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DAYBUE™ (trofinetide): Scales Used to Measure Efficacy in the LAVENDER™ Study

This letter is provided in response to your specific request for information regarding the scales used in the Phase 3 clinical trial, LAVENDER, to measure the efficacy of trofinetide in Rett syndrome (RTT).

Summary

- In the Phase 3 LAVENDER study assessing trofinetide in 187 female participants (5–20 years old) with RTT, co-primary efficacy endpoints measured symptoms using the caregiver-assessed **Rett Syndrome Behaviour Questionnaire (RSBQ)** total score (change from baseline to Week 12) and the clinician-assessed **Clinical Global Impression-Improvement (CGI-I)** (score at Week 12).[1]
- The key secondary endpoint was change from baseline to Week 12 in the **Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score (CSBS-DP-IT Social)**.[1]
- **Other secondary efficacy endpoints** included a range of caregiver- and clinician-rated scales across various several symptomatic domains of RTT.[1] However, the study was not designed or powered to show statistically significant difference from placebo for these secondary endpoints.

RSBQ

The RSBQ, which is a widely used rating scale for assessment of RTT patients, was one of the two co-primary endpoints in the Phase 3 LAVENDER study, assessed as the change in total score from baseline to Week 12.[1,2] The RSBQ is a 45-item rating scale completed by the caregiver that assesses a range of symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night-time behaviors, vocalizations, facial expressions, eye gaze, and mood) (**Table 1**).[3,4] The RSBQ is a validated instrument previously used in other studies in RTT,[5-7] including studies by other sponsors designed for submission to FDA.[8] The RSBQ has been characterized and validated across a range of ages (2 to 47 years) and genetic variations in RTT.[2,9-12]

Every patient with RTT has a different set of symptoms, therefore the total score of the RSBQ was used in LAVENDER to assess the efficacy of trofinetide compared with placebo across a variety of symptoms observed in RTT. The caregiver rates each of the 45 items as "0" (not true), "1" (somewhat or sometimes true), or "2" (very true or often true). In general, the prompts for RSBQ represent symptoms of RTT, meaning that the score of "2" indicates greater severity or frequency of symptoms.[8] Lower scores reflect lesser severity in signs and symptoms of RTT.[3] The exception is item 31 ("Uses eye gaze to convey feelings, needs, and wishes") for which the score of "2" (very true) indicates a better outcome. In LAVENDER, the score for item 31 ("Uses eye gaze to convey feelings, needs, and wishes") was reversed in the calculations of total score because the score of "2" (very true) reflects a better outcome; therefore, decreases in RSBQ total score denote improvement.[8]

In LAVENDER, the RSBQ was administered to caregivers by qualified site personnel who were required to have previous experience with neurodevelopmental disorders or previous experience facilitating patient-reported or caregiver-reported outcome instruments and to complete training on each assessment.[8]

Table 1. RSBQ Items[4]

1. There are times when breathing is deep and fast (hyperventilation)
2. Spells of screaming for no apparent reason during the day
3. Makes repetitive hand movements with hands apart
4. Makes repetitive hand movements involving fingers around tongue
5. There are times when breath is held
6. Air or saliva is expelled from mouth with force
7. Spells of apparent anxiety/fear in unfamiliar situations
8. Grinds teeth
9. Seems frightened when there are sudden changes in own body position
10. There are times when parts of the body are held rigid
11. Shifts gaze with slow horizontal turn of head
12. Expressionless face
13. Spells of screaming for no apparent reason during the night
14. Abrupt changes in mood
15. There are certain days/periods where she performs much worse than usual
16. There are times when she appears miserable for no apparent reason
17. Seems to look through people into the distance
18. Does not use hands for purposeful grasping
19. Swallows air
20. Hand movements are uniform and monotonous
21. Has frequent naps during the day
22. Screams hysterically for long periods of time and cannot be consoled
23. Although can stand independently tends to lean on objects or people
24. Restricted repertoire of hand movement
25. Abdomen fills with air and sometimes feels hard
26. Spells of laughter for no apparent reason during the day
27. Has wounds on hands as a result of repetitive hand movements
28. Makes mouth grimaces
29. There are times when she is irritable for no apparent reason
30. Spells of inconsolable crying for no apparent reason during the day
31. Uses eye gaze to convey feelings, needs and wishes
32. Makes repetitive tongue movements
33. Rocks self when hands are prevented from moving
34. Makes grimacing expressions with face
35. Has difficulty in breaking/stopping hand stereotypies
36. Vocalizes for no apparent reason
37. Spells of laughter for no apparent reason during the night
38. Spells of apparent panic
39. Walks with stiff legs
40. Tendency to bring hands together in front of chin or chest
41. Rocks body repeatedly
42. Spells of inconsolable crying for no apparent reason during the night
43. The amount of time spent looking at objects is longer than the time spent holding or manipulating them
44. Appears isolated
45. Vacant ‘staring’ spells

Abbreviation: RSBQ=Rett Syndrome Behaviour Questionnaire.

CGI-I

The CGI-I was a co-primary endpoint in the Phase 3 LAVENDER study, assessed as the score at Week 12.[1] The Clinical Global Impression (CGI) scale, which includes both the Improvement (CGI-I) and the Severity (CGI-S) scales,[13] is a well-established research rating tool used widely in clinical studies of CNS disorders,[14] including neurodevelopmental disorders.[15-17]

The CGI-I is completed by the clinician who is required to rate how much the subject's illness improved or worsened relative to the subject's illness at a baseline state. In LAVENDER, the clinician is asked *"Compared to the baseline assessment in this study, if you consider the signs and symptoms associated with this patient's Rett syndrome, how much has she changed? Rate her total improvement whether or not, in your judgment, it is due entirely to the study drug. Please consider how the patient has been doing over the past week, in particular."* A 7-point scale is used: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse. Decreases in scores denote improvement.[8]

The CGI-I ratings in LAVENDER were assessed using RTT-specific anchors across major symptom areas to assess RTT as a whole.[2] The anchors were developed by Neul et al. to provide a framework for considering the following factors related to symptom duration, onset, durability of change, and the context of sign/symptom change across the symptom domains. Information on factors to differentiate between the scores was provided (**Table 2**).[18] To ensure ratings were consistently applied in the trofinetide clinical studies, training and standardization of the CGI-I ratings by all study raters and qualification of raters was required. To achieve this, an expert panel wrote a series of clinical case vignettes. All CGI raters were trained on anchors and case vignettes and discussed the panel's "gold standard" CGI-I ratings.[2,8]

Table 2. RTT-specific CGI-I Anchors[18]

Score	CGI-I:	Rett Anchors
1	*Very much improved*	*Very Much Improved* designates marked improvement, across settings and/or across multiple behavior problems. Although a CGI-I of 1 does not strictly require that the patient qualify for a CGI-S rating better than baseline, usually the CGI-S does also improve. Such improvement must be very substantial and is usually accompanied by considerable caregiver enthusiasm. Such patients are usually noticeably improved behaviorally in the clinic as well.
2	*Much improved*	*Much Improved* may denote moderate improvement in a single symptom area, *especially if seen across settings.* Likewise, *moderate improvements in several areas,* even if confined to one setting, may warrant a rating of "Much improved." Durability of the change should be taken into account. For example, a change reported for the last few days probably would not warrant such a rating. On the other hand, a change that coincided with a dose change and was clearly in evidence for the last week or longer probably would warrant a rating of 2. It is not necessary that the patient qualify for a CGI-S rating better than baseline to receive a CGI-I rating of 2, but often (not always) the CGI-S also improves.
3	*Minimally improved*	*Minimal Improvement* indicates modest improvements, especially if confined to one setting. Trivial changes or changes that are *possibly present* or require guesswork usually would be scored as 4 (the level below this one).
4	*No change*	*No Change* indicates, by definition, the absence of change in behavior or clinical presentation from baseline to subsequent assessments. Chance

Score	CGI-I:	Rett Anchors
		fluctuations and equivocal improvements or declines should be included here.
5	*Minimally worse*	*Minimally Worse (5)* indicates some worsening in symptoms that are mild to moderate or may be confined to one setting.
6	*Much worse*	*Much Worse (6)* designates moderate to moderately severe worsening. This may include moderate levels of worsening in a single symptom area when observed across settings. Moderately severe changes that are confined to one setting may warrant a rating of "Much Worse."
7	*Very much worse*	*Very Much Worse (7)* designates significant worsening, across settings and/or across multiple symptoms.
N.B.	CGI-improvement is a rating of change; normalization is not necessary for a rating of 1, although if behavior is normalized, it suggests an Improvement score of 1. A CGI-I of 2 is appropriate for definite, unequivocal improvement of a magnitude that makes the clinician confident that the treatment is helping. An improvement score of 3 (or 5) is appropriate if variations in ratings and other criteria appear to represent more than random chance or rating error, but are not definite and unequivocal. A score of 4 is appropriate for slight variation in either direction of a magnitude that is likely due to chance, natural history, external events, or rating error.	

Abbreviations: CGI-I=Clinical Global Impression–Improvement; CGI-S=Clinical Global Impression–Severity; RTT=Rett syndrome.

CSBS-DP-IT Social

The CSBS-DP-IT Social was the key secondary endpoint in LAVENDER, assessed as change from baseline to Week 12.[1] The CSBS-DP-IT Social is intended to be a screening tool to identify potential communication issues in otherwise healthy infants/toddlers. This tool has not been validated for use in patients with RTT.

The Infant-Toddler Checklist, one of three components of the Communication and Symbolic Behavior Scales Developmental Profile™ (CSBS-DP), is a caregiver-completed questionnaire that was originally developed to assess communication and pre-linguistic skills in young children (12 to 24 months of age).[19] It has been used with older children with developmental delay,[20] including RTT.[7] Given the limited communication abilities of individuals with RTT, the CSBS-DP-IT Checklist was assessed and a subset of items were found to be appropriate for assessing communication skills of individuals with RTT 8 to 19 years of age.[21]

The Social Composite score (CSBS-DP-IT Social) evaluates a range of non-verbal communication modalities commonly used by people with RTT. It is comprised of the first 13 items of the 24 items on the checklist. The 13 items are divided into three skill areas "Emotion and Eye Gaze (items 1 to 4), "Communication" (items 5 to 8), and "Gestures" (items 9 to 13) that range from 0 to 2 points (**Table 3**). Credit of 0 points is given for items checked "Not Yet", 1 point for items checked "Sometimes", or 2 points for items checked "Often". Higher scores indicate better social communication development.[2,8,22]

Table 3. CSBS-DP-IT Social Items[22]

Emotion and Eye Gaze	1. Do you know when your child is happy and when your child is upset?
	2. When your child plays with toys, does he/she look at you to see if you are watching?
	3. Does your child smile or laugh while looking at you?
	4. When you look at and point to a toy across the room, does your child look at it?
Communication	5. Does your child let you know that he/she needs help or wants an object out of reach?
	6. When you are not paying attention to your child, does he/she try to get your attention?
	7. Does your child do things just to get you to laugh?
	8. Does your child try to get you to notice interesting objects—just to get you to look at the objects, not to get you to do anything with them?
Gestures	9. Does your child pick up objects and give them to you?
	10. Does your child show objects to you without giving you the object?
	11. Does your child wave to greet people?
	12. Does your child point to objects?
	13. Does your child nod his/her head to indicate yes?

Abbreviation: CSBS-DP-IT Social=Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score.

In LAVENDER, the CSBS-DP-IT Social was administered to caregivers by qualified site personnel who were required to have previous experience with neurodevelopmental disorders or previous experience facilitating patient-reported or caregiver-reported outcome instruments and to complete training on each assessment.[8]

Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints in LAVENDER are shown in **Table 4** and **Table 5**, assessed as the change from baseline to Week 12.[2] The study was not designed or powered to show statistically significant difference from placebo for other secondary endpoints.

Table 4. Other Secondary Efficacy Endpoints – Caregiver Assessed[2]

Domain	Endpoint Assessment	Description
Caregiver burden	RTT-CBI[23]	Caregivers use a 5-point Likert scale to rate the frequency that each statement describes their feeling or experience. Scale of 0–4 (“never” to “nearly always”) Items 1 through 24 are negatively worded, yielding the total Burden score up to 96.
Impact on family and child	ICND Scale total score[24]	Evaluates the impact that a child’s condition has on 11 aspects of the child’s and the family’s everyday life at the present time and during the previous 3 months. Scale of 0–3 (“not at all,” “a little,” “some,” “a lot”).
Quality of life	Overall Quality of Life Rating of the ICND Scale[24]	The QoL item of the ICND asks the caregiver to rate the subject’s overall quality of life on a 6-point scale from 1 (“poor”) to 6 (“excellent”).

Abbreviations: ICND=Impact of Childhood Neurologic Disability; RTT-CBI=Rett Syndrome Caregiver Burden Inventory; QoL=quality of life.

Table 5. Other Secondary Efficacy Endpoints – Clinician Assessed[2]

Domain	Endpoint Assessment	Description
Rett syndrome globally	CGI-S[13]	7-point scale to rate the severity of illness at the time of assessment compared to the clinician's experience with others who have the same diagnosis. RTT-specific anchors were used.[18] Scale of 1–7 ("normal; not at all ill" to "among the most extremely ill").
Hand function	RTT-HF*	Assessment of the participant's ability to use their hands for functional purposes. Rated on an 8-point Likert scale, from 0 = Normal function to 7 = No hand use.
Walking	RTT-AMB*	Assessment of the participant's ability to sit, stand, and ambulate. Rated on an 8-point Likert scale, from 0 = Normal function to 7 = Cannot sit without support AND Cannot stand AND Cannot walk.
Nonverbal communication	RTT-COMC*	Assessment of the participant's ability to communicate their choices or preferences, which can include the use of nonverbal means such as eye contact or gestures. Rated on an 8-point Likert scale, from 0 = Normal function to 7 = No interactions or no attempts to respond to requests even from caregivers; does not make choices.
Verbal communication	RTT-VCOM*	Assessment of the participant's ability to communicate verbally. Rated on an 8-point Likert scale, from 0 = Normal function to 7 = No words AND No vocalizations (may scream).

**Novel scale, derived from the Rett Syndrome-Clinician Domain Specific Concerns-Visual Analog Scale (RTT-DSC-VAS).[5]*
Abbreviations: CGI-S=Clinical Global Impression–Severity; RTT=Rett syndrome; RTT-AMB=Rett Syndrome Clinician Rating of Ambulation and Gross Motor Skills; RTT-COMC=Rett Syndrome Clinician Rating of Ability to Communicate Choices; RTT-HF=Rett Syndrome Clinician Rating of Hand Function; RTT-VCOM=Rett Syndrome Clinician Rating of Verbal Communication.

References

1. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med.* 2023;29(6):1468-1475. **[PubMed]**
2. Neul JL, Percy AK, Benke TA, et al. Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome. *Contemp Clin Trials.* 2022;114:106704. **[PubMed]**
3. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. **[Link]**
4. Mount RH, Charman T, Hastings RP, Reilly S, Cass H. The Rett Syndrome Behaviour Questionnaire (RSBQ): refining the behavioural phenotype of Rett syndrome. *J Child Psychol Psychiatry.* 2002;43(8):1099-1110. **[PubMed]**
5. Glaze DG, Neul JL, Kaufmann WE, et al. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. *Neurology.* 2019;92(16):e1912-e1925. **[PubMed]**
6. Khwaja OS, Ho E, Barnes KV, et al. Safety, pharmacokinetics, and preliminary assessment of efficacy of mecasermin (recombinant human IGF-1) for the treatment of Rett syndrome. *Proc Natl Acad Sci U S A.* 2014;111(12):4596-4601. **[PubMed]**

7. O'Leary HM, Kaufmann WE, Barnes KV, et al. Placebo-controlled crossover assessment of mecasermin for the treatment of Rett syndrome. *Ann Clin Transl Neurol.* 2018;5(3):323-332. **[PubMed]**
8. Acadia Pharmaceuticals Inc. Summary of Clinical Efficacy. 2022.
9. Cianfaglione R, Clarke A, Kerr M, et al. A national survey of Rett syndrome: behavioural characteristics. *J Neurodev Disord.* 2015;7(1):11. **[PubMed]**
10. Cianfaglione R, Clarke A, Kerr M, Hastings RP, Oliver C, Felce D. Ageing in Rett syndrome. *J Intellect Disabil Res.* 2016;60(2):182-190. **[PubMed]**
11. Robertson L, Hall SE, Jacoby P, Ellaway C, de Klerk N, Leonard H. The association between behavior and genotype in Rett syndrome using the Australian Rett Syndrome Database. *Am J Med Genet B Neuropsychiatr Genet.* 2006;141b(2):177-183. **[PubMed]**
12. Barnes KV, Coughlin FR, O'Leary HM, et al. Anxiety-like behavior in Rett syndrome: characteristics and assessment by anxiety scales. *J Neurodev Disord.* 2015;7(1):30. **[PubMed]**
13. Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976.
14. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont).* 2007;4(7):28-37. **[PubMed]**
15. Kolevzon A, Ventola P, Keary CJ, et al. Development of an adapted Clinical Global Impression scale for use in Angelman syndrome. *J Neurodev Disord.* 2021;13(1):3. **[PubMed]**
16. Davenport MH, Schaefer TL, Friedmann KJ, Fitzpatrick SE, Erickson CA. Pharmacotherapy for Fragile X Syndrome: Progress to Date. *Drugs.* 2016;76(4):431-445. **[PubMed]**
17. Arnold LE, Aman MG, Martin A, et al. Assessment in multisite randomized clinical trials of patients with autistic disorder: the Autism RUPP Network. Research Units on Pediatric Psychopharmacology. *J Autism Dev Disord.* 2000;30(2):99-111. **[PubMed]**
18. Neul JL, Glaze DG, Percy AK, et al. Improving Treatment Trial Outcomes for Rett Syndrome: The Development of Rett-specific Anchors for the Clinical Global Impression Scale. *J Child Neurol.* 2015;30(13):1743-1748. **[PubMed]**
19. Wetherby AM, Allen L, Cleary J, Kublin K, Goldstein H. Validity and reliability of the communication and symbolic behavior scales developmental profile with very young children. *J Speech Lang Hear Res.* 2002;45(6):1202-1218. **[PubMed]**
20. Anagnostou E, Jones N, Huerta M, et al. Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder. *Autism.* 2015;19(5):622-636. **[PubMed]**
21. Urbanowicz A, Downs J, Girdler S, Ciccone N, Leonard H. An Exploration of the Use of Eye Gaze and Gestures in Females With Rett Syndrome. *J Speech Lang Hear Res.* 2016;59(6):1373-1383. **[PubMed]**
22. Wetherby A, Prizant B. Communication and Symbolic Behavior Scales Developmental Profile–First Normed Edition. 2002. Baltimore: Paul H. Brookes.
23. Lane JB, Salter AR, Jones NE, et al. Assessment of Caregiver Inventory for Rett Syndrome. *J Autism Dev Disord.* 2017;47(4):1102-1112. **[PubMed]**
24. Camfield C, Breau L, Camfield P. Assessing the impact of pediatric epilepsy and concomitant behavioral, cognitive, and physical/neurologic disability: Impact of

Childhood Neurologic Disability Scale. *Dev Med Child Neurol.* 2003;45(3):152-159. **[PubMed]**