Neuren keeps Rest-of-World rights for Trofinetide

Share Price: A$1.15

Valuation range: A$ 4.17 – A$ 6.31

ASX: NEU

Sector: Pharmaceuticals

7 March 2019

Trofinetide goes to Phase 3 this year

Last year Neuren Pharmaceuticals partnered its lead molecule, called Trofinetide, to Acadia Pharmaceuticals. That company will start the Phase 3 trial with Trofinetide in Rett Syndrome in the second half of 2019. Neuren has declined to license the Rest-of-World rights to Acadia and is now free to explore other options for a commercial partner.

Investment case: A fast path to market

Acadia expects to take Trofinetide into Phase 3 in the second half of this year and file for FDA approval in Rett Syndrome potentially in 2021. We believe the market has misunderstood the massive opportunity Neuren and Acadia are working on with Trofinetide, particularly with regard to its speed to market. Since Orphan drugs often sell for very high prices, we see potential for Trofinetide to become a blockbuster.

Neuren has a great North American partner in Acadia for Trofinetide

Acadia Pharmaceuticals is a significant player on the US biotechnology scene, with a current market capitalisation of >US$3.8bn and membership in the elite Nasdaq Biotechnology Index. The company gained FDA approval for its first drug, Nuplazid for Parkinson's disease psychosis, in 2016 and is now seeking to grow into other indications based on strong focus and expertise in neurology.

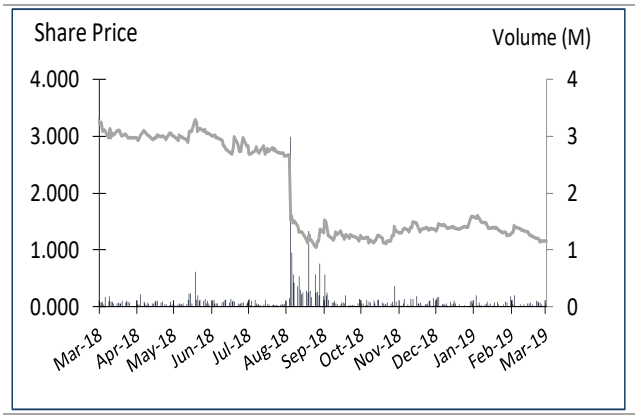
Valuation range of A$4.17 – A$6.31 per share

As per the methodology followed in our 5 December 2018 initiuation report on Neuren, we value Neuren at $4.17 per share base case and $6.31 per share optimistic case using a probability-weighted DCF approach. We believe the market has chosen to price Neuren like a Phase 2 company rather than the Phase 3 company which it really is. We see Neuren being re-rated towards our valuation range as the market starts to appreciate the quality of the deal with Acadia, and as Acadia prepares for the US pivotal study. There also remains the potential for Neuren to negotiate a deal for the ex-North America rights for Trofinetide. Currently our valuation does not include NNZ-2591, which is a further upside as Neuren provides more details on the development program.

Market Cap. (A$ m)	115.2
# shares outstanding (m)	100.2
# share fully diluted	102.7
Market Cap Ful. Dil. (A$ m)	118.1
Free Float	100%
12 months high/low	3.56 / 1.04
1 / 3 / 12-month performance	-64% / -16% / -11%
Website	neurenpharma.com

Source: Company, Pitt Street Research

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



Source: FactSet, Pitt Street Research

Valuation metrics	
DCF fair valuation range (A$)	4.17 – 6.31
WACC	15%
Assumed terminal growth rate	None

Source: Pitt Street Research

Analyst: Stuart Roberts

Tel: +61 (0)447 247 909

Stuart.roberts@pittstreetresearch.com

Table of Contents

Neuren is keeping the RoW rights to Trofinetide, for now

The Rest-of-World rights for Trofinetide are still in play. When Neuren announced its partnering deal with Acadia Pharmaceuticals for Trofinetide in August 2018, the deal related only to US and Canadian rights, with Neuren retaining the Rest-of-World rights. In late October 2018 Neuren and Acadia entered an exclusive three month negotiating period regarding Rest-of-World rights, much as they had done for North American rights the previous May. This time, however Neuren decided to keep the RoW rights once the exclusive negotiating period was concluded.

We believe the Rest-of-World rights are eminently partnerable. The thing to understand about Orphan Drugs is that it is not just big business in the US with its traditionally higher drug prices. Japan first established an Orphan Drug system in 1993 while the European Union has had one since 2000. These systems and others have made Orphan Drugs a lucrative market globally over the last two decades. In 2016 the Orphan Drug market in the US is estimated to be worth US$38bn[1], but in the European Union, even with greater pressure on reimbursement and drug pricing, the market was still worth US$24bn around the same time[2]. Europe in particular features a number of emerging companies that have been built on Orphan Drugs. We therefore see little impediment to Neuren finding an alternative partner for Trofinetide.

Trofinetide Rest-of-World rights are potentially very valuable. When we valued Neuren in December 2018, for conservatism's sake we modeled no licensing fees but assumed an extension of our estimated North American royalty rates to the Rest of the World, a one year lag on approvals, but ten years exclusivity post-approval, reflecting the 10 years exclusivity granted for all Orphan Drugs in the EU (pediatric Orphan drugs get 12[3]) and pediatric Orphan Drugs in Japan[4]. For the RoW we modeled peak sales of $0.8bn (base case) to $1.6bn (optimistic case), which assumes lower penetration of a more fragmented market and lower pricing compared with the US.

Neuren has brought in some outside help. At the same time that Neuren announced that it was keeping the Rest-of-World rights it also announced that it had retained Torreya Partners as a corporate advisor to consider various options regarding these rights as well as for the company generally. Given the quality of the Trofinetide data coming out of Phase 2, and the fact that the drug will enter Phase 3 this year, Torreya's work could unlock some interesting opportunities for Neuren's shareholders.

Trofinetide goes to Phase 3 this year

Trofinetide can gain FDA approval after a single Phase 3

Acadia has confirmed its plans for the Rett Syndrome Phase 3. When Neuren had its End-of-Phase 2 meeting with the FDA for Trofinetide in Rett Syndrome in October 2017 the Agency agreed with Neuren's plan for a single Phase 3 study where the patients would randomise 1:1 to a single dose group or placebo, the treatment duration would be six months, and the co-primary endpoints would be improvement in the RSBQ (Rett Syndrome Behavioural

[1] Source: *Orphan Drugs in the United States - Growth Trends in Rare Disease Treatments*: Iqvia Institute for Human Data Science, October 2018
[2] Source: *Orphan Drug Report 2017*, EvaluatePharma, February 2017.
[3] See Regulation (EC) No 1901/2006.
[4] Intractable Rare Dis Res. 2012 May; 1(2): 95–97.

Questionnaire) and the CGI-I (Clinical Global Impression of Improvement) where the Phase 2 data was compelling.

Acadia announced in early February 2019 that its Phase 3 for Trofinetide will commence in the second half of the current calendar year. As Neuren envisaged, this Phase 3 will recruit ~180 female Rett patients aged 5 to 20, but only dose for three months with patients randomising 1:1 to treatment and placebo. After the three month period all patients will go on Trofinetide to evaluate longer-term safety and tolerability.

We see the potential for Neuren stock to re-rate as the commencement of this study nears. Encouragingly, Acadia has confirmed that it expects to be filing for FDA approval of Trofinetide, should favourable data emerge from the study, in 2021.

NNZ-2591 demonstrates positive effects in Phelan-McDermid Syndrome

Neuren has a great follow-on drug to Trofinetide. Neuren's second drug is a cyclic dipeptide with 100% oral bioavailability called NNZ-2591. Like Trofinetide, NNZ-2591 is related to IGF-1. While it was originally just a backup candidate to Trofinetide, NNZ-2591 showed, early on, *in vivo* efficacy in a wide range of CNS disorders including Parkinson's Disease, peripheral neuropathy and mild cognitive impairment. In July 2013 Neuren was able to show, in a Fragile X animal model, that NNZ-2591 would treat Fragile X at around one third the dose required of Trofinetide. With that drug now moving into late-stage clinical work, Neuren is now actively advancing development of NNZ-2591 in neurodevelopmental disorders, including Phelan-McDermid Syndrome.

NNZ-2591 has generated good pre-clinical data in Phelan-McDermid Syndrome

NNZ-2591 has generated good pre-clinical data. Neuren announced on 18 February that scientists had tested NNZ-2591 in the SHANK3 knockout mouse model, which is the standard animal model for Pherlan-McDermid Syndrome[5]. The study compared normal mice and mice with a disrupted SHANK3 gene. In the knockout mice, deficits in anxiety, repetitive behavior, motor performance and social interaction were restored to the wild type state following treatment with NNZ-2591 for three weeks. The susceptibility to seizures also fell by 60% in the treated knockout mice. Moreover, the abnormal length of the dendrite spines between brain cells, the excess activated ERK protein (pERK) and the depressed level of IGF-1 in the knockout mice were all normalized after treatment with NNZ-2591. Neuren has already started the standard characterization and non-clinical safety studies that are required before filing an Investigational New Drug Application (IND) with the FDA to commence clinical work.

What is Phelan-McDermid Syndrome? Phelan-McDermid Syndrome is sometimes called 22q13 Deletion Syndrome, but can occur because the SHANK3 gene that lies on chromosome 22 is simply misspelled rather than deleted[6]. It is characterized by intellectual disability, sometimes including features of the autism spectrum disorders (ASD), but doesn't have as severe a level of dysmorphisms or somatic anomalies as other ASDs. Generally the

[5] Disruption of SHANK3 gene is also thought to be associated with many cases of Autism Spectrum Disorder beyond Phelan-McDermid.

[6] About 20% of people with Phelan-McDermid have a deletion, or even a duplication, that is caused by a chromosomal translocation. Other patients will have what is called a ring chromosome, or ring 22, so called because the very distal ends of chromosome 22 break off and the 'new ends' of the chromosome stick to each other to create a circular chromosome.

condition will first show up very early in life with hypotonia (low or weak muscle tone) followed by severely delayed or absent speech. Since it is typically diagnosed before adolescence, there is relatively little in the literature on adult patients. Significantly, there is no approved treatment available for Phelan-McDermid syndrome.

How rare is Phelan-McDermid? As with many rare CNS disorders that are monogenic, no reliable estimates of the prevalence of Phelan-McDermid exiss, mainly because testing to detect very small SHANK3 deletions did not become commonly available until the late 1990s. The Phelan-McDermid Syndrome Foundation, has suggested that 1% of people with an ASD have Phelan-McDermid, but not all Phelan-McDermid patients present with autism. We estimate that there could be 5,000-10,000 patients in the United States, which makes the commercial opportunity similar to Rett syndrome and means that Neuren should be able to obtain Orphan Drug designation.

Neuren can move fairly quickly with Phelan-McDermid. The aforementioned Phelan-McDermid Syndrome Foundation, based in Venice, Fl., maintains a patient registry that now has the patient details of over 2,000 individuals around the world. We believe that if Neuren chooses to move ahead with a Phelan-McDermid indication for NNZ-2591, it could gain a similar level of patient advocacy support as it has for Rett Syndrome with Rettsyndrome.org.

Background to Neuren Pharmaceuticals, ASX: NEU

Neuren Pharmaceuticals is a Melbourne-based drug developer. This company's lead compound is Trofinetide, for the treatment of two Autism Spectrum Disorders, Rett Syndrome and Fragile X Syndrome. The company has generated favourable Phase 2 data in both these conditions and in August 2018 was able to license the North American rights to Trofinetide to Acadia Pharmaceuticals[7], a US specialty pharma company based in San Diego with a current market capitalisation of >US$3.8 billion. Neuren also has a second drug candidate in active pre-clinical development for other neurodevelopmental disorders.

Neuren and Acadia may be filing for FDA approval of Trofinetide in 2021

Acadia North American deal worth US$450M

Acadia paid US$10m upfront and may pay US$105m in development and regulatory milestones and US$350m in sales milestones, plus double-digit royalties on all Trofinetide sales. Acadia will now proceed with and fully fund a Phase 3 study in Rett Syndrome and commence further clinical work on Fragile X Syndrome. The US company expects to be filing for FDA approval in Rett Syndrome potentially in 2021 ahead of a 2022 approval following a 6-month Priority Review. Significantly, Neuren retains the Rest-of-World rights to Trofinetide, having declined to grant these rights to Acadia in January 2019.

What are Trofinetide and NNZ-2591?

Trofinetide is a synthetic tripeptide drug that has its origins in the hormone Insulin-like Growth Factor 1 (IGF-1). This hormone, which is central to the normal growth and functioning of the central nervous system, has long been known to play a role in brain development[8]. In the 1990s the laboratory of Sir Peter Gluckman at the University of Auckland in New Zealand did a great deal

[7] San Diego, Ca., Nasdaq: ACAD, www.acadia-pharm.com.
[8] Neuroscience. 2016 Jun 14;325:89-99. Epub 2016 Mar 31.

of work on the neuroprotective and neurotrophic properties of Glypromate, a tripeptide[9] that cleaves off the N terminus of IGF-1[10] and is known to upregulate in the brain after hypoxic-ischemic injury[11].

Neuren has been working on Trofinetide in Rett Syndrome since 2012

Neuren Pharmaceuticals was founded in 2001 and did its IPO on the ASX in 2005 in order to develop Glypromate for the prevention of cognitive impairment following cardiac surgery, where the drug failed in Phase 3 in late 2008. Dist. Prof. Margaret Brimble and her group at the University of Auckland produced a synthetic analogue of Glypromate initially called NNZ-2566, which is more stable, able to be administered orally and more readily crosses the blood-brain barrier. The same group also produced a synthetic analogue of cyclic glycine proline (CGP), which is another active peptide that plays a role in regulating the natural biology of IGF-1 in the brain. They named that analogue NNZ-2591.

Neuren initially conducted work on Trofinetide as a potential neuroprotective agent in Traumatic Brain Injury, before shifting the development focus to the Orphan Drug programs Rett Syndrome and Fragile X Syndrome in late 2012. NNZ-2566 was renamed 'Trofinetide' in early 2015 when the World Health Organisation accepted this name for inclusion on the list of International Nonproprietary Names[12]. The effects of Trofinetide can be summarised as reducing neuroinflammation, restoring the normal function of microglia (the brain's immune cells) and improving connectivity between brain cells.

What is Rett Syndrome?

Neuren and Acadia may have the first ever drug treatment for Rett Syndrome

Rett Syndrome is a serious and debilitating neurodevelopmental condition that almost exclusively affects females. It is caused by a mutation in a gene located on the X chromosome called MeCP2. Rett Syndrome is characterised first and foremost by severe intellectual disability, but also by unsteady breathing, cardiac arrythmia and unusual hand movements. Prevalence of the condition has been estimated at 1 in 10,000 or 1 in 15,000 females[13] and we estimate that there are ~10,000 females in the US currently living with the condition.

Females with Rett have been known to live into their 40s and beyond, however many die before this, and many suddenly die because of respiratory failure, apnoea or cardiac arrhythmia[14]. As yet, there are no approved drug treatments. Neuren and Acadia hope to change all that with Trofinetide, which has performed well in two Phase 2 studies in Rett Syndrome patients. Because Trofinetide aims to improve the underlying brain biology rather than treating one symptom, the target market is the entire Rett population.

What is Fragile X Syndrome?

Fragile X Syndrome is, like Rett Syndrome, a monogenic disorder (i.e. caused by a single gene defect), in this case by mutations in the fmr1 gene, also on the X chromosome. It's called 'Fragile X' because, when viewed under a microscope, the X chromosome at the point of the mutated fmr1 is so narrow it looks as if it would break[15]. Fragile X Syndrome affects both sexes, but males more than females. The condition is characterised by intellectual disability, as

[9] Glypromate gets its name from the fact that the three peptides are GLYcine, PROline and GlutaMATE.
[10] That is, the start of the hormone's amino acid chain.
[11] Brain Res. 2001 Dec 13;922(1):42-50.
[12] This was confirmed in August 2015.
[13] Br Med J (Clin Res Ed). 1985 Aug 31;291(6495):579-82.
[14] Eur Child Adolesc Psychiatry. 1997;6 Suppl 1:71-4.
[15] Am J Hum Genet. 2012 Apr 6;90(4):579-90.

well as by a long face and other atypical physical features[16], social withdrawal, hyperactivity and seizures. We estimate there are around 40,000 Fragile X patients in the United States[17]. Neuren has completed a successful Phase 2 in Fragile X Syndrome.

Orphan drugs can command very high prices

Orphan Drugs often sell for high prices per patient p.a.

Since the 1980s many countries have had measures in place to encourage the development of so-called Orphan Drugs affecting small patient populations. In the US an Orphan Drug is defined at one affecting less than 200,000 people in that country annually. Since around 2008 there has been a strong push by US pharma and biotech companies to enter the Orphan Drug space because of the premium prices that are often charged for such drugs, and the relative ease with which they can gain regulatory approval. We estimate that Trofinetide could become a blockbuster based on Orphan-style pricing in the order of US$200,000 per patient.

If Neuren is so good, how come the share price came down markedly with the Acadia deal?

Neuren was marked down after the Acadia deal because of the low upfront. Smart investors will value the milestones

After the announcement of the Acadia deal, Neuren's share price declined from the $2.65 level of early August to a low of $1.04 by 28 August. We believe that the market was disappointed with the Acadia partnering because the headline upfront in the deal was only US$10m. We also believe such disappointment is unwarranted. Firstly, US$455m in development and sales milestones plus double-digit royalties is a large deal in anyone's book when it comes to Pharma partnering, and the deal also removed a heavy development funding burden from Neuren.

Secondly, Trofinetide is moving into Phase 3, in which it has to repeat the result that was obtained in Phase 2, so the risk of clinical failure is considerably lower than was the case in Phase 2.

Thirdly, there is potential for Trofinetide to become a blockbuster once it comes on the market after 2022.

And fourthly, Neuren's partner Acadia is a well-regarded US drug developer with a track record of success as demonstrated by Nuplazid (pimavanserin), which the FDA designated a Breakthrough Therapy for Parkinson's Disease Psychosis in 2014 and which gained marketing approval in April 2016. Nuplazid enjoyed US$125m in net sales in 2017, its first full year of commercial release, and US$224m in 2018. We see strong potential for Neuren to re-rate as the market starts to appreciate the quality of its August 2018 deal.

[16] Such as macroorchidism in the case of boys.
[17] Am J Med Genet A. 2014 Jul;164A(7):1648-58. Epub 2014 Apr 3.

Ten reasons to look at Neuren

Trofinetide turned in some good data in pediatric Rett Syndrome

1. **Neuren is a Phase 3 CNS drug developer in areas of urgent unmet need**, with Trofinetide having performed well in two Phase 2 studies in Rett Syndrome and one Phase 2 in Fragile X Syndrome. Following an end-of-Phase 2 meeting with the FDA for Rett syndrome in October 2017, Trofinetide only needs to repeat the result from the second Phase 2 trial in a single Phase 3 trial prior to Neuren's partner Acadia filing for FDA approval. Given the speed with which Neuren's previous studies have recruited, Trofinetide could potentially become an approved drug for Rett Syndrome by 2022.
2. **Neuren has a lucrative partnering deal with Acadia Pharmaceuticals**. Neuren's partnering deal with Acadia, signed in August 2018, came with total milestone payments of up to US$465m plus double-digit royalties on net sales of Trofinetide in North America. It provides a clear path to market for Trofinetide in Rett Syndrome and Fragile X Syndrome.
3. **Trofinetide performed particularly well in the Phase 2 for pediatric Rett Syndrome**. This randomised, placebo-controlled study, which completed in 2017, generated statistically significant improvements across a range of domains and core measures and helped shape the design of the upcoming Phase 3. Two of the measures that showed statistically significant improvement are the primary endpoints for the Phase 3 trial.
4. **Neuren has the support of the key physicians and advocacy groups.** Neuren's studies have been conducted with strong support and collaboration from the leading Rett Syndrome physicians and the largest patient advocacy group Rettsyndrome.org, which is critical for development and commercial success.
5. **Neuren is funded for its next stage of development.** With Neuren holding A$24m in cash as at December 2018, and Acadia funding further development of Trofinetide estimated at US$60m for Rett Syndrome alone, we see Neuren as being free from near-term funding pressures.
6. **There is potential to partner Rest-of-World rights for Trofinetide**. After a second exclusive negotiating period with Acadia between October 2018 and January 2019 Neuren has chosen to retain the Rest-of-World rights for Trofinetide for now. Should a new partner emerge there is potential for a re-rating of Neuren stock given the de-risking represented by such a transaction.
7. **Neuren is an Orphan Drug developer**. Both Rett Syndrome and Fragile X are Orphan diseases with, at present, no approved drug treatments. There is potential for Neuren and Acadia to therefore enjoy high pricing for Trofinetide should the drug come to market.
8. **NNZ-2591 has potential across a wide range of conditions.** Based on preclinical evidence, NNZ-2591 has demonstrated potent neuroprotective and neurotrophic properties across a range of CNS conditions. Active development of NNZ-2591 is now enabling Neuren to expand its drug portfolio for neurological disorders, starting with Phelan-McDermid syndrome.
9. **Neuren has a strong management team**. The company's management team is led by its Executive Chairman, Dr. Richard Treagus, who has >20 years of experience in the biopharmaceutical industry on development and commercialization of new pharmaceutical products, FDA approval for novel products, and product licensing deals. Richard is part of a well-equipped board that has extensive experience in building a successful life sciences company.
10. **Neuren is undervalued, on our numbers**. Without NNZ-2591, we value Neuren at $4.17 per share base case and $6.31 per share optimistic case using a probability-weighted DCF valuation approach. We see Neuren being re-rated towards our valuation range as the market starts to appreciate the quality of the deal with ACADIA, as Neuren negotiates a deal for the ex-North America rights for Trofinetide and as Acadia prepares for the US pivotal studies.

Risks related to Neuren

Risks specific to Neuren. We see four major risks for Neuren as a company and as a listed stock:

- Clinical risk. There is the risk that Trofinetide may fail to meet the primary or secondary endpoints in the upcoming Phase 3
- Partnering risk. There is the risk that Neuren may not succeed in partnering Rest-of-World rights for Trofinetide.
- Timing risk. There is the risk that the Trofinetide Phase 3 study in Rett Syndrome may take longer than we expect to complete.
- Regulatory risk. There is the risk that regulatory decisions may slow or stop the progress of Trofinetide in to the marketplace.

Risks related to pre-revenue Life Science companies in general. The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology and medical device 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 device 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 abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Neuren.

General advice warning, Disclaimer & Disclosures

Terms & Conditions

The information contained herein ("Content") has been prepared and issued by Pitt Street Research Pty Ltd ACN 626365615 ("Pitt Street Research"), an Authorised Representative (no: 1265112) of BR Securities Australia Pty Ltd. ABN 92 168 734 530, AFSL 456663. All intellectual property relating to the Content vests with Pitt Street Research unless otherwise noted.

Disclaimer

The Content is provided on an as is basis, without warranty (express or implied). Whilst the Content has been prepared with all reasonable care from sources we believe to be reliable, no responsibility or liability shall be accepted by Pitt Street Research for any errors or omissions or misstatements howsoever caused. Any opinions, forecasts or recommendations reflect our judgement and assumptions at the date of publication and may change without notice. Pitt Street Research will not accept any responsibility for updating any advice, views, opinions or recommendations contained in this document.

No guarantees or warranties regarding accuracy, completeness or fitness for purpose are provided by Pitt Street Research, and under no circumstances will any of Pitt Street Research officers, representatives, associates or agents be liable for any loss or damage, whether direct, incidental or consequential, caused by reliance on or use of the Content.

General Advice Warning

The Content has been prepared for general information purposes only and is not (and cannot be construed or relied upon as) personal advice nor as an offer to buy/sell/subscribe to any of the financial products mentioned herein. No investment objectives, financial circumstances or needs of any individual have been taken into consideration in the preparation of the Content.

Financial products are complex, entail risk of loss, may rise and fall, and are impacted by a range of market and economic factors, and you should always obtain professional advice to ensure trading or investing in such products is suitable for your circumstances, and ensure you obtain, read and understand any applicable offer document.

Disclosures

Pitt Street Research has been commissioned to prepare the Content. From time to time, Pitt Street Research representatives or associates may hold interests, transact or hold directorships in, or perform paid services for, companies mentioned herein. Pitt Street Research and its associates, officers, directors and employees, may, from time to time hold securities in the companies referred to herein and may trade in those securities as principal, and in a manner which may be contrary to recommendations mentioned in this document.

Pitt Street Research receives fees from the company referred to in this document, for research services and other financial services or advice we may provide to that company. The analyst has received assistance from the company in preparing this document. The company has provided the analyst with communication with senior management and information on the company and industry. As part of due diligence, the analyst has independently and critically reviewed the assistance and information provided by the company to form the opinions expressed in the report. Diligent care has been taken by the analyst to maintain an honest and fair objectivity in writing this report and making the recommendation. Where Pitt Street Research has been commissioned to prepare Content and receives fees for its preparation, please note that NO part of the fee, compensation or employee remuneration paid will either directly or indirectly impact the Content provided.