

neuren

pharmaceuticals

# IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

13 September 2021



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# INVESTMENT HIGHLIGHTS

Neuren (ASX: NEU) is a biotechnology company developing new therapies in global markets for multiple serious neurological disorders that emerge in early childhood

1

Two patented drugs (trofinetide and NNZ-2591) administered as oral liquids

2

In Phase 3 and Phase 2 clinical development for 6 orphan drug indications, all with urgent unmet need

3

Near term inflection point with Phase 3 results for trofinetide due in Q4 2021

4

Trofinetide licensed to Acadia for North America, milestones up to US\$455m + double digit % royalties + data for rest of the world

5

Accelerating Phase 2 development of NNZ-2591 in 4 indications

6

NNZ-2591 novel mechanism of action has many more potential applications

# CAPITAL RAISE FOR NEAR TERM CRYSTALLISATION OF VALUE

Raising ~A\$22m (via a A\$20m Placement and A\$2m Share Purchase Plan)

## Neuren Today

~A\$250m market cap

- Trofinetide Rett syndrome Phase 3 results Q4 2021
- Existing US partner for trofinetide; significant interest from RoW
- NNZ-2591 Phase 2 for 3 indications
- Global rights to NNZ-2591 retained
- A\$16m cash at 31 July 2021

## Post-raising

- Well capitalised to bring NNZ-2591 to Phase 3 in 4 indications
- Significant potential upside on successful trofinetide Phase 3 and US launch (US cashflow + RoW partnering)
- Proforma cash A\$37m<sup>1</sup>

## In 2023

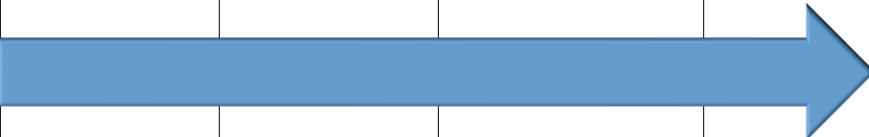



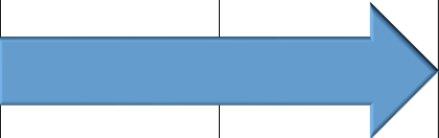
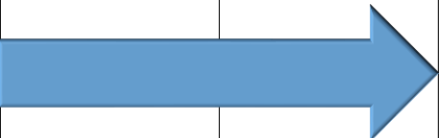
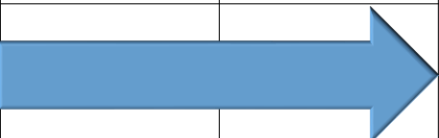
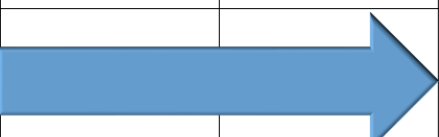
- NNZ-2591 Phase 3 ready for 4 indications with potential markets 5 x Rett syndrome<sup>2</sup>
- Self-funded with trofinetide cash generated from US and RoW<sup>3</sup>
- Multiple value creation pathways through commercial arrangements and licensing globally

<sup>1</sup> Based on A\$16m cash at 31 July 2021 plus A\$21m raising proceeds assuming full subscription of the Offer and net of costs

<sup>2</sup> Based on number of addressable patients globally

<sup>3</sup> Assuming positive results in Rett syndrome Phase 3 trial, New Drug Application (NDA) is approved by the FDA and product launch in United States

# LEADING PIPELINE IN NEURODEVELOPMENTAL DISORDERS

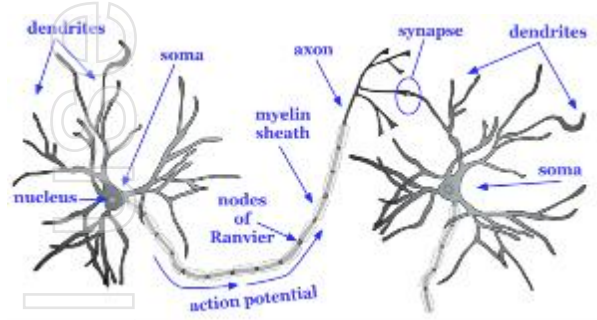
Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Commercial Partner
Trofinetide	Rett syndrome <sup>1</sup>					<b>Results expected Q4 2021</b>  (North America)
	Fragile X syndrome <sup>1</sup>					 (North America)
NNZ-2591	Phelan-McDermid syndrome <sup>2</sup>			<b>Commence expected H2 2021</b>		
	Angelman syndrome <sup>2</sup>			<b>Commence expected H2 2021</b>		
	Pitt Hopkins syndrome <sup>2</sup>			<b>Commence expected H2 2021</b>		
	Prader-Willi syndrome <sup>3</sup>			<b>Commence expected mid-2022</b>		

<sup>1</sup> Orphan Drug designation in US and EU, Fast Track designation in US

<sup>2</sup> Orphan Drug designation in US and EU <sup>3</sup> Orphan Drug designation in US

# TREATING NEURODEVELOPMENTAL DISORDERS

Rett	Fragile X	Phelan-McDermid	Angelman	Pitt Hopkins	Prader-Willi
<i>MECP2</i>	<i>FMR1</i>	<i>SHANK3</i>	<i>UBE3A</i>	<i>TCF4</i>	<i>15q11-q13</i>



Impaired communication between neurons, abnormal formation/pruning of dendrites & chronic inflammation

Neuren's drugs target the critical role of IGF-1 in this upstream process, using analogs of peptides that can be taken orally as liquids

## Severe impact on nearly every aspect of life

walking and balance issues

anxiety and hyperactivity

seizures

speech impairment

intellectual disability

breathing irregularities

impaired hand use

sleep disturbance

gastrointestinal problems



# COMMERCIAL ADVANTAGES OF ORPHAN DRUGS

Compared with existing markets that have apparently attractive large \$ sales revenue in which established products have to be displaced, **Orphan Drugs have many advantages**

Serious and urgent unmet need results in strong support from patient community and leading physicians as well as a more supportive regulatory environment

Ability to target a leadership position with little competition

Higher pricing

*Evaluate Pharma Orphan Drug Report 2019 - US Orphan Drug mean cost of US\$150k per patient per year*

Immediate access to known patients means large sales organisation less important

Exclusivity periods from regulators eliminate patent risk

Smaller and fewer Phase 3 trials

Statistics show higher probability of regulatory approval<sup>1</sup>

**~572k addressable patients across 6 indications<sup>2</sup>**

<sup>1</sup> Biomedtracker/Amplion: Clinical Development Success Rates 2006-2015

<sup>2</sup> 96k in US, 122k in EU and 354k in Asia; estimates derived by applying the mid-point of the prevalence estimate range to the populations under 60 years



# TRANSFORMING MILESTONES APPROACHING

- **Results in Q4 2021 for trofinetide Phase 3 trial in Rett syndrome**
  - Partnered with Acadia (NASDAQ:ACAD) for North America, Neuren has access to US data for ex-North America registration
  - Up to US\$455m milestone payments, plus double digit % royalties, plus one third of RPD Priority Review Voucher value<sup>1</sup>
  - ACADIA funds development and commercialisation for North America
  - Neuren potential revenue over 2022 and 2023 for Rett syndrome in the US alone of A\$111 million plus double-digit percentage royalties on net sales<sup>2</sup>
  - Positive Phase 3 results expected to enable Neuren to partner in Europe and Asia
- **Phase 2 trials for NNZ-2591 in 4 disorders**
  - **Large potential upside** - multiple indications and global rights retained
  - Potential markets for NNZ-2591 is more than 5 times Rett syndrome<sup>3</sup>

<sup>1</sup> Refer to slide 19

<sup>2</sup> Refer to assumptions on slide 20

<sup>3</sup> Based on estimates of number of addressable patients globally

# THE THREE KEY DRIVERS OF NEAR TERM VALUE

Realise Neuren's share of trofinetide value in the US through ACADIA's Phase 3 results and New Drug Application

Implement commercial strategy for trofinetide ex-North America, using US data for registration

Confirm efficacy of NNZ-2591 in Phase 2 trials for 4 valuable indications

# STRONG MOMENTUM FROM NEAR-TERM CATALYSTS

2021

## Achieved

- ✓ EU Orphan designations for Phelan-McDermid, Angelman, and Pitt Hopkins
- ✓ Successful Phase 1 trial results for NNZ-2591
- ✓ Prader-Willi syndrome added to NNZ-2591 pipeline
- ✓ Complete drug substance manufacturing for NNZ-2591 Phase 2
- ✓ Pre-IND meetings with FDA to agree NNZ-2591 Phase 2 plans
- ✓ Acadia completes enrolment in trofinetide Rett syndrome Phase 3
- ✓ NNZ-2591 IND application for Angelman submitted to FDA

**FDA Orphan designation for NNZ-2591 in Prader-Willi syndrome**

## Imminent

- Submit NNZ-2591 IND applications for Pitt Hopkins and Phelan-McDermid to FDA
- Commence three NNZ-2591 Phase 2 trials
- Trofinetide Rett syndrome Phase 3 top-line results

2022

## Expected

- Submit NNZ-2591 IND application for Prader-Willi to FDA
- Commence NNZ-2591 Phase 2 trial in Prader-Willi
- Trofinetide New Drug Application to FDA<sup>1</sup>
- Trofinetide partnering in Europe and Asia<sup>1</sup>
- Results from NNZ-2591 Phase 2 trials in each of Phelan-McDermid, Angelman and Pitt Hopkins

<sup>1</sup> Assuming positive results in Rett syndrome Phase 3 trial

# PRADER-WILLI SYNDROME OVERVIEW

- Prader-Willi syndrome (PWS) is a debilitating neurodevelopmental disorder, caused by defects in the 15q11-q13 region of chromosome 15
- The estimated incidence is 1 in 10,000 – 30,000 males and females across all races and ethnicities (potentially 76k patients in US, EU, Asia<sup>1</sup>)
- Infants with PWS have very low muscle tone and suffer from feeding difficulties
- An unregulated appetite and easy weight gain characterize the later stages of PWS, which can lead to morbid obesity
- A range of other problems can include intellectual and learning disabilities, growth hormone deficiency, sleep disturbances, speech difficulties, obsessive-compulsive symptoms, gastrointestinal complications, and difficulty controlling emotions
- Daily injection of growth hormone is the only medicine approved for PWS
- **PWS patients have sub-normal levels of IGF-1 - the mechanism of action of NNZ-2591 has the potential to address both endocrinological and neurological aspects of PWS**



<sup>1</sup> Refer to estimates on slide 25

# FUNDING PRADER-WILLI AND PHASE 3 READINESS

## Capital raise enables Neuren to accelerate NNZ-2591 to Phase 3 in 4 indications

- Pursue opportunity in Prader-Willi syndrome
  - FDA granted Orphan Drug designation on 2 September 2021
  - Compelling efficacy in *Mage12*-null mouse model - NNZ-2591 normalized fat mass, insulin levels, IGF-1 levels and all behavioural deficits<sup>1</sup>
  - File IND application and commence Phase 2 trial in mid-2022, targeting results in 2023
- Complete the foundational work for Phase 3 trials across all indications
  - Non-clinical toxicology studies for chronic dosing in Phase 3 and commercial use
  - Manufacturing scale-up and commercial product presentation
  - Validation of efficacy measures

<sup>1</sup> Refer to results on slides 40-41

# OFFER DETAILS

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# OFFER DETAILS

Neuren is conducting a capital raising of A\$22 million via an institutional placement and share purchase plan

## Offer Structure

- The Offer comprises:
  - a placement of fully paid ordinary shares in the Company (“New Shares”) to institutional investors to raise approximately A\$20 million; and
  - an offer of New Shares to eligible shareholders in Australia and New Zealand under a share purchase plan to raise approximately A\$2 million.
- The Offer is not underwritten

## Placement

- Placement to raise A\$20 million (“Placement”)
  - Approximately 9.8m new Shares under the Company’s existing placement capacity under ASX Listing Rules 7.1/7.1A
  - Represents ~8.5% of current issued capital

## Placement Pricing

- The offer price of A\$2.05 per share (“Offer Price”) represents:
  - A discount of 8.9% to the last close of A\$2.25 on 9 September 2021
  - A discount of 12.7% to the 5-day VWAP of A\$2.347 up to and including 9 September 2021

## Share Purchase Plan

- Neuren intends to offer eligible shareholders an opportunity to subscribe for up to A\$30,000 of new Shares under a Share Purchase Plan (SPP) at a price per Share equal to the Offer Price
- It is intended the SPP will be capped at approximately A\$2 million

## Ranking

- New Shares issued under the Placement will rank pari passu with existing Shares from their date of issue



# USE OF FUNDS

Uses	A\$m
IND application and Phase 2 clinical trial for NNZ-2591 in Prader-Willi syndrome	7.0
Foundational work for Phase 3 trials across all 4 indications for NNZ-2591	11.8
Working capital & Offer costs	3.2 <sup>1</sup>
<b>Total</b>	<b>22.0</b>

<sup>1</sup> Assuming full subscription of the Offer

# OFFER TIMETABLE

Event	Date, AEST
Trading halt	Thursday, 9 September 2021
Record Date for SPP	Friday, 10 September 2021
Placement announced & Shares resume trading on ASX	Monday, 13 September 2021
Placement settlement of new Shares	Thursday, 16 September 2021
Placement issue of new Shares	Friday, 17 September 2021
SPP opens	Friday, 17 September 2021
SPP closes	Friday 1 October 2021
Issue of new Shares under SPP	Wednesday, 6 October 2021

The timetable is indicative only and subject to change by the Company and Lead Managers, subject to the Corporations Act and other applicable laws.

# TROFINETIDE FOR RETT SYNDROME

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# TROFINETIDE LICENCE AGREEMENT WITH ACADIA

- Partnership commenced in August 2018, providing the necessary funding and capabilities to execute Phase 3 and commercialise trofinetide in the US
- Redacted agreement is available in ACADIA's 2018 10K filing



Territory	North America (Neuren retains all rights ex-North America)
Indications	All, including Rett syndrome and Fragile X syndrome
Future development costs	Funded by ACADIA
Use of data	Each party has access to all data for use in its territory
Development Milestones	US\$105m on achievement of 5 milestones across Rett and Fragile X
Commercial Milestones	US\$350m on achievement of 4 thresholds for total annual net sales
Royalties	Double-digit % royalties with % escalating in 4 tiers of total annual net sales
Rare Pediatric Disease Priority Review Voucher	Neuren receives 1/3 of voucher market value (recent sale average US\$100m)
Non-compete	Neuren may not develop a competing product in indications for which ACADIA develops and commercialises trofinetide

# RETT SYNDROME OPPORTUNITY

Estimates	US	Europe	Japan	China urban	Other Asia
Potential patients <sup>1</sup>	10,000	13,000	3,000	28,000	6,000
Patients currently identified	5,000	4,000	1,000	2,000	'00s

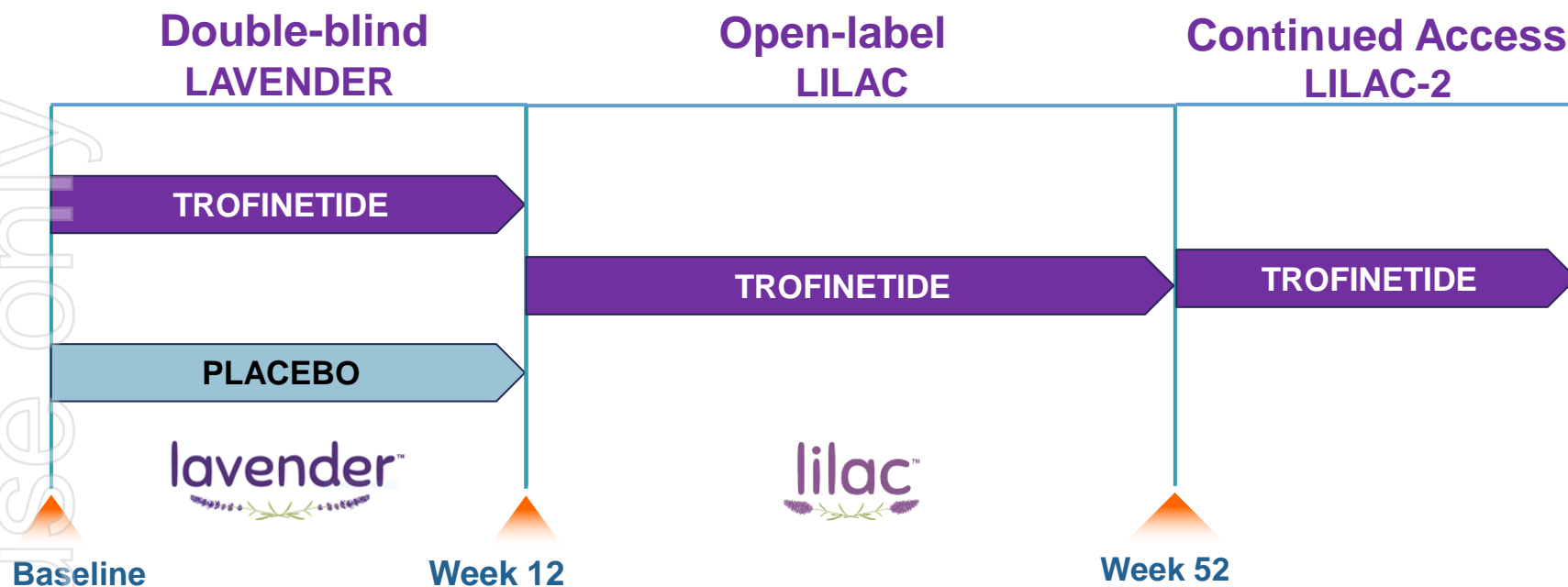
<sup>1</sup> Potential patient estimates derived by applying the mid-point of the published prevalence estimate range to the populations under 60 years

- ▣ Peak annual sales potential in US at least US\$500m<sup>2</sup>
- ▣ Neuren potential revenue over 2022 and 2023 for Rett syndrome in the US alone of A\$111 million<sup>3</sup> plus double-digit percentage royalties on net sales
- ▣ Positive Phase 3 results expected to enable Neuren to partner in Europe and Asia
- ▣ Diagnosis rates expected to increase with awareness and accelerate with availability of a treatment

<sup>2</sup> Acadia 2Q18 Earnings Call presentation and Jefferies Healthcare Conference 2 June 2021

<sup>3</sup> Assuming a New Drug Application (NDA) is approved by the FDA, the product is launched in the US, US\$33m is received as one third share of the value of a Rare Pediatric Disease Priority Review Voucher if awarded upon approval of a NDA, and a USD/AUD exchange rate of 0.75

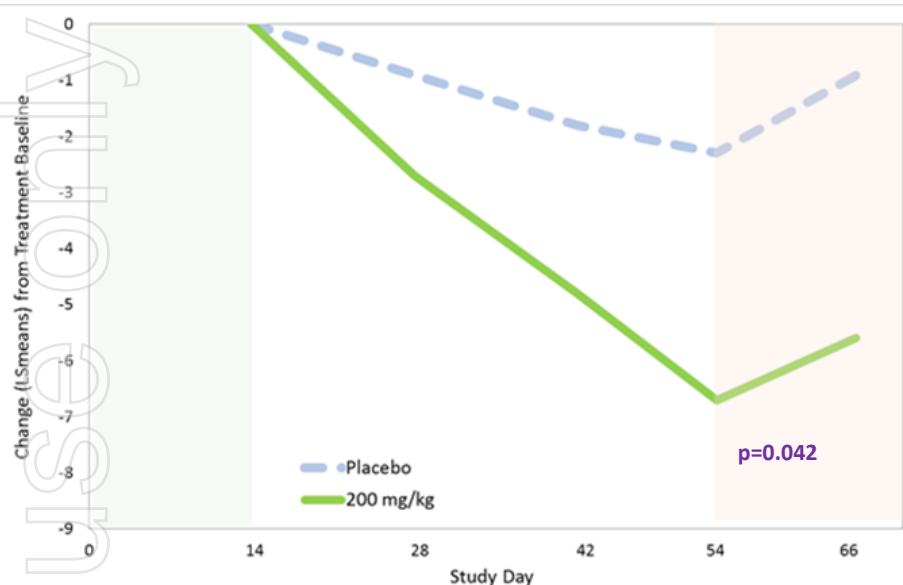
# RETT SYNDROME PHASE 3 PROGRAM



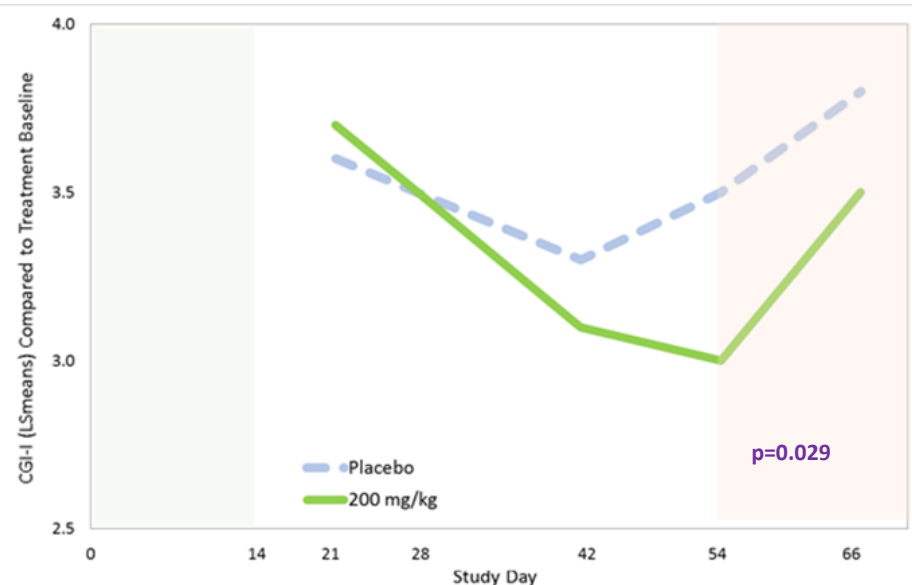
- LAVENDER™ enrolment completed – top-line results expected in Q4 2021
- 180 females aged 5 to 20 years
- RSBQ (caregiver) and CGI-I (physician) at 12 weeks are co-primary efficacy endpoints - both were positive in the Phase 2 trial
- Program includes DAFFODIL™ safety/PK trial in females aged 2 to 5 years
- Potential marketing approval in 2022 with Priority Review

# RETT SYNDROME PHASE 2 - RSBQ AND CGI-I

Clinical improvement measured by RSBQ



Clinical improvement measured by CGI-I



RSBQ is a caregiver rating, reflecting the severity of the syndrome. Mean improvements for trofinetide and placebo were, respectively, 16% and 6%

CGI-I is a clinician rating of how much the subject's overall illness has improved or worsened. 22% of subjects on trofinetide received a score of 2 ("much improved") compared with 4% of subjects on placebo

RSBQ and CGI-I measure overall syndrome rather than a particular symptom, reflecting heterogeneity of symptoms and disease-modifying action of trofinetide

Publication: <https://n.neurology.org/content/early/2019/03/27/WNL.0000000000007316>



# MAXIMISING PROBABILITY OF SUCCESS

- The Phase 3 co-primary endpoints were both positive in the Phase 2 trial
- In the Phase 2 trial clinical improvement continued increasing through to end of treatment - the Phase 3 trial at 12 weeks is twice the duration of the Phase 2 trial
- The Phase 3 sample size at approx. 90 per group is more than 3 times the Phase 2 sample size – much greater statistical power to detect a difference between active and placebo
- The dosing regimen in the active group for the Phase 3 trial is optimised, informed by the PK-PD analyses of the Phase 2 subjects
- The age range for the Phase 3 trial is 5 to 20 years, compared with 5 to 15 years in the Phase 2 trial
- Both trials are US sites only, with most Phase 2 sites participating in Phase 3

# **NNZ-2591 FOR MULTIPLE NEURODEVELOPMENTAL DISORDERS**

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# ESTIMATES OF TARGET PATIENT POPULATIONS

Disorder	Gene mutation	Published prevalence estimates	Potential patients		
			US <sup>1</sup>	Europe <sup>1</sup>	Asia <sup>1, 2</sup>
Phelan-McDermid	<i>SHANK3</i>	1/8,000 to 1/15,000 males and females	22,000	28,000	81,000
Angelman	<i>UBE3A</i>	1/12,000 to 1/24,000 males and females	14,000	18,000	52,000
Pitt Hopkins	<i>TCF4</i>	1/34,000 to 1/41,000 males and females	7,000	9,000	25,000
Prader-Willi	<i>15q11-q13</i>	1/10,000 to 1/30,000 males and females	13,000	16,000	47,000
			<b>56,000</b>	<b>71,000</b>	<b>205,000</b>

- Current opportunity for NNZ-2591 is more than 5 times the Rett Syndrome opportunity<sup>3</sup>
- There are many other neurodevelopmental disorders potentially relevant for NNZ-2591 mechanism of action

<sup>1</sup> Estimates derived by applying the mid-point of the prevalence estimate range to the populations under 60 years

<sup>2</sup> Asia comprises Japan, Korea, Taiwan, Israel and urban populations of China and Russia

<sup>3</sup> Based on number of addressable patients globally

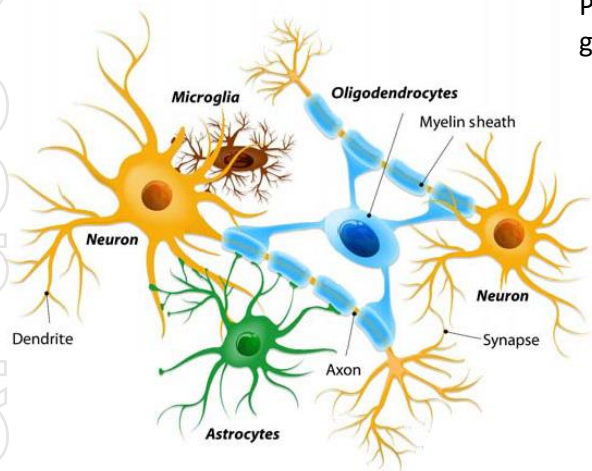
# NNZ-2591 MECHANISM OF ACTION

**NNZ-2591** is a synthetic analog of cyclic glycine proline, a peptide that occurs naturally in the brain, designed to be more stable, orally bioavailable and readily cross the blood-brain barrier

**NNZ-2591** can regulate the amount of IGF-1 that is available to activate IGF-1 receptors

The effects of **NNZ-2591** are “state-dependent” – correcting impairment, but not impacting normal cells

## NEURONS AND NEUROGLIAL CELLS



Produce essential growth factor

IGF-1

Reversible binding  
regulates bioavailability

IGF-1

IGF Binding Protein-3

Competitively binds to binding protein, regulating IGF-1 binding<sup>1</sup>

NNZ-2591

Activates PI3K–Akt–mTOR and Ras–MAPK–ERK signalling pathways in neurons, regulating formation of new synapses

IGF-1

IGF-1 receptor on cell surface

<sup>1</sup> doi: 10.1038/srep04388: Guan et al, 2017: Cyclic glycine-proline regulates IGF-1 homeostasis by altering the binding of IGFBP-3 to IGF-1

# FOUNDATIONS IN PLACE FOR MULTIPLE INDICATIONS

Neuren is leveraging experience from Rett syndrome program across all areas to execute much faster development for NNZ-2591

**2022**

Phase 2 data in multiple indications

**2021**

INDs approval by FDA

Commence Phase 2 trials in multiple indications

**2020**

Identify optimum dose

Develop and scale-up manufacturing

GMP manufacturing for Phase 2

Non-clinical safety studies

Phase 1 trial

3 EU Orphan designations

**2019**

Confirm blood brain barrier penetration

3 positive animal models

3 US Orphan designations

New patents in Europe and Japan

# IDEAL ATTRIBUTES LEADING INTO PHASE 2

- ✓ Novel mechanism of action
- ✓ Clear and consistent efficacy in mouse models of each syndrome
- ✓ Biochemical effects in the brain and optimum dose confirmed
- ✓ Demonstrated high oral bioavailability and blood-brain barrier penetration
- ✓ IND-enabling program of non-clinical toxicology and CMC studies completed
- ✓ Proprietary drug substance manufacturing process with exceptional purity and high yield, administered as patient-friendly liquid dose
- ✓ Safe and well tolerated in Phase 1 trial
- ✓ Phase 2 plans confirmed at pre-IND meetings with FDA
- ✓ Orphan designations from FDA and EMA

# THREE PHASE 2 TRIALS COMMENCING H2 2021

- Prioritising speed to data – results in H2 2022:
  - Angelman syndrome trial in Australia
  - Phelan-McDermid and Pitt Hopkins trials in US
  - Up to 20 patients in each trial
- First trials maximise opportunity to demonstrate effects:
  - Pediatric patients
  - 13 weeks' treatment
- Confirm safety and PK in pediatric patients
- Assess treatment impact across multiple efficacy measures

**Overall aim – expedite data that enables subsequent trials to be designed as registration trials**



# PHASE 1 CLINICAL TRIAL HIGHLIGHTS

- Twice daily dosing for 7 days was safe and well tolerated at all dose levels tested in healthy volunteers
- No SAEs, no clinically significant findings in lab or cardiac tests
- All AEs mild or moderate and resolved during the trial
- At highest dose all AEs were mild apart from one moderate
- Most common AE was drowsiness

**= Good safety and tolerability profile for dosing patients in Phase 2**

# APPENDIX

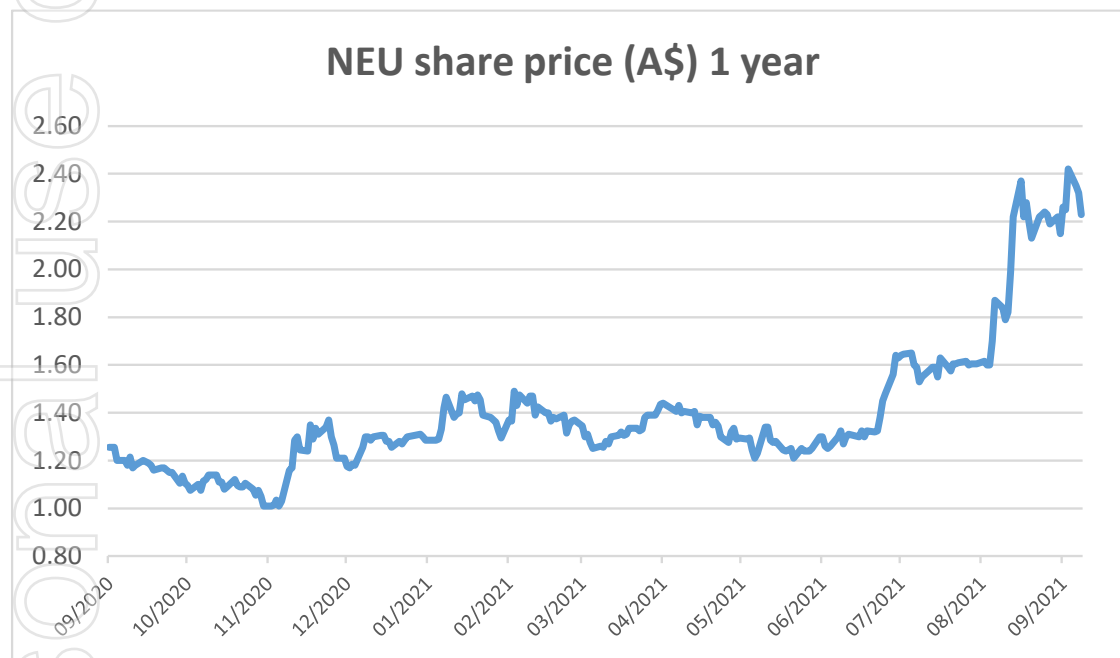
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# STOCK INFORMATION (ASX: NEU)

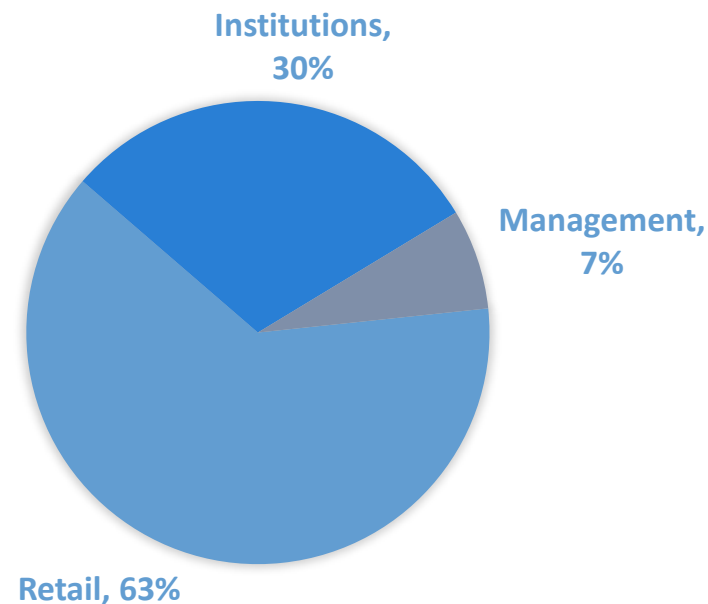
Current risk-adjusted valuation per share (MST Access) - A\$3.93

52 week price range: A\$1.00 - A\$2.53

NEU share price (A\$) 1 year



Current share register composition before Offer (114 million quoted shares – top 20 hold 50%)



A\$16.0 million cash at 31 July 2021

# MANAGEMENT AND BOARD

- Management team has devised and executed Neuren's Orphan Drug programs since 2013
- Extensive international pharmaceutical business experience
- Successfully developed drugs from pre-clinical through to FDA approval
- Executed multiple partnering transactions



Jon Pilcher  
Chief Executive Officer



Larry Glass  
Chief Science Officer



Dr Clive Blower  
VP Product Development



Dr Nancy Jones  
VP Clinical Development



James Shaw  
VP Clin/Reg Operations



Patrick Davies  
Non-exec Chairman



Dianne Angus  
Non-exec Director



Dr Jenny Harry  
Non-exec Director



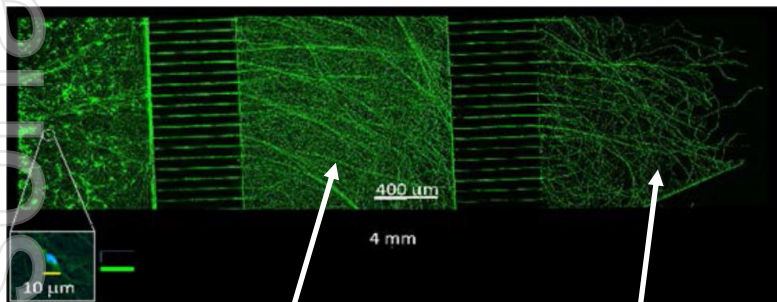
Dr Trevor Scott  
Non-exec Director



Lauren Frazer  
CFO & Co. Secretary

# CORRECTING IMPAIRED SIGNALING IN NEURONS

- Neurodevelopmental disorders result from different gene mutations, but all feature impaired signaling between neurons, with abnormal length and density of the dendritic spines that connect the neurons via synapses
- This impaired signaling causes behavioral, cognitive, motor and autonomic problems
- Trofinetide and NNZ-2591 address 3 characteristics common to these disorders:
  - Reduce inflammation associated with excessive inflammatory cytokines
  - Normalise abnormally low levels of IGF-1
  - Normalise the microglia phenotype for effective synaptic pruning and maintenance
- This restores the normal balance between protein synthesis forming new spines and maintenance of spines by microglia, correcting the length and density



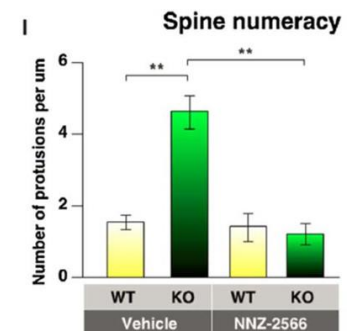
Abnormal dendrites in *shank3* knockout mice

Normalisation after treatment with NNZ-2591

## Correction of abnormal dendritic spines in mouse models:

Left - Phelan-McDermid syndrome (*shank3*)

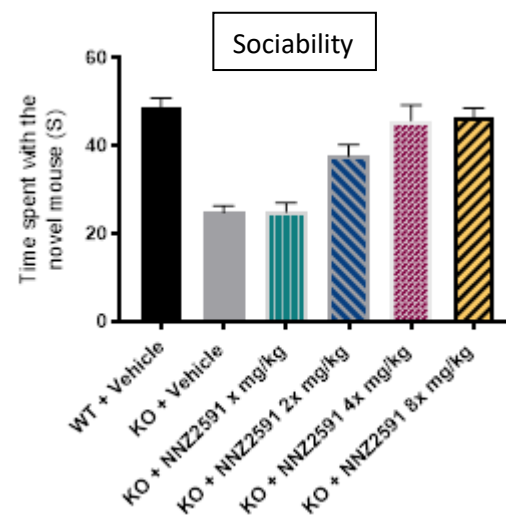
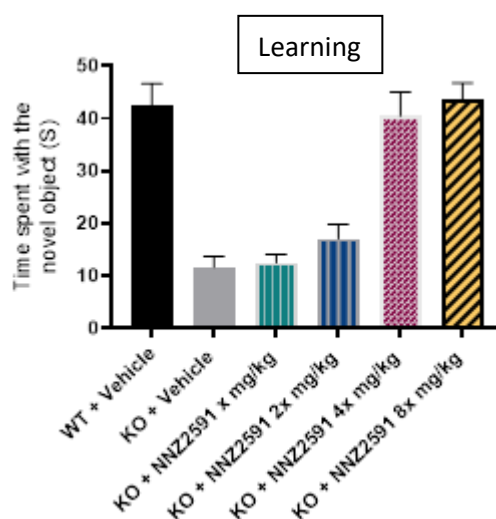
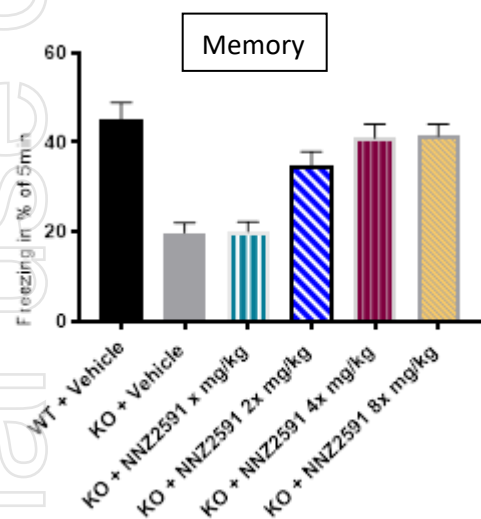
Right - Fragile X syndrome (*fmr1*)



Correction in *fmr1* knockout mice after treatment with trofinetide (NNZ-2566)

# CONSISTENT EFFICACY AND DOSE RESPONSE IN PHELAN-MCDERMID MODEL

PMS is caused by a deletion or other change in the 22q13 region of chromosome 22, which includes the *SHANK3* gene, or a mutation of the gene. In the *shank3* knockout mouse model, wild type mice and knockout mice were treated with placebo or 4 escalating dose levels of NNZ-2591 for 6 weeks. Results clearly indicate 2<sup>nd</sup> highest dose as optimum dose, informing dose selection for clinical trials in patients.

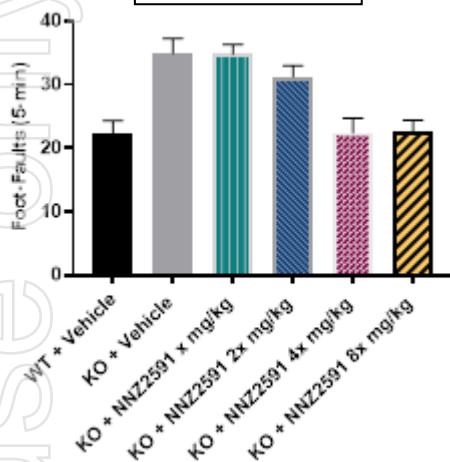


Incidence of seizures

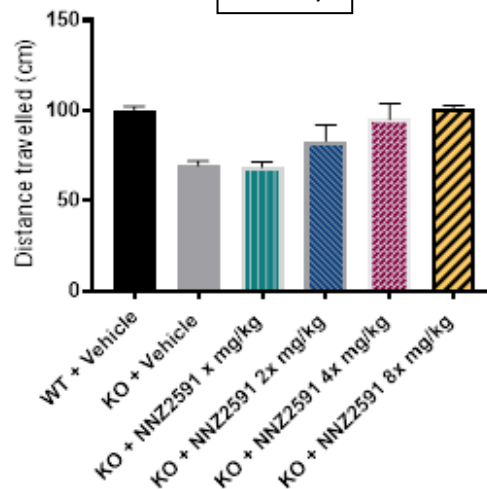
WT + vehicle	KO + vehicle	KO + x mg/kg	KO + 2x mg/kg	KO + 4x mg/kg	KO + 8x mg/kg
0%	60%	50%	30%	10%	10%

# CONSISTENT EFFICACY AND DOSE RESPONSE IN PHELAN-MCDERMID MODEL

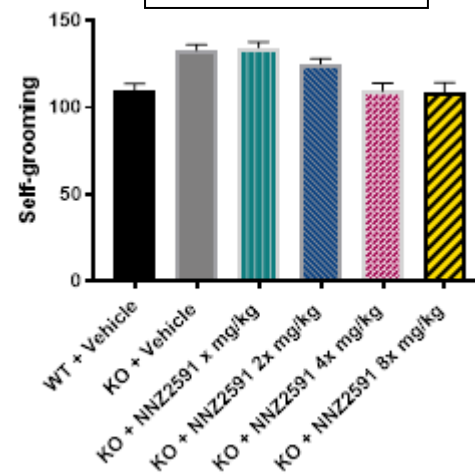
Motor function



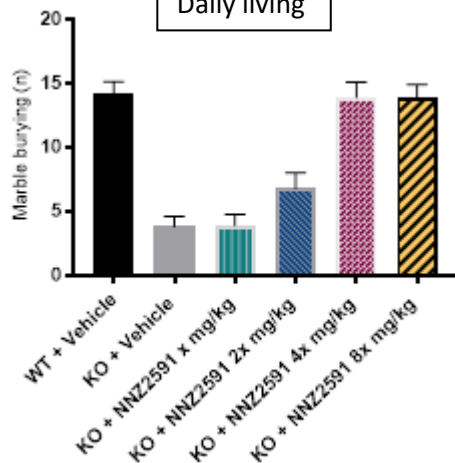
Anxiety



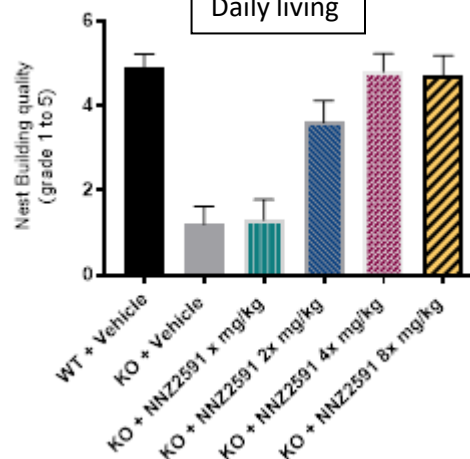
Repetitive behavior



Daily living



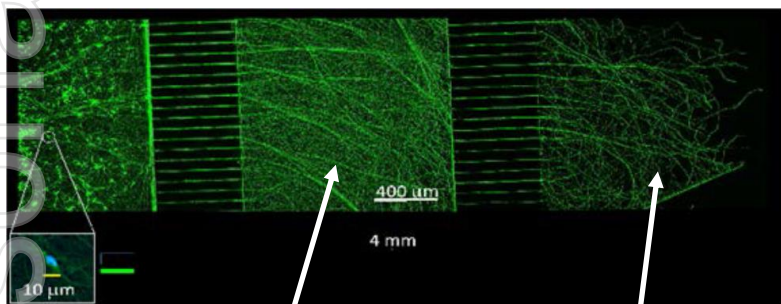
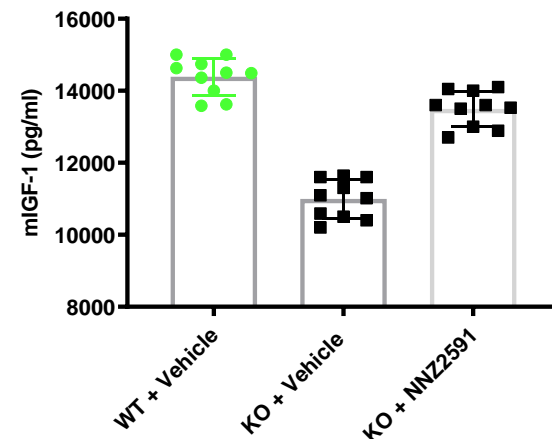
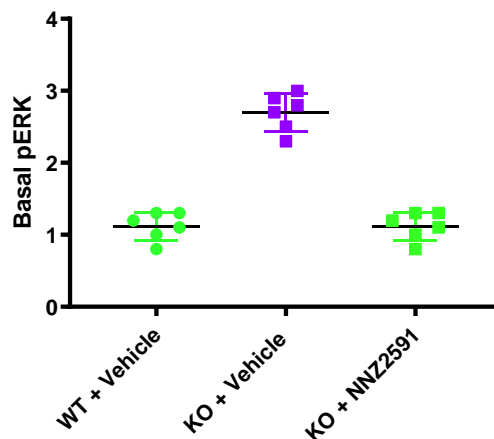
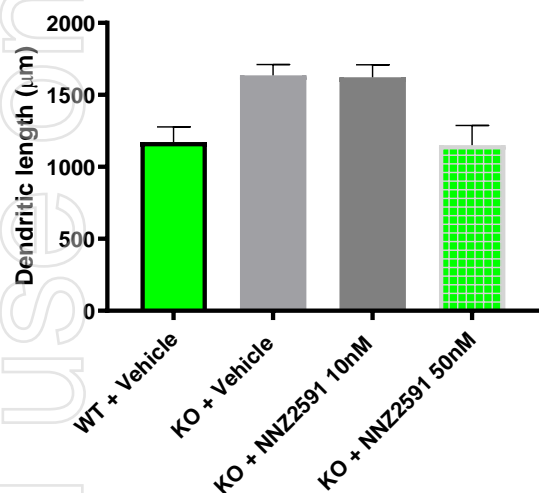
Daily living





# BIOCHEMICAL EFFECTS CONFIRMED IN *SHANK3* MODEL

In biochemical testing, NNZ-2591 was shown to normalise the abnormal length of dendrite spines between brain cells, the excess activated ERK protein (pERK) and the depressed level of IGF-1 in *shank3* knockout mice.

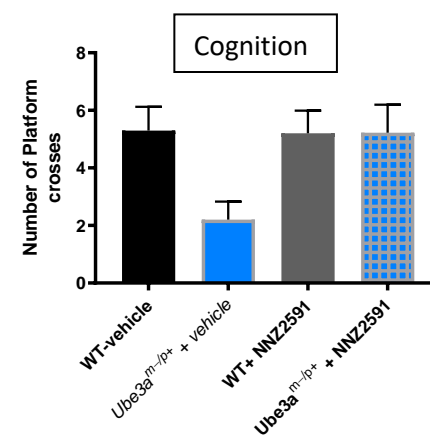
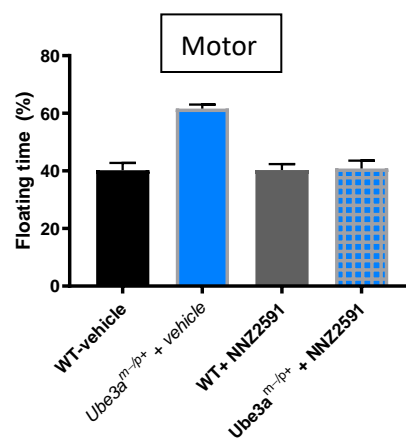
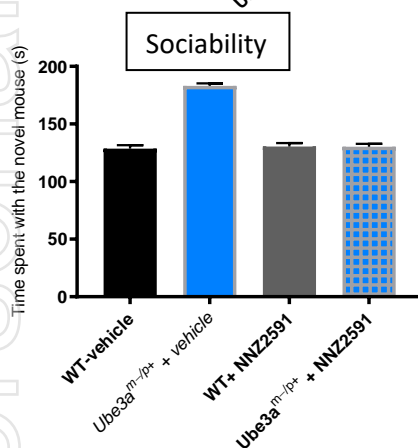
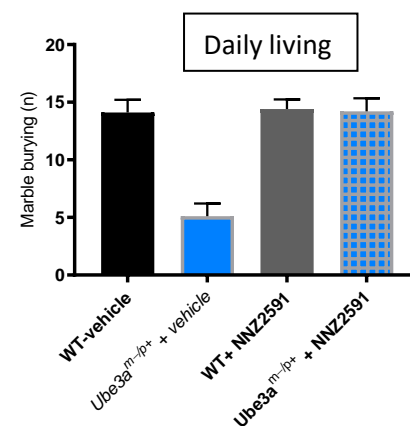
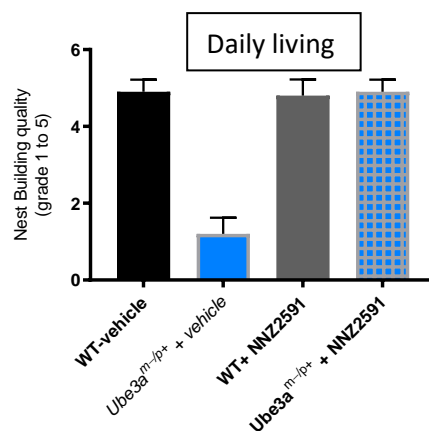
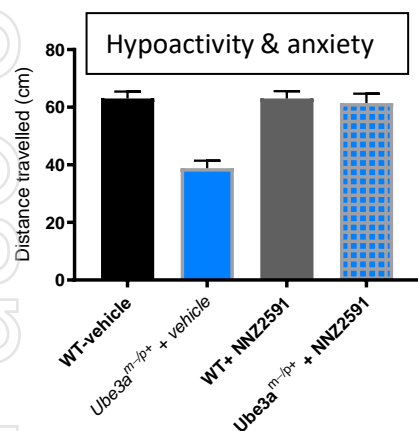


Abnormal dendrites in *shank3* knockout mice

Normalisation after treatment with NNZ-2591

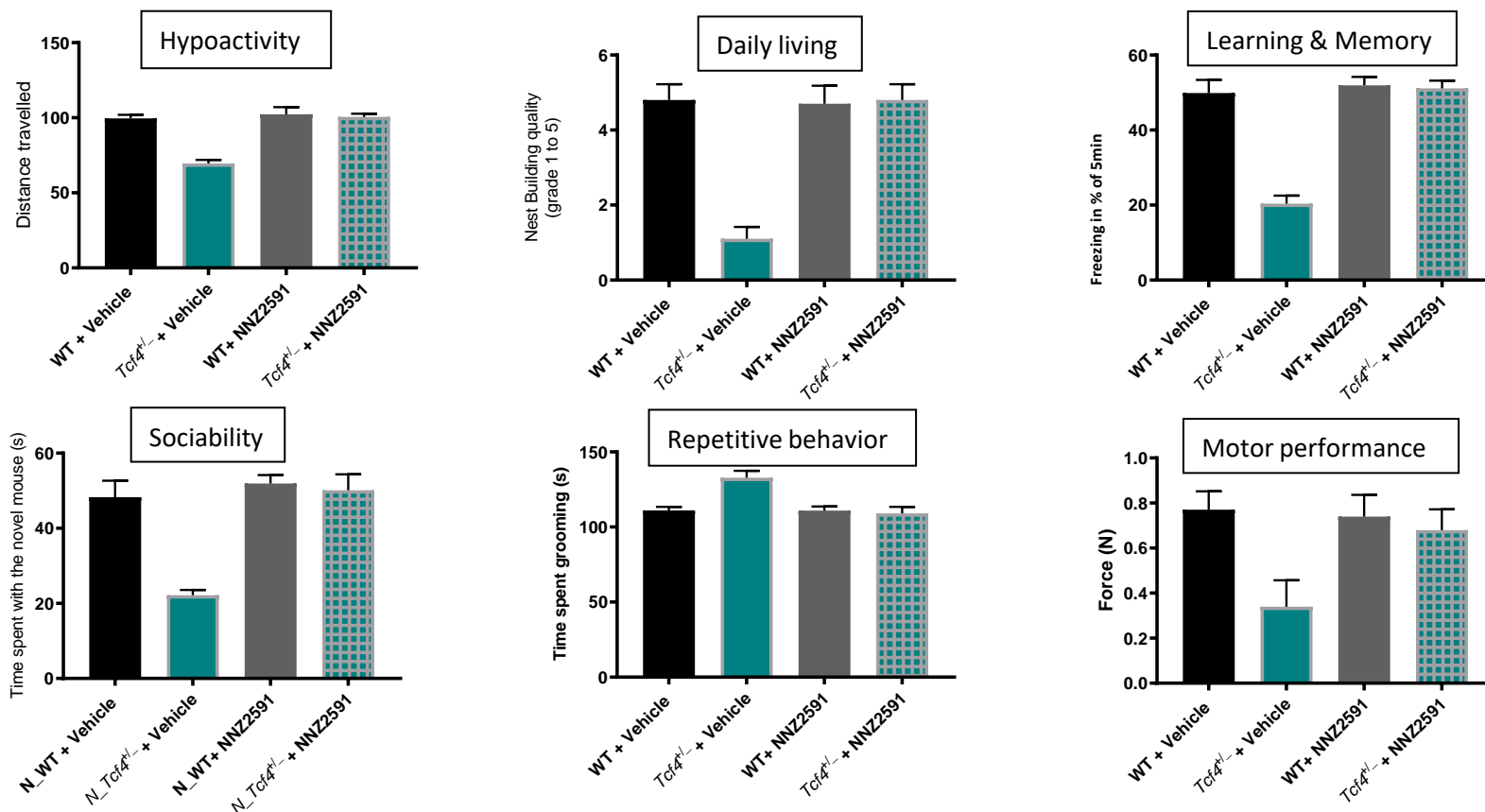
# CONSISTENT EFFICACY IN ANGELMAN MODEL

AS is caused by a deletion or mutation in the ubiquitin protein ligase E3A (*UBE3A*) gene on chromosome 15. In the *ube3a* knockout mouse model, which resembles features of AS in humans, wild type and knockout mice were each treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized all the deficits in the knockout mice, **including eliminating seizures**, and had no effect on the wild type mice.



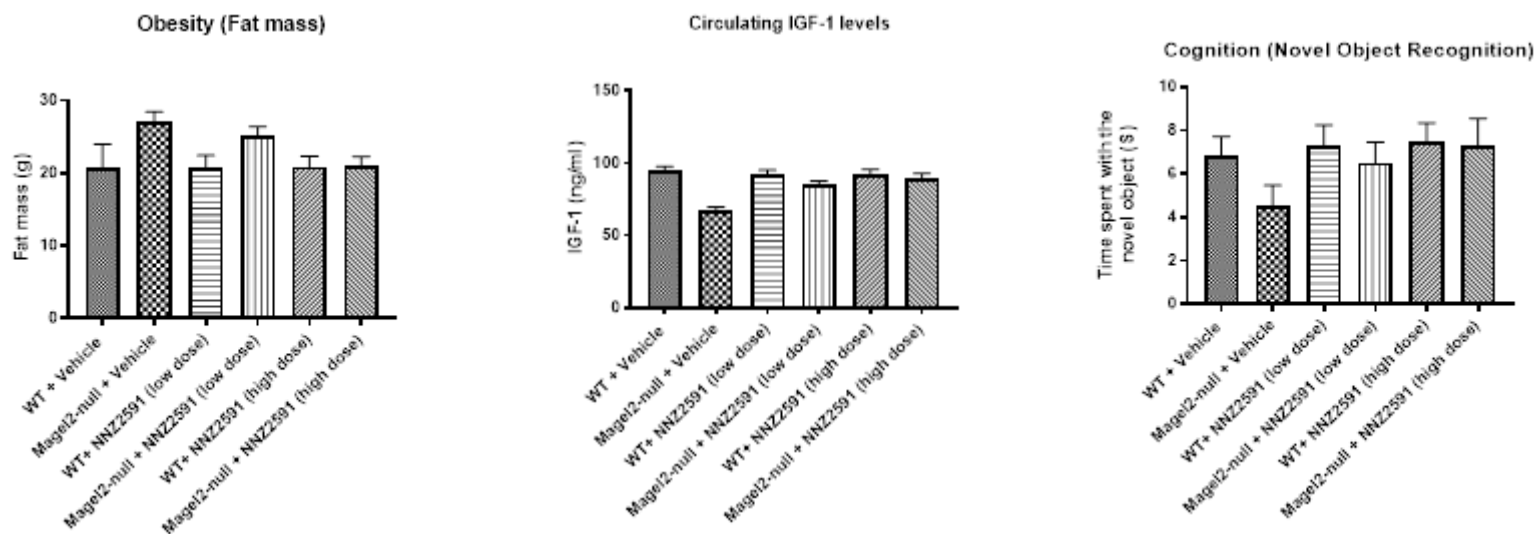
# CONSISTENT EFFICACY IN PITT HOPKINS MODEL

PTHS is caused by the loss of one copy or a mutation of the *TCF4* gene on chromosome 18. In the *tcf4* mutation mouse model, which exhibits features of PTHS in humans, wild type mice and knockout mice were treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized all the deficits in the knockout mice and had no effect on the wild type mice.



# CONSISTENT EFFICACY IN PRADER-WILLI MODEL

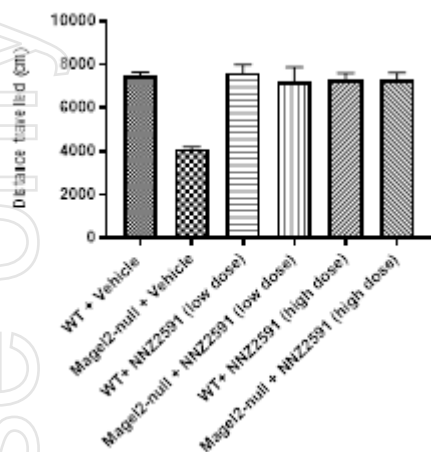
PWS is caused by mutations in the *15q11-q13* region of chromosome 15. In the *Magel2*-null mouse model, which exhibits features of PWS in humans, wild type mice and knockout mice were treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized fat mass, insulin levels, IGF-1 levels and all the behavioral deficits in the knockout mice and had no effect on the wild type mice.



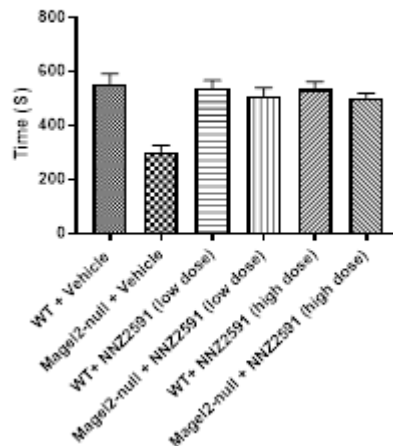
Insulin levels (pM)					
WT plus vehicle	<i>Magel2</i> -null plus vehicle	WT plus NNZ-2591 low dose	<i>Magel2</i> -null plus NNZ-2591 low dose	WT plus NNZ-2591 high dose	<i>Magel2</i> -null plus NNZ-2591 high dose
110	173	112	143	115	119

# CONSISTENT EFFICACY IN PRADER-WILLI MODEL

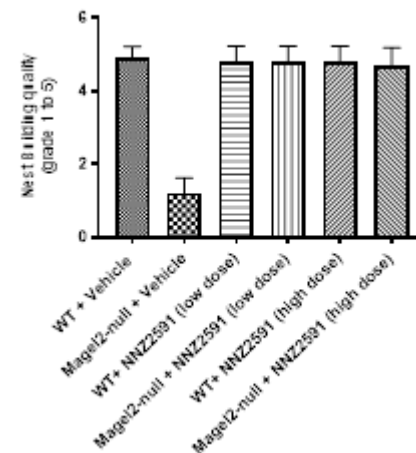
Hypoactivity (Open Field distance travelled)



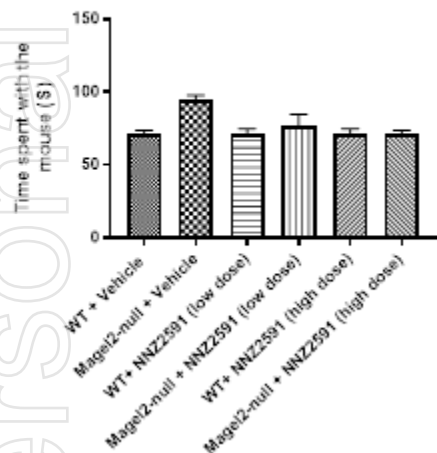
Hypoactivity (Open Field time spent active)



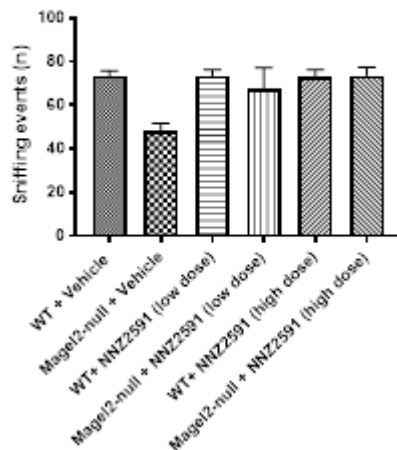
Daily living (Nest building)



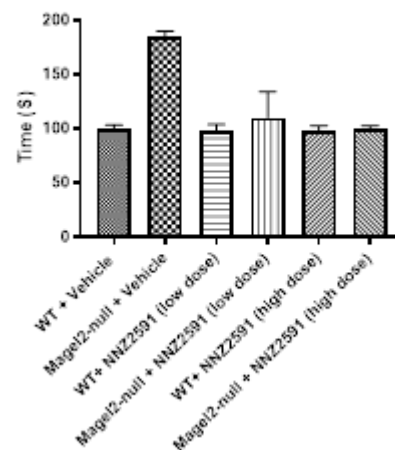
Social preference (novel mouse)



Social Interaction (Sniffing events)



Anxiety (Elevated Plus maze, time spent in open arm)



## **RISK FACTORS**

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# RISK FACTORS

This section sets out some of the key risks associated with any investment in the Company, together with risks relating to participating in the Placement and SPP which may affect the value of the Company's securities.

The risks are not set out in order of importance and do not constitute an exhaustive list of all risks involved with an investment in the Company.

Before investing in the Company, you should carefully consider the risk factors and your personal circumstances. You should also consider all publicly available information, including the Company's ASX announcements available at [www.asx.com.au](http://www.asx.com.au).

## **Business Risk Factors**

### **Reliance on key personnel**

Due to the specialised nature of the Company's technology and products, its future depends on attracting and retaining suitably qualified senior management, scientific and research personnel.

The biotechnology industry has strong competition for highly skilled scientists and researchers due to the limited number of people with the appropriate skill set. The Company currently employs, or engages as consultants, a number of key senior management, scientific and research personnel.

There is a risk that the Company will be unable to attract and retain the necessary staff to pursue its strategies. This could materially and adversely affect the Company's business, operating results and financial prospects.

### **Contract risks generally**

Neuren operates through a series of contractual relationships with licensors, sublicensees, independent contractors, distributors and suppliers. All contracts carry risks associated with the performance by the parties thereto of their obligations as to time and quality of work performed.

### **Risk as to technical capacity**

The Company intends to carry out development work using appropriately chosen scientific research organisations. As such, it will be subject to the risk that staff in those organisations may have greater or lesser technical capacity than needed to achieve the results sought to be obtained from any development programme. No development programme is thus under the sole control of the Company. If, for any reason, incompetent staff in any such organisation carry out research then the results sought to be obtained may not be obtained or results apparently obtained may be inaccurate as a result of flawed research or development.

### **Development and commercialisation of the Company's intellectual property or products**

The Company regards the content of certain of its technology as proprietary and relies primarily on a combination of copyright, patent and trade secrecy laws and employee and third party non-disclosure agreements to protect its rights. Those steps may, however, not be adequate to fully protect those rights. No assurances can be given that employees and/or third parties will not breach non-disclosure agreements or infringe or misappropriate the Company's rights.

Further, no assurance can be given that others will not challenge the ownership or validity of those proprietary rights by attacking either the Company or patent holders from whom the Company has acquired licences. In addition, effective copyright and patent protection may be unavailable or limited in certain countries.

Litigation may be necessary from time to time to enforce and protect the Company's rights. Such litigation can be costly and could have adverse effects on its activities, business, operating results and financial position. Likewise, a failure to succeed in protecting any such rights may equally have a materially adverse effect on the Company's activities, business, operating results and financial position.

It is possible that other parties may assert intellectual property infringement, unfair competition or like claims against the Company under copyright, trade secret, patent or other laws. While the Company is not aware of any claims of this nature in relation to any of the intellectual property rights in which it has interests, such claims, if made, may harm, directly and indirectly, the Company's business. If the Company is forced to defend against claims of intellectual property infringement, whether they are with or without merit or are determined in the Company's favour, the Company might face costly litigation and diversion of management's attention. As a result of such disputes, the Company may have to develop non-infringing technology or enter into royalty or licensing agreements. Such agreements, if necessary, may be unavailable on terms acceptable to the Company, or at all. If there is a successful claim of intellectual property infringement or unfair competition against the Company and it is unable to develop non-infringing technology or license the infringed or similar technology or content on a timely basis, it could harm the Company's business, operations and financial condition.

# RISK FACTORS (CONT'D)

## Competition

The Company's current and potential future competitors might include companies with significantly greater resources than Neuren. These competitors may develop products or services that are more effective and/or cheaper than those being developed by the Company, and as a consequence the Company's products or services may become uncompetitive, resulting in adverse effects on revenue, margins and profitability.

## Product development

There are many risks inherent in the development of biotechnology products. They are subject to risks of failure during clinical trials or may fail to achieve sufficient robustness and reliability. The Company cannot guarantee that the development work being undertaken will result in the development of any products, or even if they do, that those products will be commercially successful.

Further, any material delays in the clinical trial process may substantially increase the cost of development. Material delays could also result in the Company failing to commercialise its products. Delays could occur during any stage of the development and commercialisation process including during toxicology studies, regulatory approval for late-stage clinical trials, manufacture of drug substance for late-stage clinical trials, enrolment of patients into clinical trials and/or scheduling delays by suppliers.

## Sufficiency of funding

The Company has a business plan which will require a high level of expenditure until product revenue streams are established. In the future, Neuren may need to raise further financing through other public or private equity financings, collaborations or other arrangements with corporate or governmental sources, or other sources of financing to fund operations and achieve milestones. There can be no assurance that such additional financing, if available, can be obtained on terms reasonable to Neuren. In the event the Company is unable to raise additional capital, future operations may need to be curtailed or discontinued.

## Product liability

Unforeseen problems, human error, deficiencies in research, development or testing or poor production quality of one or more of the Company's products may lead to product liability risk. In addition, as with all new products, there can be no assurance that unforeseen adverse events or defects will not arise. Adverse events may expose the Company to product liability claims or litigation, result in the loss of regulatory approvals for the relevant products and/or monetary damages being awarded against the Company.

While the Company currently has product liability insurance to cover these risks, there is no guarantee that the Company will be fully insured to cover its loss.

## Regulatory risks

Operations by the Company may require approvals from regulatory authorities which may not be forthcoming or which may not be able to be obtained on terms acceptable to the Company. While the Company has no reason to believe that all requisite approvals will not be forthcoming, investors should be aware that the Company cannot guarantee that any requisite approvals will be obtained. A failure to obtain any approvals would mean that the ability of the Company to develop or operate any project may be limited or restricted either in part or absolutely.

## Investment risk factors

### Shareholder dilution

In the future, the Company may elect to issue Shares or engage in capital raisings to fund research and development or other activities, for working capital purposes or for other opportunities that the Company may decide to pursue. While the Company will be subject to the constraints of the Corporations Act, shareholders at the time may be diluted as a result of such issues of Shares and capital raisings.

### Force majeure events

Events may occur within or outside Australia that could impact upon the Australian economy, the operations of the Company and the value of the Shares. The events include but are not limited to acts of terrorism, an outbreak of international hostilities, fires, floods, earthquakes, labour strikes, civil wars, natural disasters, outbreaks of disease (including COVID-19) or other natural or man-made events or occurrences that can have an adverse effect on the demand for the Company's products and its ability to conduct business.



# RISK FACTORS (CONT'D)

## **Change in the Australian tax system**

Any future changes in Australian tax law, including changes in interpretation or application of the law by the courts or taxation authorities in Australia, may affect the taxation treatment of the acquisition, holding and disposal of the New Shares and the market price of the New Shares.

## **Share market risks generally**

Potential investors should recognise that the prices of shares fall as well as rise. Many factors affect the price of shares including local and international stock markets, movements in interest rates, economic and political conditions and investor and consumer sentiment.

## **New Shares risk**

Investments in the New Shares are an investment in the Company and may be affected by the ongoing performance, financial position and solvency of the Company. The New Shares are not guaranteed by any government, government agency or compensation scheme in Australia or by any other person or any other jurisdiction.

## **Foreign currency risk**

The underlying currency in which the Company's revenues and costs are denominated primarily in Australian dollars, US dollars and Sterling. The currency which the Company currently reports in is Australian dollars. The fact that the Company has a portion of its revenues and costs denominated in a currency other than its functional currency can and has created gains or losses arising from foreign exchange translations.

## **Political factors**

Apart from exchange risks there are a wide range of other macroeconomic and political factors beyond the control of the Company which may affect the Company's operations including the consequences of terrorist and other activities which themselves impact adversely on the global economy and share market conditions and share prices generally.

## **Coronavirus (COVID-19)**

Events related to the COVID-19 pandemic have resulted in significant market volatility. There is continued uncertainty as to ongoing and future response of governments and authorities globally as well as a likelihood of an Australian economic recession of unknown duration or severity. As such, the full impact of COVID-19 to consumer behaviour, suppliers, employees and the Company are not fully known. Given this, the impact of COVID-19 could potentially be materially adverse to the Company's financial and operational performance. Further, any government or industry measures may adversely affect the Company's operations and are likely beyond the control of Neuren. In compliance with its continuous disclosure obligations, the Company will continue to update the market in regard to any material impact of COVID-19 on its business.

## **Other**

Other risk factors that apply generally in the conduct of a business, including litigation resulting from the breach of agreements or in relation to employees or contractors (through personal injuries, industrial matters or otherwise), loss of service of key management or operational personnel, non-insurable risks, delay in resumption of activities after reinstatement following the occurrence of an insurable risk and other matters that may all interfere with the Company's business and adversely affect its performance.

# FOREIGN SELLING RESTRICTIONS

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# FOREIGN SELLING RESTRICTIONS

This presentation does not constitute an offer of new ordinary shares ("New Shares") of the Company in any jurisdiction in which it would be unlawful. In particular, this presentation may not be distributed to any person, and the New Shares may not be offered or sold in any country outside of Australia, except to the extent permitted below.

## New Zealand

This document has not been registered, filed with or approved by any New Zealand regulatory authority under the Financial Markets Conduct Act 2013 (the "FMC Act"). The New Shares are not being offered or sold in New Zealand (or allotted with a view to being offered for sale in New Zealand) other than to a person who:

- is an investment business within the meaning of clause 37 of Schedule 1 of the FMC Act;
- meets the investment activity criteria specified in clause 38 of Schedule 1 of the FMC Act;
- is large within the meaning of clause 39 of Schedule 1 of the FMC Act;
- is a government agency within the meaning of clause 40 of Schedule 1 of the FMC Act; or
- is an eligible investor within the meaning of clause 41 of Schedule 1 of the FMC Act.

## Hong Kong

**WARNING:** This document has not been, and will not be, registered as a prospectus under the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32) of Hong Kong, nor has it been authorised by the Securities and Futures Commission in Hong Kong pursuant to the Securities and Futures Ordinance (Cap. 571) of the Laws of Hong Kong (the "SFO"). No action has been taken in Hong Kong to authorise or register this document or to permit the distribution of this document or any documents issued in connection with it. Accordingly, the New Shares have not been and will not be offered or sold in Hong Kong other than to "professional investors" (as defined in the SFO and any rules made under that ordinance).

No advertisement, invitation or document relating to the New Shares has been or will be issued, or has been or will be in the possession of any person for the purpose of issue, in Hong Kong or elsewhere that is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to New Shares that are or are intended to be disposed of only to persons outside Hong Kong or only to professional investors. No person allotted New Shares may sell, or offer to sell, such securities in circumstances that amount to an offer to the public in Hong Kong within six months following the date of issue of such securities. The contents of this document have not been reviewed by any Hong Kong regulatory authority. You are advised to exercise caution in relation to the offer. If you are in doubt about any contents of this document, you should obtain independent professional advice.

## United Kingdom

Neither this document nor any other document relating to the offer has been delivered for approval to the Financial Conduct Authority in the United Kingdom and no prospectus (within the meaning of section 85 of the Financial Services and Markets Act 2000, as amended ("FSMA")) has been published or is intended to be published in respect of the New Shares.

The New Shares may not be offered or sold in the United Kingdom by means of this document or any other document, except in circumstances that do not require the publication of a prospectus under section 86(1) of the FSMA. This document is issued on a confidential basis in the United Kingdom to "qualified investors" within the meaning of Article 2(e) of the UK Prospectus Regulation. This document may not be distributed or reproduced, in whole or in part, nor may its contents be disclosed by recipients, to any other person in the United Kingdom. Any invitation or inducement to engage in investment activity (within the meaning of section 21 of the FSMA) received in connection with the issue or sale of the New Shares has only been communicated or caused to be communicated and will only be communicated or caused to be communicated in the United Kingdom in circumstances in which section 21(1) of the FSMA does not apply to the Company.

In the United Kingdom, this document is being distributed only to, and is directed at, persons (i) who have professional experience in matters relating to investments falling within Article 19(5) (investment professionals) of the Financial Services and Markets Act 2000 (Financial Promotions) Order 2005 ("FPO"), (ii) who fall within the categories of persons referred to in Article 49(2)(a) to (d) (high net worth companies, unincorporated associations, etc.) of the FPO or (iii) to whom it may otherwise be lawfully communicated (together "relevant persons"). The investment to which this document relates is available only to relevant persons. Any person who is not a relevant person should not act or rely on this document.