-significant improvement in acroparesthesias (Jardim et al. 2006 [31]; Bongiorno et al. 2003 [42]) ↓ Unknown significance, improvement (Bongiorno et al. 2003 [42]) — No change (Hughes et al. 2011 [48]; Sergi et al. 2010 [53]; Whitfield et al. 2005 [55])	↓ Significant improvement (Eng et al. 2001 [69]; Hilz et al. 2004 [77]) ↓ Non-significant improvement (Eto et al. 2005 [70]; Mignani et al. 2004 [80])
3.7.	GI outcomes	↓ Unknown significance, improvement (Jardim et al. 2006 [31]; Hoffmann et al. 2007 [46]; Hughes et al. 2011 [48]) ↑ Unknown significance, diarrhea (Hughes et al. 2011 [48];	No data from clinical or observational studies with approved dose of agalsidase beta
3.8.	QoL	↑ Non-significant improvement (Hughes et al. 2011 [48]) — No change, energy levels (Ghali et al. 2012 [100]) — No change, SF-36 (Smid et al. 2011 [54])	↑ Significant improvement (Eto et al. 2005 [70]) ↑ Unknown significance (Eng et al. 2001 [69]; Watt et al. 2010 [83])

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 reports, mixed-ERT publications, and publications with other dose regimens are not included.

CNS, central nervous system; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; EOW, every other week; GI, gastrointestinal; GL-3, globotriaosylceramide; IENFD, intra-epidermal nerve fibre density; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; LVMi, left ventricular mass index; LVWT, left ventricular wall thickness; lyso-GL-3, globotriaosylsphingosine; PNS, peripheral nervous system; pts, patients; QoL, quality of life; SF-36, 36-Item Short Form Health Survey.

two Grade 1a/c studies [where the 1a portion was placebo-controlled]), 19 OS publications (16 Grade 2 prospective OS publications, and three Grade 3 retrospective OS publications) and no CRs. For mixed ERT there were two CT publications (one from a Grade 1a RCT and another from a Grade 1c single-arm CT), 14 OS publications (nine from Grade 2 prospective OS publications, and five from Grade 3 retrospective OS publications) and no CRs.

The main findings regarding clinical outcomes of treatment with agalsidase alfa and agalsidase beta in male 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. Treatment with agalsidase alfa was associated with a reduction in plasma GL-3 in four RCT publications [25,27,29,36], of which the last two were placebo-controlled, and four single-arm CT publications [26,35,39,40] (mainly trials with ≤25 patients and follow-up periods of 2.5–54 months) and three OS publications (including 12–22 male patients followed for 12–48 months) [52,101,102]. The change from baseline in plasma GL-3 was statistically significant in one RCT [25], one placebo-controlled RCT with open-label extension [29], one placebo-controlled RCT [36] and its open-label extension [39], one publication from a single-arm CT [35] and two OS publications [52,102]. In both placebo-controlled RCTs, there was a significant decrease in plasma GL-3 in the agalsidase alfa arm compared with no changes in the placebo group [29,36]. There were two publications that reported the impact of agalsidase dose/regimen change [40,52]: in one single-arm CT publication [40], the change from agalsidase alfa 0.2 mg/kg EOW to 0.2 mg/kg weekly resulted in no change in plasma GL-3 compared with pre-switch levels, whereas in another OS publication (12 patients followed for 24–48 months), further reductions, though not statistically significant, in plasma GL-3 were observed when the dose was increased from 0.2 mg/kg EOW to 0.2 or 0.4 mg/kg weekly [52]. In one OS, the four patients with antibodies to agalsidase alfa showed a reduction in plasma GL-3 after 12 months [101] (Supplementary Table 2).

There were three RCT publications in MG populations [27,135,176], one of which reported a significant decrease from baseline in plasma GL-3 with agalsidase alfa 0.2 mg/kg EOW after 12 months [27,176]. One RCT publication reported non-significant reductions from baseline in plasma GL-3 with agalsidase alfa 0.2 mg/kg EOW and 0.2 mg/kg weekly regimens [27]; another RCT publication described no statistically significant differences in plasma GL-3 reductions between for 0.2 mg/kg EOW, 0.1 mg/kg weekly, or 0.2 mg/kg weekly schedules [135].

3.2.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, an overall reduction in plasma GL-3 was reported in four single-arm CT publications (involving 13–21 patients followed for 2.5 to > 12

months) [69–72], and five OS publications [75,76,80,101,102]. Agalsidase beta treatment resulted in normalization of plasma GL-3 levels in four publications (including three single-arm CTs [69,70,72] and an OS publication [75]) and statistically significant reductions of plasma GL-3 levels in five publications (three single-arm CTs [70–72] and two OS publications [76,102]). In one single-arm CT, plasma GL-3 levels were above the normal range at baseline, decreased significantly with the 1.0 mg/kg EOW dose to normal levels and remained stable when the dose was reduced to 0.3 mg/kg EOW [72]. In another single-arm CT, switching 15 patients from agalsidase alfa 0.2 mg/kg EOW (mean duration 3.7 years; range 1.6–14 years) to agalsidase beta 1.0 mg/kg EOW for 6 months resulted in a statistically significant further reduction in plasma GL-3 after switch [71]. Two OS publications showed that treatment with agalsidase beta 1.0 mg/kg EOW resulted in larger reductions in plasma GL-3 compared with agalsidase alfa 0.2 mg/kg EOW [100,101], of which one publication was able to demonstrate a statistically significant difference between the two treatment regimens [101]. The same publications also described that a reduction in plasma GL-3 levels can be achieved with a lower dose of agalsidase beta (0.2 mg/kg EOW) [101,102] (Supplementary Table 2). The findings of reductions in plasma GL-3 were supported by three CRs of patients treated with agalsidase beta [91,94,98].

For MG populations, there were nine publications that described the changes in plasma GL-3 with agalsidase beta [79,149,157,160,163,166,168,176,180]. These publications were derived from one RCT [176], one placebo-controlled RCT with open-label extension [149], a longer-term open-label extension study from the same RCT [157] and one study in which patients were treated through an RCT, its open-label extension and then followed further through a registry [163] (58 patients followed for up to 120 months), and five OS publications [79,160,166,168,180]. All these publications noted a general trend towards normalization of plasma GL-3 levels. In the placebo-controlled study, patients receiving agalsidase beta 1.0 mg/kg EOW experienced a decrease in plasma GL-3 while those receiving placebo experienced no change; the difference between groups was statistically significant [149]. One RCT publication reported a statistically significant reduction in plasma GL-3 with agalsidase beta 0.2 mg/kg EOW (in 36 patients followed for ≥12 months) [176]. One OS, in 19 patients followed for 60–126 months, described reduced plasma GL-3 levels after 3 months of agalsidase beta and normalization after 1–2 years [79].

3.2.1.3. Mixed ERT. The findings of reductions in plasma GL-3 were supported by an OS which combined data for agalsidase alfa and agalsidase beta [101], and two mixed-ERT CRs [120,133].

There was one relatively large mixed-ERT MG OS publication (52 patients followed for ≥12 months) which reported a statistically significant decrease in plasma GL-3 for patients treated with agalsidase alfa 0.2 mg/kg EOW or agalsidase beta 0.2 mg/kg EOW, and a non-significant decrease for patients unresponsive to 0.2 mg/kg EOW of either treatment who switched to agalsidase beta 1.0 mg/kg EOW [180]. Decreasing plasma GL-3 levels were also reported in a mixed-ERT OS publication involving 34 renal dialysis or transplant patients followed for 45–48 months [186].

3.2.2. Plasma lyso-GL-3

3.2.2.1. Agalsidase alfa 0.2 mg/kg EOW. Plasma lyso-GL-3 levels decreased significantly with agalsidase alfa in one single-arm CT publication (with data reporting for 21 patients followed for 24 months) [26] and non-significantly in two OS publications (involving 22–29 patients followed for ≥12 months) [101,102]. In one OS publication (with 14 male patients treated with agalsidase alfa for a median of 11 months), a statistically significant increase in plasma lyso-GL-3 levels was reported in patients who switched from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [54]. Lastly, plasma lyso-GL-3 was reduced in the two classic patients from an OS publication: one who received agalsidase alfa and one who switched from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [110] (Supplementary Table 3).

3.2.2.2. Agalsidase beta 1.0 mg/kg EOW. One single-arm CT publication reported a statistically significant decrease in plasma lyso-GL-3 after switching from agalsidase alfa 0.2 mg/kg EOW (mean 3.7 years, range 1.6–14 years) to agalsidase beta 1.0 mg/kg EOW (in 15 patients followed for 6 months) [71]. Two OS publications (in 22–29 male patients followed for ≥12 months) showed that the decrease in plasma lyso-GL-3 was more notable with agalsidase beta 1.0 mg/kg EOW compared with agalsidase alfa 0.2 mg/kg EOW [101,102]. Agalsidase beta at a reduced dose of 0.2 mg/kg EOW led to a decrease in plasma lyso-GL-3 in two OS publications [101,102], and a statistically significant increase in plasma lyso-GL-3 in another [54] (Supplementary Table 3). One CR also described a decrease in plasma lyso-GL-3 with agalsidase beta [94].

3.2.2.3. Mixed ERT. Statistically significant reductions in plasma lyso-GL-3 with mixed-ERT were reported in one CT publication [182], four OS publications [51,101,102,109] and one CR [133].

3.2.3. Urinary GL-3

3.2.3.1. Agalsidase alfa 0.2 mg/kg EOW. One placebo-controlled RCT [36], one placebo-controlled RCT with open-label extension [29] and three single-arm CTs [26,35 and 39, where 39 is an extension study of 36] reported a decrease in urinary GL-3 levels with agalsidase alfa (including 12–21 male patients followed for 6–54 months). In one of the placebo-controlled RCTs, urinary GL-3 declined significantly compared with the placebo group [29], and in the other, urinary GL-3 levels decreased with agalsidase alfa but increased in the placebo group [36]. One single-arm CT publication (including 12 patients followed for ≤120 months) in which patients were switched from agalsidase alfa 0.2 mg/kg EOW to the same dose weekly reported no change in urinary GL-3 [40] and another small single-arm CT reported an increase in urinary GL-3 upon switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [26]. There were two OS publications (including 6–12 patients followed for 12–48 months) [52,55], one of which noted further reductions in urinary GL-3 levels when the regimen was changed from EOW to a weekly schedule [52]. Urinary GL-3 levels increased in antibody-positive patients in one OS publication (including 29 patients followed for > 12 months) [101] (Supplementary Table 4).

There were two RCT publications which reported urinary GL-3 levels in MG populations: one reported an overall decrease [176], and the other a trend towards decline, with agalsidase alfa 0.2 mg/kg weekly [135]. In an OS publication, a decrease in urinary GL-3 in antibody-negative patients, and an increase in urinary GL-3 in antibody-positive patients was reported following treatment with agalsidase alfa 0.2 mg/kg EOW (52 patients followed for ≥12 months) [180].

3.2.3.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, three single-arm CT publications (including 13–21 patients followed for 6–18 months) showed a decrease in urinary GL-3 levels [70–72]. During one single-arm trial, urinary GL-3 levels decreased significantly with agalsidase beta 1.0 mg/kg EOW and then increased significantly when the agalsidase beta dose was reduced [72]. In a separate single-arm CT, there was a non-significant decrease in urinary GL-3 levels after switching from agalsidase alfa 0.2 mg/kg EOW to agalsidase beta 1.0 mg/kg EOW [71]. In one OS publication, antibody-positive patients showed a decrease in urinary GL-3 levels with both agalsidase beta 1.0 mg/kg EOW and 0.2 mg/kg EOW, whereas, with agalsidase alfa 0.2 mg/kg EOW, an increase was seen [101]. In another OS publication (in three patients), urinary GL-3 remained normal throughout 18 months of follow-up [80]. In a CR, urinary GL-3 decreased after 12 months [99] (Supplementary Table 4).

In MG populations, one RCT publication reported a non-significant decrease in urinary GL-3 with agalsidase beta 0.2 mg/kg EOW [176]. In two OS publications, there was a statistically significant decrease in urinary GL-3 (11 patients followed for ≤27 months) [160]; and 52 patients followed for ≥12 months [180]). In one OS publication in 19 patients followed for 60–126 months, urinary GL-3 levels declined after 3 months and normalized within 3 years [79]. One OS publication reported a decrease in urinary GL-3 with agalsidase beta 1.0 mg/kg EOW in both antibody-negative and antibody-positive patients [180]; with the agalsidase beta 0.2 mg/kg dose, there was a decline in urinary GL-3 in antibody-negative patients and an increase in antibody-positive patients [180].

3.2.3.3. Mixed ERT. One mixed-ERT study publication in males showed reductions in urinary GL-3 [101]. For MG publications, urinary GL-3 levels were undetectable both at baseline and at endpoint in one OS publication (in 34 renal dialysis and transplant patients followed for 45–48 months) [186]. A decrease in urinary GL-3 in antibody-negative patients, and an increase in urinary GL-3 in antibody-positive patients were reported in an OS involving 18 patients followed for 6–12 months [178].

3.2.4. Urinary lyso-GL-3

3.2.4.1. Agalsidase alfa/beta. There were no publications reporting on the change in urinary lyso-GL-3 following treatment with agalsidase alfa or agalsidase beta.

3.2.4.2. Mixed ERT. Urinary lyso-GL-3 levels decreased during treatment with mixed-ERT in one male patient followed for 30 months in the only publication that reported this outcome [106].

3.2.5. GL-3 accumulation: histology

3.2.5.1. Renal cells

3.2.5.1.1. Agalsidase alfa 0.2 mg/kg EOW. In one placebo-controlled RCT publication, GL-3 in kidney biopsy samples was reduced from baseline in both the agalsidase alfa and placebo groups [36] (Supplementary Table 5).

3.2.5.1.2. Agalsidase beta 1.0 mg/kg EOW. Two single-arm CT publications reported change in GL-3 levels across various renal tissues [72,73]. One publication observed statistically significant increases in the proportions of patients experiencing GL-3 clearance in six of eight different renal cell types after 6 months of treatment. Clearance levels were generally maintained when patients received the 0.3 mg/kg EOW dose during 18 months of treatment in a single-arm CT [72]. A 73% decline in podocyte GL-3 content and a 63% reduction in podocyte volume after 11–12 months of agalsidase beta was reported in the other single-arm CT publication [73]. In the same publication, there was a reduction in GL-3 score (in three of six patients) and a statistically significant increase in the number of podocytes/biopsy without visible GL-3 inclusions with agalsidase beta treatment [73]. Also, one single-arm CT showed that the accumulation of GL-3 in kidney cells was reduced with different dosing regimens in four of five patients after five infusions (2.5 months) [69] (Supplementary Table 5). In one CR, agalsidase beta decreased renal GL-3 deposits (histological analysis based on specific staining for GL-3 in renal biopsy samples) [89]. In another CR, the composite podocyte score was reduced with agalsidase beta but increased after switching to agalsidase alfa [130].

Four MG publications reported GL-3 clearance in renal capillary and non-capillary endothelial cells with agalsidase beta: the placebo-controlled RCT [149], its secondary analysis [153], and its extension study [150], and the OS [160]. In the placebo-controlled RCT, the proportion of patients achieving GL-3 clearance from renal capillary endothelial cells was significantly higher with agalsidase beta than with placebo [149]. A secondary analysis of the same study reported that, compared with placebo, significantly more patients treated with agalsidase beta achieved GL-3 clearance from glomerular capillary endothelial cells, arterial/arteriolar endothelial cells, mesangial cells, and interstitial cells [153]. The difference in proportion of patients achieving clearance was statistically significant compared with baseline in the open-label extension study of the RCT (up to 54 months' follow-up) [150] and one small OS (in 11 patients followed for ≤27 months) [160].

3.2.5.1.3. Mixed ERT. One CR noted that the adult male patient who started ERT at 18 years of age showed clearance of GL-3 deposits from podocytes, yet the paediatric male patient who started ERT at 7 years of age showed better clearance [130].

3.2.5.2. Cardiac cells

3.2.5.2.1. Agalsidase alfa 0.2 mg/kg EOW. In one placebo-controlled RCT with open-label extension, during the 6-month RCT phase the six patients who were treated with agalsidase alfa showed a non-significant reduction in GL-3 accumulation in myocardial cells while the eight patients in the placebo group experienced an increase [29] (Supplementary Table 6). A MG OS publication reported GL-3 accumulation in cardiomyocytes with agalsidase alfa (17 patients followed for ≤40 months), but data for both pre- and post-ERT were not available [143].

3.2.5.2.2. Agalsidase beta 1.0 mg/kg EOW. There was one single-arm CT publication in male patients which reported a non-significant decrease in the capillary endothelium GL-3 scores [69] (Supplementary Table 6).

In MG publications of agalsidase beta, a reduction in GL-3 accumulation in cardiac endothelial cells was reported in three publications: one was a placebo-controlled RCT with open-label extension [149], and two were longer-term open-label extensions of the same study (including 58 patients followed for up to 54 months) [150,155]. In the RCT, patients treated with agalsidase beta 1.0 mg/kg EOW experienced a decrease in cardiac GL-3 deposits, while those in the placebo group, experienced a small increase [149].

3.2.5.2.3. Mixed ERT. There were no publications from either male or MG publications describing the effect of mixed-ERT regimens on cardiac GL-3 levels.

3.2.5.3. Other cell types

3.2.5.3.1. Agalsidase alfa 0.2 mg/kg EOW. There were no publications describing change from baseline following agalsidase alfa treatment in GL-3 levels in other cell types.

3.2.5.3.2. Agalsidase beta 1.0 mg/kg EOW. One single-arm CT publication (in 15 patients followed for ≤ 2.5 months) reported a decrease in GL-3 levels in liver cells in each of the five dosing regimens [69]. In another, skin GL-3 was significantly reduced in 21 patients followed for 6 months [72]. One single-arm study found that 100% of patients had clearance of GL-3 in interstitial capillary endothelial cells with agalsidase beta 1.0 mg/kg EOW but 90% with the reduced dose of agalsidase beta 0.3 mg/kg [72]. In one OS publication, treatment achieved GL-3 clearance from skin (as measured by an increase in the number of patients with undetectable/trace levels of skin GL-3 following treatment) [75] (Supplementary Table 7). CRs described clearance of glycolipid storage deposits from sweat glands [97] and vascular endothelial cells [93].

In MG publications, one placebo-controlled RCT followed by open-label extension (in 58 patients) reported a statistically significant reduction in skin epithelial GL-3 scores compared with placebo after 5 months, and during the open-label extension (after 6–12 months follow-up), 96% of patients had total clearance of skin epithelial GL-3 [149]. These low levels were sustained in three further open-label extensions of the same study (after 30-36 months [154,157] and after 54 months [150]).

3.2.5.3.3. Mixed ERT. There were no publications for mixed-ERT regimens describing other organ GL-3 levels.

3.3. Renal outcomes

3.3.1. Estimated glomerular filtration rate (eGFR)

3.3.1.1. Agalsidase alfa 0.2 mg/kg EOW. For agalsidase alfa, eGFR was reported as a measure of kidney function during ERT in six CT publications (including one placebo-controlled RCT with open-label extension [29], one placebo-controlled RCT [36] and its two extension studies [38,39], and two single-arm studies [35,40]) and seven OS publications [41,43,44,48,49,52,54]. In the placebo-controlled RCT, renal function declined significantly more in the placebo group than in the agalsidase alfa group [36]. In one placebo-controlled RCT with open-label extension, eGFR was significantly increased compared with baseline in the seven patients receiving agalsidase alfa, while the patients receiving placebo experienced no changes [29]. Another single-arm CT publication (in 12 patients) noted an increase in eGFR after 6 months but this was not statistically significant [35]. The decline in eGFR appeared to be slowed compared with placebo or untreated patients when the 14 agalsidase alfa-treated patients from the placebo-controlled RCT [36] were followed for 48–54 months [39], in a large OS (in 360 patients, of whom 115 male patients had eGFR data, followed for 60 months) [41], and in a small OS (in 12 patients followed for 24–48 months) [52]. Other publications showed decreases in eGFR, including one open-label extension of a placebo-controlled RCT (in 26 patients followed for 12–18 months) [38], three publications from the same registry (including 115–172 patients followed for 36–134 months) [43,44,48], and one OS (in 15 patients treated for a median of 11 months with agalsidase alfa [54]). Another single-arm CT publication reported a slowed decline in eGFR on switching from agalsidase alfa 0.2 mg/kg EOW to the same dose weekly (in 12 patients followed for < 120 months) [40]. One OS publication reported stabilized eGFR in 21 male patients after 10 years [49]. Three CRs suggested that agalsidase alfa might slow the decrease in eGFR [60,62,67] (Table 2).

In MG populations, eGFR did not change significantly with agalsidase alfa. This was reported in 12 publications (five CT publications including three RCTs [27,135,176] and two single-arm studies [26,35], five OS publications [139,141,142,146,147] and two registry studies [137,144]). The five CT publications included three pure agalsidase alfa publications (one RCT [27] and two single-arm studies [35,136] in 8–44 patients followed for ≤24 months), and two mixed-ERT publications in which the agalsidase alfa arm data were reported separately (one single-arm CT publication in which 100 patients were followed for 24 months [26] and one RCT where 36 patients were followed for ≥12 months [176]). The five OS publications included a large report (234 patients) and one long-term follow-up (57 months) [139,141,142,146,147]. Of the registry studies, one followed 181 patients for 60 months and the other followed 314 patients for an average of 17 months [137,144].

The effect of switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW differed across four publications [26,177,179,181]. Two publications (one single-arm CT including 40 male switch patients [26] and one OS including 7 male switch patients [179]) described no (clinical) change in eGFR 24 months after switching. One OS showed that eGFR was reduced in 37 patients, of whom 20 were male, 12 months after switching [181], and was statistically significant decreased at 24 months after the switch [177].

3.3.1.2. Agalsidase beta 1.0 mg/kg EOW. Publications from three single-arm CT publications [70,72,73] and two OS publications [79,82] reported on the effect of agalsidase beta on eGFR. One single-arm CT (in 13 patients followed for 5 months) reported a non-significant decrease in eGFR [70], whereas another showed no change in eGFR during agalsidase beta 1.0 mg/kg EOW or after a dose reduction to 0.3 mg/kg EOW (in 21 patients who received normal dosing for 6 months and reduced dosing for 18 months) [72]. In one single-arm CT publication that reported patient-level change in eGFR, eGFR decreased in two of six patients, no change was observed in another two of six, and an increase was seen in one of six patients (one patient was not evaluable at follow-up) [73]. One large OS publication reported that early agalsidase beta treatment initiation was associated with a reduced slope of eGFR decline (in 151 patients followed for 24 months) [82] and another OS (11 patients followed for 60–126 months) reported a significantly lower eGFR decline in patients with lower proteinuria before ERT [79]. In this study, temporary agalsidase beta dose reduction resulted in a statistically significant decrease in eGFR (compared with full-dose period, seven patients) [79] (Table 2). One CR reported a decline in eGFR during 16 years of agalsidase beta treatment [84].

In MG populations, the observation that agalsidase beta had a stabilizing effect on eGFR was consistently reported in 12 publications (one RCT with open-label extension [149] and two further open-label extensions in the same patients [150,157] and one single-arm CT publication [152] and eight OS publications [159,163,165,175,177,180,181,188]). Two publications reported different effects of agalsidase beta dose reduction on eGFR: one OS publication reported a statistically significant decrease (105 patients followed for 8–16 months) [181], whereas an RCT observed no effect (52 patients followed for 12 months or longer) [176].

3.3.1.3. Mixed ERT. Eight mixed-ERT OS publications (including some large, long-term studies including ≤100 patients followed for ≤120 months) agreed that ERT might slow the decrease in eGFR [51,103,104,107,109,112,114,116]. One large, long-term OS publication reported that patients without proteinuria responded better to treatment than patients with overt proteinuria (109 patients followed for ≤116 months) [103]. Four CRs noted that eGFR remained stable or decreased during mixed-ERT [125,130–132].

In MG populations, one OS publication reported a statistically significant decline in eGFR following 80 months of mixed ERT (26 patients) [108], and another OS noted no statistically significant change in eGFR for patients treated with agalsidase alfa 0.2 mg/kg EOW or agalsidase beta 0.2 mg/kg EOW combined [180].

3.3.2. Albuminuria/proteinuria

3.3.2.1. Agalsidase alfa 0.2 mg/kg EOW. Agalsidase alfa was generally reported to have no effect on proteinuria. These findings were reported by two CT publications (first a randomized, placebo-controlled portion in which 14 patients were followed for 6 months [36], and then an open-label extension of 48–54 months in the same patients [39]) and six OS publications [42–44,48,49,52], including three large registry studies involving 77–115 patients with proteinuria data followed for 36–89 months [43,44,48]. One OS publication reporting the impact of 10 years of agalsidase alfa treatment noted no changes in patients without baseline proteinuria but a statistically significant increase in proteinuria in those with pre-existing proteinuria at baseline [49]. The only statistically significant finding in the registry studies was an increase in proteinuria in patients with chronic kidney disease stage 1 at baseline [44]. When the agalsidase alfa regimen was changed from 0.2 mg/kg EOW to 0.2 mg/kg weekly, there was a decrease in proteinuria (OS publication [52]) (Supplementary Table 8).

Effects of agalsidase alfa on proteinuria were very variable across five different CRs: two CRs showed improved proteinuria [56,62], two described worsening [65,125], and one noted no change during treatment [64]. In two CRs, the change in proteinuria was dependent on agalsidase alfa dose: patients experienced an increase in proteinuria with agalsidase alfa 0.2 mg/kg EOW dose but a decrease in proteinuria when the dose was subsequently increased to 0.4 mg/kg EOW [63,67].

For MG populations, one RCT [176], one single-arm CT publication [136] and three OS publications [139,142,147] reported no statistically significant change in proteinuria with agalsidase alfa. Two OS publications reported the effect of switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW on proteinuria/albuminuria

Table 2
Glomerular filtration rate outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
Alfa	Beck et al. 2015 [41] (N = 677) *Grade 3*	360 (53)	60	mL/min/1.73 m^2 (mean annualized eGFR slope ± SE)	eGFR at BL ≥60: NR (n = 117)	eGFR at BL ≥60: −1.68 ± 0.19 (n = 117)	↓ (95% CI −2.05, −1.31)
					eGFR at BL < 60: NR (n = 18)	eGFR at BL < 60: −2.86 ± 0.53 (n = 18)	↓ (95% CI −3.90, −1.83)
					Proteinuria at BL ≥1.0 g/24 h: Mean: 74.4 (n = 16)	Proteinuria at BL ≥1.0 g/24 h: −4.76 ± 0.56 (n = 16)	↓ (95% CI −5.85, −3.66)
					0.1–1.0 g/24 h: Mean: 101.8 (n = 74)	0.1–1.0 g/24 h: −1.62 ± 0.23 (n = 74)	↓ (95% CI −2.08, −1.17)
					< 0.1 g/24 h: Mean: 105 (n = 15)	< 0.1 g/24 h: −1.32 ± 0.48 (n = 15)	↓ (95% CI −2.26, −0.38)
	Feriozzi et al. 2009 [43] (N = 165) *Grade 3*	115 (70)	36	mL/min/1.73 m^2	94.5 [30.8] (n = 115)	81.2 [32.5] (n = 115)	↓ ($p < 0.01$)
	Feriozzi et al. 2012 [44] (N = 208) *Grade 3*	134 (64)	60–134	mL/min/1.73 m^2	97.3 [26.5] (n = 134)	79.7 [31.8] (n = 134)	↓ ($p < 0.01$)
	Hughes et al. 2008 [29] (N = 7) *Grade 1a*	15 (100)	6	mL/min/1.73 m^2	106.3 ± 13.9 (n = 7)	Increase within normal range: 106–131 mL/min	↑ ($p = 0.007$)
	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	≥48	mL/min/1.73 m^2 (median [10 − 90th percentile])	88.2 (41.1–137.0) (n = 105)	80.3 (34.2–119.7) (n = 105)	↓ ($p < 0.001$)
	Kampmann et al. 2015 [49] (N = 45) *Grade 3*	21 (47)	Median (range): 130 (115–150)	mL/min/1.73 m^2	≥90 mL/min/1.73 m^2: Values: NR	≥90 mL/min/1.73 m^2: 10 years: NC	NC (NS)
					< 90 mL/min/1.73 m^2: Values: NR	< 90 mL/min/1.73 m^2: 10 years: NC	NC (NS)
	Pastores et al. 2007 [35] (N = 22) *Grade 1c*	20 (91)	Range: 2.5–15	mL/min/1.73 m^2	Transplant pts: 64.5 ± 6 (n = 12)	Transplant pts: 71.6 ± 8.0 (n = 12)	↑ ($p = 0.07$)
	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	Creatinine clearance mL/min/1.73 m^2	92.7 ± 6.2 (n = 13)	94.8 ± 7.7 (n = 13)	↑ (NR)
	Schiffmann et al. 2006 [38] (N = 26) *Grade 1c*	26 (100)	18	mL/min/1.73 m^2	97 (n = 26)	90 (n = 25)	↓ ($p = 0.38$)
	Schiffmann et al. 2006 [39] (N = 25) *Grade 1c*	25 (100)	48–54	mL/min/1.73 m^2	88.4 [26.0] (n = 24)	Month 48: 75.1 [32.7] (n = 24)	↓ ($p = 0.039$)
	Schiffmann et al. 2007 [52] (N = 12) *Grade 2*	12 (100)	24–48	mL/min/ 1.73 m^2	77.8 [30.4] (n = 12)	53.7 [21.0] Mean change: −8.0 [2.8]/year	↓ (NR)
Beta	Eto et al. 2005 [70] (N = 13) *Grade 1c*	13 (100)	4.6	Creatinine clearance mL/min	126.6 [41.8] (n = 13)	115.3 [30.4] (n = 13)	↓ ($p = 0.216$)
	Kim et al. 2016 [79] (N = 19) *Grade 2*	15 (79) *11 adults, 4 paediatric pts*	60–126	mL/min/1.73 m^2	107.3 [28.5] (n = 11)	−3.8 [4.5]/year (n = 11)	↓ (NR)
						Stratified by BL proteinuria < 0.1g/day: −0.7 [3.8]/year (n = 3)	NC (NS)
						> 0.1 g/day: −6.3 [4.2]/year (n = 6)	NC (NS)
					During shortage: 78.3 [29.4] (n = 7)	During shortage:	NC ($p > 0.05$)

(*continued on next page*)

Table 2 (*continued*)

Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
					63.3 [37.2] (n = 7)	
Lubanda et al. 2009 [72] (N = 21) *Grade 1c*	21 (100)	5.5	mL/min/1.73m^2	Median: 92.5 (n = 21)	Median: 93.1 (n = 21)	NC (NS)
Najafian et al. 2016 [73] (N = 6) *Grade 1c*	6 (100)	11–12	mL/min/1.73m^2	Range: 111–154 (n = 6)	Range: 114–190 (n = 5)	NC/↓/↑ (NR)
Warnock et al. 2012 [82] (N = 213) *Grade 3*	151 (71)	> 24	mL/min/1.73 m^2/year	Q1[f]: 99 [22.6] (n = 37) Q2: 77 [32.9] (n = 37) Q3: 88 [38.7] (n = 38) Q4: 2 [34.3] (n = 36)	Q1: −0.1 [1.20] (n = 38) Q2: −2.1 [0.52] (n = 38) Q3: −3.8 [0.61] (n = 38) Q4: −6.7 [2.26] (n = 37)	↓ (NR)

Data are means (SD) or means ± SE or medians (range), unless otherwise indicated.
Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
↓, decrease; ↑, increase; BL, baseline; CI, confidence interval; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; h, hours; NC, no change; NR, not reported; NS, not significant; pt, patient; Q1, first quartile (based on progression of renal disease during follow-up); Q2, second quartile; Q3, third quartile; Q4, fourth quartile; SD, standard deviation; SE, standard error.
[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 male patients who were treated with ERT;
[d] Number of male, ERT-treated patients with data for the outcome at baseline;
[e] Number of male, ERT-treated patients with data for the outcome at endpoint;
[f] eGFR slope Quartile 1: −1.2 to 15.3, Quartile 2: −2.8 to -1.3, Quartile 3: −4.8 to −2.9, Quartile 4: −15.5 to −4.9.

levels [179,181]: in one, there was a statistically significant increase in albuminuria following the switch [181], and in the other, there was no change in proteinuria [179].

3.3.2.2. Agalsidase beta 1.0 mg/kg EOW. There were two single-arm CT publications [72,73] and two OS publications [79,80] which reported proteinuria/albuminuria outcomes following agalsidase beta. One single-arm CT publication reported no statistically significant changes with agalsidase beta 1.0 mg/kg EOW or following a dose reduction to 0.3 mg/kg EOW in 21 patients followed for ≤18 months [72]. A resolution of proteinuria was observed in all patients with follow-up data available in a single-arm CT publication of six patients followed for 12 months [73]. In an OS publication in 11 patients followed for 60–126 months, there was no statistically significant effect of agalsidase beta treatment on proteinuria, and no impact of baseline proteinuria on treatment outcomes [79]. Another OS publication reported that one of three patients had detectable proteinuria at baseline which resolved during treatment [80] (Supplementary Table 8). Five CRs with agalsidase beta showed an improvement in proteinuria [86,88,92,95,96], whereas one showed no change [87], and one a worsening [85].

One MG single-arm CT reported a decrease in proteinuria with agalsidase beta when used in conjunction with antiproteinuric therapy (angiotensin-converting enzyme inhibitor [ACEi] and/or angiotensin receptor blocker [ARB]) [152]. Two OS publications [164,175] showed a statistically significant reduction in proteinuria in 40 patients followed for ≥60 months and a resolution of proteinuria in some patients (in a small study of 11 patients followed for 29–58 months). One OS publication reported a statistically significant decrease in proteinuria with agalsidase beta in combination with paricalcitol [188]. One open-label extension of a placebo-controlled RCT [157] and four OS publications [159,160,165,181] reported no statistically significant change in proteinuria or albuminuria. In an RCT [176] and another OS publication [181], agalsidase beta therapy at a dose of 0.2 mg/kg EOW or with a dose reduction to 0.3–0.5 mg/kg EOW did not result in statistically significant changes in proteinuria and albuminuria.

3.3.2.3. Mixed ERT. The effects of mixed ERT on proteinuria/albuminuria are supported by four mixed-ERT OS publications, including one study investigating proteinuria in 109 patients after 116 months [103] and three smaller studies reporting changes in albuminuria [51,107,109]. In one CR, the patient had slightly elevated albuminuria levels at baseline, which decreased after 1 year of agalsidase beta 1.0 mg/kg EOW and remained stable for the next 10 years (with different ERT regimens) [130]. Proteinuria was also described in another two CRs [121,125].

In MG populations, there was one mixed-ERT OS publication including renal dialysis and transplant patients that reported a non-significant increase in proteinuria in transplanted patients [186].

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. Two RCT publications [27 and the placebo-controlled 29] and four OS publications [41,48,49,189], reported measures of LVM with agalsidase alfa therapy. In a small placebo-controlled RCT with open-label extension in six patients using magnetic resonance imaging (MRI) assessment of left ventricular mass index (LVMi) (followed for 30 months), agalsidase alfa showed a significant reduction in LVM compared with placebo [29]. In one RCT that included 26 patients followed for 12 months, a non-significant increase in LVM was seen with agalsidase alfa 0.2 mg/kg EOW, whereas no change was seen with agalsidase alfa 0.2 mg/kg weekly and a non-significant decrease with agalsidase alfa 0.4 mg/kg weekly [27]. In one registry study publication (in 172 patients followed for ≥48 months, 45 of whom had had LVM data available), LVM decreased significantly in the 22 patients with baseline LVH [48], and in another OS publication (in 360 patients followed for 60 months, 71 of whom had LVMi data available), the progression of LVH was slowed compared with untreated patients, but still increased significantly [41]. After 10 years of

agalsidase alfa there was no change in LVMi in patients without baseline LVH, but a statistically significant decrease in LVMi in patients with baseline LVH (OS in 21 patients) [49]. In the final small OS (four patients), switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW led to a small decrease in LVM [189] (Supplementary Table 9).

There were four CRs which reported an increase in LVH/LVMi with agalsidase alfa after 12 months [61], 6 years [64], 9 years [57], and 12 years [60]. Another CR described stabilization of LVMi, indicated by absence of progression to LVH, in one patient treated with agalsidase alfa [59] and in another who switched regimens (from agalsidase alfa to agalsidase beta and back to agalsidase alfa) [84]. Normalization of hypertrophy after 6 years of treatment [68], and fluctuations in LVM depending on dose, with a lower dose causing an increase in LVM and a higher dose a decrease [63], were also found in CRs.

Two RCTs [27,176] and one single-arm CT publications [26] in MG populations showed that LVM parameters remained stable. LVM was reported to decrease in two registry publications: one in 314 patients followed for 17 months [137] and the other in 181 patients followed for 60 months [144]. In one OS publication, the impact of agalsidase alfa on LVMi was variable [143], while another reported no change in LVMi when patients were switched from agalsidase beta 1.0 mg/kg to agalsidase alfa 0.2 mg/kg EOW [179].

3.4.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, five OS publications reported LVH outcomes [7,76,79–81]. LVMi decreased significantly in two large registry study publications [7,81]; LVM decreased in 115 patients followed for 59 months which was a statistically significant decrease in patients who started agalsidase beta treatment at age < 30 years; LVM increased, however, in patients who started ERT at age ≥50 years [7]. LVM did not change in the two smaller study publications (five to eleven patients followed for 10–126 months) [76,79] (Supplementary Table 9). In four CRs LVMi declined or stabilized with agalsidase beta [84,87,90,91].

LVM was reported in one MG RCT [176], one MG single-arm CT publication [151] and 14 MG OS publications [158–161,164–167,169,170,173,174,179,180], half of which reported a statistically significant reduction in LVM with agalsidase beta. One of these noted a statistically significant decrease from baseline in LVM with ERT in patients without fibrosis, but no such effect in patients with mild or severe fibrosis [174].

3.4.1.3. Mixed ERT. Findings from mixed-ERT studies were reported across nine OS publications [101,104,107,109,110,112,113,114,116] including a large study in 100 patients followed for 59–64 months [114]. One OS publication showed that patients with an abnormal baseline electrocardiogram (ECG) had a statistically significant increase in LVMi, while patients with normal ECG at baseline did not experience any statistically significant change in LVMi (neither progression nor regression) with mixed-ERT treatment (6 years' follow-up) [113]. One CR noted a deterioration in LVMi [125] but three other CRs showed a decline or stabilization in LVMi [122,124,127].

LVMi with mixed ERT was also described in one MG RCT [176], another single-arm CT publication [26], and eight OS publications [51,103,179,180,182,183,185,186]. In one of these OS publications (25 patients), there was a statistically significant decrease in LVM and LVMi after 12 months [182]. In another mixed-ERT OS publication including 40 patients, LVM decreased in the first few years after treatment initiation and increased thereafter (but neither change was statistically significant) [183].

3.4.2. Left ventricular wall thickness (LVWT)

3.4.2.1. Agalsidase alfa 0.2 mg/kg EOW. One OS including 21 males with mild hypertrophy, reported a statistically significant decrease in LVWT after 10 years of treatment with agalsidase alfa [49], while two CRs noted an increase in LVWT [57,64]. One OS reported a small decrease in LVWT after switching from agalsidase beta 1.0 mg/kg to agalsidase alfa 0.2 mg/kg EOW [189] (Supplementary Table 10).

In one large registry publication of a MG population of 314 patients, there was decreased LVWT after 12 and 24 months of agalsidase alfa [137]. In two OS publications, wall thickness measures did not change on switching from agalsidase beta 1.0 mg/kg to agalsidase alfa 0.2 mg/kg EOW (LVWT [179]; septal and posterior wall thickness [181]).

3.4.2.2. Agalsidase beta 1.0 mg/kg EOW. Wall thickness outcomes with agalsidase beta were assessed in male patients in three OS publications. One study showed a statistically significant decrease in maximal wall thickness (MWT) and left ventricular end-diastolic diameter (LVEDD) in 44 patients followed for a median of 36 months [81]. Another OS in 10 patients followed ≤12 months reported no change in LVWT parameters (MWT, LVEDD, and left ventricular end systolic diameter) [76], whereas a third OS in three patients demonstrated that wall thickness decreased in two patients and increased in one patient after 18 months [80]. LVWT stabilized or decreased in two CRs [87,91] (Supplementary Table 10).

For MG populations, agalsidase beta reduced LVWT parameters in six publications (one single-arm CT [156] and seven OS publications [159,164,167,170,173,174,179]). Agalsidase beta did not change LVWT in four OS publications [163,166,171,181], including three large studies of 56–105 patients followed for ≤58 months [163,171,181]. One of these noted that LVWT was stable in those who started therapy at age < 40 years, but was significantly higher if patients received their first dose of ERT when aged ≥40 years [163]. In one OS, agalsidase beta dose reduction did not have a statistically significant effect on posterior LVWT (median of 12 months' follow-up) [181].

3.4.2.3. Mixed ERT. Two mixed-ERT OS publications [109,113] and two CRs [122,126] indicated that LVWT parameters stabilized or decreased in male patients.

In MG populations, there was one OS that demonstrated a statistically significant decrease in intraventricular septum thickness [IVST] (25 patients treated for 12 months) [182], but three longer-term OS publications (37 to 64 months) reported no change in LVWT [184,185,187]. One mixed-ERT OS publication involving a MG population of 34 patients followed for 45–48 months reported an increased posterior LVWT in chronic haemodialysis patients and a decreased posterior LVWT in renal transplant patients [186].

3.4.3. Left ventricular ejection fraction (LVEF)

3.4.3.1. Agalsidase alfa 0.2 mg/kg EOW. One placebo-controlled RCT publication with open-label extension reported no change in LVEF following 6 months of agalsidase alfa (seven patients) [29]. An OS including 21 males reported no statistically significant change in LVEF after 10 years of treatment with agalsidase alfa [49] (Supplementary Table 11). One CR showed that the LVEF remained normal after 5 years of treatment with agalsidase alfa [57].

Two OS publications of MG populations reported no change in LVEF when patients were switched from agalsidase beta 1.0 mg/kg to agalsidase alfa 0.2 mg/kg EOW (105 patients followed for 8–16 months [181] and ten patients followed for 20 months [179]).

3.4.3.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one registry OS publication reported a statistically significant improvement in ejection fraction in 44 patients followed for a median of 36 months [81]. One OS [80] and two CRs [86,88] also described an improvement, but other CRs described stabilization [85] or worsening in LVEF [90] (Supplementary Table 11).

In MG publications, there was no change in LVEF with agalsidase beta in two single-arm CT publications [151,156] and nine OS publications [164,166–168,170,171,173,175,179] that included two large studies (40 patients followed for ≥60 months [175]; and 56 patients followed for ≤58 months [171]). One MG OS publication did report a

small but statistically significant increase in ejection fraction [161]. Dose reduction (to 0.3–0.5 mg/kg EOW) was reported not to lead to a change in LVEF in the large OS publication (in 105 patients followed for 8–16 months) [181].

3.4.3.3. Mixed ERT. One mixed-ERT OS reported no change in ejection fraction in 26 male patients [113], whereas one CR showed an increase [122].

In MG populations, the effect on LVEF was described in three OS publications [177,183,185]. Only one of these studies (the large, long-term study of 40 patients followed for 20–71 months) reported a decrease in ejection fraction in patients during the early years of ERT, with no change in ejection fraction later in treatment [183].

3.4.4. Electrocardiogram (ECG) measures

3.4.4.1. Agalsidase alfa 0.2 mg/kg EOW. One placebo-controlled RCT publication in 14 patients followed for 6 months [36] and another placebo-controlled RCT (6 months) with open-label extension (24 months) in seven patients [29] reported a decrease in QRS duration with agalsidase alfa. In a retrospective analysis including 21 males, one patient developed conduction abnormalities during ERT [49] (Supplementary Table 12). One CR described occurrence of persistent atrial fibrillation [59], another noted an increase of QRS voltages with deeply negative T waves after 9 years of treatment [57] and a third showed ST-segment depression and negative T waves [64]. There were no publications describing changes in ECG measures with agalsidase alfa from MG publications.

3.4.4.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one single-arm CT publication reported no change in ECG measures in three patients treated with agalsidase beta 1.0 mg/kg EOW and 12 patients treated with different agalsidase beta dosing regimens, all followed for 2.5 months (reported as a safety parameter in this study) [69]. One large registry OS publication (in 44 patients followed for a median of 36 months) reported a statistically significant increase in P wave duration and PQ interval and a statistically significant decrease in heart rate-corrected QT interval [81]. Another OS of three patients followed for 18 months reported that ECG measures did not change [80] (Supplementary Table 12). In a CR, ECG signs of cardiac hypertrophy were reduced [85].

For MG populations, there were no changes in ECG measures, such as PR and QRS intervals, following agalsidase beta in one relatively large placebo-controlled RCT with an open-label extension (in 58 patients followed for 26 months) [149]), and two OS reports [160,168].

3.4.4.3. Mixed ERT. For mixed ERT, two OS publications reported that ECG measures did not change [113,116].

One large mixed-ERT OS publication (in 40 patients followed for 20–71 months) did not demonstrate statistically significant changes in PQ time or QRS duration in patients in the first years of ERT. However, patients analysed after some years of ERT had increased QRS duration and a trend towards increased PQ time [183].

3.4.5. Exercise testing

3.4.5.1. Agalsidase alfa 0.2 mg/kg EOW. For agalsidase alfa, there were no publications reporting data from clinical or OS publications for male patients. One CR of a male patient demonstrated worsened cardiac symptoms, as indicated by worsening of New York Heart Association (NYHA) functional classification to class 3, after 5 years of treatment with agalsidase alfa [57].

In an MG population, one RCT publication on 44 patients followed for 12 months showed no change in exercise testing with agalsidase alfa 0.2 mg/kg EOW, 0.2 mg/kg weekly, and 0.4 mg/kg weekly [27].

3.4.5.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta there were no publications reporting data for male patients. In MG populations, one single-arm CT publication [156] and one OS publication [159] reported no statistically significant changes in exercise testing. In contrast, two OS publications demonstrated improvements in the bicycle stress test [168,174] and one OS publication demonstrated an improvement in NYHA class [170].

3.4.5.3. Agalsidase beta 1.0 mg/kg EOW. One mixed-ERT OS publication of an MG population reported no change in exercise testing [184].

3.5. Nervous system outcomes

3.5.1. Sweat function

3.5.1.1. Agalsidase alfa 0.2 mg/kg EOW. One publication describing 30–36 months' follow-up of 26 patients treated during a placebo-controlled RCT reported immediate effects of agalsidase alfa on the ANS [37]. In the short term (24–72 hrs) after a single agalsidase alfa (0.2 mg/kg) infusion, there was a statistically significant temporary improvement in sweat function, which returned to pre-infusion treatment levels after 7 days [37]. One single-arm CT [31] and two OS publications [42,48] (in 4–97 patients followed for 12–48 months) reported improvements in sweat function and two OS publications (in 11–22 patients followed for 24–36 months) reported no change in sweat function [45,52]. Improvements in sweat function were reported in one CR of a male patient for agalsidase alfa [67] (Supplementary Table 13).

In MG publications, one RCT publication reported a non-significant increase in sweat volume with 0.1 mg/kg weekly and 0.2 mg/kg weekly compared with 0.2 mg/kg EOW agalsidase alfa [135]. In one registry OS publication (in 40 patients followed for 28–150 months), there was no change in sweat function in patients who switched from agalsidase beta to agalsidase alfa [100].

3.5.1.2. Agalsidase beta 1.0 mg/kg EOW. For agalsidase beta, one single-arm CT publication (in 15 patients, of whom three received the approved dose, followed for 2.5 months) [69], and one OS publication (in 22 patients followed for ≤23 months) [77] reported subjective improvements in sweat function (Supplementary Table 13). Improvements in sweat function with agalsidase beta were also reported in three CRs in male patients [85,88,97].

In MG publications, improvements in hypohidrosis were reported in two OS publications: one study in 40 patients followed for ≥60 months [175] and another study in 11 patients followed for 29–58 months [164]. In one OS publication (in 40 patients followed for 28–150 months), there was no change in sweat function between patients switching from regular-dose to reduced-dose agalsidase beta (0.5 mg/kg EOW) [100].

3.5.1.3. Mixed dose. Two CRs in male patients reported improvements in sweat function with mixed ERT [127,129].

3.5.2. PNS nerve sensitivity

3.5.2.1. Agalsidase alfa 0.2 mg/kg EOW. PNS nerve sensitivity with agalsidase alfa was reported in one single-arm CT publications [40] and two open-label extensions of an RCT [37,38]. After 12–18 months follow-up there was a statistically significant reduction in intra-epidermal nerve fibre density (IENFD), and no change in thermal thresholds in 26 patients [38]. When the same 26 patients were followed for 30–36 months, there was a statistically significant reduction in cold and warmth detection thresholds [37]. In a single-arm CT, switching from EOW dosing to weekly dosing of agalsidase alfa 0.2 mg/kg resulted in a worsening of warmth perception, although cold perception did not change (12 patients followed for ≤120 months) [40]. Two single-arm CT publications in the same patients reported no change in neurological examination scores after 12 months [30] and 24 months [31] (Supplementary Table 14). One CR described improvements in heat intolerance with agalsidase alfa [129].

For MG populations, there were two OS publications that reported no change in PNS nerve sensitivity following the switch from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [100,181]: one study measured heat or cold tolerance in 40 patients after 28–150 months [100].

3.5.2.2. Agalsidase beta 1.0 mg/kg EOW. With agalsidase beta, nerve sensitivity was reported to significantly improve in one OS (of 22 patients followed for 18–23 months) [77] (Supplementary Table 14). One CR described improvements in sensory ulnar and sural nerve conduction with agalsidase beta [97].

In MG publications, there was no change in heat/cold tolerance or PNS nerve sensitivity when the agalsidase beta dose was reduced [100,181].

3.5.2.3. Mixed ERT. In a mixed-ERT OS publication, patients experienced an improvement in IENFD (18 patients followed for ≤103 months) [117].

3.5.3. Vestibular/auditory and other CNS outcomes

3.5.3.1. Agalsidase alfa 0.2 mg/kg EOW. Improvements in vestibular/auditory symptoms reported with agalsidase alfa were described in two CT publications: one was a placebo-controlled RCT with an open-label extension in seven patients followed for 24–30 months [28], and the other was a single-arm CT in five male patients followed for 12 months [34]. During the RCT portion, patients receiving placebo experienced a greater decline in hearing compared with the treated group, but the difference between groups was not statistically significant [28]. During the open-label portion, the placebo patients crossed over to agalsidase alfa and all patients experienced an improvement in hearing [28]. One OS publication reported stabilization of hearing in 11 patients followed for 25–73 months [53] (Supplementary Table 15). Neurological examination findings did not change with agalsidase alfa in one single-arm CT publication (in seven patients followed for 12 months) [30]. Two publications from the same placebo-controlled RCT in 14 patients followed for 6 months reported changes in cerebral blood flow with agalsidase alfa and placebo [32,33]. In both publications, cerebral blood flow decreased with agalsidase alfa and increased in the placebo group (Supplementary Table 15).

In MG publications, a significant improvement in hearing with agalsidase alfa was reported in one publication describing an RCT and its open-label extension [134] and in one OS publication [145], but no change in auditory function was reported in another publication [138]. One single-arm CT with agalsidase alfa reported no change in neurological examination scores [136].

3.5.3.2. Agalsidase beta 1.0 mg/kg EOW. Hearing loss improved with agalsidase beta in one CR [85] but worsened in another [91]. One OS found that neurological examination scores remained stable in patients who had normal scores at baseline and were followed for 18–23 months while receiving agalsidase beta [77] (Supplementary Table 15).

In a MG population, one OS showed no change in auditory function [160].

3.5.3.3. Mixed ERT. One mixed-ERT OS publication reported a decrease in hearing loss [115], another described an increased risk for tinnitus in those who were ERT antibody-positive [107], and a third reported no significant worsening in hearing acuity [105].

3.5.4. White matter hyperintensities (WMH)

3.5.4.1. Agalsidase alfa 0.2 mg/kg EOW. A CR (41-year-old male) with CNS lesions at baseline (vascular dolichoectasia with punctuated WMH in frontal lobe and basal ganglia) described no change in CNS lesions after 52 months of agalsidase alfa (two different doses: 0.2 mg/kg and 0.4 mg/kg) [63]. In a MG population, one single-arm CT publication (in eight patients followed for 24 months) also reported no change in WMH with agalsidase alfa [136].

3.5.4.2. Agalsidase beta 1.0 mg/kg EOW. In one CR of a male patient receiving agalsidase beta, treatment resulted in disappearance of most WMH [99], but another showed an increase in WMH (with full and lower dose) [84]. One MG OS publication (in 25 patients followed for a median of 27 months) showed that, in younger patients (age < 50 years), WMH remained stable in 44% of patients treated with agalsidase beta compared with 31% of patients receiving placebo [162]. Another MG OS reported no change in existing ischaemic brain lesions and no new brain lesions (in six patients followed for ≥120 months) [165].

3.5.4.3. Mixed ERT. One OS publication (in 27 patients followed for 66 months) [112] and one case study [84] described the development of WMH with mixed ERT. One OS investigated WMH and other brain pathology using positron emission tomography and MRI over 9 years in patients who received mixed ERT (agalsidase beta 1.0 mg/kg EOW who were switched to agalsidase alfa 0.2 mg/kg EOW during the temporary shortage). Of 32 patients, only six received a scan before and after start of treatment and only four patients showed progression of pathology during treatment [123].

3.5.5. Stroke/transient ischaemic attack (TIA)

Long-term and large-scale trials would be required to show any influence of ERT on stroke and/or TIA. However, these are difficult to perform in Fabry patients. Currently, the only publications available report on the number of patients with stroke/TIA, but none of them compares the number of strokes and/or TIAs per patient per year before and after ERT (agalsidase alfa: [30,39,50,59,136,137,144,147]; agalsidase beta: [148,150,157,159,163,175]; mixed ERT: [26,108,111,112,114,118,120,123,127,128,177,181,186]).

3.6. Pain outcomes

3.6.1.1. Agalsidase alfa 0.2 mg/kg EOW. With agalsidase alfa, improvements in subjectively assessed acroparaesthesiae were reported in one single-arm CT publication (in seven patients followed for 24 months) [31]. In a placebo-controlled RCT, 14 patients treated with agalsidase alfa experienced a decrease in pain and pain-related QoL while data in the 12 patients receiving placebo remained mostly unchanged [36]. Significantly improved pain scores were reported in 14 patients followed for 6 months [36]. The open-label extension study where the same patients were followed for a further 30 months reported no further decline in pain scores [37]. A large registry OS publication (in 345 patients, of whom 51 had Brief Pain Inventory [BPI] data available) followed for ≤36 months) showed improvements in average pain and present pain assessed with the BPI, but no changes in worst pain and last pain [47]. Improvements in neuropathic pain/acroparaesthesiae were seen in one OS publication with agalsidase alfa (in four patients followed for 12 months) [42]. In contrast, three other OS publications did not report statistically significant changes in pain scores (in 11 patients followed for 25–73 months [53], in 172 patients followed for 48 months in a registry study [48], and in five patients followed for ≤12 months [55]) (Supplementary Table 16). Most of the CRs of agalsidase alfa also described improvements in neuropathic pain/acroparaesthesiae or pain scores [58,60–62,64].

One MG RCT publication reported an improvement in 'pain-at-its worst' scores with agalsidase alfa 0.1 mg/kg/week and 0.2 mg/kg/week compared with pre-treatment levels, but no differences in mean pain score [135]. Two large registry OS publications reported reductions in BPI pain scores during ERT (in 181 patients followed for 60 months [144], and in 314 patients followed for a mean of 17 months [137]). One RCT publication reported no change in pain with agalsidase alfa [176], which was also seen in an OS publication in which patients switched from agalsidase beta 1.0 mg/kg EOW to agalsidase

alfa 0.2 mg/kg EOW [177]. One registry OS publication (in 40 patients followed for 28–150 months) reported no change in pain in patients who switched from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [100]. One large OS publication (in 105 patients followed for 8–16 months) reported statistically significant increases in pain attacks when switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [181].

3.6.1.2. Agalsidase beta 1.0 mg/kg EOW. With agalsidase beta, one single-arm CT publication reported a statistically significant improvement in pain scores (in 15 patients across all five dosing regimens followed for 2.5 months) [69], while another single-arm CT publication reported a near-significant reduction in pain intensity (in 13 patients followed for 5 months) [70]. One OS also found that treatment with agalsidase beta for 18 or 23 months significantly reduced the mean total symptom score for neuropathic pain in a group of 22 Fabry disease patients [77]. Pain was also improved in an OS of three patients after 18 months [80] (Supplementary Table 16). Many CRs with agalsidase beta also described reduced neuropathic pain/acroparaesthesiae or improved pain scores [84,85,89,97].

In MG publications with agalsidase beta, improvements in pain scores were reported from a placebo-controlled RCT with open-label extension in 58 patients [149], who were then followed through open-label extension studies for a further 30 months [157] and 54 months [150], and one RCT publication using a reduced dose of 0.2 mg/kg EOW [176]. During the placebo-controlled portion of the RCT, patients in both groups experienced a decline in pain scores due to a possible placebo effect, so the difference between groups was not statistically significant [149]. In one single-arm CT, patients were able to discontinue their use of analgesics [151]. Three OS publications reported decreased pain with agalsidase beta: reduction in neuropathic pain (40 patients followed for ≥60 months) [175], resolution of neuropathic pain [164] and reduction in acroparaesthesiae [168]. No change in pain symptoms was reported for agalsidase beta 1.0 mg/kg EOW, but lowering the dose to 0.3–0.5 mg/kg EOW resulted in an increase in pain crises and pain attacks in the relatively large OS in 105 patients followed for 8–16 months [181]. Another registry OS publication (in 40 patients followed for 28–150 months) reported no change in pain in patients who switched from regular- to reduced-dose agalsidase beta [100].

3.6.1.3. Mixed ERT. One mixed-ERT OS publication observed a greater improvement in pain scores in ERT antibody-negative patients compared with antibody-positive patients [107]. Most of the mixed-ERT CRs described improved pain [119,124,125,127,129]. In one CR, two patients showed an increase in pain scores after switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW, which was reversed when agalsidase beta 1.0 mg/kg EOW was reintroduced [125]. Furthermore, patients receiving agalsidase beta 1.0 mg/kg EOW were able to stop anti-neuropathic treatment or reduce medication, whereas those receiving agalsidase alfa 0.2 mg/kg EOW continued using carbamazepine during the study [125]. An 18-year-old male had acral pain at baseline, which was reduced with agalsidase beta (1.0 mg/kg EOW) but markedly increased when the patient was switched to agalsidase alfa 0.2 mg/kg EOW [130].

One mixed-ERT MG OS publication reported a reduction in acroparaesthesiae [184]. In one OS, there was a statistically significant association between time on mixed ERT and pain interference score, but no significant association with pain severity [103].

3.7. Gastrointestinal (GI) outcomes

3.7.1. Agalsidase alfa 0.2 mg/kg EOW

Improvement in GI outcomes (i.e. abdominal pain, constipation, nausea, and vomiting) with agalsidase alfa was reported in one single-arm CT (five patients followed for 24 months) [31] and two OS publications (in 33 male patients followed for 24 months [46] and in up to 77 male patients followed for on average 48 months in a registry study [48]) (Supplementary Table 17). Most (4 of 5) CRs with agalsidase alfa also observed reduced GI outcomes [59,62,67,190] but one CR described worsening abdominal pain, bloating, postprandial vomiting, and sporadic diarrhoea after 4 years of treatment [65].

One CT publication in an MG population reported a reduction in the number of patients with abdominal pain and/or diarrhoea during treatment with agalsidase alfa [140]. Switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW resulted in an increase in GI pain in two relatively large, mixed-ERT OS publications (in 105 patients followed for 8–16 months [181], and in 89 patients followed for 24 months [177]).

3.7.2. Agalsidase beta 1.0 mg/kg EOW

With agalsidase beta, improvement of GI outcomes (i.e. abdominal pain, diarrhoea, and discontinuation of GI medications) was reported in three CRs [74,85,97].

In MG publications, agalsidase beta resulted in an improvement in GI outcomes in one single-arm CT publication [151] and resolution of abdominal pain in one OS publication [164]. In one relatively large OS, there was no change in GI pain and diarrhoea with regular-dose agalsidase beta, but dose reduction led to increased GI pain (in 89 patients followed for 24 months) [177]. A relatively large, mixed-ERT OS publication reported no changes in GI outcomes (general or pain/diarrhoea) with regular- or reduced-dose agalsidase beta (in 105 patients followed for 8–16 months) [181].

3.7.3. Mixed ERT

Positive effects of ERT on GI outcomes were confirmed in a mixed-ERT OS publication in which diarrhoea was reduced in antibody-negative patients (in 24 patients followed for ≤131 months) [107], and in one CR [127]. Another CR noted that GI discomfort was reduced with agalsidase beta 1.0 mg/kg EOW but increased when the patient was switched to agalsidase alfa 0.2 mg/kg EOW [130].

One mixed-ERT OS publication reported no changes in GI outcomes (general or pain/diarrhoea) after switching from regular- to reduced-dose agalsidase beta or regular-dose agalsidase alfa (in a registry study of 40 patients followed for 28–150 months) [100].

3.8. Quality of life (QoL)

3.8.1. Agalsidase alfa 0.2 mg/kg EOW

One large registry OS publication (in 172 patients, of whom 30–37 had QoL data, followed for on average 48 months) reported non-significant improvements in health scores from the 5-dimension EuroQol questionnaire and EuroQol visual analogue scale with agalsidase alfa [48]. Another relatively large, mixed-ERT registry OS publication reported no change in self-reported energy levels (using the 36-Item Short Form Health Survey [SF-36]) with agalsidase alfa (in 32 patients treated for 12 months with agalsidase alfa) [100]. One mixed-ERT OS publication reported no statistically significant difference in SF-36 scores after a switch from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW [54] (Supplementary Table 18). A CR described an increase in motivation after 12 months with agalsidase alfa [66].

In MG publications, findings varied. In two RCTs, QoL measures did not change with agalsidase alfa 0.2 mg/kg EOW, 0.1 mg/kg weekly, or 0.2 mg/kg weekly [135], or with agalsidase alfa 0.2 mg/kg EOW, 0.2 mg/kg weekly, or 0.4 mg/kg weekly [27], but did increase (measured using the EuroQoL index) with agalsidase alfa 0.2 mg/kg EOW in a large registry OS publication (in 181 patients followed for 60 months) [144]. There was no change in Center for Epidemiologic Studies Depression Scale (CES-D) score upon switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW in one relatively large, mixed-ERT OS publication (in 105 patients followed for 8–16 months) [181].

3.8.2. Agalsidase beta 1.0 mg/kg EOW

For agalsidase beta, two single-arm CT publications reported improvements in general and mental health using the SF-36 (statistically significant in 13 patients followed for 5 months [70]), and improvements in bodily pain, general health, and vitality in the SF-36 (in 15 patients, three of whom received 1.0 mg/kg EOW, followed for 2.5 months [69]) (Supplementary Table 18). One registry OS publication (in 71 patients followed for an average of 81 months) reported a statistically significant improvement in mental and physical health (using the SF-36) after 12 months of agalsidase beta [83]. One mixed-ERT registry OS publication reported a decrease in self-reported energy levels (using the SF-36) when the agalsidase beta dose was reduced to 0.3–0.5 mg/kg EOW (in 32 patients followed for 18–74 months) [100] (Supplementary Table 18). One CR demonstrated the resolution of a diagnosis of depressive disorder after 12 months of agalsidase beta [97], while another CR showed improvements in functional independence (using the Functional Independence Measure) in six patients with agalsidase beta [98].

For MG publications with agalsidase beta 1.0 mg/kg EOW, one placebo-controlled RCT with open-label extension [149] in 58 patients, two open-label extension studies (where the same patients were followed for a further 30–36 months [157] and up to 54 months [150]), and one OS publication [165] described improvements in QoL (using the SF-36). A different OS publication (nine patients followed for 24 months) reported no change [168].

3.8.3. Mixed ERT

One mixed-ERT OS publication reported no statistically significant difference in CES-D scores [117].

In MG populations, a relatively large, mixed-ERT OS publication in 105 patients followed for 8–16 months reported no change in QoL [181]. Another mixed-ERT registry OS publication (in 32 male patients followed for 18–74 months) reported no change in QoL between patients switching from regular- to reduced-dose agalsidase beta and patients switching from regular-dose agalsidase beta to regular-dose agalsidase alfa [100].

3.9. Clinical events

Large, long-term trials are needed to show an effect of ERT on incidence rates of clinical events, such as renal, cardiac, and cerebrovascular events, and death. The majority of papers describing clinical events before or during ERT only report the number of events occurring during the study without a statistical analysis of the data. There were no agalsidase alfa publications describing an ERT effect on clinical events. One placebo-controlled RCT [148], one publication in which patients were treated during an RCT, its open-label extension and then followed through a registry [163], and two large OS publications [78,172] reported an effect of agalsidase beta 1.0 mg/kg EOW on the timing and incidence of severe clinical events. One large CT with 52 patients (including two severely affected females) showed that during 10 years of treatment 81% of patients did not experience any severe clinical event and 94% of patients were still alive at the end of the study [163]. One OS publication described a decrease in incidence rate of severe clinical events after 6 months of treatment, which was sustained during the remaining 4.5 years of the study [172]. Two registry OS publications showed that the risk of a clinical event was significantly lower when treatment was started at a younger age (< 40 years) [78,172], and one placebo-controlled RCT demonstrated a significant 81% risk reduction for life-threatening events compared with placebo when treatment was started before renal deterioration [148].

3.10. Male patients with later-onset phenotypes

Patients with later-onset phenotypes of Fabry disease often present with later-onset symptoms that may be confined to a single-organ system. Although several publications may describe outcomes for a mix of patients, including patients with classic disease, later-onset disease or variants of unknown significance, we identified outcome data specific for adult male patients with later-onset phenotypes of Fabry disease in five mixed-ERT MG OS publications. These studies included three small studies of eight to 35 patients followed for 3–90 months [105,109,115], a relatively large study in 109 patients followed for ≤116 months [103], and one study describing the results from three patients who switched from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW, and 13 patients who received agalsidase alfa 0.2 mg/kg EOW [110]. Findings from these studies are outlined below.

For 18 patients (13 males and five females) with a predominantly cardiac phenotype (IVS4 + 919G > A) who received agalsidase alfa or beta for 6–39 months, echocardiography revealed the reduction or stabilization of LVMi, IVST, and left posterior wall thickness (LPWT) [109]. However, since this mutation affects mRNA splicing, it may not be representative for the late-onset cardiac variant in patients with missense later-onset mutations in the coding *GLA* regions.

In another study of 16 patients with a predominantly cardiac phenotype (IVS4 + 919G > A) who received agalsidase alfa or beta for at least 12 months, LVMi decreased or remained stable [110]. In a relatively large study including 37 male later-onset type patients followed for ≤116 months, ERT (with agalsidase alfa or beta) was reported to reduce LVMi and improve eGFR [103].

No publications containing data for male patients with later-onset phenotypes who received ERT were identified in this analysis for urinary (lyso-) GL-3, kidney or cardiac GL-3, or GL-3 levels in other organs, ECG measures or exercise testing, other ANS, PNS, or CNS outcomes, GI symptoms, or QoL.

4. Discussion

This systematic literature review includes all types of publication with original data, any type of ERT regimen, and all Fabry disease-related outcomes in the population of male Fabry patients over the past 16 years. Spanning 166 publications including 36 CTs, it provides a comprehensive overview of outcomes achieved in male patients with Fabry disease when treated with disease-specific therapy.

Analyzing this volume of evidence was a huge undertaking, adding to the current literature in Fabry disease. First, it provides an overview of all the evidence published exclusively in male patients. Previous systematic literature reviews [197] have pooled data in male and female patients, which may not be appropriate considering the recognized differences in clinical manifestations and disease progression. Secondly, data from the current review in males and two other publications, in females [22] and paediatric patients [23], informed the development of new therapeutic goals for Fabry disease [24]. This therapeutic goals publication outlines what patients should expect to achieve in each organ system, depending on their individual disease status at baseline [24]. The therapeutic goals publication was based on the evidence published in males (current review, total 166 publications including 36 RCTs), in females (total 67 publications including 6 RCTs) and paediatric patients (total 16 publications, including 6 RCTs). As the reader can note, most of the evidence is derived from the current review, in male patients. Finally, the current review provides a comprehensive summary of the effects of ERT on all organ systems. This helps inform clinical decision-making and the management of male Fabry patients.

ERT was the first disease-specific therapy available that changed the natural history of Fabry disease. Data published in adult male patients with Fabry disease demonstrates that the effect of ERT on plasma GL-3 levels, eGFR, and cardiac outcomes is strongest and substantiated by a wide range of publications, showing consistent, dose-dependent reductions in GL-3 accumulation, a reduced decline in eGFR, and improvements in cardiac outcomes (see relevant sections within the current review). Furthermore, ERT may improve nervous system, GI, pain,

and QoL outcomes. In the context of a multisystemic condition, the impact of ERT on all affected organs is important and relevant. Some studies show no change in outcomes over time with ERT. However, considering the fact that Fabry disease is a lifetime progressive debilitating disease associated with a risk of premature mortality, no change in outcomes is an indication of disease stabilization. This indicates that a clinical benefit in preventing disease progression and avoiding deterioration of patients' well-being is seen when no difference in outcomes after ERT compared with baseline is observed.

Patients who started ERT at an earlier age achieved better outcomes [7,82,130,163,174], and, therefore, effective early treatment is needed to prevent or mitigate disease progression [196]. Regarding cardiac function, patients who started agalsidase beta treatment at age < 30 years experienced a statistically significant decline in LVM but those who started ERT at age ≥50 years reported an increase in LVM [7], and patients < 40 years of age at treatment initiation had stable LPWT and IVST over a period of 10 years, whereas patients ≥40 years of age at treatment initiation significantly progressed over time [163]. Likewise, the importance of administering ERT early was demonstrated in patients without fibrosis at baseline. They experienced a statistically significant decline from baseline in LVM and a statistically significant improvement in exercise capacity with ERT, while patients in whom treatment was started when mild or severe fibrosis was already present experienced no effect of ERT [174]. Regarding renal function, initiation of treatment before the development of significant glomerulosclerosis and proteinuria might prevent future renal disease [79,163], which correlates with the reduced slope of eGFR decline that is seen in patients who started ERT early compared with a higher slope of eGFR decline in patients who started ERT later [82]. Furthermore, two recent publications derived from the Fabry Registry demonstrated a statistically significantly lower risk of clinical events in patients who started ERT < 40 years of age compared with those who were older at start of ERT [78,172], and one placebo-controlled RCT showed that ERT initiation before the start of severe organ damage gives a lower risk of the occurrence of clinical events [148]. On a smaller scale, a case series noted that the GL-3 clearance from podocytes was more extensive in the patient who started ERT at 7 years of age compared with the patient who started at 18 years [130].

Consolidated evidence suggests a dose effect. Studies which have included both agalsidase alfa 0.2 mg/kg EOW and agalsidase beta 1.0 mg/kg EOW show more notable reductions of plasma GL-3, plasma lyso-GL-3, and urinary GL-3 with agalsidase beta 1.0 mg/kg EOW [101,102]. A dose increase of agalsidase alfa beyond the approved dose has a positive effect on several outcomes including plasma GL-3 [27,52], urinary GL-3 [52], eGFR [40], proteinuria [52,62,67], and sweat function [135]. In contrast, reducing the agalsidase beta dose or switching from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2 mg/kg EOW, negatively impacts some outcomes. The literature shows that agalsidase beta dose reduction causes worsening of plasma (lyso-) GL-3 plasma [54,72], urinary GL-3 [72], renal GL-3 [72], pain [181], GI symptoms [177], and self-reported energy levels [100]. Furthermore, the switch from agalsidase beta (1.0 mg/kg EOW) to agalsidase alfa (0.2 mg/kg EOW) also had a negative impact on plasma lyso-GL-3 [54], urinary GL-3 [26], renal GL-3 [130], albuminuria [181], pain [125,130], and GI symptoms [130,177,181]. A dose effect is further exemplified by a normalization of plasma GL-3 levels with agalsidase beta 1.0 mg/kg EOW in several studies (Supplementary Table 2) [69,70,72,75,79,102]. The largest head-to-head comparison between agalsidase alfa and agalsidase beta demonstrated that 19.4% of patients on agalsidase alfa and 13.3% of patients on agalsidase beta progressed to a composite clinical endpoint (renal, cardiovascular, or cerebrovascular events, or death) during the 59-month study duration, although differences were not significant due to limited power [114].

The design and limitations of the systematic literature analysis, which was used to identify and extract the data reported in this publication, are described in detail in a separate manuscript [21]. Data reported in patients with later-onset Fabry disease largely reflect the outcomes seen in classic male patients. However, many publications included in our analysis may have described outcomes for a mix of patients with classic disease, later-onset disease or variants of unknown significance, or did not specify whether patients had classic or later-onset disease. Therefore, the inclusion of patients with later-onset phenotypes in clinical studies looking at outcomes related to organs that are not affected in such patients could be a source of error. Our review was limited to ERT and did not include all the emerging treatment approaches for Fabry disease such as migalastat [191–193] and PRX-102 [194]. Furthermore, our analysis did not stratify the renal or cardiac outcomes according to concomitant medications, which may be relevant considering the effect of medications used to treat renal disease (ACEi and/or ARB) on the progression of Fabry nephropathy [195]. Furthermore, the use of antiproteinuric therapy is only reported for about half of the publications that report on albuminuria or proteinuria, which is important for putting results in perspective.

ERT, available since 2001, was the first disease-specific treatment for Fabry patients, providing a clinical benefit to thousands of patients to date with this rare disease. Fabry disease is a multisystemic disease and ERT has an effect on most outcomes and organ systems, resulting in slowing or halting of cardiac and renal disease progression. Evidence, mainly derived from male studies, shows that patients may benefit from treatment that starts early, before major organ damage has developed. Consolidated evidence suggests a dose effect. Together, the data described in male, female, and paediatric patient populations inform clinical practice in order to facilitate individualized treatment, aiming for optimized patient care and improvement in QoL.

Acknowledgements

The authors would like to thank Dr Michael Arad, Prof. Ralf Baron, Dr Alessandro Burlina, Prof. Ulla Feldt-Rasmussen, Dr Derralynn Hughes, Dr Lorenzo Monserrat, Prof. Alberto Ortiz, Dr Camilla Tøndel, Prof Anna Tylki-Szymańska, and Prof. Frank Weidemann for their input and interpretation of the study results as members of the expert panel.

Disclosure

This literature analysis, the development of the publication and the meetings of the international expert panel were sponsored by Sanofi Genzyme. The authors received editorial/writing support in the preparation of this manuscript from Rosalie Gadiot, PhD, and Tom Rouwette, PhD, of Excerpta Medica, which was funded by Sanofi Genzyme. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

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.
- 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.
- Victor V. Fomin has received speaker honoraria and travel support

from Novartis and Sanofi Genzyme.

- 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.
- Ana Jovanovic has received travel support from Amicus Therapeutics, Biomarin, Sanofi Genzyme and Shire; has received speaker and advisory board honoraria from Amicus Therapeutics, Sanofi Genzyme, and Shire.
- Ilkka Kantola has received speaker honoraria and travel support from Sanofi Genzyme and Shire.
- Aleš Linhart is a consultant for Amicus Therapeutics, Sanofi Genzyme, and Shire; has received speaker honoraria and travel support from Sanofi Genzyme and Shire.
- Renzo Mignani has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme.
- Mehdi Namdar has received research support, advisory board attendance and speaker honoraria, and travel support from Sanofi Genzyme; has received research support from Shire HGT.
- Albina Nowak is a consultant for Shire; has received speaker honoraria, travel support and research support from Sanofi Genzyme and Shire.
- João-Paulo Oliveira has received consulting honoraria, and unrestricted research grants and funding for research projects from Sanofi Genzyme; has received speaker honoraria from Sanofi Genzyme and Shire; has received conference and travel support from Amicus Therapeutics, Sanofi Genzyme, and Shire; is a member of the European Advisory Board of the Fabry Registry.
- Maurizio Pieroni has received advisory board honoraria from Amicus Therapeutics and Sanofi Genzyme; has received speaker honoraria from Amicus Therapeutics, Sanofi Genzyme, and Shire.
- Miguel Viana-Baptista has received consulting honoraria, speaker honoraria, conference and travel support, and unrestricted research grants and funding for research projects from Sanofi Genzyme; has received consulting and speaker honoraria from Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer-Bristol Myers-Squibb; has received conference and travel support from Boehringer Ingelheim; is a member of the Global Neurological Fabry Disease Advisory Board.
- 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.
- Marco Spada has received speaker and advisory board honoraria, and travel support from Sanofi Genzyme and Shire.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2019.100454.

References

[1] D.P. Germain, Fabry disease, Orphanet J. Rare Dis. 5 (2010) 30, https://doi.org/10.1186/1750-1172-5-30.

[2] S. Waldek, M. Patel, M. Banikazemi, et al., Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry, Genet. Med. 11 (2009) 790–796, https://doi.org/10.1097/GIM.0b013e3181bb05bb.

[3] C.M. Eng, D.P. Germain, M. Banikazemi, et al., Fabry disease: guidelines for the evaluation and management of multi-organ system involvement, Genet. Med. 8 (2006) 539–548.

[4] D.P. Germain, A new phenotype of Fabry disease with intermediate severity between the classical form and the cardiac variant, Contrib. Nephrol. 136 (2001) 234–240.

[5] D.P. Germain, P. Avan, A. Chassaing, P. Bonfils, Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients, BMC Med. Genet. 3 (2002) 10.

[6] A. Ortiz, B. Cianciaruso, M. Cizmarik, et al., End-stage renal disease in patients with Fabry disease: natural history data from the Fabry Registry, Nephrol. Dial. Transplant. 25 (2010) 769–775, https://doi.org/10.1093/ndt/gfp554.

[7] D.P. Germain, F. Weidemann, A. Abiose, et al., Analysis of left ventricular mass in untreated men and in men treated with agalsidase-β: data from the Fabry Registry, Genet. Med. 15 (2013) 958–965, https://doi.org/10.1038/gim.2013.53.

[8] K. Sims, J. Politei, M. Banikazemi, et al., Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry, Stroke 40 (2009) 788–794, https://doi.org/10.1161/STROKEAHA.108.526293.

[9] W.R. Wilcox, J.P. Oliveira, R.J. Hopkin, et al., Females with Fabry disease frequently have major organ involvement: lessons from the Fabry registry, Mol. Genet. Metab. 93 (2008) 112–128.

[10] R.J. Hopkin, J. Bissler, M. Banikazemi, et al., Characterization of Fabry disease in 352 pediatric patients in the Fabry registry, Pediatr. Res. 64 (2008) 550–555, https://doi.org/10.1203/PDR.0b013e318183f132.

[11] C. Kampmann, A. Linhart, F. Baehner, et al., Onset and progression of the Anderson-Fabry disease related cardiomyopathy, Int. J. Cardiol. 130 (2008) 367–373, https://doi.org/10.1016/j.ijcard.2008.03.007.

[12] M. Namdar, Electrocardiographic changes and arrhythmia in Fabry disease, Front Cardiovasc. Med. 3 (2016) 7, https://doi.org/10.3389/fcvm.2016.00007.

[13] M. Namdar, J. Steffel, M. Vidovic, et al., Electrocardiographic changes in early recognition of Fabry disease, Heart. 97 (2011) 485–490, https://doi.org/10.1136/hrt.2010.211789.

[14] M. Senechal, D.P. Germain, Fabry disease: a functional and anatomical study of cardiac manifestations in 20 hemizygous male patients, Clin. Genet. 63 (2003) 46–52.

[15] C. Wanner, J.P. Oliveira, A. Ortiz, et al., Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry, Clin. J. Am. Soc. Nephrol. 5 (2010) 2220–2228, https://doi.org/10.2215/CJN.04340510.

[16] R.J. Desnick, Enzyme replacement therapy for Fabry disease: lessons from two alpha-galactosidase A orphan products and one FDA approval, Expert. Opin. Biol. Ther. 4 (2004) 1167–1176.

[17] R. Desnick, E. Schuchman, Enzyme replacement therapy for lysosomal diseases: lessons from 20 years of experience and remaining challenges, Annu. Rev. Genomics Hum. Genet. 13 (2012) 307–335, https://doi.org/10.1146/annurev-genom-090711-163739.

[18] R. El Dib, H. Gomaa, R.P. Carvalho, et al., Enzyme replacement therapy for Anderson-Fabry disease, Cochrane Database Syst. Rev. 7 (2016), https://doi.org/10.1002/14651858.CD006663.pub4.

[19] S.M. Rombach, B.E. Smid, G.E. Linthorst, et al., Natural course of Fabry disease and the effectiveness of enzyme replacement therapy: a systematic review and meta-analysis: effectiveness of ERT in different disease stages, J. Inherit. Metab. Dis. 37 (2014) 341–352, https://doi.org/10.1007/s10545-014-9677-8.

[20] T. Alegra, F. Vairo, M.V. de Souza, et al., Enzyme replacement therapy for Fabry disease: a systematic review and meta-analysis, Genet. Mol. Biol. 35 (4 Suppl) (2012) 947–954.

[21] P.M. Elliott, D.P. Germain, M.J. Hilz, et al., Enzyme replacement therapy in Fabry disease – Methodology of a systematic literature review by a European panel of experts, (2019) [submitted].

[22] Germain DP, Arad M, Burlina A, et al., 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 Mol. Genet. Metab., 2018, [accepted].

[23] M. Spada, R. Baron, P.M. Elliott, et al., 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, Mol. Genet. Metab. (2018), https://doi.org/10.1016/j.ymgme.2018.04.007.

[24] C. Wanner, M. Arad, R. Baron, et al., Expert consensus statement on therapeutic goals in Fabry disease, Mol. Genet. Metab. (2018), https://doi.org/10.1016/j.ymgme.2018.06.004.

[25] J.T. Clarke, M.L. West, J. Bultas, R. Schiffmann, The pharmacology of multiple regimens of agalsidase alfa enzyme replacement therapy for Fabry disease, Genet. Med. 9 (2007) 504–509.

[26] O. Goker-Alpan, K. Nedd, S.P. Shankar, et al., Effect and tolerability of agalsidase alfa in patients with Fabry disease who were treatment naïve or formerly treated with agalsidase beta or agalsidase alfa, JIMD Rep. 23 (2015) 7–15, https://doi.org/10.1007/8904_2015_422.

[27] L. Goláň, O. Goker-Alpan, M. Holida, et al., Evaluation of the efficacy and safety of three dosing regimens of agalsidase alfa enzyme replacement therapy in adults with Fabry disease, Drug Des. Devel. Ther. 9 (2015) 3435–3444, https://doi.org/10.2147/DDDT.S80928.

[28] D. Hajioff, Y. Enever, R. Quiney, J. Zuckerman, K. Mackermot, A. Mehta, Hearing loss in Fabry disease: the effect of agalsidase alfa replacement therapy, J. Inherit. Metab. Dis. 26 (2003) 787–794.

[29] D.A. Hughes, P.M. Elliott, J. Shah, et al., Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa, Heart 94 (2008) 153–158.

[30] L. Jardim, L. Vedolin, I.V. Schwartz, et al., CNS involvement in Fabry disease: clinical and imaging studies before and after 12 months of enzyme replacement therapy, J. Inherit. Metab. Dis. 27 (2004) 229–240.

[31] L.B. Jardim, I. Gomes, C.B. Netto, et al., Improvement of sympathetic skin responses under enzyme replacement therapy in Fabry disease, J. Inherit. Metab. Dis. 29 (2006) 653–659.

[32] D.F. Moore, L.T. Scott, M.T. Gladwin, et al., Regional cerebral hyperperfusion and nitric oxide pathway dysregulation in Fabry disease: reversal by enzyme replacement therapy, Circulation 104 (2001) 1506–1512.

[33] D.F. Moore, G. Altarescu, P. Herscovitch, R. Schiffmann, Enzyme replacement reverses abnormal cerebrovascular responses in Fabry disease, BMC Neurol. 2

(2002) 4.
[34] A. Palla, U. Widmer, D. Straumann, Head-impulse testing in Fabry disease–vestibular function in male and female patients, Acta Paediatr. Suppl. 92 (2003) 38–42.
[35] G.M. Pastores, E. Boyd, K. Crandall, A. Whelan, L. Piersall, N. Barnett, Safety and pharmacokinetics of agalsidase alfa in patients with Fabry disease and end-stage renal disease, Nephrol. Dial. Transplant. 22 (2007) 1920–1925.
[36] R. Schiffmann, J.B. Kopp, H.A. Austin 3rdet al., Enzyme replacement therapy in Fabry disease: a randomized controlled trial, JAMA 285 (2001) 2743–2749.
[37] R. Schiffmann, M.K. Floeter, J.M. Dambrosia, et al., Enzyme replacement therapy improves peripheral nerve and sweat function in Fabry disease, Muscle Nerve 28 (2003) 703–710.
[38] R. Schiffmann, P. Hauer, B. Freeman, et al., Enzyme replacement therapy and intraepidermal innervation density in Fabry disease, Muscle Nerve 34 (2006) 53–56.
[39] R. Schiffmann, M. Ries, M. Timmons, J.T. Flaherty, R.O. Brady, Long-term therapy with agalsidase alfa for Fabry disease: safety and effects on renal function in a home infusion setting, Nephrol. Dial. Transplant. 21 (2006) 345–354.
[40] R. Schiffmann, C. Swift, X. Wang, D. Blankenship, M. Ries, A prospective 10-year study of individualized, intensified enzyme replacement therapy in advanced Fabry disease, J. Inherit. Metab. Dis. 38 (2015) 1129–1136, https://doi.org/10.1007/s10545-015-9845-5.
[41] M. Beck, D. Hughes, C. Kampmann, et al., Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: a Fabry Outcome Survey analysis, Mol. Genet. Metab. Rep. 3 (2015) 21–27, https://doi.org/10.1016/j.ymgmr.2015.02.002.
[42] M.R. Bongiorno, G. Pistone, M. Aricò, Fabry disease: enzyme replacement therapy, J. Eur. Acad. Dermatol. Venereol. 17 (2003) 676–679.
[43] S. Feriozzi, A. Schwarting, G. Sunder-Plassmann, et al., Agalsidase alfa slows the decline in renal function in patients with Fabry disease, Am. J. Nephrol. 29 (2009) 353–361, https://doi.org/10.1159/000168482.
[44] S. Feriozzi, J. Torras, M. Cybulla, et al., The effectiveness of long-term agalsidase alfa therapy in the treatment of Fabry nephropathy, Clin. J. Am. Soc. Nephrol. 7 (2012) 60–69, https://doi.org/10.2215/CJN.03130411.
[45] S.N. Gupta, M. Ries, G.J. Murray, et al., Skin-impedance in Fabry disease: a prospective, controlled, non-randomized clinical study, BMC Neurol. 8 (2008) 41, , https://doi.org/10.1186/1471-2377-8-41.
[46] B. Hoffmann, M. Schwarz, A. Mehta, et al., Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy, Clin. Gastroenterol. Hepatol. 5 (2007) 1447–1453.
[47] B. Hoffmann, M. Beck, G. Sunder-Plassmann, et al., Nature and prevalence of pain in Fabry disease and its response to enzyme replacement therapy - a retrospective analysis from the Fabry Outcome Survey, Clin. J. Pain 23 (2007) 535–542.
[48] D.A. Hughes, M.Á. Barba Romero, C.E. Hollak, R. Giugliani, P.B. Deegan, Response of women with Fabry disease to enzyme replacement therapy: comparison with men, using data from FOS–the Fabry Outcome Survey, Mol. Genet. Metab. 103 (2011) 207–214, https://doi.org/10.1016/j.ymgme.2011.03.022.
[49] Kampmann C, Perrin A, Beck M, Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment. Orphanet. J. Rare. Dis. 10 (2015) 125. doi: 10.1186/s13023-015-0338-2. doi: https://doi.org/10.1186/s13023-015-0338-2. [Erratum in: Orphanet. J. Rare. Dis. 11 (2016) 95.]
[50] C.R. Kaneski, D.F. Moore, M. Ries, G.C. Zirzow, R. Schiffmann, Myeloperoxidase predicts risk of vasculopathic events in hemizygous males with Fabry disease, Neurology 67 (2006) 2045–2047, https://doi.org/10.1212/01.wnl.0000247278.88077.09.
[51] H.Y. Lin, Y.H. Huang, H.C. Liao, et al., Clinical observations on enzyme replacement therapy in patients with Fabry disease and the switch from agalsidase beta to agalsidase alfa, J. Chin. Med. Assoc. 77 (2014) 190–197, https://doi.org/10.1016/j.jcma.2013.11.006.
[52] R. Schiffmann, H. Askari, M. Timmons, et al., Weekly enzyme replacement therapy may slow decline of renal function in patients with Fabry disease who are on long-term biweekly dosing, J. Am. Soc. Nephrol. 18 (2007) 1576–1583.
[53] B. Sergi, G. Conti, G. Paludetti, et al., Inner ear involvement in Anderson-Fabry disease: long-term follow-up during enzyme replacement therapy, Acta Otorhinolaryngol. Ital. 30 (2010) 87–93.
[54] B.E. Smid, S.M. Rombach, J.M. Aerts, et al., Consequences of a global enzyme shortage of agalsidase beta in adult Dutch Fabry patients, Orphanet. J. Rare. Dis. 6 (2011) 69, https://doi.org/10.1186/1750-1172-6-69.
[55] P.D. Whitfield, J. Calvin, S. Hogg, et al., Monitoring enzyme replacement therapy in Fabry disease–role of urine globotriaosylceramide, J. Inherit. Metab. Dis. 28 (2005) 21–33.
[56] G. Altarescu, D. Elstein, Fabry disease in an oligosymptomatic male, Isr. Med. Assoc. J. 13 (2011) 191–192.
[57] A. Frustaci, M.A. Russo, C. Chimenti, Paradoxical response to enzyme replacement therapy of fabry disease cardiomyopathy, Circ. Cardiovasc. Imaging. 9 (2016), https://doi.org/10.1161/CIRCIMAGING.116.005078.
[58] J. Ghali, A. Murugasu, T. Day, K. Nicholls, Carpal tunnel syndrome in Fabry disease, JIMD Rep. 2 (2012) 17–23, https://doi.org/10.1007/8904_2011_37.
[59] M. Gomez, L. Molina, M. Cladellas, et al., Phenotype and genotype characterization and twin association in patients with Anderson-Fabry cardiomyopathy, Cardiology 121 (2012) 71–75, https://doi.org/10.1159/000336168.
[60] C. Kampmann, G. Kalkum, M. Beck, C. Whybra, Successful long-term enzyme replacement therapy in a young adult with Fabry disease, Clin. Genet. 83 (2013) 395–396, https://doi.org/10.1111/j.1399-0004.2012.01916.x.
[61] A. Karras, P. De Lentdecker, M. Delahousse, et al., Combined heart and kidney transplantation in a patient with Fabry disease in the enzyme replacement therapy era, Am. J. Transplant. 8 (2008) 1345–1348, https://doi.org/10.1111/j.1600-6143.2008.02245.x.
[62] K. Nicholls, K. Bleasel, G. Becker, Severe infusion reactions to fabry enzyme replacement therapy: rechallenge after tracheostomy, JIMD Rep. 5 (2012) 109–112, https://doi.org/10.1007/8904_2011_106.
[63] C. Paliouras, G. Aperis, F. Lamprianou, G. Ntetskas, K. Roufas, P. Alivanis, Control of proteinuria with increased doses of agalsidase alfa in a patient with Fabry disease with atypical genotype-phenotype expression, Nefrologia. 35 (2015) 578–581, https://doi.org/10.1016/j.nefro.2015.08.001.
[64] M. Pieroni, A. Camporeale, R. Della Bona, et al., Progression of Fabry cardiomyopathy despite enzyme replacement therapy, Circulation 128 (2013) 1687–1688, https://doi.org/10.1161/CIRCULATIONAHA.113.002799.
[65] J. Politei, B.L. Thurberg, E. Wallace, et al., Gastrointestinal involvement in Fabry disease. So important, yet often neglected, Clin. Genet. 89 (2016) 5–9, https://doi.org/10.1111/cge.12673.
[66] Y. Tomizawa, A. Okuzumi, H. Shiotsuki, K. Noda, N. Hattori, Y. Okuma, A Patient with the GLA p.E66Q mutation exhibiting vascular parkinsonism and bilateral pulvinar lesions, Intern. Med. 54 (2015) 2503–2506, https://doi.org/10.2169/internalmedicine.54.4437.
[67] R. Torra, F. Algaba, E. Ars, S. Santin, P. Fernández-Llama, J. Ballarin, Preservation of renal function in a patient with Fabry nephropathy on enzyme replacement therapy, Clin. Nephrol. 69 (2008) 445–449.
[68] T. Yano, H. Oshima, T. Miki, et al., Late gadolinium enhancement image masquerading as hypertrophic cardiomyopathy in Fabry disease receiving enzyme replacement therapy, Int. J. Cardiol. 203 (2016) 136–137, https://doi.org/10.1016/j.ijcard.2015.10.140.
[69] C.M. Eng, M. Banikazemi, R.E. Gordon, et al., A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies, Am. J. Hum. Genet. 68 (2001) 711–722.
[70] Y. Eto, T. Ohashi, Y. Utsunomiya, et al., Enzyme replacement therapy in Japanese Fabry disease patients: the results of a phase 2 bridging study, J. Inherit. Metab. Dis. 28 (2005) 575–583.
[71] O. Goker-Alpan, M.J. Gambello, G.H. Maegawa, et al., Reduction of plasma globotriaosylsphingosine levels after switching from agalsidase alfa to agalsidase beta as enzyme replacement therapy for Fabry disease, JIMD Rep. 25 (2016) 95–106.
[72] J.C. Lubanda, E. Anijalg, V. Bzdúch, B.L. Thurberg, B. Bénichou, A. Tylki-Szymanska, Evaluation of a low dose, after a standard therapeutic dose, of agalsidase beta during enzyme replacement therapy in patients with Fabry disease, Genet. Med. 11 (2009) 256–264, https://doi.org/10.1097/GIM.0b013e3181981d82.
[73] B. Najafian, C. Tøndel, E. Svarstad, A. Sokolovkiy, K. Smith, M. Mauer, One Year of enzyme replacement therapy reduces globotriaosylceramide inclusions in podocytes in male adult patients with Fabry disease, PLoS One 11 (2016) e0152812, , https://doi.org/10.1371/journal.pone.0152812.
[74] M. Banikazemi, T. Ullman, R.J. Desnick, Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy, Mol. Genet. Metab. 85 (2005) 255–259.
[75] B. Bénichou, S. Goyal, C. Sung, A.M. Norfleet, F. O'Brien, A retrospective analysis of the potential impact of IgG antibodies to agalsidase beta on efficacy during enzyme replacement therapy for Fabry disease, Mol. Genet. Metab. 96 (2009) 4–12, https://doi.org/10.1016/j.ymgme.2008.10.004.
[76] P.M. Elliott, H. Kindler, J.S. Shah, et al., Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A, Heart 92 (2006) 357–360.
[77] M.J. Hilz, M. Brys, H. Marthol, B. Stemper, M. Dütsch, Enzyme replacement therapy improves function of C-, Adelta, and Abeta-nerve fibers in Fabry neuropathy, Neurology 62 (2004) 1066–1072.
[78] R.J. Hopkin, G. Cabrera, J. Charrow, et al., Risk factors for severe clinical events in male and female patients with Fabry disease treated with agalsidase beta enzyme replacement therapy: data from the Fabry Registry, Mol. Genet. Metab. 119 (2016) 151–159, https://doi.org/10.1016/j.ymgme.2016.06.007.
[79] J.H. Kim, B.H. Lee, J. Hyang Cho, et al., Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes, J. Hum. Genet. 61 (2016) 923–929, https://doi.org/10.1038/jhg.2016.78.
[80] R. Mignani, V. Panichi, A. Giudicissi, et al., Enzyme replacement therapy with agalsidase beta in kidney transplant patients with Fabry disease: a pilot study, Kidney Int. 65 (2004) 1381–1385.
[81] M. Motwani, S. Banypersad, P. Woolfson, S. Waldek, Enzyme replacement therapy improves cardiac features and severity of Fabry disease, Mol. Genet. Metab. 107 (2012) 197–202, https://doi.org/10.1016/j.ymgme.2012.05.011.
[82] D.G. Warnock, A. Ortiz, M. Mauer, et al., Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation, Nephrol. Dial. Transplant. 27 (2012) 1042–1049, https://doi.org/10.1093/ndt/gfr420.
[83] T. Watt, A.P. Burlina, C. Cazzorla, et al., Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: findings from the Fabry Registry, Genet. Med. 12 (2010) 703–712, https://doi.org/10.1097/GIM.0b013e3181f13a4a.
[84] M. Arends, G.E. Linthorst, C.E. Hollak, M. Biegstraaten, Discontinuation of enzyme replacement therapy in Fabry disease in the Dutch cohort, Mol. Genet. Metab. 117 (2016) 194–198, https://doi.org/10.1016/j.ymgme.2015.11.014.
[85] S. Bazan-Socha, T. Miszalski-Jamka, P. Petkow-Dimitrow, J. Musiał, Clinical stability of Fabry disease in 54 months' enzyme replacement therapy–follow-up of the first Polish study [in Polish], Pol. Arch. Med. Wewn. 117 (2007) 260–265.
[86] S. Choi, H. Seo, M. Park, et al., Fabry disease with aortic regurgitation, Ann. Thorac. Surg. 87 (2009) 625–628, https://doi.org/10.1016/j.athoracsur.2008.06.

023.
[87] G. De Schoenmakere, D. Chauveau, J.P. Grünfeld, Enzyme replacement therapy in Anderson-Fabry's disease: beneficial clinical effect on vital organ function, Nephrol. Dial. Transplant. 18 (2003) 33–35.
[88] A.L. Fauchais, S. Prey, B. Ouatara, E. Vidal, A. Sparsa, Angiokeratoma regression in a Fabry disease after treatment with agalsidase-beta: clinical effectiveness marker? J. Eur. Acad. Dermatol. Venereol. 24 (2010) 737–738, https://doi.org/10.1111/j.1468-3083.2009.03455.x.
[89] S. Hirashio, T. Taguchi, T. Naito, et al., Renal histology before and after effective enzyme replacement therapy in a patient with classical Fabry's disease, Clin. Nephrol. 71 (2009) 550–556.
[90] M. Imbriaco, G. Messalli, G. Avitabile, et al., Cardiac magnetic resonance imaging illustrating Anderson-Fabry disease progression, Br. J. Radiol. 83 (2010) e249–e251, https://doi.org/10.1259/bjr/52065763.
[91] C.P. Moura, C. Soares, D. Seixas, M. Ayres-Bastos, J.P. Oliveira, Temporal intradiploic dilative vasculopathy: an additional pathogenic factor for the hearing loss in Fabry disease? JIMD Rep. 7 (2013) 7–12, https://doi.org/10.1007/8904_2012_132.
[92] J.H. Mukdsi, S. Gutiérrez, B. Barrón, et al., A renal variant of Fabry disease: a case with a novel Gal A hemizygote mutation, J. Nephropathol. 1 (2012) 194–197, https://doi.org/10.5812/nephropathol.8123.
[93] R. Schiffmann, A. Rapkiewicz, M. Abu-Asab, et al., Pathological findings in a patient with Fabry disease who died after 2.5 years of enzyme replacement, Virchows Arch. 448 (2006) 337–343.
[94] T. Togawa, T. Kodama, T. Suzuki, et al., Plasma globotriaosylsphingosine as a biomarker of Fabry disease, Mol. Genet. Metab. 100 (2010) 257–261, https://doi.org/10.1016/j.ymgme.2010.03.020.
[95] H. Trimarchi, A. Karl, M.S. Raña, et al., Initially nondiagnosed Fabry's disease when electron microscopy is lacking: the continuing story of focal and segmental glomerulosclerosis, Case Rep. Nephrol. Urol. 3 (2013) 51–57, https://doi.org/10.1159/000351516.
[96] Trimarchi H, Forrester M, Lombi F, et al., Amiloride as an alternate adjuvant antiproteinuric agent in Fabry disease: the potential roles of plasmin and uPAR. Case Rep. Nephrol. 2014 (2014) 854521. doi: https://doi.org/10.1155/2014/854521
[97] D. Tsambaos, E. Chroni, A. Manolis, et al., Enzyme replacement therapy in severe Fabry disease with renal failure: a 1-year follow-up, Acta Derm. Venereol. 84 (2004) 389–392.
[98] K. Tsuboi, Enzyme replacement therapy in patients with Fabry's disease, J. Int. Med. Res. 35 (2007) 574–581.
[99] M. Yamadera, M. Yokoe, G. Beck, et al., Amelioration of white-matter lesions in a patient with Fabry disease, J. Neurol. Sci. 279 (2009) 118–120, https://doi.org/10.1016/j.jns.2008.12.028.
[100] J. Ghali, K. Nicholls, C. Denaro, et al., Effect of reduced agalsidase beta dosage in Fabry patients: the Australian experience, JIMD Rep. 3 (2012) 33–43, https://doi.org/10.1007/8904_2011_44.
[101] S.M. Rombach, J.M. Aerts, B.J. Poorthuis, et al., Long-term effect of antibodies against infused alpha-galactosidase A in Fabry disease on plasma and urinary (lyso)Gb3 reduction and treatment outcome, PLoS One 7 (2012) e47805, , https://doi.org/10.1371/journal.pone.0047805.
[102] M.J. van Breemen, S.M. Rombach, N. Dekker, et al., Reduction of elevated plasma globotriaosylsphingosine in patients with classic Fabry disease following enzyme replacement therapy, Biochim. Biophys. Acta 1812 (2011) 70–76, https://doi.org/10.1016/j.bbadis.2010.09.007.
[103] L.J. Anderson, K.M. Wyatt, W. Henley, et al., Long-term effectiveness of enzyme replacement therapy in Fabry disease: results from the NCS-LSD cohort study, J. Inherit. Metab. Dis. 37 (2014) 969–978, https://doi.org/10.1007/s10545-014-9717-4.
[104] H. Fujii, K. Kono, T. Yamamoto, et al., Effect of enzyme replacement therapy on serum asymmetric dimethylarginine levels, coronary flow reserve and left ventricular hypertrophy in patients with Fabry disease, Clin. Kidney J. 5 (2012) 512–518.
[105] M. Komori, Y. Sakurai, H. Kojima, T. Ohashi, H. Moriyama, Long-term effect of enzyme replacement therapy with Fabry disease, Int. J. Otolaryngol. 2013 (2013) 282487, https://doi.org/10.1007/s10545-014-9717-4.
[106] P. Lavoie, M. Boutin, C. Auray-Blais, Multiplex analysis of novel urinary lyso-Gb3-related biomarkers for Fabry disease by tandem mass spectrometry, Anal. Chem. 85 (2013) 1743–1752, https://doi.org/10.1021/ac303033v.
[107] P. M. Lenders, M. J. Stypmann, C. T. Duning, M. B. Schmitz, C. S.M. Brand, C. E. Brand, Serum-mediated inhibition of enzyme replacement therapy in Fabry disease, J. Am. Soc. Nephrol. 27 (2016) 256–264, https://doi.org/10.1681/ASN.2014121226.
[108] M. Lenders, B. Schmitz, J. Stypmann, et al., Renal function predicts long-term outcome on enzyme replacement therapy in patients with Fabry disease, Nephrol. Dial. Transplant. 32 (2017) 2090–2097, https://doi.org/10.1093/ndt/gfw334.
[109] H.Y. Lin, H.C. Liu, Y.H. Huang, et al., Effects of enzyme replacement therapy for cardiac-type Fabry patients with a Chinese hotspot late-onset Fabry mutation (IVS4 + 919G > A), BMJ Open 3 (2013), https://doi.org/10.1136/bmjopen-2013-003146.
[110] H.C. Liu, H.Y. Lin, C.F. Yang, et al., Globotriaosylsphingosine (lyso-Gb3) might not be a reliable marker for monitoring the long-term therapeutic outcomes of enzyme replacement therapy for late-onset Fabry patients with the Chinese hotspot mutation (IVS4 + 919G > A), Orphanet. J. Rare Dis. 9 (2014) 111, https://doi.org/10.1186/s13023-014-0111-y.
[111] K. Nicholls, Increased arterial stiffness is associated with high cardiovascular mortality in male Fabry patients, J. Inherit. Metab. Dis. 35 (2012) 885–889, https://doi.org/10.1007/s10545-011-9428-z.
[112] S.M. Rombach, B.E. Smid, M.G. Bouwman, G.E. Linthorst, M.G. Dijkgraaf, C.E. Hollak, Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain, Orphanet. J. Rare Dis. 8 (2013) 47, https://doi.org/10.1186/1750-1172-8-47.
[113] C. Schmied, A. Nowak, C. Gruner, et al., The value of ECG parameters as markers of treatment response in Fabry cardiomyopathy, Heart 102 (2016) 1309–1314, https://doi.org/10.1136/heartjnl-2015-308897.
[114] S.M. Sirrs, D.G. Bichet, R. Casey, et al., Outcomes of patients treated through the Canadian Fabry disease initiative, Mol. Genet. Metab. 111 (2014) 499–506, https://doi.org/10.1016/j.ymgme.2014.01.014.
[115] E.B. Suntjens, B.E. Smid, M. Biegstraaten, W.A. Dreschler, C.E. Hollak, G.E. Linthorst, Hearing loss in adult patients with Fabry disease treated with enzyme replacement therapy, J. Inherit. Metab. Dis. 38 (2015) 351–358.
[116] A.S. Talbot, N.T. Lewis, K.M. Nicholls, Cardiovascular outcomes in Fabry disease are linked to severity of chronic kidney disease, Heart 101 (2015) 287–293, https://doi.org/10.1136/heartjnl-2014-306278.
[117] N. Üçeyler, L. He, D. Schönfeld, et al., Small fibers in Fabry disease: baseline and follow-up data under enzyme replacement therapy, J. Peripher. Nerv. Syst. 16 (2011) 1304–1314, https://doi.org/10.1111/j.1529-8027.2011.00365.x.
[118] V. Di Lazzaro, F. Pilato, P. Profice, C. Feliciani, R. Renna, Cerebral hemorrhage in a paucisymptomatic young patient with Fabry disease, J. Stroke Cerebrovasc. Dis. 22 (2013) e254–e255, https://doi.org/10.1016/j.jstrokecerebrovasdis.2012.12.012.
[119] F. Iemolo, F. Pizzo, G. Albeggiani, et al., De novo mutation in a male patient with Fabry disease: a case report, BMC Res. Notes 7 (2014) 11, https://doi.org/10.1186/1756-0500-7-11.
[120] Y. Kikumoto, Y. Kai, H. Morinaga, et al., Fabry disease exhibiting recurrent stroke and persistent inflammation, Intern. Med. 49 (2010) 2247–2252.
[121] J.H. Kim, D.H. Han, M.Y. Park, et al., Fabry disease previously diagnosed as Henoch-Schonlein purpura, Korean J. Intern. Med. 30 (2015) 925–927, https://doi.org/10.3904/kjim.2015.30.6.925.
[122] K. Komamura, M. Higashi, N. Yamada, Improvement of cardiac hypertrophy and ventricular function in a man with Fabry disease by treatment with recombinant alpha-galactosidase A, Heart 90 (2004) 617.
[123] K. Korsholm, U. Feldt-Rasmussen, H. Granqvist, et al., Positron emission tomography and magnetic resonance imaging of the brain in fabry disease: a nationwide, long-time, prospective follow-up, PLoS One 10 (2015) e0143940, https://doi.org/10.1371/journal.pone.0143940.
[124] D. Maixnerová, V. Tesař, R. Ryšavá, et al., The coincidence of IgA nephropathy and Fabry disease, BMC Nephrol. 14 (2013) 6, https://doi.org/10.1186/1471-2369-14-6.
[125] J. Politei, A.B. Schenone, G. Cabrera, R. Heguilen, M. Szlago, Fabry disease and enzyme replacement therapy in classic patients with same mutation: different formulations - different outcome? Clin. Genet. 89 (2016) 88–92, https://doi.org/10.1111/cge.12590.
[126] P. Qian, D. Ross, M. Tchan, N. Sadick, A patient with recurrent disabling atrial fibrillation and Fabry cardiomyopathy successfully treated with single ring pulmonary vein isolation, Int. J. Cardiol. 182 (2015) 375–376, https://doi.org/10.1016/j.ijcard.2015.01.001.
[127] M. Rigoldi, D. Concolino, A. Morrone, et al., Intrafamilial phenotypic variability in four families with Anderson-Fabry disease, Clin. Genet. 86 (2014) 258–263, https://doi.org/10.1111/cge.12261.
[128] J.T. Saarinen, N. Sillanpää, I. Kantola, A male Fabry disease patient treated with intravenous thrombolysis for acute ischemic stroke, J. Clin. Neurosci. 22 (2015) 423–425, https://doi.org/10.1016/j.jocn.2014.07.021.
[129] Y.D. Shen, C.M. Yang, J.S. Huang, Fabry disease manifesting as chronic uveitis–treated with enzyme replacement therapy, Eye (Lond) 21 (2007) 431–432.
[130] R. Skrunes, E. Svarstad, K. Kampevold Larsen, S. Leh, C. Tøndel, Reaccumulation of globotriaosylceramide in podocytes after agalsidase dose reduction in young Fabry patients, Nephrol. Dial. Transplant. 5 (2017) 807–813, https://doi.org/10.1093/ndt/gfw094.
[131] K. Suzuki, N. Miura, W. Kitagawa, et al., Progressive renal failure despite long-term biweekly enzyme replacement therapy in a patient with Fabry disease secondary to a new α-galactosidase mutation of Leu311Arg (L311R), Clin. Exp. Nephrol. 15 (2011) 916–920, https://doi.org/10.1007/s10157-011-0486-1.
[132] C. Tesmoingt, O. Lidove, A. Reberga, et al., Enzyme therapy in Fabry disease: severe adverse events associated with anti-agalsidase cross-reactive IgG antibodies, Br. J. Clin. Pharmacol. 68 (2009) 765–769, https://doi.org/10.1111/j.1365-2125.2009.03501.x.
[133] K. Tsuboi, H. Yamamoto, Clinical course of patients with Fabry disease who were switched from agalsidase-β to agalsidase-α, Genet. Med. 16 (2014) 766–772, https://doi.org/10.1038/gim.2014.28.
[134] Hajioff D, Goodwin S, Quiney R, Zuckerman J, MacDermot KD, Mehta A, Hearing improvement in patients with Fabry disease treated with agalsidase alfa, Acta Paediatr. Suppl. 92 (2003) 28–30.
[135] D.A. Hughes, P.B. Deegan, A. Milligan, et al., A randomised, double-blind, placebo-controlled, crossover study to assess the efficacy and safety of three dosing schedules of agalsidase alfa enzyme replacement therapy for Fabry disease, Mol. Genet. Metab. 109 (2013) 269–275, https://doi.org/10.1016/j.ymgme.2013.04.015.
[136] L.B. Jardim, F. Aesse, L.M. Vedolin, et al., White matter lesions in Fabry disease before and after enzyme replacement therapy: a 2-year follow-up, Arq. Neuropsiquiatr. 64 (2006) 711–717.
[137] M. Beck, R. Ricci, U. Widmer, et al., Fabry disease: overall effects of agalsidase alfa treatment, Eur. J. Clin. Investig. 34 (2004) 838–844.

[138] G. Conti, B. Sergi, Auditory and vestibular findings in Fabry disease: a study of hemizygous males and heterozygous females, Acta Paediatr. Suppl. 92 (2003) 33–37.
[139] M. Cybulla, K.N. Walter, A. Schwarting, et al., Kidney transplantation in patients with Fabry disease, Transpl. Int. 22 (2009) 475–481, https://doi.org/10.1111/j.1432-2277.2008.00824.x.
[140] F. Dehout, D. Roland, S. Treille de Granseigne, B. Guillaume, L. Van Maldergem, Erratum: Relief of gastrointestinal symptoms under enzyme replacement therapy [corrected] in patients with Fabry disease, J. Inherit. Metab. Dis. 27 (2004) 499–505 Erratum in J. Inherit. Metab. Dis. 27 (2004) 620.
[141] F. Dehout, A. Schwarting, M. Beck, et al., Effects of enzyme replacement therapy with agalsidase alfa on glomerular filtration rate in patients with Fabry disease: preliminary data, Acta Paediatr. Suppl. 92 (2003) 14–15.
[142] S. Feriozzi, D.P. Germain, R. Di Vito, A. Legrand, R. Ricci, F. Barbey, Cystatin C as a marker of early changes of renal function in Fabry nephropathy, J. Nephrol. 20 (2007) 437–443.
[143] T.R. Hsu, S.H. Sung, F.P. Chang, et al., Endomyocardial biopsies in patients with left ventricular hypertrophy and a common Chinese later-onset Fabry mutation (IVS4 + 919G > A), Orphanet. J. Rare. Dis. 4 (2014) 96, https://doi.org/10.1186/1750-1172-9-96.
[144] A. Mehta, M. Beck, P. Elliott, et al., Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data, Lancet 374 (2009) 1986–1996, https://doi.org/10.1016/S0140-6736(09)61493-8.
[145] A. Palla, S. Hegemann, U. Widmer, D. Straumann, Vestibular and auditory deficits in Fabry disease and their response to enzyme replacement therapy, J. Neurol. 254 (2007) 1433–1442.
[146] A. Schwarting, F. Dehout, S. Feriozzi, et al., Enzyme replacement therapy and renal function in 201 patients with Fabry disease, Clin. Nephrol. 66 (2006) 77–84.
[147] S. Thofehrn, C. Netto, C. Cecchin, et al., Kidney function and 24-hour proteinuria in patients with Fabry disease during 36 months of agalsidase alfa enzyme replacement therapy: a Brazilian experience, Ren. Fail. 31 (2009) 773–778, https://doi.org/10.3109/08860220903150296.
[148] M. Banikazemi, J. Bultas, S. Waldek, et al., Agalsidase-beta therapy for advanced Fabry disease: a randomized trial, Ann. Intern. Med. 146 (2007) 77–86.
[149] C.M. Eng, N. Guffon, W.R. Wilcox, et al., Safety and efficacy of recombinant human alpha-galactosidase A–replacement therapy in Fabry's disease, N. Engl. J. Med. 345 (2001) 9–16.
[150] D.P. Germain, S. Waldek, M. Banikazemi, et al., Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease, J. Am. Soc. Nephrol. 18 (2007) 1547–1557.
[151] A. Pisani, L. Spinelli, M. Sabbatini, et al., Enzyme replacement therapy in Fabry disease patients undergoing dialysis: effects on quality of life and organ involvement, Am. J. Kidney Dis. 46 (2005) 120–127.
[152] H. Tahir, L.L. Jackson, D.G. Warnock, Antiproteinuric therapy and Fabry nephropathy: sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-β, J. Am. Soc. Nephrol. 18 (2007) 2609–2617.
[153] B.L. Thurberg, H. Rennke, R.B. Colvin, et al., Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy, Kidney Int. 62 (2002) 1933–1946.
[154] B.L. Thurberg, H. Randolph Byers, S.R. Granter, R.G. Phelps, R.E. Gordon, M. O'Callaghan, Monitoring the 3-year efficacy of enzyme replacement therapy in Fabry disease by repeated skin biopsies, J. Invest. Dermatol. 122 (2004) 900–908.
[155] B.L. Thurberg, J.T. Fallon, R. Mitchell, T. Aretz, R.E. Gordon, M.W. O'Callaghan, Cardiac microvascular pathology in Fabry disease: evaluation of endomyocardial biopsies before and after enzyme replacement therapy, Circulation 119 (2009) 2561–2567, https://doi.org/10.1161/CIRCULATIONAHA.108.841494.
[156] F. Weidemann, F. Breunig, M. Beer, et al., Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study, Circulation 108 (2003) 1299–1301.
[157] W.R. Wilcox, M. Banikazemi, N. Guffon, et al., Long-term safety and efficacy of enzyme replacement therapy for Fabry disease, Am. J. Hum. Genet. 75 (2004) 65–74.
[158] M. Beer, F. Weidemann, F. Breunig, et al., Impact of enzyme replacement therapy on cardiac morphology and function and late enhancement in Fabry's cardiomyopathy, Am. J. Cardiol. 97 (2006) 1515–1518.
[159] F. Breunig, F. Weidemann, J. Strotmann, A. Knoll, C. Wanner, Clinical benefit of enzyme replacement therapy in Fabry disease, Kidney Int. 69 (2006) 1216–1221.
[160] J.H. Choi, Y.M. Cho, K.S. Suh, et al., Short-term efficacy of enzyme replacement therapy in Korean patients with Fabry disease, J. Korean Med. Sci. 23 (2008) 243–250, https://doi.org/10.3346/jkms.2008.23.2.243.
[161] C. Collin, M. Briet, T.C. Tran, et al., Long-term changes in arterial structure and function and left ventricular geometry after enzyme replacement therapy in patients affected with Fabry disease, Eur. J. Prev. Cardiol. 19 (2012) 43–54, https://doi.org/10.1177/1741826710391118.
[162] A. Fellgiebel, M. Gartenschläger, K. Wildberger, A. Scheurich, R.J. Desnick, K. Sims, Enzyme replacement therapy stabilized white matter lesion progression in Fabry disease, Cerebrovasc. Dis. 38 (2014) 448–456, https://doi.org/10.1159/000369293.
[163] D.P. Germain, J. Charrow, R.J. Desnick, et al., Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease, J. Med. Genet. 52 (2015) 353–358, https://doi.org/10.1136/jmedgenet-2014-102797.
[164] M. Imbriaco, A. Pisani, L. Spinelli, et al., Effects of enzyme-replacement therapy in patients with Anderson-Fabry disease: a prospective long-term cardiac magnetic resonance imaging study, Heart 95 (2009) 1103–1107.
[165] P. Juan, A. Hernan, S.A. Beatriz, et al., Fabry disease: multidisciplinary evaluation after 10 years of treatment with agalsidase beta, JIMD Rep. 16 (2014) 7–14, https://doi.org/10.1007/8904_2014_310.
[166] R.J. Kalliokoski, I. Kantola, K.K. Kalliokoski, et al., The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease, J. Inherit. Metab. Dis. 29 (2006) 112–118.
[167] S. Koeppe, H. Neubauer, F. Breunig, et al., MR-based analysis of regional cardiac function in relation to cellular integrity in Fabry disease, Int. J. Cardiol. 160 (2012) 53–58, https://doi.org/10.1016/j.ijcard.2011.03.023.
[168] J.W. Koskenvuo, J.J. Hartiala, P. Nuutila, et al., Twenty-four-month alpha-galactosidase A replacement therapy in Fabry disease has only minimal effects on symptoms and cardiovascular parameters, J. Inherit. Metab. Dis. 31 (2008) 432–441, https://doi.org/10.1007/s10545-008-0848-3.
[169] W. Machann, F. Breunig, F. Weidemann, et al., Cardiac energy metabolism is disturbed in Fabry disease and improves with enzyme replacement therapy using recombinant human galactosidase A, Eur. J. Heart Fail. 13 (2011) 278–283, https://doi.org/10.1093/eurjhf/hfq211.
[170] G. Messalli, M. Imbriaco, G. Avitabile, et al., Role of cardiac MRI in evaluating patients with Anderson-Fabry disease: assessing cardiac effects of long-term enzyme replacement therapy, Radiol. Med. 117 (2012) 19–28, https://doi.org/10.1007/s11547-011-0710-9.
[171] M. Niemann, F. Breunig, M. Beer, et al., Tei index in Fabry disease, J. Am. Soc. Echocardiogr. 24 (2011) 1026–1032, https://doi.org/10.1016/j.echo.2011.05.021.
[172] A. Ortiz, A. Abiose, D.G. Bichet, et al., Time to treatment benefit for adult patients with Fabry disease receiving agalsidase β: data from the Fabry Registry, J. Med. Genet. 53 (2016) 495–502, https://doi.org/10.1136/jmedgenet-2015-103486.
[173] L. Spinelli, A. Pisani, M. Sabbatini, et al., Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease, Clin. Genet. 66 (2004) 158–165.
[174] F. Weidemann, M. Niemann, F. Breunig, et al., Long-term effects of enzyme replacement therapy on Fabry cardiomyopathy: evidence for a better outcome with early treatment, Circulation 119 (2009) 524–529, https://doi.org/10.1161/CIRCULATIONAHA.108.794529.
[175] F. Weidemann, M. Niemann, S. Störk, et al., Long-term outcome of enzyme-replacement therapy in advanced Fabry disease: evidence for disease progression towards serious complications, J. Intern. Med. 274 (2013) 331–341, https://doi.org/10.1111/joim.12077.
[176] A.C. Vedder, G.E. Linthorst, G. Houge, et al., Treatment of Fabry disease: outcome of a comparative trial with agalsidase alfa or beta at a dose of 0.2 mg/kg, PLoS One 2 (2007) e598.
[177] M. Lenders, S. Canaan-Kühl, J. Krämer, et al., Patients with Fabry disease after enzyme replacement therapy dose reduction and switch-2-year follow-up, J. Am. Soc. Nephrol. 27 (2016) 952–962, https://doi.org/10.1681/ASN.2015030337.
[178] G.E. Linthorst, C.E. Hollak, W.E. Donker-Koopman, A. Strijland, J.M. Aerts, Enzyme therapy for Fabry disease: neutralizing antibodies toward agalsidase alpha and beta, Kidney Int. 66 (2004) 1589–1595.
[179] A. Pisani, L. Spinelli, B. Visciano, et al., Effects of switching from agalsidase beta to agalsidase alfa in 10 patients with Anderson-Fabry disease, JIMD Rep. 9 (2013) 41–48, https://doi.org/10.1007/8904_2012_177.
[180] A.C. Vedder, F. Breunig, W.E. Donker-Koopman, et al., Treatment of Fabry disease with different dosing regimens of agalsidase: effects on antibody formation and GL-3, Mol. Genet. Metab. 94 (2008) 319–325, https://doi.org/10.1016/j.ymgme.2008.03.003.
[181] F. Weidemann, J. Krämer, T. Duning, et al., Patients with Fabry disease after enzyme replacement therapy dose reduction versus treatment switch, J. Am. Soc. Nephrol. 25 (2014) 837–849, https://doi.org/10.1681/ASN.2013060585.
[182] K.H. Chen, Y. Chien, K.L. Wang, et al., Evaluation of proinflammatory prognostic biomarkers for Fabry cardiomyopathy with enzyme replacement therapy, Can. J. Cardiol. 32 (2016) 1221.e1–1221.e9, https://doi.org/10.1016/j.cjca.2015.10.033.
[183] M.A. Engelen, E. Brand, T.B. Baumeister, et al., Effects of enzyme replacement therapy in adult patients with Fabry disease on cardiac structure and function: a retrospective cohort study of the Fabry Munster Study (FaMuS) data, BMJ Open 2 (2012), https://doi.org/10.1136/bmjopen-2012-000879.
[184] T. Kovacevic-Preradovic, M. Zuber, C.H. Attenhofer Jost, et al., Anderson-Fabry disease: long-term echocardiographic follow-up under enzyme replacement therapy, Eur. J. Echocardiogr. 9 (2008) 729–735, https://doi.org/10.1093/ejechocard/jen129.
[185] J. Krämer, M. Niemann, S. Störk, et al., Relation of burden of myocardial fibrosis to malignant ventricular arrhythmias and outcomes in Fabry disease, Am. J. Cardiol. 114 (2014) 895–900, https://doi.org/10.1016/j.amjcard.2014.06.019.
[186] R. Mignani, S. Feriozzi, A. Pisani, et al., Agalsidase therapy in patients with Fabry disease on renal replacement therapy: a nationwide study in Italy, Nephrol. Dial. Transplant. 23 (2008) 1628–1635.
[187] M. Niemann, F. Breunig, M. Beer, et al., The right ventricle in Fabry disease: natural history and impact of enzyme replacement therapy, Heart 96 (2010) 1915–1919, https://doi.org/10.1136/hrt.2010.204586.
[188] A. Pisani, M. Sabbatini, G. Duro, P. Colomba, E. Riccio, Antiproteinuric effect of add-on paricalcitol in Fabry disease patients: a prospective observational study, Nephrol. Dial. Transplant. 30 (2014) 661–666, https://doi.org/10.1093/ndt/gfu273.
[189] K. Tsuboi, H. Yamamoto, Clinical observation of patients with Fabry disease after switching from agalsidase beta (Fabrazyme) to agalsidase alfa (Replagal), Genet. Med. 14 (2012) 779–786, https://doi.org/10.1038/gim.2012.81.
[190] S. Feriozzi, E.S. Torre, T.V. Ranalli, P. Cardello, A. Morrone, E. Ancarani, A diagnosis of Fabry gastrointestinal disease by chance: a case report, Eur. J. Gastroenterol. Hepatol. 19 (2007) 163–165.

[191] D.P. Germain, J.Q. Fan, Pharmacological chaperone therapy by active-site-specific chaperones in Fabry disease: in vitro and preclinical studies, Int. J. Clin. Pharmacol. Ther. 47 (2009) S111–S117.
[192] D.P. Germain, D.A. Hughes, K. Nicholls, et al., Treatment of Fabry's disease with the pharmacologic chaperone migalastat, N. Engl. J. Med. 375 (2016) 545–555.
[193] D.A. Hughes, K. Nicholls, S.P. Shankar, et al., Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study, J. Med. Genet. 54 (2017) 288–296, https://doi.org/10.1136/jmedgenet-2016-104178.
[194] D. Warnock, D. Hughes, S. Boyd, et al., PRX-102 for treating Fabry disease: immunogenicity and PK results from a phase 1-2 study, Mol. Genet. Metab. 120 (2017) 1–2 (S137–S138).
[195] D.G. Warnock, C.P. Thomas, B. Vujkovac, et al., Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy, J. Med. Genet. 52 (2015) 860–866, https://doi.org/10.1136/jmedgenet-2015-103471.
[196] A. Ortiz, D.P. Germain, R.J. Desnick, et al., Fabry disease revisited: management and treatment recommendations for adult patients, Mol. Genet. Metab. 123 (2018) 416–427.
[197] R. El Dib, H. Gomaa, A. Ortiz, et al., Enzyme replacement therapy for Anderson-Fabry disease: a complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies, PLoS One 12 (2017) e0173358.
[198] G.E. Linthorst, D.P. Germain, C.E. Hollak, et al., Expert opinion on temporary treatment recommendations for Fabry disease during the shortage of enzyme replacement therapy (ERT), Mol. Genet. Metab. 102 (2011) 99–102.

Contents

Supplementary Table 1a Publications describing clinical outcomes with ERT in studies of adult male patients with Fabry disease 2
Supplementary Table 1b Publications describing clinical outcomes with ERT in mixed-gender studies (populations including ≥50% male patients with Fabry disease) .. 13
Supplementary Table 2 Plasma GL-3 outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 22
Supplementary Table 3 Plasma lyso-GL-3 outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 25
Supplementary Table 4 Urinary GL-3 outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 27
Supplementary Table 5 Kidney GL-3 accumulation outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 29
Supplementary Table 6 Cardiac GL-3 accumulation outcomes with approved dose of agalsidase alfa in adult male patients 31
Supplementary Table 7 GL-3 accumulation outcomes in other organs with approved dose of agalsidase beta in adult male patients 32
Supplementary Table 8 Proteinuria outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 33
Supplementary Table 9 Left ventricular hypertrophy outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 35
Supplementary Table 10 Wall thickness outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 38
Supplementary Table 11 Ejection fraction outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 39
Supplementary Table 12 Electrocardiography outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 40
Supplementary Table 13 Sweat function outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 42
Supplementary Table 14 Nerve sensitivity outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 44
Supplementary Table 15 Vestibular/auditory and other central nervous system outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 46
Supplementary Table 16 Pain outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 48
Supplementary Table 17 Gastrointestinal outcomes with approved dose of agalsidase alfa in adult male patients 51
Supplementary Table 18 Quality of life outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients 52

Supplementary Table 1a
Publications describing clinical outcomes with ERT in studies of adult male patients with Fabry disease

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
Agalsidase alfa	Clarke et al. 2007 [25]	Clinical: Grade 1a randomized controlled trial	0.1 mg/kg weekly 0.2 mg/kg EOW 0.2 mg/kg weekly 0.4 mg/kg EOW 0.4 mg/kg weekly	2.5	18	Plasma GL-3
	Goker-Alpan et al. 2015 [26]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	24	15 (naïve) 40 (switch)	Plasma GL-3, plasma lyso-GL-3, urinary GL-3
	Goláň L. et al. 2015 [27]	Clinical: Grade 1a randomized controlled trial	0.2 mg/kg EOW 0.2 mg/kg weekly 0.4 mg/kg weekly	12	26	Plasma GL-3, LVM
	Hajioff et al. 2003 [28]	Clinical: Grade 1a/c	0.2 mg/kg EOW	24–30	7	Hearing loss
	Hughes et al. 2008 [29]	Clinical: Grade 1a/c	0.2 mg/kg EOW	30	7	Plasma GL-3, urinary GL-3, cardiac GL-3, eGFR, LVM, EF, ECG
	Jardim et al. 2004 [30]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	12	7	Neurological examination/CNS, TIA/stroke
	Jardim et al. 2006 [31]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	24	7	Acroparaesthesia, neurological examination, GI outcomes
	Moore et al. 2001 [32]	Clinical: Grade 1a randomized controlled trial	0.2 mg/kg EOW	6	14	Cerebral blood flow
	Moore et al. 2002 [33]	Clinical: Grade 1a randomized controlled trial	ERT NS	6	14	Cerebral blood flow
	Palla et al. 2003 [34]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	12	5	Vestibular function

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Pastores et al. 2007 [35]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	6	22	Plasma GL-3, urinary GL-3, eGFR
	Schiffmann et al. 2001 [36]	Clinical: Grade 1a randomized controlled trial	0.2 mg/kg EOW	5.5	14	Plasma GL-3, urinary GL-3, kidney GL-3, eGFR, proteinuria, ECG, pain
	Schiffmann et al. 2003 [37]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	30–36	26	Sweat function, PNS nerve sensitivity, pain
	Schiffmann et al. 2006 [38]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	12–18	26	eGFR, PNS nerve sensitivity
	Schiffmann et al. 2006 [39]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	48–54	14	Plasma GL-3, urinary GL-3, eGFR, proteinuria, TIA/stroke
	Schiffmann et al. 2015 [40]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg weekly	<120	12	Plasma GL-3, urinary GL-3, eGFR, PNS nerve sensitivity
	Beck et al. 2015 [41]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	60	360	eGFR, LVM
	Bongiorno et al. 2003 [42]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	12	4	Proteinuria, sweat function, pain
	Feriozzi et al. 2009 [43]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	36	115	eGFR, proteinuria
	Feriozzi et al. 2012 [44]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	88.8	134	eGFR, proteinuria

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Gupta et al. 2008 [45]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	36	22	Sweat function
	Hoffmann et al. 2007 [46]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	24	345	GI outcomes
	Hoffmann et al. 2007 [47]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	≤36	345	Pain
	Hughes et al. 2011 [48]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	≥48	172	eGFR, proteinuria, LVM, sweating, pain, GI outcomes, QoL
	Kampmann et al. 2015 [49]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	130 (median)	24	eGFR, proteinuria, LVM, LVWT, EF, ECG
	Kaneski et al. 2006 [50]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	≤55	73	TIA/stroke
	Lin et al. 2014 [51]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	Beta: 0.7–88.6 Alfa: 12–112	9	Plasma lyso-GL-3, eGFR, albuminuria, LVM
	Schiffmann et al. 2007 [52]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW 0.2 mg/kg weekly	24–48	12	Plasma GL-3, urinary GL-3, eGFR, proteinuria, sweat function
	Sergi et al. 2010 [53]	Observational: Grade 2 prospective	0.2 mg/kg EOW	51.5 (25–73)	11	Hearing, pain

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
		observational study				
	Smid et al. 2011 [54]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	64.8 (3–123)	NR	Plasma lyso-GL-3, eGFR, QoL
	Tsuboi et al. 2012 [189]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW (pre-switch: beta 1.0 mg/kg EOW)	12	4	LVM, LVWT
	Whitfield et al. 2005 [55]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	12	6	Urinary GL-3, pain
	Altarescu et al. 2011 [56]	Case: Grade 5 case report	0.2 mg/kg EOW	8	1	Proteinuria
	Feriozzi et al. 2007 [190]	Case: Grade 5 case report	0.2 mg/kg EOW	3	1	GI outcomes
	Frustaci et al. 2016 [57]	Case: Grade 5 case report	0.2 mg/kg EOW	108	1	LVM, LVWT, EF, ECG, cardiac function (NYHA)
	Ghali et al. 2012 [58]	Case: Grade 4 case series	Agalsidase alfa dose NS	NR	3	Pain
	Gomez et al. 2012 [59]	Case: Grade 4 case series	0.2 mg/kg EOW	6–72	4	LVM, ECG, TIA/stroke, GI outcomes
	Kampmann et al. 2013 [60]	Case: Grade 5 case report	ERT NS	144	1	eGFR, LVM, pain
	Karras et al. 2008 [61]	Case: Grade 5 case report	0.2 mg/kg EOW	42	1	LVM, pain
	Nicholls et al. 2012 [62]	Case: Grade 5 case report	0.2 mg/kg EOW	60	1	eGFR, proteinuria, pain, GI outcomes
	Paliouras et al. 2015 [63]	Case: Grade 5 case report	0.2 mg/kg EOW 0.4 mg/kg EOW	52	1	Proteinuria, LVM, WMH
	Pieroni et al. 2013 [64]	Case: Grade 5 case report	0.2 mg/kg EOW	72	1	Proteinuria, LVM, LVWT, ECG, pain

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Politei et al. 2016 [65]	Case: Grade 4 case series	0.2 mg/kg EOW	48	1	Proteinuria, GI outcomes
	Tomizawa et al. 2015 [66]	Case: Grade 5 case report	0.2 mg/kg EOW	12	1	Motivation (QoL)
	Torra et al. 2008 [67]	Case: Grade 5 case report	0.2 mg/kg EOW 0.4 mg/kg EOW	72	1	eGFR, proteinuria, sweat function, GI outcomes
	Yano et al. 2016 [68]	Case: Grade 5 case report	0.2 mg/kg EOW	72	1	LVH
Agalsidase beta	Eng et al. 2001 [69]	Clinical: Grade 1c single-arm clinical trial	0.3 mg/kg EOW 1.0 mg/kg EOW 3.0 mg/kg EOW 1.0 mg/kg every 48 h 3.0 mg/kg every 48 h	2.5	15	Plasma GL-3, renal GL-3, cardiac GL-3, liver GL-3, ECG, sweat function, pain, QoL
	Eto et al. 2005 [70]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	5	13	Plasma GL-3, urinary GL-3, eGFR, pain, QoL
	Goker-Alpan et al. 2016 [71]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	6	15	Plasma GL-3, plasma lyso-GL-3, urinary GL-3
	Lubanda et al. 2009 [72]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW 0.3 mg/kg EOW	Normal dose: 6 Low dose: 18	21	Plasma GL-3, urinary GL-3, renal GL-3, dermal GL-3, eGFR, proteinuria
	Najafian et al. 2016 [73]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	11–12	6	Renal GL-3, eGFR, proteinuria
	Bénichou et al. 2009 [75]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	1.9–60.7	122	Plasma GL-3, dermal GL-3
	Elliott et al. 2006 [76]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW 2.0 mg/kg EOW	10.1 (2.3)	10	Plasma GL-3, LVM, LVWT
	Germain et al. 2013 [7]	Observational: Grade 3	0.9–1.1 mg/kg EOW	58 (22–114)	115	LVM

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
		retrospective observational study				
	Hilz et al. 2004 [77]	Observational: Grade 2 prospective observational study	0.9–1.0 mg/kg EOW	18 or 23	22	Sweat function, PNS nerve sensitivity, neurological findings, pain
	Hopkin et al. 2016 [78]	Observational: Grade 3 retrospective observational study	0.9–1.1 mg/kg EOW	52	969	Clinical events
	Kim et al. 2016 [79]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	60–126	11	eGFR, proteinuria, LVMi
	Mignani et al. 2004 [80]	Observational: Grade 2 prospective observational study	0.9–1.0 mg/kg EOW	18	3	Plasma GL-3, urinary GL-3, proteinuria, LVM, LVWT, EF ECG, pain
	Motwani et al. 2012 [81]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	36 (median)	44	LVM, LVWT, EF, ECG
	Smid et al. 2011 [54]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	64.8 (3–123)	NR	Plasma lyso-GL-3
	Warnock et al. 2012 [82]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	24	151	eGFR
	Watt et al. 2010 [83]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	81 ± 31	71	QoL

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Arends et al. 2016 [84]	Case: Grade 4 case series	1.0 mg/kg EOW and "reduced dose"	192	1	eGFR, LVM, WMH, pain
	Banikazemi et al. 2005 [74]	Observational: Grade 4 Case series	1.0 mg/kg EOW	6–7	4	GI outcomes
	Bazan-Socha et al. 2007 [85]	Case: Grade 4 case series	1.0 mg/kg EOW	54	2	Proteinuria, EF, ECG, sweat function, hearing, pain, GI outcomes
	Choi et al. 2009 [86]	Case: Grade 5 case report	1.0 mg/kg EOW	19	1	Proteinuria, EF
	De Schoenmakere et al. 2003 [87]	Case: Grade 5 case report	1.0 mg/kg EOW	19	1	Proteinuria, LVM, LVWT
	Fauchais et al. 2010 [88]	Case: Grade 5 case report	1.0 mg/kg EOW	12	1	Proteinuria, EF, sweat function
	Hirashio et al. 2009 [89]	Case: Grade 5 case report	1.0 mg/kg EOW	30	1	Renal GL-3, pain
	Imbriaco et al. 2010 [90]	Case: Grade 5 case report	1.0 mg/kg EOW	72	1	LVM, EF
	Moura et al. 2013 [91]	Case: Grade 5 case report	0.8–1.6 mg/kg EOW	30	1	Plasma GL-3, LVM, LVWT, hearing
	Mukdsi et al. 2012 [92]	Case: Grade 5 case report	90 mg EOW	36	1	Proteinuria
	Schiffmann et al. 2006 [93]	Case: Grade 5 case report	1.0 mg/kg EOW	30	1	Vascular endothelial GL-3
	Togawa et al. 2010 [94]	Case: Grade 5 case report[b]	1.0 mg/kg EOW	48	1	Plasma GL-3, plasma lyso-GL-3
	Trimarchi et al. 2013 [95]	Case: Grade 5 case report	1.0 mg/kg EOW	1	1	Proteinuria
	Trimarchi et al. 2014 [96]	Case: Grade 5 case report	Agalsidase beta dose NS	24	1	Proteinuria

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Tsambaos et al. 2004 [97]	Case: Grade 5 case report	1.0 mg/kg EOW	12	1	Sweat gland GL-3, sweat function, PNS nerve sensitivity, pain, GI outcomes, QoL
	Tsuboi et al. 2007 [98]	Case: Grade 4 case series	1.0 mg/kg EOW	NR	5	Plasma GL-3, QoL
	Yamadera et al. 2009 [99]	Case: Grade 5 case report	1.0 mg/kg EOW	12	1	Urinary GL-3, WMH
Agalsidase alfa and agalsidase beta comparison	Ghali et al. 2012 [100]	Observational: Grade 3 retrospective observational study	Alfa: NS Beta: 0.3 mg/kg EOW Beta: 1.0 mg/kg EOW	Regular dose: 73.5 Low-dose: 18	32	Sweat function, PNS nerve sensitivity, pain, GI outcomes, QoL
	Rombach et al. 2012 [101]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2–1.0 mg/kg EOW	>12	29	Plasma GL-3, plasma lyso-GL-3, urinary GL-3, LVM
	van Breemen et al. 2011 [102]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	12	22	Plasma GL-3, plasma lyso-GL-3
Treatment not specified or combination of agalsidase alfa and agalsidase beta (ERT mixed)	Anderson et al. 2014 [103]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	≤116	109	eGFR, proteinuria, LVM
	Fujii et al. 2012 [104]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	12	2	eGFR, LVM
	Komori et al. 2013 [105]	Observational: Grade 2 prospective observational study	ERT NS	46.6 (8–90)	8	Hearing
	Lavoie et al. 2013 [106]	Observational: Grade 3 retrospective	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	30	49	Urinary lyso-GL-3

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
		observational study				
	Lenders et al. 2016 [107]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	ERTi−: 58.7 ± 43.1 ERTi+: 86.2 ± 45.4	24	eGFR, proteinuria, LVM, hearing, pain, GI outcomes
	Lenders et al. 2016 [108]	Observational: Grade 3 retrospective observational study	Alfa: NS Beta: NS	81 ± 24	26	eGFR, TIA/stroke
	Lin et al. 2013 [109]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	17 ± 8.8 (6–39)	19	Plasma lyso-GL-3, eGFR, albuminuria, LVM, LVWT
	Liu et al. 2014 [110]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	13–46	18	Plasma lyso-GL-3, LVM
	Nicholls et al. 2012 [111]	Observational: Grade 2 prospective observational study	NS	≤108	33	TIA/stroke
	Rombach et al. 2013 [112]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 0.2–1.0 mg/kg EOW	66	27	eGFR, LVM, WMH, TIA/stroke
	Schmied et al. 2016 [113]	Observational: Grade 3 retrospective observational study	ERT NS	79.2	25	LVM, LVWT, EF, ECG
	Sirrs et al. 2014 [114]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	Prior ERT: 64 No prior ERT: 59	100	eGFR, LVM, TIA/stroke

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Suntjens et al. 2015 [115]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 0.2–1.0 mg/kg EOW	Classic: 72 Later-onset: 36	35	Hearing
	Talbot et al. 2015 [116]	Observational: Grade 3 retrospective observational study	ERT NS	120	25	eGFR, LVM, ECG
	Üçeyler et al. 2011 [117]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	0.1–103	18	PNS nerve sensitivity, QoL (depression score)
	Arends et al. 2016 [84]	Case: Grade 5 case report[c]	Mixed Alfa: 0.2 mg/kg EOW (1 year) Beta: 1.0 mg/kg EOW (4 years)	132	1	eGFR, LVM, WMH, pain
	Di Lazzaro et al. 2013 [118]	Case: Grade 5 case report	ERT NS	72	1	TIA/stroke
	Iemolo et al. 2014 [119]	Case: Grade 5 case report[c]	ERT NS	NR	1	Pain
	Kikumoto et al. 2010 [120]	Case: Grade 4 case series	ERT NS	72 or 84	2	Plasma GL-3, TIA/stroke
	Kim et al. 2015 [121]	Case: Grade 5 case report	ERT NS	12	1	Proteinuria
	Komamura et al. 2004 [122]	Case: Grade 5 case report	0.2 mg/kg EOW	6	1	LVM, LVWT, EF
	Korsholm et al. 2015 [123]	Case: Grade 4 case series	Switch Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	≤108	12	WMH, TIA/stroke
	Maixnerová et al. 2013 [124]	Case: Grade 5 case report[c]	ERT NS	120	1	LVM, pain
	Politei et al. 2016 [125]	Case: Grade 4 case series	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	34–144	8	eGFR, proteinuria, LVM, pain

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	ERT-treated male patients (n)	Clinical outcomes reported
	Qian et al. 2015 [126]	Case: Grade 5 case report	Alfa: 0.2 mg/kg EOW Beta: 0.2–1.0 mg/kg EOW	>156	1	LVWT
	Rigoldi et al. 2014 [127]	Case: Grade 4 case series	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	60–120	11	LVM, sweat function, TIA/stroke, pain, GI outcomes
	Saarinen et al. 2015 [128]	Case: Grade 5 case report	ERT NS	NR	1	TIA/stroke
	Shen et al. 2007 [129]	Case: Grade 5 case report	Alfa: 10.5 mg EOW Beta: 70 mg EOW	Alfa: 14 Beta: 29	1	Sweat function, heat intolerance, pain
	Skrunes et al. 2017 [130]	Case: Grade 4 case series	ERT mixed (different regimens)	96–120	3	Renal GL-3, eGFR, proteinuria, pain, GI outcomes
	Suzuki et al. 2011 [131]	Case: Grade 5 case report	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	120	1	eGFR
	Tesmoingt et al. 2009 [132]	Case: Grade 5 case report	Alfa: 0.2 mg/kg EOW Beta: 0.5–1.0 mg/kg EOW	Alfa: 32 Beta: 5	1	eGFR
	Tsuboi et al. 2014 [133]	Case: Grade 5 case report[c]	Alfa: 0.2 mg/kg EOW Beta: 0.7–1.0 mg/kg EOW	Beta 1.0 mg/kg, EOW: 27 Beta 0.7 mg/kg, EOW: 10 Alfa 0.2 mg/kg, EOW: 28	1	Plasma GL-3, plasma lyso-GL-3

[a] Duration as reported in the publication. [b] This was a Grade 2 prospective observational study, but data available at baseline and follow-up for only one patient, so classified as a Grade 5 case report. [c] These were Grade 4 case series, but data available at baseline and follow-up for only one patient, so classified as Grade 5 case report.
CNS, central nervous system; ECG, electrocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; ERTi−, enzyme replacement inhibition negative; ERTi+, enzyme replacement inhibition positive; GI, gastrointestinal; GL-3, globotriaosylceramide; LVM, left ventricular mass; LVMi, left ventricular mass index; LVWT, left ventricular wall thickness; lyso-GL-3, globotriaosylsphingosine; NR, not reported; NS, not specified; NYHA, New York Heart Association; PNS, peripheral nervous system; QoL, quality of life; TIA, transient ischaemic attack; WMH, white matter lesions.

Supplementary Table 1b
Publications describing clinical outcomes with ERT in mixed-gender studies (populations including ≥50% male patients with Fabry disease)

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
Agalsidase alfa	Goláň et al. 2015 [27]	Clinical: Grade 1a randomized controlled trial	0.2 mg/kg EOW 0.2 mg/kg weekly 0.4 mg/kg weekly	12	44	59	Plasma GL-3, eGFR, LVM, exercise testing, QoL
	Hajioff et al. 2003 [134]	Clinical: Grade 1a/c	0.2 mg/kg EOW	6–42	25	92	Hearing
	Hughes et al. 2013 [135]	Clinical: Grade 1a randomized controlled trial	0.2 mg/kg EOW 0.1 mg/kg weekly 0.2 mg/kg weekly	3	19	68	Plasma GL-3, urinary GL-3, sweat function, pain, QoL
	Jardim et al. 2006 [136]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	24	8	87	eGFR, proteinuria, neurological examination, WMH, TIA/stroke
	Pastores et al. 2007 [35]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	10.5 (median)	22	91	eGFR
	Beck et al. 2004 [137]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	17 (mean)	314	52	eGFR, LVM, LVWT, TIA/stroke, pain
	Conti et al. 2003 [138]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	NR	14	71	Hearing
	Cybulla et al. 2009 [139]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	42.4 (31.0–56.8)	20	90	eGFR, proteinuria
	Dehout et al. 2004 [140]	Observational: Grade 2 prospective	0.2 mg/kg EOW	6 or 12	11	82	GI outcomes

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
		observational study					
	Dehout et al. 2003 [141]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	12	234	NR	eGFR
	Feriozzi et al. 2007 [142]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	36 or 48	34	71	eGFR, proteinuria
	Hsu et al. 2014 [143]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	8–40	17	77	Cardiac GL-3, LVM
	Mehta et al. 2009 [144]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	60	181	70	eGFR, LVM, TIA/stroke, pain, QoL
	Palla et al. 2007 [145]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	≤60	24	63	Hearing
	Schwarting et al. 2006 [146]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	1–40	201	63	eGFR
	Thofehrn et al. 2009 [147]	Observational: Grade 2 prospective	0.2 mg/kg EOW	12–36	9	78	eGFR, proteinuria, TIA/stroke

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
		observational study					
Agalsidase beta	Banikazemi et al. 2007 [148]	Clinical: Grade 1a randomized controlled trial	1.0 mg/kg EOW	0–35	51	88	TIA/stroke, clinical events
	Eng et al. 2001 [149]	Clinical: Grade 1a/c	1.0 mg/kg EOW	6–11	58	97	Plasma GL-3, renal GL-3, cardiac GL-3, dermal GL-3, eGFR, ECG, pain, QoL
	Germain et al. 2007 [150]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	54	58	97	Renal GL-3, cardiac GL-3, dermal GL-3, eGFR, TIA/stroke, pain, QoL
	Pisani et al. 2005 [151]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	24	9	89	LVM, EF, pain, GI outcomes
	Tahir et al. 2007 [152]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	6–43	11	73	eGFR, proteinuria
	Thurberg et al. 2002 [153]	Clinical: Grade 1a/c	1.0 mg/kg EOW	6–11	58	97	Renal GL-3
	Thurberg et al. 2004 [154]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	30–36	58	97	Dermal GL-3
	Thurberg et al. 2009 [155]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	53 or 59	58	97	Cardiac GL-3
	Weidemann et al. 2003 [156]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	12	16	87	LVWT, EF, exercise testing
	Wilcox et al. 2004 [157]	Clinical: Grade 1c single-arm clinical trial	1.0 mg/kg EOW	30	58	97	Plasma GL-3, dermal GL-3, eGFR, proteinuria, TIA/stroke, pain, QoL
	Beer et al. 2006 [158]	Observational: Grade 2 prospective observational	1.0 mg/kg EOW	12	17	57	LVM

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
		study					
	Breunig et al. 2006 [159]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	12–37	26	77	eGFR, proteinuria, LVM, LVWT, exercise testing, TIA/stroke
	Choi et al. 2008 [160]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	4–27	11	73	Plasma GL-3, urinary GL-3, renal GL-3, proteinuria, LVM, ECG, hearing
	Collin et al. 2012 [161]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	54	30	94	LVM, EF
	Fellgiebel et al. 2014 [162]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	27 (median)	25	93	WMH
	Germain et al. 2015 [163]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	120 (median)	52	96	Plasma GL-3, eGFR, LVWT, TIA/stroke, clinical events
	Imbriaco et al. 2009 [164]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	29–58	11	73	Proteinuria, LVM, LVWT, EF, sweat function, GI outcomes, pain
	Juan et al. 2014 [165]	Observational: Grade 2 prospective	1.0 mg/kg EOW	≥120	6	67	eGFR, proteinuria, albuminuria, LVM, CNS neurological examinations, QoL

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
		observational study					
	Kalliokoski et al. 2006 [166]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	NR	10	70	Plasma GL-3, LVM, LVWT, EF
	Kim et al. 2016 [79]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	60–126	19	79	Plasma GL-3, urinary GL-3
	Koeppe et al. 2012 [167]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	13	25	84	LVM, LVWT, EF
	Koskenvuo et al. 2008 [168]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	24	9	56	Plasma GL-3, EF, ECG, exercise testing, pain, QoL
	Machann et al. 2011 [169]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	14	23	57	LVM
	Messalli et al. 2012 [170]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	48	16	63	LVM, LVWT, EF, cardiac function (NYHA)
	Niemann et al. 2011 [171]	Observational: Grade 2 prospective	1.0 mg/kg EOW	35 ± 23	56	57	LVWT, EF

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
		observational study					
	Ortiz et al. 2016 [172]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	60	1,044	61	Clinical events
	Spinelli et al. 2004 [173]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	12	9	78	LVM, LVWT, EF
	Weidemann et al. 2009 [174]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	36	32	82	LVM, LVWT, EF, exercise testing
	Weidemann et al. 2013 [175]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	≥60	40	78	eGFR, proteinuria, EF, sweat function, TIA/stroke, pain
Agalsidase alfa and agalsidase beta comparison	Vedder et al. 2007 [176]	Clinical: Grade 1a randomized controlled trial	Alfa: 0.2 mg/kg EOW Beta: 0.2 mg/kg EOW	≥12	34	53	Plasma GL-3, urinary GL-3, eGFR, proteinuria, LVM, pain
	Ghali et al. 2012 [100]	Observational: Grade 3 retrospective observational study	Alfa: NR Beta: 0.5 mg/kg EOW Beta: 1.0 mg/kg EOW	28–150	40	82	Sweat function, PNS nerve sensitivity, pain, GI outcomes, QoL
	Lenders et al. 2016 [177]	Observational: Grade 3 retrospective observational	Alfa: 0.2 mg/kg EOW Beta: 0.3–0.5 mg/kg EOW	24	89	63	eGFR, EF, TIA/stroke, pain, GI outcomes

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
		study	Beta: 1.0 mg/kg EOW				
	Linthorst et al. 2004 [178]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	6–12	18	89	Urinary GL-3
	Pisani et al. 2013 [179]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	Beta: ≥48 pre-switch Alfa: 20	10	70	eGFR, proteinuria, LVM, LVWT, EF
	Vedder et al. 2008 [180]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	≥12	52	54	Plasma GL-3, urinary GL-3, eGFR, LVM
	Weidemann et al. 2014 [181]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.3-0.5 mg/kg EOW Beta: 1.0 mg/kg EOW	8–16	105	59	eGFR, albuminuria, LVWT, EF, PNS nerve sensitivity, TIA/stroke, pain, GI outcomes, QoL
Treatment not specified/ combination of agalsidase alfa and agalsidase beta	Goker-Alpan et al. 2015 [26]	Clinical: Grade 1c single-arm clinical trial	Alfa: 0.2 mg/kg EOW (pre-switch: alfa or beta)	24	100	54	eGFR, LVM, TIA/stroke
	Anderson et al. 2014 [103]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	≤116	109	52	LVM, pain, GFR, proteinuria

Treatment	Study, year [reference]	Evidence Grade	Dose	Duration[a] (months)	Total N[b] (ERT-treated)	Percentage male	Clinical outcomes reported
(ERT mixed)	Chen et al. 2016 [182]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	12	25	88	Plasma lyso-GL-3, LVM, LVWT (IVS)
	Engelen et al. 2012 [183]	Observational: Grade 3 retrospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	20–71	40	53	LVM, EF, ECG
	Kovacevic-Preradovic et al. 2008 [184]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	20–55	29	69	LVWT, exercise testing, pain
	Krämer et al. 2014 [185]	Observational: Grade 2 prospective observational study	ERT NS	57.6 ± 28.8	57	52	LVM, LVWT, EF
	Mignani et al. 2008 [186]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	Dialysis: 45.1 (19.8) Transplant: 48.4 (13.2)	34	94	Plasma GL-3, urinary GL-3, proteinuria, LVM, LVWT, TIA/stroke
	Niemann et al. 2010 [187]	Observational: Grade 2 prospective observational study	ERT NS	41 ± 23	57	75	LVWT
	Pisani et al. 2014 [188]	Observational: Grade 2 prospective observational study	Mixed Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	≥12	6	53	eGFR, proteinuria

[a] Duration as reported in the publication. [b] N = number of patients in the ERT-treated mixed-gender population.
CNS, central nervous system; ECG, electrocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; GI, gastrointestinal; GL-3, globotriaosylceramide; IVS, intraventricular septum; LVM, left ventricular mass; LVWT, left ventricular wall thickness; lyso-GL-3, globotriaosylsphingosine; NR, not reported; NS, not specified; NYHA, New York Heart Association; PNS, peripheral nervous system; QoL, quality of life; TIA, transient ischaemic attack; WMH, white matter lesions.

Supplementary Table 2
Plasma GL-3 outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/95% CI)
Alfa	Clarke et al. 2007 [25] (N = 18) *Grade 1a*	18 (100)	2.5	nmol/mL (mean (range) or mean [SD])	9.72 (4.8–4.4) (n = 4)	Significant reduction of about 50%	**↓ (p < 0.001)**
	Goker-Alpan et al. 2015 [26] (N = 132) *Grade 1c* *No detailed information on prior dosing available*	81 (61)	24	nmol/mL (mean ± SE) (normal: 4.55 ± 3.9 (1.96–7.7) in healthy volunteers)	ERT-naïve group: 19.02 ± 3.11 (n = 10) Switch group: 13.36 ± 0.86 (n = 37)	Trend towards reduction from baseline (n = 3) NC (n = 18)	↓ (NR) NC
	Goláň et al. 2015 [27] (N = 44) *Grade 1a*	26 (59)	12	nmol/mL (mean)	7.2 (n = 14)	5.5 (n = 11)	↓ (95% CI −3.36, 0.13)
	Hughes et al. 2008 [29] (N = 7) *Grade 1a/c*	7 (100)	30	nmol/mL (mean ± SE)	NR (n = 7)	Decrease (n = 7)	↓ (NR)
	Pastores et al. 2007 [35] (N = 22) *Grade 1c*	20 (91)	Range: 2.5–15	nmol/mL (mean ± SE)	4.76 ± 0.47 (n = 20)	12 months: 3.40 ± 0.53 (n = 5)	**↓ (0.017)**
	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	nmol/mL (mean ± SE)	12.14 ± 0.907 (n = 14)	5.58 ± 0.536 (n = 14)	↓ (NR)
	Schiffmann et al. 2006 [39] (N = 25) *Grade 1c*	25 (100)	48–54	nmol/mL (mean ± SE)	11.4 ± 0.8 (n = 25)	Month 48: 5.0 ± 0.6 (n = 25)	**↓ (p < 0.001)**
	Schiffmann et al. 2007 [52] (N = 12) *Grade 2*	12 (100)	24–48	nmol/mL	11.8 [3.6] (n = 12)	4.2 [1.6] (n = 11)	**↓ (p < 0.05)**
Beta	Bénichou et al. 2009 [75] (N = 134) *Grade 3*	122 (91)	Range: 1.9–60.7	µg/mL (normal: >7.03 µg/mL)	Above normal (>7.03) in 80% pts (n = 122)	Levels remained normal (normalized by 6–12 months) (n = 122)	↓ (NR) Normalized

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/95% CI)
	Elliott et al. 2006 [76] (N = 5) *Grade 2*	5 (100)	10.1 [2.3]	µg/mL	NR (n = 5)	−5.3 (n = 5)	**↓ (p = 0.04; 95% CI 0.5, 10.1)**
	Eng et al. 2001 [69] (N = 15) *Grade 1c*	15 (100)	5 infusions	ng/µL (normal: <1.2)	17.1 [12.8] (n = 15)	2/3 clearance 1/3 reduction (n = 3)	↓ (NR)
	Eto et al. 2005 [70] (N = 13) *Grade 1c*	13 (100)	4.6	ng/µL	3.9 [2.7] (n = 13)	0.2 [0.8] (n = 13)	**↓ (p < 0.001)**
	Goker-Alpan et al. 2016 [71] (N = 15) *Grade 1c* *Pre-treatment with agalsidase alfa (median treatment duration), years (range): 3.7 (1.6–14)*	15 (100)	6	Absolute change, µg/mL Change, %	NR (n = 15) NR (n = 15)	−0.9 (n = 14) −17.9 (n = 14)	**↓ (p < 0.05)** **↓ (p < 0.05)**
	Lubanda et al. 2009 [72] (N = 21) *Grade 1c*	21 (100)	6[f]	µg/mL (normal: ≤7.0)	12.2 [3.4] (n = 21)	5.9 [1.1] (n = 21)	**↓ (p < 0.001) normalized**
	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	ng/µL	3.16–8.27	1.57–4.94	↓ (NR)
Alfa **Beta**	van Breemen et al. 2011 [102] (N = 43) *Grade 3*	22 (51)	12	µM (normal: <3.18)	Alfa 0.2 Ab+: 7.03 (5.95–8.80) (n = 7) Beta 1.0 Ab+: 6.56 (3.97–8.74) (n = 9)	Alfa 0.2 Ab+: 3.74 (3.07–6.42) (n = 7) Beta 1.0 Ab+: 2.77 (1.34–3.37) (n = 9)	**↓ (p < 0.01) normalized** **↓ (p < 0.01)**

	Study, year [reference] (number of patients[a]) / *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/95% CI)
Alfa	Rombach et al. 2012 [101] (N = 59) *Grade 2*	29 (49) *Ab+ (n = 14)* *Ab− (n = 12)*	≥12	µmol/L (median, range) (normal: 0.45–2.46)	Alfa 0.2 Ab+: 4.7 (4.0–7.1) (n = 4)	Alfa 0.2 Ab+: 3.6 (3.5–4.1) (n = 4)	↓ (NR) Normalized
Beta					Beta 1.0 Ab+: 5.3 (3.1–6.1) (n = 4)	Beta 1.0 Ab+: 2.0 (1.9–2.1) (n = 4)	↓ (NR)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint. [f] 6 months at normal dose (1.0 mg/kg EOW) followed by 18 months on reduced dose (0.3 mg/kg EOW). Details of dose under dose change section.
↓, decrease; ↑, increase; Ab+, antibody-positive; Ab−, antibody-negative; CI, confidence interval; EOW, every other week; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; NC, no change; NR, not reported; NS, not significant; pt, patient; SD, standard deviation; SE, standard error.

Supplementary Table 3
Plasma lyso-GL-3 outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Goker-Alpan et al. 2015 [26] (N = 132) *No detailed information on prior dosing available* *Grade 1c*	81 (61)	24	nM	ERT-naïve: 102.67 ± 19.09 (n = 10) Switch: 57.94 ± 5.11 (n = 37)	Significant reduction from baseline (n = 3) NC (n = 18)	**↓ (NR)** NC (NR)
Beta	Goker-Alpan et al. 2016 [71] (N = 15) *Grade 1c* *Pre-treatment with agalsidase alfa (median treatment duration), years (range): 3.7 (1.6–14)*	15 (100)	6	Absolute change, µg/mL Reduction, %	NR (n = 14) NR (n = 14)	−16.7 (n = 14) 39.5% [23.57] (n = 14)	**↓ (p < 0.001)** **↓ (p < 0.001)**
Alfa	Rombach et al. 2012 [101] (N = 59) *Grade 2*	29 (49)	≥12	nmol/L (normal: 0.3−0.5 in healthy controls)	Alfa 0.2 Ab+: 91 (70–119) (n = 4)	Alfa 0.2 Ab+: 65 (38–80) (n = 4)	↓ (NR)
Beta					Beta 1.0 Ab+: 76 (53–124) (n = 4)	Beta 1.0 Ab+: 17.5 (15–23) (n = 4)	↓ (NR)
Alfa	van Breemen et al. 2011 [102] (N = 43) *Grade 3*	22 (51)	12	nM (normal: <3)	Alfa 0.2 Ab+: 220 (148–250) (n = 7)	Alfa 0.2 Ab+: 118 (52–149) (n = 7)	↓ (NR)
Beta					Beta 1.0 Ab+: 189 (134–397) (n = 9)	Beta 1.0 Ab+: 55 (23–113) (n = 9)	↓ (NR)

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

[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 2, prospective observational study; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease in levels; ↑, increase in levels; Ab+, antibody-positive; ERT, enzyme replacement therapy; lyso-GL-3, globotriaosylsphingosine; NC, no change; NR, not reported; NS, not significant; SD, standard deviation; SE, standard error.

Supplementary Table 4
Urinary GL-3 outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Goker-Alpan et al. 2015 [26] (N = 132) *Grade 1c* *No detailed information on prior dosing available*	81 (61)	24	nmol/mg, creatinine-normalized	ERT-naïve group: 3.78 ± 0.83 (n = 10)	Decrease (n = 3)	↓ (NS)
					Switch group: 2.74 ± 0.51 (n = 36)	Increase (n = 18)	↑ (NS)
	Hughes et al. 2008 [29] (N =7) *Grade 1a*	7 (100)	6	nmol/24 h	NR	Decrease	↓ (NR)
	Pastores et al. 2007 [35] (N = 22) *Grade 1c*	20 (91)	Range: 2.5–15	nmol/g creatinine	≤33 (normal levels) (n = 11)	NC (n = 11)	NC
					117 (n = 1)	46 (n = 1)	↓ (NR)
	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	nmol/g creatinine	2,369 ± 308 (n = 14)	1,683 ± 443 (n = 14)	↓ (NR)
	Schiffmann et al. 2006 [39] (N = 25) *Grade 1c*	25 (100)	48–54	nmol/g creatinine	2,566 ± 299 (n = 25)	Month 36: –59.7% (n = 21)	**↓ (p < 0.001)**
	Schiffmann et al. 2007 [52] (N = 12) *Grade 2*	12 (100)	24–48	nmol/g creatinine	2,839 [1,862] (n = 12)	1,318 [901] (n = 12)	**↓ (p < 0.001)**
	Whitfield et al. 2005 [55] (N = 8) *Grade 2*	6 (75)	12	GL-3/ creatinine ratio, µmol/mmol	Range: 0.01–14.9 (n = 6)	Decrease by 8.7–20.7% (vs baseline) (n = 6)	↓ (NR)
Beta	Eto et al. 2005 [70] (N = 13) *Grade 1c*	13 (100)	4.6	nmol/filter	4,085 [2077] (n = 13)	2,687 [2,514] (n = 13)	↓ (p = 0.2440)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
	Goker-Alpan et al. 2016 [71] (N = 15) *Grade 1c* *Pre-treatment with agalsidase alfa (median (range): 3.7 (1.6-14 years)*	15 (100)	6	µg/mmol (median absolute change)	NR (n = 15)	−11.1 (n = 14)	↓ (NS)
				Median % change	NR (n = 15)	−33.8% (n = 14)	↓ (NS)
	Lubanda et al. 2009 [72] (N = 21) *Grade 1c*	21 (100)	5.5	µg/mg creatinine	221 [152] (n = 21)	109 [120] (n = 21)	**↓ (p < 0.001)**
	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	ng/µL	ND (n = 3)	ND (n = 3)	NC (NR)
Alfa	Rombach et al. 2012 [101] (N = 59) *Grade 2*	29 (49)	≥12	nmol/24 h (normal: 18–90 in healthy controls)	Alfa 0.2 Ab+: 1.786 (1,362–2,778) (n = 4)	Alfa 0.2 Ab+: 2,442 (1,714–2,720) (n = 4)	↓ (NR)
Beta					Beta 1.0 Ab+: 1,790 (669–1,812) (n = 4)	Beta 1.0 Ab+: 824 (212–1,656) (n = 4)	↓ (NR)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 2, prospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; Ab+, antibody-positive; ERT, enzyme replacement therapy; GL-3, globotriaosylsphingosine; h, hours; NC, no change; ND, not determined; NR, not reported; NS, not significant; SD, standard deviation; SE, standard error.

Supplementary Table 5

Kidney GL-3 accumulation outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	nmol/mg of tissue	19.5 ± 1.68 (n = 11)	15.6 ± 1.6 (n = 11)	↓ (NR)
Beta	Lubanda et al. 2009 [72] (N = 21) *Grade 1c*	21 (100)	5.5	% patients with zero scores	Interstitial capillary endothelial cells: 14 (n = 21)	Interstitial capillary endothelial cells: 100 (n = 21)	↑ **(p < 0.001)**
					Glomerular endothelial cells: 26 (n = 19)	Glomerular endothelial cells: 100 (n = 19)	↑ **(p < 0.001)**
					Mesangial cells: 16 (n = 19)	Mesangial cells: 100 (n = 19)	↑ **(p < 0.001)**
					Non-capillary endothelial cells: 14 (n = 21)	Non-capillary endothelial cells: 100 (n = 20)	↑ **(p < 0.001)**
					Interstitial cells: 14 (n = 21)	Interstitial cells: 86 (n = 21)	↑ **(p < 0.001)**
					Distal convoluted tubule and collecting duct cells: 10 (n = 21)	Distal convoluted tubule and collecting duct cells: 52 (n = 21)	↑ **(p = 0.004)**
					Non-capillary smooth muscle cells: 5 (n = 21)	Non-capillary smooth muscle cells: 30 (n = 20)	↑ (p = 0.06)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
					Podocytes: 0 (n = 19)	Podocytes: 0 (n = 19)	NC
Beta	Najafian et al. 2016 [73] (N = 6) *Grade 1c*	6 (100)	11–12	μm^3	Total volume of GL-3 inclusions per podocyte: NR (n = 6)	Total volume of GL-3 inclusions per podocyte: Mean: −73% (n = 6)	**↓ (p = 0.02)**
					Podocyte volume: NR (n = 6)	Podocyte volume: Mean: −63% (n = 6)	**↓ (p = 0.02)**
				ISGFN score	Podocyte GL-3: 4.0 (n = 6)	Podocyte GL-3: n = 3: NC n = 3, median (range): 0.1 (0.1–0.7)	NC/↓ (p = 0.18)
				%	Proportion of podocytes/biopsy without GL-3 inclusions: 0 (0–6.3) (n = 6)	Proportion of podocytes/biopsy without GL-3 inclusions: 12 (5–27) (n = 6)	**↑ (p = 0.008)**

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline; [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; ISGFN, scoring system for podocyte GL-3 inclusions developed by the International Study Group for Fabry Nephropathy; NC, no change; NR, not reported; SD, standard deviation; SE, standard error.

Supplementary Table 6
Cardiac GL-3 accumulation outcomes with approved dose of agalsidase alfa in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
Alfa	Hughes et al. 2008 [29] (N = 7) *Grade 1a*	7 (100)	6	nmol/µg protein	0.71 ± 0.18 (n = 7)	0.58 ± 0.18 (n = 6)	↓ (NS)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. GL-3 scores were based on microscopic evaluation. A 4-point scoring system was used, ranging from 0 (normal), to 3 (severe involvement). Case series, case reports, mixed-ERT publications, paediatric-–adult- mixed publications, and publications with other dose regimens are not included.
[a] Total number of patients included in the study who were treated with ERT. [b] Study grade: Grade 1a, randomized controlled trial. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline; [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease in GL-3 score, i.e. improvement, less accumulation of GL-3; CI, confidence interval; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; NS, not significant; SD, standard deviation; SE, standard error.

Supplementary Table 7

GL-3 accumulation outcomes in other organs with approved dose of agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Beta	Bénichou et al. 2009 [75] (N = 134) *Grade 3*	122 (91)	Range: 1.9–60.7	Number of pts	Zero scores: 2 pts Mild: 2 pts Moderate: 37 pts Severe: 15 pts (n = 56)	Zero scores: 44 pts (at 6 months or after) Mild scores: 12 pts When stratified by antibody titre, the largest proportion of non-zero scores was in the high-titre subgroup (n = 56)	↓ (NR)
	Eng et al. 2001 [69] (N = 15) *Grade 1c*	15 (100)	5 infusions	ng/mg tissue	Skin: 350 [168] (n = 14, all dosing regimens)	Skin: all reduced (n = 3)	↓ (NR)
					Liver: 176–2,410 (n = 3)	Liver: 45–185 (n = 3)	↓ (NR)
				GL-3 accumulation score	Liver sinusoid endothelial cells: 2.4 [0.74] (n = 15, all dosing regimens)	Liver sinusoid endothelial cells: −2.00 [1.00] (n = 3)	↓ (NR)
	Lubanda et al. 2009 [72] (N = 21) *Grade 1c*	21 (100)	5.5	% pts with zero score	Dermal capillary endothelium: 24% (n = 21)	Dermal capillary endothelium: 95% (n = 20)	**↑ (p < 0.001)**

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

[a] Total number of patients included in the study who were treated with ERT. [b] Study grades defined as follows: Grade 1c single-arm clinical trial; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline; [e] Number of male, ERT-treated patients with data for the outcome at endpoint.

↓, decrease; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; NR, not reported; pt, patient; SD, standard deviation; SE, standard error.

Supplementary Table 8

Proteinuria outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patient[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Feriozzi et al. 2009 [43] (N = 165) *Grade 3*	115 (70)	36	mg/24 h	415.4 [417.1] (n = 115)	481.0 [394.1] (n = 115)	NC (p = 0.39)
	Feriozzi et al. 2012 [44] (N = 208) *Grade 3*	134 (64)	60–134	mg/24 h	Total: 590.6 [832.2] (n = 84)	Total: 772.6 [1,190.1] (n = 84)	↑ (p = 0.06)
	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	≥48	mg/24 h Median (10–90th percentile)	333.0 (99.2–2,200.0) (n = 77)	370.0 (100.0–1,700.0) (n = 77)	NC (p = 0.465)
	Kampmann et al. 2015 [49] (N = 45) *Grade 3*	21 (47)	Median 130 (115–150)	mg/24 h	NR (n = 21) Pts with proteinuria: 659.0 [889.0] (n = 10)	112.5 [35.8] (n = 8) Pts with proteinuria: 297.0 [376.7] (n = 10)	NC (NS) **↑ (p = 0.0342)**
	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	g/24 h	5 pts with urinary protein excretion >1 (n = 14)	NR (n = 14)	NC (NR)
	Schiffmann et al. 2006 [39] (N = 25) *Grade 1c*	25 (100)	48–54	mg/24 h	353 (100–7,500) (n = 24)	Median: 543 (n = 20)	↑ (NR)
	Schiffmann et al. 2007 [52] (N = 12) *Grade 2*	12 (100)	24–48	mg/24 h	1,217 [1,246] (n = 12)	1,485 [1,295] (n = 12)	↑ (NR)
Beta	Kim et al. 2016 [79] (N = 19) *Grade 2*	15 (79) *11 adults, 4 paediatric pts*	60–126	mg/day	<0.1 g/day: 87 [11.9] (n = 3) >0.1 g/day: 1,352 [861.1] (n = 6)	<0.1 g/day: 65.7 [40.1] (n = 3) >0.1 g/day: 1,319.7 [1,405.6] (n = 6)	NC (NS) NC (NS)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patient[d])	End-point (number of patients[e])	Overall result (p value)
					During shortage: 1,290 [1,480]	During shortage: 910 [1,100]	NC (p>0.05)
	Lubanda et al. 2009 [72] (N = 21) *Grade 1c*	21 (100)	5.5	g protein/ g creatinine	Median: 0.3 (n = 20)	Median: 0.4 (n = 20)	↑ (NS)
	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	mg/day	ND in 2 pts, 550 in 1 pt (n = 3)	ND (n = 3)	↓ (NR)
	Najafian et al. 2016 [73] (N = 6) *Grade 1c*	6 (100)	11–12	g/g creatinine	Range: 0.10–1.62 (n = 6)	Range: <0.18–0.45 (n = 2)	↓ (NR)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 2, prospective observational study; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT.
[d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; ERT, enzyme replacement therapy; h, hours; NC, no change; ND, not determined; NR, not reported; NS, not significant; pt, patient; SD, standard deviation; SE, standard error.

Supplementary Table 9

Left ventricular hypertrophy outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
Alfa	Beck et al. 2015 [41] (N = 677) *Grade 3*	360 (53)	60	g/m$^{2.7}$/year (mean annualized LVMi slope ± SEM)	NA	Total: 0.33 ± 0.10 (n = 71) LVH at BL: 0.19 ± 0.16 (n = 29) No LVH at BL: 0.47 ± 0.13 (n = 42)	**↑ (95% CI 0.13, 0.53)** NC (95% CI −0.13, 0.50) **↑ (95% CI 0.22, 0.72)**
	Goláň L. et al. 2015 [27] (N = 44) *Grade 1a*	26 (59)	12	LVMi, g/m^2 (echo)	80.1 (n = 14)	87.4 (n = 10)	↑ (95% CI −1.81, 16.21)
	Hughes et al. 2008 [29] (N = 7) *Grade 1a*	7 (100)	6	LVM, g (echo) LVMi, g/m^2 (echo) [normal: 134] LVM, g (MRI) [mean]	NR 176 ± 10 (n = 7) NR	−20.4 ± 27.2 (n = 6) −6.4 (n = 6) −11.5 g (n = 6)	↓ (NR) ↓ (NR) ↓ (NR)
	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	≥48	LVMi, g/m$^{2.7}$ (echo)	54.7 [24.0] (n = 45) LVH at BL: NR (n = 22) Without LVH at BL: NR	52.2 [19.2] (n = 45) LVH at BL: Mean difference: −9.11 (n = 22) Without LVH at BL: Mean difference: 3.82	↓ (p = 0.247) **↓ (p = 0.0115)** ↑ (p = 0.0741)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
					(n = 23)	(n = 23)	
Alfa	Kampmann et al. 2015 [49] (N = 45) *Grade 3*	21 (47)	Median 130 (115–150)	LVMi, g/m$^{2.7}$ (echo)	LVMi <50 (% pts): 71 LVMi ≥50 (% pts): 29 (n = 21)	LVMi <50: NC (n = 15) LVMi ≥50: LS mean: −13.55 (n = 6)	NC (NR) **↓ (p = 0.0061; 95% CI −23.05, −4.06)**
Alfa	Tsuboi et al. 2012 [189] (N = 11) *Pre-treatment with agalsidase beta for a minimum of 24 months* *Grade 2*	4 (36)	12	LVMi, g/m$^{2.7}$ (echo)	53.93 [10.32] (n = 4)	49.75 [11.54] (n = 4)	↓ (p = 0.3750)
Beta	Elliott et al. 2006 [76] (N = 5) *Grade 2*	5 (100)	10.1 [2.3]	LVMi, g/m^{2} (echo)	226. 3 [54.11] (n = 5)	226.7 [39.0] (n = 5)	NC (NS)
Beta	Germain et al. 2013 [7] (N = 163) *Grade 3*	163 (100)	ERT group: 59 [22] (n = 115)	LVM slope, g/year (echo)	ERT (18–29 years): 9.5 ± 2.36 (n = 15) ERT (30–39 years): 8.4 ± 3.55 (n = 17) ERT (40–49 years): 13.4 ± 6.63 (n = 7) ERT (≥50 years): 0.4 ± 9.41 (n = 9)	ERT (18–29 years): −3.6 ± 1.62 (n = 31) ERT (30–39 years): 2.8 ± 2.2 (n = 44) ERT (40–49 years): 3.4 ± 2.87 (n = 23) ERT (≥ 50 years): 7.7 ± 4.48 (n = 17)	**↓ (p < 0.0001)** ↓ (p = 0.1760) ↓ (p = 0.1691) ↑ (p = 0.4843)
Beta	Kim et al. 2016	15 (79)	60–126	LVMi, g/m$^{2.7}$ (echo)	59.7 [26.2]	57 [22.4]	NC (NR)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
	[79] (N = 19) *Grade 2*	*11 adults, 4 paediatric pts*			(n = 11)	(n = 11) Pts with LVH (mean change/year): −2.0 [1.6] (n = 4) Pts without LVH (mean change/year): 0.5 [1.4] (n = 5)	
	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	LVM, g (echo)	403.8–934.6	402.4–832.1	↓ (NR)
	Motwani et al. 2012 [81] (N = 66) *Grade 3*	44 (67)	36	LVMi, g/m^2 (echo)	123 [2] (n = 44)	120 [26] (n = 44)	**↓ ($p < 0.001$)**

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 2, prospective observational study; Grade 3 retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; BL, baseline; CI, confidence interval; echo, echocardiography; ERT, enzyme replacement therapy; LS, least squares; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; NA. not available; NC, no change; NR, not reported; NS, not significant; pt, patient; SD, standard deviation; SE, standard error; SEM, standard error of the mean.

Supplementary Table 10

Wall thickness outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
Alfa	Kampmann et al. 2015 [49] (N = 45) *Grade 3*	21 (47)	Median 130 (115–150)	MWT, mm (echo)	12.3 [2.9] (n = 21)	LS mean change: −1.89 (n = 21)	**↓ (p < 0.0001, 95% CI −2.58, −1.19)**
Alfa	Tsuboi et al. 2012 [189] (N = 11) *Pre-treatment with agalsidase beta for a minimum of 24 months* *Grade 2*	4 (36)	12	LVWT, mm (echo)	13.2 (n = 4)	13.0 (n = 4)	↓ (NR)
Beta	Elliott et al. 2006 [76] (N = 5) *Grade 2*	5 (100)	10.1 [2.3]	Maximum LVWT, mm	NR (n = 5)	0.02 [0.3] (n = 5)	NC (NS)
Beta	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	PWT, cm (echo)	1.19–2.30	1.20–2.20	↑↓ (NR)
Beta	Motwani et al. 2012 [81] (N = 66) *Grade 3*	44 (67)	36	MWT, mm (echo)	15 [7] (n = 44)	14 [5] (n = 44)	**↓ (p < 0.001)**

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[a] Total number of patients included in the study who were treated with ERT. [b] Study grades defined as follows: Grade 2 prospective observational study; Grade 3 retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; CI, confidence interval; echo, echocardiography; ERT, enzyme replacement therapy; LS, least squares; LVWT, left ventricular wall thickness; MWT, maximal wall thickness; NC, no change; NR, not reported; NS, not significant; PWT, posterior wall thickness; SD, standard deviation; SE, standard error.

Supplementary Table 11

Ejection fraction outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Hughes et al. 2008 [29] (N = 7) *Grade 1a*	7 (100)	6	EF, % (echo)	78.7 ± 1.71 (n = 7)	81 ± 2.74 (n = 7)	NC (NR)
	Kampmann et al. 2015 [49] (N = 45) *Grade 3*	21 (47)	Median 130 (115–150)	LVEF, %	69.9 [7.3] (n = 21)	69.8 [7.0] (n = 21)	NC (p = 0.4546)
Beta	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	LVEF, % (echo)	40.0–65.2	54.0–64.0	↑ (NR)
	Motwani et al. 2012 [81] (N = 66) *Grade 3*	44 (67)	36	EF, % (echo)	62 [4] (n = 44)	64 [3] (n = 44)	**↑ (p < 0.001)**

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 2, prospective observational study; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; echo, echocardiography; EF, ejection fraction; ERT, enzyme replacement therapy; LVEF, left ventricular ejection fraction; NC, no change; NR, not reported; SD, standard deviation; SE, standard error.

Supplementary Table 12

Electrocardiography outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Hughes et al. 2008 [29] (N = 7) *Grade 1a*	7 (100)	6	ms (change in QRS duration)	NR (n = 7)	↓ by 12.9 [11.8] (n = 7)	↓ (NR)
	Kampmann et al. 2015 [49] (N = 45) *Grade 3*	21 (47)	Median 130 (115–150)	Conduction abnormalities	NR	One male pt developed conduction abnormalities	↑ (NR)
	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	ms (change in QRS duration, echo)	94.1 ± 4.85 (n = 14)	91.7 ± 2.14 (n = 14)	↓ (NR)
Beta	Eng et al. 2001 [69] (N = 15) *Grade 1c*	15 (100)	5 infusions	NR	NR	NC	NC
	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	PR interval, ms	134–170	143–168	NC (NR)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
	Motwani et al. 2012 [81] (N = 66) *Grade 3*	44 (67)	36	ms	PQ interval: 129 [10] (n = 44)	PQ interval: 142 [12] (n = 44)	↑ **(p < 0.001)**
					P-wave duration: 76 [4] (n = 44)	P-wave duration: 90 [6] (n = 44)	↑ **(p < 0.001)**
					QRS width: 95 [14] (n = 40)	QRS width: 92 [16] (n = 40)	↓ (p = 0.06)
					QTc interval: 421 [19] (n = 40)	QTc interval: 412 [16] (n = 40)	↓ **(p < 0.001)**
				RE score[6]	RE score: 5 (0-11) (n = 44)	RE score: 5.5 (0–11) (n = 44)	NC (p = 0.59)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 2, prospective observational study; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT.
[d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; ECG, electrocardiogram; echo, echocardiography; ERT, enzyme replacement therapy; LVH, left ventricular hypertrophy; NC, no change; NR, not reported; pt, patient; QTc, heart rate-corrected QT interval; RE, Romhilts–Estes (categorizes ECG as no-, probable-, or definite LVH); SD, standard deviation; SE, standard error.

Supplementary Table 13

Sweat function outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Bongiorno et al. 2003 [42] (N = 4) *Grade 2*	4 (100)	12	NR	NR (n = 4)	Improvement in hypohidrosis (n = 4)	↑ (NR)
	Gupta et al. 2008 [45] (N = 49) *Grade 2*	27 (55)	36	Skin moisture	NR	No improvement	NC (NR)
	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	≥48	Pts with hypohidrosis, % Pts with hyperhidrosis, %	45.4 (n = 97) 1.1 (n = 89)	59.8 (n = 97) 2.2 (n = 89)	↑ **(NR)** ↑ **(NR)**
	Jardim et al. 2006 [31] (N = 7) *Grade 1c*	7 (100)	24	Sweating	Score: NR (n = 7)	Improvement (n = 5)	↑ **(NR)**
	Schiffmann et al. 2003 [37] (N = 26) *Grade 1c*	26 (100)	36	µL/mm^2 sweat excretion (normal: 1.05 [0.81])	0.24 [0.33] (n = 17)	24–72 h post-infusion: 0.57 [0.71] (n = 17)	↑ **(p = 0.04)**
	Schiffmann et al. 2007 [52] (N = 12) *Grade 2*	12 (100)	24–48	µL/mm^2	NR (n = 12)	0.29 [0.22] (n = 12)	NR
Beta	Eng et al. 2001 [69] (N = 15) *Grade 1c*	15 (100)	5 infusions	NR	NR	Increased ability to sweat	↑ (NR)
	Hilz et al. 2004 [77] (N = 22) *Grade 2*	22 (100)	18–23	NR	NR (n = 22)	All pts reported subjective improvement in sweating (n = 22)	↑ (NR)

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

[a] Total number of patients included in the study who were treated with ERT. [b] Study grades defined as follows: Grade 1c, single-arm clinical trial; Grade 2, prospective observational study; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.

↓, decrease; ↑, increase; ERT, enzyme replacement therapy; h, hours; NC, no change; NR, not reported; pt, patient; SD, standard deviation; SE, standard error.

Supplementary Table 14

Nerve sensitivity outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
Alfa	Schiffmann et al. 2003 [37] (N = 26) *Grade 1c*	26 (100)	36	Nerve conduction tests	5 pts: focal nerve compression	High individual variability 3 pts : ↑ 40% 3 pts: ↓ 40% Overall, no significant changes observed (n = 25)	NC (NR)
				Sensory tests	Foot: Warm: elevated Cold: elevated Vibration: normal (n = 25)	Foot: Cold sensation: reduction Warm sensation: reduction Vibration: increase (n = 22)	**↓ (p < 0.001)** **↓ (p = 0.006)** **↑ (p = 0.006)**
					Hand: Warm: normal Cold: elevated Vibration: elevated (n = 25)	Hand: Warm: NC Cold: reduction Vibration: NC (n = 25)	NC (NR) ↓ (p = 0.08) NC (NR)
	Jardim et al. 2004 [30] (N = 8) *Grade 1c*	7 (88)	12	Neurological examination PNS score	Mean: 2.37 (n = 8)	Mean: 1.87 (n = 7)	NC (NR)
	Jardim et al. 2006 [31] (N = 7) *Grade 1c*	7 (100)	24	Neurological examination PNS score	Score: NR (n = 7)	NC (n = 5)	NC (NR)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value/ 95% CI)
	Schiffmann et al. 2006 [38] (N = 26) *Grade 1c*	26 (100)	18	fibres/mm (IENFD, thigh)	5.56 [4.12] (n = 14)	3.85 [2.84] (n = 13)	**↓ (p < 0.05, 95% CI −0.2497, −3.106)**
				Thermal threshold (JND units)	Cold sensation: 18.3 [4.3] (n = 14)	Cold sensation: 18.5 [4.6] (n = 13)	NC (NR)
					Warm sensation: 14.1 [2.4] (n = 14)	Warm sensation: 13.7 [3.7] (n = 12)	NC (NR)
Beta	Hilz et al. 2004 [77] (N=22)[f] *Grade 2*	22 (100)	18–23	VDT, JND on the first toe	15.5 [3.5] (n = 22)	14.3 [4.1] (n = 22)	**↓ (p < 0.05)**
				CDT, JND (dorsum of feet)	19.8 [11.1] (n = 22)	19.9 [10.2] (n = 22)	NC (p>0.05)
				HP 0.5, JND (dorsum of feet)	22.3 [6.7] (n = 22)	19.4 [1.3] (n = 22)	**↓ (p < 0.01)**
				HP 5.0, JND (dorsum of feet)	27.3 [5.6] (n = 22)	22.5 [2.3] (n = 22)	**↓ (p < 0.01)**

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[a] Total number of patients included in the study who were treated with ERT. [b] Study grades defined as follows: Grade 1c, single-arm clinical trial; Grade 2, prospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint. [f] Normal values for VDT, JND: 12.75 [2.73] (upper limit: 19.58); CDT, JND: 9.64 [3.57] (upper limit: 18.75); HP 0.5, JND: 17.05 [2.36] (upper limit: 22.95); HP 5.0, JND: 20.52 [1.43] (upper limit: 24.9).
↓, decrease; ↑, increase; CDT, cold-detection threshold; CI, confidence interval; ERT, enzyme replacement therapy; HP, heat-pain; IENFD, intraepidermal nerve fibre density; JND, just noticeable difference; NC, no change; NR, not reported; pt, patient; VDT, vibration detection threshold; SD, standard deviation; SE, standard error.

Supplementary Table 15

Vestibular/auditory and other central nervous system outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Hajioff et al. 2003 [28] (N = 15) *Grade 1a/c*	15 (100)	24–30	dB (high-frequency SNHL)	Overall hearing loss, Median (IQR): 25 (15.0-49.9) (n = 15)	Median: 4.9 (n = 20)	**↑ (p = 0.004 vs BL)**
	Palla et al. 2003 [34] (N = 21) *Grade 1c*	13 (62)	12	Peripheral vestibular function (average gain)	Reduced gain in 85% of pts (n = 13)	Improvement (n = 5)	↑ (NS)
	Moore et al. 2002 [33] (N = 26 pts) *Grade 1a*	26 (100)	6	mL/min/100 g tissue (regional CBF)	Resting CBF: 25.7 [3.8] (n = 26) Visual activation CBF: 29.4 [3.4] (n = 26)	Resting CBF: −2.3 [3.7] (n = 14) Visual activation: −1.75 [2.6] (n = 14)	NR ↓ NR
	Moore et al. 2001 [32] (N = 26) *Grade 1a*	26 (100)	6	mL/min/100 g tissue (resting global CBF)	CBF Fabry group: 42 [4.8] (n = 26)	↓ by 3.48 [4.57] (n = 14)	**↓ (NR)**
	Jardim et al. 2004 [30] (N = 8) *Grade 1c*	7 (88)	12	Neurological examination CNS score	Mean: 2.07 (n = 8)	Mean: 1.8 (n = 7)	NC (NR)
	Sergi et al. 2010 [53] (N = 20) *Grade 2*	11 (55)	51.5 (25–73)	Hearing threshold (dB nHL) HFHL	30.7 37.5 (16)	34.7 36.96 (15.6)	NC (p = 0.5) NC (NR)

Beta	Hilz et al. 2004 [77] (N = 22) *Grade 2*	22 (100)	18–23	Neurological examination	Normal for cranial nerve function, muscle strength, coordination (n = 20) Reduced deep tendon reflexes (n = 2)	No changes reported (n = 22)	NC (NR)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; BL, baseline; CBF, cerebral blood flow; CNS, central nervous system; dB, decibel; ERT, enzyme replacement therapy; HFHL, high-frequency hearing loss; IQR, inter-quartile range; NC, no change; nHL, normalized hearing loss; NR, not reported; NS, not significant; pt, patient; SD, standard deviation; SE, standard error; SNHL, sensorineural hearing loss.

Supplementary Table 16

Pain outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Bongiorno et al. 2003 [42] (N = 4) *Grade 2*	4 (100)	12	NR	NR	Improvement in acroparaesthesia	↓ (NR)
	Hoffmann et al. 2007 [47] (N = 714) *Grade 3*	345 (48)	≤36	Change in BPI score	NR	Pain at its worst: −0.4 (0.4) (n = 51) Pain on average: −0.6 (0.4) (n = 51 Pain at its least: −0.2 (0.3) (n = 51) Present pain: –1.1 (0.5) (n = 51)	NC (NS) **↓ (p < 0.05)** NC (NS) **↓ (p < 0.05)**
	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	>48	BPI score	Pain at its worst: 3.7 [3.0] (n = 46) Pain on average: 2.7 [2.2] (n = 46)	Pain at its worst: 3.5 [3.1] (n = 46) Pain on average: 2.6 [2.4] (n = 46)	NC (p = 0.803) NC (p = 0.762)
	Jardim et al. 2006 [31] (N = 7) *Grade 1c*	7 (100)	24	Acroparaesth-esia	Score: NR (n = 7)	General improvement (n = 5)	↓ (NR)
	Schiffmann et al. 2001 [36] (N = 14) *Grade 1a*	14 (100)	5.5	BPI severity	3.8 ± 0.44 (n = 14)	2.7 ± 0.54 (n = 14)	↓ (NR)

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
				Pain-related QoL	3.2 ± 0.55 (n = 14)	2.1 ± 0.56 (n = 14)	↓ (NR)
Alfa	Schiffmann et al. 2003 [37] (N = 26) *Grade 1c*	26 (100)	36	BPI score	18-month time-point: NR (n = 25)	18-month time-point: ↓ 1.9 [0.53] (n = 25)	**↓ (p = 0.003)**
	Sergi et al. 2010 [53] (N = 20) *Grade 2*	11 (55)	51.5 (25–73)	Pain severity (no. of pts)	Mild: n = 8 Moderate: n = 1 Severe: n = 2	Mild: n = 6 Moderate: n = 3 Severe: n = 2	NR
	Whitfield et al. 2005 [55] (N = 8) *Grade 2*	6 (75)	12	BPI score	Average pain: 0–4 (n = 5) Worst pain last 24 h: 0–7 (n = 5)	Average pain: 0–4 (n = 5) Worst pain last 24 h: 0–4 (n = 5)	NC (NR) ↓ (NR)
Beta	Eng et al. 2001 [69] (N = 15) *Grade 1c*	15 (100)	5 infusions	Short Form McGill Pain	NR	Overall pain: improved (n = 3) Present pain intensity: improved (n = 3)	**↑ (p = 0.03)** **↑ (p = 0.004)**
	Eto et al. 2005 [70] (N = 13) *Grade 1c*	13 (100)	4.6	PPI score	NR (n = 13)	Slight reduction in all median pain scores (n = 13) Reduction in PPI (n = 13)	↓ (NS) ↓ (p = 0.0630)
	Hilz et al. 2004 [77] (N=22) *Grade 2*	22 (100)	18–23	TSS	1.74 [1.97] (n = 22)	Improvement: 0.83 [1.53] (n = 22)	**↓ (p = 0.038)**
	Mignani et al. 2004 [80] (N = 3) *Grade 2*	3 (100)	18	Pain and paraesthesia	Present in 1 pt (n = 3)	Absent in all pts (n = 3)	↓ (NR)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes. Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 2, prospective observational study; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; BPI, Brief Pain Inventory; ERT, enzyme replacement therapy; h, hours; NC, no change; NR, not reported; NS, not significant; PPI, present pain intensity; pt, patient; QoL, quality of life; SD, standard deviation; SE, standard error; TSS, Total Symptom Score.

Supplementary Table 17

Gastrointestinal outcomes with approved dose of agalsidase alfa in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	≥48	Pts, %	Abdominal pain: 61.8 (n = 76) Constipation: 17.2 (n = 64) Diarrhoea: 61.0 (n = 77) Nausea: 34.3 (n = 70) Vomiting: 22.4 (n = 67)	Abdominal pain: 59.2 (n = 76) Constipation: 12.5 (n = 64) Diarrhoea: 62.3 (n = 77) Nausea: 32.9 (n = 70) Vomiting: 20.9 (n = 67)	NR NR NR NR NR
	Jardim et al. 2006 [31] (N = 7) *Grade 1c*	7 (100)	24	# of episodes, diarrhoea	Score: NR (n = 7)	Resolved (n = 5)	↓ (NR)

Data are means [SD] or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[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 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease in symptoms; ERT, enzyme replacement therapy; SD, standard deviation; SE, standard error; NR, not reported; pt, patient.

Supplementary Table 18

Quality of life outcomes with approved doses of agalsidase alfa and agalsidase beta in adult male patients

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
Alfa	Hughes et al. 2011 [48] (N = 250) *Grade 3*	172 (69)	≥48	EQ VAS health score (100 mm)	67.7 [21.7] (n = 30)	71.1 [17.6] (n = 30)	↑ (p = 0.346)
				EQ-5D health score	0.63 [0.3] (n = 37)	0.72 [0.2] (n = 37)	↑ (p = 0.079)
	Ghali et al. 2012 [100] (N = 40) *Grade 3* *Pre-treatment with agalsidase beta (minimum of 12 months)*	32 (80)	12	Self-reported energy levels scored 1–10 using SF-36	8 (range 4–9) (n = 9)	7 (range 5–9) (n = 9)	NC (p = 0.77)
Beta	Eng et al. 2001 [69] (N = 15) *Grade 1c*	15 (100)	5 infusions	SF-36 QoL	NR	Improvements reported for: bodily pain, general health, vitality (n = 3)	↑ (NR)
	Eto et al. 2005 [70] (N = 13) *Grade 1c*	13 (100)	4.6	SF-36 QoL	Role Emotional: NR (n = 13)	Role Emotional: NR (n = 13)	↑ (p = 0.063)
					General Health: NR (n = 13)	General Health: NR (n = 13)	**↑ (p = 0.023)**
					Mental Health: NR (n = 13)	Mental Health: NR (n = 13)	**↑ (p = 0.048)**

	Study, year [reference] (number of patients[a]) *Evidence grade*[b]	Male, n (%)[c]	Duration (months)	Units	Baseline (number of patients[d])	End-point (number of patients[e])	Overall result (p value)
	Watt et al. 2010 [83] (N = 130) *Grade 3*	71 (55)	81 [31]	SF-36 QoL	(n = 71 for all subscales) Physical summary score: 38.8 ± 1.29 Mental summary score: 46.0 ± 1.22	(n = 71 for all subscales) Physical summary score: >24–36 months: 41.3 ± 1.29 Mental summary score: >24–36 months: 47.3 ± 1.22	↑ (NR) ↑ (NR)

Data are means (SD) or means ± SE or medians (range), unless otherwise indicated. Red font indicates statistically significant changes.
Case series, case reports, mixed-ERT publications, paediatric–adult mixed publications, and publications with other dose regimens are not included.
[a] Total number of patients included in the study who were treated with ERT. [b] Study grades defined as follows: Grade 1c, single-arm clinical trial; Grade 3, retrospective observational study. [c] Number of male patients who were treated with ERT. [d] Number of male, ERT-treated patients with data for the outcome at baseline. [e] Number of male, ERT-treated patients with data for the outcome at endpoint.
↓, decrease in QoL; ↑, improvement in QoL; ERT, enzyme replacement therapy; EQ-5D, 5-dimension EuroQol questionnaire; EQ VAS, EuroQol visual analogue scale; NC, no change; NR, not reported; QoL, quality of life; SD, standard deviation; SE, standard error; SF-36, 36-Item Short-Form Health Survey.