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 Scales (Severity and Improvement). This effort is part of an on-going clinical trial involving adolescent and adult females with RTT, which 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

Score	CGI-S:	CGI-I:
	Provides an assessment of the patient's symptom severity at the time of assessment, based on the clinician's cumulative experience involving patients with the disorder	***Rates improvement since start of the study medication. Score can be used to separate clinical trial subjects into "responders" (CGI-I of 1 or 2) and "non-responders" (CGI-I of 3 to 7)***
1	Normal, not at all ill	Very much improved
2	Borderline ill	Much improved
3	Mildly ill	Minimally improved
4	Moderately ill	No change
5	Markedly ill	Minimally worse
6	Severely ill	Much worse
7	Extremely ill	Very much worse

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
  - o Participants have confirmed RTT and MeCP2 mutation
  - o CGI-S severity score of 4 or higher at screening
- Primary outcome: Safety as measured by adverse events
- Secondary outcomes: Efficacy and Pharmacokinetics
  - o Global outcomes measured by CGI-S and CGI-I
  - o RTT Natural History Motor Behavior Assessment (MBA)
  - o RTT Clinical Severity Score (CSS)
  - o Aberrant Behavior Checklist
  - o Vineland Adaptive Behavior Scale
  - o RTT Caregiver Burden Inventory
  - o Caregiver Top Three Concerns
  - o EEG activity and hand movements
  - o Autonomic function: respiration, hyperventilation, apneas, oxygen desaturation
- Clinicaltrials.gov ID: NCT01703533-For complete inclusion/exclusion criteria

STUDY PARTICIPANTS

Figures 1 a and b: Participant Race and Ethnicity

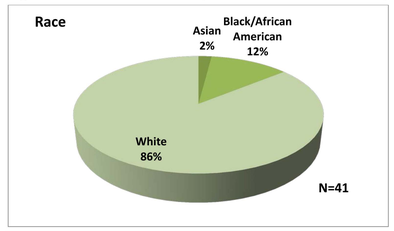
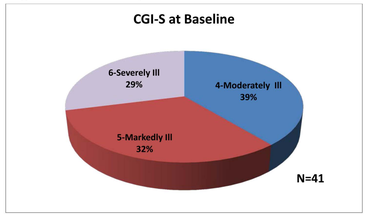


Figure 2: Severity Level at Baseline



Note: Minimum CGI-S score of 4 required for study entry.

Table 2: Participant Demographics

Enrollment to date (*Randomized*)	N=46
Mean Age	26 yrs
Age Range	16 - 44 yrs

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-I 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

CLINICAL DOMAINS	1 (CSS =0)	2 (CSS <5)	3 (CSS 5-10)	4 (CSS 10-20)	5 (CSS 20-25)	6 (CSS 25-35)	7 (CSS 35-40)
Language/ Communication	Normal	Appropriate. May have unusual features such as perseveration/echolalia. Reading disability/dyslexia	Phrases-sentences. May have conversations or echolalia	Words (<5) Babbles Makes choices 25-50%	No Words Babbles Makes choices ≤25%	Vocalizations Occasionally screams Makes No Choices or only rarely makes choices	No Words No Vocalizations Screams No Choices
Ambulation	No impairment	Normal, may have slight evidence of dystonia/ataxia/dyspraxia on careful exam	Walks, able to use stairs/run. May ride tricycle or climb	Walks Independently, unable to use stairs or run	Walks with Assistance	Stands With Support or independently May walks with support Sits independently or with support	Cannot sit Doesn't Stand or Walk
Hand Use	Completely normal, no impairment	Normal, may have slight fine motor issues	Bilateral Pincer grasp. May use pen to write but has some fine motor issues like tremor	Reaches for objects, raking grasp or unilateral pincer. May use utensils/cup	Reaches No Grasps	Rarely-Occasionally Reaches Out No Grasp	None
Social (Eye Contact)	Normal	Occasional eye gaze avoidance	Appropriate eye contact, >30 sec	Eye Contact <20 secs	Eye Contact <10 secs	Eye Contact, Inconsistent 5 secs	No eye Contact
Autonomic	None	Minimal	No or minimal breathing abnormalities (<5% of times observed) and Warm, pink extremities	Breathing Dysrhythmia <50% No Cyanosis Cool UE & LE Pink	Breathing Dysrhythmia 50% No Cyanosis Cool UE & LE Pink	Breathing Dysrhythmia, 50%-100%, maybe with Cyanosis Cold LE or UE, may be Blue	Breathing Dysrhythmia, Constantly with Cyanosis Cold UE & LE Mottled/Blue
Seizures	None	None or controlled	None, with or without meds	Monthly-Weekly	Weekly	Weekly-Daily	Daily
Attentiveness	Entirely normal	Occasional inattention	Attentive to conversation and follows commands	50-100% of Time	50% of Time	Less than 50% time	0%

Table 4: CGI Severity Anchor Example

Score	Description of Anchors
5. *Markedly ill*	Markedly ill would describe another large proportion of individuals eligible for the RETT-001 study. This level of severity is characterized by breathing dysrhythmia which is observed 50% of the time, but there is no distinct cyanosis. She has cool, but pink upper and lower extremities. Seizures occur weekly. The individual walks with assistance, and can reach for objects but not grasp. Social and communication skills are impaired. The individual babbles but uses no words functionally, and makes choices < 25% of the time. She may be attentive 50% of the time and typically makes eye contact for less than 10 seconds.

Table 5: Examples of Anchors from the CGI-I

Score	Description of Anchors	Score	Description of Anchors
2-*Much Improved*	Much Improved may denote moderate improvement in a single symptom area, especially if seen across settings. Likewise, moderate improvements in several areas, even if confined to one setting, may warrant a rating of "Much improved." Durability of the change should be taken into account.	**3-*Minimally Improved***	Minimally Improved indicates modest improvements, especially if confined to one setting. Trivial changes or changes that are possibly present or require guesswork usually would be scored as 4 (the level below this one).

RESULTS

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

Visit	CGI Score	Descriptor
Baseline	**Severity: 5**	She is 29yo who walks without trouble initiating and without retropulsion. She screams and vocalizes; she does not make consonant sounds. She reaches out for objects but cannot grasp or hold on to any object for more than a few seconds. She makes infrequent eye contact for 5-10 seconds, although she is very attentive to particular shows on TV. She has minimal breath holding and no hyperventilation. Her hands and feet are pink and cool. She has no seizures and is stable on her seizure medications.
Day 14	**Severity: 5 Improvement: 3**	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.

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

Busner J, Targum SD, and Miller DS (2009). The Clinical Global Impressions scale: errors in understanding and use. Comprehensive Psychiatry 50:257-262.

Guy W (1976). Clinical global impressions. In: Guy W, editor. ECDEU assessment manual for psychopharmacology (Revised). Rockville, Maryland, National Institute of Mental Health: 217-221.

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

ACKNOWLEDGEMENTS

The study is sponsored by Neuren Pharmaceuticals, and funded by Neuren Pharmaceuticals and the International Rett Syndrome Foundation. We acknowledge the participating centers, Baylor College of Medicine (PIs: Drs. Daniel Glaze and Jeffrey Neul), the University of Alabama, Birmingham (PI: Dr. Alan Percy), and Gillette Children's Specialty Healthcare (PIs: Drs. Timothy Feyma and Art Beisang) and their contributions to the development of CGI calibration vignettes. We also thank the families who have participated in the study.