Neuren presents at annual International Meeting for Autism Research

Melbourne, Australia, 21 May 2014: Neuren Pharmaceuticals (ASX: NEU) presented the attached poster at the International Meeting for Autism Research (IMFAR) in Atlanta on 15 May 2014. The poster describes the development of a Clinical Global Impression Scale (CGI) with measures specific to the signs and symptoms of Rett Syndrome. The CGI, which measures severity of illness and improvement in illness, is being used as one of several indicators of clinical efficacy in Neuren’s Phase 2 clinical trial of NNZ-2566 in Rett Syndrome. The trial is the first commercial multi-site clinical trial in Rett Syndrome.

To date 51 subjects have been enrolled in the trial. Neuren expects to complete enrolment in June 2014 and announce top-line results from the trial in the fourth quarter of 2014.

About Rett Syndrome

Rett Syndrome is a post-natal neurological disorder that occurs almost exclusively in females following apparently normal development for the first six months of life. 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. They experience a variety of motor problems including increased muscle tone (spasticity) and abnormal movements. These individuals are never able to provide for their own needs. It is a rare disorder and is believed to be second only to Down Syndrome as a genetically-determined cause of chronic neurological problems in females that include severe communication, motor disabilities and epilepsy. Rett Syndrome is caused by mutations on the X chromosome on a gene called MECP2. There are more than 200 different mutations found on the MECP2 gene. Rett Syndrome strikes all racial and ethnic groups and occurs worldwide in approximately 1 in every 10,000 live female births.

About NNZ-2566

NNZ-2566 is a synthetic analogue of a naturally occurring neurotrophic peptide derived from IGF-1, a growth factor produced by brain cells. In animal models, NNZ-2566 exhibits a wide range of important effects including inhibiting neuroinflammation, normalising the role of microglia and correcting deficits in synaptic function. In the Fragile X model, these actions resulted in statistically significant improvement in all core anatomic and behavioural features of the disorder that were assessed. NNZ-2566 is being developed both in intravenous and oral formulations for a range of acute and chronic conditions. The intravenous form of NNZ-2566 is presently in a Phase 2 clinical trial in patients with moderate to severe traumatic brain injury. The oral form of NNZ-2566 is in Phase 2 trials in Rett Syndrome and Fragile X Syndrome. All three programs have received Fast Track designation from the US FDA and the Fragile X Syndrome program has also received Orphan Drug designation. Neuren intends to implement a Phase 2 clinical trial with the oral form of NNZ-2566 in patients with concussion (mild traumatic brain injury).
About Neuren

Neuren Pharmaceuticals Limited (Neuren) is a publicly listed biopharmaceutical company focusing on the development of new therapies for brain injury, neurodevelopmental and neurodegenerative disorders. The novel drugs target chronic conditions such as Rett Syndrome and Fragile X Syndrome as well as acute neurological injuries. Neuren presently has a clinical stage molecule, NNZ-2566 in three Phase 2 clinical trials as well as NNZ-2591 in pre-clinical development.

Forward-looking Statements

This ASX-announcement contains forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks and important factors that may cause the actual results, performance or achievements of Neuren to be materially different from the statements in this announcement.

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Improving outcome measures for Rett Syndrome (RTT) clinical trials: the development of RTT-specific anchors for the Clinical Global Impression Scale

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INTRODUCTION

High-quality outcome measures are a critical component of well-designed clinical trials in subjects with Rett Syndrome (RTT). We describe the development of novel anchors specific to RTT signs and symptoms for the Clinical Global Impression Scale (CGI) for use in trials involving adolescent and adult females with RTT. This is the first industry-sponsored, multi-site clinical trial in this clinical population.

• The Clinical Global Impression Scale (CGI) (Guy, 1976) is a measure of global clinical change with strong face validity that has been widely used as an outcome measure in CNS clinical trials, including trials in neurodevelopmental disorders such as autism and Fragile X syndrome.
• The CGI is a 7-point Likert rating scale that reflects expert clinical judgment. It includes independent severity of illness (CGI-S) and improvement (CGI-I) scales.
• Despite its favorable assay sensitivity in clinical trial settings involving a number of different neuropsychiatric disorders, a disadvantage of the CGI has been its lack of focus on the specific signs and symptoms of the disorder under study (Busner et al. 2009).

Development of specific anchors for the scale that are keyed to gradations in the signs and symptoms of the disorder being assessed holds promise for enhancing the validity and reliability of the CGI for specific disorders.

Table 1: CGI Scales

<table>
<thead>
<tr>
<th>Score</th>
<th>CGI-S</th>
<th>CGI-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, not at all ill</td>
<td>Very much improved</td>
<td></td>
</tr>
<tr>
<td>Borderline</td>
<td>Much improved</td>
<td></td>
</tr>
<tr>
<td>Mildly ill</td>
<td>Minimally improved</td>
<td></td>
</tr>
<tr>
<td>Moderately II</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Markedly II</td>
<td>Minimally worse</td>
<td></td>
</tr>
<tr>
<td>Severely II</td>
<td>Much worse</td>
<td></td>
</tr>
<tr>
<td>Extremely II</td>
<td>Very much worse</td>
<td></td>
</tr>
</tbody>
</table>

METHODS

Utilizing information obtained from the RTT Natural History Study (ClinicalTrials.gov ID: NCT00299312), a classification grid of symptom severity was created, then developed into anchors describing progressive levels of impairment in symptoms. The CGI anchors provide examples of sign/symptom change as well as a framework for considering the duration, onset, durability of change, and context of sign/symptom change across these domains.

Table 3: Initial assignment of RTT-CSS severity scores and symptoms to CGI-S rating score

STUDY PARTICIPANTS

STUDY OVERVIEW

• Double-blind, placebo-controlled study of NNZ-2566 ([1-3] IGF-1 analog) versus placebo
• Adolescent and adult females ages 16-45 years old
• Participants have confirmed RTT and MeCP2 mutation
• Clinical Global Impression (CGI) scale provides an overall clinical impression of overall status of disorder
• CGI-S severity score of 4 or higher at screening
• CGI-S severity score of 4 or higher at screening
• Participants have confirmed RTT and MeCP2 mutation

Table 4: CGI Severity Anchor Example

FUTURE RESEARCH/IMPLICATIONS

The rating scheme captures clinically relevant gradations in severity and improvement of RTT-related signs and symptoms, offering the prospect of more consistent and relevant administration across research sites and studies. This report describes early development of this novel format for the CGI in the context of a clinical trial involving adolescent and adult females with RTT. Future analyses with the full pool of subjects will examine the psychometric properties and feasibility of this RTT-specific version of the CGI scales in the context of this clinical trial.

REFERENCES


ACKNOWLEDGEMENTS

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Copies of the CGI-S and CGI-I RTT anchors can be obtained by emailing: Nancy Jones, PhD at njones@neurenpharma.com

RESULTS

Table 6: Example Calibration Vignettes with CGI-S and CGI-I Scores

Visit | CGI Score | Descriptor
--- | --- | ---
Baseline | Severity: 5 | Description
No negative symptoms or events reported. Caretaker reports she is more attentive and seems to do certain things faster and more frequently, such as urinating and giving high-fives. She is observed to hold her eye gaze longer and walk with a little more fluidity.

Figures 1 a and b: Participant Race and Ethnicity

Figure 2: Severity Level at Baseline

Table 2: Participant Demographics

Table 5: Examples of Anchors from the CGI-I

Table 4: CGI Severity Anchor Example

Table 6: Example Calibration Vignettes with CGI-S and CGI-I Scores