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New Hope: Novel and Emerging Treatment Options for Rett Syndrome

Announcer:
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Dr. Neul:
Hi, my name is Jeff Neul, and today I'm going to talk about New Hope: Emerging Treatment Options for Rett Syndrome.

In the late 2000s, of a group in Scotland developed a mouse model that allowed them to turn the gene back on in a time-dependent fashion. And they turned this gene on after the animals were clearly symptomatic. And the animals got better and survived. And this was repeated in female mice, and it's been shown repeatedly. And this really demonstrates that the disorder is not irreversible, and provided hope to develop disease modifying or reversing treatments. One of the first work was done in 2009, where mice were treated - Rett syndrome mice were treated with a tripeptide that was derived from the amino terminus of insulin-like growth factor-I, and that is shown in the center with a tripeptide being glycine-proline-glutamate, or called glypromate. And this again improved features of these mice.

This led to the development of clinical trials based on similar compounds, and one of them is trofinetide. So on the left, you can see the structure of the glypromate, the tripeptide that was used to treat the mice. And trofinetide it is exactly the same structure, it just has a methyl group placed in it, which improves the drug quality and allows it to be taken orally and has a longer half-life.

There were two phase 2 trials conducted in Rett syndrome in both adults and children in Rett syndrome. They showed that this was safe and had signals of efficacy. This led to a phase 3 trial of trofinetide, which was a randomized, double-blind, placebo-controlled, multi-site study, where 187 young girls and women between 5 and 20 years old with Rett syndrome, were enrolled, and randomized to 1:1 to either trofinetide or placebo for 12 weeks with a coprimary endpoints being the change in a caregiver scale, and the change in clinician improvement scale, called CGI-I.

Now here are their top-level results. On the left is the caregiver scale, the Rett Syndrome Behavior Questionnaire, and on the right is the clinician scale, the Clinical Global Impression of Improvement. In both cases, lower numbers are better. And you can see in blue, the trofinetide showed a better improvement in the caregiver and the clinician scale, compared to those people on placebo.

In terms of treatment- emergent adverse events, there were 90 people - 90% of the people on trofinetide had any treatment-emergent adverse event compared to 50% in the placebo group, whereas the serious treatment-emergent adverse events were similar percentages between the two. Now the largest of the top adverse events were diarrhea seen 80% of people with trofinetide, compared to 20% on placebo; and vomiting, which was 27% in trofinetide, and about 10% in placebo. And the bomb - the diarrhea was one of the larger issues leading to withdrawal of the drug during the trial. There were no fatalities during this. Trofinetide was approved by the FDA on March 12, 2023, for Rett syndrome, for treatment of people with Rett syndrome over 2 years old.

There is also currently a drug development in a drug called blarcamesine. And this was a stigma-1 agonist, which was also used in Rett models, mouse models and showed improvement. And there have been top-level results from this reported in ongoing clinical trials.

In addition to these trials, there are more trials in Rett syndrome that are initiating or being proposed. One are things like repurposing

drugs such as ketamine, for the treatment of Rett syndrome. The other are things like gene therapy trials, and two companies have announced that they're initiating gene therapy trials in Rett syndrome. Preclinically, there's been a lot of work being done using a variety of different techniques such as X-chromosome reactivation, DNA editing, or RNA Editing; all of which have the potential of eventually moving to clinical trials.

So in closing, I want to talk about how mouse models of Rett syndrome are - can reproduce many of the features of the disease and have shown that they can be reversible or modifiable. And the preclinical use of these models has been used to identify new treatment approaches and will continue to do so to guide clinical development. Clinical trials have shown the potential to develop targeted therapies. Trofinetide is the first FDA approved drug for Rett syndrome. Additional trials of small molecules are underway, and gene therapy trials have been announced and are initiating. And new approaches are being developed preclinically.

So thank you all for watching, and thanks to all my friends with Rett Syndrome who have taught me everything I need to know.

Announcer:
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