NEWS

# Debut drug for Rett syndrome at edge of approval

BY **SHAENA MONTANARI**

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Margaret Brimble was a new professor in 1999 at the University of Auckland in New Zealand. The country was not exactly known as a hotbed of drug development, but Brimble was an optimist, a dedicated chemist and maybe even a bit of a dreamer — she was working to create new drugs for traumatic brain injuries at a spinout company called Neuren Pharmaceuticals.

She and three chemists from her lab were focused on analogs of a natural peptide of insulin-like growth factor 1 (IGF-1), chasing one in particular they called NNZ-2566. The peptide was intriguing, but it needed to be synthesized at just the right temperature and on an exact timeline — and even then the reaction was capricious.

It was nearly enough to make them give up. But **Brimble** slid it to the back burner and let it simmer while she and her colleagues explored other leads. And then one day in 2002 during a weekly lab meeting, the biologists on the **Neuren** team presented promising in-vitro data for NNZ-2566, showing it possessed clear neuroprotective effects.

It was the data they had been looking for. This is our drug, Brimble thought. Here it is.

> “Are you seeing improvements? Because there's no point in taking a drug if you’re not.”
> David Lieberman

That drug, renamed trofinetide, was eventually licensed to the American company **Acadia Pharmaceuticals** and now stands on the cusp of approval, though for the genetic neurodevelopmental condition **Rett syndrome**, not traumatic brain injury. Acadia said in its **2022 earnings call** on Monday that it is “eagerly awaiting” communication from the U.S. Food and Drug Administration (FDA), but, if cleared, trofinetide would also be welcomed by a community that has waited even longer than Acadia for this treatment.

The FDA has set a Prescription Drug User Fee Act, or PDUFA, date — the deadline the agency sets itself to respond to a new drug application — of 12 March for trofinetide. The regulator gave it priority review in a nod to the unmet need for the patient population, which has only drugs to treat independent symptoms such as seizures and sleep issues.

Acadia acquired the drug after positive **phase 2 results** in Neuren's two clinical trials, the second of which ended in 2017. The companies entered a **North American license agreement** in 2018, with Acadia paying Neuren $10 million for exclusive rights to trofinetide in North America. The companies formed a committee to direct development of trofinetide for other conditions, such as **fragile X syndrome**, and Acadia agreed to pay up to $455 million plus royalties if the drug hits development and sales milestones.

For now, though, trofinetide is aimed at Rett syndrome. The condition mainly affects girls, with motor and communication skills beginning to regress between 6 and 18 months of age. Rett is caused by a mutation in the X-linked gene **MECP2**, which encodes the MECP2 protein. The protein is a transcription factor and is linked to the expression of thousands of genes. Because of this broad reach, those with Rett have a range of neurodevelopmental difficulties, including gait abnormalities, stereotypical hand movements, breathing issues and intellectual disability. Rett syndrome also shares characteristics with autism — social withdrawal and communication difficulties in particular — and was formerly classified as an autism spectrum disorder in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders.

Trofinetide is a synthetic analog of glycine-proline-glutamate (GPE), the amino-terminal tripeptide of IGF-1. The mode of action of GPE is unknown, but in a mouse model of Rett, the presence of GPE restored synaptic function in the mice, improving motor abilities and breathing.

Acadia initiated the phase 3 trial for trofinetide in 2019, enrolling 187 girls and women with Rett syndrome between the ages 5 of 20. The 12-week randomized, double-blind study had two primary endpoints, the first measured by the Rett Syndrome Behavior Questionnaire (RSBQ), which is administered by caregivers, and the second by the Clinical Global Impression Scale-Improvement (CGI-I), a survey conducted by clinicians.

The lower the RSBQ score, the less prominent the person's Rett-related traits. In the **phase 3 trial**, RSBQ scores in the trofinetide group fell from baseline by 5.1 points; in the placebo group, the drop was just 1.7. Overall, all eight categories that the RSBQ questionnaire measures, which includes metrics for hand behaviors and anxiety, improved against placebo.

The clinician-assessed scale also showed positive results, though it was on the "minimally improved end of things," says **David Lieberman**, a physician in the neurology department at Boston Children's Hospital in Massachusetts, who was involved in the phase 3 and extension trials. Still, this is a big stride, Lieberman says: Researchers have tried a raft of other compounds for neurodevelopmental conditions, and none of the drugs have shown anything even close to this

level of success.

Clinical trials for conditions such as Rett are challenging because endpoints rarely capture all aspects of the disease, says **Kathie Bishop**, senior vice president and head of rare disease and external innovation at Acadia Pharmaceuticals. A pivotal trial that has two co-primary endpoints is a "high hurdle," she says, but their drug cleared it.

Rett occurs in 1 in 10,000 women and girls in the United States alone. That means there are thousands of children and adults dealing with the vast constellation of Rett syndrome traits who could benefit from trofinetide, the first Rett drug that has even reached the FDA's desk for review.

Although approval depends on the success of the trial's primary endpoints, Bishop notes that one of the secondary endpoints, the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist — Social, which is administered by parents or caregivers, also saw a statistically significant improvement over placebo. The survey assesses nonverbal communication, and that, Bishop says, is "??the No. 1 symptom that caregivers say matters."

Those data can only help the drug's chances, but trofinetide approval is not a certainty. The RSBQ has its critics, and a **2020 study** concluded it does not "achieve acceptable standards" for a clinical trial metric. This is a known issue in the Rett world.

"That's kind of a problem that we as a community are working on," says Lieberman, who sees more than 100 Rett patients each year. The RSBQ was created before MECP2 testing became available, meaning it was based on people who were not genetically confirmed to have Rett syndrome.

Beyond evaluating the drug's efficacy, the FDA also needs to consider its side effects. In the phase 3 trial, about 80 percent of those who took the drug dealt with diarrhea, and about 27 percent experienced vomiting, which led some 17 percent of participants in the drug group to withdraw from the study. But Bishop says there are no safety concerns, and no hospitalizations occurred in the trial.

More than 90 percent of participants opted to roll over into an open-label extension, Acadia noted, and there is also an ongoing open-label study for girls with Rett syndrome aged 2 to 5. The company announced top-line results from the first open-label extension in its earnings call, with Bishop noting a "sustained and continued improvement" on both the RSBQ and CGI-I scores over the course of 40 weeks. However, more than 20 percent of the participants dropped out of the trial because of adverse events, and the overall discontinuation rate was 46 percent.

> "I'm really amazed that it's got to this stage, but you still can't relax until you actually get that little word: Approved." Margaret Brimble

So clinicians and patients would need to weigh the risk versus benefit, as with any drug. The big question, Lieberman says, is, “Are you seeing improvements? Because there’s no point in taking a drug if you’re not.”

If the drug is approved, Lieberman plans to try it with patients on a case-by-case basis. The condition is diagnosed based on issues with walking, loss of hand use, regression of verbal communication, and repetitive hand movements, and Lieberman says there is “nothing I can use that targets those four features that make up Rett syndrome.”

Acadia already has an approved drug, a Parkinson’s disease psychosis medication called Nuplazid. It brought the company $517.2 million in net sales in 2022, but trofinetide has weighed on the bottom line. The company posted a net loss of $216 million for the year, which includes $362 million spent on research and development, and $30 million specifically for the drug’s commercial supply build and the $10 million payment to Neuren.

That is the nature of drug development. It is long, and costly. This is something Brimble herself knows. After that day in 2002, when she and her team knew they had a drug that had an effect in the body, they put it into a clinical trial for head injury. There were five trials of trofinetide for traumatic brain injury, but they never progressed past phase 2 and finally flamed out in 2016. Meanwhile, Neuren used the compound for a Rett syndrome trial in 2012 and then gained momentum in the phase 2 that drew Acadia’s attention.

Since then, Brimble has met girls and women with Rett syndrome from all over — at home in New Zealand and as far away as San Diego, California. She has become invested in not only the drug and the FDA’s verdict, but also the community that awaits it.

It has been decades, but the “Mother of Trofinetide” — a nickname her students gave her — can finally see the end of the course, one way or another.

“I’m really amazed that it’s got to this stage,” she says, but “you still can't relax until you actually get that little word: Approved.”

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