Psychometric validation of the Inflammatory-Rasch-built Overall Disability Scale (I-RODS) and Modified Rasch-built-Fatigue Severity Scale (R-FSS) in adult patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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Introduction

- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a rare autoimmune disease characterized by chronic progressive or recurrent weakness and numbness, sensory dysfunction, and impaired or absent tendon reflexes, with over half of individuals living with CIDP unable to walk unaided at times (1-3).
- Fatigue reported in up to 80% of patients and correlates over time with increased disability and worse quality of life (4).
- Currently, a phase 2 riliprubart trial (NCT04658472) in adults with CIDP is ongoing. Evaluation of psychometric properties of instruments in the trial within the target population is needed, including the Inflammatory-Rasch-built Overall Disability Scale (I-RODS) and the Modified Rasch-built-Fatigue Severity Scale (R-FSS).

Objectives

- To conduct psychometric validation of and derive meaningful change thresholds for the I-RODS and the R-FSS, in CIDP patients enrolled in Sanofi's phase 2 riliprubart trial (NCT04658472).

Methodology

Study design

- Multinational, multicenter, open-label, non-randomized, proof-of concept phase 2 study to evaluate the efficacy, safety, and tolerability of SAR445088 in adults with CIDP (Table 1).
- Subgroups: Standard Of Care (SOC) Naïve, SOC-Refractory and SOC-Treated.
- Analyses using pooled population.
- Data collected throughout initial 24 weeks of treatment period (cutoff date: April 12th, 2023) with data for I-RODS at Days 1, 22, 50, 78, 106 and 162 and for R-FSS at Days 1, 78 and 162.

Instruments

- **I-RODS:** 24-item patient reported outcome (PRO) assessing activity and social participation limitations in chronic CIDP with recall period of "currently"; total score from 0-100 (higher score=fewer limitations); 2 domains: activity and social participation.
- **R-FSS**: 7-item PRO assessing severity and impact of fatigue over past 7 days; score=raw sum of all items; observed range 0-21 in present study (higher score=more severe fatigue).
- **Other measures**: EuroQoL 5-Dimension 5-Level (EQ-5D-5L)(5), Inflammatory Neuropathy Cause and Treatment (INCAT)(6), Martin Vigorimeter Grip Strength (7), Physician's Global Assessment of disease severity (PhysGAS), Patient Global Impression of disease Change (PGI-C), PGI-C Fatigue (PGIC-F), Patient Global Impression of Severity (PGI-S) and PGI-S Fatigue (PGIS-F).

Psychometric analysis:

- Item-level analysis
- Reliability
- Construct Validity
- Structural validity (Rasch)
- Responsiveness
- Meaningful change threshold

Results

- **Population:** 64 patients (47 males and 17 females), mostly diagnosed with typical CIDP (Table 1).

Table 1: Description of studied population

Variables, n (%)	SOC-NAIVE (N=11)	SOC-REFRACTORY (N=19)	SOC-TREATED (N=34)	Total (N=64)
Age [mean (SD)]	62.62 (14.64)	63.74 (14.64)	57.35 (13.97)	60.16 (14.38)
Male, n (%)	8 (72.7%)	12 (63.2%)	27 (79.4%)	47 (73.4%)
CIDP Phenotype				
Typical CIDP, n (%)	8 (72.7%)	15 (78.9%)	25 (73.5%)	48 (75.0%)
Pure Motor CIDP, n (%)	0 (0.0%)	0 (0.0%)	2 (5.9%)	2 (3.1%)
Lewis-Summer Syndrome, n (%)	3 (27.3%)	4 (21.1%)	7 (20.6%)	14 (21.9%)

- **Floor/Ceiling effect**: Floor and ceiling effects for some I-RODS and R-FSS items, but not on total scores. All timepoints considered.
- **Internal consistency**: Very good evidence: Cronbach's alpha > 0.90 for both I-RODS and R-FSS. All timepoints considered.
- **Test-retest**: Very good evidence found with Intraclass Correlation Coefficients (ICC) assessed at Day 1 and Day 78 (ICC=0.848 for I-RODS; ICC=0.861 for R-FSS).
- **Convergent validity**: I-RODS correlated moderately with PGI-S and strongly with EQ-5D-5L Mobility and Usual Activities domains, Martin Vigorimeter, and PhysGAS, while R-FSS strongly correlated with PGIS-F (Table 2). All timepoints considered.
- **Discriminant validity**: Though still moderate, I-RODS correlated more weakly with EQ-5D-5L – Anxiety/depression domain than others more conceptually similar (Table 2). All timepoints considered.

Table 2: Convergent/Discriminant Validity: Pearson Correlations

Measure	I-RODS Total Score Correlation (p-value)	R-FSS Rasch-Built Score Correlation (p-value)
Convergent Validity		
INCAT Disability Scale Score	-0.75 (<.001)	0.24 (0.006)
Martin Vigorimeter Grip Strength	0.56 (<.001)	-0.12 (0.156)
EQ-5D-5L – Mobility Domain	-0.77 (<.001)	0.39 (<.001)
EQ-5D-5L – Usual Activities Domain	-0.79 (<.001)	0.43 (<.001)
PGI-S	-0.46 (<.001)	0.32 (<.001)
PGIS-F	-0.44 (<.001)	0.54 (<.001)
PhysGAS	-0.72 (<.001)	0.29 (<.001)
Discriminant Validity		
EQ-5D-5L – Anxiety/depression Domain	-0.41 (<.001)	0.31 (<.001)

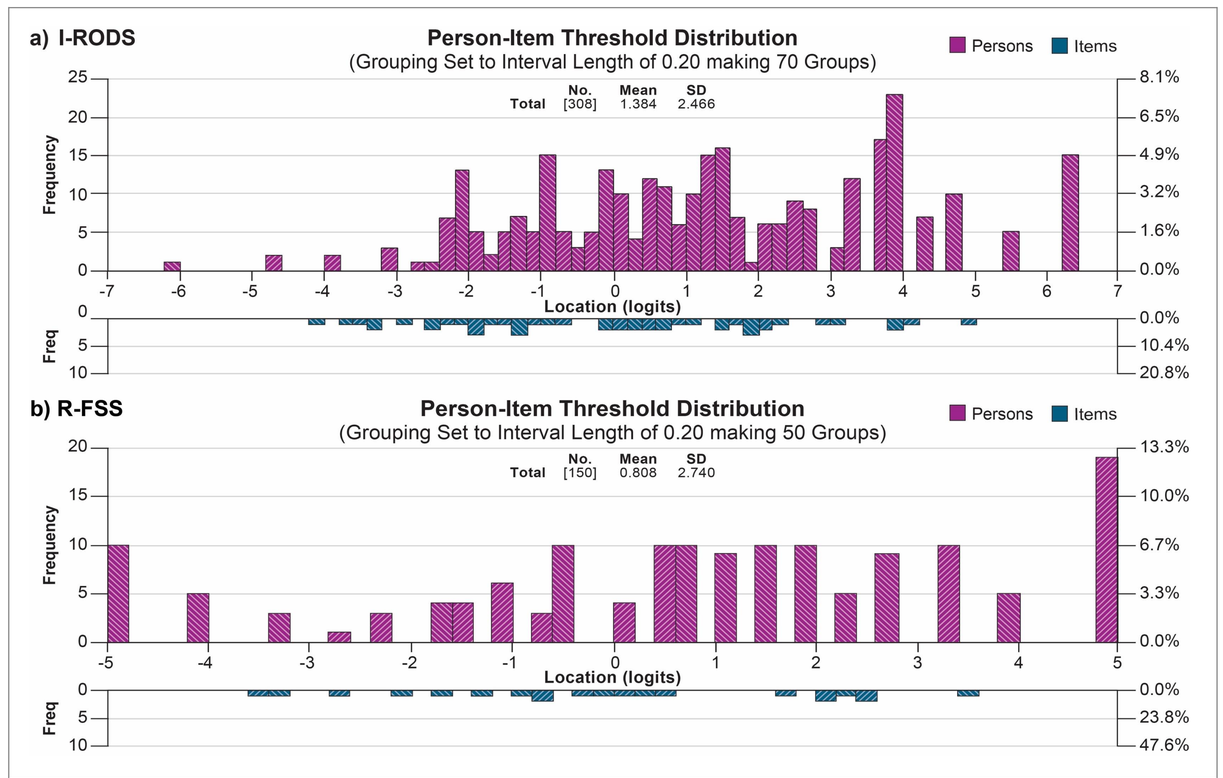
Strong correlation (r≥0.5) Moderate correlation (0.30≤r<0.5)

Higher overall INCAT Disability Scale Score=more disability; adjusted scores used.
Higher Martin Vigorimeter Grip Strength Score=more grip strength; score computed based on dominant hand.
Higher I-RODS Score=fewer limitations.
Higher R-FSS Score=more severe fatigue.
Grey font=Relationships not hypothesized a priori.
Correlations assessed via repeated measures correlations using data from all timepoints.

Results (continued)

- **Structural validity (by Rasch analysis)**:
  - The I-RODS and the R-FSS differentiated sufficiently between low and high scores (Person Separation Index: 0.948 and 0.903).
  - Average item fit residuals and their Standard Deviations (SD) (I-RODS: -0.911 [SD=1.662] and R-FSS: -0.120 [1.330]) were within recommended ranges (0+/-2.5 [1+/-2.5]).
  - Andrich thresholds were monotonically ordered, and person-item threshold distributions (Figure 1) supported alignment between item and person measures for both PROs.
  - Item misfit was observed for 10 items of the I-RODS.

Figure 1: Person-Item Threshold Distributions for I-RODS and R-FSS



Using data from Days 1, 22, 50, 78, 106 and 162 for a) I-RODS and data from Days 1, 78 and 162 for b) R-FSS.

- **Responsiveness**: Moderate changes between Days 1 and 162 for Improved categories of PGI-S and PGI-C in I-RODS, and PGIS-F and PGIC-F in R-FSS (0.50 ≤ Effect Size / Standardized Response Mean < 0.80). No significance (p<0.05) between change categories of anchors for both PROs likely due to small sample size.
- **Responder Definition (RD; within patient difference)**: Between Days 1 and 162, RD range of 3-16 for I-RODS, and 2-8 for R-FSS (Table 3). Analysis of I-RODS and PGI-S not considered because of poor correlation between the two measures (r<0.3)
- **Clinically Important Difference (CID; between group difference)**: Between Days 1 and 162, range of 8-10 for I-RODS, and 3-4 for R-FSS (Table 3).

Table 3: Overview of RD and CID estimates and triangulation result for the I-RODS and R-FSS

	I-RODS	R-FSS	
	PGI-C Improved vs No Change/ Worsened	PGIS-F improved vs No Change/ Worsened	PGIC-F Improved vs No Change/ Worsened
RD Anchor-Based (CDF difference in change score at percentile)			
25%	-3.0	8.0	4.0
50%	-8.0	4.0	3.0
75%	-16.0	3.0	3.0
90%	-10.0	7.0	7.0
ROC analyses – Youden	8	-6	2/-4
RD (individual level)	**3-16**	**2-8**	
CID Anchor-Based			
Mean Change Difference	-8.26	3.48	3.88
CID Distribution-Based			
0.5 SD (Baseline SD/2)	10.269	3.237	
Observed CID (group level)	**8-10**	**3-4**	

Based on data from Day 1 to Day 162; RD=Responder Definition; CID=Clinically Important Difference; CDF=Cumulative Distribution Curve; SD=Standard Deviation

Discussion

Strengths:

- Data from several timepoints were analyzed.
- Analyses were conducted using classical test theory and Rasch analysis.

Limitations:

- Limited sample sizes within subgroups and overall (due to the rare nature of CIDP).
- Intervals between assessments for test-retest reliability were rather large (11 weeks).

CONCLUSIONS

Considering regulatory standards and FDA guidelines, generally moderate to strong evidence was found to support the psychometric properties of the I-RODS and the R-FSS in adults with CIDP, thus indicating their acceptability as endpoint measures in clinical trials in CIDP patients.

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CONFLICT OF INTERESTS
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