DISEASE REGISTRY REPORT

Compound(s): GZ/SAR402671 (venglustat)

Registry Title: An Observational Study to Assess the Psychometric Properties of a Patient Reported Outcome (PRO) Instrument in Patients with Fabry Disease

Registry number: OBS14422

Registry name: PROOF Study

Registry initiation date [date first patient in (FPI)]: 10-Jan-2017

Registry completion date [last patient completed/last patient out (LPO)]: 30-Nov-2017

Registry design:

This is a prospective, longitudinal, international, observational study.

Non interventional on the therapeutic strategy

The Fabry Disease Patient-Reported Outcome (FD-PRO) instrument was completed daily via an electronic diary for 30 consecutive days. Patient Global Impression of Change (PGIC) and Patient Global Impression-Static (PGIS) was completed weekly via an electronic diary. Other patient reported outcomes (PRO) instruments (Short Form-36 Health Survey version 2 [SF-36v2], Beck Depression Inventory- Second Edition [BDI-II], Irritable Bowel Syndrome- Quality of Life [IBS-QOL], Fabry Disease Severity Scoring System (DS3), Physician Global Assessment) were collected via paper in the clinic on Day 1 and Day 30, while Estimated Meaningful Change in Symptoms Questionnaire and Stool Frequency and Consistency Questionnaire were collected via paper in the clinic only on Day 30.

Date of interim report: 10-July-2019

Report date: 25-March-2020

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

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SYNOPSIS

Title of the registry:	An Observational Study to Assess the Psychometric Properties of a patient reported outcome (PRO) Instrument in Patients with Fabry Disease (FD).
Design:	This is a prospective, longitudinal, international, observational study. The Fabry Disease Patient-Reported Outcome (FD-PRO) instrument was completed daily via an electronic diary for 30 consecutive days. Patient Global Impression of Change (PGIC) and Patient Global Impression-Static (PGIS) was completed weekly via an electronic diary. Other patient reported outcomes (PRO) instruments (Short Form-36 Health Survey version 2 [SF-36v2], Beck Depression Inventory- Second Edition [BDI-II], Irritable Bowel Syndrome- Quality of Life [IBS-QOL], Fabry Disease Severity Scoring System (DS3), Physician Global Assessment) were collected via paper in the clinic on Day 1 and Day 30, while Estimated Meaningful Change in Symptoms Questionnaire and Stool Frequency and Consistency Questionnaire were collected via paper in the clinic only on Day 30.
Objectives:	This was a prospective, longitudinal, non-interventional study designed to evaluate the psychometric properties (item-level distributional characteristics, domain structure, reliability, construct validity, scoring and responder definitions) of the novel FD-PRO instrument.
Participants:	Approximately one hundred and fifty male and female patients diagnosed with Fabry Disease (FD) were targeted for screening to ensure that 125 FD patients are enrolled in the study with a minimum of 85 enzyme replacement therapy (ERT) treated and a minimum of 40 treatment naïve patients. The target was approximately 25 clinical sites located across Asia, Europe, Latin America, and North America. Patients eligible for enrollment were required to meet the following inclusion/exclusion criteria. INCLUSION CRITERIA I 01. Patient is male or female adult ≥18 years.

	I 02. Patient has a diagnosis of FD historically confirmed at the site through the following means: • Male patients: FD diagnostic confirmed enzymatic deficiency as documented by leukocyte or plasma αGAL activity assay (local lab). GLA genotype to be collected, if available, • Female patients: FD diagnostic confirmed by documented causative GLA genotyping. αGAL levels to be collected, if available. I 03. Patient may be ERT treated or naïve to treatment: • ERT treated patients should be stable at the recommended label dose for at least the previous 6 months, • Patients not treated must be naïve to any Fabry specific treatment including ERT, chaperone, or substrate reduction therapy (SRT). I 04. Patient is willing and able to provide written informed consent. I 05. Patient is willing and able to complete study questionnaires. I 06. Patient meets symptom-severity stratification criteria. EXCLUSION CRITERIA E 01. Patient has active, or a history of, clinically significant organic disease (with the exception of the symptoms related to Fabry disease), including clinically significant cardiovascular, hepatic, pulmonary, neurological, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstances that, in the opinion of the Investigator, would preclude participation in the study or interfere with the interpretation of data. E 02. Patient has participated in a study employing an investigational drug within 30 days from the start of the study.

	E 03. Patient plans to start ERT within next month after screening period.
Scientific committee & members:	Not applicable
Publications (reference):	Hamed A, DasMahapatra P, Iaconangelo C, Serrano S, Gwaltney C (2019). Measurement Properties of the Fabry Disease Patient-Reported Outcome (FD-PRO), a New Instrument to Measure Symptoms in Fabry Disease (abstract presented at *WorldSymposium*, Orlando, FL, USA)
Introduction - Background/rationale:	Fabry disease (FD) is a rare, multi-systemic lysosomal storage disorder associated with severe renal, cardiac, and cerebrovascular clinical manifestations, and decreased life expectancy. Signs and symptoms in the severe "classic" phenotype begin in early childhood and persist in adults, and negatively impact quality of life (QoL)[1,2]. A key clinical goal is to reduce symptom burden and improve patients' QoL in FD. Severity of such symptoms experienced by the patient is best assessed by a patient-reported outcome (PRO) measure[3], however, no disease specific PRO has been validated for clinical use in FD. A novel Fabry Disease Patient-Reported Outcome (FD-PRO) instrument was developed via qualitative research, including (1) concept elicitation via literature review, key opinion leader (KOL) interviews, and patient interviews, and (2) cognitive debriefing of the items in the questionnaire to assess symptoms experienced by patients with FD. The objective of this study was to evaluate the psychometric properties and develop a scoring algorithm of the FD-PRO questionnaire
Methodology:	**(a) Site and patient selection:** Sites were selected based on: ability to recruit, in the needed timeframe, using patient medical record information; availability of the staff to screen patients against eligibility criteria; participation in the Institutional Review Board/Independent Ethics Committee (IRB/IEC) application process; and ability to

	ensure patient compliance with the protocol requirements. Potentially eligible patients were identified by the study coordinator or clinician(s) at each site. These patients were scheduled for a clinic visit to sign their consent, complete the screening and enrollment process, including filling in the Symptom Screening Questionnaire. This study enrolled patients who are experiencing variable level of severity of gastrointestinal (GI) and neuropathic symptoms which are among the most commonly reported symptoms of FD. In order to guarantee an appropriate patient representativeness for FD PRO validation, patients were stratified in four groups of different intensity of symptoms (absent, mild, moderate, and severe) based upon the patient response to screening questionnaire items that assess: a) pain, burning, and numbness in the hands/arms, b) tingling in the hands/arms, c) pain, burning, numbness in the feet/legs, d) tingling in the feet/legs, e) diarrhea, f) abdominal pain, and g) tiredness. The stratification plan based on the symptomatology observed at screening was regularly checked during the enrollment period and adjusted, as necessary. **(b) Data collection:** Nine (ten including screening) questionnaires was filled in by the patient included either as an electronic diary (daily for FD PRO including Bristol Stool Form Scale [BSFS] and weekly for PGIC and PGIS) or as a paper diary for other PRO instruments to assess the symptoms, quality of life and patient well-being using PRO measures (**Table 1**). The clinician also assessed the patient with two instruments via paper for Clinician Reported Outcome

	(ClinRO). (Table 1) Of note, the **FD-PRO** is a PRO instrument to assess patient-reported symptoms associated with FD. Seventeen items assess presence and severity of each symptom using a numerical rating scale (NRS) ranging from 0 (none) to 10 (as bad as you can imagine). One item (yes/no/not sure) assesses whether the patient was in a situation that would have led to sweating. The final item assesses difficulty engaging in regular physical activities using an NRS ranging from 0 (no difficulty) to 10 (difficulty as bad as you can imagine). This latter item (physical activity) was not included in the scoring of the FD-PRO. The FD-PRO was administered as an electronic daily diary and was the subject of psychometric evaluation in this study. **(c) Safety data collection:** N/A **(d) Data management, review, validation:** Data was collected on electronic dairy (DIARY PRO) and eCRF. **(e) Statistical considerations:** Analyses described in this Clinical Study Report (CSR) fall into the following broad categories, described in detail hereafter: 1. Sample Characterization Compliance 2. Response Pattern Evaluation 3. Empirical Domain Specification 4. Scoring Method 5. Reliability 6. Concurrent Validity 7. Known-Groups Validity 8. Sensitivity to Change 9. Thresholds for Clinically-Meaningful Change This broad description was detailed for each major component outlined in the CSR. (f) **Data analyses:** Distributions of the weekly averaged

	FD-PRO items were analyzed by empirical domain specification (EDS), which included exploratory factor analysis (EFA) to determine the domain structure of the FD-PRO, and an item-response theory (IRT) model to evaluate the relative strength of items in measuring the FD-PRO disease domains and to define a model-based score that maximizes the precision and reliability of the FD-PRO. A goal of the analyses was to develop a total symptom score (TSS); an Omega coefficient >0.80 was used as criterion to evaluate whether the score determined by the confirmatory factor model was representative of a unit-weighted composite score. The following psychometric analyses of the FD-PRO TSS were performed: internal consistency, test-retest reliability, concurrent validity, and known-groups validity.
Registry period:	This report includes data reported to the PROOF Registry as of cutoff 15-Jan-2018
RESULTS	

Participants (actual):	**Patient Demographic and Clinical Characteristics** The study enrolled 138 patients diagnosed with FD (enzyme deficiency in males; GLA genotyping in females) from 11 countries and 18 sites. The mean age of patients was 43 years (range 18–72 years). The division between male and female was close to even, with slightly more males (52.9%) than females (47.1%). The sample was majority white (84.1%). The countries most heavily recruited from were Argentina and Portugal, each of which contributed approximately 14.5% of the sampled population. Most patients (72%) were treated with enzyme replacement therapy (ERT). Regarding disease severity, patients with moderate disease comprised the largest group (**Table 2**).
Participant characteristics and primary analyses:	**Domain Specification and Modern Psychometric Evaluation** With a categorical model (IRT) approach, the strength of association among the items revealed a neuropathy component comprising the first 8 items of the FD-PRO (pain in hands/arms, burning feeling in hands/arms, numbness in hands/arms, tingling in hands/arms, pain in feet/legs, burning feeling in feet/legs, numbness in feet/legs, tingling in feet/legs). Inter-item correlations among these 8 items ranged from 0.64–0.89. Categorical EFA with 1- and 2-factor loadings confirmed the grouping of the 8 items into a neuropathy parcel. The sweating items (items 17 and 18) did not load on any factor in either the 1-factor or 2-factor categorical EFA models, indicating that these items were not related to the overall FD-PRO structure; thus, these items were not considered in the FD-PRO analysis. Local dependence and redundant items analyses supported grouping 3 items into an audiovisual parcel; G2 statistical analyses indicated that item pairs formed from tinnitus, hearing impairment, and vision impairment exhibit local dependence ($P<0.05$).[4] A total symptom score (TSS) was generated that included the neuropathy and audiovisual parcels (items within each parcel were averaged and treated as a single item), and the remaining 5 items of the FD-PRO

	(headache, abdominal pain, heat intolerance, swelling in lower extremities, tiredness/fatigue). (**Figure 1**) The parameters and model fit statistics were within ranges of acceptable values: lower bound of the confidence interval for root mean square error of approximation (RMSEA) ≤0.05, and confirmatory fit index = 0.97 and Tucker-Lewis Index = 0.96. **Scoring** The confirmatory factor model that was fit to parcel scored data supported use of the 7-item scale (Omega = 0.90). All daily diary entries were first parceled into 7 items. Next, these 7 responses were averaged to obtain a daily mean score. The algorithm is as follows: Note that "Integer" indicates a function for rounding a number to the nearest integer. Then, the daily diary mean scores from each week were averaged to create a weekly diary final score, the FD-PRO TSS which corresponds to the mean of 7 items: neuropathy parcel, audiovisual parcel, headache, abdominal pain, heat intolerance, swelling, and tiredness/fatigue (**Figure 1**) **Measurement Characteristics of the FD-PRO TSS** (a) Internal consistency (Cronbach's alpha) of the FD-PRO TSS was ≥0.89 across weeks. (b) Test-retest reliability (intraclass correlation coefficient) was ≥0.91 (Table 3). (c) Concurrent validity analyses showed that the absolute correlations between the TSS and the criterion variables at baseline were high, suggesting that the TSS captured a range of relevant symptoms. Note that some of the DS3 clinical variables (i.e., renal, CNS, and cardiac assessments) are only tangentially related to the TSS and thus the correlation was not expected to be high (**Figure 2**). (d) FD-PRO TSS scores discriminated moderate and severe from least severe (no symptoms) FD groups in known-groups validity analyses using either Physician Global Assessment (PGA)

	(P=0.00), PGIS (P=0.00), symptom cohort (P=0.00 and P=0.04, respectively) or DS3 (P=0.00) patient anchors.

Other analyses:	**Patient Compliance and Time to Completion** Patient compliance was high; ≥87% completed at least 4 FD-PRO entries each week. Mean completion time ranged from 171 seconds in Week 1 to 117 seconds in Week 4.
Discussions:	Establishing a scoring algorithm for the FD-PRO was a key objective of the study. An initial evaluation of the items revealed severe skew toward the low end of the response scale (i.e., 0 on a scale of 0 to 10). This occurred throughout the study and reflected the generally low symptom severity of a sample consisting of a majority of clinically stable patients. This severe skew violated distribution assumptions of linear exploratory factor analysis (EFA), and, in response, response categories were collapsed and generalized linear EFA (hereafter references as EFA) was used instead. Item properties were assessed via generalized linear confirmatory factor models (i.e., item response theory (IRT) models). The inter-item correlations, 1-factor and 2-factor EFA loadings indicated that the Sweating item was not related to the other items and was dropped from the analysis. The inter-item correlations, 2-factor EFA loadings, and unusually large IRT slopes suggested redundancy among the 8 items measuring peripheral neuropathy symptoms. Three items measuring hearing and vision impairments also appeared to be redundant, based on empirical evidence and the shared content of the item prompt. The investigation into local dependence via the G2 statistic provided corroborating evidence of potential redundancy. The final determination was made by a likelihood ratio test comparing the fit of two models: the full model was an IRT model fit to 16 items, and the reduced model was an IRT model with two sets of constraints: (1) parameters of neuropathy items constrained to equality, and (2) parameters of impairment items constrained to equality. The results indicated that the constrained model fit the data statistically identically, providing empirical evidence that the neuropathy and impairment item sets were each functioning as a single item. These redundancies were addressed via parcel scoring. Items 1-8 were considered the neuropathy parcel, and items 13, 15, and 16 were considered the impairment parcel. The average of each

	parcel was computed and treated as a single item response. This resulted in the creation of a 7-item scale out of the original 17-item instrument (plus a gatekeeper item). A traditional linear confirmatory factor model was fit to the parcel-scored data in the raw (uncategorized) response metric to confirm the model fit and corroborate the results from the IRT framework in the raw response metric. Statistics indicated that unit-weighted scores were highly correlated with the model-based, empirically weighted scores. Thus, a weekly mean of the parcel-scored FD-PRO instrument was determined as the appropriate final score. This score includes the key symptoms of Fabry disease and is conceptualized as a total symptom score (TSS). Internal consistency of the TSS, assessed via Cronbach's alpha, exceeded the pre-specified acceptability criterion of 0.7. Test-retest reliability estimated via intraclass correlation coefficient, for which symptom stability was defined by patient and clinician anchors, exceeded the pre-specified criterion of 0.75. Known-groups validity estimated stratifying TSS scores on the same patient and clinician anchors showed that TSS scores incremented properly across most of the known health groups and each higher health severity group significantly differed from the least severe known health group. Although the Sweating item was not included in the scoring, the DS3 clinical assessment of sweating was a statistically significant predictor of TSS. Similarly, an investigation into the convergent validity showed that correlations of the TSS with a clinical assessment as well as patient-reported assessments exceeded the pre-specified criterion of $r > |0.4|$. Computation of sensitivity to change and meaningful change estimates offered limited evidence that the TSS may be capable of detecting change in disease. The meaningful change estimate for the TSS should be revisited in future longitudinal trials with more subjects reporting greater severity of symptoms at baseline and having a greater likelihood of exhibiting change over time during the study. The findings from this observational study support the scoring algorithm, reliability, and validity of the FD-PRO instrument. The TSS provides a single indicator of

	overall Fabry disease symptom severity. The FD-PRO is ready to be implemented in longitudinal studies where treatment may be administered. **Strengths and Limitations** The FD-PRO is the first disease specific measure in FD that has been developed to measure symptom severity. The study results are generalizable across a broad population of classic and late-onset Fabry patients. Future studies with longer follow up are needed to determine a threshold of meaningful within-patient change on the FD-PRO
Conclusions:	The study demonstrated strong measurement properties of the FD-PRO, a novel disease-specific patient-reported instrument that measures FD symptoms. The FD-PRO is a reliable, valid, and robust measure that can quantify the total symptom severity of FD.
Date of report:	25-March-2020

APPENDICES

APPENDIX I – ADMINISTRATIVE AND LEGAL CONSIDERATIONS

1.1 ETHICAL CONSIDERATIONS

1.1.1 Ethical principles

This registry was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments.

1.1.2 Laws and regulations

This study was conducted in accordance with the guidelines for Good Epidemiology Practice (US[5] and European[6]).

Each participating country were responsible locally to ensure all necessary regulatory submissions (eg, IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

1.2 DATA PROTECTION

The patient's personal data and physician's personal data which were included in the Company's databases were treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the physician and/or to the patients, the Company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

1.3 RECORD RETENTION

The Investigators arranged for the retention of study documentation until the end of the study. In addition, the Investigator complied with specific local regulations/ recommendations with regards to patient record retention.

1.4 THE COMPANY AUDITS AND INSPECTIONS BY COMPETENT AUTHORITIES (CA)

The Investigators agreed to allow Sponsor auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

1.5 CENTRAL LABORATORY

Not applicable

1.6 OWNERSHIP OF DATA AND USE OF REGISTRY RESULTS

No use of the data will be possible without the authorisation of Sponsor conducting the study.

1.7 REGISTRY CONSULTANTS

1.7.1 Scientific Committee and Charter

Not applicable

1.7.2 National coordination

Not applicable

1.7.3 Other experts/consultants

Not applicable

1.8 PARTICIPATING PHYSICIANS

The physicians performed the registry in accordance with the protocol, applicable local regulations and international guidelines.

The physician or a person designated by the physician, fully informed the patient, in language and terms they were able to understand, to the fullest extent possible, about the registry, objectives, constraints, duration, and patient's rights.

It was the responsibility of the physician's or a person designated by the physician to obtain written and signed informed consent from patients prior to inclusion. The patient's legal representative could also sign the written informed consent form (ICF) on behalf of the patient. A copy of the signed and dated written ICF was provided to the patient and/ or his legal representative.

List of participating investigators

Country	Site number	Principal Investigator
Argentina	032-001	Juan Politei
Argentina	032-004	Judith Gaite
Australia	036-001	Kathy Nicholls
Australia	036-002	Mark Thomas
Brazil	076-001	Ana Maria Martins

Brazil	076-002	Roberto Giugliani
Canada	124-001	Daniel Bichet
Czech Republic	203-001	Gabriela Dostalova
Germany	276-001	Christine Kurschat
Japan	392-001	Koichiro Sugimura
Japan	392-002	Norio Sakai
Portugal	620-001	Olga Azevedo
South Korea	410-001	Yoo-Mi Kim
Taiwan	158-001	Yin-Hsiu Chien
United States	840-001	Ozlem Goker-Alpan
United States	840-003	Amel Karaa
United States	840-004	Raphael Schiffmann
United States	840-005	William Wilcox

1.9 REGISTRY PERSONNEL

1.9.1 Personnel involved in the registry

This report was prepared by:

• Pronabesh DasMahapatra, Head of Health Economics and Value Assessment, Rare Disease

• Frederic Le-Foll, Global Study Manager

• Julie Pinard, Global Study Manager

• Laurence Salin, Clinical Study Director

1.9.2 The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the registry.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

1.9.3 Service Provider

(a) Data collection for paper based and electronic PRO was performed by eResearch Technology (ERT) and Linical

Contact information for ERT : Beate Vought, Project Manager
eResearch Technology
225 West Station Square Drive
Pittsburgh, PA 15219

Contact information for Linical : Rafael Castillo, Data Project Manager
C/Rosa de Lima, 1-bis, Edificio Alba
28290 Las Matas (Madrid)
Spain

(b) Data management and statistical analyses were conducted by Pharmerit International

Contact Information: Charlie Iaconangelo, PhD

Daniel Serrano, PhD

Pharmerit International

4350 East West Highway, Suite 1100

Bethesda, MD 20814

2 APPENDIX II – TABLES AND GRAPHS

Table 1. Patient Reported Outcome (PRO) and Clinician Reported Outcome (ClinRO) Assessed in the Study

Instruments	Topics	Time of assessment
PRO		
FD-PRO	FD symptoms, 19 items (plus the Bristol Stool Rating Scale)	Daily
SF-36v2	HRQoL (generic), 36 items, 8 domains (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health)	Day 1 and Day 30 (Week 4)
BDI-II	Depression symptoms, 21 items	Day 1 and Day 30 (Week 4)
IBS-QoL	IBS impact on HRQoL, 34 items, 8 subscales (Dysphoria, Interference with Activity, Body Image, Health Worry, Food Avoidance, Social Reaction, Sexual, Relationships)	Day 1 and Day 30 (Week 4)
DS3 FD Severity Scoring System Patient Item	Overall patient well-being in the last month	Day 1 and Day 30 (Week 4)
PGIS	FD symptoms, single-item	Day 1, Week 1– Week 4
ClinRO		
PGA	FD patient's signs and symptoms, single-item	Day 1 and Day 30 (Week 4)
DS3 PNS domain	FD severity: sweating, GI, and pain subdomains	Day 1 and Day 30 (Week 4)
DS3 Renal domain	FD severity: eGFR, proteinuria, and eGFR slope assessments	Day 1 and Day 30 (Week 4)
DS3 Cardiac domain	FD severity: LVH, arrhythmia, and NYHA class assessments	Day 1 and Day 30 (Week 4)
DS3 CNS domain	FD severity: white matter lesions and TIA/stroke assessments	Day 1 and Day 30 (Week 4)

Table 2. Baseline Participant Characteristics

Characteristics	FD Patient Data (N=138)
Age in years, mean (SD)	43.0 (13.7)
Male, n (%)	73 (52.9)
Race, n (%)	
White	116 (84.1)
Asian	20 (14.5)
Multiracial	1 (0.7)
American Indian or Alaska native	1 (0.7)
Ethnicity, n (%)	
Hispanic or Latino	68 (49.3)
Not Hispanic or Latino	68 (49.3)
Not reported	2 (1.4)
Country, n (%)	
Argentina	20 (14.5)
Australia	18 (13)
Brazil	18 (13)
Canada	8 (5.8)
Czech Republic	18 (13)
Germany	1 (0.8)
Japan	8 (5.8)
Portugal	20 (14.5)
South Korea	2 (1.4)
Taiwan	10 (7.2)
USA	15 (10.9)
Previous treatment, n (%)	
ERT-treated	99 (71.7)
Treatment naïve	39 (28.3)
Symptom severity at screening [a], n (%)	
Absent	16 (11.6)
Mild	34 (24.6)
Moderate	55 (39.9)
Severe	33 (23.9)

Figure 1. FD-PRO Score Generation

		Domain		Parcel Scoring	
Item		**Neuropathy Domain**	**Other Fabry Symptoms**	**Neuropathy Parcel**	**Impairment Parcel**
1	Pain in hands or arms	✓		✓	
2	Burning feeling in hands or arms	✓		✓	
3	Numbness in hands or arms	✓		✓	
4	Tingling in hands or arms	✓		✓	
5	Pain in feet or legs	✓		✓	
6	Burning feeling in feet or legs	✓		✓	
7	Numbness in feet or legs	✓		✓	
8	Tingling in feet or legs	✓		✓	
9	Headache		✓		
10	Abdominal pain		✓		
11	Heat intolerance		✓		
12	Swelling in lowe extremeties		✓		
13	Tinnitus		✓		✓
14	Tiredness/fatigue		✓		
15	Hearing impairment		✓		✓
16	Vision impairment		✓		✓
17	Sweating				

The FD-PRO items were built into a daily via electronic diary. The nature of the device ensured that patients that responded to the diary completed all items. That is, for a given diary, subjects either responded to all items or did not respond to any items. Thus, for purposes of analyzing the data it is not necessary to use imputation strategies or likelihood-based approaches to address the missing data within an individual assessment. Likewise, when scoring, there was no need to determine how to score cases with less than 100% missing data. Daily data should be averaged over 7 days to create weekly scores. In order for a patient's weekly score to be included in the analyses, *at least 4 out of 7 diaries* must have been completed by the subject that week. Fewer than 4 completed diaries result in the subject score for that week being considered missing.
Scoring instructions: The daily diary data was scored as follows: All weekly diary entries were first parceled into 7 items. Next, these 7 responses were averaged to compute a daily mean score. The algorithm can be written as,

$$\frac{Integer\left(\frac{\sum_{i=1}^{8} item_i}{8}\right) + \sum_{i=9}^{12} item_i + item_{14} \; + \; Integer\left(\frac{\sum item_{13}\; item_{15}\; item_{16}}{3}\right)}{7}$$

where "*Integer*" indicates a function for rounding a number to the nearest integer.

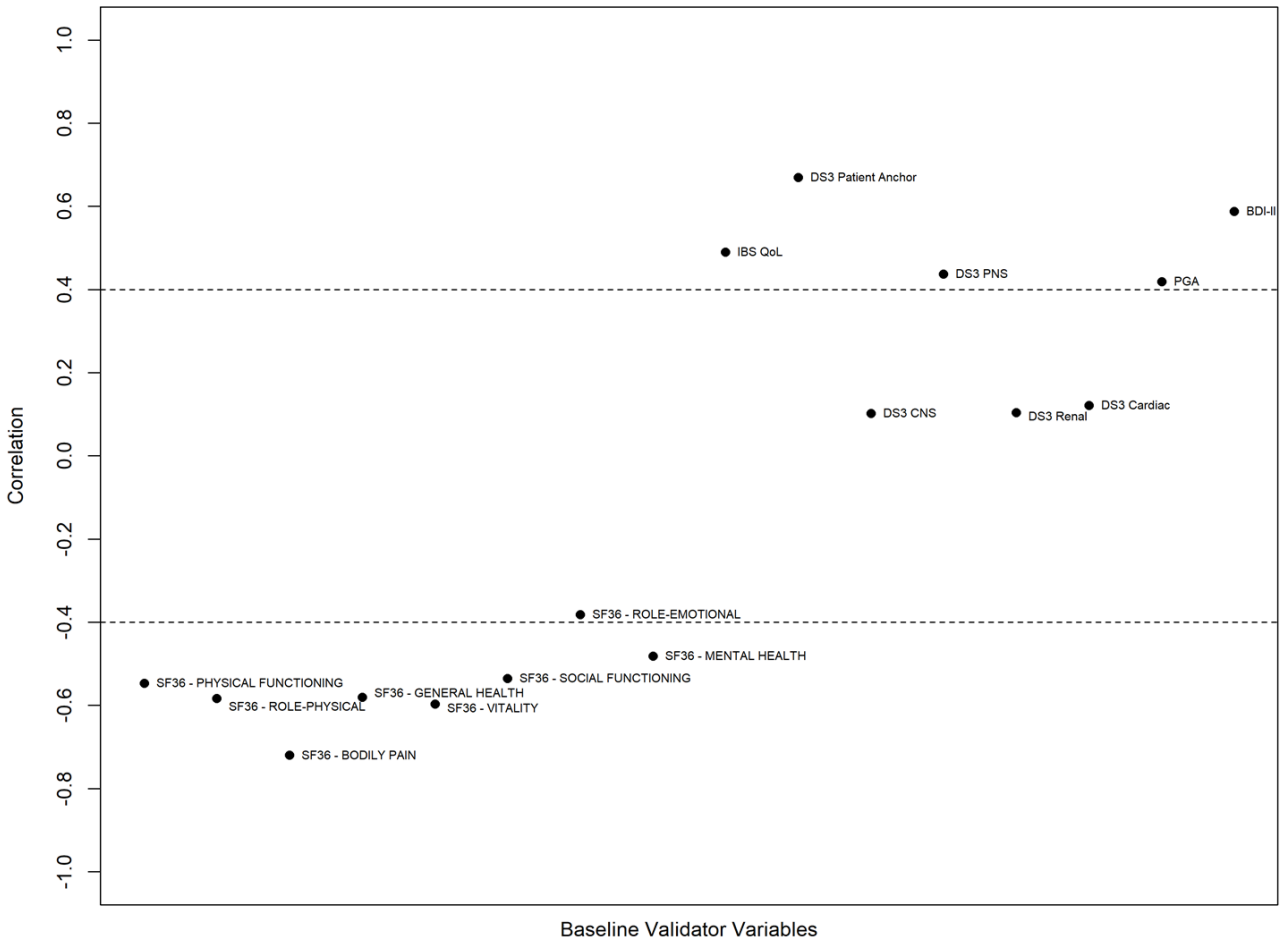
The daily diaries are then averaged to the week level. To compute weekly diary scores, the daily diary mean scores from each week were averaged to create a final score. This weekly score is labeled the FD-PRO Total Symptom Score (TSS).

1. Diary entries for items in the function are parceled into 7 items (as shown in the function)

2. Response are averaged at a day level to get daily scores

3. Daily scores are then averaged for a week to get weekly scores (assuming at least 4 out of 7 completed days)

Figure 2. Correlation between the FD-PRO and other assessments



3 APPENDIX III – SUPPORTIVE DOCUMENTS

3.1 PROTOCOL

Available on request

3.2 STATISTICAL ANALYSIS PLAN (SAP)

3.2.1 Final Statistical Analysis Plan

Available on request

3.2.2 Changes from the final Statistical Analysis Plan

Available on request

3.3 CASE REPORT FORM (CRF)/ PATIENT QUESTIONNAIRE

Available on request

3.4 PATIENT INFORMED CONSENT

Available on request

4 APPENDIX IV - PUBLICATIONS

4.1 REFERENCES

4.2 PUBLICATIONS/ABSTRACTS OF THE REGISTRY RESULTS

Hamed A, DasMahapatra P, Iaconangelo C, Serrano S, Gwaltney C (2019). Measurement Properties of the Fabry Disease Patient-Reported Outcome (FD-PRO), a New Instrument to Measure Symptoms in Fabry Disease (abstract presented at *WorldSymposium*, Orlando, FL, USA)

4.3 PUBLICATIONS CITED IN THE REFERENCE LIST

1. El-Abassi R, Singhal D, England JD. Fabry's disease. J Neurol Sci. 2014;344(1-2):5-19.

2. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30.

3. US Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, 2009.

4. Chen W-H, Thissen D. Local dependence indexes for item pairs using item response theory. J Edu Behav Stat. 1997;22(3):265-289

5. International Society for Pharmocoepidemiology, April 2007. 'Guidelines for Good Pharmacoepidemiology Practices'

6. Good Epidemiological Practice (GEP) proper conduct in epidemiology research - IEA European Federation (April 2007)