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Neuren Pharmaceuticals (NEU)

Nearing a payday with NNZ-2566

Recommendation
Spec Buy
Price
\$0.017
Target (12 months)
\$0.12

Expected Return

Capital growth	606%
Dividend yield	0
Total expected return	606%

Company Data & Ratios

Enterprise value	\$9.6m
Market cap	\$19.4m
Issued capital	1,141.6m
Free float	100%
Avg. daily vol. (52wk)	1.7m
12 month price range	0.0127-0.0227

GICS sector

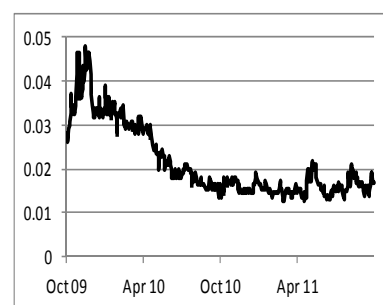
Healthcare Equipment and Services

Disclosure: Bell Potter Securities acted as lead manager in the July 2011 placement and rights issue and received fees for that service.

Price Performance

	(1m)	(3m)	(12m)
Price (A\$)	0.02	0.02	0.01
Absolute (%)	0.00	6.25	17.23
Rel market (%)	-1.17	12.40	27.69

Absolute Price



SOURCE: IRESS

This report initiates Bell Potter Securities' coverage of Neuren Pharmaceuticals.

NNZ-2566 is an exciting clinical-stage opportunity

Neuren's NNZ-2566 drug for the treatment of Traumatic Brain Injury (TBI) has performed well in various pre-clinical studies, demonstrating neuroprotective as well as neuromodulatory properties. An IV version of the drug is now in Phase II for moderate-to-severe TBI with significant funding (ie around US\$23m) being provided by the US Army, backed by the support of key opinion leaders. We expect data from this trial late next year. If successful, the FDA has indicated that only one Phase III trial would be necessary, putting NNZ-2566 on track to enter the US market by 2017. An oral version of NNZ-2566 is planned for the treatment of mild TBI. Following on from TBI there is also potential for oral NNZ-2566 to be useful in stroke recovery and an autism spectrum disorder called Rett Syndrome.

A large market awaits NNZ-2566

With around 1.7 million TBIs per year in the US and no approved therapies in this indication, there is a potential US\$2-4bn market opportunity should NNZ-2566 perform well in the clinic.

Neuren has an encouraging pipeline

Neuren is also in Phase II with Motiva, a drug for the treatment of post-stroke apathy. This drug has a strong safety profile, having been initially developed by the Japanese drug company Daiichi Sankyo. There is also potential with NNZ-2591 for Parkinson's and peripheral neuropathy, and for various anti-cancer antibodies.

Neuren has a solid management team

We have a high regard for the Neuren management team led by Larry Glass, who brings strong relationships with the Army Medical R&D command as well as strong business development skills. We think that the Neuren board under Chairman Robin Congreve and including Dr John Holaday, the QRxPharma CEO, is a good one.

Neuren is undervalued given the potential

Neuren was subject to a clinical failure in late 2008 related to a product called Glypromate, and the timing of this, in the middle of the Global Financial Crisis, as well as its choice to fund itself via a convertible note facility from late 2009 to mid-2011, considerably hampered the stock. We feel NNZ-2566's trial structure is much better than Glypromate's was, raising the chance of clinical success. We value Neuren on a probability-weighted DCF valuation at 12 cents base case and 21 cents optimistic case. Our 12 cent price target sits at the low point of this valuation range. We see the market marking up Neuren as Motiva and NNZ-2566 near the end of their Phase II trials, and as awareness grows of the interest of key opinion leaders in NNZ-2566 as the Next Big Thing in Traumatic Brain Injury. We also expect that a favourable partnering outcome for NNZ-2566 could lead to a significant re-rating of the stock.

Neuren Pharmaceuticals – nearing a payday with NNZ-2566

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Figure 1 - Major developments for Neuren since February 2005



SOURCE: NEUREN, BELL POTTER

“We are confident that the study’s design and the painstaking groundwork that has been laid will pay off in the successful execution of the trial. Knowing that, between the financing announced at the end of 2009 and funding from the US Army, we have access to all of the capital resources needed to complete the study contributes significantly to our level of confidence”. – Neuren CEO Larry Glass, commenting on the May 2010 commencement of NNZ-2566’s Phase II trial, called INTREPID-2566.

Introducing Neuren, ASX Code NEU

What is Neuren? Neuren is a start-up biotech company based in Auckland, New Zealand, with offices in Bethesda, Md where CEO Larry Glass is located. The company's lead compound is NNZ-2566, for the treatment of Traumatic Brain Injury (TBI). NNZ-2566 is now in Phase II and is on track to be FDA-approved and marketed by 2017. Neuren is also in Phase II for Motiva, a cognition-enhancement drug it acquired in 2007 that was initially developed by the Japanese drug company Daiichi Sankyo. Neuren currently anticipates developing Motiva for the treatment of Apathy Syndrome in stroke recovery patients. Neuren is doing pre-clinical work on NNZ-2591, for the treatment of Parkinson's disease and peripheral neuropathy, while a Neuren subsidiary called Perseis Therapeutics is working on monoclonal antibodies to breast and other cancers.

What is NNZ-2566? NNZ is a synthetic analogue of the first three amino acids of Insulin-like Growth Factor-I, a tripeptide known to have neuroprotective properties. It is believed that administration of NNZ-2566 in the hours after a Traumatic Brain Injury (TBI) would prevent the subsequent death of brain cells that results in permanent damage. Currently no such neuroprotection drug is available. NNZ-2566 entered its Phase II trial for this indication in 2010. We expect this trial will complete in late 2012, which could lead to a single US pivotal Phase III under Fast Track and SPA procedures. Fast Track designation has already been granted. The NNZ-2566 currently in the clinic is by infusion only and is indicated for moderate-to-severe TBI. Neuren is currently working on an orally-available formulation of NNZ-2566 which could be used in mild TBI as well as stroke recovery.

What is Traumatic Brain Injury? TBI is the loss of cognitive and other neurological function that results from a blow to the head. It can be mild, moderate, or severe. After a TBI there is a 'window of opportunity' of up to five days before brain cells die from the biochemical cascade that follows the initial blow. Neuren believes that NNZ-2566, administered during this window, could be used to protect brain cells. There are around ~1.7 million TBIs in the US each year¹ and currently there are no treatments that are considered neuroprotective. Neuren estimates that the US market alone could be worth US\$2bn for mild TBI and another US\$2bn for moderate-to-severe TBI.

Why is the US Army funding NNZ-2566's clinical development? In order to continually improve as a fighting force, the US Armed Forces conducts considerable medical research activity through various agencies and programmes, with estimated expenditure of US\$2.8bn in FY11. Part of this is spent by the US Army Medical Research and Materiel Command (USAMRMC), based at Fort Detrick, Md. The largest of USAMRMC's labs is the Walter Reed Army Institute of Research at Silver Springs, Md, whose focus is neuroscience and infectious diseases. Given the prevalence of TBI in the US armed forces throughout the world (~25,000 cases in 2010 among active personnel), the Army has a strong interest in developing drugs that are neuroprotective. It has therefore chosen to fund Neuren's NNZ-2566 drug to the tune of US\$22.8m, sufficient to cover the Phase II trial.

If Neuren is so good why does it have an enterprise value of less than A\$10m? Neuren's Glypromate product, which is simply the first three amino acids of Insulin-like Growth Factor-I, failed in December 2008 in a Phase III trial measuring the ability of the drug to prevent cognitive decline following Coronary Artery Bypass Graft. Understandably, this failure helped depress the stock price. However we argue in this note that the Glypromate trial outcome reflects a poor choice of trial structure (see Appendix IV for more), with all the data raising the chances for a better outcome for NNZ-2566 in TBI. Consequently we think that Neuren's current stock price is undervaluing the potential.

The US Army is funding Neuren's Phase II trial for NNZ-2566

¹ Source: CDC.

Nine reasons to buy Neuren

Neuren's Phase II trial of Motiva is being funded by an NH&MRC grant

- 1 **NNZ-2566 is a viable neuroprotection drug.** Neuren has gathered strong pre-clinical data on the neuroprotection properties of its NNZ-2566 small molecule, for the treatment of Traumatic Brain Injury (TBI). We see significant upside from this drug given that there are 1.7 million TBIs per year in the US, no approved therapies in this indication, a potential US\$2-4bn market opportunity should NNZ-2566 perform well in the clinic, and strong support from the US Army and key opinion leaders.
- 2 **Neuren is making progress with its Phase II trial in Traumatic Brain Injury.** NNZ-2566 entered a Phase II clinical trial in May 2010 under an IND, but recruitment was initially slow. The trial is now accruing patients at a faster rate thanks to changes to the trial protocol and FDA grant of Exemption From Informed Consent. We expect that the trial will complete late in 2012. We expect that in the event of clinical success only one pivotal trial would be required prior to approval, with flexibility to be expected from the regulators in terms of trial structure and the choice of endpoints.
- 3 **The US government is funding the Phase II trial in full.** The US Army has provided significant funding for the NNZ-2566 Phase II trial (ie around US\$23m) as part of its effort to get a neuroprotection drug onto the market that would be useful in treating TBI in its soldiers. This allows the company to conserve its shareholders' funds.
- 4 **There is strong potential upside from new indications for NNZ-2566.** Following on from the TBI application there is also potential for orally available versions of the drug to be useful in stroke recovery and a genetic disorder called Rett Syndrome (one of the autism spectrum disorders), as well as numerous other applications.
- 5 **Neuren is also in Phase II with Motiva, a drug for the treatment of post-stroke apathy.** This drug has a strong safety profile, having been initially developed by the Japanese drug company Daiichi Sankyo. More importantly there is Phase II clinical data showing its effectiveness in post-stroke apathy, and another Phase II trial is now underway in Australia, fully funded by an NH&MRC grant. Given high industrialised world stroke incidence, and prevalence and the high number of stroke survivors with Apathy Syndrome, we see a large market opportunity.
- 6 **Neuren has an encouraging early-stage pipeline.** Neuren is also at pre-clinical with NNZ-2591 for Parkinson's and peripheral neuropathy, while a subsidiary called Perseis Therapeutics, in which Neuren has a majority stake, is working on anti-cancer antibodies. There is potential for upside to be generated from these projects through outlicensing.
- 7 **Neuren has a solid management team.** We have a high regard for the Neuren management team led by Larry Glass, who brings strong relationships with the Army Medical R&D command as well as strong business development skills. We think that the Neuren board under Chairman Robin Congreve and including Dr John Holaday, the QRxPharma CEO, is a good one.
- 8 **Neuren has a very low burn rate.** With US and Australian Government funding for its two lead molecules Neuren only burns around A\$180,000 per month, so it is well funded for its current stage of clinical development.
- 9 **Neuren is undervalued given the potential.** We value Neuren on a probability-weighted DCF valuation at 12 cents base case and 21 cents optimistic case. Our 12 cent price target sits at the low point of this valuation range. We see the market marking up Neuren as Motiva and NNZ-2566 near the end of their Phase II trials, and as awareness grows of the interest of key opinion leaders in NNZ-2566 as the Next Big Thing in Traumatic Brain Injury. We also expect that a favourable partnering outcome for NNZ-2566 could lead to a significant re-rating of the stock.

Valuing Neuren

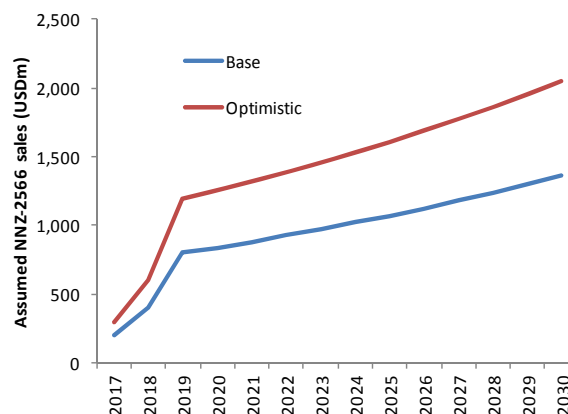
We value Neuren on a probability-weighted DCF valuation at 12 cents base case and 21 cents optimistic case. Our 12 cent price target sits at the low point of this valuation range.

Figure 2 - Our valuation of Neuren

	Base case	Optimistic case
NNZ-2566 (A\$m)	196.5	353.2
Motiva (A\$m)	126.5	179.3
NNZ-2591 (A\$m)	38.0	76.0
TFF antibodies (A\$m)	6.5	13.5
R&D overhead (A\$m)	-9.6	-9.6
Cash as at Jun 2011 (A\$m)	9.8	9.8
Cash from options (A\$m)	6.2	6.2
Cash to be raised	20.0	90.0
Total value (A\$m)	393.8	718.3
Total diluted shares on issue (million)	3,354.3	3,401.0
Value per share	\$0.117	\$0.211
Valuation midpoint	\$0.164	
Share price now	\$0.017	
Upside to valuation midpoint	866.5%	

SOURCE: BELL POTTER SECURITIES ESTIMATES

Figure 3 - Assumed sales profile for NNZ-2566



SOURCE: BELL POTTER SECURITIES ESTIMATES

We value Neuren at 12 cents base case and 21 cents optimistic case

We value Neuren on the basis of potential payoffs across the pipeline. To attempt a valuation of Neuren we looked at the pipeline as a whole and assumed outlicensing after completion of early stage trials and minimal extra investment in the programmes by Neuren. We then conducted probability-weighted DCF valuations of the products should they gain regulatory approval using certain sales levels reached at the point of maximum sales growth in year 3, after which sales only rise 5% pa (see the example chart above). We assumed royalties are collected for around 13 years after first sales. We valued this royalty stream using a 25% discount rate, a 30% tax rate, and a 0.85 AUD/USD exchange rate². We also assumed a 15% chance of clinical success for all products.

Figure 4 – Key parameters for valuing Neuren's pipeline

Product	Sales pa at maximum growth rate base (USD)	Sales pa at maximum growth rate optimistic (USD)	Neuren remaining investment base (USD)	Neuren remaining investment optimistic (USD)	Royalty base	Royalty optimistic	Upfronts and milestone payments base (USDm)	Upfronts and milestone payments optimistic (USDm)	Launch year	Probability of successful launch
NNZ-2566 (100%)	800	1200	0	0	12%	15%	200	300	2017	15%
Motiva (100%) ³	500	750	0	0	10%	12%	300	400	2018	15%
NNZ-2591 (100%)	500	750	0	0	6%	8%	175	350	2021	15%
TFF antibodies (50%)	300	500	0	0	6%	8%	50	100	2021	15%

SOURCE: BELL POTTER SECURITIES ESTIMATES

Valuing the underlying burn rate. We assumed that going forward, Neuren burns around \$200,000 per month, or A\$2.4m pa, on R&D and admin, and discounted the after-tax value of this burn at 25% in perpetuity.

We assume another \$20m in capital needs to be raised. We assume that Neuren will seek to raise around A\$20m over time in order to fully develop the potential of the pipeline.

² Bell Potter's current long term assumption.

³ Neuren will owe a royalty on sales of this drug to Daiichi Sankyo, the Japanese drug company which originated the compound. We estimate this royalty to be in the low double-digits, but in our modelling we assume that the end-licensee of the drug assumes the liability.

While Neuren has been very careful with its capital and has been generously funded by the US government and other granting bodies we think the company can use \$20m to add value to programmes such as NNZ-2591, for the treatment of Parkinson's, and other 'deep pipeline' opportunities. As at June 2011 the company had A\$10m cash, funding it into 2012 and beyond.

We see a number of catalysts to potentially re-rate Neuren to 12 cents in 2012

Target price 12 cents

We see the following important potential developments over the rest of 2011 and into 2012 as having the capacity to re-rate the stock to our target price:

- Progress on recruitment for the NNZ-2566 trial in TBI, including further trial sites;
- Progress on the NNZ-2566 collaboration in Rett Syndrome;
- Progress on recruitment for the Motiva Phase II trial;
- Further grants to the various Neuren programmes;
- Further grants over Neuren's vast estate of patent applications;
- Completion of development work on oral NNZ-2566, and initiation of a clinical trial for mild TBI with this formulation;
- Selection of lead antibodies for Perseis Therapeutics.

NNZ-2566 has strong potential as a neuroprotection drug

Neuren's lead compound, NNZ-2566, is a neuroprotective small molecule that is currently in a Phase II clinical trial for the treatment of Traumatic Brain Injury (TBI). This trial is expected to complete in late 2012. After examining the available data on NNZ-2566 we believe that the drug has a good chance of preserving brain function in treated patients, opening up a large commercial opportunity in a field where there are no currently approved drugs and a ~US\$4bn addressable market based on annual incidence of TBI.

What is NNZ-2566?

NNZ-2566 is a synthetic analogue of Glypromate, a drug known to have neuroprotective properties. Glypromate, a peptide drug, is simply the first three amino acids of Insulin-like Growth Factor I. A large body of science has demonstrated that Glypromate is neuroprotective, and Neuren did its 2005 IPO on the ASX in order to take the drug into the clinic with the aim of having one of the first successful neuroprotective drugs on the market. However the company made the mistake, between 2004 and 2008, of testing Glypromate clinically for its ability to preserve cognitive function following Coronary Artery Bypass Surgery (CABG). After this programme was initiated science began to suggest that there is relatively little cognitive decline after CABG, meaning that neuroprotective compounds can make negligible difference vis-a-vis placebo to treatment outcomes. Consequently Glypromate failed at Phase III in December 2008. We profile Glypromate's neuroprotective properties, and the drug's experience in CABG in Appendix IV of this note.

NNZ-2566 is better than Glypromate. Neuren developed NNZ-2566 around 2002 by methylation of the proline moiety of Glypromate in order to confer protease resistance to the drug, something that would enable it to be delivered orally, whereas Glypromate had been delivered by infusion. Neuren began collaborating with the Walter Reed Army Institute of Research on NNZ-2566 in 2004, exploring its potential for the treatment of TBI, and that year demonstrated that NNZ-2566 could have oral bioavailability⁴. NNZ-2566's current clinical trial in moderate-to-severe TBI involves infusion delivery, however an oral drug is currently being developed for mild TBI. In pre-clinical work the infusion form of the drug surprised researchers by enabling higher blood plasma concentrations than Glypromate, as well as having four times the plasma half life⁵.

The world needs a good neuroprotection drug

Traumatic Brain Injury represents a large market opportunity. Every year in the US around 1.7 million people sustain a Traumatic Brain Injury, that is, a loss of cognitive and other neurological functions that results from a blow to the head. Such an injury can be mild, moderate, or severe, depending on the number of brain cells that are affected by the blow. Of the 1.7 million TBIs, around 1.4 million, being mild, are treated in the emergency department and sent home. Another ~250,000-300,000, however, are hospitalised with moderate and severe brain injury, and ~50,000 die from their injuries⁶. It is estimated that around 5 million people, or 1.7% of the US population, is living with some sort of TBI.

There are around 1.7 million Traumatic Brain Injuries in the US every year

⁴ Source: Neuren's IPO prospectus, page 11.

⁵ See Example 8 of U.S. Patent 7,605,177, filed 20/12/2005.

⁶ Source: CDC: Traumatic Brain Injury in the United States - Emergency Department Visits, Hospitalizations and Deaths 2002-2006.

The molecular cascade following a TBI opens up various points for a drug-based intervention

In TBI, not all brain cells die straight away. When the subject of a TBI suffers a blow to the head, some brain cells die at the moment of impact, but many others die over the next few days during a cascade of secondary events:

- *Too much glutamate floods the brain.* Glutamate is an 'excitatory neurotransmitter' in the central nervous system, meaning that it is able to turn up electrical signals being generated by neurons. It does so by interacting with so-called NMDA receptors on the surface of the receiving neuron. Too much glutamate means that neurons are, in effect, excited to death⁷.
- *Too much calcium flows into nerve cells.* Part of the problem with glutamate activation of NMDA receptors is that calcium influx triggers various events that lead to cell damage⁸;
- *There is too much free radical production.* The calcium influx prompts the production of free radicals, which in turn damage cells through oxidative stress⁹;
- *All the cellular damage generates an inflammatory response,* with cytokines and other inflammatory molecules being activated to clean up the mess. This can also prove damaging to cells¹⁰.

The result of this cascade is effectively two waves of cell death. The first wave kills brain cells via necrosis, that is, 'premature' death of cells through cell damage, and takes place soon after the injury. The second wave kills brain cells through 'apoptosis', in which mechanisms for 'programmed' cell death are triggered by the molecular cascade described above.

An effective neuroprotection drug could limit the damage in TBI. It is the apoptosis wave that suggests a window of opportunity to treat TBI – in various TBI animal models apoptotic death of brain cells has been observed to go on for days after induction of injury¹¹. Consequently any drug that can combat the glutamate, calcium, free radicals or inflammation, if administered to the patient within hours of the injury, has the potential to limit the damage and therefore the potential disability following a TBI.

Why there are currently no neuroprotection drugs on the market. Neuroprotection is an opportunity not just in TBI but also in strokes as well as in neurodegenerative disorders like Alzheimer's and Parkinson's, all of which have large Western world incidences. Consequently a potential multi-billion dollar market awaits any successful neuroprotection drug, and in the 1990s and into the 2000s pharma companies were very interested in drugs that would be neuroprotective. However all of the drugs that were developed failed, leading to headlines such as:

- *Astra hit by drug failure - AstraZeneca's experimental stroke drug NXY-059 has failed to pass a pivotal clinical trial, dealing a fresh blow to the group's already depleted new product pipeline*¹².
- *Ono Pharma shares decline after stroke drug failure – Ono Pharmaceutical Co., a Japanese drugmaker, fell in stock trading after tests of its experimental stroke medicine, Arocyte, failed to show it was effective when compared with a placebo*¹³.

These failures have led to neuroprotection drug development being described as a 'graveyard'¹⁴. They have caused Big Pharma to almost abandon the area¹⁵, and have left

⁷ See *Neurochem Int.* 2006 Apr;48(5):394-403. Epub 2006 Feb 13.

⁸ See *Biorheology.* 2003;40(1-3):401-9.

⁹ See *Surg Neurol.* 1997 Jun;47(6):575-81.

¹⁰ See *Neurochem Res.* 1998 Mar;23(3):329-40.

¹¹ See, for example, Conti et. al (*J Neurosci.* 1998 Aug 1;18(15):5663-72) in which significant apoptosis in the rat cortex occurred at 24 hours but with a second, more pronounced round of apoptosis at one week after injury.

¹² *The Telegraph*, 26/10/2006

¹³ Bloomberg story by Kanoko Matsuyama, 2/10/2008. The story refers to arundic acid or ONO-2506, an Ono-developed modulator of astrocyte activation. For early clinical data showing a favourable trend on NIHSS see *J Neuro Sci.* 2006 Dec 21;25(11-12):50-6. Epub 2006 Nov 7.

¹⁴ See, for example, *Search for the brain's first defense* by Melissa Healy, the Los Angeles Times, 9/4/2007.

academic teams as the only serious proponents of neuroprotection other than Neuren and a few other small companies¹⁶. We note, however that the number of scientific papers on neuroprotection has continued to increase in recent years¹⁷, as has the number of US patents related to neuroprotection¹⁸, meaning that knowledge about what may work therapeutically is rising all the time.

Some of the more prominent neuroprotection failures of the last fifteen years are profiled in Appendix VI of this report. We argue there are four basic reasons why such drugs have failed:

- *Mechanisms of action have been limited* – the main drug development approaches to date have been targeting NMDA receptors to deal with the glutamate issue, and scavenging of free radicals. Ideally neuroprotection drugs will deal with the inflammation issue as well.
- *Stage of delivery has been too late* – Often a drug will be delivered after the neuroprotection window has closed. So, for example, in the Intravenous Magnesium Efficacy in Stroke trial measuring the neuroprotective effects of magnesium sulphate, the drug only had to be administered within 12 hours¹⁹. Another ongoing trial pushes this back to two hours²⁰.
- *Animal models weren't predictive of human outcomes* – Often the animal testing prior to clinical studies hasn't been as good as it could have been²¹.
- *There was difficulty measuring outcomes*. There are various ways to measure the outcome of a neuroprotection drug. The Modified Rankin Scale, for example, evaluates stroke disability whereas the NIH Stroke Scale measures neurocognitive function following a stroke. This measurement, with its element of subjectivity, is likely to have hampered drug candidates.

All of which begs the question as to why Neuren has a chance to succeed with NNZ-2566 where AstraZeneca and other companies much larger than Neuren have failed. To answer this question, let's look first at the pre-clinical evidence for NNZ-2566 before looking at how the current Phase II trial in Traumatic Brain Injury has been structured for an optimal outcome.

Evidence that NNZ-2566 works

Over the last five years Neuren has gathered strong evidence of NNZ-2566's efficacy in neuroprotection:

- *Neuroprotection in vitro*. NNZ-2566 was able to protect neurons from the cortex, striatum and cerebellum of rats against damage from neurotoxic chemicals over a 24 hour period²²;
- *Neuroprotection in hypoxic-ischemic brain injury*. 25 rats with hypoxic-ischemic brain injury but treated with NNZ-2566 from one to five hours after the injury experienced much less tissue damage in the injured part of the brain ($p < 0.001$) than did the 28 rats in the control group. There was much less damage in parts of the cortex and striatum in

Neuren has gathered strong evidence of NNZ-2566's efficacy in neuroprotection

¹⁶ Not quite, however. Pfizer is in Phase II with a stroke recovery drug called PF-03049423. And GSK is in Phase II with a myelin-associated glycoprotein monoclonal antibody (see J Neuropathol Exp Neurol. 2003 Jan;62(1):25-33).

¹⁸ Emory University in Atlanta, for example, has done serious clinical work on progesterone for TBI neuroprotection. The ProTECT III trial is a multi-site NIH-sponsored clinical study enrolling 1,140 patients at 17 centres under the leadership of Dr David Wright, Emory's Professor of Emergency Medicine. See NCT00822900 at www.clinicaltrials.gov and Ann Emerg Med. 2007 Apr;49(4):391-402, 402.e1-2. Epub 2006 Sep 29.

¹⁷ In 2000 there were 109 scientific papers that had 'neuroprotection' in the title. In 2010 there were 304 (Source: Pubmed).

¹⁸ In 2000 there were 23 US patents that had 'neuroprotection' or 'neuroprotective' in the title or abstract. In 2010 there were 31 (Source: US Patent and Trademark Office).

¹⁹ See Lancet. 2004 Feb 7;363(9407):439-45.

²⁰ The FAST-MAG Phase III trial (www.fastmag.info) sponsored by NIH will evaluate the effectiveness of magnesium administered within 1-2 hours of a stroke. For pilot data related to FAST-MAG see Stroke. 2004 May;35(5):e106-8. Epub 2004 Mar 11.

²¹ For many years now the Stroke Therapy Academic Industry Roundtable has worked on recommendations for optimal preclinical work in stroke drugs, but in the view of some the adherence to these guidelines has been variable. See Stroke. 2009 Feb;40(2):577-81. Epub 2008 Dec 12.

²² See the sole example in WO/ 2002/094856.

the treated rats, and none of the rats experienced non-convulsive seizures whereas 9 control rats did²³. Subsequent work in hypoxic-ischemic brain injury showed that treated rats had less expression of the pro-inflammatory cytokine interleukin-6 and higher level of new blood vessel formation²⁴.

- *Neuroprotection in a stroke model.* 13 rats in which a Middle Cerebral Artery Occlusion (MCAo) had been induced to model the effects of a stroke in the rat brain²⁵ had infarct volumes around half the size of 15 control rats ($p < 0.05$) when treated with NNZ-2566 between 5 and 9 hours after the ischemia. There was also less activation of astrocytes and microglia, indicating a much lower inflammatory response in the brain, although the numbers were not statistically significant²⁶. A later experiment established that NNZ-2566 could reduce seizures in the MCAo model - 10 rats treated with NNZ-2566 for 12 hours beginning 30 minutes post-occlusion experienced 36% less non-convulsive seizures and 56% less time in such seizures compared to 13 controls. The drug-treated group also had a lower infarct size. These results were dose-dependent and were statistically significant²⁷.
- *Neuroprotection in a Traumatic Brain Injury model.* Rats used to model 'experimental penetrating ballistic-like brain injury'²⁸, when treated with NNZ-2566 30 minutes after the injury, demonstrated fewer 'foot faults' and other neurological disabilities than control rats, and there was also less evidence of microglial activity in the treated rats²⁹. Moreover the effect was dose-dependent. Subsequent work in this model established that treated rats had less expression of the pro-apoptosis proteins Bax and more expression of the anti-apoptosis protein Bcl-2³⁰.
- *Neuroprotection in the ageing brain.* Ageing rats, when administered NNZ-2566, registered increased levels of choline acetyltransferase (ChAT), the enzyme that makes the neurotransmitter acetylcholine, than control rats. Treated rats were therefore much better performers at memory tests. They were also found to be generating more neuroblasts (neuron precursors), and had less activation of astrocytes³¹.
- *Neuroprotection associated with noticeably lower levels of inflammation.* In the experimental penetrating ballistic-like brain injury model described above, NNZ-2566 was able to significantly reduce levels of the pro-inflammatory cytokines IL-1 β , TNF- α , e-selectin and IFN- γ , but did not impact levels of IL-6 as an anti-inflammatory³².

NNZ-2566 can combat the inflammation that causes cell death after TBI

NNZ-2566 is well placed to succeed in the current Phase II trial

NNZ-2566 entered the clinic in May 2010 under an IND³³. NNZ-2566's Phase II trial in Traumatic Brain Injury, called INTREPID-2566, will study NNZ-2566 in patients with moderate-to-severe TBI that is non-penetrating³⁴. It will enrol 260 patients moderate and severe TBI patients, as measured by the Glasgow Coma Scale (GCS), and the trial will randomise two-thirds to drug and one-third to placebo. The drug will be administered within 6 to 8 hours of injury, with continuous infusion after an initial bolus infusion out to 72 hours.

²³ See Example 4 of U.S. Patent 7,605,177, filed 20/12/2005.

²⁴ See Dev Neurosci. 2007;29(4-5):393-402.

²⁵ More specifically, a 'focal stroke', in which only part of the brain is effected.

²⁶ See Example 5 of U.S. Patent 7,605,177, filed 20/12/2005. This work was later published in the Journal of the Neurological Sciences – see J Neuro Sci. 2009 Mar 15;278(1-2):85-90. Epub 2009 Jan 20. The paper also established the longer half-life of NNZ-2566 as opposed to Glypromate.

²⁷ See Example 3 of U.S. Patent 7,714,020, filed 4/4/2006. This work was later published in the Journal of Cerebral Blood Flow & Metabolism – see J Cereb Blood Flow Metab. 2009 Dec;29(12):1924-32. Epub 2009 Jul 29.

²⁸ Through insertion of a probe into the brain.

²⁹ See Example 6 of U.S. Patent 7,605,177, filed 20/12/2005.

³⁰ See J Neurotrauma. 2009 Jan;26(1):141-54.

³¹ See Examples 4-6 of US 2007/0004641, another continuation in part of U.S. Patent 7,041,314.

³² J Neuroinflammation. 2009 Aug 5;6:19. Note that Interleukin-6 can act as either a pro-inflammatory or an anti-inflammatory cytokine.

³³ See NCT00805818 at www.clinicaltrials.gov. Neuren reported in January 2007 that a Phase Ia trial of NNZ-2566 in 28 healthy volunteers had found the drug to be safe and well tolerated. The current Phase II took a while to get started – the IND opened in March 2009.

³⁴ That is, no gunshot or stab wounds to the head. Neuren took the decision to focus on non-penetrating TBI, even though the drug worked well in pre-clinical models of penetrating TBI, because this kind of injury was considered more challenging.

There will be three cohorts (20 mg/kg bolus followed by 1, 3 or 6 mg/kg/hr infusion for 72 hrs). And there will be the possibility of an interim analysis to be conducted after 100 patients³⁵.

The Phase II trial is making progress on recruitment. INTREPID-2566 is currently enrolling in Emergency Departments at 11 hospitals across America, with a further five intended to be recruiting by the end of 2011. Initially recruitment was slow, with the 30th patient taking until May 2011 to enrol. Two changes, however, have speeded recruitment since May:

- With FDA approval, the investigators has expanded the inclusion criteria from males only aged 18-70 years to both males and females aged 16-75;
- The FDA has also accepted a new IND permitting EFIC, that is, Exception from Informed Consent for Emergency Research. Previously a 'legally authorised representative' would have to grant informed consent³⁶, and obtaining this consent was causing the investigators to miss the eight hour treatment window. EFIC allows that requirement to be waived, in return for the treatment window being reduced to six hours³⁷.

We believe these changes put Neuren on track to be able to complete INTREPID-2566 by late 2012.

Why NNZ-2566 has a good chance of succeeding in Phase II. Obviously in an area as historically problematic as neuroprotection, nothing is anywhere near certain. That said, we think NNZ-2566 is well placed to report a positive outcome from INTREPID-2566, for five reasons:

- *NNZ-2566 is something of an Orphan Drug.* Ordinarily an Orphan Drug is one that treats a disease affecting less than 200,000 patients in the US. Designation as an Orphan Drug by the FDA often brings with it favourable regulatory treatment, particularly if it is the only drug going after the indication. TBI is not an Orphan indication in the sense that more than 200,000 people have to be hospitalised every year in the US because of such an injury. However Neuren argues that NNZ-2566 is something of an Orphan Drug, since there is currently no approved neuroprotection drug even though there is significant unmet need and the US Army badly needs such a drug. Consequently the company expects a certain amount of flexibility in its dealings with the Agency, including a consideration of cost-benefit analysis when the company files for FDA approval³⁸, as well as a willingness to look at new endpoints for approval.
- *Multiple functional endpoints raise the chances of success.* The investigators will track the functional outcome of the patients using the Glasgow Outcome Scale-Extended (GOS-E) and the Mayo-Portland Adaptability Index. GOS-E is an 8 point score where a physician makes a very general assessment of the general functioning of the patient with the TBI and rates him on a scale from 1 (dead) to 8 (a very good recovery). By contrast the Mayo-Portland Adaptability Index tracks functional improvement across a wide range of measures from everyday activities to emotion to cognition. Measuring functional outcome more than one way makes it more likely that NNZ-2566 will succeed - a statistically significant improvement over placebo with either measure in a Phase III setting would likely gain FDA approval for NNZ-2566.
- *Data on seizures could prove to be powerful.* As we noted above, in animal models NNZ-2566 markedly reduced non-convulsive seizures in the animal models of hypoxic-ischemic brain injury. The INTREPID-2566 investigators will track the patients' experience of seizures during the three days of infusion using continuous EEG. There's

NNZ-2566's performance will be measured in multiple ways

³⁵ This is not in the trial protocol but something that Neuren has contemplated. The final decision on an interim analysis will be made by the trial investigators, guided by the Data and Safety Monitoring Board.

³⁶ Since the patient himself is in a coma or close to it.

³⁷ See NCT01366820 at www.clinicaltrials.gov.

³⁸ That is, evaluating the drug for what benefits it could bring, however small, rather than whether it missed certain conventional endpoints.

clear evidence that non-convulsive seizures worsen outcomes for TBI patients³⁹, so seizures may prove one of the 'new endpoints' the FDA will be willing to consider as approvable for NNZ-2566, even if the functional endpoints don't work so well.

- *The mechanism of action makes sense.* We noted above that not all parts of the brain injury molecular cascade had been adequately addressed in late stage trials of neuroprotection drugs. We think the growing evidence of the causal relationship between inflammation and apoptosis in a brain undergoing TBI⁴⁰ stands NNZ-2566 in good stead.
- *The investigators have taken heed of the animal data.* The design of INTREPID-2566, including the trial's powering, was largely shaped by the animal data that has been gathered in recent years. For example, the three day infusion window for NNZ-2566 was suggested by the inflammation evidence we noted above, which showed that the drug could inhibit inflammation and brain cell apoptosis for up to three days post-injury. The animal data also helped shape the 6-8 hour window on drug delivery.

Neuren has partnered with the US government on NNZ-2566's clinical development

An important aspect of NNZ-2566's clinical development is the fact that Neuren does not have to spend much money on the drug, with the US government covering all trial expenses for INTREPID-2566. Uncle Sam is also covering other non-trial costs up to commencement of a pivotal.

Uncle Sam desperately wants a neuroprotection drug. We noted above that Neuren has been collaborating on NNZ-2566 with the Walter Reed Army Institute of Research (WRAIR) since 2004. This collaboration arises out of the US Army's desperate need for a neuroprotection drug. In order to continually improve as a fighting force, the US Army conducts considerable medical research activity through its Medical Research and Materiel Command (USAMRMC), based at Fort Detrick, Md. USAMRMC's budget in FY11 was US\$170-180m⁴¹. The largest of USAMRMC's labs is WRAIR at Silver Springs, Md, whose focus is neuroscience and infectious diseases. TBI has become a serious issue for the Army, and therefore for the WRAIR, in recent years:

- In the wars in Iraq and Afghanistan, the use by the terrorists of improvised explosive devices (IEDs) has greatly increased the potential for US soldiers to sustain a TBI – between 2001 and 2007, for every 10,000 men fighting in these campaigns for a year, around 25 suffered a TBI in Afghanistan and 42 in Iraq⁴²
- A survey of 2,500 soldiers returned from Iraq found that 4.9% had experienced injuries with loss of consciousness⁴³;
- At six months post-injury, soldiers with mild TBI were five times more likely to report a major negative change in health as compared to other soldiers with other mild injuries⁴⁴.
- As well as combat-related injuries the US armed forces continues to suffer TBI among its active personnel around the world each year, with ~25,000 cases in 2010 alone⁴⁵

Uncle Sam has picked NNZ-2566 as a candidate to back, and fully funded the Phase II trial. The US government's involvement has been manifold:

³⁹ For example, they increase intracranial pressure and the lactate/pyruvate ratio, indicative of not enough glucose being consumed by brain cells. See Crit Care Med. 2007 Dec;35(12):2830-6.

⁴⁰ See, for example, Neuroscience. 2010 Dec 29;171(4):1273-82. Epub 2010 Oct 13.

⁴¹ Source: Association of American Medical Colleges, FY 2012 Department of Defense Medical Research Funding.

⁴² See Am J Prev Med. 2010 Jan;38(1 Suppl):S108-16.

⁴³ See N Engl J Med. 2008 Jan 31;358(5):453-63. Epub 2008 Jan 30.

⁴⁴ See Injury. 2011 Aug 18. [Epub ahead of print]

⁴⁵ Source: Defense and Veterans Brain Injury Center. Note by contrast there were only ~5,700 US service personnel wounded in Iraq and Afghanistan in 2010 (source: US DOD).

- WRAIR personnel have been active in the research demonstrating pre-clinical effectiveness⁴⁶;
- The government has contributed US\$23m to fully fund the Phase II trial, US\$4m through the Department of Defence's Congressionally Directed Medical Research Program⁴⁷ and the rest through USAMRMC's 'Combat Casualty Care' programme⁴⁸;
- Before the money was granted NNZ-2566 had to go through competitive, peer-reviewed grant applications, further strengthening the credibility of the drug.

Probably the greatest benefit of the US government's backing is the fact that Neuren retains all future commercial rights to NNZ-2566 outside the drug's use by the US military. We see the possibility that Uncle Sam will choose to fund the pivotal as well, although this is not guaranteed.

NNZ-2566 could be worth US\$4bn for TBI in the US alone. Neuren has estimated that at a price of US\$12,000 per IV dose for moderate-to-severe TBI (30% of the market) and of US\$3,000 per dose for mild TBI (the other 70%), 1.5 million TBIs each year in the US would make for a US\$4bn market⁴⁹. That this pricing is realistic is suggested by the Roche/Genentech drug Activase⁵⁰, which works to break up a blood clot which is causing a stroke if administered within three hours of the stroke. Activase sells for around US\$2,200 per dose in the US and at that price is considered highly cost effective⁵¹, having prompted Medicare in 2005 to raise average reimbursement per acute stroke patient by US\$6,700 to more than US\$11,500⁵², when that patient is treated with Activase.

The path forward for NNZ-2566

A pivotal trial in moderate-to-severe TBI from 2013. We expect that NNZ-2566 will move forward quickly after the current trial, being already the holder of a Fast Track designation by the FDA⁵³. We think, given the strong unmet medical need, that the FDA may be prepared to require only a single pivotal trial of NNZ-2566, under a Special Protocol Assessment (SPA)⁵⁴, prior to approval. That pivotal trial could commence in 2013 with a possible rolling NDA submission under Fast Track procedures beginning in 2013 or 2014, putting Neuren on track to be completing the pivotal in 2015 and gaining FDA approval in 2016. Should this timetable be met, the drug would launch around 2017.

Success in moderate-to-severe TBI opens up other possibilities for NNZ-2566 as an IV drug. Obviously if NNZ-2566 is successful in non-penetrating TBI, Neuren will look to explore its use in penetrating TBI, in stroke, in cardiac arrest and neonatal asphyxia, and in non-convulsive seizures associated with other CNS conditions. Together this has potential to make NNZ-2566 a blockbuster drug.

An oral NNZ-2566 formulation is coming for mild TBI. In mid-2010 Neuren initiated development of an oral NNZ-2566 formulation for use in mild TBI as well as stroke recovery. This drug would further extend the NNZ-2566 franchise, opening up its use in transient ischemic attacks (ie 'mini strokes'), in chemotherapy-induced neuropathy and in a rare autism spectrum disorder called Rett Syndrome as well as other autism spectrum

We see other indications emerging for NNZ-2566

⁴⁶ See the aforementioned papers in J Neuroinflammation, J Cereb Blood Flow Metab. and J Neurotrauma.

⁴⁷ Where the US Congress appropriates funds for medical research and makes the funds available for laboratory grants. See <http://cdmmp.army.mil>. Neuren announced its CDMRP funding in January 2008.

⁴⁸ See Neuren's announcements of 4/9/2008 and 1/7/2009.

⁴⁹ See the company's 24 June 2011 presentation to Ausbiotech New York, slide 6.

⁵⁰ See www.activase.com. Activase, which is recombinant tissue plasminogen activator or TPA, gained FDA for its stroke indication in 1996. The drug had originally gained FDA approval in 1988, indicated for treating blood clots in heart attack patient but was a commercial disaster for Genentech with the drug not priced competitively against other therapies. The result of this was that Roche was able to buy majority ownership of the weakened Genentech in 1990.

⁵¹ See Stroke. 2010 Oct;41(10 Suppl):S59-62.

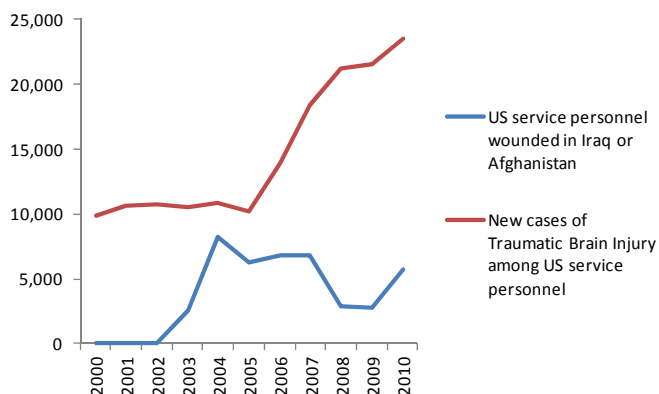
⁵² See Stroke. 2008 Mar;39(3):924-8. Epub 2008 Jan 31.

⁵³ This was granted in June 2009.

⁵⁴ A declaration by the FDA that a pivotal trial's clinical endpoints are acceptable for FDA approval of the drug. It effectively ensures that the FDA can't change its mind with regard to approval and ask for further data when the final results of the trial come in.

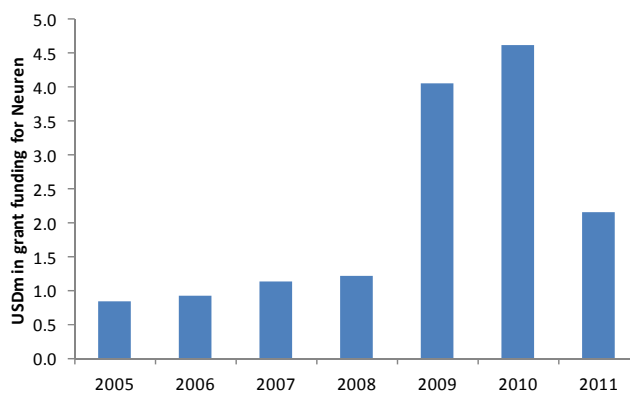
disorders. Neuren believes that it can complete development of oral NNZ-2566 late in 2011 and take this into the clinic for a mild TBI trial in mid-2012⁵⁵.

Figure 5 - The US Armed Services suffered 25,000 TBIs among active personnel in 2010



SOURCE: DEFENCE AND VETERAN'S BRAIN INJURY CENTER, US GOVERNMENT

Figure 6 - Neuren has enjoyed ample grant funding in recent years, including US\$23m from the US government



SOURCE: NEUREN

NNZ-2566 may be the first effective treatment for Rett's Syndrome

Rett Syndrome opens up new vistas for NNZ-2566

Perhaps the most interesting application of NNZ-2566 so far contemplated is in **Rett Syndrome**, a rare neurodevelopmental disorder of the grey matter of the brain that affects only girls⁵⁶. Rett's girls are characterised by small hands and feet, and a deceleration of the rate of head growth. They generally have no verbal skills and half never learn to walk. In February 2009 scientists in the laboratory of Professor Mriganka Sur at MIT, studying Rett's in mice lacking the mutant MECP2 protein which causes the disease, found that they could partially reverse the symptoms using, to quote the Sur lab's paper⁵⁷, '*an active peptide fragment of Insulin-like Growth Factor 1 (IGF-1)*'. Effectively the Sur team had used Neuren's drug.

Neuren is now working on Rett's. Subsequent to this paper Neuren began working on NNZ-2566 in the same mouse model that had generated MIT data. To this end It collaborated with two US labs, the collaboration being sponsored by the Connecticut-based Rett Syndrome Research Trust, which is the main charity globally funding work on Rett's⁵⁸. The programme has apparently yielded encouraging results.

Where Rett Syndrome could take NNZ-2566. Success in pre-clinical could conceivably move NNZ-2566 onto the market very quickly. We think it's reasonable, in the event of pre-clinical success, to expect strong support from the Rett Syndrome Research Trust, and other patient advocacy groups, for a push into the clinic. Moreover we expect to see grant funding for the project emerge over time. A Rett's indication would definitely qualify for Orphan status, and would probably be granted manageable hurdles in terms of clinical endpoints and study powering by the FDA. The effect of all this could be an earlier arrival on the market for NNZ-2566, and potentially a faster track to approval for other indications such as TBI, as well as a path to a solid partnering deal.

⁵⁵ See NCT01420042 at www.clinicaltrials.gov.

⁵⁶ In Australia cumulative incidence has been estimated at 0.96 per 10,000 females to age 12 years. See *Eur Child Adolesc Psychiatry*. 1997;6 Suppl 1:8-10.

⁵⁷ See *Proc Natl Acad Sci U S A*. 2009 Feb 10;106(6):2029-34. For the MIT press release on the work see <http://web.mit.edu/newsoffice/2009/rett-0209.html>.

⁵⁸ See <http://www.rsrt.org>.

Reprofiling Motiva into a new area of unmet medical need

Around 20% of stroke survivors suffer from Apathy Syndrome

Neuren's second drug candidate after NNZ-2566 is Motiva, a drug that was originally developed by Daiichi Pharmaceutical of Japan⁵⁹ for various CNS conditions and which Neuren is now developing as a drug to treat 'Apathy Syndrome' in stroke patients, for which there is currently no drug-based treatment and a large patient population.

What is Apathy Syndrome? Apathy is indifference and lack of emotion, and psychiatrists have coined the term 'Apathy Syndrome' to describe a set of apathetic signs and symptoms that tend to occur together in certain patient groups⁶⁰. Apathy Syndrome is common in stroke patients, with prevalence of around 20%, because of the disruption in various neural networks⁶¹:

- A survey in Italy found apathy in 15% of patients⁶², while a survey in Japan found apathy in around 20-40% of stroke patients⁶³.
- An Australian study found apathy in 27% of patients versus 5% in the matched controls⁶⁴ after 3-6 months.

Since apathy is also common in other CNS disorders such as Parkinson's, Alzheimer's, schizophrenia and TBI, an apathy drug is potentially a blockbuster⁶⁵. Neuren itself has conservatively estimated sales five years post launch in the order of US\$700m⁶⁶.

A post-stroke apathy drug has potential for strong healthcare economics. A stroke survivor with apathy is not only much less likely to pursue rehabilitation and also less likely to cope with the activities of daily living. Consequently such patients will cost more in terms of nursing home or related care, as well as conventional health care. This in turn means that a drug that can treat Apathy Syndrome has potential to be cost effective for Western world healthcare systems. We estimate that the lifetime cost of a survivor of acute ischemic stroke in the US is around US\$224,000⁶⁷.

There is a high incidence and prevalence of stroke in industrialised countries. Each year in the US around 795,000 people experience a new or recurrent stroke (610,000 first attacks, 185,000 recurrent)⁶⁸. Cerebrovascular diseases including stroke is the fourth leading cause of death in the US, with ~129,000 deaths in 2009, and people who survive a stroke join a patient population of around 7 million Americans, which is 3% of the adult population. Europe is understood to be better placed in terms of stroke than the US, with American men having 61% higher odds of having a stroke than European men⁶⁹. However that would still leave a European stroke survivor community in the order of 1.5% of the adult population or 5-6 million people⁷⁰.

What is Motiva? Motiva, generic name nefiracetam, is one of the class of drugs known as 'racetams' that originated in the early 1970s with Nootropil (piracetam), a drug used to treat a variety of memory and balance problems, and includes the 1990s blockbuster drug

⁵⁹ Now Daiichi Sankyo after a 2005 between Daiichi Pharmaceutical and Sankyo Co.

⁶⁰ For example, Kalechstein et. al. have identified Apathy Syndrome in cocaine dependence. See *Psychiatry Res.* 2002 Jan 31;109(1):97-100.

⁶¹ See *Can J Psychiatry.* 2010 Jun;55(6):350-4.

⁶² See *Arch Gerontol Geriatr Suppl.* 2004;(9):315-23.

⁶³ See *Int J Geriatr Psychiatry.* 2007 Oct;22(10):1046-51.

⁶⁴ See *Psychol Med.* 2005 Dec;35(12):1707-16. Epub 2005 Oct 5.

⁶⁵ This has attracted companies such as Novartis, which is testing its Exelon Alzheimer's drug as a potential treatment for Parkinsonian apathy. See NCT00767091 at www.clinicaltrials.gov.

⁶⁶ See Neuren AGM presentation, May 2008.

⁶⁷ Using costs from Taylor et. al (*Stroke.* 1996 Sep;27(9):1459-66), updated using medical care inflation data from the BLS.

⁶⁸ Source: American Heart Association, *Heart Disease and Stroke Statistics*, 2011 update.

⁶⁹ American Stroke Association International Stroke Conference 2008: Abstract 120. Presented February 21, 2008

⁷⁰ Bell Potter Securities estimate.

There is already a large body of science related to Motiva

Keppra (levetiracetam)⁷¹, for the treatment of epilepsy. The racetams, by acting on glutamate receptors, have important effects on memory, which is why they are often called 'smart drugs' or 'nootropics'⁷². Nefiracetam was developed in the early 1990s by Daiichi for the treatment of senile dementia, however it was rejected for that indication by Japan's drug regulators in 1999 after a five year wait. In 2004 nefiracetam was out-licensed to an American start-up called Hamilton Pharmaceuticals, which was granted exclusive rights for the US and EU. Hamilton branded the drug Motiva, and, based on Phase II data, proposed to reprofile it as a treatment for the psychological and cognitive disorders resulting from stroke, TBI, Alzheimer's and Parkinson's disease, with an initial focus on post-stroke depression. Neuren acquired Hamilton in mid-2007 for US\$4.1m of its shares⁷³.

A large body of science has grown up around Motiva over the last 20 years. The drug is a cyclic GABA agonist that is understood to improve memory and cognition by facilitating cholinergic neurotransmission, in part by targeting presynaptic nicotinic acetylcholine receptors. We profile some of the more interesting papers demonstrating the drug's apparent versatility in various CNS disorders in Appendix V of this note. Various trials in senile dementia and in stroke across all Phases of clinical development have seen around 1,700 patients treated with the drug, indicating that it has a robust safety profile.

Daiichi trialled Motiva as a stroke drug. From 1999 to 2002 Daiichi conducted two Phase III trials of Motiva in Japan as a drug to improve outcomes in stroke patients. The first of these was a success, with 32% of patients registering a statistically significant improvement on the 'Global Improvement Rating' scale versus 10% on placebo ($p < 0.001$). The second, however, was controlled not by placebo but by idebenone, an antioxidant drug from Daiichi's competitor Takeda⁷⁴. This trial saw Motiva outperform idebenone but without statistical significance (38% versus 27%, $p = 0.068$).

Daiichi discovered the post-apathy application. After this failure Daiichi studied Motiva in post-stroke depression, since around 40% of stroke patients will become depressed at some time after the event⁷⁵. After an initial study in Japan⁷⁶, a Phase II randomised, placebo-controlled clinical trial for the US and Canada was initiated under an IND. 159 stroke patients that were also diagnosed with depression were given Motiva or placebo within three months of the stroke. This trial failed to show a significant time by treatment interaction⁷⁷, however at the highest dose of 900 mg there was a significant improvement in depression for the most depressed patients⁷⁸. More importantly, for 70 patients that also had apathy, a post-hoc analysis suggested significant time-by-treatment interaction for both a 900 mg and 600 mg dose, although the 900 mg dose worked better⁷⁹. This work suggested that apathy was the correct indication for Motiva.

Motiva is moving forward without much expenditure required from Neuren. In March 2010 Neuren announced that Australia's National Health and Medical Research Council⁸⁰ would fund a Phase II trial of 122 post-stroke apathy patients at two sites in Western Australia. Patients will randomise 1:1 between 900 mg Motiva or placebo, and be assessed for functional capacity and apathy at 12 and 36 weeks. We expect that this trial can complete by mid-2013, allowing a move into pivotal trials under the still-open IND.

⁷¹ Both drugs developed by the Belgian drug company UCB.

⁷² Greek for 'acting on the mind'.

⁷³ It satisfied this with 13.6 million shares at 30 cents per share.

⁷⁴ Now marketed in Europe by the Swiss drug company Santhera as Catena, for the treatment of the rare CNS disorder Friedreich's Ataxia.

⁷⁵ See Expert Opin Pharmacother. 2008 Jun;9(8):1291-8.

⁷⁶ A 150 mg dose of Motiva generated a significant improvement in apathy, or, as the Japanese put it, 'reduced spontaneity' and the drug worked best in recent stroke patients on an analysis of Activities of Daily Living.

⁷⁷ That is, relationship between changed disease status and drug over time.

⁷⁸ See J Neuropsychiatry Clin Neurosci. 2008 Spring;20(2):178-84.

⁷⁹ See J Neuropsychiatry Clin Neurosci. 2009 Spring;21(2):144-51.

⁸⁰ Australia's answer to the National Institutes of Health.

More potential value in the early pipeline

In addition to NNZ-2566 and Motiva, Neuren also has two other potentially lucrative projects in its pipeline:

NNZ-2591 – A potential Parkinson’s drug. Since IPO Neuren has been working on a class of compounds called diketopiperazines or DKPs. These are cyclic compounds formed by peptide bonds between two amino acids. Neuren’s diketopiperazine programme aimed to create Glypromate-style molecules with greater potency and greater bioavailability through rational drug design. The best drug from this programme was NNZ-2591⁸¹ which was found in pre-clinical work to be effective in hypoxic-ischemic brain injury in rats⁸², in a rat model of Parkinson’s disease⁸³ and in a rat model of mild cognitive impairment⁸⁴. The drug also appears to be useful in peripheral neuropathy⁸⁵. Currently Neuren is interested in moving this compound forward as a Parkinson’s treatment, which is a lucrative, underserved drug market. Around 1-2% of people over the age of 55 may have Parkinson’s disease, a degenerative movement disorder⁸⁶. That would translate to around 0.9-1.0 million patients in the US alone⁸⁷, where total health care costs are estimated to be US\$5-6bn and where the disease is the 15th largest cause of death⁸⁸. What makes Parkinson’s a particularly lucrative target for drug developers is the relatively long time a patient will be on medication – in many instances close to 20 years⁸⁹ – and the fact that there are relatively few treatment options beyond L-Dopa.

Trefoil Factors – Potential cancer drug targets. Another programme ongoing for Neuren since IPO has been research on growth hormone, in particular the impact of growth hormone on cancer. This work has zeroed in on the Trefoil Factors, which are estrogen-related genes that are also acted on by growth hormone and IGF-1 and appear to play a role in cancer⁹⁰. By 2006 Neuren had identified two targets of interest, called Trefoil Factors 1 and 3, and had raised monoclonal antibodies against those targets⁹¹. These antibodies have generated favourable pre-clinical data in breast cancer both *in vitro* and *in vivo*, and there is also some interesting data in gastric cancer. In April 2009 Neuren announced that a new Auckland-based company called Perseis Therapeutics⁹² would take over the Trefoil Factors programme, with New Zealand’s Breast Cancer Research Trust⁹³ coming in as a new shareholder. Neuren retains a 72% interest in Perseis, which is currently selecting antibody candidates to take into the clinic. The commercial case for Perseis lies in the potential for its antibodies to become cancer antibody blockbusters like Herceptin (US\$5.2bn in global sales in 2010) and Avastin (US\$6.2bn).

Neuren’s work on growth hormone may have led to a breast cancer drug

⁸¹ See WO/ 2005/023815

⁸² See Neuropharmacology. 2007 Nov;53(6):749-62. Epub 2007 Aug 19.

⁸³ The 6-OHDA model, in which the neurotoxin 6-hydroxydopamine is used to selectively kill dopaminergic and noradrenergic neurons. See Br J Pharmacol. 2009 Feb;156(4):662-72. Epub 2009 Jan 16.

⁸⁴ In which acute memory loss is induced in rats using the amnesia drug scopolamine. See Behav Brain Res. 2010 Jul 11;210(2):221-8. Epub 2010 Feb 25.

⁸⁵ See WO/ 2011/037644.

⁸⁶ See a Dutch study, done in the city of Rotterdam, which suggested prevalence in over 55s of 1.4% (Neurology. 1995 Dec;45(12):2143-6).

⁸⁷ Adapting Kaiser data from California gathered in the mid-1990s (see Am J Epidemiol. 2003 Jun 1;157(11):1015-22) to the US population structure in 2009, we estimated US incidence of ~44,000 patients per year, around twice the number of deaths where Parkinson’s is a primary cause.

⁸⁸ Source: CDC, Deaths, Preliminary data for 2009.

⁸⁹ One UK study estimated an anticipated age at the time of death for Parkinsonians who were diagnosed over the age of 65 at only three years less than non-Parkinsonians of the same age. See J Neurol Neurosurg Psychiatry. 2007 Dec;78(12):1304-9. Epub 2007 Mar 30. Average age of onset of Parkinson’s is around 60, while the average American aged 60 can expect to live to age 82 (source: 2011 Statistical Abstract of the United States, Table 103). This suggests well over a decade of life expectancy for Parkinson’s patients.

⁹⁰ See Trends Endocrinol Metab. 2008 Mar;19(2):74-81. Epub 2007 Dec 3.

⁹¹ See WO/ 2008/042435 and WO/ 2009/147530. TFF-1 is expressed on most breast cancer tumours and is negatively associated with patient survival. TFF-3 is associated with tamoxifen resistance in breast cancer.

⁹² See www.perseis.co.nz.

⁹³ See www.breastcancer.org.nz.

Good leadership

Larry Glass has built strong contacts with government people focused on Uncle Sam's biomedical research mission

We have a high regard for the leadership team at Neuren

CEO **Larry Glass**, who runs Neuren from offices in Bethesda, Md, was formerly CEO of SRA Life Sciences, the Virginia-based contract research organisation⁹⁴ which pioneered HIV diagnostic testing in clinical research and clinical trials in the US under his watch. Following on from SRA's background of providing research services to U.S. government agencies, and its groundbreaking work in undertaking the first large, prospective epidemiological study of HIV/AIDS at the US Army's request, Larry has built strong contacts with government people focused on Uncle Sam's biomedical research mission. He is therefore highly skilled at tapping grant revenue as well as collaborating with the NIH and the Army Medical R&D Command. Clearly these skills have proved useful in tapping into Walter Reed funding for the NNZ-2566 trial. We think Larry has the skills to help position NNZ-2566 and Neuren's other compounds for maximum commercial upside.

CMO **Dr Doug Wilson** brings many years working in academia in fields such as haematology, molecular pathology and immunology, as well as many years at the privately held drug German major Boehringer Ingelheim, where he was successively Head of US and then global Head of Medical and Regulatory Affairs. In these latter roles he oversaw multiple drug discovery programmes at all stages of development.

Director of Clinical Operations **Maggie Scott** brings to Neuren around 20 years experience with the Green Lane Coordinating Centre, a New Zealand contract research organisation which has grown over the years through services to the likes of J&J, Merck & Co and GSK⁹⁵.

Director of Preclinical R&D **Dr Mike Bickerdike** formerly led research teams at the UK biotech company Vernalis, whose focus has traditionally been central nervous system drugs⁹⁶. He therefore has experience in preparing products in the same league as NNZ-2566 for an IND filing.

CFO **Rob Turnbull** brings financial skills acquired at PricewaterhouseCoopers in various cities around the world, as well as an understanding of biotech gained initially at the New Zealand biotech Virionyx⁹⁷ prior to his joining Neuren.

The Neuren board, which includes Wilson but not Glass, has the range of skills necessary to build a commercial biotech company.

- **Robin Congreve**⁹⁸ (the Chairman) and **Trevor Scott** bring corporate skills from their respective backgrounds in law and accounting;
- **Dr Graeme Howie** brings product development skills honed from his years at Pfizer⁹⁹;
- **Dr John Holaday** is an experienced biotech veteran, having been involved in a number of start-ups over the years including his current company, QRxPharma¹⁰⁰.

⁹⁴ SRA was acquired in 2000 by Virco, a Belgian company which owned a US diagnostic testing company focused on HIV. Virco in turn was bought by J&J in 2002. Under Larry SRA employed around 250 people and turned over US\$25m pa.

⁹⁵ For example, GLCC participated in trials of J&J's Xarelto blood thinning drug, Merck's Vytorin cholesterol-lowering drug combo and GSK's darapladib drug for the treatment of Acute Coronary Syndrome.

⁹⁶ He was involved, for example, in Vernalis' work on 5-HT_{2c} receptor agonists for the treatment of obesity, a programme which attracted Roche as a collaborator.

⁹⁷ Virionyx had been developing HRG214, a passive immunotherapy drug for the treatment of HIV infection. The company changed its name to Innate Therapeutics in 2009. It is now focusing its passive immunotherapy approach on Multiple Sclerosis.

⁹⁸ Congreve is best known in New Zealand for his taxation law expertise, built up in the country's leading law firm, Russell McVeagh.

⁹⁹ He also has some small company experience, having briefly been CEO of the failed Perth-based cancer drug developer Solbec Pharmaceuticals.

¹⁰⁰ John Holaday was a founder of Medicis, now a highly successful supplier of dermatological products, as well as Entremed, which helped pioneer the science of anti-angiogenesis drugs for the treatment of cancer. For more background on QRxPharma see our comprehensive research note dated 21/9/2011 and headlined 'Near-term immediate release of profits'.

The risks

Biotechnology is risky

The stocks of biotechnology companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology companies in Australia fit this description, the speculative moniker also applies to the entire sector. The fact that biotechnology's intellectual property base lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology ought to be regarded. Investors are advised to be cognisant of this risk before buying any ASX-listed biotech stock including Neuren.

Neuren is not without risk

We see five major risks specifically related to Neuren as a company and a stock:

- 1 **Clinical risk** – There is the risk that Neuren's NNZ-2566 clinical trial could fail in terms of not being able to outperform placebo with statistical significance.
- 2 **Timing risk** – There is the risk that Neuren and the Walter Reed Army Institute of Research could take much longer to complete the NNZ-2566 trial than the roughly two years we have postulated in this note.
- 3 **IP risk** – There is the risk that Neuren could find itself locked in disputes over patent infringement. All key patents (including the composition of matter and oral formulation for NNZ-2566) are issued.
- 4 **Burn rate** – As at June 2011 Neuren had around A\$3m cash, but raised A\$2m in a placement and A\$6.8m in a 1:1 rights issue at 1.3 cents in July. It has burned around A\$650,000 per month since its 2005 IPO and raised A\$52.5m in equity capital since that time. While the burn rate has been cut considerably since then – it now runs at around A\$180,000 per month - Neuren will probably have to raise more capital to fund later stage work on NNZ-2566 and the other elements of its pipeline
- 5 **'SpringTree risk'** - In November 2009 Neuren entered into an agreement in relation to a convertible loan facility from the New York-based SpringTree Global Investors¹⁰¹, an alternative asset management company. The SpringTree facility provided A\$100,000 per month to Neuren through 2010 and A\$60,000 per month in 2011 with those funds converting at 15% discount to market. In addition to the shares issued to pay for this drawdown, Neuren also had to issue one four-year option exercisable at 120% of the conversion price for every new share. In all, the facility yielded Neuren A\$2.26m before it was closed out in June 2011. By that time Neuren had issued 137.5 million shares (12% of the current register, for an average entry price of 1.64 cents per share) and 136.4 million options to SpringTree¹⁰². Since SpringTree has never gone substantial on the Neuren register it appears that it has been a seller of shares although it has yet to exercise any options.

SpringTree's average entry price was 1.64 cents per share

¹⁰¹ See www.springtreegi.com. Neuren's facility was with the SpringTree Special Opportunities Fund.

¹⁰² This included 8.1 million shares as a commitment fee for the facility.

Appendix I – Neuren’s capital structure

The stock. Neuren is only traded on the ASX.

Liquidity. Neuren has traded on 90% of days the ASX is open but volumes are small, with average daily trade value since listing of \$45,000.

Figure 7 - Neuren's capital structure

Shares (ASX Code NEU)	1,141,614,932		Price (c)	1.7
Shares from options options	212,726,662	(18.9% of total)	Undiluted cap (\$m)	19.4
Total diluted shares	1,354,341,594		F.D. Cap (\$m)	23.0
Options schedule	Number	Exercise price	Expiry date	Cash
SpringTree options ¹⁰³	136,420,488	\$0.0247	25-Aug-14	3,374,558
ESOP options	26,000,000	\$0.0300	25-Mar-15	780,000
Other options	50,306,174	\$0.0397	18-Jan-14	1,995,992
Total	212,726,662	\$0.0289	30-Jul-14	6,150,550

SOURCE: NEUREN, BELL POTTER. NOTE, THE EXERCISE PRICE AND EXPIRY DATE OF THE SPRINGTREE AND 'OTHER' ARE AVERAGES. 10,000,000 OF THE 'OTHER' OPTIONS, EXERCISABLE AT 1.54 CENTS BEFORE 6 MAY 2014, ARE HELD BY BELL POTTER.

Figure 8 - Neuren's capital raising history

Date	Shares (million)	% of current shares on issue	Price	Amount raised (\$m)	Discount to market	Type of raising
Feb-05	37.5	3.3%	\$0.400	15.0		IPO
Dec-05	12.0	1.1%	\$0.530	6.4	11.7%	Placement
Sep-06	15.0	1.3%	\$0.400	6.0	4.8%	Placement
Nov-06	4.1	0.4%	\$0.400	1.6	9.1%	SPP
Dec-07	50.7	4.4%	\$0.140	7.1	30.0%	1 for 2 rights issue
Aug-08	11.9	1.0%	\$0.080	1.0	11.1%	Placement
Sep-08	25.6	2.2%	\$0.080	2.1	-14.3%	SPP
Aug-09	27.2	2.4%	\$0.030	0.8	0.0%	SPP
Nov-09 - Jun-11	137.5	12.0%	\$0.016	2.3	32.6%	SpringTree funding
Dec-09	40.3	3.5%	\$0.038	1.5	-8.9%	Placement
May-11	153.8	13.5%	\$0.013	2.0	7.1%	Placement
Jul-11	523.7	45.9%	\$0.013	6.8	21.5%	1 for 1 rights issue
Total	1,039.3	91.0%	\$0.051	52.5	14.2%	

SOURCE: NEUREN, BELL POTTER

Neuren has raised around A\$52.5m since its 2005 IPO on the ASX

¹⁰³ As at the date of this report SpringTree had yet to exercise any of its options. These options represent 10.1% of Neuren's current fully diluted capital.

Appendix II – Comparable companies

We think the best comparables to Neuren are companies which are working on:

- neuroprotection;
- the treatment of stroke;
- therapies for Parkinson's or Alzheimer's that have yet to advance to Phase III.

We have identified eight companies that best fit this description. We think Neuren is currently undervalued compared to this range of comparables.

Figure 9 - Neuren comparables¹⁰⁴

Name	Location	Code	Market cap (USDm)	Web site
Oxygen Biotherapeutics	Morrisville, SC	Nasdaq: OXBT	58.7	www.oxybiomed.com
SYGNIS Pharma	Heidelberg, Germany	FWB: LIOK	42.5	www.sygnis.de
Transition Therapeutics	Toronto, On	Nasdaq: TTHI	41.1	www.transitiontherapeutics.com
BrainStorm Cell	Petah Tikva, Israel	OTCBB: BCLI	39.2	www.brainstorm-cell.com
Phytopharm	Huntington, UK	LSE: PYM	37.3	www.phytopharm.com
ReNeuron	Guildford, UK	LSE: RENE	31.8	www.reneuron.com
Allon Therapeutics	Vancouver, BC	TSX: NPC	15.4	www.allontherapeutics.com
Stem Cell Therapeutics	Calgary, Ab	CVE: SSS	10.0	www.stemcellthera.com

SOURCE: BELL POTTER SECURITIES

Allon Therapeutics was also a victim of the 'CABG cognition hypothesis'

Allon Therapeutics. This company's lead product, a peptide drug called davunetide, is now in a US Phase III under an SPA for an orphan indication called Progressive Supranuclear Palsy (PSP). Davunetide failed in Phase II in August 2008 as a treatment for cognitive decline in CABG patients, around four months before Neuren's Glypromate compound met a similar end. Davunetide and a range of neuroprotectant drugs at the pre-clinical stage of development were identified from two naturally-occurring proteins known to have neuroprotective properties.

BrainStorm Cell Therapeutics. This stem cell company, whose focus is the treatment of CNS disorders such as Parkinson's disease and Lou Gehrig's disease, is based on technology to differentiate marrow-derived mesenchymal stem cells into cells capable of releasing neurotrophic factors, including glial-derived neurotrophic factor (GDNF), making it useful to the treatment of ALS and Parkinson's¹⁰⁵.

Oxygen Biotherapeutics. This company's core Oxycyte technology involves the use of chemicals called perfluorocarbons as delivery agents for oxygen. The company has launched cosmetic indications based on the technology and is also exploring its application in wound healing. Oxycyte, as an intravenous emulsion, is in Phase II in Europe as a treatment for Traumatic Brain Injury.

Phytopharm. This company is working on sapogenin compounds¹⁰⁶ that are neurotrophic factor inducers. Cogane, which stimulates the release of brain-derived neurotrophic factor (BDNF) and GDNF, is in Phase II for the treatment of Parkinson's disease. The drug has also been evaluated in animal models of ALS and of glaucoma.

ReNeuron. This stem cell company has been built on various cell lines that have been immortalised using the c-MycER fusion protein, and that can proliferate after a chemical

¹⁰⁴ Market capitalisations as at 17 October close on Nasdaq and elsewhere.

¹⁰⁵ BrainStorm achieves this differentiation using, among other things, docosahexaenoic acid, an omega-3 fatty acid known to be good for nerve cells.

¹⁰⁶ That is, the non-saccharide, portions of the family of natural products known as saponins.

**Believe it or not,
publicly traded
biotech companies
are still developing
stroke drugs**

constituent of the growth media is removed. The company encapsulates the cells so as to protect them from an immunological response in the recipient, the claim being that this allows them to be used allogeneically. ReNeuron is focused in particular on neural cells, and initiated a Phase I clinical trial in disabled stroke patients in November 2010 that will evaluate changes in both motor and cognitive function over a two year period.

Stem Cell Therapeutics. This company's lead product, NTx-265 for the treatment of acute ischemic stroke, is currently in Phase II. It involves the use of the hormones chorionic gonadotropin¹⁰⁷ and erythropoietin¹⁰⁸, both approved drugs, to stimulate the growth and differentiation of new neurons to replace the brain cells that were lost or damaged by the stroke. The company also wants to work on the application of this technology in Traumatic Brain Injury, while it has evidence that prolactin, the hormone that stimulates milk production after childbirth, may be useful in the treatment of MS.

SYGNIS Pharma. This company's AX200 drug is an analogue of granulocyte colony-stimulating factor (G-CSF)¹⁰⁹ that SYGNIS has found to be neuroprotective and neuroregenerative. The product is in Phase II for the treatment of stroke with potential applications in ALS and spinal cord injury. SYGNIS is also working on KIBRA modulators for the treatment of Alzheimer's¹¹⁰, and SY300, a small-molecule drug designed to induce the differentiation of adult neural stem cells into neurons.

Transition Therapeutics. This company's ELND005 a small molecule drug for the treatment of Alzheimer's disease completed Phase II in 2010. Interesting, while the drug missed its primary outcome in terms of memory, Executive Function and Activities of Daily Living, the drug appeared to demonstrate a biological effect on the target amyloid-beta protein in the cerebrospinal fluid, which has encouraged Transition to plan for a Phase III study. Transition is at a pre-clinical stage on inflammation and diabetes compounds.

¹⁰⁷ Such as Novarel from the Swiss drug company Ferring Pharmaceuticals, used as an ovulation inducer.

¹⁰⁸ Such as Amgen's Epogen drug, used in the treatment of anemia.

¹⁰⁹ Such as Amgen's Neupogen drug, which is used to treat neutropenia since it stimulates the bone marrow to increase production of neutrophils. The drug is also routinely used to increase the number of hematopoietic stem cells in the blood before collection by leukapheresis for use in hematopoietic stem cell transplantation.

¹¹⁰ KIBRA is a gene associated with memory – see Science. 2006 Oct 20;314(5798):475-8.

Appendix III – Neuren’s intellectual property

Neuren’s intellectual property is currently covered by around 29 patent groups.

- 1 **New peptide antagonists at glutamate and NMDA receptors**¹¹¹, WO/ 1994/026301 (Priority date 14/5/1993; Invented by Jean-Pierre Bourguignon for Pharmacia¹¹²)

This patent application covers the use of IGF-I(1-3) as an NMDA receptor antagonist, which, by blocking the excitatory effect of the receptor, theoretically helps prevent brain cell death.

- 2 **Composition and methods to improve neural outcome**¹¹³, WO/ 1995/017204 (Priority date 23/12/1993; Invented by Sir Peter Gluckman and Chris Williams¹¹⁴)

This patent application is the original intellectual property around Glypromate, covering the use of the tripeptide glycine-proline-glutamine (known as GPE, after the traditional symbols for these three amino acids) in inhibiting nerve cell death. Experiment 3 of the patent application demonstrates reduced neuronal damage with GPE administration two hours after brain injury in animal models.

- 3 **Regulation of neural enzymes**, WO/ 1998/014202¹¹⁵ (Priority date 4/10/1996; Invented by Sir Peter Gluckman, Chris Williams and Jian Guan¹¹⁶)

This patent application covers the use of GPE in increasing levels in the CNS of three enzymes - choline acetyltransferase (ChAT), glutamic acid decarboxylase (GAD) and nitric oxide synthase (NOS) – that are lacking in a broad range of CNS disorders from Alzheimer’s (ChAT) to GAD (epilepsy) to stroke (NOS).

- 4 **Neuronal rescue agent**, WO/ 1999/015192 (Priority date 19/9/1997; Invented by Sir Peter Gluckman, Chris Williams, Dahao Wu, Paul Hughes and Maggie Lai)

This patent application covers the use in neuroprotection of a naturally-occurring growth factor called activin.

- 5 **Regulation of tyrosine hydroxylase**, WO/ 1999/065509¹¹⁷ (Priority date 16/5/1998; Invented by Sir Peter Gluckman, Jian Guan and Tajrena Alexi)

This patent application covers the use of GPE in increasing levels in the CNS of an enzyme called tyrosine hydroxylase. Since this enzyme helps turn L-tyrosine into the neurotransmitter DOPA, GPE is potentially useful in the treatment of Parkinson’s Disease, which is caused by a drop in the levels of DOPA in the CNS¹¹⁸.

- 6 **Neuroprotection**, WO/ 2000/013650¹¹⁹ (Priority date 3/9/1998; Invented by Arjan Scheepens¹²⁰, Chris Williams, Sir Peter Gluckman and Ross Clark¹²¹)

This patent application covers the use of growth hormone in neuroprotection.

¹¹¹ This patent was granted in the US as No 5,804,550 in September 1998 and in Europe as EP 0 697 886 in August 2003.

¹¹² This patent was ultimately vended into a Neuren precursor company by Pfizer, which acquired Pharmacia in 2002. The patent reflects work which Bourguignon, an authority on endocrinology at the University of Liège in Belgium, was doing at the time on the use of IGH-I(1-3) to inhibit release of GnRH. See Endocrinology. 1994 Mar;134(3):1589-92.

¹¹³ This patent was granted in the US as Nos 6,187,906 (February 2001 - 15/6/1998 priority), 6,780,848 (August 2004 - 23/12/1993 priority) and 6,812,208 (November 2004 - 23/12/1993 priority).

¹¹⁴ Associate Professor Chris Williams is now doing bionic eye research at the Bionics Institute in Melbourne.

¹¹⁵ This patent was granted in the US as No 6,365,573 in April 2002.

¹¹⁶ Dr Jian Guan does research on insulin-like growth factors at the Liggins Institute.

¹¹⁷ This patent was granted in the US as Nos 6,617,311 in September 2003 and 6,933,282 in August 2005. Granting of US Patent 6,933,282 was announced to the ASX.

¹¹⁸ Scientists working with Neuren have demonstrated that GPE prevents the loss of tyrosine-hydroxylase-positive neurons in rats with OHDA induced nigral lesions, which is an animal model of Parkinson’s (see Brain Res. 2000 Mar 24;859(2):286-92) and can improve functional deficits in those rats (See Neuroreport. 2004 Jul 19;15(10):1601-4).

¹¹⁹ This patent was granted in the US as No 7,304,029 in December 2007.

¹²⁰ Dr Arjan Scheepens is now a senior scientist at the New Zealand Institute for Plant & Food Research.

¹²¹ The late Professor Ross G. Clark was an authority on growth hormone and IGF-I. He led Genentech’s original development of IGF-I and a company he founded, Tercica, gained FDA approval in 2005 for Increlex, which was IGF-I in-licensed from Genentech. Tercica was bought by the French drugmaker Ipsen in 2008 for ~US\$400m.

- 7 **GPE analogs**, WO/ 2002/016408¹²² (Priority date 24/8/2000; Invented by Sir Peter Gluckman and Tajrena Alexi)

This patent application covers the use of analogues to GPE in neuroprotection, where each amino acid in GPE is replaced by others that are roughly equivalent.

- 8 **Treatment of demyelinating diseases**, WO/ 2002/030447 and WO/ 2002/030447¹²³ (Priority date 12/10/2000; Invented by Geoff Krissansen¹²⁴ and Jagat Kanwar¹²⁵)

These patent applications¹²⁶ basically cover the use of GPE in treating multiple sclerosis. In MS lymphocytes from the immune system attack the myelin sheath that encloses and protects the axons of nerve cells, damaging nerve function. In 2000 American researchers¹²⁷ found, in animal models of MS, that they could reduce glutamate-induced myelin destruction using drugs which block the AMPA/kainate receptors, located on the oligodendrocytes which produce myelin. This patent application demonstrates that GPE is synergistic with AMPA/kainate receptor blockers, presumably because the tripeptide inhibits glutamate binding to the receptors as well.

- 9 **Functional proteomics using double phage display screening**, WO/ 2002/046754 (Priority date 8/12/2000; Invented by Robert Gilmour and Keith Marvin)

This patent application covers the use of standard phage display techniques to identify proteins of interest. It arises from the interest Neuren's scientists had in identifying proteins that respond to IGF-I.

- 10 **Anti-GPE antibodies, their uses, and analytical methods for GPE**¹²⁸, WO/ 2002/074245 (Priority date 16/3/2001; Invented by Greg Thomas, Bernhard Breier and David Batchelor)

This patent application covers antibodies to GPE, which can be used for diagnostic purposes and can potentially boost the half-life of GPE by preventing the tripeptide from degradation or non-specific binding.

- 11 **Regulation of weight**, WO/ 2002/076208¹²⁹ (Priority date 23/3/2001; Invented by Tajrena Alexi)

This patent application covers the use of GPE's neuroprotective and neuromodulatory properties in driving weight gain for people who are underweight due to a CNS disorder. Weight loss is a problem in head injury patients¹³⁰.

- 12 **GPE analogs and peptidomimetics**, WO/ 2002/094856¹³¹ (Priority date 24/5/2001; Invented by Norman Abood and Margaret Brimble¹³²)

This patent application is similar to WO/ 2002/016408 above however instead of simply proposing amino acid swaps in the GPE tripeptide it involves the substitution of synthetic analogues. WO/ 2002/094856 is the composition of matter patent application for G-2Methyl-PE, which is Neuren's NNZ-2566 molecule. The patent application's example demonstrates that the G-2Methyl-PE¹³³, has comparable neuroprotection to GPE.

The composition of matter patent for NNZ-2566 has a 2001 priority date

¹²² This patent was granted in the US as No 7,112,570 in September 2006.

¹²³ This patent was granted in the US as No 7,192,931 in March 2007.

¹²⁴ Associate Professor Geoff Krissansen leads the Molecular and Cellular Biology Group at The University of Auckland.

¹²⁵ Associate Professor Jagat Kanwar is now at Deakin University in Australia, focused mainly on immunology research.

¹²⁶ The second of these two applications added an anti-inflammatory to the GPE+kainite inhibitor combination.

¹²⁷ See Nat Med. 2000 Jan;6(1):67-70.

¹²⁸ This patent was granted in the US as No 7,282,342 in October 2007.

¹²⁹ This patent was granted in the US as No 6,682,753 in January 2004.

¹³⁰ See Neurosurgery. 1985 Nov;17(5):784-91.

¹³¹ This patent was granted in Europe as EP 1 401 808 in July 2009 and in the US as Nos 7,041,314 (May 2006), 7,605,177 (October 2009), 7,714,020 (May 2010) and 7,863,304 (January 2011). Granting of US Patent 7,041,314 was announced to the ASX.

¹³² Professor Margaret Brimble is the Chair of Organic and Medicinal Chemistry at the University of Auckland. She continues to consult to Neuren.

¹³³ The exact synthesis method is not described in the Examples section of the patent application, however it is disclosed in U.S. Patent 7,605,177 (Example 2). The drug is made by alpha methylation of the proline moiety (see J Neurol Sci. 2009 Mar 15;278(1-2):85-90. Epub 2009 Jan 20). For a description of how Neuren creates GPE analogues generally, see three papers published by the Neuren scientists in the journal Bioorganic & Medicinal Chemistry (Bioorg Med Chem. 2005 Jan 17;13(2):501-48).

- 13 Neuroprotection and/or neurorestoration via the neural Activin Type IIb receptor**, WO/ 2003/000281 (Priority date 22/6/2001; Invented by Paul Hughes, John Fernandez and Sumit Raniga)
- This patent application covers the use of the ActRIIB receptor, which appears to mediate the neuroprotective function of the activin protein covered in WO/ 1999/015192.
- 14 Use of Insulin-Like Growth Factor I for promoting remyelination of axons**, WO/ 2003/049761 (Priority date 12/8/2000; Invented by Jian Guan, Alistair Gunn, Laura Bennet and James Egan)
- This patent application is similar to WO/ 2002/030447 but instead of GPE covers the use of whole IGF-I in treating MS.
- 15 Neuroprotective macrocyclic compounds and methods for their use**, WO/ 2004/084809 (Priority date 20/3/2003; Invented by Paul Harris and Margaret Brimble)
- This patent application covers synthetic GPE analogues with neuroprotective properties where one end of the peptide analogue is bound to the other to create a large ring structure. The company demonstrates two neuroprotective macrocyclic compounds, one called '48' and another called '68'.
- 16 Somatogenic therapy using a 20kda placental growth hormone variant**, WO/ 2005/018659 (Priority date 20/8/2003; Invented by Sir Peter Gluckman, Stewart Gilmour, Mark Vickers¹³⁴ and Bernhard Breier¹³⁵)
- This patent application covers placental growth hormone as an alternative to conventional growth hormone therapy (which is pituitary growth hormone), the disadvantage of the latter being its lactogenic effect¹³⁶.
- 17 Neuroprotective bicyclic compounds and methods for their use¹³⁷**, WO/ 2005/023815 (Priority date 3/9/2003; Invented by Margaret Brimble, Jian Guan and Frank Sieg¹³⁸)
- This patent application covers a number of diketopiperazine compounds including cyclic glycyl-2-allyl proline, that is, NNZ-2591 (see WO/ 2008/063311 and WO/ 2011/037644 below).
- 18 Neuroprotective effects of gly-pro-glu following intravenous infusion**, WO/ 2005/042000 (Priority date 23/10/2003; Invented by Jian Guan, Greg Thomas, David Batchelor and Sir Peter Gluckman)
- This patent application, which describes the pharmacokinetics of GPE, covers both infusions and bolus injections of the tripeptide.
- 19 GPE and G-2MePE, caffeine and alkanol for treatment of CNS injury**, WO/ 2005/097161 (Priority date 30/3/2004; Invented by James Grotta¹³⁹ and Sir Peter Gluckman)
- This patent application covers the combination of Glypromate, NNZ-2566, and caffeine¹⁴⁰ in the recovery of sensory motor function after a stroke.
- 20 Non-diabetogenic therapy using a 20kda placental growth hormone variant**, WO/ 2006/012525 (Priority date 23/7/2004; Invented by Sir Peter Gluckman, Stewart Gilmour and Mark Vickers)

¹³⁴ Dr Mark Vickers does research on metabolic diseases at the Liggins Institute.

¹³⁵ Professor Bernhard Brier has the Chair of Human Nutrition at Massey University in New Zealand.

¹³⁶ Which can potentially cause gynecomastia, that is, male breast enlargement.

¹³⁷ This patent was granted in the US as No. 7,776,876 in August 2010. Neuren's scientist's had previously filed for patent protection over *Cyclo(Prolyl-Glycine) and methods of use to treat neural disorders* (WO/ 2003/039487, priority date 11/9/2001) but dropped this application in favour of WO/ 2005/023815.

¹³⁸ Dr Frank Sieg works on developmental neurobiology at The Liggins Institute. He is Chief Scientist of CuroNZ, which is commercialising the Neural Regeneration Peptide technology that had been developed by Neuren between 2005 and 2008.

¹³⁹ Dr James Grotta chairs the University of Texas Medical School at Houston's Department of Neurology. He has served on Neuren's Scientific Advisory Board. The work that went into this patent was done at Houston. See *Stroke*. 2005 Jan;36(1):129-34. Epub 2004 Nov 29.

¹⁴⁰ A combination of caffeine and ethanol known to have neuroprotective properties (see *Stroke*. 2003 May;34(5):1246-51. Epub 2003 Apr 10).

This patent application is similar to WO/ 2005/018659 but covers an additional benefit from placental growth hormone variant, namely, that it does not interfere with the activity of insulin, a common side effect of conventional growth hormone therapy¹⁴¹.

- 21 **Trefoil factors and methods of treating proliferation disorders using same**, WO/ 2006/069253 (Priority date 22/12/2004; Invented by Peter Lobie¹⁴²)

This patent application covers peptide antagonists and interfering RNA molecules to Trefoil Factors 1 and 3 as a treatment for tamoxifen-resistant breast cancer.

- 22 **Method for treating apathy syndrome**, WO/ 2006/113937 (Priority date 20/4/2005; Invented by Albert Cha¹⁴³)

This patent application covers Neuren's Motiva drug, that is, the use of the old Daiichi compound nefiracetam in the treatment of apathy.

- 23 **Analogs of glycyl-prolyl-glutamate**¹⁴⁴, WO/ 2006/127702 (Priority date 23/5/2005; Invented by Margaret Brimble, Paul Harris and Frank Sieg)

This patent application covers a library of GPE analogues beyond those covered in WO/ 2002/094856.

- 24 **Oral formulations of glycyl-2-methylprolyl-glutamate**¹⁴⁵, WO/ 2007/106555 (Priority date 14/3/2006; Invented by Jingyuan Wen, Greg Thomas and Mike Bickerdike)

This patent application covers Neuren's orally available version of NNZ-2566.

- 25 **Infusion pump**, WO/ 2007/119178 (Priority date 23/1/2006; Invented by Suded Emmanuel and Chris Williams)

This patent application covers Neuren's wireless controlled implantable micropump system, which allows precise delivery of small volumes of drug directly into the brain.

- 26 **Conformation-specific antibodies that bind trefoil factors and methods of treating cancers and proliferation disorders using same**, WO/ 2008/042435 (Priority date 3/10/2006; Invented by Peter Lobie)

This patent application is similar to WO/ 2006/069253 above but focuses on monoclonal antibodies to Trefoil Factors 1 and 3.

- 27 **Cyclic glycyl-2-allyl proline improves cognitive performance in impaired animals**, WO/ 2008/063311 (Priority date 11/10/2006; Invented by Mike Bickerdike and Jian Guan)

This patent application covers the use of Neuren's cyclic glycyl-2-allyl proline diketopiperazine (NNZ-2591), first covered in WO/ 2005/023815, in treating cognitive impairment.

- 28 **Conformation specific antibodies that bind trefoil factors**, WO/ 2009/147530 (Priority date 6/6/2008; Invented by Peter Lobie)

This patent application provides more monoclonal antibodies for Trefoil Factor 1 than were covered in WO/ 2008/042435.

- 29 **Cyclic glycyl-2-allyl proline and its use in treatment of peripheral neuropathy**, WO/ 2011/037644 (Priority date 25/9/2009; Invented by Mike Bickerdike, Margaret Brimble and Ernest Sirimanne)

This patent application covers the use of Neuren's cyclic glycyl-2-allyl proline diketopiperazine (NNZ-2591), first covered in WO/ 2005/023815, in the treatment of peripheral neuropathy.

¹⁴¹ Growth hormone suppresses the abilities of insulin to, firstly, stimulate uptake of glucose in peripheral tissues and, secondly, enhance glucose synthesis in the liver.

¹⁴² Professor Peter Lobie heads the breast cancer research group at the Liggins Institute.

¹⁴³ Dr Albert Cha is Managing Partner of Vivo Ventures of Palo Alto, Ca, a venture capital firm which was an early investor in Hamilton Pharmaceuticals.

¹⁴⁴ This patent was granted in the US as No. 7,863,304 in January 2011.

¹⁴⁵ This patent was granted in the US as No. 7,887,839 in February 2011.

Appendix IV – The story of Glypromate

An important aspect of understanding the Neuren story today is Glypromate, which was Neuren's lead product from its 2005 IPO up until its clinical failure in December 2008, and from which Neuren has derived what we regard as a much better compound, NNZ-2566.

Glypromate is derived from Insulin-like Growth Factor I

Glypromate is a neuroprotective compound

The scientific story for Glypromate begins with IGF-I. The Insulin-Like Growth Factor I is a hormone similar in structure to insulin whose job within the body is to promote cell growth and multiplication by binding to various IGF receptors to be found on the surface of cells. Back in the late 1980s scientists at the Karoliska Institutet in Sweden, intrigued by the fact that a slightly truncated IGF-I could be found in the human brain, figured out that a peptide made up of the leftmost three amino acids in the hormone¹⁴⁶ - a glycine, a proline and a glutamate - would boost release of the neurotransmitter acetylcholine¹⁴⁷, which in turn could play an important role in boosting brain function¹⁴⁸. Later on, at the University of Auckland, the laboratory of one of New Zealand's better known biomedical researchers, Professor Sir Peter Gluckman¹⁴⁹, whose background is paediatrics and endocrinology, spent a good deal of the 1990s studying this mysterious tripeptide, renamed Glypromate¹⁵⁰.

The early work on Glypromate was promising. What was special about Glypromate was that, *in vitro* as well as in animal experiments modelling a variety of brain impairment states, the tripeptide demonstrated that it played a serious role in neuroprotection:

- The drug enhanced survival of CA1-2 hippocampal neurons following an excitotoxic insult *in vitro*¹⁵¹.
- In lab rats suffering hypoxic-ischemic brain injury, there was much less cell death in Glypromate-treated rats¹⁵²;
- Glypromate was shown to be effective in neuroprotection following stroke, with reduced brain damage following microsphere-induced embolic damage in rats¹⁵³;

Glypromate was more than a glutamate antagonist. Gluckman et. al. spent a lot of time thinking about how Glypromate did its neuroprotection thing. The team knew from the earlier Swedish work that their tripeptide was a partial glutamate antagonist, which made it potentially useful in neuroprotection because, as we noted previously, injured brains tend to accumulate an excessive amount of glutamate. That said, having a glutamate antagonist was nothing to write home about, because by the turn of the 21st Century other glutamate antagonists with names like eliprodil, selfotel and aptiganel¹⁵⁴ had already been tried without success as potential neuroprotectants, in good measure because of the side effects involved. No, Glypromate's potential went way beyond battling the evil forces of

¹⁴⁶ Technically, the 'N-terminal tripeptide' of IGF-I.

¹⁴⁷ See *Biochem Biophys Res Commun.* 1989 Dec 15;165(2):766-71, and some later work by researchers at the University of Uppsala (*Neuroreport.* 1993 Sep;4(9):1111-4).

¹⁴⁸ See *Ann N Y Acad Sci.* 1993 Aug 27;692:183-91.

¹⁴⁹ Sir Peter helped build the University of Auckland into a world leader in the areas of developmental endocrinology and neuroscience. He was the founding director in 2001 of Auckland's Liggins Institute (www.liggins.auckland.ac.nz), a large-scale research institute focused on perinatology. Sir Peter was named the New Zealand Prime Minister's Chief Science Adviser in 2009.

¹⁵⁰ The Auckland team originally called it GPE (after the initials biologists use to denote the three amino acids involved - 'E' is glutamate because 'G' is already taken by glycine) before giving it the much more euphonious name of Glypromate (GLYcine-PROline-glutaMATE).

¹⁵¹ See *Neuroreport.* 1999 Jan 18;10(1):161-4.

¹⁵² This grew out of Sir Peter's interest in paediatrics. Hypoxic-ischemic brain injury is what happens to infants when complications in pregnancy or a difficult birth cuts off the flow of blood and oxygen to the baby's brain, resulting in varying degrees of brain damage. Compared to the controls Glypromate engineered a statistically significant reduction in cortical damage and neuronal loss in the CA1 and CA2 subregions of the hippocampus. Importantly, it helped reduce the loss of neurons in the striatum containing the neuronal enzymes ChAT and GAD and the hormone somatostatin. It also boosted the number of neurons in the striatum containing the enzyme NOS. Consequently Glypromate, as well as being neuroprotective, appears to have a favourable influence on neuronal activity after hypoxic-ischemic injury. See *Neuroscience.* 1999 Mar;89(3):649-59.

¹⁵³ See *Neurosci Lett.* 2009 Apr 17;454(1):53-7. Epub 2009 Mar 5.

¹⁵⁴ All NMDA receptor antagonists - see *Lancet Neurol.* 2002 Oct;1(6):383-6.

Glypromate cut down on apoptosis in animal models of brain damage

glutamate, even if the drug was naturally occurring in the brain and therefore not a big chance of having side effects.

Glypromate had a favourable effect on glial cells as well as neurons. What was really exciting about Glypromate was that the drug binds to glial cells, and not to neurons, in the white matter tracts, the cortex and the striatum¹⁵⁵. Glial cells, which in the brain outnumber neurons ten to one, are, if you will, the neurons' support network - they don't communicate nerve signals but they repair and maintain neurons and they clean up the mess when a neuron dies.

- One type of glial cell called the astrocyte seemed to be helped by Glypromate, which was encouraging among other things because astrocytes help regulate neurotransmitter levels in the brain.
- Another kind of glial cell, the microglia, whose ordinary role is to run the brain's special immune system and which seem to go out of control in cases of brain impairment, were, apparently, down-regulated by Glypromate.
- Glypromate cut down on apoptosis of neurons, that is, the 'naturally-occurring' death of these cells¹⁵⁶.

Glypromate had other favourable qualities, namely

- *It could be effective for a long time after brain injury*, working well for up to 7 hours after the injury event via intravenous infusion. As we understand it, other compounds struggled to do any good after about three hours.
- *It was small*. Being only a string of three amino acids, it was likely to be cheap to make and easy to store, and would be so small that it would easily slip above the blood brain barrier, that biochemical Berlin Wall that keeps the brain somewhat safe from bad stuff going on in the rest of the body¹⁵⁷.

Neuren worked on Glypromate between 2000 and 2008. Neuren's precursor company NeuronZ was funded in 2000 in order to take over the relevant intellectual property of Glypromate and develop it. As its first project NeuronZ chose to investigate Glypromate's potential to prevent cognitive decline following a Coronary Artery Bypass Graft, and to that end the drug entered Phase I in 2004. The 2005 IPO on the ASX of Neuren was intended to fund the CABG indication into later stage trials, and it was a Phase III CABG trial where Glypromate failed in December 2008.

CABG was the wrong model in which to study Glypromate

CABG was supposed to lead to substantial cognitive decline in patients. Coronary Artery Bypass Graft, or 'CABG'¹⁵⁸ commonly known as 'heart bypass' surgery, is a surgical treatment for coronary artery disease¹⁵⁹ that has been performed since the 1960s. In the mid-2000s it represented a large market opportunity, with ~350,000 CABGs performed in US hospitals in 2003¹⁶⁰, even though the procedure was in decline¹⁶¹. CABG is a lengthy procedure – generally 4 to 6 hours – and traditionally the procedure has involved stopping the heart and providing blood supply to the rest of the body via cardiopulmonary bypass (CPB), an artificial circulation system¹⁶². Even with CPB there were understood to be frequent shortfalls in oxygen supply to the brain resulting in noticeable cognitive decline for

¹⁵⁵ See Brain Res. 2001 Dec 13;922(1):42-50.

¹⁵⁶ For the astrocyte, microglial and neuronal apoptosis evidence see Neuropharmacology. 2004 Nov;47(6):892-903.

¹⁵⁷ While the aforementioned Neuropharmacology paper established Glypromate's availability above the blood brain barrier, another paper (Neuropeptides. 2005 Apr;39(2):81-7. Epub 2005 Jan 28) showed that the drug could get above the blood-brain barrier after intraperitoneal administration, and its half life could be extended by peptidase inhibitors.

¹⁵⁸ Pronounced 'cabbage', as in, the cultivated plant, *Brassica oleracea*.

¹⁵⁹ The coronary arteries are those which supply heart muscle with oxygen-rich blood. Coronary artery disease is the buildup of plaque inside the coronary arteries, leading to occlusion or blockage. In CABG a section of vein, usually from the patient's leg, is used to create an alternative pathway for blood to reach the heart muscle.

¹⁶⁰ Source: Agency for Healthcare Research and Quality, Procedures in U.S. Hospitals, 2003.

¹⁶¹ The US rate per head of the adult population declined 38% between 2001 and 2008 due in part to the increasing popularity of stenting. See JAMA. 2011 May 4;305(17):1769-76.

¹⁶² More recently doctors have started to perform 'off pump' CABGs in which the heart is left beating.

CABG proved to be the wrong setting in which to trial Glypromate

the patients in the months after the operation. For example, one study published in the New England Journal of Medicine in 2001¹⁶³, estimated that more than 50% of CABG patients saw a substantial decline in at least one measure of cognitive function at surgical discharge¹⁶⁴, while around 25% of patients remained similarly impacted at six months post-surgery. Going into Glypromate's Phase III trial Neuren took the view that 'almost 70% of patients who have cardiac surgery with cardiopulmonary bypass experience cognitive decline at discharge and up to 35% of patients' exhibit cognitive impairment three months after the operation'¹⁶⁵. Neuren had expected that Glypromate, administered to patients at the end of their surgery, would protect patients against such cognitive decline. It didn't happen.

The bad news - there wasn't much cognitive decline for control patients in Glypromate's Phase III trial. In December 2008 it was Neuren's melancholy duty to inform the market that of the 325 CABG patients evaluated at 12 weeks, 'only a small proportion (approximately 20%) evidenced any degree of cognitive decline at 12 weeks and, among those with decline, the average change was small. Approximately 80% of patients in both the placebo and Glypromate groups actually showed improvement in cognitive function'¹⁶⁶. In other words, not enough brain damage resulted from CABG for Glypromate to make a difference. Apart from bad luck¹⁶⁷, we suggest several reasons for this sub-optimal (from Neuren's perspective) result:

- *Neuren's trial was performed at centres with better outcomes.* Neuren's trial centres were generally more prestigious and therefore busier centres¹⁶⁸. For CABG the busier the centre, the better the outcome for the patient¹⁶⁹, meaning that there was likely to be less cognitive decline in Neuren's patients than if they were treated at relatively unprestigious hospitals.
- *Neuren's study may have measured cognitive decline differently to others,* there being no uniform criteria for assessing cognitive decline¹⁷⁰.
- *CABG may generate less cognitive decline today than in the past.* A good rule of thumb with any surgical procedure is that surgeons as a group get better at performing it over the years. That appears to be the case with CABG, with rates of strokes in CABG patients having steadily declined since the late 1980s¹⁷¹. There may have been a comparable improvement in cognitive decline outcomes since the NEJM study we cited above, which drew data from the years 1989 to 1993¹⁷².
- *CABG may have always generated less cognitive decline than many people thought.* The wide divergence in estimates of cognitive decline¹⁷³ have suggested to some that the cognitive decline traditionally associated with CABG may in fact be cognitive decline associated with cardiovascular disease¹⁷⁴, in which case CABG was definitely the wrong clinical model in which to study Glypromate.

¹⁶³ See N Engl J Med. 2001 Feb 8;344(6):395-402.

¹⁶⁴ ie >20%, which is roughly one standard deviation. The study measured four 'domains' of cognitive function.

¹⁶⁵ Source: Neuren market release, 31/5/2007. We have not been able to identify all the peer-reviewed sources for these estimates however they fit with scientific consensus (see Acta Cardiol. 2010 Oct;65(5):557-64). The Octopus Study, which compared the three month cognitive outcome of 'off-pump' versus 'on pump' CABG, found declines of 21% and 29% respectively (see JAMA. 2002 Mar 20;287(11):1405-12)

¹⁶⁶ Source: Neuren market release, 24/12/2008. That's right – Neuren delivered the bad news to the market on Christmas Eve. The stock fell from 5 cents to 1.1 cents before that day's traditional early close.

¹⁶⁷ Meaning, in this instance, recruitment of the 'wrong' patients. There is emerging evidence that postsurgical cognitive outcomes for CABG vary depending on the patient. For example, the patient's number of years of education may be inversely correlated with cognitive decline while a patient's living alone may be positive correlated (see Ann Thorac Surg. 2004 Feb;77(2):597-603).

¹⁶⁸ The first patient, for example, was treated at the Christ Hospital in Cincinnati, Oh, which is ranked the 50th best hospital in the US for cardiology and heart surgery using the well-regarded US News and World Report methodology (2011-12 survey).

¹⁶⁹ See Health Aff (Millwood). 2007 Jan-Feb;26(1):162-8.

¹⁷⁰ See Ann Thorac Surg. 1996 May;61(5):1342-7.

¹⁷¹ See JAMA. 2011 Jan 26;305(4):381-90.

¹⁷² Although no two published studies have comparable measurement criteria to make this assessment.

¹⁷³ From 20 to 70% at discharge and from 10-40% at six weeks. See Acta Cardiol. 2010 Oct;65(5):557-64.

¹⁷⁴ Cognitive decline seems to be the same for patients with comparable risk factors for coronary artery disease not undergoing surgery (see Ann Thorac Surg. 2003 May;75(5):1377-84), suggesting that whatever cognitive decline related to surgery is relatively mild and resolves within two-to-three months. One group has estimated 'true' CABG-generated cognitive decline could be as low as 8% at three months (see Acta Anaesthesiol Scand. 2005 Oct;49(9):1232-5).

Glypromate-treated patients had a much lower death rate

The good news – less deaths in the Glypromate group may be evidence of neuroprotection. So it's fair to say that the Glypromate Phase III was a disaster. There was, however, one intriguing piece of data from the trial. The death rate for the Glypromate group was only 0.59% versus 3.59% for placebo. While that was not statistically significant ($p=0.067$) it potentially suggests that Glypromate was neuroprotective, and that the drug improved CABG survival by lowering the level of stroke and therefore stroke-related mortality¹⁷⁵.

NNZ-2566 is a better drug than Glypromate with a better trial setting

Since Glypromate's failure, Neuren has been developing NNZ-2566, a synthetic analogue of Glypromate, as its new lead molecule. We regard Neuren's prospects as much better for this drug:

- Looking at the available data, we believe NNZ-2566 has performance characteristics more or less equivalent to what is known about Glypromate¹⁷⁶, although there is some evidence that the new drug may be superior¹⁷⁷.
- The trial setting, in Traumatic Brain Injury, is clearly one in which true neuroprotective compounds can make a difference¹⁷⁸
- The new drug has a much better half-life and blood concentrations than Glypromate.

¹⁷⁵ Interestingly, serum levels of IGF-I fall after CABG (see J Endocrinol Invest. 2005 Sep;28(8):711-9) while IGF-I is known to be cardioprotective (see Proc Natl Acad Sci U S A. 1995 August 15; 92(17): 8031–8035).

¹⁷⁶ Compare, for example, NNZ-2566's performance in hypoxic-ischemic brain injury at 0.3 mg/kg (see Example 4 of U.S. Patent 7,605,177, data estimated from Figure 16A) with Glypromate's performance at the same dose (See table 2 in Example 7 of WO/2005/042000). We estimate that Glypromate reduced neural damage scores in the striatum, various regions of the hippocampus (CA1-2, CA3, and the dentate gyrus) and the cortex by 64%. The comparable performance by NNZ-2566 was 69%.

¹⁷⁷ Guan and Gluckman (Br J Pharmacol. 2009 July; 157(6): 881–891) argue that NNZ-2566 is '*more potent in neuroprotection*' than Glypromate, citing a 2004 rat study (Stroke. 2005;36:129–134) that looked at neuroprotection after MCAo, where a dose of NNZ-2566 one tenth the size of the Glypromate dose was still neuroprotective compared to placebo, and where this dose was synergistic with caffeine whereas Glypromate was not. Guan and Gluckman also cite work from 2007 showing that NNZ-2566 could bring about reduced overall brain injury seven days after hypoxic-ischemic brain injury in neonatal rats, in part because of vascular remodeling. (Dev Neurosci. 2007;29(4-5):393-402).

¹⁷⁸ See Example 4 of U.S. Patent 7,605,177, filed 20/12/2005.

Appendix V – Some of the science behind Motiva

There have been around 119 papers published on Motiva since 1992

There have been around 119 papers published on Motiva since 1992. Below is a selection of some of the more interesting papers:

Hiramatsu et. al., *European Journal of Pharmacology*, June 1992. This paper showed that Motiva could boost memory acquisition and consolidation in rats through boosting cholinergic neuronal function. *Eur J Pharmacol.* 1992 Jun 5;216(2):279-85.

Nishizaki et. al., *Molecular Pharmacology*, January 1998. This paper showed the mechanism of action for Motiva as a cognition enhancer, which involves activation of two signal transduction pathways. *Mol Pharmacol.* 1998 Jan;53(1):1-5.

Yamada et. al., *British Journal of Pharmacology*, January 1999. This paper showed that Motiva could improve β -amyloid-(1-42)-induced learning and memory impairments in rats, suggesting that it may be useful in the treatment of Alzheimer's. *Br J Pharmacol.* 1999 January; 126(1): 235-244.

Nishizaki et. al., *Brain Research*, May 1999. This paper showed that Motiva could strengthen synapses to the point where they could be considered to have reached 'long-term potentiation'. *Brain Res.* 1999 May 1;826(2):281-8.

Nishizaki et. al., *Molecular Brain Research*, August 2000. This paper showed that Motiva could facilitate hippocampal synaptic transmission by targeting nicotinic acetylcholine receptors, strengthening the case that the drug would work against Alzheimer's. *Brain Res Mol Brain Res.* 2000 Aug 14;80(1):53-62.

Itoh et. al., *Behavioural Brain Research*, October 2000. This paper showed that Motiva could play a role in ending morphine dependence or tolerance. *Behav Brain Res.* 2000 Oct;115(1):65-74.

DeFord et. al., *Pharmacology Biochemistry and Behavior*, July 2001. This paper showed that Motiva could improve cognitive function in rats following Traumatic Brain Injury. *Pharmacol Biochem Behav.* 2001 Jul-Aug;69(3-4):611-6.

Rashid and Ueda, *Journal of Pharmacology and Experimental Therapeutics*, October 2002. This paper showed that Motiva had analgesic properties potentially useful in neuropathic pain. *J Pharmacol Exp Ther.* 2002 Oct;303(1):226-31.

Takeo et. al., *British Journal of Pharmacology*, February 2003. This paper showed that Motiva preserved cognitive function, or prevented cognitive dysfunction, after sustained cerebral ischemia. *Br J Pharmacol.* 2003 Feb;138(4):642-54.

Ueda et. al., *Journal of Pharmacology and Experimental Therapeutics*, April 2004. This paper showed that Motiva could prevent both necrosis and apoptosis in ischemic/hypoxic neuronal injury. *J Pharmacol Exp Ther.* 2004 Apr;309(1):200-7. Epub 2004 Jan 12.

Kitano et. al., *Epilepsia*, June 2005. This paper showed that Motiva was an effective anticonvulsant comparable to UCB's Keppra drug. *Epilepsia.* 2005 Jun;46(6):811-8.

Moriguchi et. al., *Molecular Pharmacology*, February 2007. This paper showed that Motiva potentiates NMDA receptors, further evidence of its potential use in Alzheimer's. *Mol Pharmacol.* 2007 Feb;71(2):580-7. Epub 2006 Nov 9.

Han et. al., *Brain Research*, April 2009. This paper showed that Motiva could improve depressive behaviours in rats and suggested a mechanism of action for this. *Brain Res.* 2009 Apr 10;1265:205-14. Epub 2009 Feb 21.

Appendix VI – Failed neuroprotection drugs

Drugs like Cerovive and Cerestat have led to stroke being described as a drug 'graveyard'

Selfotel (CGS-19755), Ciba-Geigy¹⁷⁹, December 1995. This NMDA receptor antagonist failed in both stroke and TBI¹⁸⁰.

Eliprodil (SL-820715), Synthelabo¹⁸¹, February 1996. This NMDA receptor antagonist failed to show benefit in a sequential analysis of the first 483 stroke patients enrolled in a Phase II/III trial¹⁸².

ProSynap (Lubeluzole), J&J, May 1998. This drug, which acts on extracellular glutamate, didn't work to improve stroke outcomes when measured by neurological status (European Stroke Scale), functional outcome (Barthel Index) or disability level (Rankin Scale)¹⁸³.

Ceraxon (citicoline), Interneuron Pharmaceuticals¹⁸⁴, January 2000. This drug, which strengthens brain cell membranes¹⁸⁵, failed in Phase III on its primary endpoint (NIHSS improvement), but succeeded in its secondary endpoint (Rankin Scale improvement)¹⁸⁶.

Gavestinel (GV-150526), GSK, June 2000. This NMDA receptor antagonist performed about as well as placebo when measured using the Barthel Index in a 1,800 patient trial¹⁸⁷.

Cervene (Nalmefene), IVAX¹⁸⁸, June 2000. This opioid receptor antagonist, traditionally used in the management of alcohol dependence, was considered a good stroke candidate because of its apparent ability to decrease excessive neuronal excitation. It didn't outperform placebo on either the Barthel Index or the Glasgow Outcome Scale¹⁸⁹.

Cerestat (aptiganel), Boehringer Ingelheim, December 2001. This NMDA receptor antagonist¹⁹⁰, failed in Phase III after showing no improvement using the Modified Rankin Scale¹⁹¹. It suggested that glutamate blockade may have detrimental effects.

Magnesium, UK Medical Research Council, February 2004. Magnesium is a NMDA receptor blocker, however it failed to improve outcomes for stroke patients in the aforementioned 2,600 patient Intravenous Magnesium Efficacy in Stroke trial.

Cerovive (NXY-059), AstraZeneca, October 2006. This free radical scavenger¹⁹² failed in a second Phase III in stroke patients after a first had shown reduced disability in the treated patients using the Modified Rankin Scale. The second trial showed no difference with placebo¹⁹³.

¹⁷⁹ Ciba-Geigy, a Swiss company, was a Novartis precursor.

¹⁸⁰ See J Neurosurg. 1999 Nov;91(5):737-43.

¹⁸¹ Synthelabo, a French drug company, was a Sanofi-Aventis precursor.

¹⁸² See Synthelabo's Eliprodil Fails In Stroke Trials, the pharmaletter, 12/2/1996.

¹⁸³ See Cerebrovasc Dis. 1998 May-Jun;8(3):172-81.

¹⁸⁴ This company changed its name to Indevus in 2003. It was later acquired by Endo Pharmaceuticals for US\$370m and US\$267m in sales milestones. By then the company's lead compound was Nebido, for the treatment of hypogonadism.

¹⁸⁵ It is a naturally-occurring precursor to phosphatidylcholine, a phospholipid.

¹⁸⁶ See Neurology. 2001 Nov 13;57(9):1595-602.

¹⁸⁷ See Lancet. 2000 Jun 3;355(9219):1949-54.

¹⁸⁸ IVAX was a US generic drug maker bought by TEVA in 2006.

¹⁸⁹ See Stroke. 2000 Jun;31(6):1234-9.

¹⁹⁰ It was originally developed by Cambridge Neurosciences and licensed to Boehringer Ingelheim. Cambridge Neurosciences was bought by CeNeS Pharmaceuticals in 2000, which in turn was bought by PAION AG, the German biotech company, in 2008.

¹⁹¹ See JAMA. 2001 Dec 5;286(21):2673-82.

¹⁹² Originally developed by Centaur Pharmaceuticals, which had collaborated with AstraZeneca since 1995. Centaur was acquired by Renovis in 2002, and that company in turn was bought by the German drug discovery company Evotec in 2007.

¹⁹³ For the initial results announcement see 'AstraZeneca announces SAINT II trial results showed no efficacy in acute ischaemic stroke', AstraZeneca press release, 26/10/2006. For the trial results see N Engl J Med. 2007 Aug 9;357(6):562-71.

Appendix VII – A Neuren glossary

Agonist – A drug that stimulates or enhances activity of cell receptors.

Alzheimer's disease (also called presenile dementia) – A brain disorder that affects parts of the brain that control thought, memory, and language.

Amino – A nitrogen-based organic compound derived from ammonia (NH₃) in which one or more of the hydrogens are replaced by a side chain. Amino acids, of which there are twenty occurring naturally, are the building blocks of proteins.

Analogue – A drug that resembles a naturally-occurring substance.

Antagonist – A drug that blocks the action of a particular receptor.

Antibodies – Immune system proteins that can bind to an antigen and help to neutralise the potentially harmful effects of the cells carrying the antigen. Antibodies are commonly used in drug therapy for this reason.

Apathy Syndrome – Lack of motivation, initiative or enthusiasm, as well as low variety of expression, often resulting from stroke.

Apoptosis – 'Programmed' cell death, that is, death that is naturally-occurring.

Astrocyte – A glial cell which helps regulate neurotransmitter levels in the brain.

Autism spectrum disorder – A developmental disability with similar symptoms to autism. Rett's Syndrome is considered an autism spectrum disorder.

Axon – An extension of a neuron responsible for nerve transmission. Axons are sheathed in myelin.

Bax – A pro-apoptosis protein.

Bcl2 – An anti-apoptosis protein.

CABG – Short for Coronary Artery Bypass Graft, that is, 'heart bypass' surgery.

CA1, CA2 – Two subregions of the hippocampus.

Caspase 8 – An effector of apoptosis.

Central Nervous System (CNS) – The brain and the spinal column, which is mostly made up of nerve cells.

Choline acetyltransferase (ChAT) – A neuronal enzyme that makes the neurotransmitter acetylcholine, important for functions such as muscle contraction, the regulation of heart rate and learning. In Alzheimer's disease ChAT is less active than in non-Alzheimer's brains.

Cortex – The outermost part of the brain, where all the important mental processes occur.

Cytokines – Molecules in the human body that regulate inflammation. TNF is a cytokine.

Diketopiperazines – Cyclic organic compounds that result from peptide bonds between two amino acids to form a lactam. They are the smallest possible cyclic peptides. NNZ-2591 is a diketopiperazine.

Endpoint – The outcome or outcomes that a clinical trial is designed to evaluate, such as disease progression or death. Generally clinical trials have primary and secondary endpoints.

Excitatory neurotransmitter – A neurotransmitter designed to turn up the frequency on other nerve system signals.

FDA – The Food and Drug Administration, the American government body which regulates the pharmaceutical industry and from whom approval must be received before a drug can be marketed in the US.

Fast Track – An FDA designation that accelerates the approval of investigational new drugs. Companies with drugs on the Fast Track receive more frequent meetings and written correspondence with the FDA.

Free radicals – Molecules with unpaired electrons that have to combine with complementary molecules before they become stable. If a free radical bonds with a positive charge molecule, its charge is neutralised. Oxygen in the free radical form can damage cells in the body in a process called oxidative stress.

G-2Methyl PE – See NNZ-2566.

GABA – Short for Gamma Amino Butyric Acid, an inhibitory neurotransmitter that is the subject of a number of anti-epilepsy drugs.

GAD – See Glutamic acid decarboxylase.

Glasgow Coma Scale – A measure of consciousness that ranges between 3 (indicating deep unconsciousness) and either 15 (full conscious), evaluated using tests of the ability to open eyes, speak and move. Patients suffering severe TBI have GCS scores between 4 and 8 while patients with moderate TBI have GCS scores of 9 to 12.

Glial cells – Cells that surround and support neurons.

Glutamate – A salt or ester of glutamic acid. Glutamate is an excitatory neurotransmitter.

Glutamic acid – One of the amino acids, common abbreviation E (because G is already taken by glycine).

Glutamic acid decarboxylase (GAD) – An enzyme that makes the neurotransmitter GABA.

Glycine – An amino acid, common abbreviation G.

Glypromate – Neuren's name for IGF-1(1-3). The name comes from GLYcine-PROline-GlutaMATE.

GPE – Another name for Glypromate, which comes from the common abbreviations for each of the amino acids in the tripeptide – Glycine (G), Proline (P) and Glutamate (E).

Growth hormone – A peptide hormone that stimulates growth, cell reproduction and regeneration.

Hippocampus – A part of the brain information for memory and spatial navigation.

Hypoxic-ischemic injury – Brain damage caused by reduced blood flow to the brain (ischemia) as well as reduced brain oxygen (hypoxia). This can be modelled in rats and mice by tying up one of the carotid arteries and then placing them in a chamber with low levels of oxygen.

IGF-1(1-3) – The first three amino acids in Insulin-like growth factor 1. Neuren initially trialled IGF-1(1-3) as Glypromate but is now focused on a Glypromate derivative called NNZ-2566.

IND – Short for Investigational New Drug, an FDA designation of a drug that has been approved for clinical trials in the US.

Infarct – A localised area of dead tissue resulting from failure of blood supply.

Inhibitory neurotransmitter – A neurotransmitter designed to turn down the frequency on other nerve system signals, so as to keep recipient nerve cells from being overwhelmed with too much information.

Insulin-like Growth Factor I (IGF-I) – A protein similar to insulin that plays a role in growth and metabolism. Glypromate is the first three amino acids of IGF-I.

Interleukins – Cytokine important in the process of inflammation.

INTREPID-2566 – The current Phase II clinical trial of NNZ-2566.

Ischemia – Restriction in blood supply to tissue.

Macrocyclic – A drug with a large ring structure.

Microglia – Specialised cells which provide the brain with its own immune system by attacking and engulfing foreign bodies.

Middle Cerebral Artery occlusion (MCAo) – The most frequently used model in experimental stroke research, in which a blockage is placed inside the middle cerebral artery, stopping blood flow into the cerebral area.

Modified Rankin Scale – A measure of stroke disability.

Monoclonal antibody – An antibody specific to a single target.

Motiva – A Neuren drug, generic name nefiracetam, for the treatment of Apathy Syndrome in stroke victims as well as Parkinson's and Alzheimer's patients.

Myelin – The protein which surrounds and protects the axons.

NDA – Short for New Drug Application, a filing with the FDA asking for marketing approval of a drug.

Nefiracetam – The generic name for Motiva.

Neonatal asphyxia – Inability to breath at birth by a newborn infant, often resulting in brain damage.

Neuromodulation – Alteration of nervous system activity, often achieved through drugs.

Neurons – Nerve cells or brain cells.

Neuroprotection – The ability to keep brain cells from dying when stressed.

Neurotransmitters – Chemicals that neurons use to communicate with each other.

NH&MRC – The National Health and Medical Research Council, an Australian government agency that provides grants to medical research.

Nitric oxide synthase (NOS) – An enzyme that helps make nitric oxide, a cellular signalling molecule.

NMDA receptor – A brain cell receptor normally triggered by glutamate. Over-excitation of the NMDA receptor has also been shown to cause nerve damage.

NNZ-2566 – A Neuren drug for the treatment of Traumatic Brain Injury that is a synthetic analogue of Glypromate. NNZ-2566 is G-2Methyl PE. Neuren has worked on intravenous and oral formulations of NNZ-2566. As well as TBI, Neuren believes the drug can be used in stroke recovery as well as in Rett Syndrome.

NNZ-2591 – A diketopiperazine drug developed by Neuren for the treatment of Parkinson's disease and peripheral neuropathy.

Non-convulsive seizure – A brain seizure characterised by behaviour such as staring, lapses of awareness and abrupt loss of muscle tone, but no convulsion.

NOS – See Nitric oxide synthase.

Orally available – Drugs that can be reduced to pill form with obvious advantages in terms of delivery to patients.

Orphan Drug – A drug that benefits less than 200,000 potential patients in the US. Orphan drug designation provides tax benefits as well as market exclusivity.

Oxidative stress – Cell damage that results from oxygen-linked free radicals.

Parkinson's disease – A neurodegenerative disease associated with a drop in dopamine levels. Parkinson's is characterised by tremors, speech impediments, movement difficulties, and often dementia.

Penetrating TBI – TBI resulting from penetration into the brain area of an object such as a bullet or a knife.

Peptides – Strings of amino acids.

Peripheral neuropathy – Damage to the peripheral nervous system, that is, the nerves outside of the brain and spinal cord.

Perseis Therapeutics – A Neuren subsidiary developing monoclonal antibodies to breast and other cancers.

Pharmacokinetics – The way in which the body absorbs, distributes, metabolises and excretes a drug.

Phase I – A clinical trial in humans to test safety in a small sample.

Phase I/II – An early-stage safety study (a Phase I study) but one conducted in patients rather than in healthy volunteers.

Phase II – A clinical trial in humans to test efficacy in a small sample.

Phase III – A clinical trial in humans to test efficacy in a large sample.

Proline – An amino acid, common abbreviation P.

Reperfusion – The return of blood supply to tissue after a period of ischemia.

Reprofiling – The process of taking a drug that has failed in one indication and retrialing it in another where it has shown promise.

Rett Syndrome – An autism spectrum disorder that affects only girls.

Special Protocol Assessment (SPA) – A declaration by the FDA that a pivotal trial's clinical endpoints are acceptable for FDA approval of the drug. It effectively ensures that the FDA can't change its mind with regard to approval and ask for further data when the final results of the trial come in.

Striatum – A brain region known to be important for learning and that governs habitual actions.

Stroke – Brain damage which results from blockage of an artery (acute 'ischemic stroke') or, less commonly, from breakage of a blood vessel ('hemorrhagic strokes'), interrupting blood flow to an area of the brain.

TBI – See Traumatic Brain Injury.

TNF- α – Short for Tumour Necrosis Factor alpha, a pro-inflammatory cytokine.

Transient ischemic attack – Often called a 'mini stroke', a transient episode of neurologic dysfunction caused by loss of blood flow to the brain but without tissue death.

Traumatic Brain Injury – The loss of cognitive function that results from a blow to the head. Traumatic brain injury is classified as mild, moderate, or severe.

Trefoil Factors – Estrogen-regulated proteins secreted by cancer cells that act as growth factors to the cancer. Neuren has developed antibodies to Trefoil Factors 1 and 3.

Tripeptide – A peptide made up of three amino acids. Glypromate is a tripeptide.

WRAIR – Walter Reed Army Institute of Research.

White matter – The part of the brain mostly containing myelin, as opposed to grey matter, which contains mostly neuronal cell bodies and glial cells.

Neuren Pharmaceuticals

COMPANY DESCRIPTION

Neuren Pharmaceuticals (ASX: NEU), based in Bethesda, Md, is a drug discovery company focused on drugs to treat disorders of the Central Nervous System. The company is in Phase II with Motiva, for the treatment of post-stroke apathy, and with NNZ-2566, for the treatment of Traumatic Brain Injury. The company is also doing pre-clinical work on NNZ-2591 as a potential treatment for Parkinson's disease and peripheral neuropathy, as well as monoclonal antibodies for the treatment of breast and other cancers.

INVESTMENT STRATEGY

We see the market marking up Neuren as Motiva and NNZ-2566 near the end of their Phase II trials, and as awareness grows of the interest of key opinion leaders in NNZ-2566 as the Next Big Thing in Traumatic Brain Injury. We also expect that a favourable partnering outcome for NNZ-2566 could lead to a significant re-rating of the stock.

VALUATION

We value Neuren on a probability-weighted DCF valuation at 12 cents base case and 21 cents optimistic case. Our 12 cent price target sits at the low point of this valuation range.

RISKS

We see the main risk in Neuren as being clinical risk – that the current Phase II trials of Motiva and NNZ-2566 fail to meet their primary endpoints. A second risk is timing, with the potential for Neuren to not recruit for the trials at the pace at which we are expecting. A third risk is burn rate – Neuren has burned around A\$650,000 per month since its 2005 IPO and raised A\$52.5m in equity capital since that time. While the burn rate has been cut considerably since then – it now runs at around A\$180,000 per month - It will probably have to raise more capital to fund later stage work on NNZ-2566 and the other elements of its pipeline. A fourth risk is the risk that the New York-based SpringTree, which funded the company through a convertible note facility between late 2009 and mid-2011, may choose to be a seller of its shares and options in the company, which could depress the share price.

Recommendation structure

Spec Buy: Expect >30% total return on a 12 month view but carries significantly higher risk than its sector

Buy: Expect >15% total return on a 12 month view

Accumulate: Expect total return between 5% and 15% on a 12 month view

Hold: Expect total return between -5% and 5% on a 12 month view

Reduce: Expect total return between -15% and -5% on a 12 month view

Sell: Expect <-15% total return on a 12 month view

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Bell Potter Securities holds 10 million Neuren options exercisable at 1.54 cents by 6 May 2014.