



Neuren (NEU) - ASX Announcement

26 April 2016

Results of Phase 2 trial in moderate to severe traumatic brain injury

Melbourne, Australia, 26 April 2016: Neuren Pharmaceuticals (ASX: NEU) today announced top-line results from its Phase 2 clinical trial of trofinetide in moderate to severe traumatic brain injury (TBI). The trial (known as "INTREPID") was conducted in collaboration with the U.S. Army Medical Research and Materiel Command. The results have been reviewed and interpreted with the assistance of military medical experts and trial investigators.

The safety results from INTREPID, which was the primary endpoint of the trial, identified no treatment-related or dose-dependent trends in adverse events or laboratory results.

The trial did not demonstrate a difference between drug and placebo in the 3 core efficacy measures, which were the Extended Glasgow Outcome Scale (GOS-E), the Mayo-Portland Adaptability Inventory (MPAI-4) and mortality. GOS-E has been used as the primary efficacy measure in previous large TBI clinical trials. MPAI-4 is a validated measure of functioning in activities of daily living following TBI. The overall rate of mortality in the INTREPID trial was lower than was observed in prior trials, but there was no significant difference between drug and placebo.

Superiority of drug over placebo was demonstrated in the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which was one of the exploratory efficacy measures in the INTREPID trial. RBANS is a validated series of tests completed by the patient for assessing cognitive impairment that is commonly used in the diagnosis and tracking of dementia. RBANS has also been validated for use in moderate-to-severe TBI. Further analysis is being conducted to evaluate the clinical implications of this positive RBANS finding and to consider the remaining exploratory efficacy measures, which also assessed cognitive and neuropsychological functioning.

Two factors appear to have contributed to the outcomes in the core efficacy measures. These were the composition of the enrolled patient population and the drug levels that were achieved.

A common challenge in clinical trials in TBI is the high degree of variability in the characteristics of injuries and patient populations. The 260 patients enrolled in the INTREPID trial included a higher than expected proportion of patients who were severely injured and, in particular, subjects who had sustained severe injuries to the chest and other parts of the body and were less likely to respond positively to a drug targeting brain injury. Further, the randomization of patients to either drug or placebo resulted in a higher proportion of severely injured patients being assigned to the drug group rather than placebo in the largest cohort of 200 subjects receiving the highest dose. This imbalance between groups was accounted for in the pre-specified statistical analysis of the results, but the adjustment only partially compensated for the disadvantage in the drug group.



The dosing regimen used in this trial, which was a bolus dose of 20 mg/kg followed by 1, 3 or 6 mg/kg per hour for 72 hours, was determined in 2009 within the context of INTREPID being the very first trial of trofinetide in human patients. Much has since been learned about trofinetide dosing and Neuren's more recent trials in Rett syndrome and Fragile X syndrome have confirmed an excellent safety profile, allowing for much higher doses to be administered for longer periods in order to maximize total drug exposure and potential clinical efficacy. Furthermore, the pharmacokinetic analysis of blood samples in the INTREPID study showed a significantly higher rate of clearance of trofinetide from patients compared with that observed in healthy volunteers, Rett syndrome patients and Fragile X syndrome patients. This may have been caused by the large volume of intravenous fluid replacement and diuretics that are frequently administered during acute critical care. The increased clearance resulted in significantly lower exposure in INTREPID patients to the drug than had been targeted.

Further detailed analyses of the INTREPID trial data are underway to help inform and define the optimum patient population, dose levels, duration of treatment and efficacy measures should another trial be conducted. Neuren and the U.S. Army are discussing the feasibility of funding and executing such a trial.

The Phase 2 trial of trofinetide in concussion being conducted by Neuren and the U.S. Army has been placed on hold while the implications and learnings from the INTREPID trial, in particular dose levels, are fully considered.

The INTREPID trial achieved a number of important advances for the design and execution of TBI trials. Biomarkers were shown to be a highly effective tool for measuring severity of injury and predicting outcomes. Neuren also has successfully developed a more sophisticated method of accounting for baseline severity in the analysis of outcomes. The detailed results of the trial will be published in due course. An overview of the trial will be presented at the 6th Annual Traumatic Brain Injury Conference on 12 May 2016 in Washington D.C.

Neuren's Chief Science Officer, Larry Glass, commented: "Combined with the safety information from the Rett and Fragile X syndrome trials, the results from the INTREPID trial support the use of considerably higher doses in TBI patients. We have also made advances in the use of biomarkers and other measures of baseline severity that would improve the design and analysis of a future trial. After further analysis, we will determine with our U.S. Army colleagues the best way forward for trofinetide in brain injury."

The U.S. Army Medical Research and Materiel Command's Principal Assistant for Acquisition, Dr. Kenneth Bertram commented: "There remains an urgent need for promising solutions across the spectrum of traumatic brain injury. We are continuing to collaborate with Neuren on further analysis of the trial data. The advances in the use of biomarkers that have been made during this trial will be an important tool for selecting and characterizing study populations in potential future clinical trials."



About trofinetide

Trofinetide is a synthetic analogue of a naturally occurring neurotrophic peptide derived from IGF-1, a growth factor produced by brain cells. In animal models, trofinetide exhibits a wide range of important effects including inhibiting neuroinflammation, normalizing the role of microglia, correcting deficits in synaptic function and regulating oxidative stress response. Trofinetide is being developed both in intravenous and oral formulations for a range of acute and chronic conditions. The intravenous form of trofinetide is in Phase 2 development for moderate to severe traumatic brain injury. The oral form of trofinetide is in Phase 2 development in Rett syndrome, Fragile X syndrome and concussion. Three programs have received Fast Track designation from the US FDA and the Rett syndrome and Fragile X syndrome programs have also received Orphan Drug designation in the United States and the European Union.

About Neuren

Neuren Pharmaceuticals Limited (Neuren) is a biopharmaceutical company developing new therapies for brain injury, neurodevelopmental and neurodegenerative disorders. The novel drugs target chronic conditions as well as acute neurological injuries. Neuren presently has a clinical stage molecule, trofinetide in Phase 2 clinical trials as well as NNZ-2591 in preclinical 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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