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Trofinetide benefits the ability to communicate in Rett syndrome: a plain language summary of the LAVENDER trial

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Where can I find the original article on which this summary is based?

You can read the original article, called 'Trofinetide treatment demonstrates a benefit over placebo for the ability to communicate in Rett syndrome' at: [https://www.pedneur.com/article/S0887-8994\(23\)00405-8/fulltext](https://www.pedneur.com/article/S0887-8994(23)00405-8/fulltext)

Summary

What is this summary about?

This summary reports communication-related results from the LAVENDER study, which was published in *Pediatric Neurology* in March 2024; the main results from LAVENDER were previously published in *Nature Medicine* (and the PLSP in *Future Rare Diseases*). The LAVENDER study involved girls and young women with a rare genetic condition called Rett syndrome, which affects the way the brain develops. One of the main symptoms of Rett syndrome is the partial or complete loss of spoken words (or verbal communication). As a result, most people with Rett syndrome rely on nonverbal communication with their caregivers by using body movements or eye gazing/pointing to indicate wants or needs. Researchers wanted to find out if a medicine called trofinetide could benefit the ability to communicate using either nonverbal methods or by using spoken words.

What happened during the LAVENDER study?

A total of 187 girls and young women took trofinetide (brand name DAYBUE™) liquid or a placebo (looks the same as the trofinetide liquid but does not contain medicine) 2 times a day either by drinking it or through a tube into the stomach called a gastrostomy tube for 12 weeks. Using questionnaires, caregivers (parent or guardian) were asked to rate verbal communication, and nonverbal communication involving only body movements or eye gazing/pointing to select objects or items from a list, and study doctors (clinicians) were asked to rate nonverbal communication and social interaction skills.





What were the communication-related results?

After 12 weeks of treatment, there was a significant difference between trofinetide and placebo in the ability to communicate nonverbally. As expected, there was no difference in verbal communication as most people with Rett syndrome are unable to speak any words.

What do the results mean?

This is the first study to show that a medicine, trofinetide, can benefit the ability to communicate in Rett syndrome relative to placebo. Communication is the single most important issue for caregivers; therefore, any benefit in communication could potentially reduce the caregiver burden and improve the quality of life for both caregiver and the individual with Rett syndrome.

How to say (download PDF and double click sound icon to play sound)...

- **Trofinetide:** troh-fin-uh-tide 
- **DAYBUE:** day-byoo 
- **Glycine-proline-glutamate:** gly-seen pro-leen gloo-tah-mate 
- **Chromosome:** krow-muh-sowm 

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research.

Trofinetide (DAYBUE™) is approved to treat the condition under study that is discussed in this summary.

Who is this summary for?

This summary may help parents and family members of people with Rett syndrome, or anyone who is a caregiver or has contact with someone with Rett syndrome including friends, to understand the results from the LAVENDER study that were related to the ability to communicate. It may also be helpful for patient advocates and healthcare professionals – this includes anyone who is looking for treatment options for people with Rett syndrome.

Who sponsored this study?

Acadia Pharmaceuticals Inc. **sponsored** this study.

Sponsor: A company organisation that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is Rett syndrome?

Rett syndrome is a rare genetic disorder that affects between 1 in 15,000 and 1 in 10,000 females (even rarer in males). Rett syndrome affects the way the brain develops and usually involves a change or mutation in a **gene** called **MECP2**, which is found on the X **chromosome**.

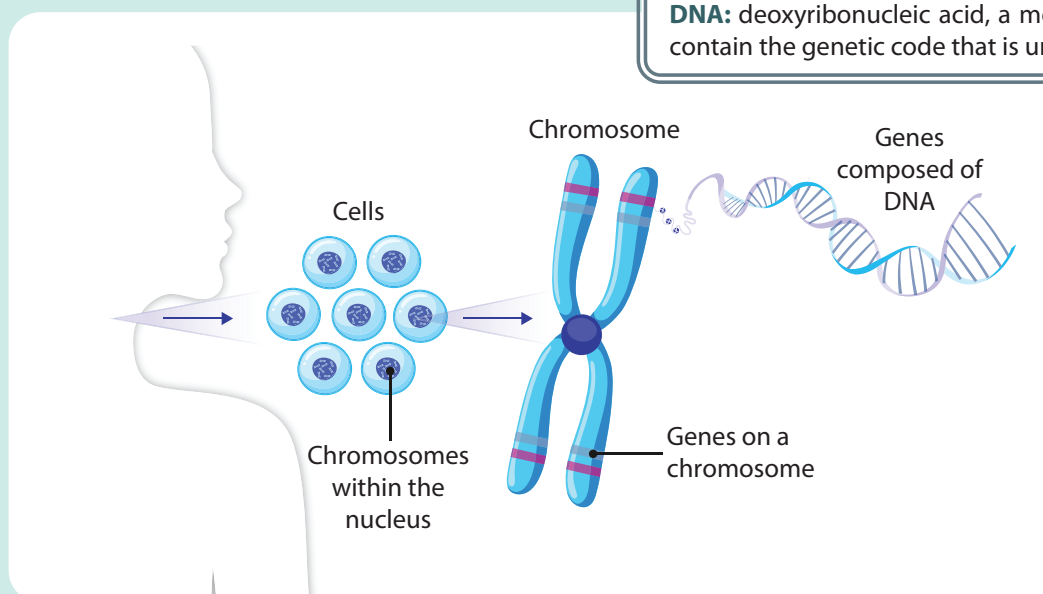
Gene: A section of DNA that contains the instructions to make a specific protein.

MECP2: The gene responsible for making methyl-CpG-binding protein 2 (**MeCP2**).

MeCP2: Methyl-CpG-binding protein 2, which is essential for the normal function of nerve cells.

Chromosomes: Thread-like structures made of protein and deoxyribonucleic acid (**DNA**) that are located in the cell nucleus; each cell has 23 pairs of chromosomes (46 in total) including the sex chromosomes (XX in females or XY in males).

DNA: deoxyribonucleic acid, a molecule consisting of two strands that contain the genetic code that is unique to every individual.



Most human cells have 23 pairs of chromosomes, and one of these pairs is the sex chromosomes of which there are 2 X chromosomes in females and 1 X and 1 Y chromosome in males.

Each gene consists of a segment of deoxyribonucleic acid (DNA), which carries instructions for making a specific protein. When the structure of the gene is altered by a mutation, the DNA sequence is altered, and the body is either unable to make the protein or makes an abnormal version of the protein that the body can't use properly.

When the *MECP2* gene undergoes a mutation or structural change, it is no longer able to produce the **MeCP2** protein properly, which is necessary for nerve cells in the brain to develop normally.

Most people with Rett syndrome look healthy for the first 6 months of their life, but symptoms start during early childhood (around 6–30 months of age) and, by 3–5 years of age, the main symptoms are clearly noticeable.

Rett syndrome affects a wide range of abilities controlled by the brain, including the absence or loss of ability to speak.

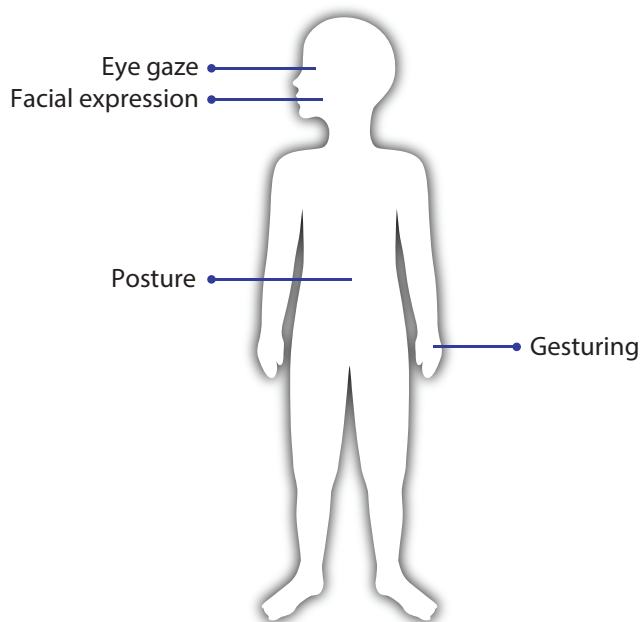
For further information on 'What is Rett syndrome' please refer to the previous plain language summary of publication of the primary results from the LAVENDER study: <https://doi.org/10.2217/frd-2023-0010>

What is the impact of Rett syndrome on communication?

Most children with Rett syndrome stop speaking by 3 years of age or are limited to a few words, with many individuals relying on nonverbal communication such as eye gazing/pointing (eyes serve same function as finger pointing by looking at an object, picture, symbols, or words), body movements (facial expressions, posture, and gestures), or through the use of an eye gaze assistive/augmentative device (cameras detect eye activity allowing the user to stare at a phrase/symbol and "activate" it like a mouse click to activate a computer screen).

An inability to control purposeful, voluntary movement (called apraxia) can also make it difficult to communicate nonverbally.

Typical nonverbal communication methods in the individual with Rett syndrome



Each day is a challenge for the caregiver because the inability to effectively communicate is a problem throughout life, and many people with Rett syndrome can live until they are 50 years or older.

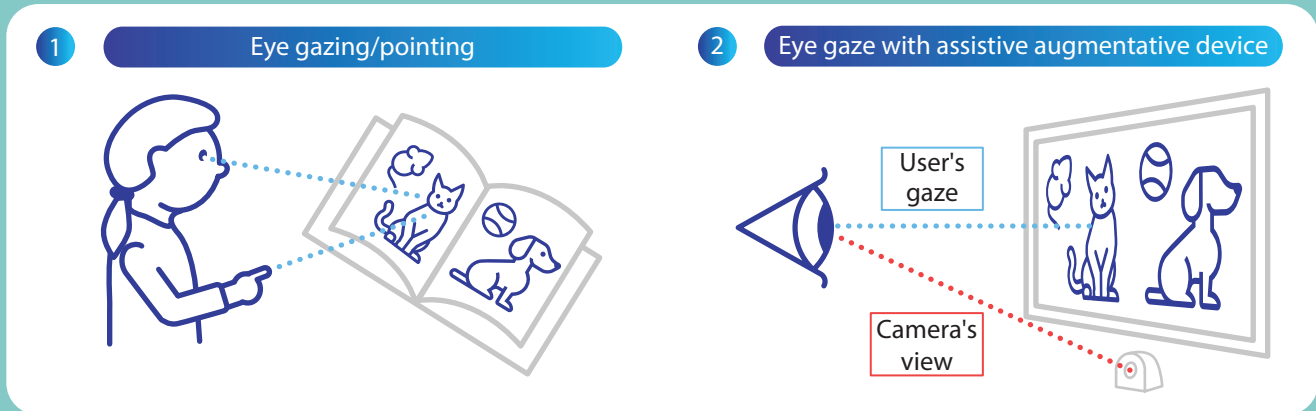
The lack of communication makes it difficult for caregivers to interpret or understand an individual's wants or needs such as hunger, choice of an object, or desires.

Improving the ability to communicate would make a big difference to the lives of caregivers because communication is the most commonly reported aspect of Rett syndrome that caregivers would like to change.

How is communication assessed in Rett syndrome?

Measuring nonverbal communication is most relevant in studies in Rett syndrome because most individuals are unable to speak or have difficulty forming words from about 3 years of age.

Nonverbal communication skills can be assessed by measuring the ability to choose an object, picture, or photograph using eye gazing/pointing or body movements (facial expressions, posture, and gestures), or through the use of an eye gaze assistive/augmentative device.



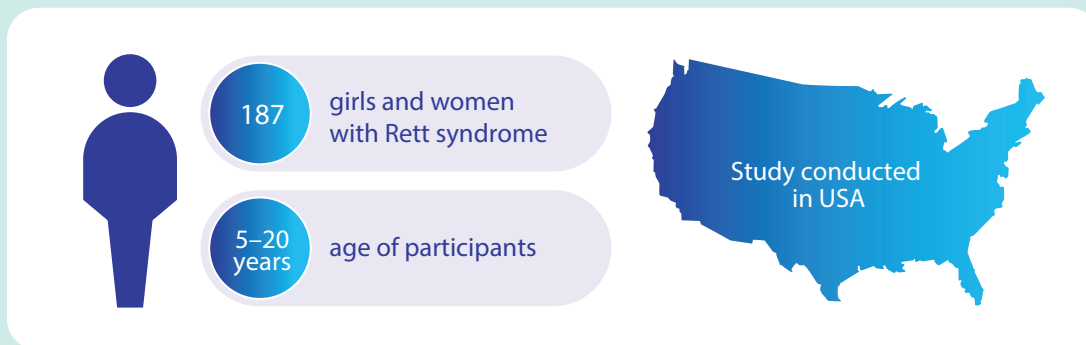
What is trofinetide?

Trofinetide is a more stable version of a peptide (small molecules that join together to form proteins) called glycine-proline-glutamate (GPE), which helps nerve cells in the brain to develop and grow.

In a study in mice with the genetic mutation (change in DNA sequence) that causes Rett syndrome, GPE improved the symptoms of Rett syndrome and the survival of the mice.

When trofinetide was first studied in people with Rett syndrome in small clinical studies, it improved symptoms compared with the placebo, which looked the same as trofinetide and was taken the same way but contained no medication.

Who took part in the LAVENDER study?



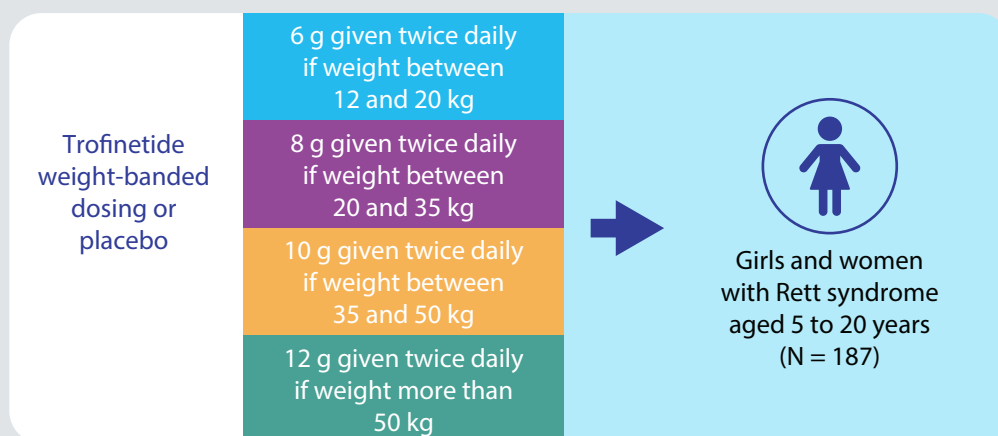
What happened in the LAVENDER study?

The LAVENDER study was a randomized, double-blind, placebo-controlled study.

- Placebo-controlled means that one of the treatments in the study did not contain medication but looked the same as trofinetide and was taken in the same way.
- Randomized means that the participants were assigned to trofinetide or placebo by chance.
- Double-blind means that the study researcher and the participant did not know which treatment was being taken.

Researchers in the LAVENDER study looked at symptoms of Rett syndrome over 12 weeks in a total of 187 girls and young women who were in one of three age groups (5–10 years old, 11–15 years old, and 16–20 years old) and who were randomly (i.e., by chance) put into 2 equally sized groups:

- Trofinetide was given to 93 participants in the form of a liquid that was delivered 2 times a day either by mouth or into the stomach with a gastrostomy tube.
 - » Four different doses (or quantity of medicine) of trofinetide were given depending on the weight of the participant.
- Placebo was given to 94 participants and was taken the same way as trofinetide.



The main results from LAVENDER were previously published and showed that after 12 weeks of treatment, trofinetide demonstrated **statistically significant** (i.e., the benefit was unlikely to be caused by chance) improvements in the Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression-Improvement (CGI-I) scale compared with placebo.

- The RSBQ evaluates the presence and/or severity of common symptoms in Rett syndrome including breathing problems, hand behaviors, and walking/standing.
- The CGI-I evaluates the overall clinical status (general health) of the individual.

Statistically significant: A mathematical measure of difference between groups. When the difference between groups is statistically significant, it means that it was unlikely that the difference was caused by chance.

For further information on the primary results of the LAVENDER study please refer to the previous plain language summary of publication: <https://doi.org/10.2217/frd-2023-0010>

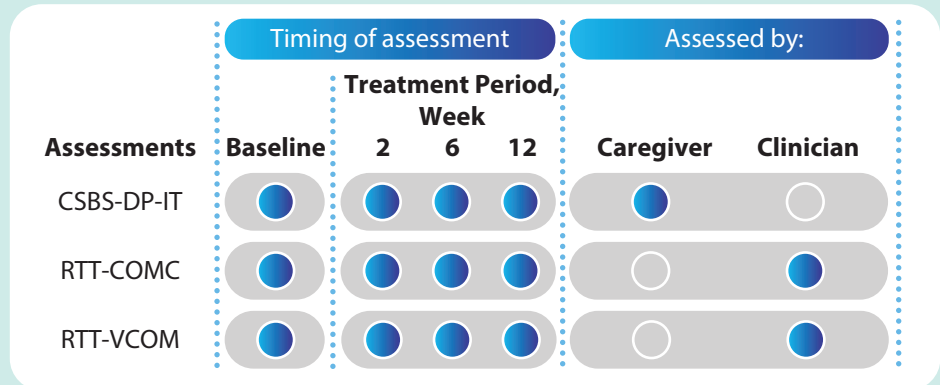
How was communication assessed in the LAVENDER study?

Researchers used 3 communication-related questionnaires or scales to measure the ability to communicate by asking caregivers or study doctors to rate how much nonverbal or verbal communication had improved or worsened at each study visit. These questionnaires or scales are currently only used for research purposes in clinical trials and are not used in everyday clinical practice to assess communication.

- The “Social Composite” score on a questionnaire called the Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler (CSBS-DP-IT) checklist.
- The Rett Syndrome Clinician Rating of Ability to Communicate Choices (RTT-COMC).
- Rett Syndrome Clinician Rating of Verbal Communication (RTT-VCOM).

The Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist (CSBS-DP-IT) Social Composite score

- The CSBS-DP-IT Social Composite score assesses communication and social interaction skills in children based on 13 questions on the CSBS-DP-IT Checklist divided into 3 skill areas: “Emotion and Eye Gaze”, “Communication”, and “Gestures”.
- For each question, the caregiver rated skills as 0 = “not yet”, 1 = “sometimes”, or 2 = “often”.
- The total score ranges from 0 to 26; a higher score indicates a better ability to communicate.



Items of the CSBS-DP-IT Social Composite Score

Caregiver rating for each question
 “Not yet”=0 “Sometimes”=1 “Often”=2

Skill area: emotion and eye gaze

1. Do you know when your child is happy and when your child is upset?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. When your child plays with toys, does he/she look at you to see if you are watching?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Does your child smile or laugh while looking at you?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. When you look at and point to a toy across the room, does your child look at it?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Skill area: communication

5. Does your child let you know that he/she needs help or wants an object out of reach?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. When you are not paying attention to your child, does he/she try to get your attention?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Does your child do things just to get you to laugh?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
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?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Skill area: gestures

9. Does your child pick up objects and give them to you?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Does your child show objects to you without giving you the object?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Does your child wave to greet people?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Does your child point to objects?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Does your child nod his/her head to indicate yes?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Total score

0 to 26
 (higher score indicates a better ability to communicate)

Rett Syndrome Clinician Rating of Ability to Communicate Choices (RTT-COMC)

The RTT-COMC is a new and original scale that is specific to Rett syndrome and is rated by the study doctor (clinician).

The RTT-COMC assesses the ability to communicate nonverbally (and sometimes verbally) by measuring the ability to express a preference by selecting from several objects or photographs/pictures using body movements or eye-gazing/pointing with or without an assistive technology device.

- Changes in communication were measured based on an 8-point scale (0 [normal functioning] to 7 [most severe impairment]).
- Lower scores were associated with:
 - » Forced choices (i.e., chooses from a list of items) as opposed to unforced choices (e.g., randomly grabs an object).
 - » Choosing from items that are pictorial representations of real objects rather than real objects or photographs of objects.
 - » Less restrictive choices (i.e., chooses from 4 items instead of 2 items).

How would you rate the patient's ability to communicate choices, focusing on the past week? Your rating may rely on both the report of caregivers and your own observation and examination.

8-point scoring scale

0	1	2	3	4	5	6	7
Normal	Makes a forced choice between 2 or more drawings or symbolic representations	Makes a forced choice between 4 photographs of objects	Makes a forced choice between 2 photographs of objects	Makes a forced choice between 2 real-life items (e.g., food, toys, videos, shapes)	Makes unforced choices (e.g., chooses food, a toy, a video)	Responds to name by looking at speaker Does not make choices	No interactions or no attempts to respond to requests even from caregivers Does not make choices

Rett Syndrome Clinician Rating of Verbal Communication (RTT-VCOM)

The RTT-VCOM is a new and original scale that is specific to Rett syndrome and is rated by the study doctor (clinician).

The RTT-VCOM was developed to evaluate verbal communication by measuring the ability to use spoken language.

- Changes in verbal communication were measured based on an 8-point scale (0 [normal functioning] to 7 [most severe impairment]).
- Higher verbal communication skills (lower scores) were associated with the ability to speak several words (> 20 words) and use short, fixed phrases that are context appropriate.

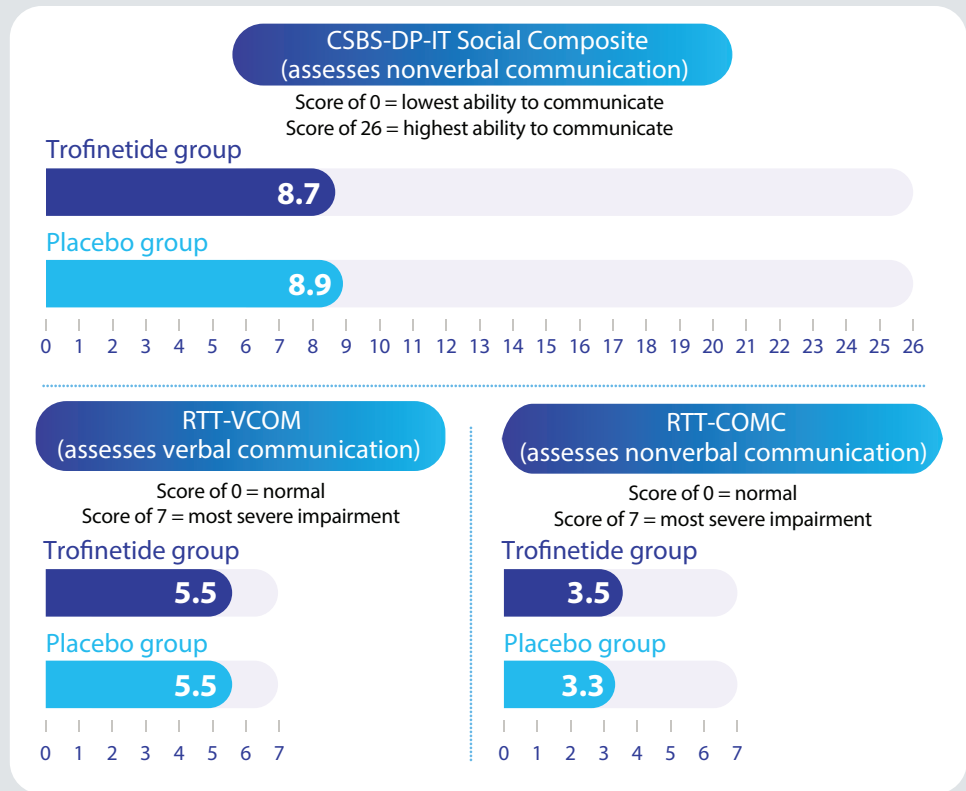
How would you rate the patient's spoken language, focusing on the past week? Your rating may rely on both the report of caregivers and your own observation and examination.

8-point scoring scale

0	1	2	3	4	5	6	7
Normal, no impairment	Uses phrases (not exclusively "fixed phrase") or sentences	Uses many words (>20) May include short "fixed phrases" used as if they were a single word	Uses a few words (5-20) AND the words are generally context-appropriate	Uses <5 words AND the words are not necessarily context-appropriate	No words BUT babbles (makes consonant-vowel combination sounds)	No words AND makes vocalizations (vowel-only sounds) BUT does not babble (i.e., does not make consonant-vowel combination sounds)	No words AND no vocalizations (may scream)

What was the ability to communicate at baseline in LAVENDER?

Baseline scores (the score before treatment started) indicated that communication was moderately to severely affected in the overall study population.



What was the impact of trofinetide on communication?

After 12 weeks of treatment, trofinetide benefited the ability to communicate compared with placebo based on the CSBS-DP-IT Social Composite and RTT-COMC scores.

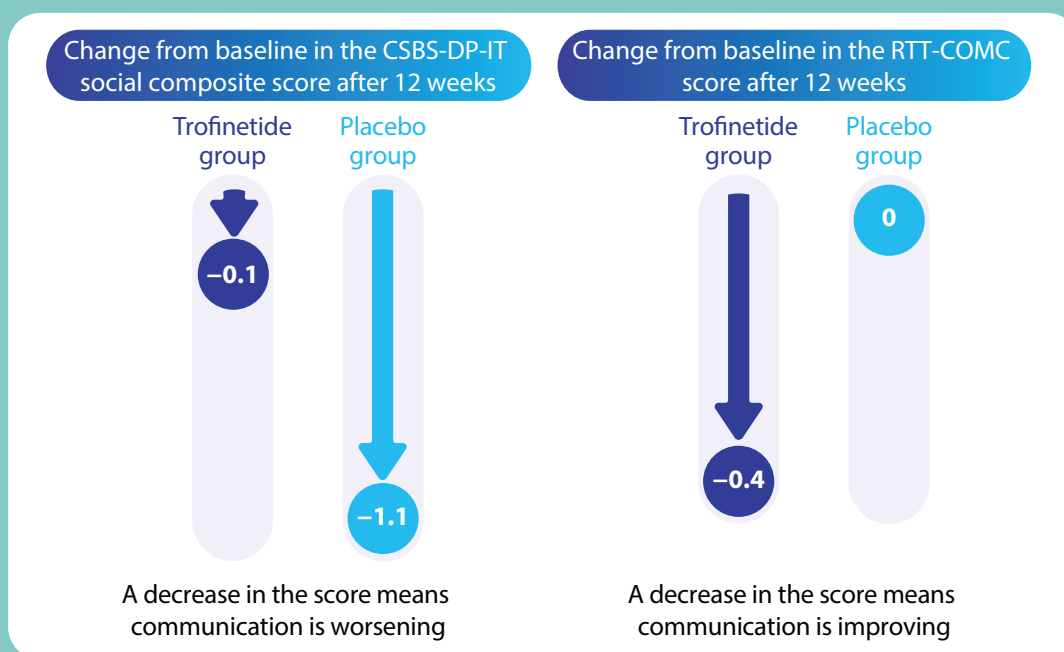
For the CSBS-DP-IT Social Composite score, the difference between the average trofinetide and placebo score (the average is a value that best represents a set of data) was statistically significant, so the benefit with trofinetide was unlikely to be caused by chance.

- The ability to communicate got worse for participants in the placebo group (score decreased or worsened by 1.1) but stayed mostly the same for participants in the trofinetide group (score decreased or worsened by 0.1).

For the RTT-COMC, the difference between the average trofinetide and placebo score was also significant and showed a benefit with trofinetide, but because it was not tested using the same statistical method as the CSBS-DP-IT Social Composite it was referred to as a nominally significant difference.

Researchers also looked at the communication results in different age groups (5–11, 12–16, and 17–20 years of age). A similar benefit on the ability to communicate using the CSBS-DP-IT Social Composite and RTT-COMC was seen with trofinetide compared with placebo across all age groups.

There was no change from baseline in the RTT-VCOM in the trofinetide and placebo groups, but this result was expected as almost all people with Rett syndrome are either unable to speak any words or can form very few coherent words.



What do the communication-based results of this study mean?

Both study doctors and caregivers agreed that trofinetide benefited the ability to communicate relative to placebo, which can be considered a clinically meaningful change in communication.

Given that communication is the single most important issue for caregivers, any benefit in communication could potentially reduce the caregiver burden and improve the quality of life for both caregiver and the individual with Rett syndrome.

This is the first time that a treatment has shown a potential benefit in the ability to communicate in Rett syndrome and complements the primary results from the LAVENDER study in which trofinetide was shown to improve many other symptoms of Rett syndrome.

Based on the evidence from the LAVENDER study, in March 2023, the US FDA approved trofinetide (DAYBUE™) for the treatment of Rett syndrome in individuals aged 2 years and older.

Where can I find more information on this study?

The original article that reported the communication results from LAVENDER was published in *Pediatric Neurology*, and the article is free to access at the following link: [https://www.pedneur.com/article/S0887-8994\(23\)00405-8/fulltext](https://www.pedneur.com/article/S0887-8994(23)00405-8/fulltext)

The primary results from the LAVENDER study were previously published in *Nature Medicine*, and the article is free to access at the following link: <https://www.nature.com/articles/s41591-023-02398-1>

A plain language summary of publication of the primary results from the LAVENDER study was previously published in *Future Rare Diseases*, and the article is free to access at the following link: <https://doi.org/10.2217/frd-2023-0010>

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Declaration of interest

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