Supplementary Material

# Patient Reported Outcome Measures

## Pain

Aspects of pain and its interference on daily life were measured using the Brief Pain Inventory (BPI) and the Patient Reported Outcomes Measurement Information System (PROMIS) Short Form v1.1 – Pain Interference 8a (PI-8a). The BPI is a validated measure used to assess pain originally developed for use in cancer related pain, and later used in a wide variety of diseases including Pompe disease, multiple sclerosis, neuropathic pain, and fibromyalgia (Cleeland and Ryan, 1994; Tan et al., 2004; Cleeland, 2009; Güngör et al., 2013). The long form of the BPI was administered to patients after permission for use was obtained. Answers were scored on two domains, pain interference and pain severity, as outlined in The BPI User Guide distributed by survey developers (Cleeland, 2009). Variations in ratings of pain have previously been used and reported (Serlin et al., 1995; Li et al., 2007; Deandrea et al., 2008; Güngör et al., 2013). Pain was defined here as no interference (0), mild (1-3), moderate (4-6), and severe (7-10). The PI-8a is validated patient reported metric to assess the impact of pain on various aspects of an individual’s life (Amtmann et al., 2010). The PI-8a was scored using the HealthMeasures Scoring Service, powered by Assessment Center (https://www.assessmentcenter.net/ac\_scoringservice), which reported raw scores and t-scores for each respondent assuming a population statistics (mean = 50, SD = 10) with the general population used as the centering sample and the general population and a clinical sample used as the calibration sample (Amtmann et al., 2010; Cella et al., 2010; Rothrock et al., 2010). Patient t-scores were averaged and standard deviations away from population mean were obtained by subtracting the population mean from the patient average t-score and dividing by the standard deviation of 10. T-score cut offs for normal, mild, moderate, and severe pain interference are defined as less than 55, 55 to less than 60, 60 to less than 70, and 70 and greater (HealthMeasures; Cella et al., 2010; Rothrock et al., 2010).

## Fatigue

Fatigue and its impact on quality of life were measured using the Brief Fatigue Inventory (BFI) and the PROMIS Short Form v1.0 – Fatigue 13a (FACIT-Fatigue). The BFI is a validated metric initially used to measure fatigue in cancer patients, but has also been used in a variety of different conditions (Mendoza et al., 1999; Shahid et al., 2012; Liu et al., 2022; Ritchie et al., 2023). BFI was administered to patients and permission for use was obtained prior to distribution. BFI global fatigue score was calculated by averaging values across all nine domains assessed (Mendoza et al., 1999; Shahid et al., 2012). Scores were subsequently averaged across patients. Average domain scores are also reported. Fatigue is categorized as no fatigue (0), mild (1-3), moderate (4-6), and severe (7-10) (Mendoza et al., 1999; Shahid et al., 2012; Liu et al., 2022; Ritchie et al., 2023). The FACIT – Fatigue is a metric used to assess generalized fatigue and has utility in multiple conditions (Lai et al., 2011; Cella et al., 2016). The FACIT- Fatigue was scored using the HealthMeasures Scoring Service, powered by Assessment Center (https://www.assessmentcenter.net/ac\_scoringservice), which reported raw scores and t-scores for each respondent assuming a population statistics (mean = 50, SD = 10) with the general population used as the centering and calibration sample (Cella et al., 2010; Rothrock et al., 2010; Cella et al., 2016). Patient t-scores were averaged and standard deviations away from population mean were obtained by subtracting the population mean from the patient average t-score and dividing by the standard deviation of 10. T-score cut offs for normal, mild, moderate, and severe pain interference are defined as less than 55, 55 to less than 60, 60 to less than 70, and 70 and greater (HealthMeasures; Cella et al., 2010; Rothrock et al., 2010).

## Quality of Life

Quality of life was measured using the EuroQol Research Foundation EQ-5D-5L survey and the RAND 36 Item Health Survey 1.0 (SF-36). The EQ-5D-5L is a health-related quality of life metric used around the world and validated for use in the United States population (Janssen et al., 2013; Devlin et al., 2018; Janssen et al., 2018; Pickard et al., 2019). It has also been used in glycogen storage disorders types 1a and 2 (Hubig et al.; Kanters et al., 2011; Ghajarzadeh et al., 2018; Attal et al., 2021; Mawla et al., 2021; Kruger et al., 2023). The EQ-5D-5L measures quality of life across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. After permission was received from EuroQol Research Foundation, surveys were distributed to patients. Patient responses were mapped to specific health states as described in the EQ-5D-5L User Guide; health states were then converted into a utility index value using a standard validated value set for the United States that attributing weights to each dimension (EQ-5D, 2019; Pickard et al., 2019). Individual patient utility index values were then compared to published norm values (Jiang et al., 2021). The SF-36 is a widely used health related QoL measure initially developed in 1992 (RAND Corporation; Ware and Sherbourne, 1992; Hays et al., 1993; VanderZee et al., 1996). The RAND corporation has made SF-36 version 1 available for open access use. The SF-36 assesses QoL in the following eight domains: Physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. Patient responses were scored as recommended by the RAND corporation; scores were generated for all 8 domains described (RAND Corporation). Scores are assigned such that a score of 0 corresponds to the lowest possible health status and a score of 100 corresponds to the best possible health status (RAND Corporation). Patient scores were averaged and compared to population norms provided by the RAND corporation (RAND Corporation; Jiang et al., 2021).

# Supplementary Table 1

PROs were used to assess individual health states and results for each patient are displayed in addition to averaged values where appropriate. \*Represents standard deviations away from population mean or parameter

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| **Pain** |
| **Brief Pain Inventory** | **Patient 1** | **Patient 2** | **Patient 3** | **Average Value (n=3)** |
| Pain severity score  | 3.5 | 6 | 7 | 5.5 |
| Pain interference score | 4.0 | 5.7 | 8.7 | 6.1 |
| ***Pain descriptors***  |  |  |  | ***No. of Patients*** |
| Aching | Yes | No | Yes | 2 |
| Throbbing | No | No | Yes | 1 |
| Shooting  | No | No | No | 0 |
| Stabbing | No | No | Yes | 1 |
| Gnawing | Yes | No | Yes | 2 |
| Sharp | No | No | Yes | 1 |
| Tender | No | Yes | No | 1 |
| Burning | No | No | Yes | 1 |
| Exhausting | Yes | No | Yes | 2 |
| Tiring | Yes | No | Yes | 2 |
| Penetrating | Yes | No | Yes | 2 |
| Nagging | Yes | No | Yes | 2 |
| Numb | No | No | Yes | 1 |
| Miserable | No | Yes | Yes | 2 |
| Unbearable | No | No | Yes | 1 |
| **PROMIS Pain Interference - SF 8a** | **Patient 1** | **Patient 2** | **Patient 3** | **Average Value (n=3)** |
| Raw score | 24 | 16 | 37 |   |
| t-score | 61.4 | 55.9 | 70.7 | 62.7 |
| Standard deviation\* |  |  |  | 1.3 |
| **Fatigue** |
| **Brief Fatigue Inventory**  | **Patient 1** | **Patient 2** | **Patient 3** | **Average Value (n=3)** |
| Current fatigue  | 3 | 8 | 8 | 6.3 |
| Usual fatigue  | 5 | 7 | 8 | 6.7 |
| Worst fatigue | 8 | 9 | 9 | 8.7 |
| General activity | 3 | 7 | 9 | 6.3 |
| Mood | 3 | 5 | 9 | 5.7 |
| Walking ability | 5 | 10 | 9 | 8.0 |
| Normal work | 2 | 8 | 10 | 6.7 |
| Relations with others | 3 | 3 | 8 | 4.7 |
| Enjoyment | 5 | 5 | 7 | 5.7 |
| Global fatigue score | 4.1 | 6.9 | 8.6 | 6.5 |
| **PROMIS - Fatigue Short Form 13a** | **Patient 1** | **Patient 2** | **Patient 3** | **Average Value (n=3)** |
| Raw scores | 31 | 36 | 51 | 39.3 |
| t-score | 55.3 | 58.2 | 66.5 | 60.0 |
| Standard deviation\* |  |  |  | 1.0 |
| **Quality of Life** |
| **SF - 36** | **Patient 1** | **Patient 2** | **Patient 3** | **Average value (n=3)** |
| Physical functioning | 65 | 0 | 5 | 23.3 |
| Role functioning/ physical | 75 | 0 | 0 | 25.0 |
| Role functioning/ emotional | 66.7 | 0 | 100 | 55.6 |
| Energy/ fatigue | 30 | 20 | 10 | 20.0 |
| Emotional well-being | 60 | 44 | 64 | 56.0 |
| Social functioning | 62.5 | 12.5 | 0 | 25.0 |
| Pain  | 55 | 57.5 | 10 | 40.8 |
| General Health | 30 | 20 | 15 | 21.7 |
| **EQ-5D-5L** | **Patient 1** | **Patient 2** | **Patient 3** |   |
| Health states | 32233 | 54532 | 42442 |   |
| Utility index | 0.5 | 0.048 | 0.044 |   |
| Standard deviation\* | 1.7 | 3.9 | 3.9 |   |

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