EQ-5D Utility Values for Clinical Health States in Fabry Disease (FD): Insights from Pegunigalsidase Alfa Clinical Trials

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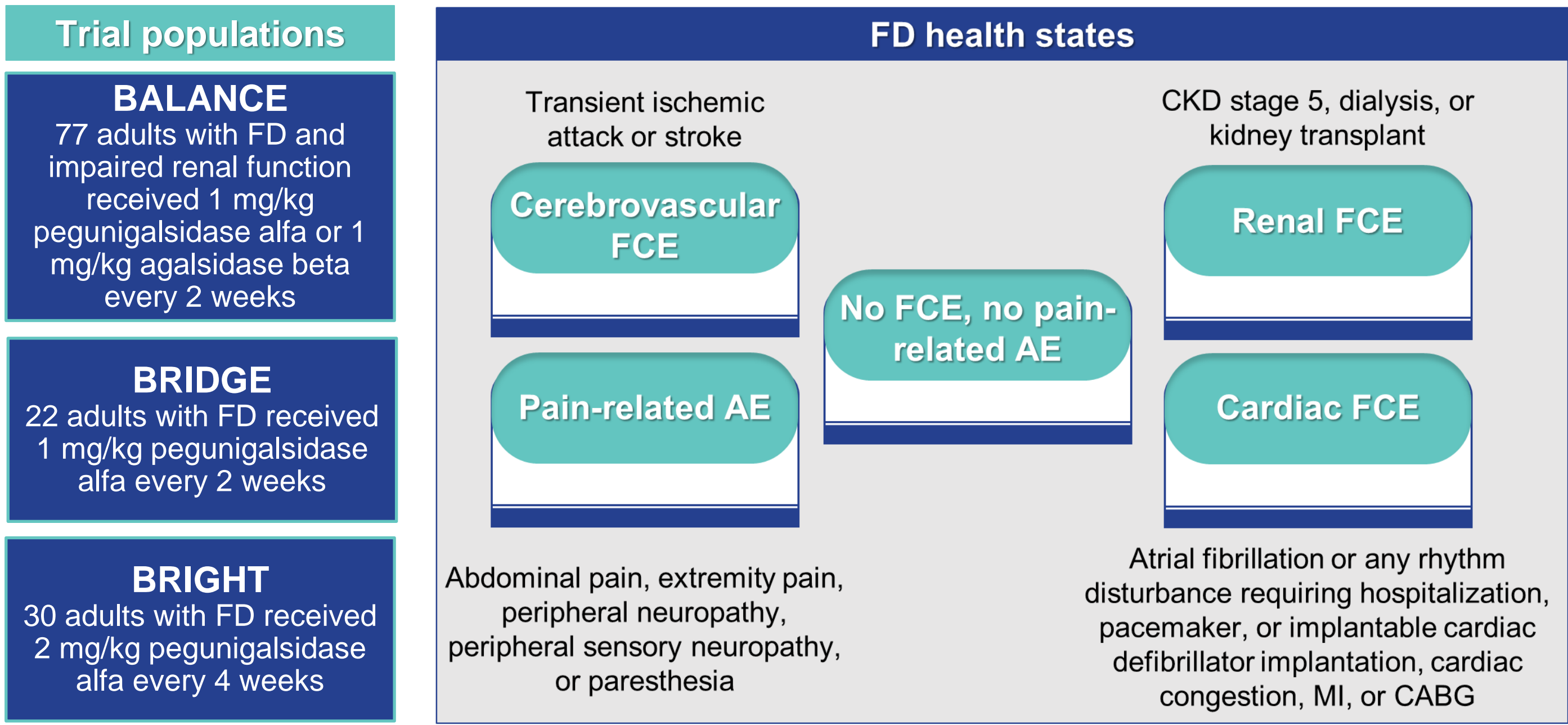[1]Chiesi USA, Boston, MA; [2]Cytel, Waltham, MA, USA

Introduction

- Fabry disease (FD), also known as Anderson Fabry disease, is a rare, devastating, and progressive X-linked lysosomal storage disorder caused by mutations in the GLA gene, resulting in deficiency of the α-galactosidase A enzyme[1,2]
- Health-related quality of life (HRQoL) is a multidimensional concept representing the impact of illness and its treatment on a patient's physical, psychological, and social functioning[3]
- The BALANCE, BRIDGE, and BRIGHT studies were phase 3 trials evaluating the safety and efficacy of pegunigalsidase alfa in adults with FD
  - In all three trials, HRQoL data were collected in the form of the EQ-5D-5L
  - The National Institute for Health and Care Excellence (NICE) recommends mapping from the EQ-5D-5L to the EQ-5D-3L[4]
- Health state utility values are necessary for understanding patient HRQoL and conducting economic evaluations. These values range between 0 (representing death) and 1 (perfect health).

Objective

- To estimate EQ-5D-3L utility values for FD health states from the BALANCE, BRIDGE, and BRIGHT trials
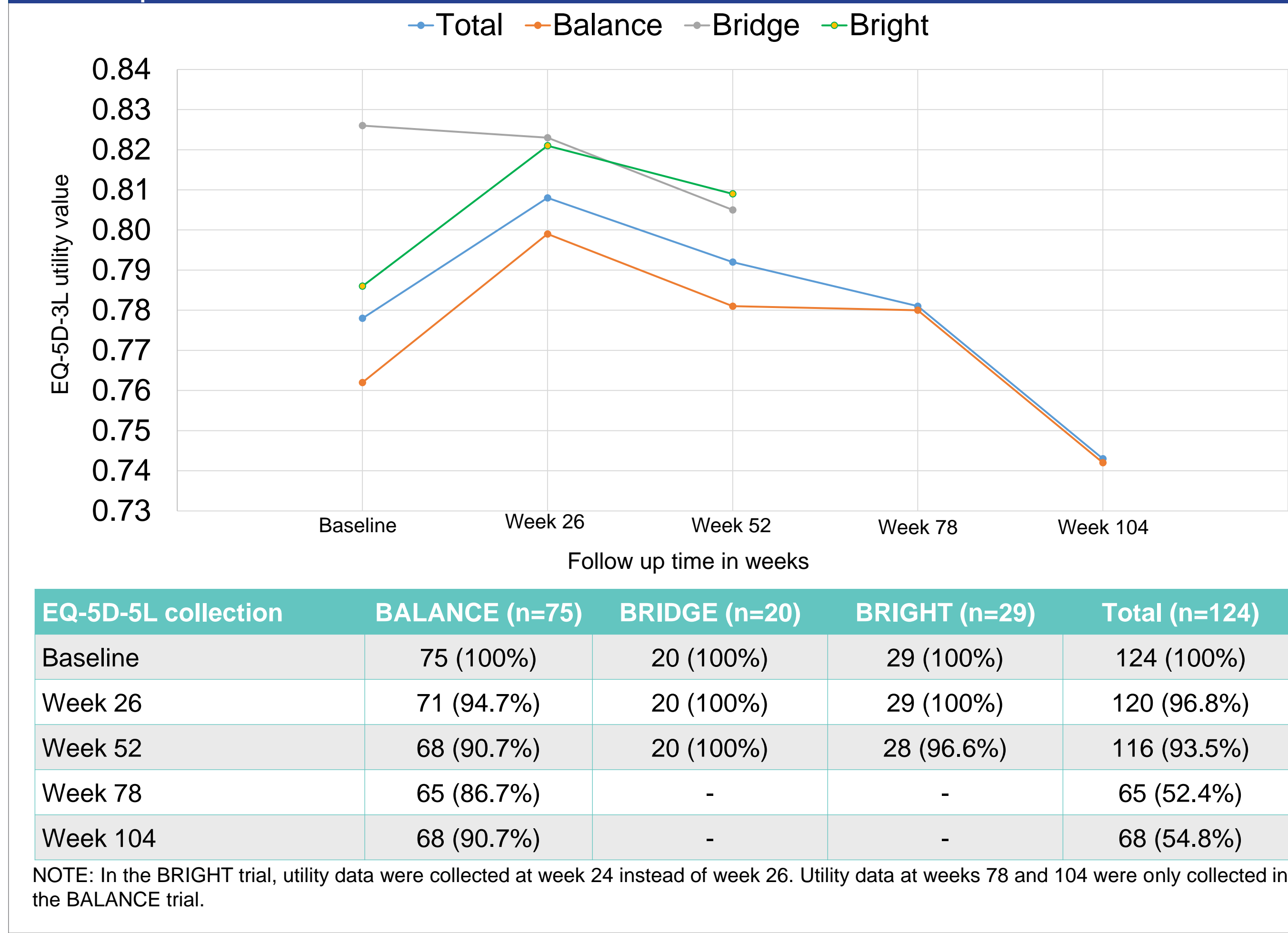
Methods

- Individual patient-level EQ-5D-5L data from all three trials were included in the analysis
- Of the 129 participants across the three trials, 124 had at least one EQ-5D-5L follow-up measurement
  - Data from both treatment arms of the BALANCE trial were included in the analysis
- The EQ-5D-5L was mapped to the EQ-5D-3L, as recommended by NICE, using the "eq5dmap" function within the "eq5d" R package[5-7]
  - Country was set to "UK" when computing utility values
- Health states were based on patient experience of one or more types of Fabry clinical event (FCE) or pain-related adverse event (AE)[9-10]

Trial populations	FD health states
BALANCE 77 adults with FD and impaired renal function received 1 mg/kg pegunigalsidase alfa or 1 mg/kg agalsidase beta every 2 weeks	Transient ischemic attack or stroke — **Cerebrovascular FCE**; **No FCE, no pain-related AE**; CKD stage 5, dialysis, or kidney transplant — **Renal FCE**
BRIDGE 22 adults with FD received 1 mg/kg pegunigalsidase alfa every 2 weeks	**Pain-related AE**; **Cardiac FCE**
BRIGHT 30 adults with FD received 2 mg/kg pegunigalsidase alfa every 4 weeks	Abdominal pain, extremity pain, peripheral neuropathy, peripheral sensory neuropathy, or paresthesia; Atrial fibrillation or any rhythm disturbance requiring hospitalization, pacemaker, or implantable cardiac defibrillator implantation, cardiac congestion, MI, or CABG

Abbreviations: AE, adverse event; CABG, coronary artery bypass grafting; FCE, Fabry clinical event; FD, Fabry disease; MI, myocardial infarction.

- A mixed effects linear regression approach was used to model the impact of different covariates on follow-up EQ-5D-3L utility values
  - Covariates included study, age, sex, disease type, treatment arm, baseline estimated glomerular filtration rate (eGFR), eGFR at time of EQ-5D measurement, baseline utility value, serious AE, pain-related AE, cardiac FCE, cerebrovascular FCE, and renal FCE
  - Random effects included subject identification and visit time
- Backward stepwise model selection was performed to determine the best-fitting model
- Models were evaluated according to their Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and log-likelihood value results

Figure 1. Mapped EQ-5D-3L utility values at each follow-up visit in patients with 1+ follow-up

EQ-5D-5L collection	BALANCE (n=75)	BRIDGE (n=20)	BRIGHT (n=29)	Total (n=124)
Baseline	75 (100%)	20 (100%)	29 (100%)	124 (100%)
Week 26	71 (94.7%)	20 (100%)	29 (100%)	120 (96.8%)
Week 52	68 (90.7%)	20 (100%)	28 (96.6%)	116 (93.5%)
Week 78	65 (86.7%)	-	-	65 (52.4%)
Week 104	68 (90.7%)	-	-	68 (54.8%)

NOTE: In the BRIGHT trial, utility data were collected at week 24 instead of week 26. Utility data at weeks 78 and 104 were only collected in the BALANCE trial.

Results

- Average utility values across the three trials were 0.778 at baseline and ranged from 0.808 to 0.742 at weeks 26 to 104 of follow-up (Figure 1)
- Results of the mixed effects model showed that baseline utility value had a statistically significant impact on follow-up utility values (p<0.0001), whereas all other covariates were found not to be statistically significant and were eliminated from the model
  - Regardless of statistical significance, health state variables remained in the model
- As age is typically included in utility analyses, and male patients with FD tend to have more severe symptoms than female patients, the final model included these two variables (Table 1)
- Final model-derived utility values were 0.800 for no FCE/no pain-related AE, 0.774 for pain-related AE, 0.719 for cardiac FCE, 0.792 for cerebrovascular FCE, and 0.688 for renal FCE
  - These estimated utility values were in line with published EQ-5D utility values in the FD research literature, with the exception of the utility value for renal FCE, which was likely affected by low frequency of this type of FCE (Table 2)

Table 1. Final model summary

	Coefficient	Standard error	p-value
Intercept	0.2870	0.0736	0.0002
Age	-0.0005	0.0011	0.6488
Sex (male)	0.0039	0.0235	0.8668
Baseline utility value	0.6849	0.0519	<0.0001
Pain-related AE	-0.0268	0.0262	0.3099
Cardiac FCE	-0.0816	0.0453	0.0747
Cerebrovascular FCE	-0.0082	0.0640	0.8982
Renal FCE	-0.1124	0.1523	0.4612
AIC: -364.7336	BIC: -321.7148	Log-likelihood: 193.3668	

Abbreviations: AE, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; FCE, Fabry clinical event
Final model formula: EQ5D = 0.2870 - 0.0005*Age + 0.0039*Male + 0.6849*Baseline EQ5D - 0.0268*Pain-related AE - 0.0816*Cardiac FCE - 0.0082*Cerebrovascular FCE - 0.1124*Renal FCE

Table 2. Final utility values and external validation

	Present study	Arends et al., 2018[8]
No FCE/no pain-related AE	0.800	0.851
Pain-related AE	0.774	0.725
Cardiac FCE	0.719	0.705
Cerebrovascular FCE	0.792	0.732
Renal FCE	0.688	0.828

Abbreviations: AE, adverse event; FCE, Fabry clinical event

Limitations

- It is important to note the limitations of the present study that affected statistical power
  - Small sample size
  - Low frequency of each FCE, especially renal FCE
- Although the study-level effect was not found to have a statistically significant impact on utility values, heterogeneity between trials was present
  - Difference in EQ-5D follow-up time points
  - Different inclusion criteria and follow-up duration in the BALANCE study
  - Different pegunigalsidase alfa dosing schedule in the BRIGHT study

Conclusions

- By leveraging the HRQoL data from the BALANCE, BRIDGE, and BRIGHT trials, this study estimated utility values for the FD health states of no FCE/no pain-related AE, pain-related AE, cardiac FCE, cerebrovascular FCE, and renal FCE
- Baseline utility value was the only covariate found to have a statistically significant impact on follow-up utility values
- Results from the present study yielded utility values that are generally in line with published EQ-5D utility values in the FD research literature, thereby making a significant contribution to the literature in the form of health state utility values from three FD clinical trials

Abbreviations

AE, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; eGFR, estimated glomerular filtration rate; FCE, Fabry clinical event; FD, Fabry disease; EQ-5D-5L, EuroQol- 5 Dimension; EQ-5D-3L, EuroQol- 3 Dimension, HRQoL, health-related quality of life; NICE, National Institute for Health and Care Excellence;

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