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Assessing Minimal Clinically Important Difference Estimates for the Rett Syndrome Behaviour Questionnaire Using Data From the Trofinetide Clinical Program

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INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disease caused by loss-of-function mutations in the *MECP2* gene[1]
  - Core RTT symptoms include partial or complete loss of purposeful hand skills and spoken language, alongside gait abnormalities and stereotypic hand movements[2,3]
  - Patients with RTT typically have limited nonverbal skills and several comorbidities including seizures, scoliosis, impaired sleep patterns, and behavioral and gastrointestinal issues[2,3]
- One of the most frequently used measures in clinical programs assessing change in outcomes of Rett Syndrome is the Rett Syndrome Behaviour Questionnaire (RSBQ), a caregiver assessment of the key symptoms of RTT[4]
  - The RSBQ includes 45 items, rated as 'not true' (0), 'somewhat or sometimes true' (1), and 'very true' (2), that assess general mood, breathing problems, hand behaviors, repetitive face movements, body rocking and expressionless face, nighttime behaviors, fear/anxiety, and walking/standing[4]
- In RETT-002 and LAVENDER, phase 2 and 3 placebo-controlled studies of trofinetide in female patients with RTT, respectively, trofinetide improved the core symptoms of RTT based on RSBQ scores[5,6]
  - The least squares mean (LSM) change from baseline in RSBQ total score at day 56 (6 weeks) in RETT-002 was -6.7 (1.46) and -2.3 (1.54) for trofinetide 200 mg/kg and placebo, respectively (P = 0.042; Cohen's d effect size = 0.49)[5]
  - The LSM change from baseline in RSBQ total score at week 12 in LAVENDER was -4.9 (0.94) and -1.7 (0.90) for trofinetide and placebo, respectively (P = 0.0175; Cohen's d effect size = 0.37)[6]
  - In both RETT-002 and LAVENDER, the Cohen's d effect size indicates a medium size effect between trofinetide and placebo
- Trofinetide is approved for the treatment of RTT in patients aged ≥2 years in the United States and patients aged ≥2 years weighing ≥9 kg in Canada[7,8]
- A couple of recent reviews of RTT outcome measures have described the RSBQ instrument properties and compared it to alternate RTT outcomes measurements, concluding that more research and assessment of all RTT measures are warranted[9,10]
- The minimal clinically important difference (MCID) is a useful threshold for the interpretation of change from an intervention as measured by a scale
  - A MCID for the RSBQ total score has not been approximated or reported to date
  - Based on the method for pooling standard deviations (SDs) suggested by Furukawa et al.,[11] Watt et al. approximated the MCID using distribution-based methods by pooling SDs across multiple trials in a neuropsychiatric disorder[12]

OBJECTIVE

- To estimate the MCID in RSBQ total score for patients with RTT using pooled data from the trofinetide clinical studies

METHODS

- Data from RETT-002 (NCT02715115), a 6-week, double-blind, randomized, placebo-controlled phase 2 study and LAVENDER (NCT04181723), a 12-week, double-blind, randomized, placebo-controlled phase 3 study were used for the MCID estimation
- A distribution-based method using the pooled SDs from both treatment arms of RETT-002 and LAVENDER were used for the MCID estimation[11]
  - The baseline RSBQ mean total score and mean change from baseline values were used to derive a range of plausible MCIDs at the 0.4 and 0.5 SD thresholds based on the methods published by Furukawa et al.[11]

$$\mathrm{SDpooled} = \sqrt{\frac{\sum(n_i - 1)SD_i^{\,2}}{\sum(n_i - 1)}}$$

- A couple of limitations of the current methodological approach are worth noting until further research is available
  - The statistical approach used to determine the MCID in this study evaluates the extent to which the difference between treatment groups is clinically relevant for the trial populations studied (it may not be the point change that is relevant for individual patients)
  - An estimation of the MCID using anchor-based methodology was not possible with the study data available for analysis

RESULTS

Demographic and Clinical Characteristics

- Overall, 82 females from RETT-002 and 187 females from LAVENDER were included in this analysis (**Table 1**)

Estimation of MCID

- The pooled total RSBQ score SD (standard error [SE]) at baseline was 11.39 (0.84) and 11.87 (0.87) for RETT-002 and LAVENDER, respectively (**Table 2**)
- Using the 0.4 and 0.5 SD MCID thresholds at baseline, the RSBQ MCIDs ranged from 4.56–5.93 for RETT-002 and LAVENDER (**Table 2**)

Table 1. Demographic and Clinical Characteristics

	RETT-002 (N = 82)	LAVENDER (N = 187)
Mean (SD) age, years	9.7 (3.4)	10.9 (4.6)
Age categories, n (%)		
≤10 years	52 (63)	101 (54)
>10 years	30 (37)	86 (46)

Table 2. Estimation of MCID with RETT-002 and LAVENDER RSBQ Total Scores

	Placebo, mean (SD)	Trofinetide, mean (SD)	Pooled SD	MCID (0.4 x SD)	MCID (0.5 x SD)
RETT-002					
Baseline RSBQ total score	39.5 (11.83)	42.2 (10.99)	11.39	4.56	5.70
Change from baseline in RSBQ total score at week 6	-2.0 (6.92)	-5.8 (8.99)	8.06	3.23	4.03
LAVENDER					
Baseline RSBQ total score	44.5 (12.20)	43.7 (11.52)	11.87	4.75	5.93
Change from baseline in RSBQ total score at week 12	-1.7 (9.05)	-5.1 (8.67)	8.87	3.55	4.44

MCID, minimal clinically important difference; RSBQ, Rett Syndrome Behaviour Questionnaire

- At the end of study assessments, the MCIDs based on change from baseline in total RSBQ score ranged from 3.23–4.03 for RETT-002 and 3.55–4.44 for LAVENDER (**Table 2**)
- Taken together, the MCID for the RSBQ total score across the trofinetide clinical trial program is likely to be within a 3- to 6-point difference

CONCLUSIONS

- Providing a plausible MCID range can be a meaningful starting point for trial result interpretation, discussion, and to encourage further research
- Our findings provide an initial estimation using data from the trofinetide clinical program and suggest that the MCID for the RSBQ total score is likely to be within a 3- to 6-point difference
  - Changes in outcomes greater than this range are likely clinically important, based on natural variability observed in the data
  - Smaller changes likely reflect measurement error rather than true clinical changes
- The estimated MCID for the RSBQ total score in patients with RTT is currently limited to the distribution-based approach used here; these analyses should be confirmed via further investigation and expert consultations

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DISCLOSURES

MVS, **NR**, **RR**, and **JMY** are employees and stakeholders in Acadia Pharmaceuticals Inc.

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