



# **Company Overview**

December 2007

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# **Company Overview**

- Robust product portfolio focused on psychiatric and cognitive effects of neurological injury and disease
- 3 drugs in late stage clinical trials for 4 central nervous system indications with efficacy results in 2009
- Potentially only 1-2 more pivotal trials prior to NDA (new drug application)
- One of the strongest and most advanced biotech pipelines in Australasia
- Strong preclinical pipeline in neurology, cancer and metabolic diseases presenting significant partnership opportunities
- International presence: Australia, New Zealand, US
- Highly experienced management: big pharma, biotech, contract research, management consulting, finance



## **Corporate Structure**

- ASX Code: **NEU**
- Ordinary Shares on Issue: 144.7m
- Market Cap: A\$30.4m @ \$0.21
- Market Cap (Fully Diluted): A\$34.7m
- Cash as at 30/9/07 NZ\$1.5m + US\$3.0m convertible note (Oct 07)

#### Significant Shareholders as at 31 Oct

K One W One	6.7%
ANZ Nominees	5.8%
Pfizer, Inc	5.6%
National Nominees	5.0%
NeuronZ	4.9%
Biotech Dev. Fund	4.1%
UCA Growth Fund	3.8%
Тор 20	61.9%





# **Neuren Product Pipeline**



# **Expected Efficacy Results in 4 Indications in 2009**



#### In 2009, 4 potential NDAs and registration will be only 1-2 trials away



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# **Neuren's CNS Portfolio: Significant Market Opportunities**

Multiple applications for both acute and chronic indications

Acute Indications	Chronic Indications
<ul> <li>Stroke</li> </ul>	<ul> <li>Alzheimer's Disease (AD)</li> </ul>
<ul> <li>Mild Cognitive Impairment (MCI)</li> </ul>	<ul> <li>Parkinson's Disease Dementia (PDD)</li> </ul>
post cardiac surgery	<ul> <li>Post stroke psychiatric disorders (PSPD)</li> </ul>
<ul> <li>Traumatic Brain Injury (TBI)</li> </ul>	<ul> <li>Peripheral Neuropathy (PN)</li> </ul>

Large and growing markets with unmet needs

Indication	Patients p/a	Market Size	Current Treatments
MCI post cardiac surgery	1.0m	US\$1.5b	Nil
TBI	3.0m	US3.0b	Nil
PSPD	1.5m	US\$1.5b	Limited
PD Dementia	1.1m	US\$1.5b	Exelon®
PN	3.0m	US\$6.0b	Limited
AD	5.0m	US\$10.0b	Aricept®



# **Preclinical Pipeline Partnership Opportunities**

### Cancer program

- Monoclonal antibodies directed against Trefoil Factor proteins (TFFs), involved in the growth of multiple cancers
- Overcomes tamoxifen resistance in breast cancer lines
- Partnership discussions with 3 global pharma companies
- Antibodies hottest therapeutic class of drugs at present
- Average value of deals for pre-clinical cancer programs (2005) – US\$479m in upfront/milestones

NNZ-2591 Parkinson's/Dementia 

- Lead compound in Neuren's diketopiperazine family
- Neuroprotective and neural repair properties
  - Strong results in preclinical development and memory models
  - 100% orally available; highly soluble; crosses blood-brain barrier; excellent safety profile
- Partnership discussion with EU specialty pharma company



# Upside for Investors 9

# **Management Team with Proven Execution Experience**

Larry Glass Co-CEO (US)	Life sciences industry consultant with broad international experience; former CEO of SRA Life Sciences
<b>Dr. Parmjot Bains</b> Co-CEO (AU/NZ)	Drug and biotech product development and management consulting experience (Fonterra Cooperative Group Ltd, McKinsey & Co.); Medical Doctor
<b>Dr. Douglas Wilson</b> Chief Medical Officer	Former SVP of Medicine and Regulatory Affairs and Worldwide Head of Corporate Medicine, Boehringer Ingelheim
<b>Dr. Peter Gluckman</b> Chief Scientific Officer	Founder of the Liggins Institute; former Dean of Medicine at University of Auckland and Asst. Professor at UCSF; Fellow of the Royal Society and Institute of Medicine
<b>Rob Turnbull</b> Chief Financial Officer	Biotech finance and fiscal management experience; former PricewaterhouseCoopers consultant
<b>Dr. Mike Bickerdike</b> Group Science Director	Neuropharmacologist with strong industry experience in R&D and preclinical development; former Vernalis program manager



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# **Glypromate<sup>®</sup> Phase III Trial - Rationale for CPB Surgery**





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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<sup>®</sup>: 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<sup>(1)</sup>
  - Primary factor diminishing quality-of-life benefits of the surgery
  - Increases risk of Alzheimer's disease<sup>(2)</sup>
- Significant pharmaco-economic benefit
  - Potential to reduce costly utilization of hospital/intermediate care services and total cost of care
- Unmet medical need
  - Accepted target for therapeutic intervention by FDA and EMEA
  - Defined as a therapeutic goal by the ACC and AHA
  - No approved drugs (\$1.5 billion worldwide market opportunity)



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- Newman et al. Longitudinal Assessment of Neurocognitive Function After Coronary Artery Bypass Surgery. 13 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.

# **Glypromate<sup>®</sup> Trial Progress**



- All sites in AU, NZ and US operational and either started recruiting or ready to start
- No logistical or operational issues encountered
- PIs are enthusiastic and engaged



- 52 patients enrolled to date and sites ramping up
  - Some sites projecting to enroll up to 100 patients each by the end of study
- On track to complete enrolment by end of 2008



- No unexpected or reportable safety adverse effects (to FDA)
- In line with expected clinical events in this patient population



# Motiva<sup>™</sup> (nefiracetam) Acquisition

- Member of well-known class of drugs with sales >US\$1.5b in 2007
- Well-understood mechanism of action and pharmacology
- Phase II/III clinical efficacy data in post-stroke patients
  - Statistically significant effects on apathy, global improvement, cognition
  - Well-defined patient population: within 3 months of cortical stroke
- One trial remaining before launching registration studies
- Short, low-cost trial design
- Exceptional safety experience (>1700 patients)
- More than US\$20m invested to date
- Strong potential for licensing/partnership revenue in Alzheimer's disease and epilepsy
- Low cost of goods; fully validated, inexpensive manufacturing



# Motiva<sup>™</sup> Planned Development

- Two completed clinical trials in post-stroke depression in 255 patients
  - Statistically significant benefits



- Post-stroke depression and apathy randomized, placebo-controlled, double blind trial
  - Enrolment within 10 days to 3 months of stroke
  - Efficacy evaluations at week 6 and week 12

#### Potentially other indications:

- Stroke
- Alzheimer's Disease
- Parkinson's Disease
- Epilepsy
- Traumatic brain injury



## Motiva<sup>™</sup> Summary

- Statistically significant Phase IIb/III data across multiple jurisdictions
- Aust equities market rewards drug developers (with novel compounds) with Phase 2/3 efficacy data:

- AVX, Phase IIb data in HIV market cap \$233m
- PGL, Phase IIb data in liver cancer market cap \$152m
- CXS, Phase IIb/III data in leukaemia market cap \$203m
- CUV, Phase II data in sun disorders market cap \$128m
- PXS, Phase IIb/III data in CF, bronchiectasis market cap \$800m
- PEP, Phase IIb data in skin cancer market cap \$127m



# **NNZ-2566**

- Patented analogue of Glypromate<sup>®</sup>
- Improved pharmacokinetics; orally available
- Initially being developed as an IV formulation
  - Phase Ib completed in Nov. 2007



- Partnership with U.S. Army since 2004 for TBI
  - U.S. Army has proposed to cover one-half the external cost of both mild-moderate and severe TBI trials (US\$4.0m)
- Eligible for Fast Track and Orphan designation
- Pre-IND meeting being scheduled for Q1 2008
- IND to be submitted in Q2 2008
- Phase IIa (severe) and Phase II (mild-moderate) trials to start mid-2008





# **TBI Market Opportunity**



#### neuren Sources:

• Traumatic Brain Injury in the United States: A Report to Congress, Center Disease Control and Prevention, December 1999.

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• Guerrero JL, et al., Brain Inj Vol 14 (2000), 181, Emergency department associated with traumatic brain injury: United States, 1995 – 1996.

# TBI top priority for US Army; NNZ-2566 is the only drug in clinical development

- "The US army says that 20% of its soldiers and marines have suffered from "mild traumatic brain injury" from blows to the head or shockwaves caused by explosions"
  - The Guardian, 27.10.07
- "If US predictions are correct, as many as 20,000 UK troops could be at risk"
  - The Guardian, 27.10.07
- "US Senate approves \$330 M in funding for traumatic brain injury"
  - July 26 2007
- 60% of patients seen at Walter Reed have a brain injury.

"In the past year, we have partnered with industry to discover a potent new neuroprotective drug [NNZ-2566] that shows great promise in reducing the effects of ... head injury... If the drug performs in humans as well as it has in rats, it will revolutionize the care of our soldiers with head injuries and will give our medics a real tool to treat head injuries."

US Army Surgeon General response to US House Armed Services Committee inquiry



ARMY RDT&E BUDGET ITEM J	February 2007	
BUDGET ACTIVITY	PE NUMBER AND TITLE	PROJECT
3 - Advanced technology development	0603002A - MEDICAL ADVANCED TECHNOLOGY	840
biological agents) that accelerate bone regeneration to select best bone substit trauma biomarkers. Brain trauma research is coordinated with related efforts in PE 0602787A, project 878. In FY07, begin an expanded human safety and (NNZ2566) as a treatment for acute silent seizures resulting from a brain inju FY08, will continue clinical development of NNZ2566 and complete clinical extensive multi-center clinical validation of most promising tissue regeneration efficacy clinical trials for NNZ2566; integrate validated biomarkers and stand and pH) in a prototype device for brain trauma biomarker diagnostics and test	under the Military Operational Medicine Research Program efficacy trial for an experimental neuroprotectant drug ry and continue evaluation of brain trauma biomarkers. In validation of brain trauma biomarkers. In FY09, will begin on treatment regimens, complete expanded human safety and lard physiological parameters (i.e. blood oxygen, chemistry,	

NNZ-2566 expressly written into Army Budgets US\$4.0m in joint clinical development funding expected 4Q CY07



# **Traumatic Brain Injury Cascade**



NNZ-2566: multiple modes of action at all stages of TBI injury cascade increases likelihood of success in clinical trials



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Compound	Clinical Status (CY08)	Indication	Est. Net Cost
Glypromate®	Phase III	MCI	US\$10.0m
Motiva™	Phase IIb	Post Stroke Dep.	US\$3.0m
NNZ-2566	Phase IIa	Sev. TBI	US\$2.5m*
NNZ-2566	Phase II	Mild-Mod TBI	US\$2.5m*

\* Assumes US Army Funding in 4Q CY07

Mid/Late Stage Efficacy for 3x NCEs in 4x Efficacy Studies for US\$18.0m Unencumbered Markets (Limited or No Approved Drugs)

Very Significant "Bang" For the Biotech Dollar

**Compare to Other Australian Biotechnology late stage trials:** 

Avexa (AVX): 2x Phase 3 in HIV - >US\$50m Progen Pharma (PGL): 1x Phase 3 in Liver Cancer >US\$50m



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# **Committed to Out-Licensing/Co-Development Strategy**



## Multiple future partnership opportunities



- NNZ-2591 (European CNS specialty pharma company)—exclusive
- Anti-TFF mAbs (global EU pharma company) negotiating exclusive
  - Peripheral nervous system indications outside of CNS and peripheral neuropathy (global US pharma company)—exclusive
- Glypromate<sup>®</sup> marketing/co-development
- NNZ-2566 marketing/co-development
- NNZ-2566 IV for stroke
- NNZ-2566 oral for stroke and TBI recovery
- Motiva<sup>™</sup> for AD and PD dementia, epilepsy
- NRPs for peripheral neuropathy
- Anti-GH cancer program
- GH variant for GH deficiency and metabolic syndrome

# **Value Proposition**

#### Superb clinical pipeline

- 3 drug compounds
- 4 indications
- New Drug Application 1-2 trials away
- Rich preclinical portfolio
  - Substantial partnership opportunities
  - Discussions underway for 3 license/co-development agreements

#### Strong management team

- Proven execution ability
- Presence in AU, US, NZ
- Reduced operating costs
  - Streamlined staffing
  - External funding

Enterprise (Technology) Value of ~\$A29m for NEU

Compares <u>very</u> favourably with ASX mid/late stage drug developers (majority single drug, single/multiple indications) :

CXS, PXS, AVX, PGL, NRT, PEP, CUV



## **Questions**

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# **Scientific Appendices**



# pharmaceuticals



# **Glypromate**<sup>®</sup>



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





# **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	<ul> <li>CABG surgery +/- valve replacement/repair with CPB</li> <li>Able to undergo all cognitive and ADL testing</li> <li>≥50 years old</li> </ul>
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



# **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	<ul> <li>CABG surgery +/- valve replacement/repair with CPB</li> </ul>	<ul> <li>Healthy volunteers</li> </ul>
	■ ≥60 years old	
Dose	<ul> <li>1 mg/kg/hr (4 hr. infusion)</li> <li>3 mg/kg/hr (4 hr. infusion)</li> </ul>	<ul> <li>0.3, 1.0 and 3.0 mg/kg/hr (15 min. infusion)</li> <li>1 mg/kg/hr (4 hr. infusion)</li> <li>3 mg/kg/hr (4 hr. infusion)</li> </ul>
Safety and Tolerability	<ul> <li>No drug-related AEs or SAEs</li> </ul>	<ul><li>No SAEs</li><li>No drug-related AEs</li></ul>



# Motiva<sup>™</sup> efficacy data in stroke patients: Japan

3 Phase IIa open- label studies	;	165 patients; dosing up to 16 weeks Endpoint: Global Improvement Rating (GIR) GIR results: Min = 12.5%; Max = 58.8% (450 mg/day x 16 weeks)
1 Phase IIb randomised, placebo controlled study	•	321 patients; 3 doses for 8 weeks; 150, 300, 450 mg/day GIR results: 24.5%, 28.4%, 41.7% (dose dependent)
2 Phase III randomised, placebo controlled studies	•	<ul> <li>Study 1 <ul> <li>268 patients; 450 mg/day or placebo x 8 weeks</li> <li>GIR results for all patients: drug vs placebo = 32.3% vs 10.1% (p&lt;0.001);</li> <li>GIR results for patients &lt;3 months post-stroke: drug vs placebo = 68.4% vs 0.0% (P&lt;0.001)</li> </ul> </li> </ul>
neuren pharmaceuticals	•	<ul> <li>Study 2         <ul> <li>267 patients; 450 mg/day nefiracetam or 90 mg/day idebenone x 8 weeks</li> <li>GIR results: nefiracetam vs idebenone = 37.6% vs</li> </ul> </li> </ul>

26.9% (p=0.068)

# Motiva<sup>™</sup> efficacy data in stroke patients: US/Canada

#### Phase IIb (under US IND)

- 159 patients; 600 mg/day, 900 mg/day or placebo X 12 weeks
- Primary endpoint: Hamilton Depression Scale (HAM-D)
- Secondary endpoints: Apathy Scale, Symbol Digit Modality Test (SDMT), Burden Inventory (BI), other ADL and psychiatric tests

#### Results

- HAM-D: not significant
- Apathy (patients with cortical lesions) for 900 mg/day vs placebo: -6.35 vs -0.96 (p=0.038)
- Apathy (patients with cortical lesions and high baseline apathy scores) for 900 mg/day vs placebo: -14.57 vs -4.9 (p=0.014)
- BI: dose dependent trend (-0.2, 0.75, 2.4 for 900 mg/day, 600 mg/day and placebo)
- SDMT (patients with cortical lesions and ≤28 days from stroke) for 900 mg/day vs placebo: 10.15 vs 2.4 (p=0.043)



## **NNZ-2566**



#### Orally available analogue of $Glypromate \ensuremath{\mathbb{R}}$

#### NNZ-2566 Non-Convulsive Seizure Time Course





#### **Inflammatory & Apoptosis-Associated Gene Expression**





\*

PBB-NNZ

\*

PBBI-NNZ

\*

PBBI-NNZ

# **NNZ-2566: two clinical trials**

- Phase II (severe: GCS 4-8)
  - Efficacy study in ~100 patients
  - Safety, PK and efficacy outcomes
  - 20 mg/kg bolus + 6mg/kg/hr 72 hour continuous infusion
  - Endpoints: mortality, non-convulsive seizures, biomarkers
  - Sites: Univ of Miami, US Army Institute of Surgical Research, Univ of California Los Angeles, Fairfax (Virginia)

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

- Double-blind, placebo controlled study in ~180 patients
- 20 mg/kg bolus + 6 mg/kg/hr 24 hour continuous infusion
- Endpoints: cognitive function, mood, ADLs, biomarkers
- Sites: Auckland, Christchurch, Van Der Veer Institute, Univ of Rochester (New York), Univ of Miami, Fairfax (Virginia)



# **Anti – TFF Antibody Selected Animal Data**

 2B10 (lead mAb) shows a strong dose-response in human gastric cancer cells



 2B10 effect in TFF-1 positive human mammary cancer cells also shows an excellent dose response





# Anti – TFF Antibody Selected Animal Data (cont.)

# TFF-1 antibody produces regression of human mammary tumour in a xenograft model



