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DAYBUE® (trofinetide): Scales used to measure efficacy in the LAVENDER™ study



SUMMARY



LAVENDER was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study that evaluated trofinetide in 187 female participants (5–20 years old) with RTT, using the caregiver-reported RSBQ total score and the clinician-rated CGI-I as co-primary endpoints at Week 12^{1,2}

Click on each icon to learn more about each scale 

Co-primary Endpoints

RSBQ

Change from baseline to Week 12 in the caregiver-assessed RSBQ total score¹



RSBQ Items



RSBQ in LAVENDER

CGI-I

Score at Week 12 in the clinician-assessed CGI-I¹



RTT-specific CGI-I anchors and their use in LAVENDER

Key secondary endpoint

CSBS-DP-IT Social

Change from baseline to Week 12 in the CSBS-DP-IT Social Composite score¹



RTT-specific CSBS DP-IT Social anchors and their use in LAVENDER

Other secondary endpoints

Other Scales

A range of caregiver- and clinician-rated scales across various symptomatic domains of RTT^{*1}



Caregiver Assessed



Clinician Assessed

*The study was not designed or powered to show statistically significant differences from placebo for these secondary endpoints.

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TRO-US-MED-00685

Abbreviations and References

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SUMMARY

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RSBQ in RTT

The RSBQ is a widely used, 45-item rating scale for the assessment of RTT patients,^{3,4} which is:



Administered to the caregiver to assess a range of neurological and behavioral symptoms of RTT^{3,4}



A validated instrument previously used in other studies in RTT,⁵⁻⁷ including studies by other sponsors designed for submission to the FDA⁸



Characterized and validated across a broad age range (2-47 years) and genetic variations in RTT^{2,9-12}

RSBQ items

The RSBQ comprises 45 items that can be categorized under different groups⁴



General mood



Breathing problems



Hand behaviors



Repetitive face movements



Body rocking and expressionless face



Nighttime behaviors



Fear/anxiety



Walking/standing



Others/uncategorized

Click on each icon for the RSBQ items under each category

Abbreviations and References

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SUMMARY

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RSBQ: Items



General mood⁴

- Spells of screaming for no apparent reason during the day
- Abrupt changes in mood
- There are certain days/periods where she performs much worse than usual
- There are times when she appears miserable for no apparent reason
- Screams hysterically for long periods of time and cannot be consoled
- There are times when she is irritable for no apparent reason
- Spells of inconsolable crying for no apparent reason during the day
- Vocalizes for no apparent reason



Breathing problems⁴

- There are times when breathing is deep and fast (hyperventilation)
- There are times when breath is held
- Air or saliva is expelled from the mouth with force
- Swallows air
- Abdomen fills with air and sometimes feels hard

DAYBUE® (trofinetide): Scales used to measure efficacy in the LAVENDER™ study



SUMMARY

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RSBQ: Items



Hand behaviors⁴

- Does not use hands for purposeful grasping
- Hand movements are uniform and monotonous
- Has frequent naps during the day
- Restricted repertoire of hand movement
- Has difficulty in breaking/stopping hand stereotypies
- The amount of time spent looking at objects is longer than the time spent holding or manipulating them



Repetitive face movements⁴

- Makes repetitive hand movements involving fingers around the tongue
- Makes mouth grimaces
- Makes repetitive tongue movements
- Makes grimacing expressions with the face

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SUMMARY

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RSBQ: Items



Body rocking and expressionless face⁴

- Expressionless face
- Seems to look through people into the distance
- Uses eye gaze to convey feelings, needs, and wishes
- Rocks self when hands are prevented from moving
- Tendency to bring hands together in front of chin or chest
- Rocks body repeatedly



Night-time behaviors⁴

- Spells of screaming for no apparent reason during the night
- Spells of laughter for no apparent reason during the night
- Spells of inconsolable crying for no apparent reason during the night

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SUMMARY

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RSBQ: Items



Fear/anxiety⁴

- Spells of apparent anxiety/fear in unfamiliar situations
- Seems frightened when there are sudden changes in own body position
- There are times when parts of the body are held rigid
- Spells of apparent panic



Walking/standing⁴

- Although can stand independently, tends to lean on objects or people
- Walks with stiff legs

DAYBUE® (trofinetide): Scales used to measure efficacy in the LAVENDER™ study



SUMMARY

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RSBQ: Items



Others/uncategorized⁴

- Spells of laughter for no apparent reason during the day
- Has wounds on the hands as a result of repetitive hand movements
- Shifts gaze with slow horizontal turn of head
- Makes repetitive hand movements with hands apart
- Appears isolated
- Grinds teeth
- Vacant 'staring' spells

DAYBUE® (trofinetide): Scales used to measure efficacy in the LAVENDER™ study



SUMMARY

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RSBQ in the LAVENDER study

In the Phase 3 LAVENDER study, the RSBQ was one of the co-primary endpoints assessed as the change in total score from baseline to Week 12^{1,2}



The RSBQ was administered to caregivers by qualified site personnel who were required to have⁸

- Previous experience with neurodevelopmental disorders
- OR
- Previous experience facilitating patient-reported or caregiver-reported outcome instruments and to complete training on each assessment

The caregiver assesses and rates each of the 45 items as “0”, “1”, or “2”⁸

Item question:⁸

Responses:⁸

0

**Not
true**

1

**Somewhat or
sometimes true**

2

**Very true or
often true**



Higher scores (score “2”) indicate greater severity or frequency of RTT symptoms,⁸ while lower scores reflect lesser severity in signs and symptoms³



Exception: For the item “Uses eye gaze to convey feelings, needs, and wishes”, the score of “2” (very true) indicates a better outcome^{8,a}

Every patient with RTT has a different set of symptoms; therefore, in the LAVENDER study, the total score of the RSBQ across the 45 items was used to assess the efficacy of trofinetide compared with placebo across a variety of symptoms observed in RTT

^aIn LAVENDER, the score for this item (item 31) was reversed in the calculations of total score because the score of “2” (very true) reflects a better outcome; therefore, decreases in the RSBQ total score denote improvement.⁸

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RTT-specific CGI-I anchors and their use in LAVENDER

The CGI-I was a co-primary endpoint in the Phase 3 LAVENDER study, assessed as the score at Week 12¹



The 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 disorders¹⁵⁻¹⁷

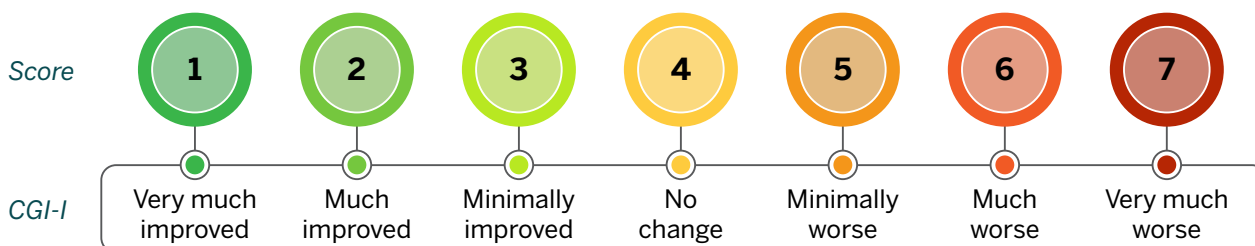


In LAVENDER, the CGI-I is completed by the clinician who is required to rate on a 7-point scale how much the subject's illness improved or worsened relative to the subject's illness at a baseline state⁸

Question:⁸

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.

Response:⁸



Click on the icons for more details on CGI-I scores

Interpretation:⁸

Decreases in scores denote improvement



In LAVENDER, the CGI-I ratings are assessed using RTT-specific anchors developed by Neul et al. to provide a framework for considering the factors related to:^{2,18}

- Symptom duration
- Onset
- Durability of change
- Context of sign/symptom change across the symptom domains



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.^{2,8}

- 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

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CGI-I in RTT

RTT-specific CGI-I anchors¹⁸

Score	CGI-I	RTT anchors
1	Very much improved	Designates marked improvement, across settings and/or across multiple behavior problems. Improvement must be very substantial and are usually accompanied by considerable caregiver enthusiasm. Such patients are usually noticeably improved behaviorally in the clinic as well. ^a
2	Much improved	Moderate improvement in a single symptom area (especially if seen across settings) or moderate improvements in several areas (even if confined to one setting). Durability of the change should be considered. Example: a change reported for the last few days may not warrant such a rating; however, a change that coincided with a dose change and was clearly seen for the last week or longer may warrant a rating of 2. The patient may not necessarily 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. ^b
3	Minimally improved	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). ^c
4	No change	The absence of change in behavior or clinical presentation from baseline to subsequent assessments. Chance fluctuations and equivocal improvements or declines should be included here. ^d
5	Minimally worse	Some worsening in symptoms that are mild to moderate or may be confined to one setting. ^c
6	Much worse	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	Significant worsening, across settings and/or across multiple symptoms.

^aCGI-I 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. ^bA CGI-I of 2 is appropriate for definite, unequivocal improvement of a magnitude that makes the clinician confident that the treatment is helping. ^cAn 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. ^dA 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.

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SUMMARY

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RTT-specific CSBS-DP-IT Social anchors and their use in LAVENDER

The CSBS-DP-IT Social was the key secondary endpoint in LAVENDER, assessed as change from baseline to Week 12¹



Designed as a screening tool for communication issues in healthy infants/toddlers, but not validated for use in patients with RTT



The Infant-Toddler Checklist (a component of CSBS-DP) is a caregiver-completed questionnaire that assesses communication in children aged 12–24 months but has also been applied in older children with developmental delays,^{19,20} including RTT⁷



A subset of the CSBS-DP-IT checklist was identified for assessing the communication skills of individuals with RTT aged 8 to 19 years²¹

CSBS-DP-IT Social*

The CSBS-DP-IT Social evaluates a range of nonverbal communication modalities commonly used by individuals with RTT and is comprised of the first 13 items of the 24 items on the CSBS-DP-IT checklist. The 13 items are divided into three skill areas^{2,8,22}



Emotion and eye gaze
(items 1 to 4)



Communication
(items 5 to 8)



Gestures
(items 9 to 13)

[Click on the scores for the description of CSBS-DP-IT Social Items](#)



The caregiver assesses and rates each of the items as “0”, “1”, or “2”^{2,8,22}

Item question:^{2,8,22}

Responses:^{2,8,22}

0

Not yet

1

Sometimes

2

Often

Higher scores indicate better social communication development^{2,8,22}

*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 assessment⁸

Abbreviations and References

DAYBUE® (trofinetide): Scales used to measure efficacy in the LAVENDER™ study



SUMMARY

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CSBS-DP-IT Social items



**Emotion and
eye gaze
(items 1 to 4)²²**

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
(items 5 to 8)²²**

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
(items 9 to 13)²²**

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?

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Caregiver-assessed secondary endpoints in LAVENDER*

The RTT-CBI, ICND scale total score, and overall quality of life rating of the ICND scale were the caregiver-assessed secondary endpoints of LAVENDER, assessed as the change from baseline to Week 12²

	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 of 4 conditions or health problems 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 Quality of Life 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")

*Note: The study was not designed or powered to show statistically significant differences from placebo for other secondary endpoints.²

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Clinician-assessed secondary endpoints in LAVENDER

The CGI-S, RTT-HF, RTT-AMB, RTT-COMC, and RTT-VCOM were the clinician-assessed secondary endpoints of LAVENDER, assessed as the change from baseline to Week 12²

	Domain	Endpoint Assessment	Description
	RTT 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 used¹⁸ - Scale of 1-7 ("normal; not at all ill" to "among the most extremely ill")
	Hand function	RTT-HF ^a	- 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 ^a	- 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 ^a	- 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 ^a	- 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)

Note: The study was not designed or powered to show statistically significant differences from placebo for other secondary endpoints.²

^aNovel scale, derived from the RTT-Clinician Domain Specific Concerns-Visual Analog Scale.⁵

Abbreviations and References

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SUMMARY

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Abbreviations and References

Abbreviations: **CGI**, Clinical Global Impression; **CGI-I**, Clinical Global Impression–Improvement; **CGI-S**, Clinical Global Impression–Severity; **CNS**, central nervous system; **CSBS-DP**, Communication and Symbolic Behavior Scales Developmental Profile™; **CSBS-DP-IT Social**, Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score; **FDA**, Food and Drug Administration; **ICND**, Impact of Childhood Neurologic Disability; **RSBQ**, Rett Syndrome Behaviour Questionnaire; **RTT**, Rett syndrome; **RTT-AMB**, Rett Syndrome Clinician Rating of Ambulation and Gross Motor Skills; **RTT-CBI**, Rett Syndrome Caregiver Burden Inventory; **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.

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