Trofinetide for the Treatment of Girls and Women 2–20 Years of Age With Rett Syndrome: Results From Phase 3 Trials

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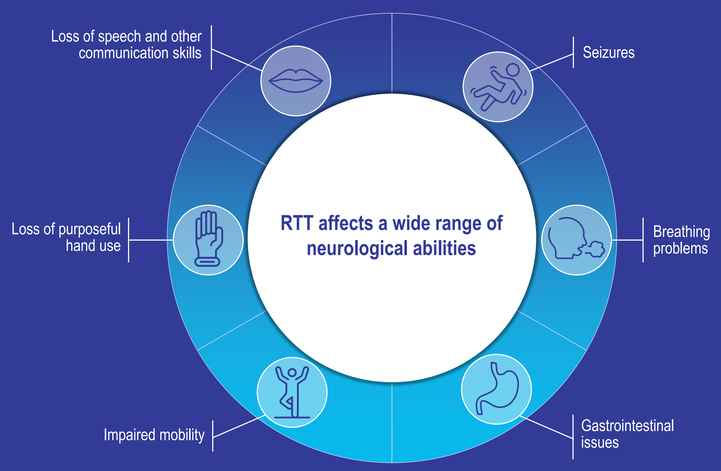
WHAT ARE THE MAIN FINDINGS?

- The LAVENDER study (ClinicalTrials.gov identifier: NCT04181723) found that girls and women who were 5–20 years of age with Rett syndrome (RTT) and were treated with trofinetide had improvements in symptoms compared with those in the placebo group
- The DAFFODIL study (ClinicalTrials.gov identifier: NCT04988867) showed that treatment with trofinetide had an acceptable safety profile in girls 2–4 years of age with RTT

WHAT IS RTT?

- RTT is a rare genetic disorder that affects central nervous system development
- RTT is much more common in females than males; it is rare for boys or men to have RTT
- Symptoms of RTT usually start at around 6–18 months of age



WHAT IS TROFINETIDE?

- Trofinetide is a more stable form of the GPE (glycine-proline-glutamate) molecule naturally found in the brain

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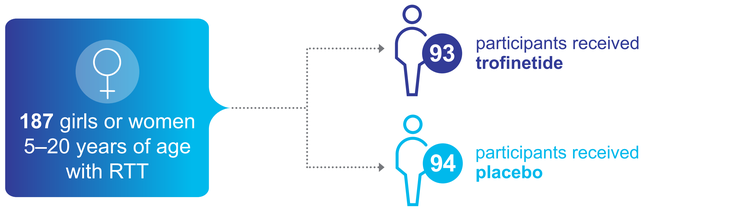
THE LAVENDER STUDY

Why Did Researchers Do This Study?

- Trofinetide improved RTT symptoms in smaller clinical trials, so researchers wanted to test these results in a larger group of people

What Did This Study Examine?

- The LAVENDER study compared RTT symptoms over 12 weeks in 2 groups of girls and women who were 5–20 years of age:
  - One group was treated with trofinetide twice daily
  - The other group was given a placebo that looked like trofinetide but did not contain any medication



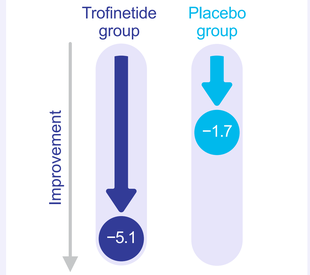
What Are the Findings of This Study?

Did Trofinetide Affect RTT Symptoms?

- Caregivers or parents of the participants with RTT were asked to complete the Rett Syndrome Behaviour Questionnaire (RSBQ), which assesses core RTT symptoms, such as night-time crying, mood changes, and repetitive movements
  - The caregivers rated 45 symptoms on a scale of 0 = "not true," 1 = "somewhat or sometimes true," or 2 = "very true"
  - A lower score indicates fewer or less severe RTT symptoms
  - After 12 weeks, the average RSBQ scores decreased in both the trofinetide and the placebo groups; however, the decrease was larger in the trofinetide group

The results were significant based on a prespecified, widely accepted standard; this suggests that RTT symptoms improved more in the trofinetide group than in the placebo group

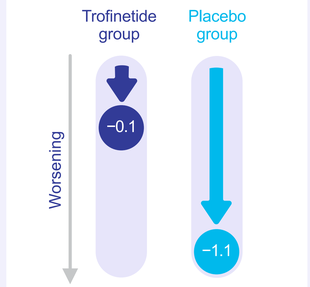
Improvements (decreases) in the RSBQ score after 12 weeks



- On the Clinical Global Impression–Improvement (CGI-I) scale, clinicians rated how much RTT-related signs and symptoms had improved in the participant
  - Scoring ranges from 1 = "very much improved" to 7 = "very much worse," so lower scores indicate greater improvements
  - After 12 weeks, the average CGI-I score was 3.5 in participants who were treated with trofinetide, which was lower than the score of 3.8 in the placebo group

This indicates greater improvements in RTT symptoms with trofinetide compared with placebo

Changes in the CSBS-DP-IT Social Composite score after 12 weeks



- The Communication and Symbolic Behavior Scales-Developmental Profile™-Infant Toddler (CSBS-DP-IT) Social Composite scale assesses communication and social interaction skills in children
  - The caregivers rated skills as 0 = "not yet," 1 = "sometimes," or 2 = "often"
  - A higher score indicates a better ability to communicate
  - After 12 weeks, in participants who were treated with trofinetide, the CSBS-DP-IT Social Composite scores were similar to the scores at the start of the study; in the placebo group, the CSBS-DP-IT Social Composite scores were lower after 12 weeks than at the start of the study

This indicates that, during the study, the participants' ability to communicate got worse for those in the placebo group but stayed mostly the same for those in the trofinetide group

What Side Effects Were Seen in the Participants of This Trial?

- A side effect is an unwanted symptom that happens after someone starts taking a new treatment; it may or may not be caused by the treatment
- The 2 most common side effects were diarrhea and vomiting
- Serious side effects were reported in 3% of those who received trofinetide or placebo
- No deaths occurred during the study

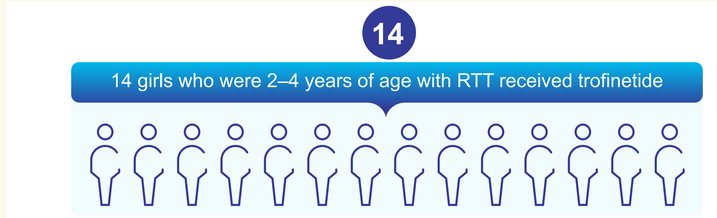
THE DAFFODIL STUDY

Why Did Researchers Do This Study?

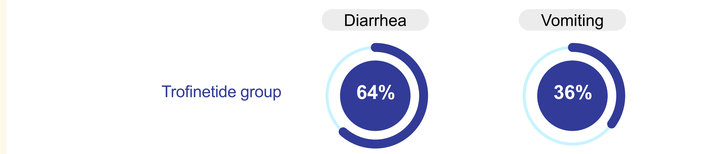
- RTT is commonly diagnosed around 2–3 years of age in the United States, so researchers wanted to see if trofinetide was safe for use in younger children

What Did This Study Examine?

- The DAFFODIL study recorded what side effects girls with RTT had and if trofinetide improved their symptoms
  - The girls were 2–4 years of age
  - All the participants took trofinetide twice a day for 12 weeks
  - This is a report of initial preliminary data for only the 12-week portion of the study



What Are the Findings of This Study?



- The 2 most common side effects were diarrhea and vomiting
- All side effects were mild or moderate
- No serious side effects were reported
- No deaths occurred during the study
- Generally, the side effects in the DAFFODIL trial were similar to those reported in the LAVENDER trial

CONCLUSIONS

- In the LAVENDER trial in girls 5–20 years of age with RTT, trofinetide showed statistically significant separation from placebo in clinical efficacy endpoints important in RTT
- In the DAFFODIL trial in girls 2–4 years of age with RTT, trofinetide was generally well tolerated, with diarrhea and vomiting the most commonly reported side effects

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