NEUREN SHAREHOLDER UPDATE

Highlights:

- Neuren to locate its investor relations and some administrative functions in Australia
- Clinical development and operations to be consolidated in the USA
- First subject in Phase 2 Rett Syndrome study now enrolled
- Decision to proceed with Phase 2 clinical study in Fragile X Syndrome

SYDNEY, Australia, 15 April 2013: Neuren Pharmaceuticals Limited (ASX:NEU) is pleased to announce that following a strategic review the Board has unanimously decided to locate the company's investor relations and some administrative functions in Australia and, further, to consolidate all clinical development and operations in the USA. Commenting on this move, Neuren's Chairman, Richard Treagus said, "Being an ASX-listed company, this move will allow us to align our business more closely with the capital markets and shareholders and to better realise the value of our pipeline. By locating our full clinical team in the USA, we expect to benefit from a greater level of operational efficiency and effectiveness."

Neuren's corporate strategy is to increase the value of its key assets by extending the therapeutic focus from acute brain injury to include chronic conditions requiring longer term dosing. The expanded focus emphasises opportunities with five crucial attributes: solid scientific rationale, significant unmet medical need, compelling market opportunity, favourable regulatory treatment with a clear path to approval, and potential for development of additional conditions.

The two chronic therapeutic indications that have been selected are **Rett Syndrome**, a devastating neurodevelopmental disorder occurring almost exclusively in females and **Fragile X Syndrome**, the single largest known cause of intellectual disability and autism in males.

NNZ-2566 is Neuren's lead clinical stage compound and has been shown in animal models to significantly inhibit neuroinflammation and to normalise the critical functions of microglia, a type of brain cell that is central to maintenance of synaptic connections and communication between neurons. Inflammation and microglial dysfunction are hallmarks of acute traumatic brain injury and concussion, as well as neurodevelopmental disorders such as Rett Syndrome and Fragile X. NNZ-2566 is protected by both composition of matter and therapeutic use patents as well as a number of pending applications.

Traumatic Brain Injury

The *INTREPID* study is a randomised, double-blind, placebo-controlled, dose escalation trial to test intravenous NNZ-2566 as a treatment for acute, moderate to severe Traumatic Brain Injury (TBI). 260 subjects between 16 and 75 years of age will be enrolled in one of three, sequential dose cohorts

(30 subjects at 1 mg/kg/hr, 30 subjects at 3 mg/kg/hr and 200 subjects at 6 mg/kg/hr, all administered for 72 hours by continuous infusion following a bolus loading dose of 20 mg/kg) with 2:1 randomisation of active to placebo.

105 subjects have now been enrolled in the study – 30 in cohort 1, 30 in cohort 2 and 45 in cohort 3. The three best performing sites (Arrowhead Regional Medical Centre, University of Pittsburgh and the University of California at Davis) have collectively enrolled 68 (66%) of subjects. All three of those centres are participating in the Exception from Informed Consent (EFIC) protocol. While the FDA approved enrolment under EFIC in July 2011, separate approval is required for clinical trials utilising Department of Defense (DOD) funding. As sites complete the community consultation and public disclosure (CCPD) process required by FDA regulations and obtain local IRB approval, their documentation is submitted for DOD review and approval. Final DOD approval for the EFIC protocol and for the first site participating under EFIC was received on 14 January 2013. Five sites have obtained local IRB approval. A second site, the University of California at Davis, received DOD approval on 3 April 2013. Applications from the remaining sites with local IRB approval are pending review by DOD. Five additional sites are currently completing the CCPD process. Once these sites have obtained local IRB approval, their application packages will be submitted for DOD review and approval.

As the EFIC protocol is implemented, Neuren expects an increase in enrolment by participating sites. Eleven new sites are in the process of being activated and are expected to receive DOD approval by July which will mean a total of 18 sites actively enrolling, 10 under the EFIC protocol. Neuren is committed to and focused on accelerating enrolment on the *INTREPID* trial with completion scheduled for 4Q2014.

Concussion Study

The IND for use of the oral formulation of NNZ-2566 to treat concussion was approved by the FDA at the end of 2011 and enabled the Phase 1 study that also supports the Rett Syndrome trial. The final Phase 1 study report was received in late October 2012. Neuren believes that acute concussion is a viable and important target for NNZ-2566, supported by preclinical evidence and representing significant unmet medical need and market opportunity.

In preparation for a Phase 2 trial, Neuren conducted site qualification and feasibility assessments at candidate sites with the proposed study protocol. These assessments identified unexpected logistical challenges with respect to enrolling subjects from the civilian population within the 24-hour time window in part because standard of care is rest for the first 24 hours prior to evaluation and in part because the majority of sports-related injuries occur on Fridays and Saturdays when the concussion clinics are typically closed. This has led the company to consider alternative and more cost-effective approaches to conducting the trial.

Neuren has subsequently held productive discussions with the US Army Medical Research & Material Command in order to evaluate the feasibility of conducting the trial in a military population. The major Army training centres have dedicated concussion clinics on base. Soldiers who sustain a concussion are typically referred to the clinics for assessment immediately following injury. Prior to deployment, all service members have a baseline Automated Neuropsychological Assessment Metrics (ANAM), which is the functional equivalent of the ImPACT assessment and would preserve

our capability to enrol subjects with a pre-injury baseline assessment thereby enabling evaluation of subject-specific recovery which we believe will increase the power and precision of the study.

Neuren will provide further details in relation to study timing and trial design once the feasibility and costs of this military option have been fully determined.

Rett Syndrome Study

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. They are never able to provide for their own needs. Rett Syndrome is caused by mutations on the X chromosome of a gene called MeCP2. Rett Syndrome strikes all racial and ethnic groups and occurs worldwide in up to 1 of every 10,000 female births and affects some 20,000 girls and women in the U.S. alone.

Neuren previously collaborated with the Rett Syndrome Research Trust in testing NNZ-2566 in the MeCP2 mouse model of Rett Syndrome. This preliminary study showed positive effects on synaptic plasticity, dendritic morphology and survival. The putative mechanism of action is inhibition of neuroinflammatory cytokines and normalization of microglial function, which are key molecular and cellular processes that are abnormal in Rett Syndrome.

The Phase 2 Rett Syndrome clinical study is now actively recruiting and the first patient has been enrolled. A US$600,000 grant from the International Rett Syndrome Foundation to the principal investigators at Baylor College of Medicine is covering part of the cost for the study which is the first sponsor-led trial in Rett Syndrome.

Approximately 120 families of patients who meet the primary inclusion criteria have been identified by Baylor and are being screened for enrolment and randomisation. The trial will enrol up to 60 subjects from 16-40 years of age, allowing for some early discontinuation, in order to have 48 who complete all dosing and assessments. The study will involve two dose cohorts (35 mg/kg and 70 mg/kg twice daily). A DSMC review will be conducted on completion of the lower dose cohort. Assessments include safety, autonomic measures (respiratory function, heart rhythm and rate), EEG abnormalities, behaviour and global and functional measures out to day 28. The study is forecast to complete enrolment and follow-up by mid-2014, with top-line results announced in 2H 2014.

Fragile X Study

Fragile X Syndrome, like Rett Syndrome, is a genetically caused neurodevelopmental disorder. It is the most common inherited form of intellectual disability in males with approximately 60,000 people affected. NNZ-2566 was recently tested in a mouse model of Fragile X Syndrome. A range of behavioural and anatomic outcomes were assessed at 42 days following 28 days of treatment. NNZ-2566 normalized the anatomic, biochemical and behavioural features of the disorder with results that achieved statistical significance in all outcome measures. Full results were presented at the American Neuropsychiatric Association meeting in Boston, USA on 4th April 2013. *(Abstract attached)*

The results appear to be among the most compelling obtained with any molecule in a validated model that has been posited to predict the outcome of clinical studies in human patients. We believe that NNZ-2566 has the potential to represent a major breakthrough in this therapeutic area. Due to existing programs in Fragile X, the clinical and regulatory framework and assessment tools are already well-defined. It is possible that NNZ-2566 may qualify for Orphan Drug and Fast Track designation for this indication.

In light of the preclinical results, Neuren has made a decision to proceed with the planning and implementation of a Phase 2 clinical study. It is intended that this study will commence in 2H2013 and complete subject enrolment in 4Q2014. The Company's decision to launch this trial is an important element of our strategic commitment to increase the value of key assets by extending the therapeutic focus from acute brain injury to chronic conditions. Like Rett Syndrome, Fragile X meets all of the criteria by which we judge the value of opportunities: scientific rationale, unmet medical need, market opportunity, and favourable regulatory treatment with a clear path to approval.

NNZ-2591 is a cyclic dipeptide (diketopiperazine or DKP) and Neuren's lead preclinical molecule. It is a synthetic analogue of the DKP cyclo-(Gly-Pro) which, like Glypromate, the parent molecule of NNZ-2566, occurs naturally in the brain and has been described as having neuroprotective, anxiolytic and nootropic (memory enhancing) effects.

NNZ-2591 significantly attenuates activation of microglia following injury. The molecule has excellent oral bioavailability (~100%) and is currently being assessed as a clinical candidate for the treatment of a number of chronic neurological disorders. NNZ-2591 is protected by both composition of matter and therapeutic use patents as well as a number of pending applications.

In January 2013 Neuren entered into a Collaborative Research and Development Agreement (CRADA) with the neurosciences group at Walter Reed Army Institute of Research. This research is further investigating the effects of 28 days of orally administered NNZ-2591 on mTOR (a key molecular pathway involved in neuroplasticity and neurite outgrowth that plays a significant role in Rett and Fragile X Syndromes as well as recovery from TBI and concussion) and biomarkers of synaptic plasticity, inflammation and apoptosis. Neuren is also testing NNZ-2591 in the same *fmr*1 mouse model of Fragile-X Syndrome in which NNZ-2566 was tested.

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.

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 two Phase 2 clinical trials as well as NNZ-2591 in pre-clinical development. Neuren currently has operations in New Zealand and the United States.

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The Impact of NNZ-2566 on the *fmr1* Knockout Mouse Model of Fragile X Syndrome

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Background

Fragile X Syndrome is a neurodevelopmental disorder caused by mutation of the fragile X mental retardation 1 (*fmr1*) gene, and characterized by intellectual disability, social anxiety, attention-deficit hyperactivity disorder and abnormal physical characteristics such as macro-orchidism (enlarged testes). Mutant *fmr1* knockout (KO) mice recapitulate this phenotype and represent a preclinical model for assessment of putative drug treatments.

NNZ-2566 is a peptidase-resistant analogue of the terminal tripeptide of IGF-1, and is currently in clinical development for the treatment of traumatic brain injury and autism spectrum disorders. The current study evaluated the potential of NNZ-2566 to reverse the Fragile X phenotype exhibited by *fmr1* KO mice.

Drug Treatment

Fmr1 KO and wild-type mice (C57BL/6J background) were dosed with either vehicle or NNZ-2566 (100 mg/kg i.p.) 1/day, starting at 14 weeks of age, for 28 days. Various behavioral and anatomic outcomes were assessed following treatment.

Results

At baseline, *fmr1* KO mice manifested numerous phenotypic changes compared with wild-type mice, including: hyperactivity in the open-field ($p < 0.01$) and successive alley tests ($p < 0.01$); decreased contextual-fear conditioned learning ($p < 0.01$); increased social sniffing ($p < 0.01$); macro-orchidism ($p < 0.01$); increased dendritic spine density and increased phosphorylation of brain ERK and Akt ($p < 0.01$). Treatment with NNZ-2566 significantly ameliorated all of these aberrant features of the *fmr1* KO mouse phenotype.

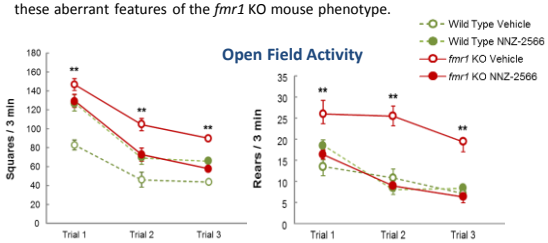

Figure 1. *Open field activity.* Fmr1 *KO mice show hyperactivity, as measured by squares crossed (left panel) and rears (right panel), which are reversed by treatment with NNZ-2566.*

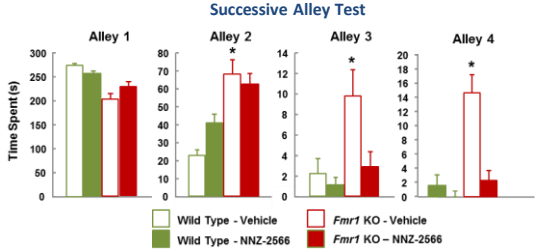

Figure 2. *Successive alley test. Wild-type mice show diminishing propensity to enter successive alleys that are increasingly neophobic (lighter, lower walled as the mouse progresses from alley 1 through alley 4). Fmr1 KO mice show significantly greater impartiality, most likely due to hyperactivity. NNZ-2566 reverses this phenotype.*

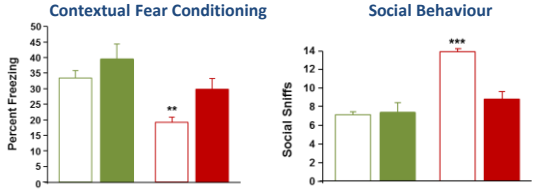

Figure 3. *Assessments of cognition and memory. Fmr1 KO mice show decreased behavioural freezing when reintroduced to an aversive environment (contextual fear conditioning), as well as enhanced sniffing of a reintroduced conspecific (social memory) – indicative of learning and memory impairment. NNZ-2566 reverses both of these effects.*

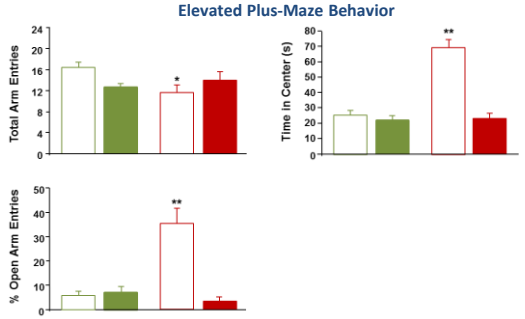

Figure 4. *Assessment of behavior in the elevated plus-maze test. Fmr1 KO mice show increased entries of the 'open' arm, which can indicate reduced anxiety. However, the considerable increase seen in time spent in the center of the maze suggests the KO mice spend an exaggerated time choosing which arm to enter, and then make an impartial decision. This behavioural profile may therefore represent impaired cognition or memory. NNZ-2566 treatment completely normalised this profile.*

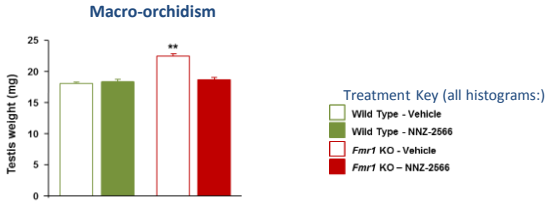

Figure 5. *An anatomical feature of Fragile X syndrome, also observed in fmr1 KO mice, is enlarged testes (macro-orchidism). This aberrant phenotype was clearly observed in the current mouse study, and was reversed by 28 day treatment with NNZ-2566 (100 mg/kg, i.p.)*

Acknowledgment:
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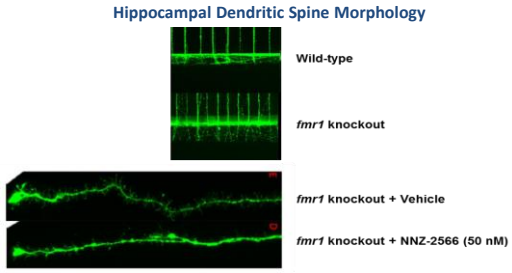

Figure 5. *Photomicrographs of dendritic spine morphology in wild-type and fmr1 KO mouse hippocampal cells (obtained at E14-E16 and cultured to 14-21 DIV). Dissociated hippocampal cells were plated in 15 mm multi-well vessels and a plating medium of MEM-Eagle's salts (supplied glutamine free) was supplemented with 10% fetal bovine serum. After 3 days (culture conditions: 37 °C in humidified 5% CO_2), green-fluorescent protein (GFP) was applied to monitor dendritic spine morphogenesis during culture. Dendritic spines are usually formed between 7 and 14 days in vitro (DIV). By 14 DIV most dendritic protrusions are spines; however, their maturation continues until 21 DIV. Fmr1 KO significantly increased spine density - an effect that is reversed by in vitro treatment with NNZ-2566 (50 nM).*

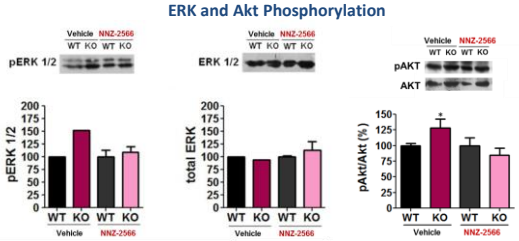

Figure 6. *Western blot analysis was conducted on extracellular-signal-regulated kinase (ERK), and Akt from wild-type and fmr1 KO mouse brain (obtained ex vivo, following 28 day treatment with either vehicle or NNZ-2566). ERK is a classical MAPK signal transduction protein, responsible for growth factor transduction, proliferation, cytokine response to stress and apoptosis. Akt is a key component in the PI3K/Akt/mTOR signalling pathway and regulates cellular survival and metabolism by binding and regulating many downstream effectors, such as Nuclear Factor-κB (NfκB) and Bcl-2 family proteins. Excess activation (phosphorylation) of both has been implicated in autism spectrum disorders. Fmr1 KO increased ERK and Akt activation in the current study. This effect was reversed by treatment with NNZ-2566.*

Conclusions

NNZ-2566 treatment for 28 days appears to normalize the phenotype of *fmr1* KO mice. The efficacy of the drug was observed not only in behavioral studies but also in studies of dendrite morphology and ERK/Akt activation. Significantly, a complete reversal of macro-orchidism was also seen following NNZ-2566, indicative of a potential for disease-modifying effects involving not just the CNS but also other tissues that are affected adversely in Fragile X Syndrome. Taken together, these data suggest that the novel small molecule, NNZ-2566, may represent a potentially important treatment for Fragile X Syndrome. Further studies are ongoing to expand our understanding of the mechanism of action of NNZ-2566 in *fmr1* KO mice, and to extend studies to other models of autism spectrum disorders.