

## HEALTH TECHNOLOGY BRIEFING MAY 2021

### Trofinetide for Rett syndrome

<b>NIHRIO ID</b>	8692	<b>NICE ID</b>	10455
<b>Developer/Company</b>	Neuren Pharmaceuticals Ltd	<b>UKPS ID</b>	N/A

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials.
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### SUMMARY

Trofinetide is in clinical development for the treatment of females with Rett syndrome (RTT). RTT is a rare genetic disorder that affects brain development, resulting in severe mental and physical disability. In RTT, a protein called insulin-like growth factor 1 (IGF-1) in the brain is lower than normal and it is thought that nerve function is affected as a result. It is characterised by loss of speech and regression of acquired skills between 6 and 18 months of age. The disease severity varies in affected people, and whilst many may reach adulthood, some people die at a young age as a result of several complications. There is currently no approved medicines for RTT.

Trofinetide is made up of a molecule derived from IGF-1. It is an oral medicinal product expected to restore IGF-1 activity in the brain, thus restoring normal functioning of brain cells and improving the symptoms of the disease. If licensed, Trofinetide would become the first therapy approved for treatment of RTT patients.

*This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.*

## PROPOSED INDICATION

Treatment of girls and women aged 2 and older with RTT.<sup>a</sup>

## TECHNOLOGY

### DESCRIPTION

Trofinetide (NNZ-2566, glycyl-L-2-methylpropyl-L-glutamic acid) is a synthetic analogue of a naturally occurring neurotrophic peptide, which is the terminal tripeptide of IGF-1 produced by brain cells.<sup>1</sup> IGF-1 is a protein in the body important for the correct development and functioning of the nervous system. In RTT, IGF-1 in the brain is lower than normal and it is thought that nerve function is affected as a result. Trofinetide is expected to restore IGF-1 activity in the brain, thus restoring normal functioning of brain cells and improving the symptoms of the disease.<sup>2</sup>

Trofinetide is in clinical development for the treatment of RTT. In the phase III clinical trial (NCT04181723), patients aged 5 to 20 years old will receive trofinetide solution of 30 – 60ml based on the subject's weight at baseline, administered twice daily by mouth or gastrostomy tube.<sup>3</sup> In the phase II trial (NCT02715115), patients aged 5 to 15 years received trofinetide 200mg/kg twice a day for 28 days.<sup>4,5</sup>

### INNOVATION AND/OR ADVANTAGES

Current treatments focus on managing symptoms, however trofinetide is developed to restore normal functioning of brain cells and improve the symptoms of the disease.<sup>2</sup>

RTT mouse models demonstrated that treatment with the terminal tripeptide of IGF-1 improves disease symptoms. Across the core efficacy measures in the phase II clinical trial (NCT02715115), improvement was seen in clinically important symptom areas core to RTT: breathing problems, repetitive movements (including hand function), mood dysfunction (including nighttime behaviors), ambulation, and seizures. All dose levels of trofinetide were generally safe and well-tolerated in children and adolescents with RTT.<sup>4,5</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Trofinetide does not currently have Marketing Authorisation in the EU/UK for any indication.

Trofinetide has the following regulatory designations:

- Orphan drug designation in the EU in 2015 for the treatment of RTT.<sup>2</sup>
- Fast Track designation from the US Food and Drug Administration (FDA) in 2015 for the treatment of RTT.<sup>6</sup>

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<sup>a</sup> Information provided by Neuren Pharmaceuticals Ltd

### DISEASE BACKGROUND

RTT is a debilitating neurological disorder that occurs primarily in females following apparently normal development for the first six months of life. It is caused by mutations on the X chromosome on a gene called *MECP2* (methyl CpG binding protein 2). There are more than 200 different mutations found on the *MECP2* gene that interfere with its ability to generate a normal gene product.<sup>7</sup> The *MECP2* gene contains instructions for producing a particular protein (MeCP2), which is needed for brain development. The gene abnormality prevents nerve cells in the brain from working properly.<sup>8</sup> Typically, between 6 to 18 months of age, patients experience a period of rapid decline with loss of purposeful hand use and spoken communication. Many patients have recurrent seizures and experience a variety of motor problems including increased muscle tone (spasticity) and abnormal movements.<sup>9</sup> There is usually no family history of RTT; almost all cases (over 99%) are spontaneous, with the mutation occurring randomly.<sup>8</sup>

RTT is described in 4 stages, although symptoms will often overlap between each stage.<sup>8</sup>

- The symptoms of stage 1 (early signs), sometimes described as “stagnation” include: low muscle tone, difficulty feeding, unusual repetitive hand movements, delay with development of speech, mobility problems and lack of interest in toys. This stage can often go unnoticed because the changes occur gradually and may be subtle.
- In stage 2, known as “regression” or “rapid destructive stage”, the child will gradually or suddenly start to develop severe problems with communication and language, memory, mobility, co-ordination and other brain functions. Later on during regression, the child may experience periods of rapid breathing (hyperventilation) or slow breathing, including breath-holding.
- Stage 3 (plateau) of RTT can begin as early as 2 years or as late as 10 years. It often lasts for many years, with many children remaining in this stage for most of their lives. During stage 3, some of the stage 2 symptoms may get better with improvements in alertness, attention span, communication and walking, however, other symptoms at this stage include: seizures and irregular breathing problems.
- The stage 4 (deterioration in movement) can last for years with symptoms such as development of a spinal curve (scoliosis), muscle weakness and spasticity, and losing the ability to walk.

### CLINICAL NEED AND BURDEN OF DISEASE

RTT affects all racial and ethnic groups and occurs worldwide in approximately 1 in every 10,000 to 15,000 live female births.<sup>9</sup>

According to European data, the prevalence of RTT is estimated to be 10 in 100,000 people, with a 5 in 100,000 birth prevalence.<sup>10</sup> In 2017, there were 679,106 live births in England and Wales, so we can estimate that approximately 34 people are born with RTT per year.<sup>11</sup>

The annual death rate in classic RTT has been estimated at about 1.2% in the UK. Most of deaths are between the ages of 15 and 20 years with causes related to the disorder (for example, pneumonia and epilepsy). However, individuals have potential for prolonged survival with approximately 60% surviving to early middle age.<sup>12</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

A co-ordinated multidisciplinary specialist team approach, preferably with close involvement of the primary care team, is the best model for care of this complex illness. Early intervention and comprehensive lifelong management of RTT can significantly improve the health and longevity of affected people.<sup>12</sup>

Treatments for RTT focus on management of specific symptoms, such as speech and language therapy, or medications for breathing and mobility problems.<sup>8,13</sup> Other treatments and aids include:<sup>8</sup>

- physiotherapy, attention to mobility, careful attention to the child's sitting posture (to minimise the chances of scoliosis developing), and frequent changes in posture. If scoliosis does become established, a back brace and sometimes spinal surgery may be used to prevent the spine curving further
- a high-calorie diet to help maintain sufficient weight, with the use of a feeding tube and other feeding aids if necessary
- occupational therapy to help develop the skills needed for dressing, feeding and other daily activities
- an ankle-foot orthosis (lower leg brace) to enable walking independently
- a hand splint to help control hand movements

### CURRENT TREATMENT OPTIONS

Current treatment options for RTT include:<sup>2,8</sup>

- Beta blocker medicine or a pacemaker to control their heart rhythm.
- Medicines to control seizures
- Laxatives
- Painkillers

### PLACE OF TECHNOLOGY

If licensed, trofinetide will offer a pharmacological treatment option for RTT in girls and women aged 2 and older.

## CLINICAL TRIAL INFORMATION

### Trial

[NCT02715115](#), **Neu-2566-RETT-002**; A Randomized, Double-blind, Placebo-controlled, Dose-ranging Study of the Safety and Pharmacokinetics of Oral NNZ-2566 in Pediatric Rett Syndrome

**Phase II** – completed

**Location(s):** US

	<b>Study completion date:</b> January 2017
<b>Trial design</b>	Randomised, parallel assignment, placebo-controlled, quadruple-blinded
<b>Population</b>	N=82; Subjects with diagnosis of classic/typical RTT with a documented mutation of the MeCP2 gene; female; aged 5 to 15 years
<b>Intervention(s)</b>	Trofinetide supplied as a lyophilized powder for reconstitution with strawberry flavored solution 0.5% v/v in water for injection
<b>Comparator(s)</b>	Strawberry flavored solution and water for injection
<b>Outcome(s)</b>	<p>Primary outcome measures :</p> <ul style="list-style-type: none"> <li>Adverse events [Time frame: through study completion, an average of 11 weeks]: Incidence of adverse events (AEs), including serious adverse events (SAEs), will be compared across the three NNZ-2566 doses and placebo. SAEs and AEs will be examined throughout the study.</li> </ul> <p>See trial record for full list of other outcomes</p>
<b>Results (efficacy)</b>	Trofinetide demonstrated statistically significant evidence of clinical improvement ( $p < 0.05$ ) for the 200 mg/kg bid dose over placebo in 3 core measures: RSBQ (total score, core neurobehavioral RTT symptoms, $p = 0.042$ ), CGI-I (overall clinical status, $p = 0.029$ ), and RTT-DSC (most concerning aspects of RTT identified by clinicians, $p = 0.025$ ). <sup>5</sup>
<b>Results (safety)</b>	Safety and tolerability of trofinetide was very good at all 3 dose levels. No deaths occurred in the study. Four SAEs occurred in 3 participants: 1 participant receiving placebo, 1 participant receiving 100 mg/kg bid, and 1 participant receiving 200 mg/kg bid. All the SAEs were deemed not related to study medication and resolved by the end of the study. <sup>5</sup>

<b>Trial</b>	<a href="#">NCT01703533</a> , <b>Neu-2566-RETT-001</b> ; A Phase II Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Escalation Study of NNZ-2566 in Rett Syndrome <b>Phase II</b> – completed <b>Location(s):</b> US <b>Study completion date</b> - September 2014
<b>Trial design</b>	Randomised, parallel assignment, placebo-controlled, quadruple-blinded
<b>Population</b>	N= 67; Subjects with diagnosis of RTT with proven mutation of the MeCP2 gene; female; 16 to 45 years
<b>Intervention(s)</b>	Trofinetide supplied as a lyophilized powder (2g in 50mL vials) for reconstitution with strawberry flavored solution 0.5% v/v in water for injection
<b>Comparator(s)</b>	Strawberry flavored solution and water for injection

<b>Outcome(s)</b>	<p>Primary Outcome Measures :</p> <ul style="list-style-type: none"> <li>Adverse events [Time frame: through to day 40]: Incidence of adverse events (AE), including Serious adverse events (SAE), will be evaluated between the two NNZ-2566 doses and placebo. SAEs will be examined from randomization through to day 40. AEs will be examined from dosing through to day 40.</li> </ul> <p>See trial record for full list of other outcomes</p>
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

<b>Trial</b>	<p><b>LAVENDER</b>, <a href="#">NCT04181723</a>; <b>ACP-2566-003</b>; A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Trofinetide for the Treatment of Girls and Women With Rett Syndrome  <b>Phase III</b> – ongoing  <b>Location(s)</b>: US  <b>Primary completion date</b> – September 2021</p>	
<b>Trial design</b>	Randomised, parallel assignment, placebo-controlled, quadruple-blinded	
<b>Population</b>	N=184; Subjects with classic/typical RTT with a documented disease-causing mutation of the MeCP2 gene; female; 5 years to 20 years	
<b>Intervention(s)</b>	Trofinetide solution of 30-60 mL based on the subject's weight at baseline, administered twice daily by mouth or gastrostomy tube (G-tube)	
<b>Comparator(s)</b>	Matched placebo	
<b>Outcome(s)</b>	<p>Primary Outcome Measures :</p> <ul style="list-style-type: none"> <li>Rett Syndrome Behaviour Questionnaire (RSBQ) total score - Change from baseline to week 12 [Time frame: 12 weeks treatment duration]</li> </ul> <p>See trial record for full list of other outcomes</p>	
<b>Results (efficacy)</b>	-	
<b>Results (safety)</b>	-	

<b>Trial</b>	<p><b>LILAC</b>; <a href="#">NCT04279314</a>; <b>ACP-2566-004</b>; A 40-Week, Open-label Extension Study of Trofinetide for the Treatment of Girls and Women With Rett Syndrome  <b>Phase III</b> – ongoing  <b>Location(s)</b>: US  <b>Primary completion date</b> - October 2022</p>	<p><a href="#">NCT04776746</a>; <b>ACP-2566-005</b>; An Open-Label Extension Study of Continuing Treatment With Trofinetide for Rett Syndrome  <b>Phase III</b> – ongoing  <b>Location(s)</b>: US  <b>Primary completion date</b> - January 2023</p>
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<b>Trial design</b>	Open label, single group assignment	Open label, single group assignment
<b>Population</b>	N=180; Subjects that have completed the week 12/end-of-treatment visit of the antecedent study, Study ACP-2566-003; female; 5 years to 21 years	N=153; Subjects that have completed the EOT visit of the antecedent trofinetide Study ACP-2566-004 (i.e., have completed 40 weeks); female; 5 years to 21 years
<b>Intervention(s)</b>	Trofinetide solution of 30-60 mL based on subject's weight at baseline, administered twice daily by mouth or gastrostomy tube (G-tube)	Trofinetide is administered twice a day for up to approximately 32 months. Doses may be taken orally or administered by gastrostomy (G) tube. The subject's assigned dose for this study will be the final dose from the antecedent study (ACP-2566-004).
<b>Comparator(s)</b>	No comparator	No comparator
<b>Outcome(s)</b>	<p>Primary Outcome Measures :</p> <ul style="list-style-type: none"> <li>Percentage of subjects with treatment-emergent adverse events (TAEs), percentage of subjects with serious adverse events (SAEs), and percentage of subjects withdrawals due to adverse events (AEs) [Time frame: 40 weeks treatment duration ]</li> </ul> <p>See trial record for full list of other outcomes</p>	<p>Primary Outcome Measures :</p> <ul style="list-style-type: none"> <li>Percentage of subjects with treatment-emergent adverse events (TAEs), percentage of subjects with serious adverse events (SAEs), and percentage of subjects withdrawals due to adverse events (AEs) [Time frame: 32 months]</li> </ul> <p>See trial record for full list of other outcomes</p>
<b>Results (efficacy)</b>	-	-
<b>Results (safety)</b>	-	-

## ESTIMATED COST

The cost of trofinetide is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- No relevant NICE guidance identified.

## NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract Paediatric Neurosciences: Neurodisability. E09/S/c.

## OTHER GUIDANCE

- Rett Syndrome. Management and Care Guidelines. 2013.<sup>13</sup>

## ADDITIONAL INFORMATION

Neuren Pharmaceuticals Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## REFERENCES

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