Humanistic burden of Fabry disease and associated utility values

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Azimpour K[1], Dorling P[2], Igbelina CD[3], Kwon CS[3], Rizzo M[4]

[1]Chiesi, Woodbridge, ON, Canada; [2]Chiesi, Boston, MA, USA; [3]Cytel Inc, Waltham, MA, US; [4]Cytel Inc, London, UK

Introduction

- Fabry disease (FD) is a rare, debilitating, and progressive X-linked lysosomal storage disorder resulting from mutations in the *GLA* gene that cause α-galactosidase A (α-Gal A) enzyme deficiency and subsequent accumulation of globotriaosylceramide (Gb3) in lysosomes[1,2]
- Gb3 accumulation in lysosomes impacts multiple organ systems in patients, as such the signs and symptoms can include episodes of severe burning pain in the hands and the feet (acroparesthesia), impaired sweat production, heat intolerance, gastrointestinal problems, dark red or purple skin lesions (angiokeratomas), corneal dystrophy, chronic fatigue, lymphedema, tinnitus, and vertigo[1,2]
- The progression of FD over time leads to a diverse range of complications including cardiovascular, renal, cerebrovascular, ocular, auditory, gastrointestinal, and dermatological manifestations that can cause pain, substantial morbidity, or premature death[2]
- The signs, symptoms, and long-term manifestations of FD can have an unfavorable impact on patients' overall quality of life both physically and mentally, especially difficulty in daily and social activities, maintaining full-time employment, depression, and anxiety[3]

Objective

- Previous systematic literature reviews (SLRs) on the humanistic burden of Fabry disease were published almost a decade ago[3-5]
- We conducted an SLR to update the knowledge on the humanistic burden associated with FD considering the evolving therapeutic landscape.
- Additionally, our aim was to evaluate patient-reported outcomes (PROs) and disease severity between treatment naïve/pretreated and treated patients, with the goal of understanding patient health states and associated utilities

Table 1. PICOS criteria for the SLR

Category	Inclusion criteria
Population	• Patients diagnosed with FD (Anderson Fabry disease, Anderson disease, Fabry syndrome, alpha-galactosidase deficiency, Fabry dyslipidosis)
Interventions	• Any pharmacological treatments for FD • No treatments
Comparators	• No restrictions
Outcomes	• General questionnaires SF-36, SF-12, SF-6-dimensions, EQ-5D • Fabry-specific questionnaires (MSSI, DS3) • Pain (BPI) • Utility/Disutility
Study type	• Prospective interventional trials (RCTs, single-arm trials, non-randomized comparative trials) • Observational studies (including patient registries) • Retrospective analyses • Systematic reviews and meta-analyses (for cross-checking only) • Pooled analysis (for cross-checking only
Language	• English language
Countries	• Studies from US, Canada, and Europe

Methods

- The SLR was conducted in May 2022 and later updated in April 2023 to identify studies reporting humanistic burden and utility data in patients with FD using Population, Intervention, Comparator, Outcome, and Study Design (PICOS) criteria in **Table 1**
- The SLR followed established guidance and methods described by the National Institute for Health and Care Excellence, and the Cochrane Handbook[6,7]
- Utilizing the Ovid platform and the grey literature search, studies reporting data for patients with FD who were either under no treatment or any pharmacological treatments such as enzyme replacement therapy (ERT, i.e., pegunigalsidase alfa, agalsidase alfa, agalsidase beta), and other treatments (migalastat, venglustat, and lucerastat) were selected based on prespecified inclusion criteria (**Table 1**)
- Utility data (quality of life [QoL] measure), Mainz Severity Score Index (MSSI) (disease severity measure) and PROs for pain (Brief Pain Inventory [BPI]), self reported measure of health (36-Item Short Form Survey [SF-36]), fatigue, and gastrointestinal symptoms scores were extracted

Results

- The SLR identified a total of 127 studies, of which 120 reported on PROs and disease severity (MSSI) and 31 studies reported utility scores associated with FD
- Of the 31 studies that reported utility, most were real-world evidence studies (n=18), followed by economic studies (n=6), interventional studies (n=5), and one each for modeling and vignette studies
- The EQ-5D (EuroQol five-dimension) was the most used utility elicitation method followed by EQ-VAS (EuroQol visual analogue scale) index
- Other PROs included BPI (35 studies) and SF-36, a measure of general health (33 studies)
- Fifty-five studies evaluated humanistic burden using the MSSI, a disease-specific measure

Utility Scores: ERT Treatment Patients in FD

- Of the 31 studies, 13 studies reported utility score (ED-5D/EQ-VAS index) comparisons between cohorts of treatment naïve, pretreated, or mixed (treatment naïve and pretreated ERT) patients and currently on ERT treatment patient cohorts (**Table 2**)
- Among the five studies comparing utility scores between treatment-naïve and ERT treated patients, two showed improvement, two showed stable, and for one, statistical analysis was not available (**Table 2**)
- Of seven studies comparing utility scores between ERT pretreated and ERT currently treated patients, three showed stable, one showed improvement, and three reported only descriptive analysis
- Three studies comparing utility scores between mixed treatment population and ERT currently treated patients demonstrated either stable or improved scores.
- The baseline treatment status of the patients was unclear in one study[9] (**Table 2**)

Utility comparison: Male versus Female

- The numerically higher utility scores were observed for females compared to males except in two studies[11,21] analyzing Spanish patients from the Fabry Outcome Survey
- The EQ-5D scores ranged from 73.6 to 84.7 among females and 71.1 to 87.3 among males across the identified studies
- EQ-5D index scores were reported to be lower for males compared to females with FD (0.74 vs. 0.88 points). Frequency of motility problem (among any problems in individual domains) was higher among males than females (45% vs. 15%; p=0.09)[12]

Table 2: Utility associated with baseline/untreated and treated patients with FD

Studies	N	Baseline/ Treatment naive score	ERT treated score		p-value	Patient status post treatment
EQ-5D, EQ-VAS index; Mean [SD], Median (range)						
Beck et al. 2004[2]	59 (year 1)	Baseline: Mix of ERT pretreated and naïve patients (Proportion of ERT treated males:30-100%, females: 11-69%)	Significant improvement (year 1)		p<0.05	Improved
	28 (year2)		improvement maintained (year 2)		p<0.05	
Hoffmann et al. 2005[8]	59	Treatment naïve 0.64 (0.32)	0.74 [0.26] (year 1); improvement maintained (year 2)		p<0.05	Improved
Hoffman et al. 2007[9]	18	Previous treatment status: Unclear 0.63 [0.37]	0.71 [0.31] (2 years)		NS	Stable
Mehta et al. 2009[10]	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed); Mean [SD] with mean deviation scores from EuroQol values		Mean [SD] with mean deviation scores from EuroQol values			-
			Mean QoL	Mean change	p-value	
	41 (year 1)	−0·24 [0·29]	−0·15 [0·26]	0·09 [0·25]	p<0.05	Improved
	48 (year 2)	−0·24 [0·30]	−0·13 [0·23]	0·11 [0·23]	p<0.05	Improved
	44 (year 3)	−0·25 [0·29]	−0·19 [0·25]	0·06 [0·24]	NS	Stable
	51 (year 5)	−0·24 [0·30]	−0·17 [0·28]	0·07 [0·25]	p<0.05	Improved
Hughes et al. 2011[11]	37 (M); 23 (F)	Baseline: Pretreated ERT for at least 4 years: 0.63 [0.3] (M) 0.72 [0.2] (F)	0.72 [0.2] (M) 0.69 [0.3] (F) (4 years)		NS	Stable
		Baseline: Pretreated ERT for at least 4 years: 67.7 [21.7] (M) 66.8 [26.3] (F)	71.1 [17.6] (M) 73.6 [19] (F) (4 years)		NS	Stable
Zuraw et al. 2011[12]	20*	Treatment naïve 0.58	0.80 (3.4 years)		p<0.05	Improved
		Treatment naïve 65	65		NS	Stable
Hughes et al. 2013[13]	18	ERT pretreated for 3 months: Baseline NR	74.3 [20.1]		p-value: NR But stated as NS	Stable
Barba-Romero et al. 2016[14]	3 (UF); 11 (TM)	Baseline: Mix of ERT pretreated and naive patients (total of 53 (60.2%) patients received ERT; males: 87.2%; females: 38.8%) UF: 0.8 (0.7-1.0)	TM: 0.8 (0.3-0.8)		p<0.05	Stable (other comparisons NS)
Goker-Alpan et al. 2016[15]	14 (week 55)	Treatment naïve 0.7	HUI2: Change from baseline to 0.1		NA	
		Treatment naïve 0.6	HUI3: Change from baseline to 0.0			
Arends et al. 2018[16]	61	Treatment naïve 0.79 (-0.16 to 1.00)	unchanged		NS	Stable
Concolino et al. 2017[17]	72	ERT pretreated for at least 3 months (before home infusion)	42 (58%) showed either stable or improved; 30 (48%) showed worsened (home infusion)			Majority stable/improved
CSR BRIGHT trial[18]€	29	Baseline: Pretreated ERT for at least 3 years: 78.3 [16.8]	82.1 [14.8] (week 52); change from baseline to 1 year n=27, 3.0 [11.3]		Only descriptive statistics used	
CSR BALANCE trial[19]€	52 (pegunigalsidase alfa)	Baseline: Pretreated ERT for at least 1 year: 74.6 [22.4]	75.8 [16.6] (week 104); change from baseline to 2 year n= 46, 2.0 [12.8]		Only descriptive statistics used	
	25 (agalsidase beta)	Baseline: Pretreated ERT for at least 1 year: 75.9 [14.6]	78.0 [17.8] (week 104); change from baseline to 2 year n= 22, 1.2 [16.2]		Only descriptive statistics used	
CSR BRIDGE trial[20]€	20	Baseline: Pretreated ERT for at least 2 years: 71.8 [19.0]	76.9 [20.1] (week 52); change from baseline to 1 year n= 20, 5.1 [14.6]		Only descriptive statistics used	

EQ-5D, HUI2, and HUI3 scores are reported 0 to 1 where 1 represents perfect health and 0 represents death; EQ-VAS scores are reported 0 to 100, with 100 being best imaginable health and 0 being worst imaginable
*Patients treated with migalastat (SRT) and not ERT
€Mean [SD] scores of mapped EQ-5D-3L utility values at each follow-up were previously reported in Khashayar A et al. 2023[46]

Utility scores by FD patient characteristics or health states

- A recent study[22] was the only one that utilized vignette (scenario) construction and valuation and assessed the main complications of FD in the general population using time trade-off methodology. The lowest mean utility value was for the end-stage renal disease health state, followed by the cardiovascular disease health state and the stroke health state (0.119, 0.278, and 0.385, respectively)
- In a modeling study using EQ-5D questionnaire methodology among patients (with almost 50% pre-treated ERT), the results showed higher utility scores for asymptomatic patients (0.87), followed by symptomatic patients (0.76), those having a single complication (0.74), and those with multiple complications (0.58) [23]
- The health state utility values used in the model[23] for two HTA (NICE and CADTH) documents[24,25] indicated the lowest utility values for health state involving multiple complications including end-stage renal disease, cardiac and stroke (0.584), followed by single complication of end-stage renal disease, cardiac complications, and stroke (0.744 each), pain (without other signs of clinically evident disease and with clinically evident FD health states; 0.762 each) among patients (with almost 50% pre-treated ERT)
- The discrepancy in the results between the recent study[22] and the two HTA reports[24,25] is attributed to the use of different methodologies and the assessment of different populations

Table 3: SF-36 scores in patients with FD

Studies	Results
SF-36, overall scores	
Gold et al. 2002[26]	Compared to general population • Fabry cohort showed large to very large differences across all eight domains with differences in effect size ranging from 0.9 for mental health to 2.5 for general health
Eto et al. 2005[27]	Compared to untreated population • Patients treated with ERT showed improvement in all categories • However, statistically significant improvement was observed for the General Health and the Mental Component Scale
Hopkin et al. 2008[28]	Compared to general population • Fabry Registry males reported significantly poorer QoL in 7/8 domains (all but Role Emotional) • Fabry Registry females reported significantly poorer QoL in 2/8 subscales (Body Pain and General Health)
Koskenvuo et al. 2008[29]	Compared to baseline • Mean scores post ERT was 58.6 (versus 59.0 at baseline): no significant difference in QoL
Bouwman et al. 2011[30]	Compared to general population • Fabry males scored significantly lower in the domains of physical functioning and bodily pain Fabry females scored significantly lower in the domain of general health perception
Pisani et al. 2012[31]	Compared to pre-switch period • No differences in mean scores after ERT treatment in all 8 domains
Lohle et al. 2015[32]	Compared to control population • Post ERT treatment patients with AFD had a markedly reduced QoL (total mean [SD] scores of control: 85.4 [12.2] versus AFD: 65.2 [24.2]
Germain et al. 2016[33]	Compared to patients with symptoms at baseline • Patients treated with migalastat showed improvements (increases in scores for the vitality and general health domains
Gaisl_SB_2020[34]	Compared to control population • In FD population, severity of obstructive sleep apnea was significantly associated physical role functioning, general health perceptions, social role functioning, and mental health

Table 4: BPI associated with baseline/untreated and treated patients in FD

Studies	N	Baseline/ Treatment naïve score	ERT treated score	Treatment follow-up (years)	p-value	Patient status post treatment
BPI Scores in Mean, Mean [SD] or Mean change (95% CI)						
Hoffmann et al. 2005[8] (pain on average)	20	Treatment naïve 4.1	3.4	1	NS	Stable
	20	Treatment naïve 4.1	3.2	2	p<0.05	Improved
Mehta et al. 2009[10] (pain on average)	33	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 3.6 [2.3]	3.1 [2.7]	1	NS	Stable
	45	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 3.7 [2.4]	2.6 [2.3]	2	p=0.002	Improved
	44	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 3.8 [2.4]	2.9 [2.5]	3	p=0.013	Improved
	53	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 3.7 [2.3]	2.5 [2.4]	5	p=0.002	Improved
Whybra et al. 2009[35] (pain at its worst)	36	Treatment naïve 4.6 [2.9]	3.3 [2.9]	1	p=0.001	Improved
Anderson et al. 2014[36] (pain severity score)	149	Baseline: Mix of ERT pretreated and naïve patients (about 70% received ERT for 0-9.7 years) 2.3	0.07 (−0.49-0.64)	<1	NS	Stable
			−0.29 (−0.70-0.12)	1-3		
			−0.26 (−0.69-0.17)	>3		
Hughes et al. 2017[37] (pain severity score)	34*	Baseline: Pretreated ERT for at least 1 year: 1.29	NR	1.6	Change from baseline 0.15 (-0.56 - 0.88); NS; Stable	
	17	Baseline: Pretreated ERT for at least 1 year: 2.12	NR	1.6	Change from baseline -0.19 (-0.98 - 0.59); NS; Stable	
CSR BRIGHT trial[18] (pain on average)	29	Baseline: Pretreated ERT for at least 3 years: 2.0 [1.8]	2.0 [2.3] Change from baseline: n=27, 0.1 [2.2];	1	Only descriptive statistics used	
CSR BALANCE trial[19] (pain on average)	52 (pegunigalsidase alfa)	Baseline: Pretreated ERT for at least 1 year: 2.2 [2.2]	2.6 [2.9] Change from baseline: n=45, 0.4 [2.3]	2	Only descriptive statistics used	
	25 (agalsidase beta)	Baseline: Pretreated ERT for at least 1 year: 2.2 [2.0]	2.5 [2.5] Change from baseline: n=22, 0.2 [1.9]	2	Only descriptive statistics used	
CSR BRIDGE trial[20] (pain on average)	20	Baseline: Pretreated ERT for at least 2 years: 1.9 [2.0]	1.9 [2.1] Change from baseline: 0.1 [1.1]	1	Only descriptive statistics used	

Higher BPI scores represent worse pain
*Patients treated with migalastat (SRT) and not ERT

SF-36 Scores: Patients with FD

- Of the 33 studies that reported SF-36 values, nine studies reported scores in all eight domains (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health or emotional wellbeing) (**Table 3**)
- Compared to baseline or untreated cohort, two studies showed no difference and two studies reported improvement in at least two domains post ERT treatment. Eto et al. 2005[27] showed improvement in two domains general health and mental component scale and Germain et al. 2016[33] showed improvement in vitality and general health domains
- Compared to control or general population, patients with FD reported reduced QoL in four studies

BPI and MSSI scores: ERT Treated Patients in FD

- Studies comparing BPI and MSSI scores between cohorts of treatment naïve, pretreated, or mixed (treatment naïve and pretreated ERT) patients and treated patients are presented in **Table 4-5**
- Two studies comparing BPI scores between treatment naïve and treated patients and two studies comparing mixed treatment population and treated patients demonstrated either stable or improved scores.
- Of four studies comparing ERT pretreated and treated patients, three reported only descriptive analysis (**Table 4**)
- Four studies comparing MSSI scores between treatment naïve and treated patients showed improved or stable scores. Three studies comparing mixed treatment group and treated patients showed mostly stable scores (**Table 5**)
- Three studies comparing MSSI scores between ERT pretreated and treated patients reported only descriptive analysis (**Table 5**)
- In one study, MSSI scores remained stable between ERT pretreated and treated patients at week 52. However, there was an improvement in MSSI scores by week 104[18] (**Table 5**)
- Although two studies[14,42] reported worsened disease severity in males treated with ERT compared to untreated males (**Table 5),** their MSSI scores indicate mild disease (<20)[41]

Table 5: MSSI associated with baseline/untreated and treated patients in FD

Studies	N (Baseline/ Treatment naive)	Baseline/ Treatment naïve score	N (ERT treated)	ERT treated score	p-value	Patient status post treatment
MSSI Scores in Median or Median [range]						
Parini et al. 2008[38]	30§	Previous treatment status: Unclear 17.0	30	11.5	p<0.05	Improved
Imbriaco et al. 2009[39]	11§	Previous treatment status: Unclear 18.0	11	9.0	p<0.05	Improved
Motwani et al. 2012[40]	66	At baseline evaluation no patient was receiving ERT 16 [2–39]	66	14 [2–36]	p<0.001	Improved
Barba-Romero et al. 2016[14]	5 (M)	Baseline: Mix of ERT pretreated and naive patients (total of 53 (60.2%) patients received ERT; males: 87.2%; females: 38.8%) 0.0 [0.0–1.0]	34 (M)	15.0 [7.5–26.5]	p<0.05	Worsened
	30 (F)	Baseline: Mix of ERT pretreated and naive patients (total of 53 (60.2%) patients received ERT; males: 87.2%; females: 38.8%) 8.0 [4.5–10.0]	19 (F)	11.0 [6.0–17.0]	NS	Stable
MSSI Scores in Mean [SD] or Mean (SEM)						
Whybra et al. 2004[41]	39	Treatment naïve NR	Median decrease of nine points (interquartile range, 6-12)		p<0.001	Improved
Whybra et al. 2009[35]	36	Treatment naïve ~28*	36	~22*	p<0.01	Improved
Tavakoli et al. 2009[42]	10 (M)	Previous treatment status: Unclear 3.7 (1.7)	6 (M)	13.0 (2.8) (M)	p<0.0001	Worsened
	10 (F)	Previous treatment status: Unclear 3.7 (1.7)	6 (F)	22.7 (4.5) (F)	NS	Stable
Lenders et al. 2020[43]	20 (M)	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 20 [1]	20 (M)	22 [11]	NS	Stable
	12 (F)	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 19 [9]	12 (F)	21 [9]	NS	
Lenders et al. 2021[44]	27 (M)	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 20.6 [9.1]	27 (M)¥	19.9 [10.0]	NS	Stable
	26 (F)	Baseline: Mix of ERT pretreated and naïve patients (proportions undisclosed) 14.9 [8.3]	26 (F)¥	16.3 [8.7]	NS	
Camporeale et al. 2023[45]	16	Treatment naïve Median (percentile range): 5.0 (3.0-6.0)	16¥	Median (percentile range): 5.0 (2.0-6.0)	NS	Stable
CSR BRIGHT trial[18]	29	Baseline: Pretreated ERT for at least 3 years: 20.5 [9.7]	27	19.2 [8.6] Change from baseline: -0.2 [3.5]; (Week 52)	Only descriptive statistics used	
CSR BALANCE trial[19]	49 (pegunigalsidase alfa)	Baseline: Pretreated ERT for at least 1 year: 23.2 [10.0]	46	22.1 [12.2] Change from baseline: -2.1 [5.1]; (Week 104)	Only descriptive statistics used	
	25 (agalsidase beta)	Baseline: Pretreated ERT for at least 1 year: 25.2 [10.7]	23	27.1 [11.0] Change from baseline: 2.0 [5.3]; (Week 104)	Only descriptive statistics used	
CSR BRIDGE trial[20]	20	Baseline: Pretreated ERT for at least 2 years: 20.3 [10.0]	20	19.3 [10.5] Change from baseline: -1.0 [4.2]; (Week 52)	Only descriptive statistics used	

MSSI scores represent disease severity with <20 as mild, 20–40 as moderate, and >40 as severe disease state
§ Individual patient values were used to calculate the total median value
*Approximate mean values were derived from a figure reported in the study
¥ Patients treated with migalastat (SRT) and not ERT

Conclusions

- **Studies identified in this SLR add to our understanding of the humanistic burden of FD by evaluating PROs such as EQ-5D, SF-36, and BPI as well as disease severity (MSSI) outcomes. These assessments provide insights into the quality of life experienced by patients**
- **Compared to treatment naïve, pretreated, or mixed treatment cohorts, the findings evaluating PROs and MSSI scores revealed the overall humanistic burden of ERT treated patients has either improved or remained consistent over time for most patients**
- **Long-term data with existing therapies for the treatment of FD may offer additional insights on patient-relevant outcomes, including pain, disease severity, and quality of life**

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Abbreviations: AFD, Anderson-Fabry disease; BPI, Brief Pain Inventory; CADTH, Canadian Agency for Drugs and Technologies in Health; CSR, clinical study report; EQ-D5, EuroQol five-dimension; EQ-VAS, EQ visual analogue scale; ERT, enzyme replacement therapy; FD, Fabry disease; F, females; FRSC, fatigue-related symptom score; HUI, Health Utilities Index; M, males; MSSI, Mainz Severity Score Index; NICE, National Institute for Health and Care Excellence; NA; not available; NR, not reported; NS, not significant; PRO, patient-reported outcome; QoL, quality of life; RCT, randomized controlled trial; SD, standard deviation; SEM, standard error of mean; SF-12/36, 12/36 Items Short Form Survey; SLR, systematic literature review; SRT, substrate reduction therapy; TM, treated males; UF; untreated females

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