PITT STREET RESEARCH

Nyrada Inc

Cholesterol drug pioneer

Share Price: A$0.20

ASX: NYR
Sector: Healthcare
5 November 2020

Nyrada is a preclinical stage, drug discovery, and development company specialising in novel small molecule drugs to treat cardiovascular, neurological, and inflammatory diseases. The Company has two main programs, in cholesterol lowering and brain injury, each targeting market sectors of significant size and considerable unmet clinical need.

A potential cholesterol drug breakthrough

PSCK9 inhibitors are potent drugs that lower LDL cholesterol. Two PSCK9 inhibitors are already on the market, but both are expensive monoclonal antibodies where cost and inconvenience are causing market resistance. Nyrada is aiming to develop a first ever oral, small molecule PCSK9 inhibitor with the convenience and cost-competitiveness of a pill that the market is seeking.

A neuroprotectant for brain injury

Neuroprotectant drugs can potentially be given in the days following a stroke or sustaining head trauma, to block a process known as excitotoxicity. This wave of death of brain cells that propagates from the initial injury can more than double the final size of the area of brain death. Excitotoxicity accounts for much of the long-term disability suffered by brain injury victims and currently, there are no effective treatments. Nyrada aims to be the first pharma to develop a drug capable of addressing this large unmet health need.

Three-to-five-year turnaround

Nyrada's business model is to focus on discovery and early-stage development (Phase I/IIa), and, after safety has been confirmed and an efficacy signal obtained, sell the intellectual property or partner the program within three to five years.

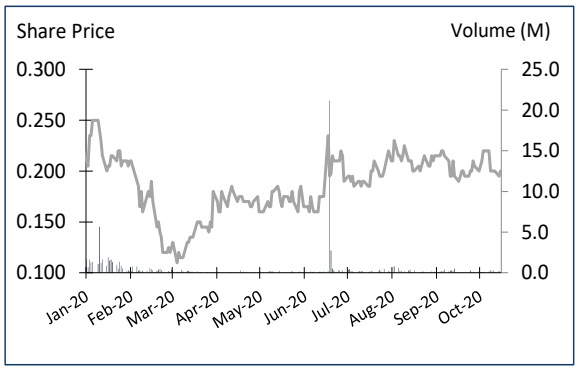
Undervalued on our numbers

We value Nyrada on a probability-weighted risk-adjusted DCF basis at A$0.51 per share base case and A$0.96 per share optimistic case. We see Nyrada being re-rated by the market as the business progresses its cholesterol lowering and brain injury programs into clinical trials. Key risks we see in Nyrada are 1) risk that the company's products may fail to meet the primary or secondary end-points in the clinical studies, 2) funding risk, 3) company taking longer than expected to get to the clinic, and 4) regulatory risk.

Market Cap. (A$ m)	21.3
# shares outstanding (m)	109.4
# share fully diluted	168.6
Market Cap Ful. Dil. (A$ m)	33.7
Free Float	55% (45% escrowed)
12-month high/low	A$0.11 - A$0.37
Avg. 12M daily volume ('1000)	281
Website	nyrada.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (M, r.h.s.)



Source: Thomson Reuters, Pitt Street Research

Valuation metrics	
Fair valuation (A$)	0.51 – 0.96
WACC	15.0%
Assumed terminal growth rate	None

Source: Pitt Street Research

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Introducing Nyrada Inc (ASX: NYR)

Nyrada is an early-stage drug development company. It was formed by Noxopharm in 2017 and registered as a new company around three non-oncology projects, including one developed by a company connected with ex-Noxopharm and now Nyrada director, Ian Dixon. Nyrada subsequently raised A$4m in new capital via a convertible note issue in February 2018 and then raised $8.5 in its 2020 IPO at a pre-money valuation of $13.4m. There currently are four programs, one concerned with cardiovascular disease, one with neuroprotection, and two with chronic inflammatory diseases.

A PCSK9 inhibitor for lowering cholesterol. PSCK9 inhibitors are usually used in combination with commonly prescribed statin drugs to lower LDL or "bad" cholesterol levels. Statins are suboptimal as a treatment in about half of all patients who take them, largely because of a countering effect of the blood protein, PCSK9. Two PSCK9 inhibitors are already on the market, but both are expensive monoclonal antibodies where cost and inconvenience are causing market resistance. Nyrada is aiming to develop a first-ever oral, small molecule PCSK9 inhibitor with the convenience and cost-effectiveness that the market is seeking. We see the early development of a PCSK9 inhibitor as having the potential to drive significant increases in shareholder value, with large interest by the global pharmaceutical industry in what up to recently was the single largest drug sector in the world, with global annual sales of cholesterol-lowering drugs reaching US$45bn.

A neuroprotectant for brain injury. Neuroprotectants can potentially be given in the days following head trauma or stroke to block a process known as excitotoxicity, which is a wave of death of brain cells that propagates out from the initial injury resulting in a much larger area of brain damage. Excitotoxicity affects survivability and accounts for much of the long-term disability suffered by TBI and stroke victims. Currently, there are no FDA-approved treatments for TBI, with only limited treatment options available for stroke. Nyrada aims to be the first pharma to develop a drug capable of addressing this large unmet health need.

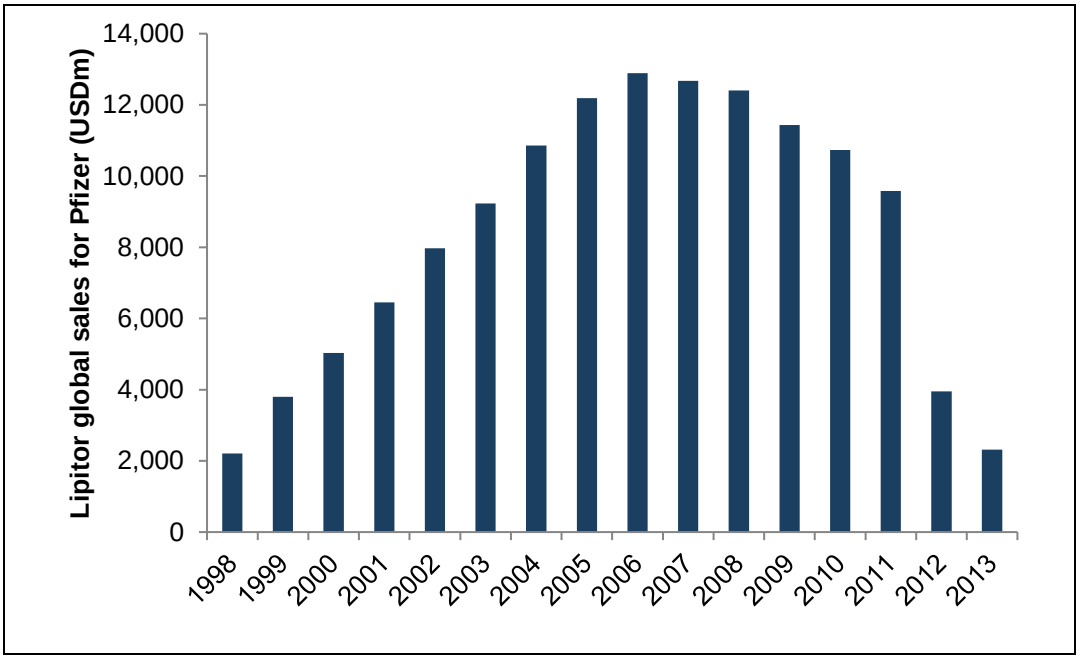
An anti-inflammatory for peripheral nerve pain. NYX-205 is being developed to treat pain associated with damage to peripheral nerves. This is an area of considerable unmet need, with a large range of diseases known as peripheral neuropathies associated with pain and loss of nerve function. Sciatica is a common example of peripheral neuropathic pain.

Another drug for chronic inflammatory diseases. This early-stage discovery program is aiming to develop a drug against the protein IRAK4, recently identified as a key player in diseases such as psoriasis, lupus, and rheumatoid arthritis.

NYX-PCSK9i – A new cholesterol-lowering agent

Nyrada's PCSK9 inhibitor, research code NYX-PCSK9i, offers enormous opportunity as a cholesterol-lowering agent. Nyrada's front-line drug development program, formerly known as NYX-330, has the potential to become one of the 'Next Big Things' in cardiovascular drug development. The statin class of cholesterol-lowering drugs, typified by Pfizer's blockbuster Lipitor®, made billions for their developers because of the huge number of people in most advanced industrial countries with high LDL-cholesterol (so-called 'bad' cholesterol) levels (Figure 1). At about the same time that the patent for Lipitor lapsed and generic statins became available in 2011, the pharmaceutical industry was handed a lifesaver with the discovery of a blood protein known as PCSK9. The role of PCSK9 in the body is to keep LDL-cholesterol in the blood, the very opposite of what statins are trying to do. And it was found that if you blocked the action of PCSK9 at the same time as giving a statin, suddenly the statins worked a great deal better, including in the 50% of patients where statins don't work all that well[1]. Suddenly a whole new drug class was born with the promise of replicating the annual US$45bn market we saw before the generic statins became available.

Figure 1: Lipitor Global Sales for Pfizer (US$M)



Source: Pfizer

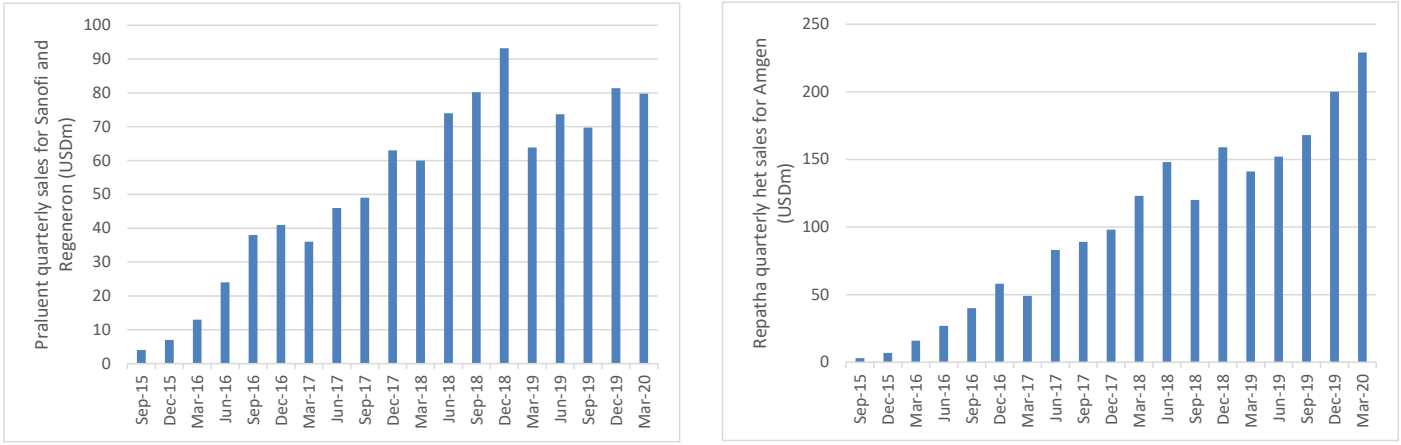
[1] A recent British study showed that half the patients have a 'suboptimal' response to statin therapy (defined as <40% reduction in 24 months) – see Heart. 2019 Jul;105(13):975-981. Epub 2019 Apr 15. A Finnish study found that about 68% of patients with ACS who are treated with statins failed to achieve guideline LDL-C over two years (Leskeläa et. al., Atherosclerosis Volume 296, March 2020, Pages 4-10)

Pfizer's Lipitor was a US$12.9bn drug at its peak

Two PCSK9 inhibitors came to market in 2015 to great fanfare. But they came with two major downsides 1) high cost (>US$5,000 p.a. per patients in the US), and 2) inconvenience, in the form of biweekly or monthly injections on top of statin treatment for most patients. The opportunity for NYX-PCSK9i lies in it being a potentially cheap to manufacture small molecule that can be combined with a statin in an orally administered pill.

The demand for better anti-cholesterol treatments remains high. High levels of LDL-cholesterol in the blood are accepted as a major risk factor for cardiovascular disease (heart attack and stroke) and is still the major cause of premature death in the developed world[2]. The reason the statins became bestsellers after their introduction in the 1980s[3] – Pfizer's Lipitor enjoyed peak sales of US$12.9bn in 2006[4] – was simple: Over 33% of all US adults, representing more than 70 million people in the years 2005-2008, had high LDL-cholesterol[5] and with statin treatment usually able to reduce levels into the normal range. But here's the problem: in about 50% of cases, statins don't drop LDL-cholesterol to a level that minimises the risk of cardiovascular disease, particularly where the clinical guidelines moved towards the "lower is better" paradigm. On top of this, it is estimated that up to 15% of patients cannot tolerate statins because of side-effects[6], meaning that they either have to stop using them or they need to reduce the statin dose to a much lower level.

Figure 2: Quarterly sales for Sanofi and Regeneron (LHS) and Amgen (RHS) (US$M)



Source: Sanofi, Regeneron, Amgen

[2] If we all were sufficiently disciplined to lead a blameless lifestyle (good diet, lots of exercise, no tobacco or alcohol, and no obesity), then we would not need cholesterol-lowering drugs. But discipline is not a developed world's strong point, so we have an ongoing need for drugs to lower LDL-cholesterol levels.

[3] The first was Merck & Co.'s lovastatin, FDA approved in September 1987.

[4] At the time it was the biggest-selling drug ever. Lipitor's peak was surpassed in 2015 by AbbVie's Humira drug for the treatment of rheumatoid arthritis.

[5] MMWR Morb Mortal Wkly Rep. 2011 Feb 4;60(4):109-14.

[6] Arch Med Sci. 2015 Mar 16;11(1):1-23. Epub 2015 Mar 14.

PSCK9 inhibitors have been the Next Big Thing in anti-cholesterol therapy

PCSK9 inhibitors make statin therapy work better. The PCSK9 inhibitors are meant to be used in combination with statins to boost their effectiveness, in particular in helping the roughly 50% of statin users achieve their target LDL-cholesterol levels, or in allowing statin-intolerant individuals to use lower dosages of statins in combination with a PCSK9 inhibitor. Cholesterol is an essential compound in the body, forming an important structural element of many tissues. The liver is central to cholesterol metabolism and to maintaining a healthy level of LDL-cholesterol in blood via two opposite functions - on the one hand, making cholesterol and putting into the blood in the form of LDL particles, and on the other hand, removing the LDL particles from the blood. PCSK9 plays a role in the removal of LDL-cholesterol by acting as a handbrake on the liver's capacity to remove it from the bloodstream[7]. The statins work by blocking the liver's ability to make cholesterol.[8] One consequence of this is now known to be the body compensating to lower levels of cholesterol in the blood by increasing levels of PCSK9[9]. Thus, statins effectively are giving with one hand and taking with the other. It was no surprise to find therefore that adding a PCSK9 inhibitor to statin therapy can lower LDL-cholesterol by an additional 50% to 70%.[10]

Disappointing sales for the currently approved PCSK9 inhibitors open the door for Nyrada's program

The PCSK9 inhibitors were seen as the next boom in LDL-cholesterol therapy. As we noted above, the first two PCSK9 inhibitors were both FDA approved in 2015. They were Praluent™[11] from Sanofi and Regeneron, in July and Amgen's Repatha™[12] in August (Figure 2). In each case, the main approval was for patients with heterozygous familial hypercholesterolemia (HeFH), an inherited condition in which the body produces dangerously high levels of LDL-cholesterol. Only around one in 250 adults in the US, or ~800,000 people, have HeFH[13], an estimated <1% of the total market for people likely to benefit from LDL-cholesterol lowering therapy. Sales in 2019 of Repatha and Praluent were US$661m and US$289m respectively[14]. And while many drugs would be regarded as successes if they achieved those sales figures, in the context of the cholesterol-lowering market, they are considered to be highly disappointing.

There has not been widespread uptake of Repatha and Praluent. Despite those drugs being approved by the FDA to prevent heart attacks and strokes in patients with established cardiovascular disease, there has not been widespread uptake of Repatha and Praluent, including in people with HeFH, with the main reason being cost. Both drugs were placed on the market at a price in excess of US$14,000 p.a.[15], a reflection of their higher clinical effectiveness as highly targeted monoclonal antibody drugs, and the higher cost of their production[16]. Both suppliers have recently halved the price of the drugs[17] but there remains the problem of delivery – as monoclonal antibodies, they need to be injected every two to four weeks for life (by a nurse, with self-injection at home generally not allowed) with injection site problems not uncommon. The market generally understands that greater market penetration is going to require a considerably lower-priced and more convenient-to-use medication.

[7] Short for Proprotein Convertase Subtilisin/Kexin type 9, PCSK9 was first discovered in the early 2000s – see Proc Natl Acad Sci U S A. 2003 Feb 4;100(3):928-33. Epub 2003 Jan 27.
[8] J Cell Mol Med. 2001 Oct-Dec;5(4):378-87.
[9] Lipids Health Dis. 2008 Jun 11;7:22.
[10] For the ODYSSEY Phase 3 studies of Praluent, see Future Cardiol. 2016 Mar;12(2):115-28. Epub 2016 Jan 20. For the RUTHERFORD-2 Phase 3 study of Repatha, see Lancet. 2015 Jan 24;385(9965):331-40. Epub 2014 Oct 1.
[11] Generic name alirocumab, see praluent.com.
[12] Generic name evolocumab, see repatha.com.
[13] Cardiol Clin. 2015 May; 33(2): 169–179.
[14] The growth in 2019 was strong for Repatha but Praluent declined by 6%.
[15] See *These Cholesterol-reducers may save lives. So why aren't heart patients getting them?* by Gina Kolata, the New York Times, 2 October 2018.
[16] Chemical Engineering Science, Volume 141, 17 February 2016, Pages 63-74.
[17] See *Amgen tones down TV ad for Repatha with disco music and wedding revelry* by Beth Snyder Bulik, FiercePharma, 22 April 2019.

Nexletol® does not represent a threat to PCSK9 in the long run. With FDA approval in January 2020 of Nexletol, from a US drug developer called Esperion[18], doctors have the first oral, once-daily, non-statin LDL-C lowering medicine since 2002. Nexletol was approved for heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) where more lowering of LDL-C is needed. Nexletol, which is bempedoic acid, inhibits ATP citrate lyase, a key enzyme in the cholesterol biosynthesis pathway that works upstream of HMG-CoA which is the target of the statins. The drug, however, is underwhelming – not only is it still expensive, at US$300 a month, it also doesn't lower cholesterol by all that much (only 17% when taken alone[19]) and comes with an increased risk of gout.

The early pre-clinical work on NYX-PCSK9i has been promising

NYX-PCSK9i represents a potential small-molecule alternative to the PCSK9 monoclonal antibodies. Nyrada, with its small molecule alternative, believes it can bring to market a lower cost, orally available alternative to the monoclonal antibody drugs. Repatha and Praluent were developed because early attempts as developing a classic small molecule to block PCSK9 were unsuccessful. The problem lay in the surface of the PCSK9 protein being seen to be too flat to provide a binding site for a small molecule.[20] The challenge of coming up with a small molecule has attracted various research groups[21], with a Melbourne-based company, Cardio Therapeutics Pty Ltd, using proprietary software to come up with a breakthrough. Nyrada acquired Cardio Therapeutics in 2017 and continued the development program, eventually filing a patent on a novel family of compounds that inhibit PCSK9 function in early 2018[22]. The fact that Big Pharma would find Nyrada's programme intriguing is suggested by AstraZeneca's recent acquisition of a preclinical oral PCSK9 inhibitor programme from a private company called Dogma Therapeutics [23].

NYX-PCSK9i is currently being optimised. Nyrada announced in August 2018 that NYX-330, the first generation PCKS9 inhibitor, had performed well in various laboratory tests of effectiveness, including a dose-response reduction in LDL-cholesterol levels in the treated mice as a monotherapy[24]. In July 2020 Nyrada announced that an *ex vivo* study in human white blood cells had shown increased efficacy compared to Praluent and Repatha in terms of an increase in LDL receptors

NYX-1010 - a neuroprotection drug useful in stroke and head trauma

NYX-1010 may reduce the rehabilitation time of stroke and TBI victims

NYX-1010 intends to ameliorate the long-term effects following acquired brain injury such as from a stroke or traumatic brain injury (TBI). NYX-1010 is a small molecule drug that the company believes could markedly reduce the degree of brain damage associated with stroke and TBI. A neuroprotectant is not intended to repair the primary damage from acquired brain injuries – instead, it is meant to improve survivability and reduce the severity and extent of disability following a stroke or TBI. The key aim is to

[18] Ann Arbor, Mi., Nasdaq: ESPR, esperion.com
[19] N Engl J Med . 2019 Mar 14;380(11):1022-1032.
[20] Acta Pharmacol Sin. 2017 Mar; 38(3): 301–311.
[21] Bioorg Med Chem Lett. 2018 Apr 15;28(7):1155-1160. Epub 2018 Feb 26.
[22] *Heterocyclic inhibitors of PCSK9*, WO/2018/165718, priority date 17 March 2017, invented by Herbert Treutlein, Jun Zeng, Ian Dixon, Ian James, and James Palmer. His initial compound targets five amino acids in PCSK9- 212, 221, 223, 258 and 263.
[23] See the AstraZeneca press release dated 17 September 2020 and headlined '*AstraZeneca acquires oral PCSK9 inhibitor programme from Dogma Therapeutics*'.
[24] See Bioorg Med Chem. 2020 Mar 15;28(6):115344. Epub 2020 Jan 31.

reduce rehabilitation times and lower the 65% incidence of stroke survivors who are permanently disabled[25], many requiring rest-of-life assisted living.

Strokes are commonplace. A stroke is a 'brain attack' that results from the brain's blood supply being cut off. Most strokes (i.e. >80%[26]) are 'ischaemic' strokes where a blood clot blocks the blood flow[27]. Less common are 'hemorrhagic' strokes where a blood vessel feeding the brain bursts. Strokes are commonplace in the Western world - there are ~7.2 million stroke survivors in the US alone, their number rising regularly due to the 800,000 stroke cases in the US every year, of which ~600,000 are first-time strokes.[28]. Most stroke survivors – one estimate suggests around two in three – will be permanently disabled in some way[29]. We estimate the global market for a new stroke drug would be >US$4bn p.a.

Brain injury following TBIs. In the US, it is estimated that around 2.8 million people sustain a TBI annually and approximately 10% of these are related to sports and recreational activities in young people under 19 years[30,31]. For military service members a TBI is typically caused in combat by a blast or penetrating ballistic (bullets/shrapnel) injury. In the last 20 years, over 400,000 service members had suffered a TBI[32].

Stroke and TBI involve two regions of brain cell death. The first region is the primary injury area. The primary injury results from a blood clot (83 - 85% of all strokes) or rupture of a blood vessel in the brain, and in TBI, results from mechanical trauma to the head. In both injuries, a region of the brain is deprived of oxygen and blood. This area of the brain dies within minutes of the injury and never recovers. The area immediately surrounding the primary injury is known as the 'penumbra' region; it has some, albeit reduced, blood supply and is a mix of dead, dying, and struggling brain cells. This penumbra region is the secondary injury area that spreads out from the primary injury over the next 5-7 days, eventually producing an area of brain death over twice the size of the original injury. The primary injury to the brain is irreversible, however, the penumbra region can be salvaged with treatment that blocks secondary brain damage. This reduction in secondary injury should significantly reduce the resultant loss of life and loss of function in patients suffering from stroke or TBI.

Nyrada's therapy would address the excitotoxicity process. The only FDA-approved treatment for stroke aims to restore blood flow via clot-busting drugs or surgical removal of the clot. To have any chance of success, these treatments need to be given no more than 4.5 hours after a stroke, the result of which is less than 15% of stroke patients receiving the treatment in time. Nyrada aims to reduce the secondary brain damage and the expansion of the penumbra as much as possible, thereby 1) increasing the likelihood of full recovery, 2) shortening rehabilitation times, and 3) reducing the global economic burden. Nyrada's neuroprotectant drug is targeting a cellular hallmark of secondary brain injury known as excitotoxicity.

What is excitotoxicity? Brain cells (neurons) transmit their electrical signals to other neurons via junction boxes known as synapses. Each neuron is connected to hundreds of other neurons, with electrical impulses crossing

[25] Stroke. 1997 Mar;28(3):531-6.
[26] S D Med. 2014 Nov;67(11):455, 457-61, 463-5.
[27] Where this kind of stroke is minor it is called a Transient Ischemic Attack or TIA.
[28] American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135:e229-e445.
[29] Stroke. 1997 Mar;28(3):531-6.
[30] Centres for Disease Control and Prevention. *TBI: Get the Facts*. 2019; Available from: https://www.cdc.gov/traumaticbraininjury/get_the_facts.html.
[31] BrainLine. *Get the Stats on Traumatic Brain Injury in the United States*. 2017; Available from: https://www.brainline.org/article/get-stats-traumatic-brain-injury-united-states
[32] https://dvbic.dcoe.mil/dod-worldwide-numbers-tbi

those synapses via chemicals known as neurotransmitters[33]. The main neurotransmitter is glutamate, which works by causing levels of calcium ions (Ca^{2+}) to rise in the receiving neuron, with this rise in Ca^{2+} triggering an electrical impulse. A neuron's immediate response to damage (e.g. being deprived of oxygen) is to dump its stores of neurotransmitters into its synapses, creating excessive levels of neurotransmitters that result in catastrophically high levels of Ca^{2+} that over-excite the receiving neurons to death[34]. The death of these previously undamaged neurons then repeats this over-excitement process, creating a wave of cell death that runs over 5-7 days before it eventually runs out of steam. This wave of cell death, secondary to the original stroke, is referred to as excitotoxicity and can result in an area of brain death as much as double the size of the original injury. Currently, there is no effective neuroprotective treatment to prevent excitotoxicity.

NYX-1010 has been designed to block excessive Ca^{2+} build-up in cells

Preventing excitotoxicity by blocking cellular calcium entry. For many years drug developers, seeking drugs to prevent excitotoxicity, looked at blocking the ability of the glutamate released into the synapses to activate the glutamate receptors in the synapses[35]. While this did dampen the excitotoxicity process by blocking Ca^{2+} levels from rising catastrophically in damaged neurons, these drugs also blocked normal neurotransmission in all brain cells[36], leading to unacceptable toxicity. Unlike these drugs, the Nyrada drug family blocks Ca^{2+} channels downstream of the glutamate receptors, which are not critical to normal brain function thereby hopefully avoiding the toxic side-effects that others have encountered.

Preclinical studies. The initial proof-of-concept study was performed with Nyrada's first-generation compound NYX-104, which was shown to block Ca^{2+} build up in cells through a collaboration between Nyrada and a research team led by Prof. Gary Housley, Director of the Translational Neuroscience Facility and Head of the Department of Physiology at the University of New South Wales, Sydney. The Housley lab has long had an interest in Ca^{2+} signalling as a key player in glutamate-induced excitotoxicity. In this study, mice underwent brain injury through the creation of a highly reproducible block of blood flow to the brain (mimicking stroke).

The result of this stroke model was an injury size with a surface area of ~5.7 mm^2 in the brain at 2 hours. This represents the irreversible core injury (primary injury) which then expanded to an average surface area of ~8.9 mm^2 over the next five days in untreated mice (penumbra expansion).

In mice that were treated daily with NYX-104 (100 mg/kg; administered via suppository), beginning on the day of injury for 5 days, there was a 38% reduction in the expansion of the brain injury volume compared to the untreated mice, five days post-injury. An abstract related to this data was published by the US Military Health System Research Symposium (MHSRS) in July 2020. The MHSRS is the foremost scientific meeting of the US Department of Defense for presenting new scientific knowledge resulting from military research and development.

Nyrada's current preclinical candidate compound, NYX-1010, was developed using a molecular modelling approach and blocks Ca^{2+} in cells with 10-times greater potency. In a pharmacokinetic (PK) study it was determined that this compound can cross the blood-brain-barrier (BBB), an important characteristic of a drug for the treatment of neurological conditions. Following continuous intravenous infusion delivery of NYX-1010 in animals, it

[33] Including the NMDA, AMPA/kainite, and metabotropic receptors.
[34] Prog Neurobiol. 2014 Apr;115:157-88. Epub 2013 Dec 17.
[35] Restor Neurol Neurosci. 1998;13(1-2):3-10.
[36] Expert Opin Biol Ther. 2003 Oct;3(7):1093-104.

was shown that therapeutic levels of this drug could be maintained in the brain. Continuous intravenous infusion is the preferred method of drug delivery for treating stroke and TBI patients.

Stroke is a huge market opportunity for any drug that works

Stroke is a large and growing market opportunity for Nyrada. We noted above the high incidence of stroke. Despite this large patient population, there have been no new stroke drugs since the Roche/Genentech clot-busting drug Activase[37] gained FDA approval for its stroke indication in 1996[38]. Every drug that has made it to Phase III has failed since the 1990s. While this has led to the widespread belief in the pharma industry that stroke is a 'drug developer's graveyard'[39], we argue that the opportunity for NYX-1010 is wide open. For one thing, most clinical failures have involved glutamate receptor antagonist approaches, with Ca^{2+} channel blockers yet to be seriously tried[40]. For another, the tools for measuring the effectiveness of stroke drugs have improved over time and can be reasonably expected to improve more in the years ahead[41].

A market in the billions. Management of TBI is currently limited to symptomatic relief, where the cost of not being able to mitigate TBI is ~US$40B per year in the US alone. An Australian suffers a Stroke every 9 minutes and 40% of the current half a million survivors face lifelong disability ('No postcode untouched – Stroke in Australia 2017'). In 2017, drug sales in the Stroke market were ~US$7.2B, with the thrombolysis 'clot-buster' drug Alteplase, the only FDA approved drug for the treatment of acute ischaemic Stroke, generating US$1.2B per annum across the eight major markets. Alteplase increased in cost by 111% between 2005 and 2014, against a background rise of 30% for all prescription drugs. This indicates the premium placed on treating immediate post-stroke hospital admissions. Globally, the Stroke drug market is set to reach US$40.2B by 2024. The Nyrada brain injury drug would be indicated across all stroke admissions (expanding the treatment window days beyond the current 4.5-hour indication for use of Alteplase for acute ischaemic stroke, limiting current treatment to ~8% of cases in Australia (2015 National Stroke Audit; Au. Comm. Safety Quality Health Care, Acute Stroke - the Case for Improvement, May 2016)). Given the unmet clinical need, the commercial potential for a drug that significantly improves survival and recovery from TBI and Stroke is in the order of US$10B in the US alone (benchmarked to US$11K Alteplase treatment cost[42] and 940,000 Stroke and moderate to severe TBI ED admissions p.a.). The potential expansion of therapeutic indications for Nyrada's drug to other brain injuries, such as concussion (prominent in sporting codes), spinal injury, epilepsy, and transient ischaemic attacks (TIA), broaden the commercial base and indicate future revenue streams.

Nyrada is currently working on analogues of NYX-1010. Following a successful improvement in the efficacy of NYX-104 in blocking cellular Ca^{2+}, Nyrada will continue to take the computational modelling approach to further improve the potency and drug-like properties of NYX-1010. Nyrada will continue to optimise the NYX-1010 compound series with the aim of selecting the clinical candidate in 2021. Also, an intranasal dose form is being developed for use in mild TBI (concussion).

[37] See activase.com. Activase is recombinant tissue plasminogen activator or TPA. For the data on improved clinical outcomes in acute ischemic stroke see N Engl J Med. 1995 Dec 14;333(24):1581-7.

[38] 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.

[39] See, for example '*Ischemic stroke continues to be a graveyard for drug development*', The Parma Letter, 18 November 2009.

[40] Nimodipine, a calcium-channel blocker with known efficacy in the prevention of complications from subarachnoid haemorrhage, was studied without success in Phase 3 a long time ago – see Stroke. 2001 Feb;32(2):461-5.

[41] Cerebrovasc Dis 2013;36:250-256.

[42] Below we use a figure of US$7K, which we believe is the cost of drug only (100mg). US$11k is the average overall per patient treatment cost (in 2013).

The way forward for the brain injury program. Nyrada continues to conduct lead optimisation and in parallel will test its current preclinical candidate NYX-1010 in models of TBI and stroke for assessing *in vivo* efficacy. Nyrada is aggressively seeking non-dilutive funding to support this preclinical program. With TBI being an area of critical importance to the military, Nyrada has endeavoured to establish a relationship with the US Department of Defense. Nyrada showcased its technology at the 2019 Defense TechConnect held in National Harbour, MD engaging with key stakeholders and researchers in the field. Once a final candidate has been selected, it will progress into preclinical safety and toxicology studies before a Phase I healthy subject study commencing in 2022. We anticipate the first Phase II study in brain-injured patients to commence in 2023.

Revenue Model

Nyrada PCSK9 inhibitor NYX-PCSK9i

Milestone Revenue

We model Nyrada out-licensing NYX-PCSK9i to a large pharma company at the end of a Phase IIb study in 2024. We assume that the license deal includes an upfront payment of US$20M and US$60M of milestone payments, with all milestone payments contingent upon the achievement of clinical and regulatory milestones. Our forecast pre-risk adjusted milestone revenues for NYX-PCSK9i are as follows:

- Upfront payment of US$20M in 2024 post completion of Phase IIb trial;
- Revenue of US$15M in 2025 upon initiation of a Phase III trial;
- Revenue of US$15M in 2026 upon successful Phase III trial; and
- Revenue of US$30M in 2027 subject to FDA approval.

To de-risk milestone revenues, we adjust them with probability factors that reflect Nyrada's likelihood of passing each clinical and regulatory hurdle.

Market Size & Market Share

We apply a top-down approach to forecast sales revenues of NYX-PCSK9i when and if it gets commercialised. We forecast future sales volume by estimating the size of the patient group and the potential market penetration of the drug.

Global sales of cholesterol-lowering drugs in 2017 totalled US$19B and is expected to increase at a CAGR of 4.9%[43]. The number of high LDL-cholesterol patients taking statin medication in the US is estimated to be at 27 million, of which 19 million patients have a suboptimal response after taking medication[44]. We believe this sub-optimal patient group serves to be the target market for NYX-PCSK9i.

In terms of market share, we conservatively assume NYX-PCSK9i will eventually capture 12% base case and 15% optimistic case, of the total market. Our assumption is based on the presence of a competitive drug market as several PCSK9 inhibitors are already on the market now and several competing therapies are also currently under development. We expect NYX-PCSK9i to hold a modest initial market share in the single-digit

[43] Visiongain Market Research -Global Cholesterol-Lowering Drugs Market 2017-2027: Statins and Fixed-Dose Combinations, Cholesterol Absorption Inhibitors, Ion Exchange Resins, Fibrates, PCSK9 Inhibitors, Novel Drugs

[44] Wong ND et al. Prevalence of the American College of Cardiology/American Heart Association statin eligibility groups, statin use, and low-density lipoprotein cholesterol control in US. J Clin Lipidology. 2016

percentage range from years 2028 to 2031. We assume NYX-PCSK9i to hit its peak sales year in 2032.

Pricing

Before March 2020, PCSK9 inhibitors available on the market were injectable only and priced at about US$5,000 per year. In March 2020, Esperion launched Bempedoic acid, also known as Nexletol, an oral drug developed for use with a statin. Nexletol is currently priced at US$3,600 per year.

In our view, NYX-PCSK9i, if approved, will be highly differentiated because of its single-pill treatment and therefore likely able to attract higher pricing as sub-optimal patients no longer need to obtain statin medication. For NYX-PCSK9i, our base case estimates an average revenue per patient of US$3,960, whilst our optimistic case prices it at US$4,140.

Royalty Revenue

As NYX-PCSK9i is yet to initiate Phase I trial, we assume a royalty of 6% base case and 8% optimistic case based on sales revenues beginning in 2028. Further, our royalty revenues for NYX-PCSK9i are probability-weighted by 10.4% in our DCF model to factor in the early-stage development risk associated with this drug[45]. When and if each milestone is met, we will increase our probability factor accordingly.

NYX-1010

Milestone Revenue

On NYX-1010, we believe that the most likely option is that Nyrada executes a licensing deal with a large pharma company at the end of a Phase IIb study in 2025. We assume that the license deal includes an upfront payment of US$20M and US$60M of milestone payments, with all milestone payments contingent upon the achievement of clinical and regulatory milestones. Our gross milestone revenues for NYX-1010 are as follows:

- Upfront payment of US$20M in 2025 post completion of Phase IIb trial;
- Revenue of US$15M in 2026 upon initiation of a Phase III trial;
- Revenue of US$15M in 2027 upon successful Phase III trial; and
- Revenue of US$30M in 2028 subject to FDA approval.

We de-risk milestone revenues by adjusting them with probability factors that reflect Nyrada's likelihood of overcoming each clinical and regulatory hurdle.

Market Size & Market Share

Once again, we apply a market share approach to derive sales of NYX-1010.

In the US, it is estimated that moderate to severe traumatic brain injury amounts to approximately 270,000 hospitalisations per annum[46], and that stroke amounts to around 650,000 hospitalisations per annum. Within this patient group, it is estimated that approximately 700,000 patients (i.e. 75% of sufferers) would present themselves within the nominal 12-hour therapeutic window[47], for which we base our target market for NYX-1010 on.

Due to a lack of current treatment options, we assume NYX-1010 will capture 50% of the target market base case and 60% optimistic case. Our assumptions

[45] Nature Biotechnology. "Clinical development success rates for investigational drugs," Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal.
[46] Beyond this is the massive opportunity in concussion (2.5M/year of the total 2.87M TBIs in the US), and CTE (caused by the cumulative effect of repeat concussions).
[47] Energias Market Research, Global Traumatic Brain Injuries Treatment Market Outlook, Trend and Opportunity Analysis, Competitive Insights, Actionable Segmentation & Forecast 2024

reflect the absence of a competitive drug market, as well as the largely unmet clinical need for a brain injury drug. We forecast NYX-1010 to hold a modest market share upon its commercial launch in 2029, after which we expect this indication to sequentially ramp up to its peak sales by 2033.

Pricing

Currently, the closest treatment option for brain injury is tissue plasminogen activator (tPA), a clot-buster drug used to treat acute ischaemic strokes, which is the most common type of stroke that comprises 88% of all stroke patients[48]. tPA helps break up blood clots if consumed within a 4.5-hour window after the stroke. tPA is priced at approximately US$7,000[49].

In our view, NYX-1010 should command a significant premium to tPA because it is anticipated to have a much larger treatment window (12-hrs vs 4.5hrs) and is highly unlikely to have the same adverse long-term side effects. Moreover, NYX-1010, if and when it gets approved, has a wider application than tPA, in which it could be potentially used to also treat non-stroke patients sustaining a traumatic brain injury due to motor vehicle accidents, falls, or contact sports.

Therefore, NYX-1010 is likely to be highly differentiated from its very limited competitors as it is a new drug with a novel mechanism of action. For NYX-1010, our base case estimates an annual revenue per patient of US$10,500, whilst our optimistic case prices it at US$11,200.

Royalty Revenue

As NYX-1010 is yet to initiate Phase I trial, we assume a royalty of 6% base case and 8% optimistic case based on sales revenues beginning in 2029. Further, our royalty revenues for NYX-1010 are probability-weighted at 10.4% in our DCF model reflecting the associated risks of drug development[50]. When and if each milestone is met, we will increase our probability factor accordingly.

Valuing Nyrada

We value Nyrada on a probability-weighted risk-adjusted DCF basis at A$0.46 per share base case and A$0.87 per share optimistic case (Figure 4). Figure 5 shows our drugs NPV split.

Our approach is as follows:

- We forecast future milestone payments and royalty streams for each of Nyrada's leading drug candidates, NYX-PCSK9i and NYX-1010. We then derive and add together the risk adjusted NPV of each drug to arrive at a fair value of the Nyrada's drug portfolio. We do not include NYX-205 in our valuation model at this stage;
- We assume around 12 years of commercial exclusivity for both NYX-PSCK9i and NYX-1010, with no follow-on revenue from authorised generics or continued branded sales;
- As NYX-PSCK9i and NYX-1010 are yet to enter Phase I clinical trials, we assume a 10.4% probability of reaching FDA approval (i.e. 1 in 10)[51] for each drug.

[48] http://www.strokecenter.org/patients/about-stroke/ischemic-stroke/
[49] T.M. Leslie-Mazwi, R.V. Chandra and J.A. Hirsch, American Journal of Neuroradiology August 2017, 38 (8) 1464-1466; DOI: https://doi.org/10.3174/ajnr.A5263
[50] Nature Biotechnology. "Clinical development success rates for investigational drugs," Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal.
[51] Nature Biotechnology. "Clinical development success rates for investigational drugs," Michael Hay, David W Thomas, John L Craighead, Celia Economides & Jesse Rosenthal.

- Our discount rate is set at 15% to price in the high-risk nature of drug development story; and
- We assume Nyrada will be able to secure partners to fund future clinical trials of NYX-PSCK9i and NYX-1010.

Our key DCF assumptions are shown in Figure 3.

Figure 3: Our key DCF assumptions

DCF Assumptions	NYX-PCSK9i	NYX-1010
Launch	2028	2029
Estimated patients size (M)	19	0.7
CAGR	4.9%	5.0%
Potential market penetration	12% - 15%	50% - 60%
Realised price (US$)	3,960 - 4,140	10,500 - 11,200
Peak sales (US$B)	9.0 - 11.8	3.7 - 4.7
Peak sales year	2032	2033
Gross milestone revenue (US$M)	80	80
R&D grant revenue (US$M)	4.0	4.5
Patent expires	2039	2040
Drug development cost (US$M)	42	44
Discount rate	15%	15%
Royalty rate	6% - 8%	6% - 8%
Tax rate	27%	27%
Probability of success	10.4%	10.4%
Risk-adjusted NPV (A$M)	42.6 - 86.8	8.5 - 13.5
rNPV per share (A$)	0.56 - 1.14	0.11 - 0.18

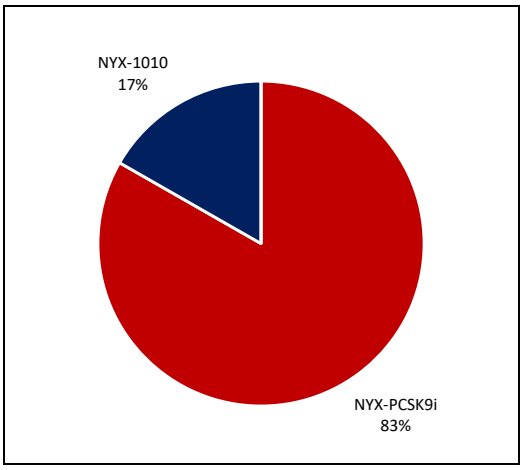
Source: Pitt Street Research

Figure 4: SOTP valuation summary

Sum-of-the-Parts Valuation for NYR	Base Case		Bull Case	
Drugs	**A$M**	**A$ps**	**A$M**	**A$ps**
NYX-PCSK9i	43	0.39	87	0.79
NYX-1010	9	0.08	14	0.12
NYX-205	0	0.00	0	0.00
rNPV	**51**	**0.47**	**100**	**0.92**
Cash	5.1	0.05	5.1	0.05
Debt	0.3	0.00	0.3	0.00
Equity Value	**56**	**0.51**	**105**	**0.96**
Current Price		0.20		0.20
Upside		*156%*		*380%*

Source: Pitt Street Research

Figure 5: Drugs NPV split



Source: Pitt Street Research

Companies to watch

Nyrada is a rare Life Sciences company in that the indications it is principally working on, namely, neuroprotection in stroke and cholesterol reduction, don't tend to be worked in by smaller public companies. That said, the following companies provide a rough guide for Nyrada in terms of providing 'çomparables' at a similar stage of development. Please note, stroke and Alzheimer's are very different indications in terms of the associated pathology, however the market is likely to price stroke companies similar to Alzheimer's companies due to the perception of both conditions having a high 'degree of difficulty' in terms of clinical development.

Acasti Pharma (Laval, Qc, TSX-V: ACST, acastipharma.com, market cap US$18.3m[52]). This company develops prescription drugs using omega-3 fatty acids derived from krill oil. Acasti's lead product candidate is CaPre® (omega-3 phospholipid), which Acasti is developing initially for the treatment of severe hypertriglyceridemia. This product is now in Phase III.

Annovis Bio (Berwyn, Pa., NYSE American: ANVS, annovisbio.com, market cap US$30m). This company's lead product, ANVS401, is able to inhibits the production of multiple neurotoxic brain proteins that have been shown to impair axonal transport and lead to nerve cell death. ANVS401 is in Phase II in Alzheimer's.

DiaMedica Therapeutics (Minneaoplis, Mn., Nasdaq: DMAC, diamedica.com, market cap US$82.4m). This company has aa number of recombinant proteins in its pipeline. The lead candidate, DM199 is a recombinant form of the human serine protease, KLK1, which is known to play a role in neurogenesis. A Phase II study in Acute Ischaemic Stroke for which top line data became available in May 2020 showed a demonstrated therapeutic effect in participants not pre-treated with thrombectomy.

NervGen Pharma (Vancouver, BC, TSX-V: NGEN, nervgen.com, market cap US$43m). This company's NVG-291 drug targets a receptor called protein tyrosine phosphatase sigma (PTPσ), inhibition of which has been shown to promote regeneration of damaged nerves. The company has thought of

[52] All market caps as at 2 November 2020.

potential indications in spinal cord injury, multiple sclerosis and Alzheimer's disease. The drug is expected to enter the clinic in 2021.

ProMIS Neurosciences (Toronto, On., TSX: PMN, promisneurosciences.com, market cap US$27.4m). This company develops drugs that targets on toxic oligomers in neurodegenerative diseases. The company's has developed lead candidates for Alzheimer's targeting amyloid beta and tau which are now in IND-enabling studies.

Vaccinex (Rochester, NY, Nasdaq: VCNX, vaccinex.com, market cap US$35.6m). This company's lead candidate, a monoclonal antibody called pepinemab, blocks SEMA4D, a key driver of neuroinflammation. Vaccinex intends to study pepinemab as a disease-modifying treatment for Huntington's, Alzheimer's, and other neurodegenerative diseases. The drug is in Phase II in Huntington's.

Nyrada's management team

We believe Nyrada has the leadership skills to grow into a substantial company:

- **CEO James Bonnar** brings broad drug development skills particularly in the field of neurology products, honed at the biotech company Neuren Pharmaceuticals
- **CSO Benny Evison** brings a cancer research background at the cutting edge, as evidenced by his focus at St Jude Children's Research Center in Nashville Tn., where he worked on DNA Damage Repair inhibitors
- **The Nyrada board** has a range of skills highly relevant in building a Life Sciences company. Chairman **John** Moore brings a long career in the US biotech scene**. Christopher Cox** was Chief Commercial Officer at The Medicines Company. That company did a deal with Novartis worth USD9.7B for inclisiran (the second largest ever single drug deal). **Ruediger Weseloh** is a senior Business Development Executive at Merck KGaA. **Marcus Frampton** brings a fund management background[53]. Peter Marks brings corporate governance skills. And **Dr. Ian Dixon** is an accomplished bio-entrepreneur best known for founding the regenerative medicine companies Cynata (ASX: CYP) and Exopharm (ASX: EX1)
- The **Nyrada Scientific Advisory Board** also has credibility. **Prof. Gary Housley** is a leading researcher in the mechanisms of brain injury. **Prof. Gilles Lambert** is a leading researcher in PCSK9 and its role in lipid metabolism. **Prof. David Burke** is a thought leader in clinical neurology. **Prof. Junichi Nabekura** is an authority on neural circuit plasticity in the injured brain. And **Dr. Jim Palmer** brings pharmacology expertise.

[53] When he was Chief Investment Officer at Alaska Permanent Fund Corporation the fund took a large, and early, position in the CAR-T pioneer Juno Therapeutics, now owned by Bristol-Myers Squibb.

Appendix I – A Nyrada glossary

Blood-brain barrier – A wall of cells that line the blood vessels in the brain so tightly that only selected substances are permitted to pass through.

Ca^{2+} - Calcium ions

Excitotoxicity – The overstimulation of nerve cells by nerve impulses, causing the cells to be damaged or killed.

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

G Protein-Coupled Receptor (GPCR) – A protein on the surface of cells whose function is to transduce extracellular stimuli into intracellular signals.

Ion channel – A 'tunnel' in a cell's membranes through which ions - mainly sodium, potassium, calcium, and chloride - travel in and out.

Ions – Atoms or group of atoms with an electrical charge.

Ischaemic stroke – Stroke caused by inadequate blood flow to the brain**.**

LDL – Short for 'low-density lipoprotein', LDL is 'bad' cholesterol because it can be deposited in the arteries, increasing the risk of heart attack or stroke.

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

NYX-104 – Nyrada's first-generation brain injury drug.

PCSK9 – Short for 'Proprotein Convertase Subtilisin/Kexin type 9, PCSK9 is a protein naturally produced by the body that plays an important role in LDL metabolism. The main action of PCSK9 is to hold LDL-cholesterol in the blood by degrading LDL receptors (LDLR). Inhibition of PCSK9 function, therefore, causes a welcome increase in the LDLRs on the surface of cells improving the body's ability to clear LDL-cholesterol from the bloodstream.

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

Stroke – A 'brain attack' that results from the brain's blood supply being reduced or cut off.

Synapse – A junction between two nerve cells.

Appendix II – Nyrada's other programs

NYX-205 is being developed to treat peripheral nerve pain. NYX-205 has been selected for its anti-inflammatory properties to treat chronic inflammation and pain in peripheral nerves.

- **Nyrada has shown that NYX-205 can be delivered into the peripheral nerves of rats.** Nerves are similar to the brain in having a protective barrier that excludes most foreign chemicals. In the brain, it is known as the blood-brain barrier, and in peripheral nerves as the blood-nerve barrier. The blood-nerve barrier serves as an effective barrier to many anti-inflammatory drugs seeking to treat nerve conditions known as peripheral neuropathies. An associated benefit of NYX-205 is that it spares the inflammatory eicosanoids such as prostaglandins, an important feature of any anti-inflammatory to be used on a long-term basis given the problem of side-effects such as gastric ulceration associated with prostaglandin inhibition with common anti-inflammatories such as aspirin, paracetamol, and ibuprofen.
- **The market opportunities for NYX-205 are significant**. Peripheral neuropathy associated with pain and loss of function occurs in about 60% of cancer patients receiving chemotherapy[54] and 20% of diabetics. It also is associated with crush injury such as sciatica. NYX-205 currently is being looked at for use in the treatment of pain and inflammation in nerve crush injuries such as sciatica.

Nyrada is looking at a potential autoimmune disease program. Autoimmunity is chronic inflammation where the body's immune system attacks its own body. A lot of recent research has identified a protein known as IRAK4 as being involved in diverting inflammation into autoimmunity, with many companies currently looking at developing drugs to inhibit this protein. Nyrada is joining some big names in the pharmaceutical world in developing IRAK4 inhibitors. This program is very early stage, but already they have shown that they can inhibit this protein. With diseases such as psoriasis on their horizon, the opportunity here is considerable, but there is a long way to go.

Appendix III – IP Position

The core intellectual property with which Nyrada is working relates to two published patents, as well as provisional patent applications covering second-generation compounds

WO/2018/165718, *Heterocyclic inhibitors of PCSK9*, priority date 17 March 2017, invented by Herbert Treutlein, Jun Zeng, Ian Dixon, Ian James, and James Palmer.

- This patent application covers the original suite of drugs including NYX-330.

WO/2019/051562, *Treatment of excitotoxicity*, priority date 15 September 2017, invented by Graham Kelly, Benny Evison, and Gary Housley.

- This patent application covers the method of use for NYX-104.

[54] Pain. 2014 Dec;155(12):2461-70. Epub 2014 Sep 23.

Appendix IV – Capital structure

Class		% of fully diluted	Note
Ordinary shares, ASX Code NYR (million)	109.4	72.6%	
Unlisted options (million)	41.2	27.4%	Exercise price 20 cents, average expiry date 06-May-2024
Fully diluted shares	150.6		

Current market cap:	A$21.9 million (US$15.9 million)
Current share price	$0.200
Twelve month range	$0.11 - $0.25
Average turnover per day (last three months)	370,000

Appendix V – Major Shareholders

Nyrada currently has three major shareholders:

- Noxopharm (30.5%)
- Eleanore Goodridge (9.0%)
- Ian Dixon (9.1%)

Appendix VI – Risks for Nyrada

Risks specific to Nyrada. We see four major risks associated with Nyrada as a company and as a listed stock.

- **Clinical risk**. There is a risk that the company's products may fail to meet the primary or secondary endpoints in clinical studies.
- **Financial risk**. There is a risk that Nyrada may not be able to obtain sufficient funds to continue development.
- **Timing risk**. Nyrada could take longer than expected to get to the clinic
- **Regulatory risk**. Regulatory decisions may slow down or stop the market authorisation process of Nyrada's future products.

Risks related to pre-revenue life sciences companies in general. The stocks of biotechnology and medical devices companies without revenue streams from products or services should always be regarded as speculative. As most biotechnology and medical devices companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector. The fact that the intellectual property base of most biotechnology and medical devices lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the above-mentioned specific and general risks before buying any biotechnology or medical device stocks mentioned in this report, including Nyrada.

Appendix VII - Analyst Qualifications

Stuart Roberts, lead analyst on this report, has been an equities analyst since 2002.

- Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
- Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research specialty at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies such as CSL, Cochlear, and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
- After 15 months in 2015 and 2016 doing Investor Relations for two ASX-listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Science companies.
- In July 2016, with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Science companies.
- Since 2018 Stuart has led Pitt Street Research's Resources Sector franchise, spearheading research on both mining and energy companies.

Cheng Ge is an equities research analyst at Pitt Street Research.

- Cheng obtained a B. Com in Finance and LL. B from the University of New South Wales, in 2013, and has passed all three levels of the CFA Program.
- Before joining Pitt Street Research, he has worked for several financial services firms in Sydney, where his focus was on financial advice.
- He joined Pitt Street Research in January 2020.

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