Contents

Supplementary Table 1a

Publications describing clinical outcomes with ERT in female patients with Fabry disease

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
Agalsidase alfa	Baehner et al. 2003 [14]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	<13	15	Plasma GL-3, urinary GL-3, eGFR, LVM, ECG, QoL
	Palla et al. 2003 [15]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	12	8	Auditory
	Whybra et al. 2009 [16]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW	48	36	Plasma GL-3, urinary GL-3, eGFR, proteinuria, LVM, exercise testing, pain
	Goker-Alpan et al. 2015 [17]	Clinical: Grade 1c single-arm clinical trial	0.2 mg/kg EOW (naïve patients and patients switched from agalsidase beta during shortage period)	24	46	Plasma GL-3, plasma lyso-GL-3, urinary GL-3
	Goláň et al. 2015 [18]	Clinical: Grade 1a randomized controlled trial	0.2 mg/kg EOW 0.2 mg/kg weekly 0.4 mg/kg weekly	12	18	Plasma GL-3, LVM
	Whitfield et al. 2005 [19]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	≤21	2	Urinary GL-3, pain
	Palla et al. 2007 [20]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	≤60	14	Hearing/vestibular loss
	Hoffmann et al. 2007	Observational: Observational:	0.2 mg/kg EOW	≤24	203	GI outcomes

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
	[21]	Grade 3 retrospective observational study				
	Hoffmann et al. 2007 [22]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	≤36	393	Pain
	Feriozzi et al. 2009 [23]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	36	50	eGFR, proteinuria
	Feriozzi et al. 2012 [24]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	60–134	74	eGFR, proteinuria
	Sergi et al. 2010 [25]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	25–73	9	Hearing loss, pain
	Hughes et al. 2011 [26]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	≥48	78	eGFR, proteinuria, LVM, pain, GI outcomes, QoL
	Beck et al. 2015 [27]	Observational: Grade 3 retrospective observational	0.2 mg/kg EOW	60	317	eGFR, LVM

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
		study				
	Kampmann et al. 2015 [28]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	130 [median]	24	LVMi, EF, wall thickness, eGFR, proteinuria
	Mougenot et al. 2008 [29]	Case: Grade 4 case series	0.2 mg/kg EOW	24 or 30	2	GI outcomes, hearing outcomes
Agalsidase beta	Bénichou et al. 2009 [30]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	1.9–60.7	12	Plasma GL-3
	Watt et al. 2010 [31]	Observational: Grade 3 retrospective observational study	0.9 ± 0.22 mg/kg EOW	41 ± 22	59	QoL
	Motwani et al. 2012 [32]	Observational: Grade 3 retrospective observational study	1.0 mg/kg EOW	36 [median]	22	LVM, wall thickness, EF, ECG
	Warnock et al. 2012 [33]	Grade 3 retrospective observational study	1.0 mg/kg EOW	48	62	eGFR
	Kim et al. 2016 [34]	Observational: Grade 2 prospective observational	1.0 mg/kg EOW	82–125	4	eGFR, proteinuria, LVMi

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
		study				
	Senocak Tasci et al. 2015 [35]	Case: Grade 4 case series	1.0 mg/kg EOW	7–9	2	eGFR, proteinuria
	Waldek et al. 2003 [36]	Case: Grade 5 case report	1.0 mg/kg EOW	24	1	Cardiac GL-3, EF, ECG
	Tsuboi et al. 2007 [37]	Case: Grade 4 case series	1.0 mg/kg EOW	NR	6	Plasma GL-3, QoL
	Wang et al. 2008 [38]	Case: Grade 5 case report	1.0 mg/kg EOW	>48	1	LVM, wall thickness, sweat function, pain
	Abaterusso et al. 2009 [39]	Case: Grade 5 case report	1.0 mg/kg EOW	10	1	eGFR
	Masugata et al. 2009 [40]	Case: Grade 5 case report	1.0 mg/kg EOW	18	1	LVM, wall thickness, EF
	Bouwman et al. 2010 [41]	Case: Grade 4 case series*	1.0 mg/kg EOW	36	1	Placental GL-3
	Politei et al. 2010 [42]	Case: Grade 5: case report	1.0 mg/kg EOW	24	1	eGFR
	Thurberg et al. 2012 [43]	Case: Grade 5 case report	1.0 mg/kg EOW	24	1	Placental GL-3
	Kitai et al. 2016 [44]	Case: Grade 5 case report	Dose NR	144	1	Proteinuria, LVH
	Wakakuri et al. 2016 [45]	Case: Grade 5 case report	70 mg EOW	12	1	EJ, eGFR, cardiomegaly
	Arends et al. 2016 [46]	Case: Grade 4 case series*	1.0 mg/kg EOW	144	1	GFR, exercise tolerance, WMH

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
	Prinz et al. 2010 [47]	Case: Grade 5 case report	1.0 mg/kg EOW	12	1	LV function, ST segment abnormalities
	Germain et al. 2010 [48]	Case: Grade 5 case report	1.0 mg/kg EOW	11	1	Proteinuria
Agalsidase alfa and agalsidase beta comparison	Smid et al. 2011 [49]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.5, 1.0 mg/kg EOW, 0.5 mg/kg monthly	Pre-switch: 65 Post-switch: 26	18	Plasma lyso-GL-3, eGFR, LVM, pain, QoL
	Van Breemen et al. 2011 [50]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2, 1.0 mg/kg EOW	12	21	Plasma GL-3, plasma lyso-GL-3
	Tsuboi et al. 2012 [51]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.3, 1.0 mg/kg EOW	Pre-switch: 24 Post-switch: 12	7	LVM, wall thickness
	Tsuboi et al. 2015 [52]	Case: Grade 4 case series*	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	Alfa: 28 Beta: 27	1	Plasma GL-3, plasma lyso-GL-3, eGFR, LVM, wall thickness
	Politei et al. 2016 [53]	Case: Grade 4 case series	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	34–132	4	LVM, pain, proteinuria, eGFR
Treatment not specified or	Buechner et al. 2008 [54]	Observational: Grade 3 retrospective observational study	ERT NS	26	7	WMH
	Üçeyler et al. 2011	Observational: Grade 2	Alfa: 0.2 mg/kg EOW	48	14	Pain, QoL

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
combination of agalsidase alfa and agalsidase beta (mixed ERT)	[55]	prospective observational study	Beta: 1.0 mg/kg EOW			
	Ghali et al. 2012 [56]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW, Beta: 0.3, 0.5, or 1.0 mg/kg EOW	Alfa: 114 Beta: 36	8	QoL
	Fujii et al. 2012 [57]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	12	2	eGFR, LVM
	Lavoie et al. 2013 [58]	Observational: Grade 3 retrospective observational study	ERT NS	9	1	Urinary GL-3, urinary lyso-GL-3
	Rombach et al. 2013 [59]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2, 1.0 mg/kg EOW	66	27	eGFR, LVM, WMH
	Rombach et al. 2012 [60]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2, 1.0 mg/kg EOW	>12	30	Plasma GL-3, plasma lyso-GL-3, urinary GL-3, WMH
	Komori et al. 2013 [61]	Observational: Grade 2 prospective observational	ERT NS	8–90 [46.6]	9	Hearing loss

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
		study				
	Lin et al. 2013 [62]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	17 ± 8.8 [6 – 39]	17	Plasma lyso-GL-3, eGFR, LVM, LVMi, wall thickness parameters, albuminuria
	Anderson et al. 2014 [63]	Observational: Grade 3 retrospective observational study	ERT NS	≤ 116 [3.34 [2.25] yr]	103	eGFR, proteinuria
	Liu et al. 2014 [64]]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	13–46	18	Plasma lyso-GL-3, LVM
	Prabakaran et al. 2014 [65]	Observational: Grade 3 retrospective observational study	Beta: 1.0 mg/kg EOW followed by alfa 0.2 mg/kg EOW for most patients	≤ 84	13	eGFR, albuminuria
	Sirrs et al. 2014 [66]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	59–64	85	eGFR, LVM

Treatment	Study, year [reference]	Evidence grade	Dose	Duration[1] (months)	ERT-treated females patients (n)	Clinical outcomes reported
	Suntjens et al. 2014 [67]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2, 1.0 mg/kg EOW	84	7	Hearing outcomes
	Schmied et al. 2016 [68]	Observational: Grade 3 retrospective observational study	ERT NS	81.6	12	LVMi, wall thickness, EF, ECG
	Korsholm et al. 2015 [69]	Case: Grade 4 case series	Switch Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	≤108	20	WMH, cerebrovascular disease
	Takahashi et al. 2015 [70]	Case: Grade 5 case report	ERT NS	11	1	eGFR
	Tuttolomondo et al. 2015 [71]	Case: Grade 5 case report*	ERT NS	24	1	WMH

[1] Duration as reported in the publication. *These were Grade 4 case series, but data available at baseline and follow-up for only 1 female patient, so classified as Grade 5 case reports.

ECG, electrocardiography; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; GFR, glomerular filtration rate; GI, gastrointestinal; GL-3, globotriaosylceramide; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; lyso-GL-3, globotriaosylsphingosine; NR, not reported; NS, not specified; QoL, quality of life; WMH, white matter hyperintensities; yr, year.

Supplementary Table 1b

Publications describing clinical outcomes with ERT in mixed-gender studies (populations including ≥50% female patients with Fabry disease)

Treatment	Study, year [reference]	Study type	Dose	Duration[1] (months)	Total N[2] [ERT-treated]	Percentage female	Clinical outcomes reported
Agalsidase alfa	Hoffmann et al. 2007 [22]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	≤36	639	52.3	Pain
	Pereira et al. 2014 [72]	Observational: Grade 2 prospective observational study	0.2 mg/kg EOW	6–12	17	65.0	eGFR, albuminuria, LVM, pain
	Kampmann et al. 2015 [28]	Observational: Grade 3 retrospective observational study	0.2 mg/kg EOW	130 [median]	45	53.3	eGFR, proteinuria, LVMi, wall thickness, EF
Agalsidase beta	Faggiano et al. 2006 [73]	Observational: Grade 2 prospective observational study	1.0 mg/kg EOW	14–16	10	50.0	QoL
Agalsidase alfa and agalsidase beta comparison	Smid et al. 2011 [49]	Observational: Grade 3 retrospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.5, 1.0 mg/kg EOW Beta: 0.5 mg/kg monthly	65 [median]	35	50.0	Plasma lyso-GL-3, LVM, pain, QoL
	Tsuboi et al, 2012 [51]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.3, 1.0 mg/kg EOW	Pre-switch: 24 Post-switch: 12	11	63.6	Plasma GL-3, eGFR, pain (BPI), QoL

Treatment	Study, year [reference]	Study type	Dose	Duration[1] (months)	Total N[2] [ERT-treated]	Percentage female	Clinical outcomes reported
	Tsuboi et al. 2014 [follow-up of Tsuboi 2012 cohort] [74]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 1.0 mg/kg EOW	Pre-switch: 47.8 ± 19.4 Post-switch: 36	11	63.6	Plasma GL-3, plasma lyso-GL-3, eGFR, proteinuria, LVMi, wall thickness, pain, QoL
Treatment not specified or combination of agalsidase alfa and agalsidase beta (mixed ERT)	Turker et al. 2016 [75]	Clinical: Grade 1c single-arm clinical trial	ERT NR	10	13	NR: "most were female"	Pain, QoL
	Biegstraaten et al. 2010 [76]	Observational: Grade 2 prospective observational study	ERT NR	NR	30	56.7	Autonomic symptom profile scores
	Rombach et al. 2012 [77]	Observational: Grade 2 prospective observational study	Alfa: 0.2 mg/kg EOW Beta: 0.2, 0.25–0.5, 1.0 mg/kg EOW	68	67	50–61	Lyso-GL-3
	Lenders et al., 2016 [78]	Observational: Grade 3 retrospective observational study	ERT NS	80 ± 19	54	51.8	eGFR, renal, cardiac, neurological endpoints

[1] Duration as reported in the publication.
[2] N = number of patients in the ERT-treated mixed-gender population.
BPI, Brief Pain Inventory; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EOW, every other week; ERT, enzyme replacement therapy; GL-3, globotriaosylceramide; LVM, left ventricular mass; LVMi, left ventricular mass index; lyso-GL-3, globotriaosylsphingosine; NR, not reported; NS, not specified; QoL, quality of life.

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

	Study (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value)
Alfa	Goker-Alpan et al. 2015 [17] (N=100) *Pre-treatment with agalsidase beta (1 mg/kg EOW; n=71): 55 months (4–146)* *Grade 1c*	46 (46)	24	nM	ERT-naïve: 27.59 ± 15.40 (n=14) Switch: 13.82 ± 1.16 (n=29)	ERT-naïve: Significant decrease (n=3) Switch: NR (n=19)	↓ (NR) NC (NS)
Alfa	Van Breemen et al. 2011 [50] (N=43) *Grade 3*	21 (49)	12	nM (normal <3)	Alfa 0.2: 23 (12–26) (n=7) Beta 1.0: 8 (0–143) (n=9)	Alfa 0.2: 13 (6-19) (n=7) Beta 1.0: 5 (0–35) (n=9)	↓ (NR) ↓ (NR)
Beta							

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.
↓, decrease in levels; ↑, increase in levels; CT, clinical trial; ERT, enzyme replacement therapy; lyso-GL-3, globotriaosylsphingosine; MG, mixed gender; NC, no change; NR, not reported; NS, not significant; OS, observational studies; SD, standard deviation; SE, standard error..

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

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Whybra et al. 2009 [16] (N=36) *Grade 1c*	36 (100)	48	Plasma GL-3 score[1] (normal <0.03 mg/mmol GL-3/creatinine ratio or <0.6 molar ratio of GL-3 /sphingomyelin) Patients, n (%)	1.67 [0.72] (n=36) Prevalence stratified by GL-3 score[6]: 1: 13 (36.1) 2: 20 (55.6) 3: 3 (8.3) (n=36)	12 months:1.29 [0.52] (n=36) Prevalence stratified by GL-3 score[6]: 1: 26 (72.2) 2: 10 (27.7) 3: 0 (0.0) (n=36)	**↓ (p<0.001)**
	Baehner et al. 2003 [14] (N=15) *Grade 1c*	15 (100)	13	nmol/24h (range)	89–1,856 (n=15)	6 months: NS decrease (n = 11)	↓ (NS from BL)
	Goker-Alpan et al. 2015 [17] (N=100) *Pre-treatment with agalsidase beta (1 mg/kg EOW; n=71): 55 months (4–146)* *Grade 1c*	46 (46)	24	nmol/mg (normal <0.03 nmol/mg creatinine)	ERT-naïve: 2.48 ± 1.82 (n=14) Switch: 0.16 ± 0.049 (n=28)	ERT-naïve: NR (n=3) Switch: NR (n=18)	NC (NR) NC (NR)
	Whitfield et al. 2005 [19] (N=8) *Grade 2*	2 (25)	≤12	GL-3/ creatinine ratio, µmol/mol	Range: 0.1–0.3 (n=2)	Decrease (n=2)	↓ (NR)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint; [6] GL-3 values were converted to a 3-point scale as follows: (1) in the normal range; (2) >normal, but ≤2 x ULN; and (3) >2 x ULN.↓, decrease in levels; ↑, increase in levels; BL, baseline; CR, case report; CT, clinical trial; ERT, enzyme replacement therapy; h, hour; MG, mixed gender; NC, no change; NR, not reported; NS, not significant; OS, observational studies; SD, standard deviation; SE, standard error; ULN, upper limit of normal range.

Supplementary Table 4
eGFR outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Baehner et al. 2003 [14] (N=15) *Grade 1c*	15 (100)	13	mL/min/1.73 m^2 (range)	65–73 (n=15)	Stable throughout treatment (n=15)	NC (NR)
	Feriozzi et al. 2009 [23] (N=165) *Grade 3*	50 (30)	36	mL/min/1.73 m^2	71.6 [17.1] (n=50)	66.6 [19.6] (n=50)	**↓ (p<0.01)**
	Hughes et al. 2011 [26] (N=250) *Grade 3*	78 (31)	≥48	mL/min/1.73 m^2 (median, 10^{th} –90^{th} percentile)	Overall: 71.8 (56.5–87.6) (n=78)	Overall: 69.6 (44.8 – 91.1) (n=78)	**↓ (p=0.007)**
	Whybra et al. 2009 [16] (N=36) *Grade 1c*	36 (100)	48	mL/min/1.73 m^2	Overall: 91.0 [31.2] (n=36) Stratified by BL eGFR: >135: 159.0 [19.7] (n=4) 90–135: 106.6 [14.9] (n=9) 60–89: 76.6 [8.5] (n=20) 30–59: 50.2 [7.3] (n=3) Use of ACEi/ARB at BL: 74.5 [10.4] (n=7) Initiating ACEi/ARB during study: 87.7 [29.6] (n=6)	Overall: 91.0 [25.6] (n=36) Stratified by BL eGFR: >135: 128.3 [4.6] (n=4) 90–135: 100.4 [16.4] (n=9) 60–89: 85.9 [20.2] (n=20) 30–59: 47.3 [14.0] (n=3) Use of ACEi/ARB at BL: 65.0 [13.5] (n=7) Initiating ACEi/ARB during study: 83.0 [33.4] (n=6)	NC (NS) **↓ (p<0.01)** ↓ (NS) **↑ (p<0.01)** ↓ (NS) ↓ (NS) ↓ (NS)

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
	Feriozzi et al. 2012 [24] (N=208) *Grade 3*	74 (36)	60–132	mL/min/1.73 m^2	78.6 [18.5] (n=74)	≥60 months: 73.9 [19.4] (n=74)	↓ **(p≤0.01)**
	Beck et al. 2015 [27] (N=677) *Grade 3*	317 (47)	60	mL/min/1.73 m^2/year (normal: 99.8 mL/min/1.73 m^2)	eGFR ≥60 at BL: NR (n=111) BL eGFR <60 at BL: NR (n=22) Proteinuria at BL ≥1.0 g/24h: Mean: 65.7 (n=17) 0.1–1.0 g/24h: Mean: 87.3 (n=70) <0.1 g/24h: Mean: 80.2 (n=22)	BL eGFR ≥60 at BL: −0.43 ± 0.21 (n=111) BL eGFR <60 at BL: 0.36 ± 0.42 (n=22) Proteinuria at BL ≥1.0 g/24h: −0.41 ± 0.51 (n=17) 0.1–1.0 g/24h: −0.44 ± 0.26 (n=70) <0.1 g/24h: −0.16 ± 0.42 (n=22)	NC (NR, 95% CI −0.83, −0.02) NC (NR, 95% CI −0.47, 1.19) NR (95% CI −1.42, 0.59) NR (95% CI −0.95, 0.07) NR (95% CI −0.97, 0.66)
	Kampmann et al. 2015 [28] (N=45) *Grade 3*	24 (53)	130 (115–150)	mL/min/1.73 m^2	≥90 mL/min/1.73 m^2: Values: NR (n=5) <90 mL/min/1.73 m^2: Values: NR (n=11)	≥90 mL/min/1.73 m^2: 10 years: NC (n=5) <90 mL/min/1.73m^2: 10 years: NC (n=11)	NC (NS) NC (NS)
Beta	Warnock et al. 2012 [33] (N=213) *Grade 3*	62 (29)	48	mL/min/1.73 m^2	Q1: 88 [16] (n=14) Q2: 90 [23.9] (n=14) Q3: 95 [27.6] (n=16) Q4: 78 [35.6] (n=14)	Annual change: Q1: 2.7 [1.65] (n=15) Q2: 0.1 [0.41] (n=16) Q3: -1.3 [0.66] (n=16) Q4: −4.4[1.58] (n=37)	↑ (NR NC (NR) ↓ (NR) ↓ (NR)

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	**Female, n (%)[3]**	**Duration (months)**	**Units**	**Baseline (number of patients[4])**	**End-point (number of patients[5])**	**Overall result (p value/95% CI)**
	Kim et al. 2016 [34] (N=19) *Grade 2*	4 (21)	82-125	mL/min/1.73 m^2	115.9 [28.8] (n=4)	103 [27.8] Decline: −1.5 [3.4]/year (n=4)[6]	↓ (p>0.05)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint; [6]Including 23 months of dose reduction.
↓, decrease; ↑, increase; ACEi; angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BL, baseline; CI, confidence interval; CR, case report; CT, clinical trial; ERT, enzyme replacement therapy; eGFR, estimated glomerular filtration rate; h, hour; MG, mixed gender; NC, no change; NR, not reported; NS, not significant; OS, observational studies; Q, quartile; SD, standard deviation; SE, standard error.

Supplementary Table 5
Proteinuria outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Feriozzi et al. 2009 [23] (N=165) *Grade 3*	50 (30)	36	mg/24h	310.0 [320.9] (n=50)	299.3 [266.8] (n=50)	NC (p=0.88)
	Whybra et al. 2009 [16] (N=36) *Grade 1c*	36 (100)	48	mg/24h	Overall: 377 [546] (n=33) Proteinuria >300 at BL: 858 [751] (n=11) Use of ACEi/ARB at BL: 1,349 [1,760] (n=7)	Overall: 263 [167] (n=33) Proteinuria >300 at BL: 339 [230] (n=11) Use of ACEi/ARB at BL 425 [531] (n=7)	↓ (NS) **↓ (p<0.01)** ↓ (NR)
	Hughes et al. 2011 [26] (N=250) *Grade 3*	78 (31)	≥48	mg/24h (median, 10th–90th percentile)	199.5 (50.0–910.0)	206.0 (80.0–800.0)	NC (p=0.800)
	Feriozzi et al. 2012 [24] (N=208) *Grade 3*	74 (36)	60–132	mg/24h	Total: 331.1 [416.2] (n=46) Stratified by CKD CKD1: 275.8 [321.5] (n=10) CKD2: 387.7 [493.9] (n=27) CKD3: 222.8 [192.9] (n=9)	Total: 420.0 [944.8] (n=46) Stratified by CKD CKD1: 184.3 [156.1] (n=10) CKD2: 307.7 [345.5] (n=27) CKD3: 1018.9 [2022.4] (n=9)	NC (p=0.56) ↓ (p=0.45) ↓ (p=0.39) ↑ (p=0.28)
	Kampmann et al. 2015 [28] (N=45) *Grade 3*	24 (53)	130 (115–150)	mg/24h	Without proteinuria[6] at BL: NR (n=6) With proteinuria at BL: NR (n=7)	Without proteinuria at BL: 115.3 [48.0] (n=6) With proteinuria at BL: 507.6 [388.9] (n=7)	NC (NS) NC (NS)

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Beta	Kim et al. 2016 [34] (N=19) *Exploratory low dose (during shortage)* *Grade 2*	4 (21)	82-125	mg/day	72.3 [17.2] (n=4)	51.3 [27.5][7] (n=4)	↓ (p=0.14)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint; [6]Proteinuria defined as urine protein >200 mg/24 h at baseline; [7]Including 23 months of dose reduction.
↓, decrease; ↑, increase; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BL, baseline; CI, confidence interval; CKD, chronic kidney disease; CR, case report; CT, clinical trial; ERT, enzyme replacement therapy; h, hour; MG, mixed gender; NC, no change; NR, not reported; NS, not significant; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 6
Left ventricular hypertrophy outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Goláň et al. 2015 [18] (N=44) *Grade 1a*	18 (41)	12	g/m$^{2.7}$ (LVMi, Echo) (normal <47)	66.7 (n=6)	64.7 Change, %: −7.3 (n=5)	↓ (95% CI −15.24, 5.74)
	Baehner et al. 2003 [14] (N=15) *Grade 1c*	15 (100)	≤13	g/m^2 (LVMi)	148.1 ± 10.17 (n=15)	9 months: 122.5 ± 9.43 (n=7)	**↓ (p=0.021)**
	Whybra et al. 2009 [16] (N=36) *Grade 1c*	36 (100)	48	g/m$^{2.7}$ (LVMi, Echo)	Prevalence of LVH,[6] n (%): 25 (69) (n=36) LVMi at BL: >85 g/m$^{2.7}$: 131.9 [43.3] (n=9) 60–85 g/m$^{2.7}$: 76.3 [9.9] (n=9) 48–60 g/m$^{2.7}$: 56.0 [2.1] (n=8) <48 g/m$^{2.7}$: 40.7 [6.4] (n=11)	Prevalence of LVH,[6] n (%): 19 (53) (n=36) LVMi at BL: >85 g/m$^{2.7}$: 91.9 [29.7] (n=9) 60–85 g/m$^{2.7}$: 62.0 [17.7] (n=9) 48–60 g/m$^{2.7}$: 48.7 [4.1] (n=8) <48 g/m$^{2.7}$: 36.2 [7.1] (n=11)	↓ (NR) **↓ (p<0.001)** **↓ (p<0.001)** **↓ (p<0.001)** **↓ (p<0.01)**
	Hughes et al. 2011 [26] (N=250) *Grade 3*	78 (31)	≥48	g/m$^{2.7}$ (LVMi)	LVMi overall: 48.2 [17.0] (n=24) LVH at BL: NR (n=12) No LVH at BL: NR (n=12)	LVMi overall: 43.7 [14.3] (n=24) LVH at BL: Mean difference: −8.49 (n = 12) No LVH at BL: Mean difference: −0.67 (n = 12)	**↓ (p=0.031)** **↓ (p=0.034)** NC (p=0.604)
	Beck et al. 2015 [27] (N=677) *Grade 3*	317 (47)	60	g/m$^{2.7}$/year	Mean: 51.0 (n=93)	Overall: 0.48 ± 0.09 (n=93) LVH at BL: 0.77 ± 0.14 (n=45)	**↑ (95% CI 0.30, 0.66)** **↑ (95% CI 0.49, 1.05)**

						No LVH at BL: 0.19 ± 0.11 (n=48)	NC (95% CI −0.03, 0.41)
	Kampmann et al. 2015 [28] (N=45) *Grade 3*	24 (53)	130 (115–150)	g/m$^{2.7}$, (LVMi, Echo)	LVMi <50, n (%): 8 (33) (n=24) LVMi ≥50, n (%): 16 (67) (n=24)	LVMi <50: NC (n=8) LVMi ≥50: 10 years: NC (n=16)	NC (NR) 10 years: NC (NR)
	Tsuboi et al. 2012 [51] (N=11) *Pre-treatment with agalsidase beta 1.0 mg/kg EOW for a minimum of 24 months* *Grade 2*	7 (64)	12	g/m$^{2.7}$ (LVMi)	60.43 [18.35] (n=7)	52.64 [18.27] (n=7)	**↓ (p=0.0469)**
Beta	Motwani et al. 2012 [32] (N=66) *Grade 3*	22 (33)	36 (median)	g/m^2 (LVMi, Echo)	101 [22] (n=22)	98 [20] (n=22)	**↓ (p<0.001)**
	Kim et al. 2016 [34] (N=19) *Exploratory low dose (during shortage)* *Grade 2*	4 (21)	82-125	g/m$^{2.7}$ (LVMi)	No LVH[6] (n=2) 28.9-59.1 (n=2)	No LVH[6] (n=2) 32.6-55.3[7] (n=2)	NC (NR) NC (NR)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint; [6]LVH defined as LVM >48 g/m$^{2.7}$; [7]Including 23 months of dose reduction.
↓, decrease; ↑, increase; BL, baseline; CI, confidence interval; CR, case report; CT, clinical trial; Echo, echocardiography; ERT, enzyme-replacement therapy; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMi, left ventricular mass index; MG, mixed gender; NC, no change; NR, not reported; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 7
Wall thickness outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Kampmann et al. 2015 [28] (N=45) *Grade 3*	24 (53)	130 (115−150)	mm, MWT (Echo)	11.7 [2.5] (n=24)	LS mean change: −0.48 (n=21)	↓ (p<0.0999, 95% CI −1.05, 0.09)
Alfa	Tsuboi et al. 2012 [51] (N=11) *Pre-treatment with agalsidase beta 1.0 mg/kg EOW for a minimum of 24 months* *Grade 2*	7 (64)	12	mm, IVST	12.3 [3.1] (n=7)	10.7 [2.5] (n=7)	↓ (NS)
				mm, LPW	11.8 [2.3] (n=7)	10.6 [2.5] (n=7)	↓ (NS)
Beta	Motwani et al. 2012 [32] (N=66) *Grade 3*	22 (33)	Median: 36	mm. MWT	12 [4] (n=22)	11 [3] (n=22)	**↓ (p<0.001)**

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.↓, decrease; CI, confidence interval; CR, case report; CT, clinical trial; Echo, echocardiography; EOW, every other week; ERT, enzyme-replacement therapy; IVST, interventricular septum thickness; LPW, left posterior wall; LS, least squares; MG, mixed gender; MWT, maximal wall thickness; NS, not significant; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 8
Ejection fraction outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Kampmann et al. 2015 [28] (N=45) *Grade 3*	24 (53)	130 (115–150)	% LVEF	71.9 [7.6] (n=23)	68.4 [6.9] (n=23)	**↓ (p=0.022, 95% CI −6.74, −0.54)**
Beta	Motwani et al. 2012 [32] (N=66) *Grade 3*	22 (33)	Median 36	% EF	63 [4] (n=22)	63 [3] (n=22)	NC (p=0.92)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.CI, confidence interval; CR, case report; CT, clinical trial; EF, ejection fraction; LVEF, left ventricular ejection fraction; MG, mixed gender; NC, no change; ERT, enzyme-replacement therapy; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 9
Electrocardiogram outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Baehner et al. 2003 [14] (N=15) *Grade 1c*	15 (100)	13	ms (QRS duration)	100.15 ± 3.95 (n=15)	9 months: 92.4 ± 3.49 (n=5)	NC (p=0.121)
Beta	Motwani et al. 2012 [32] (N=66) *Grade 3*	22 (33)	Median 36	ms	PQ interval: 137 [16] (n=22)	PQ interval: 150 [15] (n=22)	↑ **(p<0.001)**
					P wave duration: 76 [6] (n=22)	P wave duration: 91 [7] (n=22)	↑ **(p<0.001)**
					QRS width: 92 [13] (n=22)	QRS width: 91 [12] (n=22)	NC (p=0.07)
					QTc interval: 412 [14] (n=22)	QTc interval: 406 [14] (n=22)	↓ **(p<0.01)**
				RE score[6]	RE score: 4 (0–10) (n=22)	RE score: 4 (0–10) (n=22)	NC (p=1.0)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint; [6] RE score reported as median (range).
↓, decrease; ↑, increase; CI, confidence interval; CR, case report; CT, clinical trial; NC, no change; QTc, corrected QT interval; RE, Romhilt-Estes; ERT, enzyme-replacement therapy; MG, mixed gender; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 10
Exercise testing outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Whybra et al. 2009 [14] (N=36) *Grade 1c*	36 (100)	48	NYHA classification	1.83 [0.94] (n=36)	1.31 [0.52] (n=36)	↓ **(p<0.001)**

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; CI, confidence interval; CR, case report; CT, clinical trial; ERT, enzyme-replacement therapy; MG, mixed gender; NYHA, New York Heart Association; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 11
Vestibular and auditory outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Palla et al. 2003 [15] (N=21) *Grade 1c*	8 (38)	12	Peripheral vestibular function (average gain)	**Head impulses:** towards weaker side: 0.68 (n=8) towards stronger side: 0.84 (n=8)	Non-significant improvement (n=3)	↑ (p=0.10)
	Sergi et al. 2010 [25] (N=20) *Grade 2*	9 (45)	51.5 (25–73)	Hearing threshold (dB nHL) HFHL	32.1 43.67 [25]	33.1 42 [24.13]	NC (p=0.9) NC (NR)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.
↑, increase; CI, confidence interval; CR, case report; CT, clinical trial; dB nHL, decibel above normal adult hearing level; ERT, enzyme replacement therapy; HFHL, high frequency hearing loss; MG, mixed gender; NC, no change; NR, not reported; OS, observational studies; SD, standard deviation; SE, standard error.

Supplementary Table 12
Pain outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Hoffmann et al. 2007 [22] (N=714) *Grade 3*	369 (52)	≤36	Change in BPI score (VAS)	NR	Pain at its worst: −1.3 ± 0.7 (n=21) Pain at its least: −0.4 ± 0.3 (n=21) Pain on average: −0.8 ± 0.5 (n=21) Pain right now: −0.9 ± 0.7 (n=21)	↓ (NS) ↓ (NS) **↓ (p<0.05)** **↓ (p<0.05)**
	Hughes et al. 2011 [26] (N=250) *Grade 3*	78 (31)	≥48	BPI score	Worst pain: 4.0 [3.3] (n=27) Pain on average: 3.6 [3.2] (n=27)	Worst pain: 3.8 [3.4] (n=27) Pain on average: 3.1 [2.7] (n=46)	NC (p=0.714) NC (p=0.353)
	Sergi et al. 2010 [25] (N=20) *Grade 2*	9 (45)	51.5 (25–73)	Pain severity (n)	Moderate: n=2 Mild: n=4 None: n=3	Moderate: n=3 Mild: n=3 None: n=3	NC (NR)
	Whitfield et al. 2005 [19] (N=8) *Grade 2*	2 (25)	≤12	BPI score (range)	Average pain: 6–7 (n=2) Worst pain last 24h: 8 (n=2)	Average pain: 0–4 (n=2) Worst pain last 24h: 0–4 (n=2)	↓ (NR) ↓ (NR)

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
	Whybra et al. 2009 [14] (N=36) *Grade 1c*	36 (100)	48	BPI score	Pain at its worst: 4.6 [2.9] (n=36)	Pain at its worst: Month 12: 3.3 [2.9] (n=36)	↓ **(p=0.001)**

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; BPI, Brief Pain Inventory; CI, confidence interval; CR, case report; CT, clinical trial; ERT, enzyme replacement therapy; h, hour; MG, mixed gender; NC, no change; NR, not reported; NS, not significant; OS, observational studies; SD, standard deviation; SE, standard error; VAS, visual analogue scale.

Supplementary Table 13
Gastrointestinal outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Hoffmann et al. 2007 [21] (N=714) *Grade 3*	25 of 62 with ERT data available (40.3)	12 or 24	Patients, %	Abdominal pain: 12 months: NR (n=21) 24 months: 40 (n=25) Diarrhoea: 12 months: NR (n=21) 24 months: 12% (n=25)	Abdominal pain: 12 months: decrease by 10% (n=21) 24 months: 20 (n=25) Diarrhoea: 12 months: decrease by10% (n=21) 24 months: 16% (n=25)	↓ (NR) ↓ (NR) ↓ (NR) ↑ (NR)
	Hughes et al. 2011 [26] (N=250) *Grade 3*	78 (31)	≥48	Patients, %	Abdominal pain: 43.6 (n=39) Constipation: 43.2 (n=37) Diarrhoea: 31.6 (n=38) Nausea: 23.1 (n=39) Vomiting: 15.4 (n=39)	Abdominal pain: 43.6 (n=39) Constipation: 35.1 (n=37) Diarrhoea: 26.3 (n=38) Nausea: 28.2 (n=39) Vomiting: 15.4 (n=39)	NC (NR) ↓ (NR) ↓ (NR) ↑ (NR) NC (NR)

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.

↓, increase; ↑, decrease; CI, confidence interval; CR, case report; CT, clinical trial; ERT, enzyme replacement therapy; MG, mixed gender; NC, no change; NR, not reported; NS, not significant; NC, no change; NR, not reported; OS, observational studies; SD, standard deviation; SE, standard error

Supplementary Table 14
Quality of life outcomes with approved doses of agalsidase alfa and agalsidase beta in adult female patients

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
Alfa	Baehner et al. 2003 [14] (N=15) *Grade 1c*	15 (100)	13	SF-36 scores	(n=15 for all subscales)	Change from BL at 6 months (n=10/11 for all subscales)	
					Mental function summary (MCS): 39.8 [14.74]	Mental function summary: 3.8 [16.94]	NC (NS)
					Physical function summary (PCS): 35.1 [11.85]	Physical function summary (PCS): 6.6 [6.02]	↑ **(p<0.025)**
					Physical functioning: 48.0 [29.78]	Physical functioning: 8.6 [9.00]	↑ (NS)
					Role-physical: 25.0 [35.36]	Role-physical: 27.3 [26.11]	↑ **(p<0.00625)**
					General health: 41.1 [21.56]	General health: 19.3 [15.69]	↑ **(p<0.00625)**
					Bodily pain: 46.5 [32.07]	Bodily pain: 6.8 [16.62]	↑ (NS)
					Vitality: 31.7 [22.65]	Vitality: 13.2 [25.81]	↑ (NS)
					Social function: 60.0 [28.03]	Social function: 5.7 [31.31]	↑ (NS)
					Role-emotional: 37.8 [45.19]	Role-emotional: 21.2 [52.22]	↑ (NS)
					Mental health: 57.1 [25.32]	Mental health: 2.2 [25.82]	↑ (NS)

	Study, year [reference] (number of patients[1]) *Evidence grade*[2]	Female, n (%)[3]	Duration (months)	Units	Baseline (number of patients[4])	End-point (number of patients[5])	Overall result (p value/95% CI)
	Hughes et al. 2011 [26] (N=250) *Grade 3*	78 (31)	≥48	EQ VAS health score (100 mm) EQ-5D health score	66.8 [26.3] (n=20) 0.61 [0.4] (n=23)	73.6 [19.0] (n=20) 0.69 [0.3] (n=23)	NC (p=0.246) NC (p=0.055)
Alfa	Ghali et al. 2011 [56] (N=40) *Pre-treatment with agalsidase beta (minimum of 12 months)* *Grade 3*	8 (20)	12	Self-reported energy levels scored 1–10 using SF-36	4 (range 4–6) (n=3)	4 (range 4–7) (n=3)	NC (p=1.0)
Beta	Watt et al. 2010 [31] (N=130) *Grade 3*	59 (45)	81 [31]	SF-36 QoL	(n=59 for all subscales) Physical summary score: 36.8 ± 1.53 Mental summary score: 45.9 ± 1.41	(n=59 for all subscales) Physical summary score: >12–24 months: 38.5 ± 1.48 Mental summary score: >12–24 months: 48.8 ± 1.36 Overall: improved scores in 6 of 8 scales after 12–24 months of treatment	↑ (NR) **↑ (p<0.05)** **↑ (p<0.05)**

Case series, case reports, mixed-ERT publications, paediatric-adult-mixed publications, and publications with other dose regimens are not included.
Data are means [SD] or means ± SE or medians (range), unless stated otherwise. Red font indicates statistically significant changes.
[1] Total number of patients included in the study who were treated with ERT; [2] 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; [3] Number of female patients who were treated with ERT; [4] Number of female, ERT-treated patients with data for the outcome at baseline; [5] Number of female, ERT-treated patients with data for the outcome at endpoint.
↓, decrease; ↑, increase; BL, baseline; CI, confidence interval; CR, case report; CT, clinical trial; EQ-5D, 5-dimension EuroQol questionnaire; EQ VAS, EuroQol visual analogue scale; ERT, enzyme replacement therapy; MCS, mental component summary; MG, mixed gender; NC, no change; NS, not significant; NS, not significant; OS, observational studies; PCS, physical component summary; SD, standard deviation; SE, standard error; SF-36, 36-item Short-Form Health Survey.