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# Company Overview

## August 2007

# Company Overview

- New Zealand company; listed on the ASX; operations in NZ and US
- Strong drug discovery, clinical development, clinical trial management
- 3 new chemical entities in clinical trials for 4 CNS indications
  - Glypromate® Phase III for post-operative cognitive impairment in cardiac surgery
  - NNZ-2566 Phase II for mild-to-moderate traumatic brain injury(1)
  - NNZ-2566 Phase IIa for severe traumatic brain injury(1)
  - Motiva™ Phase II for post-stroke depression(1)
- Drug attributes of lead molecules well-suited to CNS therapy
  - Wide safety margins
  - Long therapeutic time windows
  - Modes of action target inflammatory and apoptotic cascades, multiple cell types
- Glypromate® is currently in a well-designed Phase III clinical trial
  - Clinical indication directly relevant to known actions of the drug
  - Clinically meaningful endpoints linked both to drug actions and preclinical data
  - Clinical outcome measures, analysis methods support trial objectives and execution

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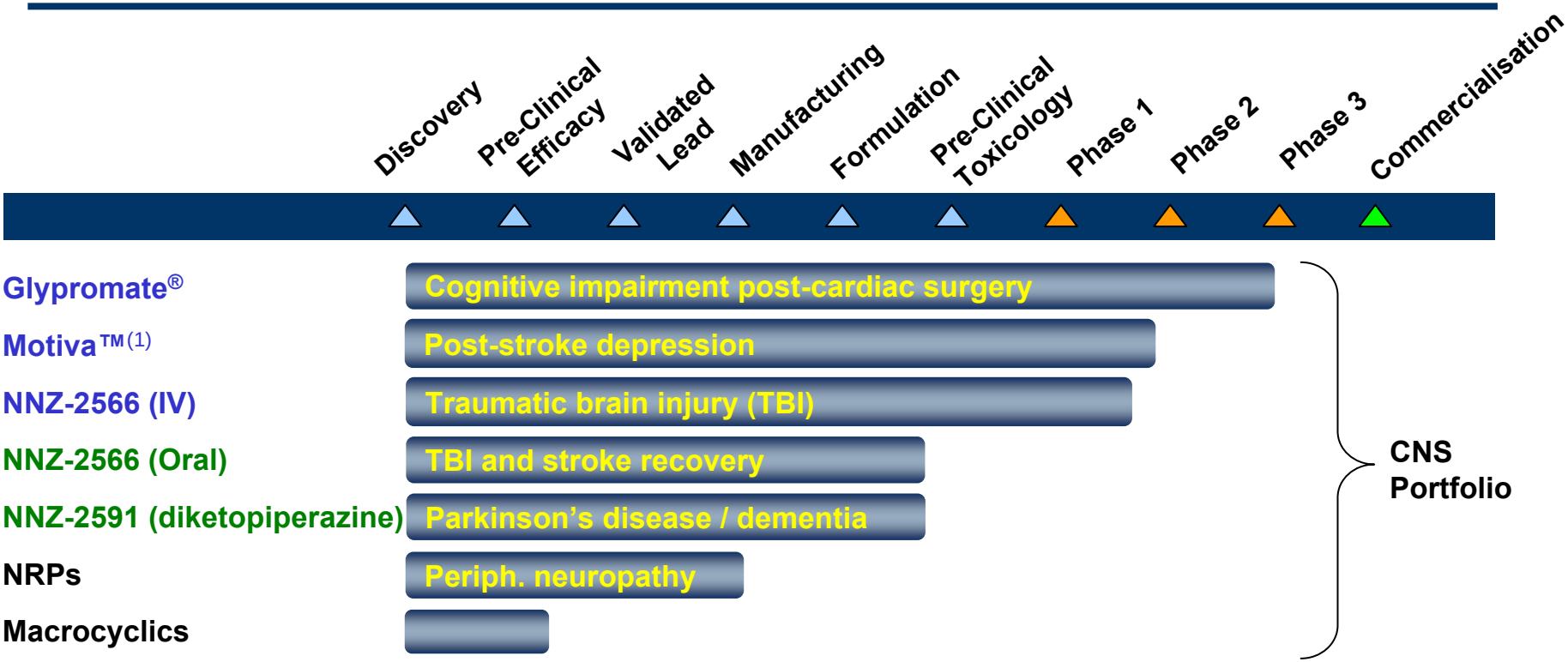
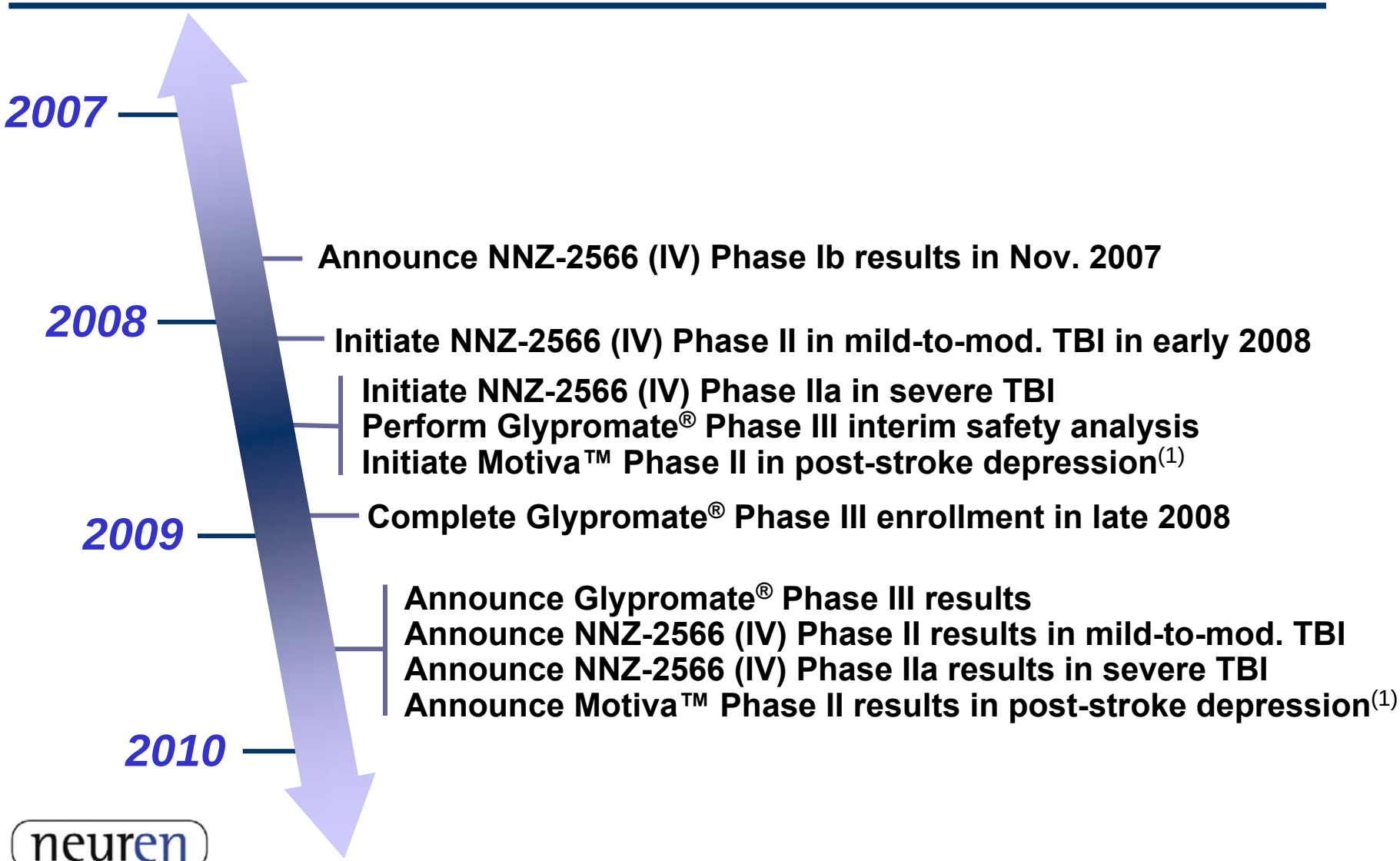
(1) Trial expected to be initiated in 2008.

# Product Candidate Pipeline




(1) Addition of Motiva™ to pipeline is subject to completion of the pending acquisition of Hamilton Pharmaceuticals.

# Anticipated Milestones

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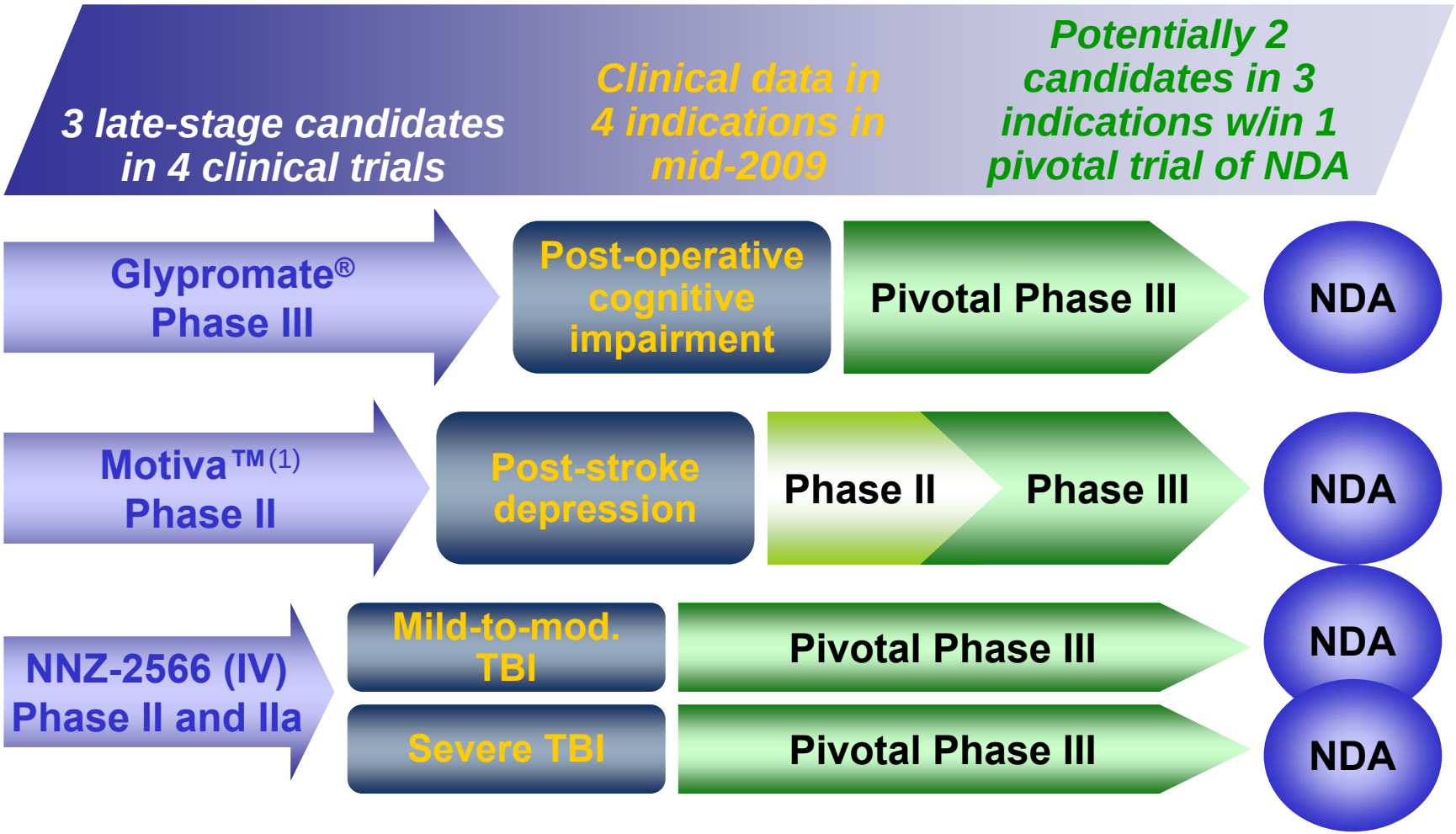
(1) Addition of Motiva™ to pipeline is subject to completion of the pending acquisition of Hamilton Pharmaceuticals.

# Neuren's Lead Product Candidates in 2009

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(1) Addition of Motiva™ to pipeline is subject to completion of the pending acquisition of Hamilton Pharmaceuticals.

# Glypromate® Pivotal Phase III (First of Two Phase IIIs)

| | |
|---|---|
| **Design** | Randomized, double-blind, placebo-controlled |
| **Patients** | Approx. 600 |
| **Sites** | 24 in U.S., Australia and New Zealand |
| **Inclusion Criteria** | ▪ CABG surgery +/- valve replacement/repair with CPB<br>▪ Able to undergo all cognitive and ADL testing<br>▪ ≥50 years old |
| **Dose** | 1 mg/kg/hr (4 hr. infusion) |
| **Randomization** | 1:1 |
| **Primary Endpoints** | Change from baseline in composite cognitive score and comparative levels in ADL composite score |

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# Previous Glypromate® Clinical Trials

| | Phase IIa | Phase I |
|---|---|---|
| **Design** | Randomized, double-blind, placebo-controlled | Randomized, double-blind, placebo-controlled |
| **Patients** | 33 (2 open label) | 30 |
| **Inclusion Criteria** | ▪ CABG surgery +/- valve replacement/repair with CPB<br>▪ ≥60 years old | ▪ Healthy volunteers |
| **Dose** | ▪ 1 mg/kg/hr (4 hr. infusion)<br>▪ 3 mg/kg/hr (4 hr. infusion) | ▪ 0.3, 1.0 and 3.0 mg/kg/hr (15 min. infusion)<br>▪ 1 mg/kg/hr (4 hr. infusion)<br>▪ 3 mg/kg/hr (4 hr. infusion) |
| **Safety and Tolerability** | ▪ No drug-related AEs or SAEs | ▪ No SAEs<br>▪ No drug-related AEs |

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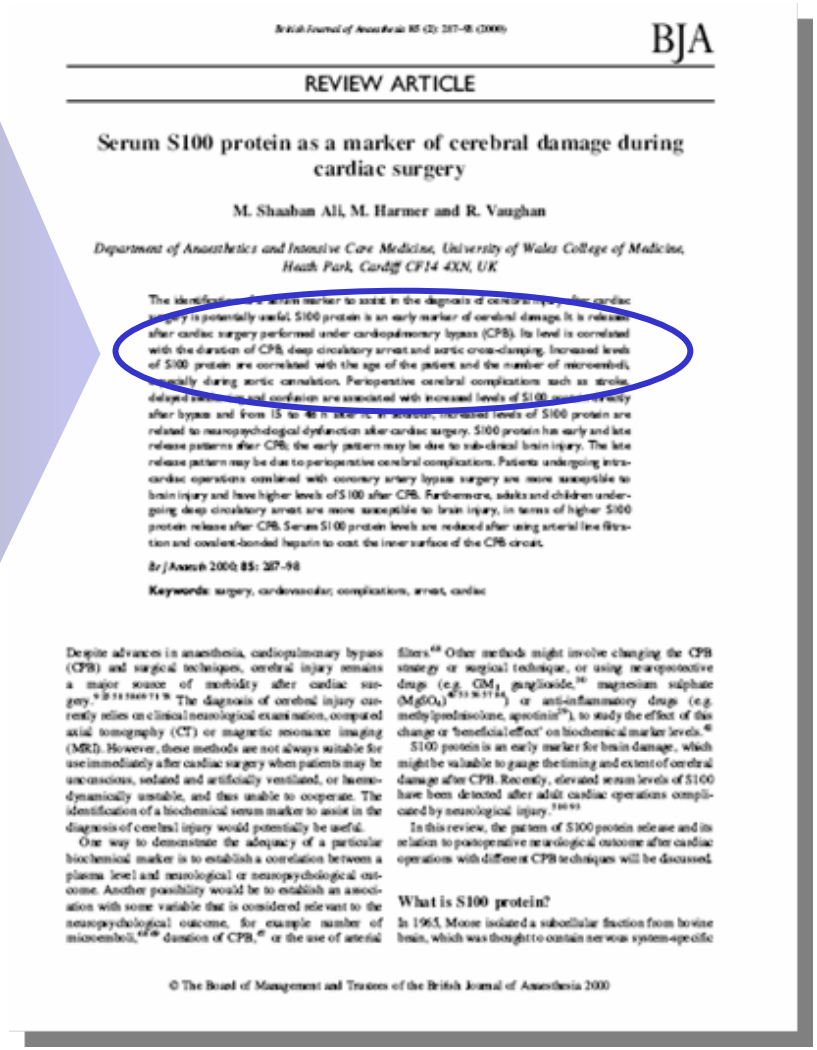
# S100 as an Early Biomarker for Brain Damage

"S100 protein is an early marker of cerebral damage. It is released after cardiac surgery performed under cardiopulmonary bypass (CPB). Its level is correlated with the duration of CPB, deep circulatory arrest and aorta cross-clamping."



British Journal of Anaesthesia 85 (2): 287–98 (2000)

BJA

REVIEW ARTICLE

## Serum S100 protein as a marker of cerebral damage during cardiac surgery

M. Shaaban Ali, M. Harmer and R. Vaughan

*Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, UK*

The identification of a serum marker to assist in the diagnosis of cerebral injury after cardiac surgery is potentially useful. S100 protein is an early marker of cerebral damage. It is released after cardiac surgery performed under cardiopulmonary bypass (CPB). Its level is correlated with the duration of CPB, deep circulatory arrest and aortic cross-clamping. Increased levels of S100 protein are correlated with the age of the patient and the number of microemboli, especially during aortic cannulation. Perioperative cerebral complications such as stroke, delayed awakening and confusion are associated with increased levels of S100 protein. Briefly after bypass and from 15 to 48 h after CPB, increased levels of S100 protein are related to neuropsychological dysfunction after cardiac surgery. S100 protein has early and late release patterns after CPB; the early pattern may be due to sub-clinical brain injury. The late release pattern may be due to perioperative cerebral complications. Patients undergoing intracardiac operations combined with coronary artery bypass surgery are more susceptible to brain injury and have higher levels of S100 after CPB. Furthermore, adults and children undergoing deep circulatory arrest are more susceptible to brain injury, in terms of higher S100 protein release after CPB. Serum S100 protein levels are reduced after using arterial line filtration and covalent-bonded heparin to coat the inner surface of the CPB circuit.

*Br J Anaesth* 2000; 85: 287–98

**Keywords:** surgery, cardiovascular; complications, arrest, cardiac

Despite advances in anaesthesia, cardiopulmonary bypass (CPB) and surgical techniques, cerebral injury remains a major source of morbidity after cardiac surgery.[1–3] The diagnosis of cerebral injury currently relies on clinical neurological examination, computed axial tomography (CT) or magnetic resonance imaging (MRI). However, these methods are not always suitable for use immediately after cardiac surgery when patients may be unconscious, sedated and artificially ventilated, or haemodynamically unstable, and thus unable to cooperate. The identification of a biochemical serum marker to assist in the diagnosis of cerebral injury would potentially be useful.

One way to demonstrate the adequacy of a particular biochemical marker is to establish a correlation between a plasma level and neurological or neuropsychological outcome. Another possibility would be to establish an association with some variable that is considered relevant to the neuropsychological outcome, for example number of microemboli,[4,5,6] duration of CPB,[7] or the use of arterial filters.[8] Other methods might involve changing the CPB strategy or surgical technique, or using neuroprotective drugs (e.g. $GM_1$ ganglioside,[9] magnesium sulphate ($MgSO_4$)[8,10,11,12]) or anti-inflammatory drugs (e.g. methylprednisolone, aprotinin[13]), to study the effect of this change or 'beneficial effect' on biochemical marker levels.[8]

S100 protein is an early marker for brain damage, which might be valuable to gauge the timing and extent of cerebral damage after CPB. Recently, elevated serum levels of S100 have been detected after adult cardiac operations complicated by neurological injury.[10,11]

In this review, the pattern of S100 protein release and its relation to postoperative neurological outcome after cardiac operations with different CPB techniques will be discussed.

### What is S100 protein?

In 1965, Moore isolated a subcellular fraction from bovine brain, which was thought to contain nervous system-specific

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

**Excerpt from:**
**M. Shaaban Ali, M. Harmer and R. Vaughn, *British Journal of Anaesthesia*, 2000; 85(2):287-298.**

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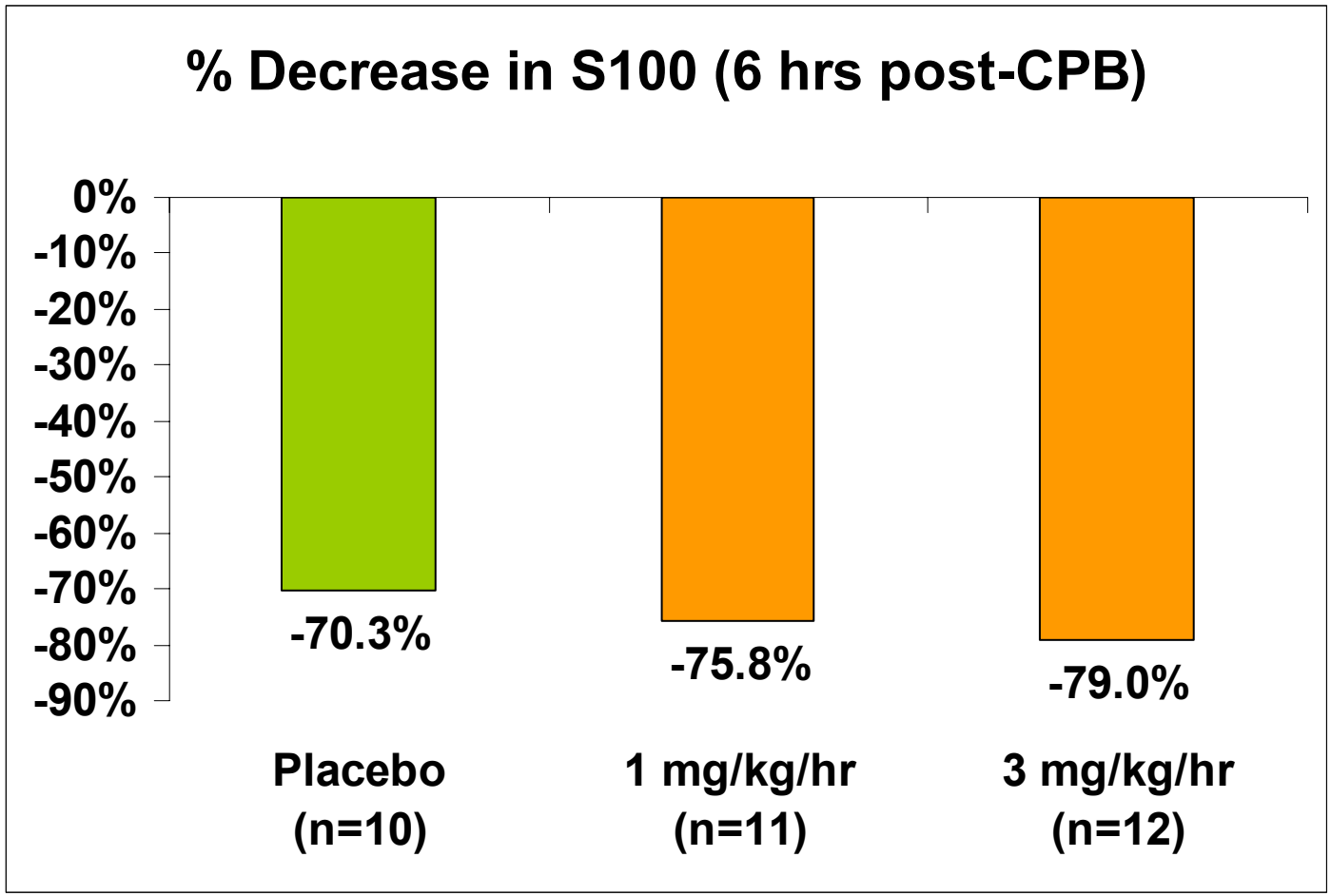
# Glypromate® Phase IIa: S100 Biomarker Data

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# Glypromate® Phase III Trial Rationale

- **CABG/CPB inherently controls treatment parameters**
  - Time of injury is known (i.e., at point of aorta unclamping)
  - No ambiguity in diagnosis and ability to control time at which therapy is initiated (i.e., unlike stroke trials)
  - Each patient serves as own baseline
- **Relatively inexpensive trial – approximately US$10 MM in direct costs**
- **Adequately powered to detect an effect**
  - Many trials have been underpowered
  - Change score is more sensitive than dichotomous or responder analysis
  - Targeting modest effect
- **Cognitive decline is significantly associated with less ability to engage in activities of daily living**(1)
- **CRO with extensive experience in hospital-based cardiology trials**
- **Automated system for capturing cognitive performance (CDR) is well-validated**

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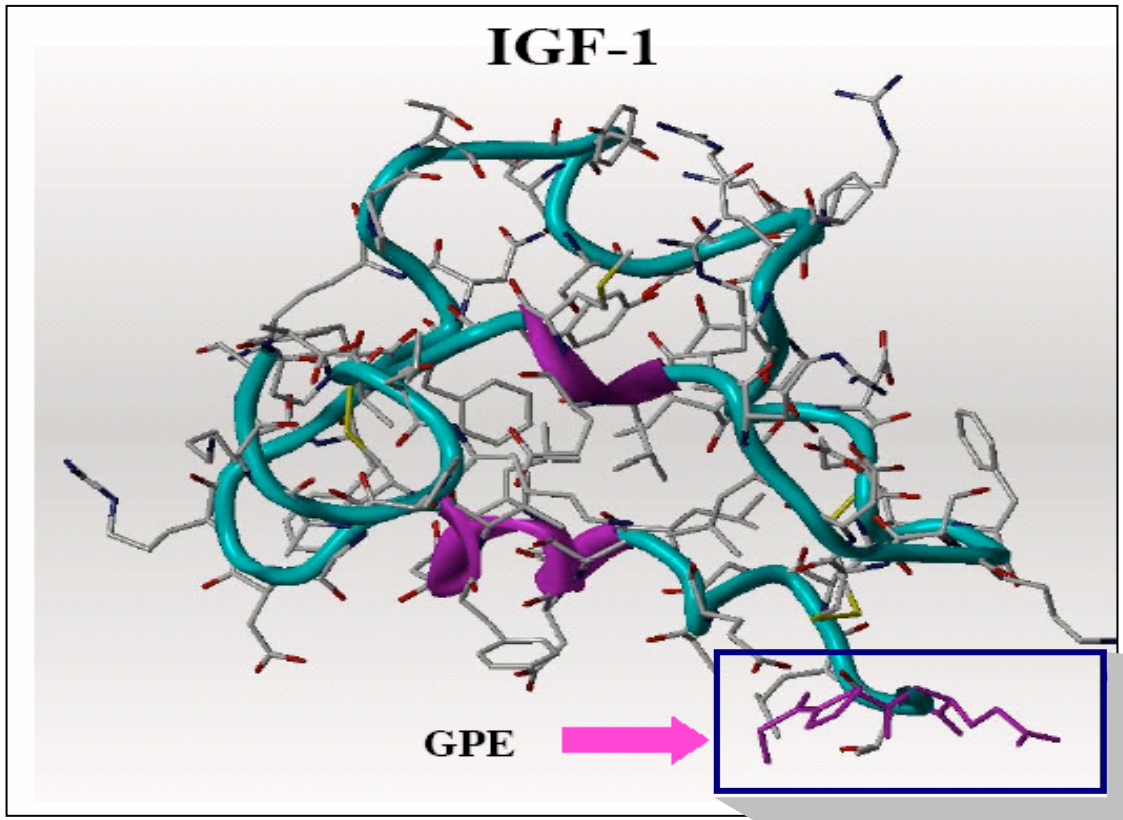
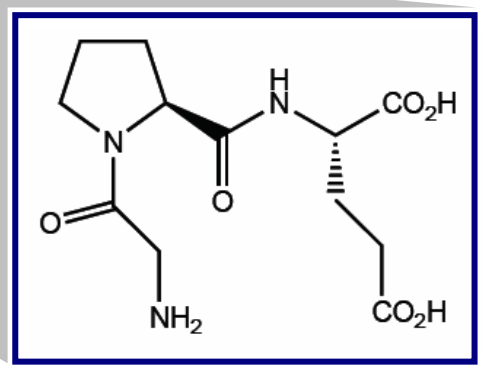
(1) Phillips-Bute et al. Association of Neurocognitive Function and Quality of Life 1 Year After Coronary Artery Bypass Graft (CABG) Surgery. *Psychosomatic Medicine,* 2006; 68:369-375.

# Glypromate®




- **Small molecule tripeptide cleaved from IGF-1**
- **Readily crosses blood brain barrier**(1)
- **Rapidly cleared**
- **Inexpensive to synthesize**




(1) Guan et al. Neuroprotective effects of the N-terminal tripeptide of insulin-like growth factor-1, glycine-proline-glutamate (GPE) following intravenous infusion in hypoxic-ischemic adult rats. *Neuropharmacology,* 2004; 47:892-903.

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# Glypromate® Exhibits Multiple Mechanisms of Action(1)

- **Inhibition of inflammatory cytokines**
- **Inhibition of apoptosis**
- **Inhibition of microglial activation**
- **Prevention of delayed or secondary necrosis**
- **Protection of astrocytes**
- **Protection of neurons and neuronal function**

(1) Based on data from preclinical studies.

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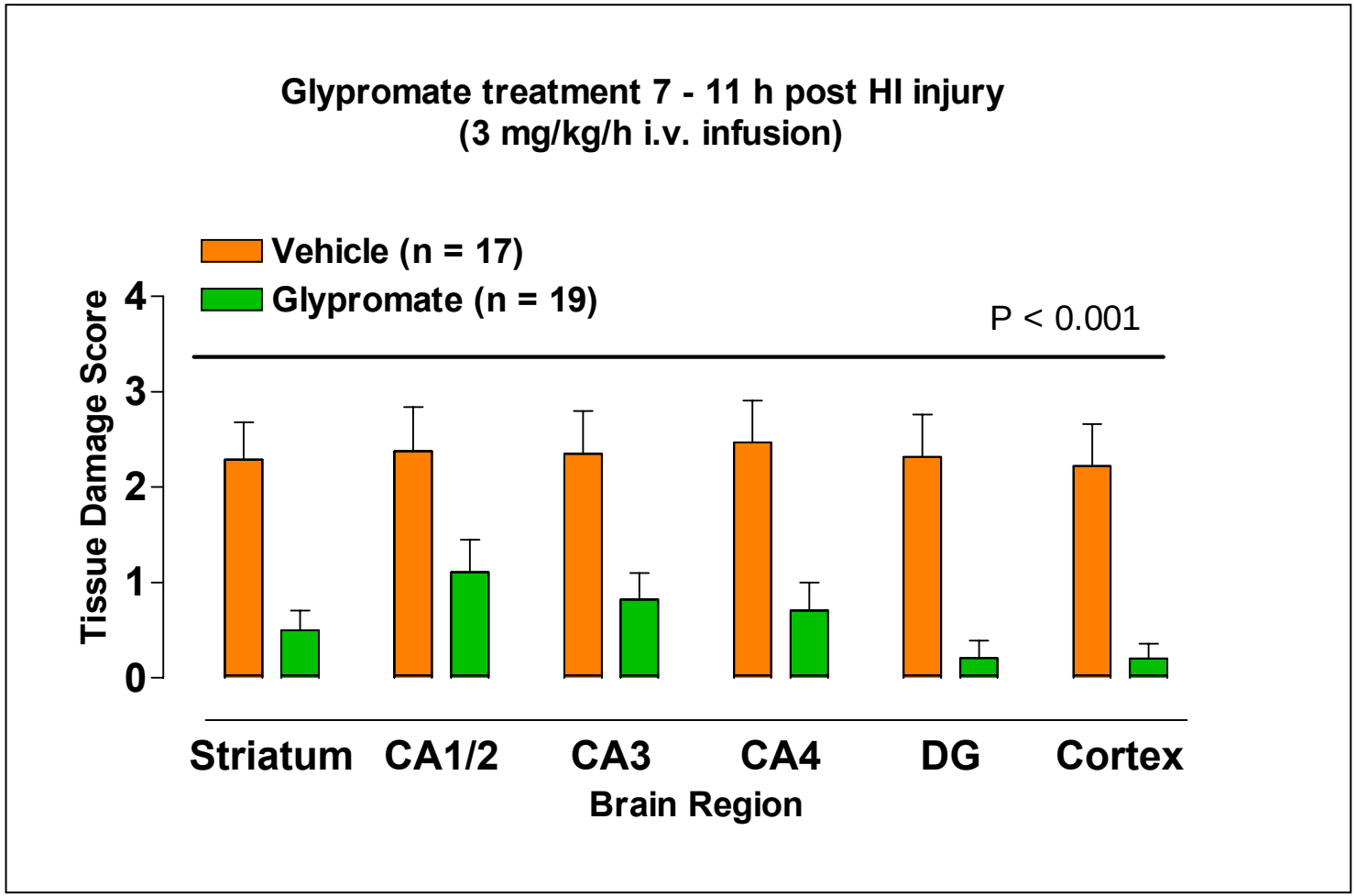
# Glypromate® in HI Model of Acute Brain Injury

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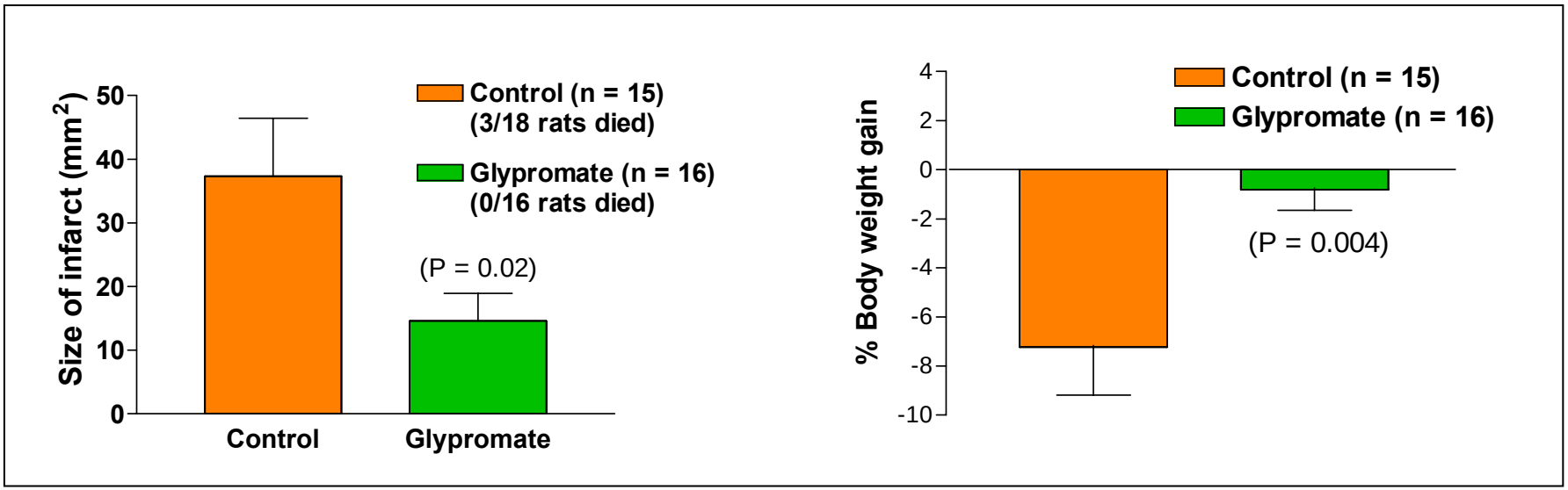
# Glypromate® in MCAO Model of Acute Brain Injury




**3 mg/kg/h i.v. infusion**
**5-9 hour treatment window**

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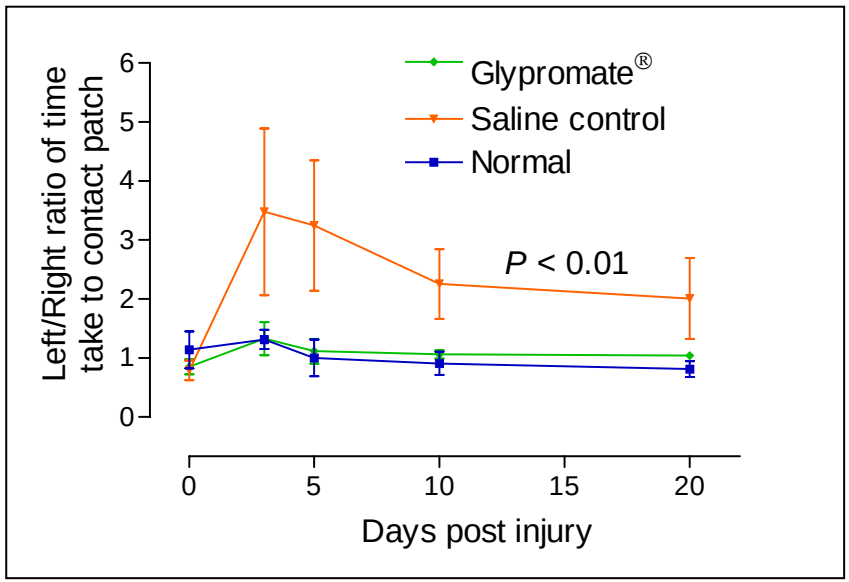
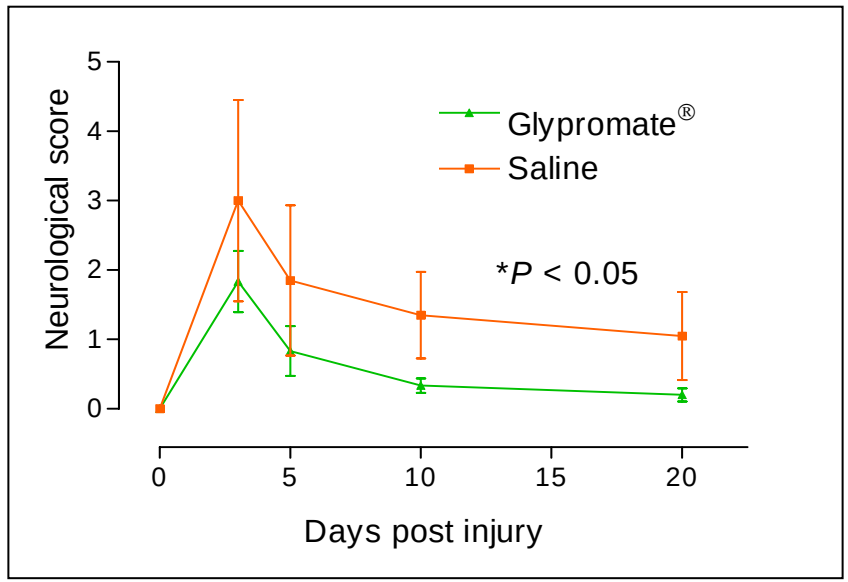
# Glypromate® Effect on Functional Recovery in HI Model

- **Improved behavioral outcome**
- **Improved neurological outcome**
- **Improved histological outcome**




**Glypromate® 3 mg/kg/h i.v. 1-5 hours post-injury**
**n = 8 per group**

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# Glypromate®: Why CABG and Valves?

- **CABG and CPB result in over 350,000 patients with persistent cognitive impairment**
  - **Equivalent to the difference in function between a 40-year old and a 60-year old**
  - **>50% impaired at discharge, >20% at 6 months, >40% at 5 years**(1)
  - **Primary factor diminishing quality-of-life benefits of the surgery**
  - **Increases risk of Alzheimer's disease**(2)
- **Significant pharmacoeconomic benefit**
  - **Potential to reduce costly utilization of hospital/intermediate care services and total cost of care**
- **Unmet medical need**
  - **Accepted as a target for therapeutic intervention by FDA and EMEA**
  - **Defined as a therapeutic goal by the ACC and AHA**
  - **No approved drugs ($1+ billion worldwide market opportunity)**

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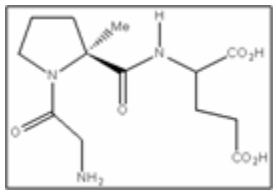
(1) Newman et al. Longitudinal Assessment of Neurocognitive Function After Coronary Artery Bypass Surgery. *New England Journal of Medicine*, 2001; 344(6):395-402.

(2) Lee et al. Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. *Journal of Alzheimer's Disease*, 2005; 7:319-324.

# NNZ-2566

- **Orally available analogue of Glypromate®**




- **Initially being developed in IV formulation**
  - **Phase Ib trial currently enrolling healthy volunteers with data expected in Nov. 2007**
  - **Drug was safe and well tolerated in Phase Ia trial in 28 healthy volunteers**
- **Partnership with U.S. Army since 2004 for TBI**
  - **$600 MM available for the treatment of TBI and Post Traumatic Stress Disorder until September 30, 2008(1)**
  - **$150 MM available for TBI R&D in FY07 Dept. of Defense budget**
- **Eligible for Fast Track and Orphan designation**

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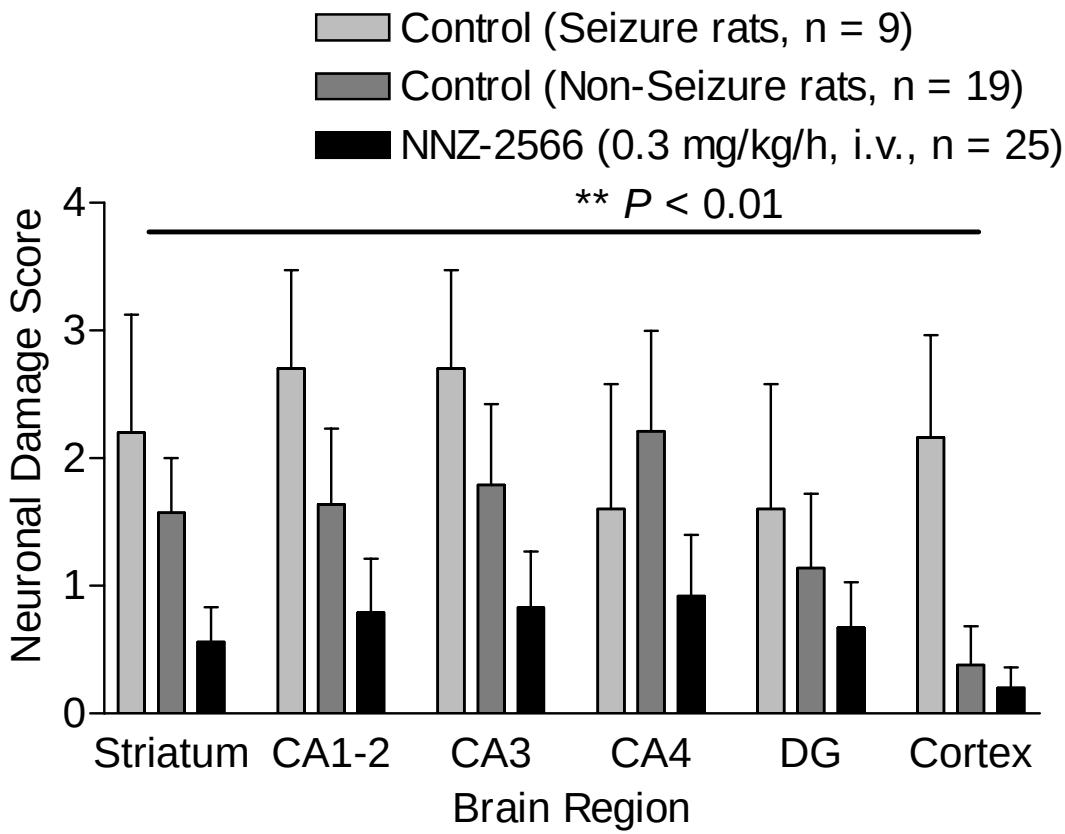
(1) Defense Supplemental Appropriation as passed by the House and Senate, April 2007.

# NNZ-2566 is highly neuroprotective




Global HI model; IV administration

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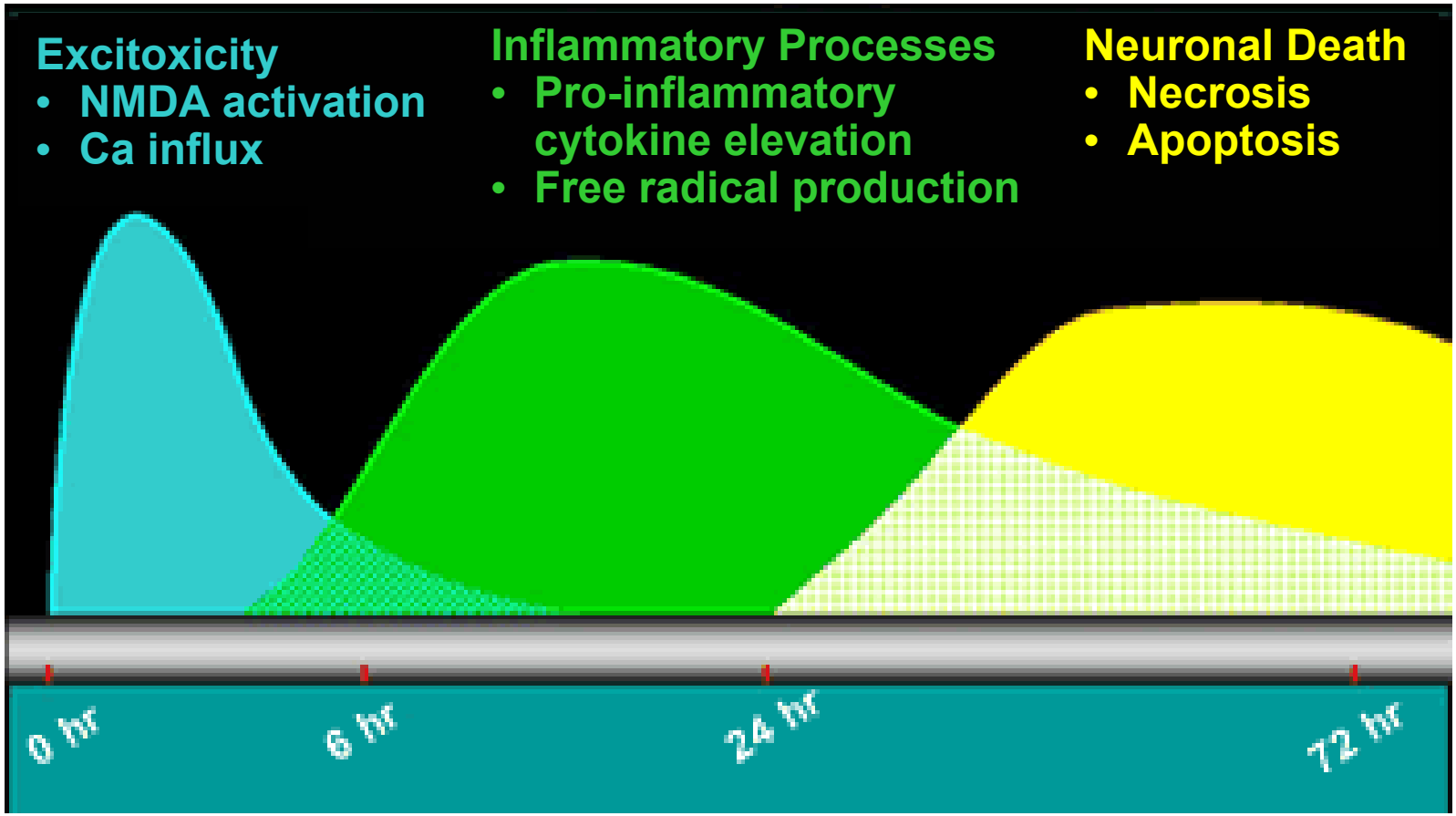
# Traumatic Brain Injury Cascade

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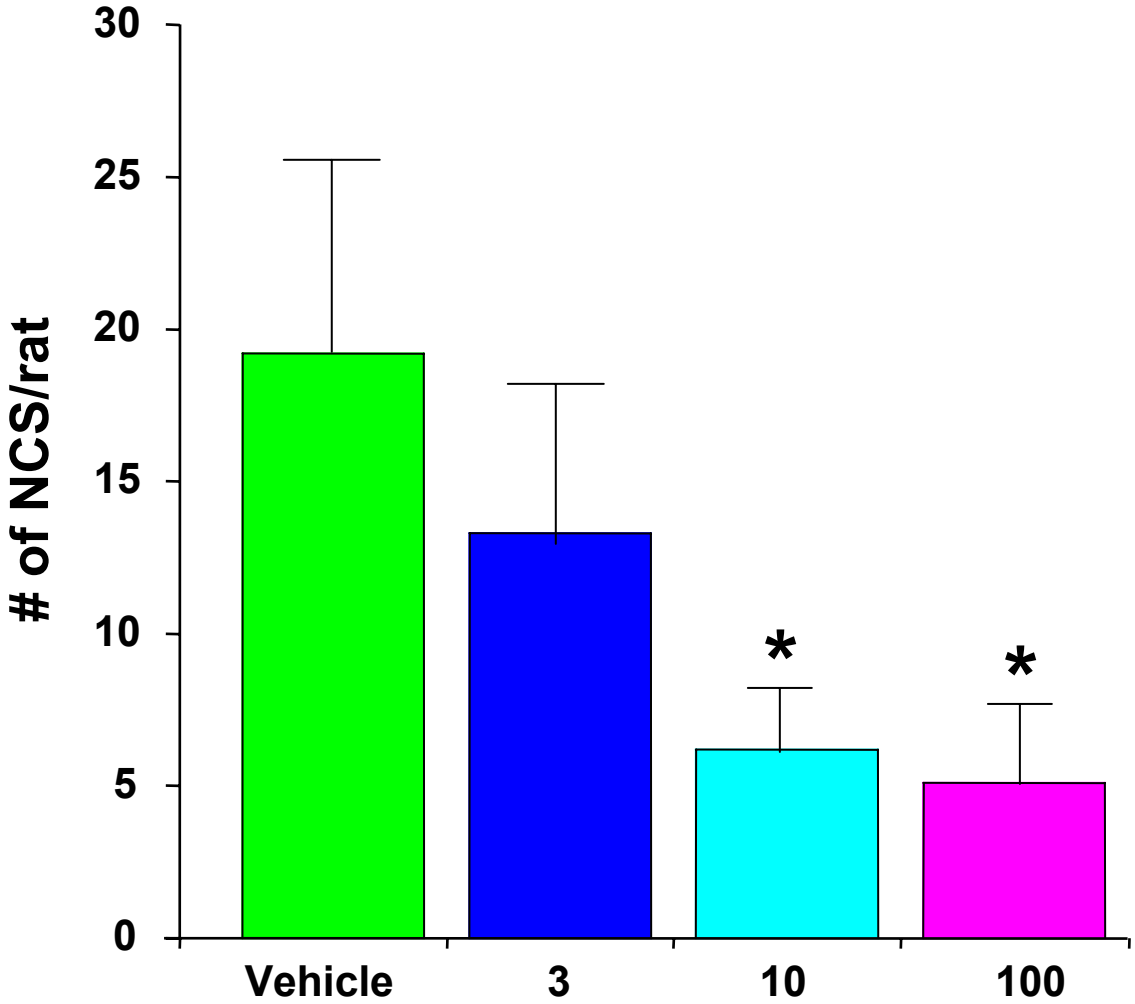
# NCS frequency

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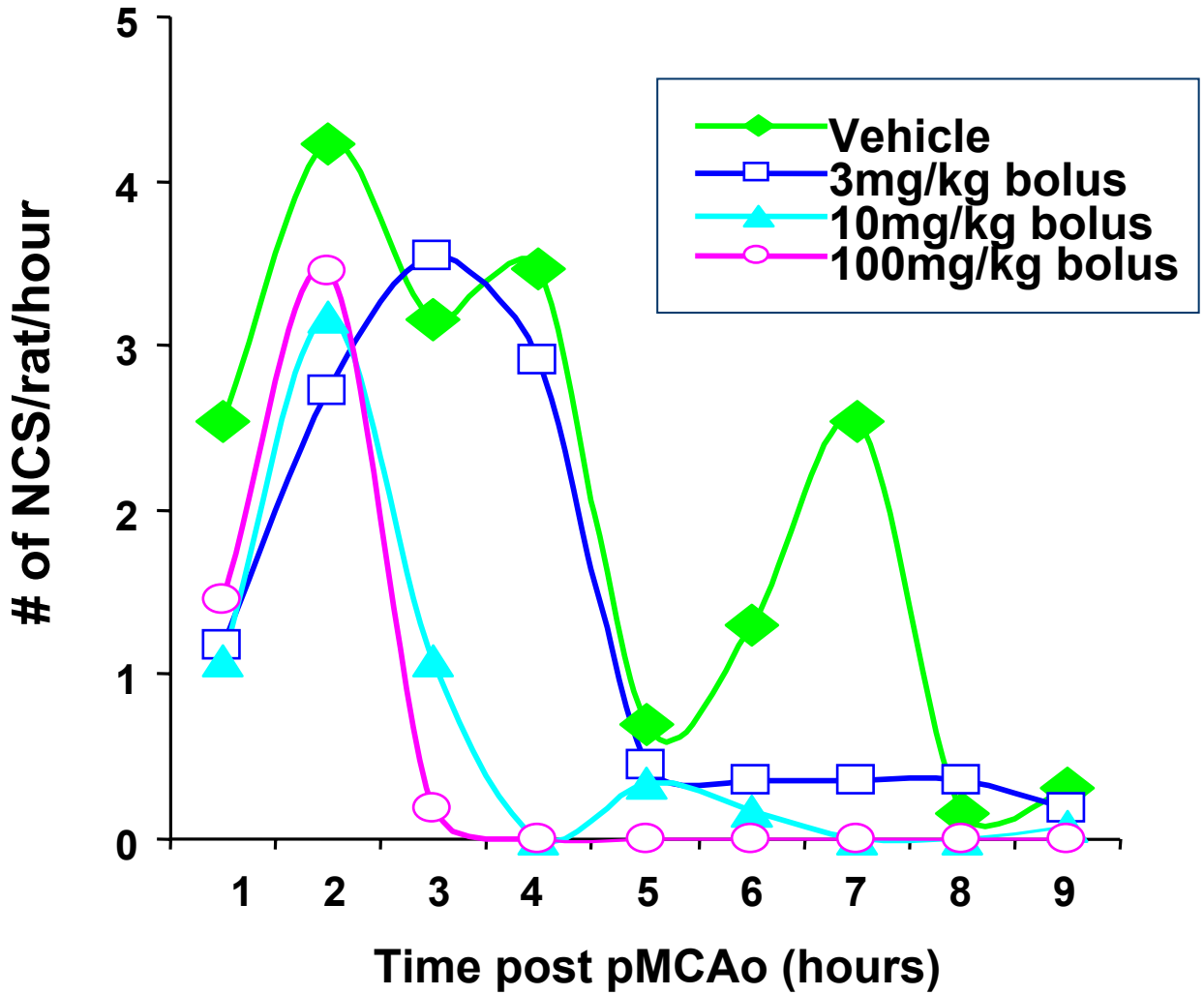
# NNZ-2566: Non-Convulsive Seizure Time Course

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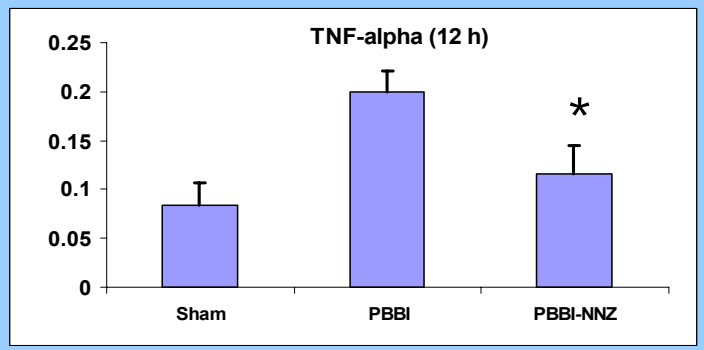
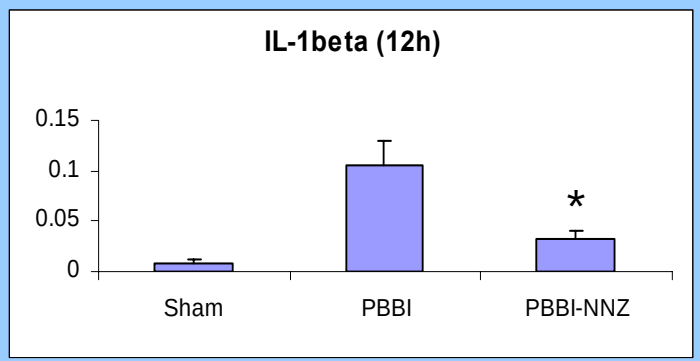
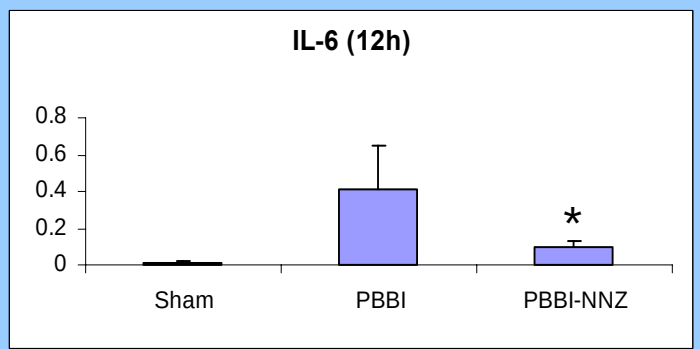
# Inflammatory & Apoptosis-Associated Gene Expression

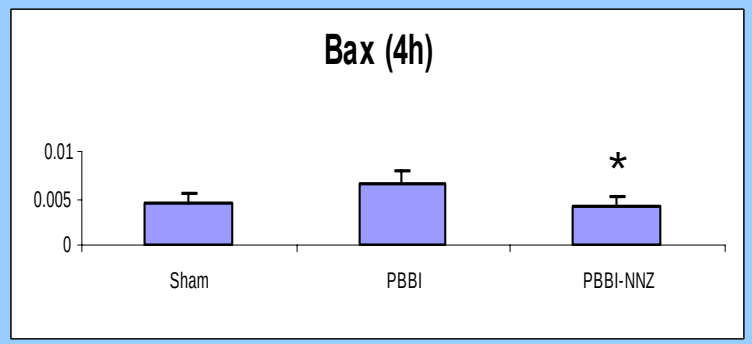
## Inflammation-Related Genes

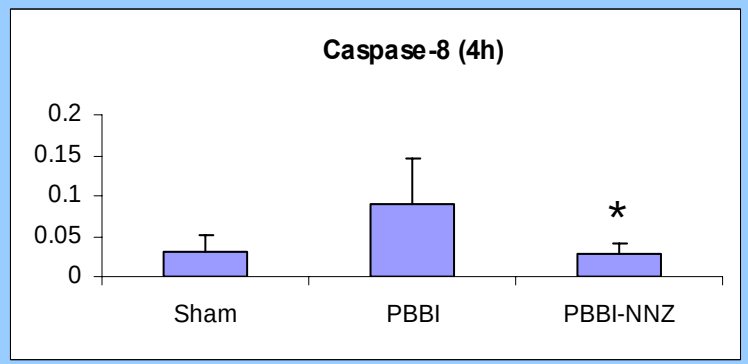


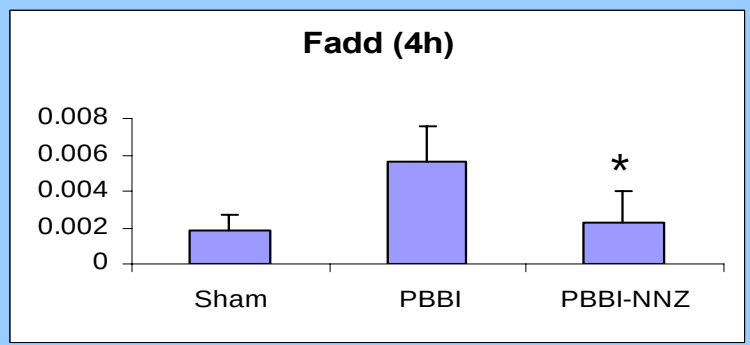




## Apoptosis-Related Genes



# Phase IIa (severe: GCS 4-8)

- Open label, dose escalation study in ~65 patients
- Within-patient and historical cohort comparisons
- 20 mg/kg bolus + 72 hour continuous infusion (2 doses)
- Endpoints
  - Mortality
  - Non-convulsive seizures and other EEG abnormalities
  - Biomarkers (inflammatory and apoptotic)
  - GOSE
  - ICP
  - Cognitive function
  - Depression

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# Phase II (mild-moderate: GCS 9-15)

- **Double-blind, placebo controlled, dose escalation study in ~180 patients admitted for ≥ 24 hours**
- **20 mg/kg bolus + up to 24 hour continuous infusion (2 doses)**
- **Endpoints**
  - **Cognitive function panel (CDR)**
  - **Profile of Mood States**
  - **Disability Rating Scale**
  - **GOSE**
  - **Rivermead Post-Concussive Syndrome**
  - **May-Portland Adaptability Index**
  - **Biomarkers (inflammatory and apoptotic)**

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# Motiva™ (nefiracetam)[1]

- **Novel cyclic GABA derivative**
- **Belongs to class of compounds called acetams**
  - **Approved acetams had sales of over US$700 MM in 1H 2007**
- **Studied in 1,700+ patients in Phase I, IIa and IIb trials**
  - **No drug-related adverse safety or toxicity**
- **Two completed randomized, controlled clinical trials in post-stroke depression in 255 patients**
  - **Statistically significant benefit in those patients with recent stroke (≤3 months), based on an apathy scale, and in those patients with cortical lesions, based on FIM and SDMT endpoints[2]**
- **Neuren plans to initiate a Phase II trial in post-stroke depression in 2008**

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(1) Addition of Motiva™ to pipeline is subject to completion of the pending acquisition of Hamilton Pharmaceuticals.
(2) Functional Independence Measure, or FIM, is a measure of activities of daily living, and the Symbol Digit Modalities Test, or SDMT, is a standard assessment of frontal lobe cognitive function.

# Hamilton Acquisition Terms

- **On July 31, 2007, entered into binding term sheet to acquire Hamilton Pharmaceuticals**
  - **Upon closing, will issue US$4.4 MM in ordinary shares to Vivo Ventures, Index Ventures and CNF Investments**
  - **Upon closing, Vivo and CNF will invest US$3.0 MM in a convertible note**
- **Future milestone payments due to Hamilton shareholders:**
  - **US$0.5 MM in warrants on completion of Motiva™ Phase II**
  - **US$0.5 MM in warrants on initiation of Motiva™ pivotal Phase III**
  - **US$1.0 MM in ordinary shares on Motiva™ NDA filing**
  - **US$2.0 MM in ordinary shares on Motiva™ NDA approval**
- **No retention of Hamilton personnel**
- **Motiva™ is subject to future milestone payments and royalties to Daiichi**

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# Partnering Strategy

- Committed to out-licensing or co-development strategies
- Existing development partnerships with Metabolic Pharmaceuticals and U.S. Army
- Three material transfer agreements executed
  - NNZ-2591
  - Anti-TFF mAbs
  - Peripheral nervous system indications outside of CNS and peripheral neuropathy
- Multiple future partnership opportunities

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# Key Financial Metrics

- **Cash: US$3.5 MM (NZ$4.5 MM) as of June 30, 2007**
- **Cash spending:**
  - **6 months ended June 30, 2007: US$4.7 MM (NZ$6.1 MM)(1)**
  - **Projected cash spend: US$1.1 MM per month**
- **Pending investment from Vivo Ventures and CNF Investments(2)**
  - **US$3.0 MM in note convertible into ordinary shares on same terms of next major financing**
- **Ordinary shares outstanding: 131,113,810(3)**
- **Market capitalization:**
  - **US$31.7 MM (AU$39.3 MM)(4)**
  - **US$36.1 MM pro forma for pending Hamilton acquisition**

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(1) Assumes exchange rate of NZ$1.00 for US$0.773 as of June 30, 2007.
(2) Subject to the completion of the pending acquisition of Hamilton Pharmaceuticals.
(3) Excludes $4.4 million of ordinary shares to be issued upon the completion of the acquisition of Hamilton Pharmaceuticals.
(4) Based on share price of A$0.30 and exchange rate of A$1.00 for US$0.8062 as of August 22, 2007.

# Projected Financial Assumptions

- **Glypromate®**
  - **Peak forecast sales** **$237 MM**
  - **Peak forecast market penetration** **12.5%**
  - **Estimated cost of goods** **11%**

- **NNZ-2566 (IV and oral)**
  - **Peak forecast sales** **$341 MM**
  - **Peak forecast market penetration** **18%**
  - **Estimated cost of goods** **17%**

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# Management Team with Proven Execution Experience

| Name/Title | Prior Experience |
|---|---|
| **David Clarke**<br>Chief Executive Officer | Former CEO of South Auckland Health Limited (leading public hospital system in New Zealand) |
| **Dr. Douglas Wilson**<br>Chief Medical Officer | Former SVP of Medicine and Regulatory Affairs and worldwide Head of Corporate Medicine at Boehringer Ingelheim |
| **Dr. Peter Gluckman**<br>Chief Scientific Officer | Founder of the Liggins Institute; former Dean of Medicine at University of Auckland and Asst. Professor at UCSF |
| **Dr. Parmjot Bains**<br>Chief Operating Officer | Fonterra Cooperative Group Limited; McKinsey & Co.; World Health Organization |
| **Larry Glass**<br>Executive Vice President | Former CEO of SRA Life Sciences |
| **Rob Turnbull**<br>Chief Financial Officer | PricewaterhouseCoopers |
| **Dr. Mike Bickerdike**<br>Group Science Director | Vernalis |

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