



Neuren Announces Glypromate[®] Trial Preliminary Results

SYDNEY, Australia, 24 December 2008: Neuren Pharmaceuticals announced preliminary results today for its pivotal clinical trial of Glypromate[®] to reduce cognitive impairment in patients undergoing cardiac surgery with cardiopulmonary bypass. Preliminary results from the study indicate that Glypromate[®] had no observable effect in this population. In contrast to the incidence of deficits reported in the published literature, among the 325 patients who completed the study, only a small proportion (approximately 20%) evidenced any degree of cognitive decline at 12 weeks and, among those with decline, the average change was small. Approximately 80% of patients in both the placebo and Glypromate[®] groups actually showed improvement in cognitive function. Furthermore, there was no evidence of impairment in ability to perform activities of daily living in either group at baseline or 12 weeks. No significant difference was noted between patients receiving the active drug and those receiving placebo on either change in composite cognitive score or activities of daily living from baseline to 12 weeks.

Commenting on the results of the study, Dr. Douglas Wilson, Neuren's Chief Medical Officer, said: "Obviously, we are very disappointed with the outcome of the trial. While the results of this study may not be applicable to all patients, our findings clearly indicate that, at least at the centres where the study was conducted, the surgery had little negative impact on cognition and activities of daily living, in contrast to most reports in the literature. To the contrary, our data suggest that these types of cardiac surgery result in improved cognitive function although the study does not shed any light on the factors that may be responsible for this observation. The data from the Neuren study are similar to recent findings from Allon Therapeutics, Inc. that were released in late August 2008 and also reported no significant cognitive impairment in a study of 234 coronary artery bypass graft patients. These discouraging results for Neuren may, in fact, be good news for patients."

Larry Glass, Neuren's US CEO, noted that "The Company will discontinue development of Glypromate[®], focusing its efforts on the other molecules in its pipeline. Neuren has an extremely promising portfolio of highly differentiated compounds addressing unmet needs in neurology, psychiatry and oncology and we will now be turning our full attention to developing these assets."

Neuren's product portfolio includes NNZ-2566, in development as a treatment for traumatic brain injury with the US Army; Motiva[™], being developed as a therapy for apathy and depression in recovering stroke patients; three families of preclinical compounds in development for acute and chronic neurological conditions including Parkinson's disease and neuropathy; and two programs focused on the treatment of cancer.

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SNUG-II Trial Design and Results

SNUG-II was an international, multicentre, randomised, Phase III, double-blind, placebo-controlled clinical trial of Glypromate[®] in patients undergoing cardiopulmonary bypass (CPB) for coronary artery bypass graft (CABG) surgery with or without valve replacement and/or repair. The primary objectives of the study were to evaluate the efficacy of Glypromate[®] compared to placebo in the reduction of cognitive decline and differences in functional activities of daily living (ADL) based on scores taken at baseline and 12-14 weeks after surgery.

Neuren enrolled 355 patients who were over the age of 50 years and scheduled for non-emergency CABG surgery with or without valve replacement/repair with CPB. Patients were enrolled from across 23 sites in the US, Australia and New Zealand. The study was initially designed to recruit 600 treated patients; however, a review of the statistical variance on complete follow-up data from the first 100 patients in the trial determined that, with complete follow-up data on 320 treated patients, the trial would be sufficiently powered to determine a statistically significant result. Patients were assigned to one of two groups (active treatment or placebo) in a 1:1 ratio, with 176 patients assigned to Glypromate[®] and 179 patients assigned to placebo. The safety population comprised 337 patients. 325 patients completed the assessments required for determination of efficacy (the modified Intent-to-Treat population).

Patient demographic attributes, including age, gender, IQ and type of surgery, were similar for the two groups. Patients received a continuous 4-hour infusion of 1 mg/kg/hr i.v. Glypromate[®] or placebo (sodium chloride 0.9% for injection) which commenced on completion of bypass.

The cognitive measure includes tests of memory, attention, recall, concentration and executive function summed to calculate the composite score. The differences between composite preoperative baseline scores and 12-14 week postoperative composite scores for each patient were used to create a standardised composite change or Z score which represents the co-primary endpoint.

The battery of cognitive tests was selected based on an extensive review of previous studies in the field. Previous studies have shown that a significant proportion of the population experienced neurocognitive deficits following surgery. These changes manifest as difficulties with memory, attention, concentration and speed of motor and mental response (Stygall and Newman 2003). In 2004, the American College of Cardiology/American Heart Association (ACC/AHA) Task Force reported that 53% of CPB-CABG patients experienced abnormal neurocognitive function at the time of hospital discharge. Six months after surgery, abnormalities could still be identified in 24% of patients (Eagle et al. 2004).

Preliminary analysis of the results of the SNUG-2 trial indicates that the majority of both treated and untreated patients did not experience a decline in cognitive function or in activities of daily living. Only 64 of the 325 patients (20%) who completed the trial experienced any cognitive decline. There was no significant difference between the Glypromate[®] treated group and the placebo treated group in the cognitive co-primary end point scores among these patients.

Preliminary analysis of the Activities of Daily Living questionnaire demonstrated minimal baseline impairment, no decline in function post-operatively and no difference between the Glypromate[®] treated group and placebo treated groups.

The data confirm that Glypromate[®] is safe and well tolerated. No adverse events or serious adverse events were considered related to study drug. The overall incidence of adverse events and serious adverse events was similar between the placebo and Glypromate[®] treated groups. Of the 9 deaths that occurred in the study, 1 occurred in the Glypromate[®] treated group (0.59% mortality rate) and 6 (3.59% mortality rate) in the placebo treated group. Two patients died before receiving any drug.

References

Eagle KA, Guyton RA, Davidoff R, Edwards FH, Ewy GA, Gardner TJ et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee to update the 1999 guidelines for coronary artery bypass graft surgery). *Circulation*, 2004; 110:340-437.

Stygall J, Newman SP, Fitzgerald G, Steed L, Mulligan K, Arrowsmith JE et al. Cognitive change 5 years after coronary artery bypass surgery. *Health Psychology*, 2003; 22:579-586.