

# Neuren Pharmaceuticals

**Regulatory strategy behind a  
novel treatment for traumatic brain injury**

---

**Bioshares Biotech Summit  
July 2011**

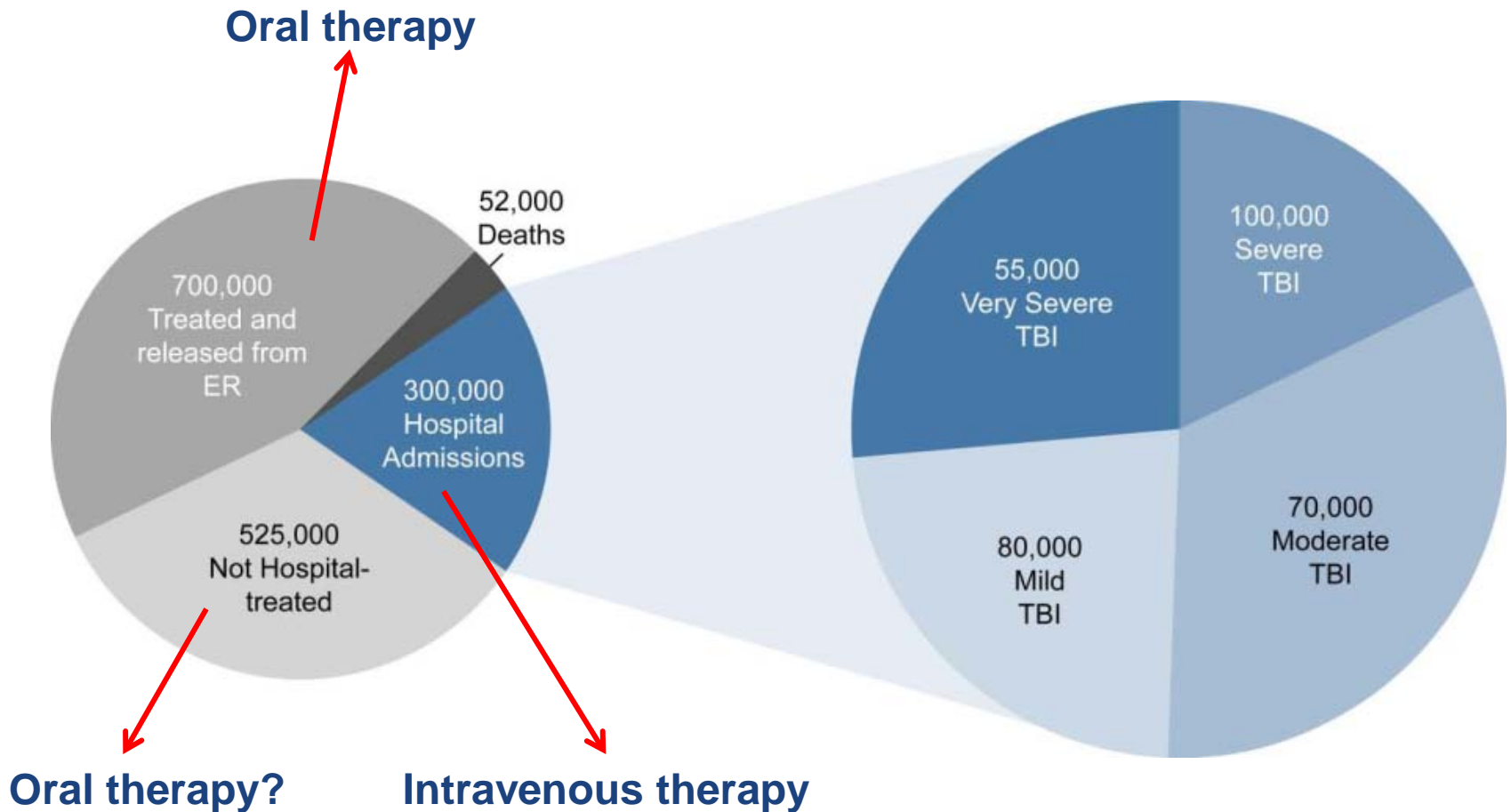
# Forward Looking Statement

---

This presentation contains forward looking statements that involve risks and uncertainties. Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Neuren can give no assurance that these expectations will prove to be correct.

Actual results could differ materially from those anticipated. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.

# Annual TBI incidence and patient disposition (US)



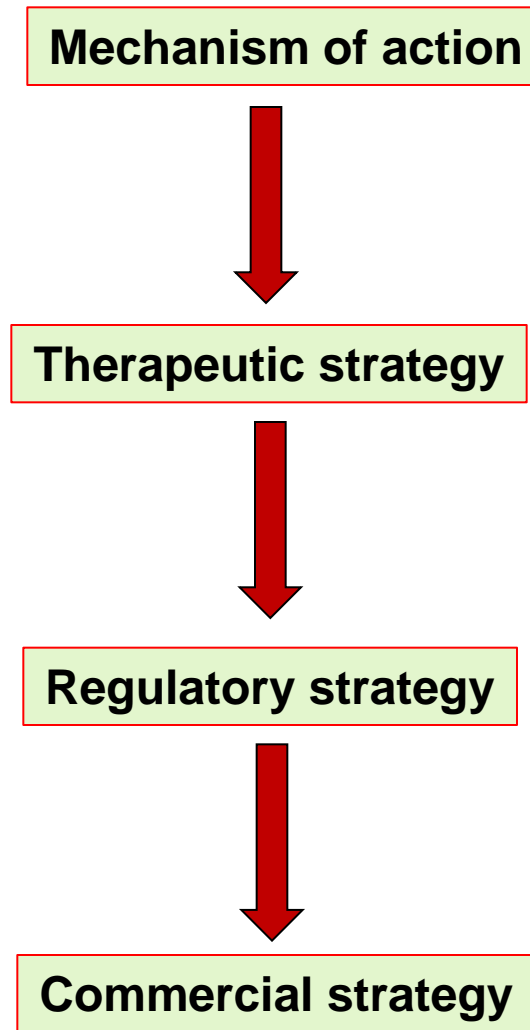
# Background on US Army TBI program

---

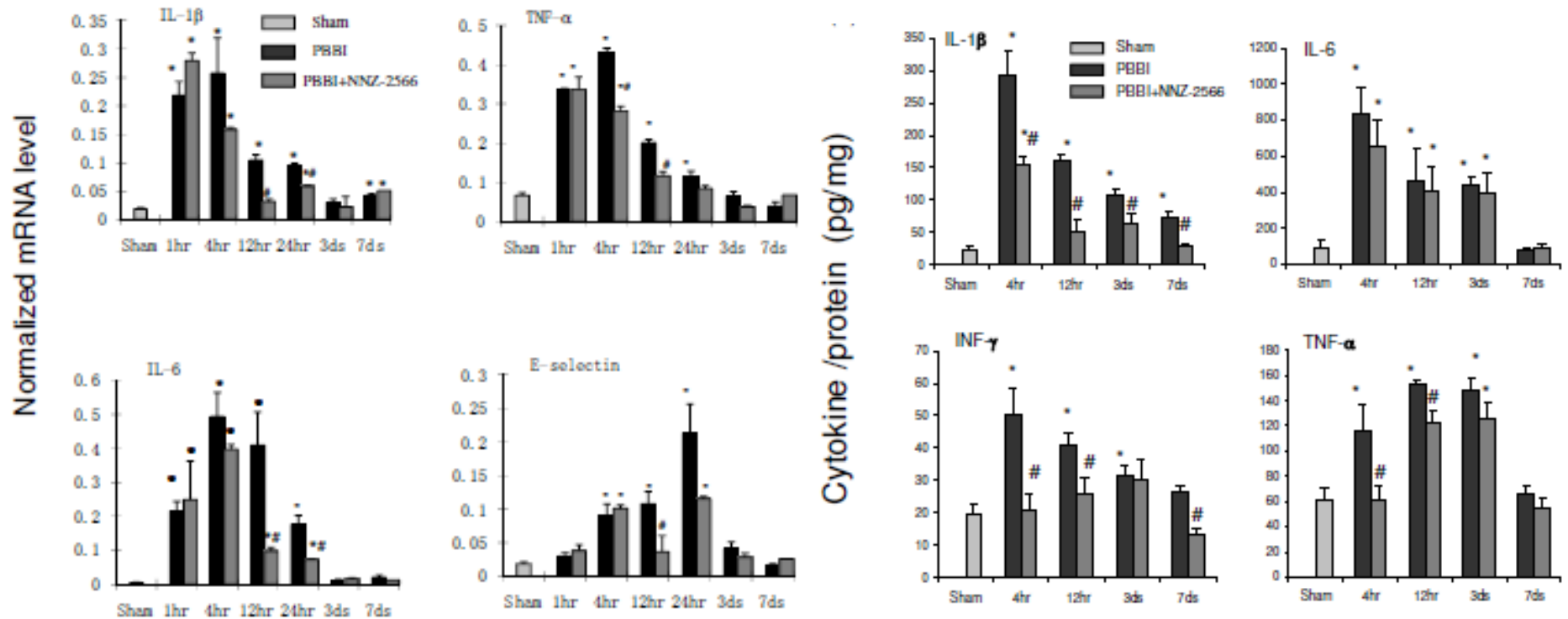
- TBI is the second leading cause of death and disability in combat; >70% mild
- Army Medical Research and Materiel Command (USAMRMC) is the lead US agency involved in TBI R&D
- Acute TBI research focuses on two goals: neuroprotection **and** prevention of post-injury seizures
- Army has extensive capabilities in preclinical R&D, clinical development and regulatory affairs
- Collaborative R&D Agreement funded by Neuren since 2004; Army focused on pharmacology, MOA
- Funding of the NNZ-2566 program has resulted from competitive, peer-reviewed grant applications
  1. Congressionally Directed Medical Research Program: \$4m
  2. USAMRMC Broad Agency Announcement (Combat Casualty Care): \$18.8m

# Integrated, logical strategy = life cycle risk management

---



# Mechanism of action: inflammatory cytokine inhibition

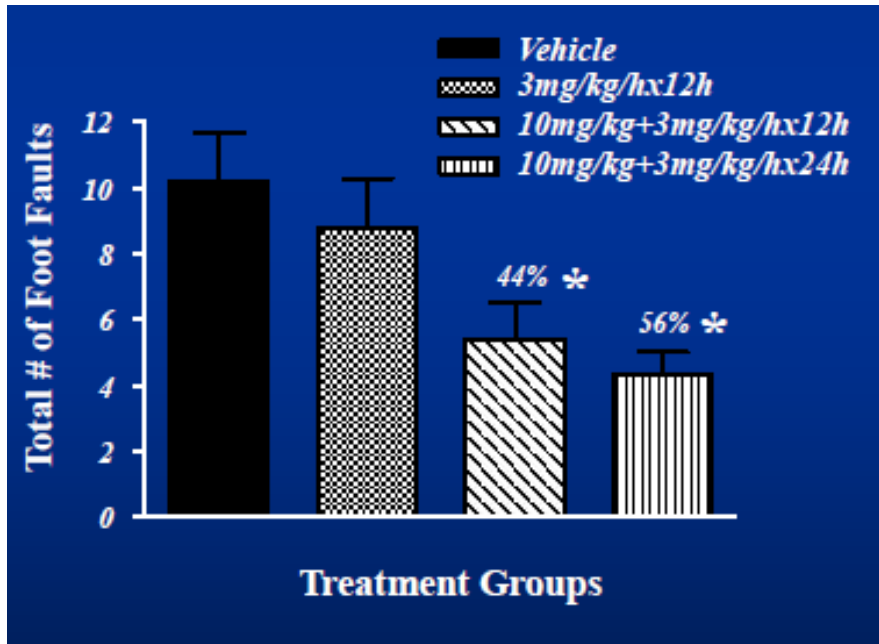


Gene expression

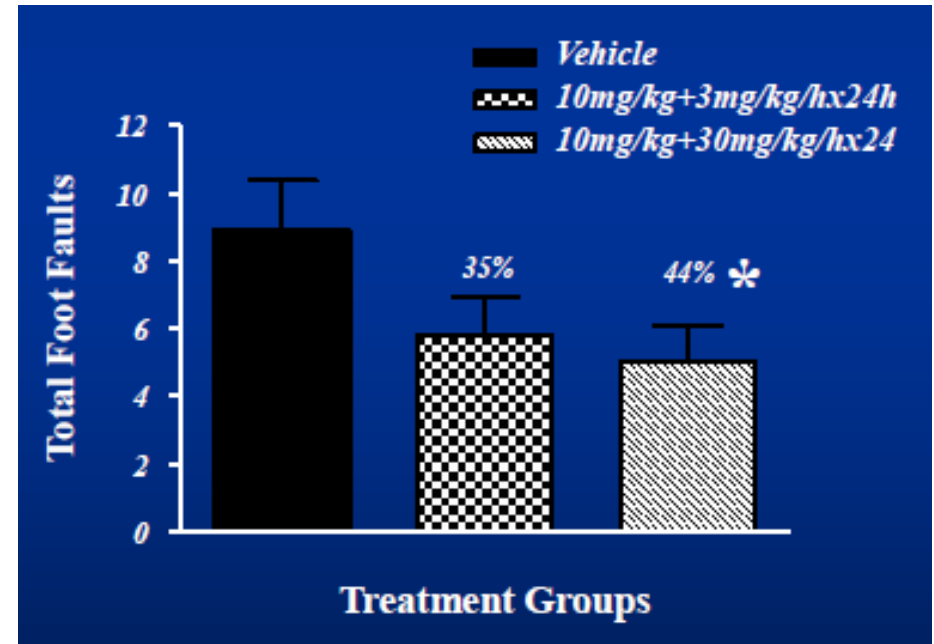
Protein expression

# Mechanism of action: dose-dependent neuroprotection

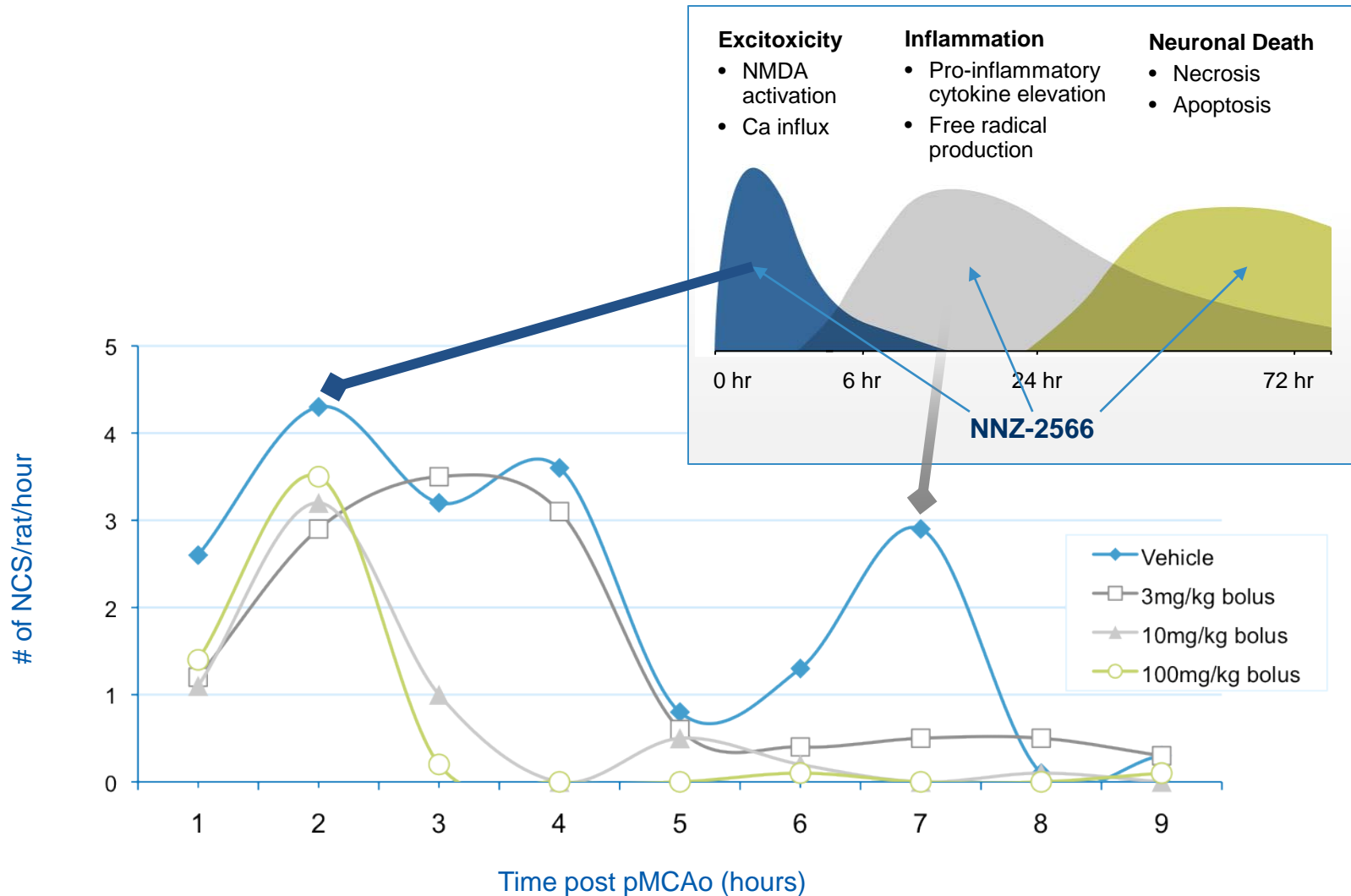
**2 hr** post-injury treatment  
(72 hr recovery )



**4 hr** post-injury treatment  
(72 hr recovery )



# Mechanism of action: dose-dependent prevention of seizures





# Therapeutic strategy

---

- Synthetic analogue of naturally occurring neuroprotective peptide—the brain's response to injury
- Prevent secondary brain injury—damage to cells adjacent to the primary injury (penumbra)
- Blocking the inflammatory response inhibits cell death (apoptosis and necrosis)
- Blocking the inflammatory response normalizes brain cell function (dendritic outgrowth, long term potentiation)
- Blocking the inflammatory response prevents convulsive and non-convulsive seizures which cause secondary brain injury

# Preclinical research directly informs clinical trial design

---

## Neuroprotection in multiple models:

- Bolus dosing + infusion enhances efficacy and extends therapeutic time window
  - ➔ **Bolus dosing and infusion in Phase II trial**

## Anti-seizure actions against non-convulsive and convulsive seizures

- Dose-dependent effect, reduced injury severity and reduced mortality
  - ➔ **Continuous EEG in Phase II trial**

## Mechanism of action studies:

- Inhibits inflammatory cytokine and pro-apoptotic expression up to 3 days post-injury
- Normalizes pro- and anti-apoptotic gene expression
  - ➔ **Dosing for 72 hours post-injury**
  - ➔ **Biomarker testing in Phase II trial**

## Neurofunctional studies:

- Improved neurofunctional/neurocognitive performance in animal models at 28 days
  - ➔ **Neuropsychological endpoints in Phase II trial**

# Regulatory framework

---

- **Kefauver Harris Amendment** to the Federal Food, Drug and Cosmetic Act (Requirement for drug manufacturers to provide proof of the effectiveness and safety before approval)
- **21CFR312.84** Risk-benefit analysis in review of marketing applications for drugs to treat life-threatening and severely-debilitating illnesses
  - “FDA's application of the statutory standards for marketing approval shall recognize the need for a medical risk-benefit judgment in making the final decision on approvability.”
- **21CFR314.510** Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses; Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity
  - “FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.”

# TBI regulatory strategy

---

## Approach to FDA Pathway

- Any validated endpoint plus a functional measure is approvable
- Prevention of post-injury seizures is approvable alone
- No *a priori* standard for magnitude of effect; must be “clinically meaningful”
- Acceptability of exploratory endpoints
- Exception from Informed Consent for Emergency Research (EFIC)

## Planning for a Single Pivotal Phase III

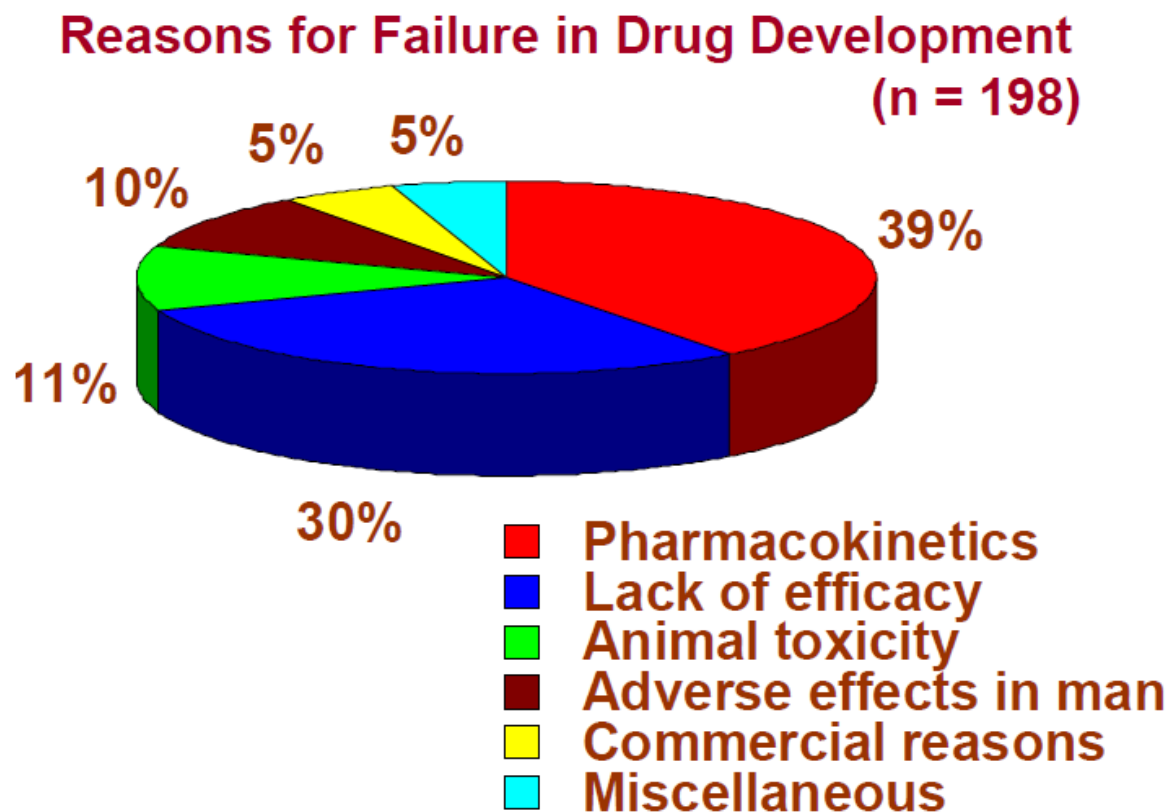
- Negotiate Special Protocol Assessment at the end of Phase II meeting
- Fast Track designation facilitates communication with FDA
- Phase II designed and powered to deliver definitive results across multiple, approvable endpoints
- All non-clinical and CMC activities for pivotal trial will be completed prior to end of Phase II
- Preclinical and clinical data from intravenous formulation driving development of oral form for mild TBI and other indications

# Phase II Protocol Designed to Deliver Definitive Data

- Double-blind, placebo controlled, rising dose
- 260 acute, non-penetrating TBI patients (Glasgow Coma Scale 4-12)
- Patients 16-75 years old
- Randomized 2:1 drug to placebo
- Administration of drug within 8 hours of injury (6 hours under EFIC)
- 20 mg/kg bolus (10-min infusion) followed by 1, 3 or 6 mg/kg/hr infusion for 72 hrs (30, 30 and 200 patients, respectively).
- Endpoints
  1. Safety
  2. Pharmacokinetics
  3. Efficacy
    - a) Functional outcomes: **Glasgow Outcome Scale-Extended (GOS-E)\***; **Mayo-Portland Adaptability Index**; neuropsychological measures; mood
    - b) Biological effects: **Seizures** detected by continuous EEG; serum biomarkers of neuronal, glial and axonal cell damage; intracranial pressure
- Efficacy endpoints directly correlate with molecular, physiological and behavioral findings in multiple animal models

**\*Outcomes in red are approvable endpoints.**

# Why drugs fail



H. Kubinyi. Drug Research: Myths, Hype and Reality, *Nature Reviews Drug Discovery* (2003).

# NNZ-2566: TBI profile largely de-risked

## Pharmacokinetics, lack of efficacy, animal toxicity, and adverse events in man are the leading causes of failure in drug development

### Pharmacokinetics (39%)

- Blood-brain barrier penetration ✓
- Linear pharmacokinetics (PK) ✓
- Comparable PK in healthy volunteers and patients ✓
- Oral bioavailability ✓

### Animal toxicity (11%)

- Safe and well-tolerated with good safety margin ✓
- Reproductive toxicology—underway but no data yet ?

### Adverse effects in patients (10%)

- Drug appeared to be safe, well-tolerated in Cohort 1 ✓
- Safety at higher dose—to be determined ?
- Cardiovascular safety—low risk but no data yet ?

### Miscellaneous (5%)

- Manufacturing—fully validated; suitable for Phase III; simple oral formulation ✓
- Regulatory—Fast Track; good relationship with FDA ✓
- Intellectual property—key patents issued ✓
- Staff and CRO resources—in place and working well ✓

### Commercial reasons (5%)

- Market competition—none now, limited in the future ✓
- Reimbursement not expected to be an issue ✓
- Strong partnering opportunities ✓
- Financing—shareholders plus US Army ✓

### Lack of efficacy (30%)

- Mechanism of action—directly relevant to TBI pathology ✓
- Preclinical efficacy—MOA addresses complex, post-injury cascade; dose-response in diverse brain injury models ✓
- Clinical trial design—endpoints directly translated from preclinical findings; powered to detect approvable benefit ✓

# Orphan Disease model

---

TBI is not an orphan disease (incidence >200,000), but...

- Significant risk and cause of mortality and permanent disability
- No approved or effective therapy
- Significant unmet need
- Priority target for FDA, US Army and NIH

## Regulatory flexibility

- Benefit-cost analysis in NDA review
- Tolerance for novel, exploratory endpoints
- No *a priori* standard for magnitude of effect

## Limited risk of competition from big pharma

- Only a single course of therapy for each patient
- Specialized marketing and sales force required
- Expensive post-marketing surveillance

## Significant attraction for potential partners

- Limited pricing pressure; little or no competition
- Small number of KOLs drive prescription practice among a small universe of prescribers
- Strong potential for other indications, including chronic conditions



# NNZ-2566—a growing franchise

## Intravenous administration

Moderate to severe TBI

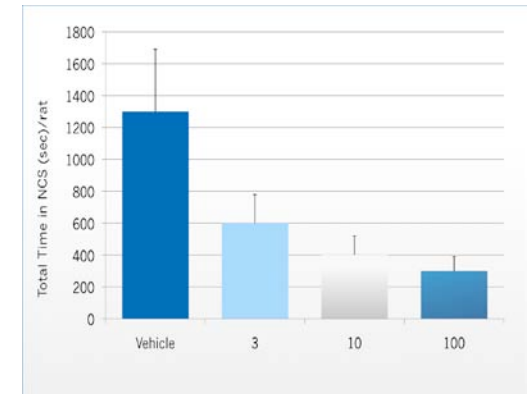
Stroke

Cardiac arrest

Perinatal asphyxia

Penetrating brain injury

Non-convulsive seizures in other CNS injuries/conditions



## Oral administration

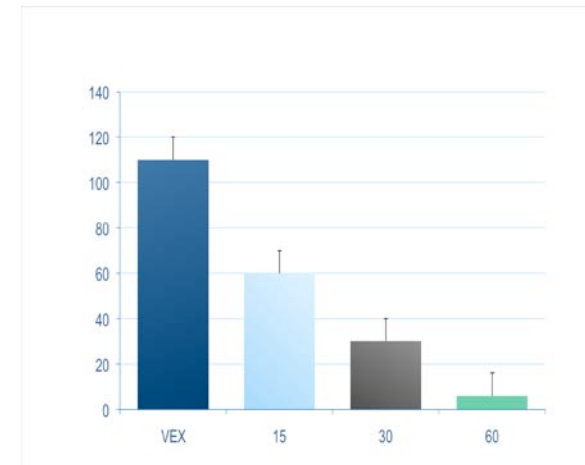
Mild TBI

Rett Syndrome/autism spectrum disorders

Post-stroke recovery

Prophylaxis following transient ischemic attack

Chemotherapy-induced neuropathy



# Further Information

---

Larry Glass, CEO

+1 (301) 941 1830

lglass@neurenpharma.com

## New Zealand

Level 2, 57 Wellington Street  
Freemans Bay 1011, Auckland  
New Zealand

+64 (9) 3700 200

1 800 259 181 (Australia Freephone)

## USA

3 Bethesda Metro Center, Suite 700  
Bethesda, Maryland 20814 USA