Neuren Pharmaceuticals

Annual Shareholders’ Meeting

May 2010
2009: A Watershed Year for Neuren

- Prioritized focus on NNZ-2566 and Motiva™
- Reduced operating costs
- Obtained approval and Fast Track designation for NNZ-2566 IND
- Secured a further $14 million in non-dilutive funding from U.S. Army (US$18m total)
- Established subsidiary, Perseis Therapeutics, to develop oncology assets in partnership and with funding from the NZ Breast Cancer Research Trust
- Developed strategic relationship with Cato Research, a U.S. based global CRO
- Enhanced board of directors—Dr. John Holaday
- Secured new funding
Positioned for Success

- **Strong clinical candidates in neurology**
  - Two drugs in Phase II clinical trials for CNS indications
  - Opportunities to leverage NNZ-2566 in niche indications
    - Chemo therapy induced ototoxicity and neuropathy
    - Non-convulsive seizures associated with brain lesions (cancer, stroke)
    - Perinatal asphyxia
  - Opportunities for Motiva™ in additional indications
    - Parkinson’s disease, depression, traumatic brain injury

- **Highly promising cancer portfolio (Perseis Therapeutics)**

- **Pipeline backed by strong patent estate**

- **Experienced, dedicated staff**

- **Proven ability to execute on clinical trials**

- **Funded through 2011 by combination of equity, convertible debt and grants**
Focused pipeline with two dynamic clinical programs

- **Motiva™ (nefiracetam)**
  - Treatment for psychiatric and behavioral effects of stroke, TBI and other chronic CNS disorders
  - Clinical efficacy data in multiple Phase II and III trials including Phase IIb under US IND
  - Phase IIb trial to be initiated in Q2 2010
    - Apathy in post-stroke patients
    - Funded by grant from the National Health & Medical Research Council to the University of Western Australia (Sergio Starkstein, MD, PhD)

- **NNZ-2566**
  - Phase II INTREPID\textsuperscript{2566} trial initiated in May 2010 for traumatic brain injury
  - Partnership with US Army since 2004
  - New patent for non-convulsive seizures
  - Four peer reviewed papers in 2009, numerous posters and abstracts
  - Development largely funded by U.S. Army grants
NNZ-2566

- **Composition**
  - Synthetic analogue of IGF-1(1-3) – composition of matter and method of use patent issued: expires in 2023

- **Multiple modes of action**
  - Molecular: inhibits inflammatory cytokine and apoptotic gene expression
  - Cellular: inhibits microglial activation and neutrophil infiltration
  - Functional: inhibits post-injury seizures

- **Improved pharmacokinetics and oral availability**
  - Intravenous formulation for moderate to severe TBI
  - Oral formulation for mild TBI

- **Phase II INTREPID\(^{2566}\) trial initiated in May 2010**
  - Phase Ib completed in Nov. 2007; drug safe and well tolerated
  - IND opened Feb 2009; Fast Track designation granted June 2009

- **Partnership with U.S. Army since 2004 ~ US$18M**
  - Mechanisms of action and pharmacology discovered by Army scientists
Major Concern with No Available Therapy

- **Large and growing problem**
  - Traumatic brain injuries (TBIs) account for 1.7 million hospital visits and 52,000 deaths each year -- almost a third of injury-related fatalities in the U.S.
  - Major cause of accidental death among young people
  - Leading cause of mortality and disability among military personnel

- **Current treatment options**
  - Very little can be done to reverse the initial brain damage caused by trauma
  - Supportive care focuses on stabilizing patient and preventing secondary injuries

- **Secondary injuries**
  - Up to 80% of cell death results from processes caused by the primary injury

- **Provides clear development path**
  - Time of injury known
  - Time to admission in trauma center and possible treatment relatively short
  - Standard, widely-used assessments provide validated endpoints
Non-convulsive Seizures (NCS): Secondary Injuries

- NCS are associated with significantly worse outcomes in TBI patients
  - Frequently lead to spreading cortical depression, status epilepticus and death
  - Not effectively prevented or treated with anti-epileptic drugs
- Dual strategy: prevent onset and stop or reduce frequency after onset

<table>
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<tr>
<th>Brain Region</th>
<th>Neuronal Damage Score</th>
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<tr>
<td>Striatum</td>
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<tr>
<td>CA1-2</td>
<td>3.3</td>
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<td>CA3</td>
<td>3.9</td>
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<tr>
<td>CA4</td>
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<tr>
<td>DG</td>
<td>1.5</td>
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<tr>
<td>Cortex</td>
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Control (Seizure rats, n = 9)
Control (Non-Seizure rats, n = 19)
NNZ-2566 (0.3 mg/kg/h, i.v., n = 25)

**P <0.01
Leading Edge TBI Program

- **Dose-dependent efficacy in all brain injury models**
  - Penetrating and concussive TBI, NCS, 2 focal stroke and 1 global HI model
  - Models with hemorrhagic, hypoxic, ischemic, reperfusion components
  - Therapeutic time window: up to 4 hrs in TBI; up to 7 hrs in stroke/HI models

- **Multiplicity of effects**
  - Neuroprotection, seizures, gene expression, cell regulation, functional recovery

- **Clinical trial design**
  - Stratification—2:1 (moderate : severe)
  - Randomization—2:1 (active : placebo)
  - Wide range of clinical and physiological endpoints (incl. EEG) supported by preclinical data
  - Neuropsychological endpoints are approvable and more sensitive than GOS-E
  - Dose-escalation—primarily safety but with dose-ranging component

- **Regulatory strategy**
  - No particular endpoint or pre-specified magnitude of effect required by FDA
  - One validated measure + one functional measure = approval
  - Approval possible with single pivotal trial
Motiva™ (nefiracetam) Overview

- **Origins**
  - Drug licensed from Daiichi by Hamilton Pharmaceuticals
  - Belongs to well-known class of compounds (acetams)
  - Well-characterized effects in neurobehavioural, cognition, epilepsy models
  - Safety confirmed in 1,700+ patients in multiple clinical trials

- **Confirmed clinical efficacy in trials in stroke patients**
  - Japan: 3 Phase IIa, 1 Phase Ib, 2 Phase III trials
  - US/Canada: 1 Phase IIb trial (stroke patients with diagnosed depression)
    - Double-blind, placebo-controlled, 2 dose trial
    - 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
    - Statistically significant, time and dose-dependent effect on apathy (70 patients)
      - Repeated measures ANOVA for time (p=0.001)
      - Repeated measures ANOVA for time by treatment group (p=0.05)
      - Repeated measures ANOVA for time by 900 mg/day vs. placebo (p=0.01)
      - Dose-dependent effect on remission (75% reduction in apathy score) (p=0.031)
Apathy: Prevalence in Multiple Disorders

- Post Stoke: 35%
- Post-TBI: 50%
- Frontotemporal Dementia: 75%
- Alzheimer’s: 55%
- Schizophrenia: 67%
- Depression: 20%
- Parkinson’s: 40%
## Drugs in Development for Apathy as Primary or Secondary Endpoint

<table>
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<th>Study</th>
<th>Sponsor</th>
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<td>Study of Rivastigmine to Treat Parkinsonian Apathy Without Dementia</td>
<td>Novartis</td>
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<td>(CHoPA-I)</td>
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<td>Carbidopa/Levodopa/Entacapone Verses Immediate Release (IR)</td>
<td>Novartis</td>
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<td>Carbidopa/Levodopa on Non-Motor Symptoms in Patients with Idiopathic</td>
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<td>Parkinson’s Disease</td>
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<td>A comparison of Sertraline-Reboxetine Combination Therapy Versus</td>
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<td>Methylphenidate for Apathy in Alzheimer's Dementia</td>
<td>Dept of Veterans Affairs</td>
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<td>Rasagiline and Apathy in Parkinson’s Disease</td>
<td>L'Hospital de la Santa Creu I Sant Pau (Spain)</td>
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<td>Apathy Associated with Alzheimer’s Disease</td>
<td>Sunnybrook Health Sciences Center</td>
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<td>Wellbutrin XP Effects on SSRI Induced Changes</td>
<td>Indiana University School of Medicine</td>
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<td>Amantadine for the Treatment of Behavioral Disturbance in</td>
<td>Johns Hopkins University (NIH)</td>
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<td>Frontotemporal Dementia (FTD)</td>
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<td>Acteylcholinesterase Inhibitors to Improve Cognitive Function and</td>
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<td>Overall Rehabilitation after a stroke</td>
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<tr>
<td>Antidepressant medication plus donepezil for treating Late-Life</td>
<td>National Institution of Mental Health/ NIH</td>
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<td>Depression</td>
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Perseis Therapeutics: Profile

- Developing antibody therapeutics for the treatment of breast and other cancers
  - Established April 2009 by Neuren Pharmaceuticals and the Breast Cancer Research Trust
  - Seed funding of NZ$1.18M from Breast Cancer Research Trust
  - New Zealand Company

- Three associated research programs aimed at targeting cancers (breast, prostate, colorectal and gastric cancer) with monoclonal antibodies
  - Targets the Trefoil Factors (TFF-1 and TFF-3) and Growth Hormone found to play a significant role in the growth and spread of cancer
  - TFF-3 strongly associated with tamoxifen resistance in breast cancer

- First major development milestone expected Q4 2010
  - *in vivo* efficacy of antibodies to support selection of therapeutic candidates for further development or partnering discussions
TFF-3 role in breast cancer survival
Further Information

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