Neuren Pharmaceuticals

Clinical Development Strategy for NNZ-2566 in Traumatic Brain Injury

2006 ATACCC Conference

Larry Glass

Program overview

"The combined research approach of brain trauma scientists, subject matter experts, and a pharmaceutical drug development company will provide a unique opportunity for conducting advanced pre-clinical research in seizure control, neuroprotection and brain injury."*

"The ultimate goal of this CRADA is the development and delivery of an efficacious, fieldable drug-based therapy amenable to rapid, far-forward medical application to both brain injured soldiers and civilians."*

*Quotes from US Army-Neuren Cooperative Research Development Agreement

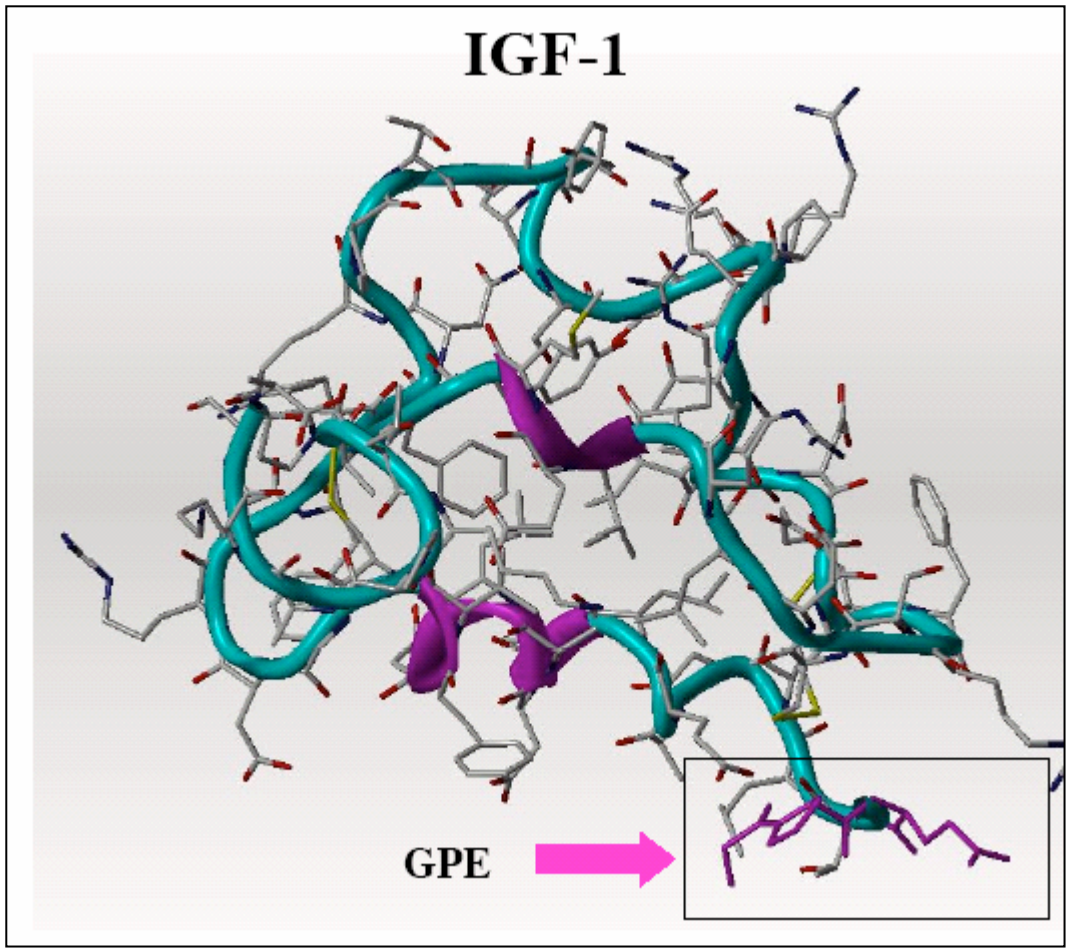
Neuren background

- Drug development company targeting neuroprotectants for cognitive impairment, traumatic brain injury, Parkinson's disease and Alzheimer's disease
- Strong portfolio
  - 6 families of compounds
  - 2 drugs in clinic for acute CNS indications
- Company operations
  - Neuren Ltd (Auckland): HQ, preclinical R&D, clinical affairs
  - Neuren Inc (Bethesda): regulatory/government affairs, CMC, pharm/tox, US/EU operations and clinical trials
- Strong research and drug development partnerships including US Army

Collaborators and Advisors

- Frank Tortella, PhD (Army; neuropharmacologist)
- COL Geoffrey Ling, MD, PhD (Army; neurologist)
- COL James Ecklund, MD (Army; neurosurgeon)
- Ron Hayes, PhD (Banyan/U of Florida; neuropharmacologist)
- Paul Vespa, MD (UCLA; neurointensivist)
- Jamie Cooper, MD (NTRI, Melbourne; neurologist)
- MAJ Jed Hartings, PhD (Army; neuropharmacologist)
- Anthony Williams, PhD (Army; neuropharmacologist)

Glypromate® and NNZ-2566



Glypromate®

- N-terminal tripeptide of IGF-1 (gly-pro-glu)
- Discovered during research into neuroprotective role of IGF-1 in brain-injured neonates
- Drug-like molecule (MW: 301 g/mol)
- Wide therapeutic window in stroke models
- No adverse effects in animals at maximum feasible dose (MFD)
- No interactions with >80 common targets (including IGF-1 receptor)
- No drug-related AEs in Phase I and IIa studies
- Entering Phase III Q4 2006 to prevent cognitive impairment in cardiopulmonary bypass patients

Multiple modes of action

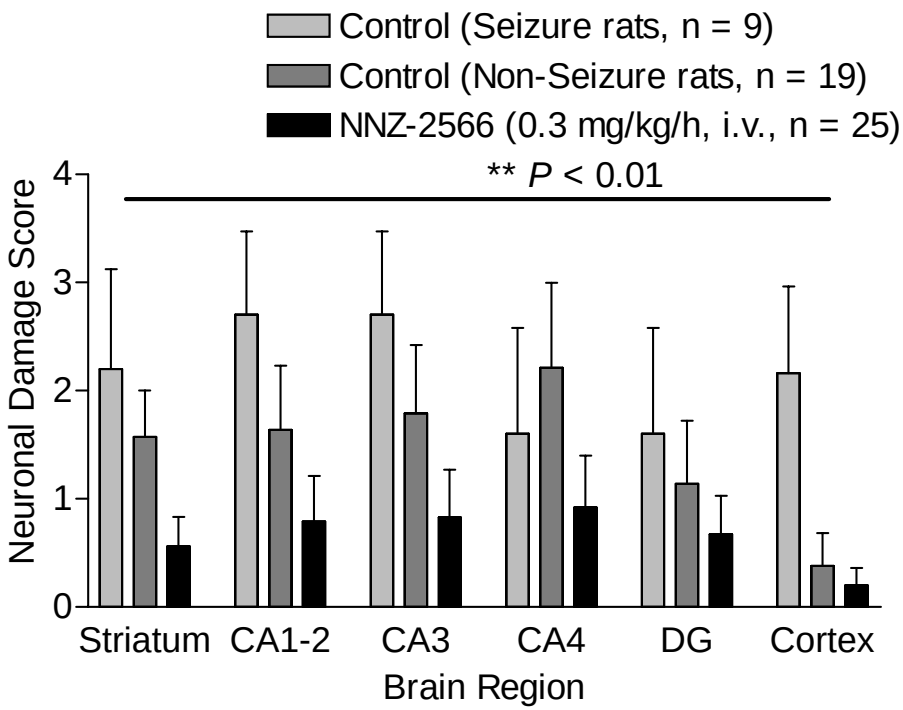
- Inhibits caspase-3 dependent apoptosis
- Inhibits microglial activation
- Protects astrocytes as well as neurons
- Inhibits secondary necrosis
- Preserves neuronal function

NNZ-2566

- Molecule
  - Glypromate® analog (gly-2 methyl-pro-glu)
  - Improved pharmacokinetics
  - Inexpensive to manufacture and formulate; good stability
  - Similar efficacy, therapeutic window in animal models
  - Comparable safety profile in safety pharmacology/toxicology studies and Phase I
  - Orally bioavailable
- Development status
  - Safe and tolerated in rats and dogs
  - Phase Ia (bolus dose escalation) underway
  - Phase Ib (continuous infusion)
  - Phase II (two studies) being planned for 2007

NNZ-2566 is neuroprotective

No seizures in NNZ-2566 treated rats



Clinical development goals

- Drug for acute treatment of TBI that…
  - Reduces neurological damage and sequelae
  - Has a reasonable (2+ hrs) therapeutic window
  - Can be administered safely to all TBI patients (mild to severe; penetrating and closed-head)
  - Can be administered prior to or without CT or MRI
  - Can be administered IV by combat medics or EMTs
- Clinical trials that…
  - Maximize opportunities for detecting an effect
  - Accommodate heterogeneity in patients
  - Utilize biologically relevant endpoints
  - Focus on clinically relevant outcomes
  - Accelerate path to marketing approval

Study 1: Phase II (severe)

- Open-label, observational study in TBI patients with GCS 4-8 to evaluate…
  - Safety
  - Penetration of drug to injured brain
  - Preliminary evidence of efficacy in modifying acute disease/injury processes
- Within subjects and cohort comparison analyses
- Drug administered within 24 hours of injury as IV bolus followed by 72 hrs of infusion (days 1-5)
- Planned enrollment: 50 closed; 15 penetrating
- Stratification by closed (focal vs. diffuse) and penetrating

Study 1 (severe) Within-subjects comparisons

- Incidence of hypotension
- Percent time of elevated intracranial pressure
- Mean global EEG percent alpha variability (PAV) score
- Incidence of epileptiform activity/non-convulsive seizures
- Biomarkers (measured in CSF at 24, 36, 72, 96 hrs)
  - Alpha II-spectrin breakdown product SBDP145 (Calpain-mediated acute cell death / necrosis)
  - Alpha II-spectrin breakdown product SBDP120 (caspase-mediated delayed cell death / apoptosis)
  - Neuroinflammation marker IL-6
- Study drug concentration in brain microdialysis samples
- Mortality
- Safety (AEs and SAEs)

Study 1 (severe) Cohort Comparisons

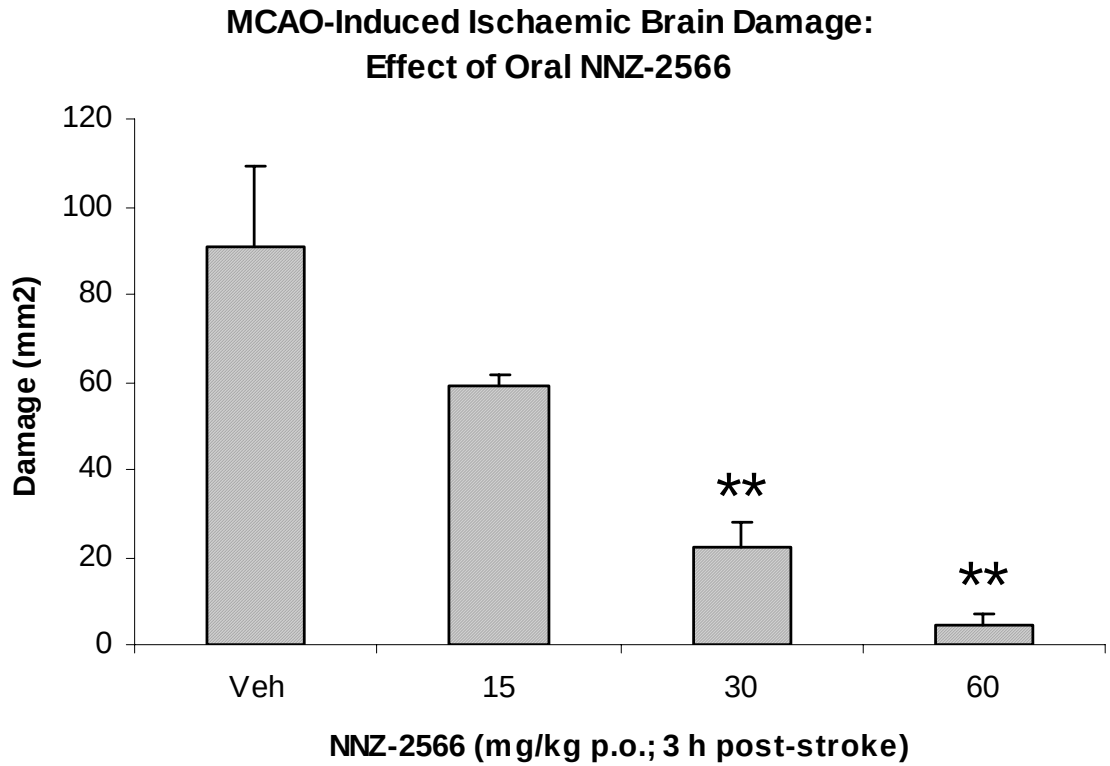
- Historical cohorts
  - Maas et al. Lancet Neurology 2006
  - Vespa et al. J Neurosurgery 2002
  - Vespa et al. J Neurosurgery 1999
  - Hebb et al. J Neurotrauma (submitted) 2006
- Mortality at 30 days
- GOSE at 6 months
- Percent time of elevated intracranial pressure
- Neuropsychological (CDR) test battery at 6 months
- Mean global EEG PAV during post injury days 0-5
- Percent time of microdialysis lactate:pyruvate ratio (LPR) > 25
- Incidence of electrographic epileptiform activity during study drug infusion compared with non-infusion period during post injury days 1-5
- Therapy Intensity Level values

Study 2: Phase II (mild-moderate)

- Randomized, double-blind, placebo controlled, dose-escalation study in patients with GCS 9-15 to evaluate safety and efficacy
- Intended enrollment = 200 (3:2 active : placebo randomization)
- Interim analysis of efficacy and safety with ~50 completed patients
- Drug administered within 12 hours of injury as IV bolus followed by 8-24 hrs continuous infusion
- Primary outcome measures
  - Neurocognitive outcome at 6 months (CDR)
  - Hamilton depression scale at 6 months
  - Global quality of life (SF36) at 6 months
  - Safety (hypotension, mortality, AEs, SAEs prior to discharge)
- Secondary outcome measures
  - cEEG (PAV, epileptiform activity)
  - MRS N-acetylaspartate (NAA) at 6 months*
  - MRI volume analysis at 6 months*

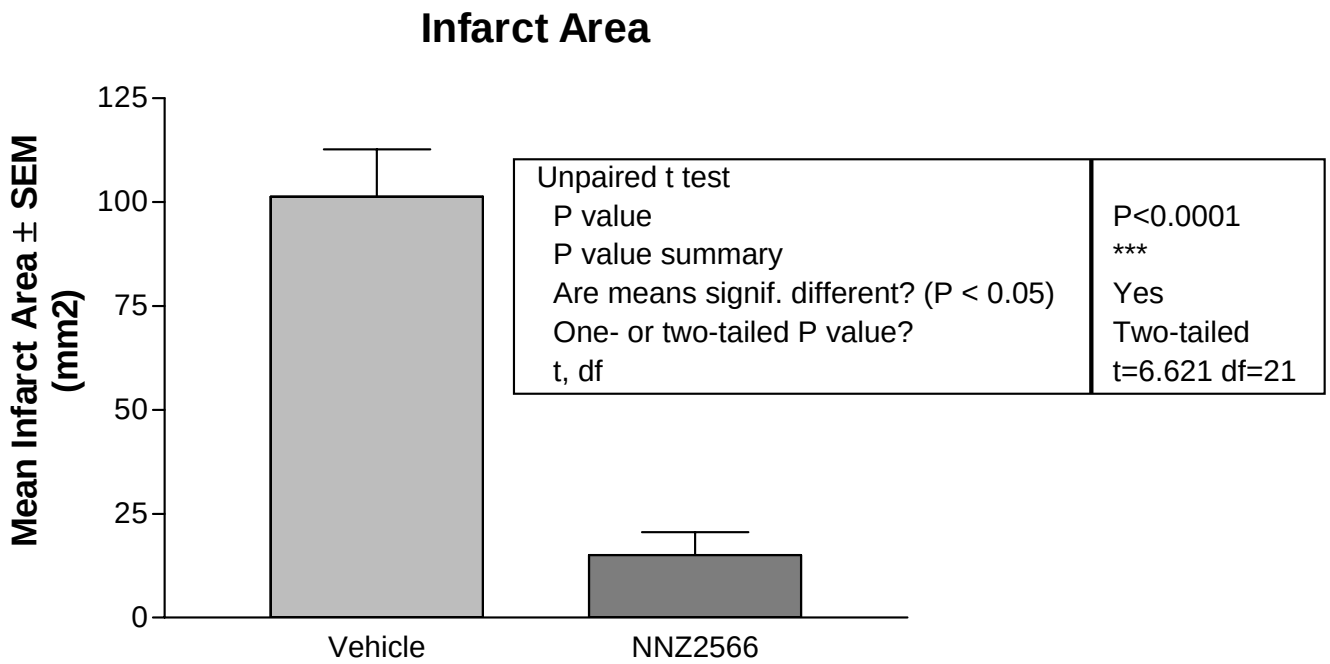
* May be performed on a subset of patients depending on cost and logistical considerations

NNZ-2566 Oral (single dose)



** P < 0.01, ANOVA with Dunnett's post-hoc test. Group sizes: Veh (9), 15 mg/kg (8), 30 mg/kg (8), 60 mg/kg (7)

NNZ-2566 Oral (2 doses)



Effect of microemulsion NNZ2566 given orally at 2 and 4 hours post Et-1 induced MCAO.Total dose is 80mg/kg. Vehicle (n = 12),NNZ2566 (n=11)

Conclusion

- Excellent progress on TBI program
- Moving toward clinical trials in 2007
- Active Army and civilian involvement in clinical trial design
- Separate clinical trials planned for severe and mild to moderate head injury
- Potential for Fast Track designation and Orphan Drug status for severe TBI