neuren pharmaceuticals

IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

25 February 2022

FORWARD LOOKING STATEMENTS

This presentation contains forward looking statements that involve risks and uncertainties. Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Neuren can give no assurance that these expectations will prove to be correct. Actual results could differ materially from those anticipated. Reasons may include risks associated with drug development and manufacture, risks inherent in the regulatory processes, delays in clinical trials, risks associated with patent protection, future capital needs or other general risks or factors.

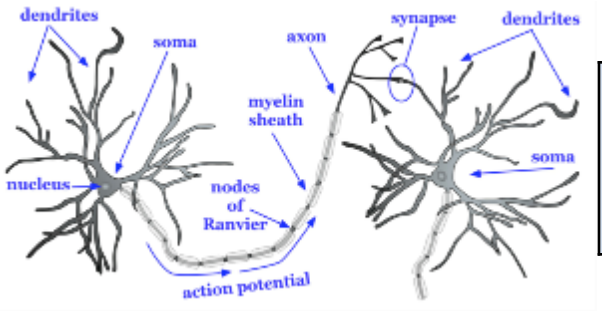
POSITIVE PHASE 3 RESULTS BEGIN NEUREN TRANSFORMATION

- **Robustly positive top-line results for trofinetide Phase 3 trial in Rett syndrome:**
  - Statistically significant improvement over placebo for both co-primary efficacy endpoints: RSBQ (p=0.0175) and CGI-I (p=0.0030), as well as key secondary endpoint: caregiver scale of ability to communicate (p=0.0064)
- **Rett syndrome NDA submission expected mid-2022, with potential for approval Q1 2023**
- **Neuren potential revenue from Acadia over 2022 and 2023 for Rett syndrome in the US alone of A$115 million[1] plus double-digit percentage royalties on net sales**
- **Partnering interest from multiple companies for ex-North America**
- **Large potential upside from NNZ-2591:**
  - Multiple indications and global rights retained
  - Funded for Phase 2 trials and Phase 3 preparation in 4 disorders
  - Potential markets more than 5 times Rett syndrome

[1] 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 0.72

TREATING NEURODEVELOPMENTAL DISORDERS

Rett	Fragile X	Phelan-McDermid	Angelman	Pitt Hopkins	Prader-Willi
MECP2	*FMR1*	*SHANK3*	*UBE3A*	*TCF4*	*15q11-q13*



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

LEADING PIPELINE IN NEURODEVELOPMENTAL DISORDERS

Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Commercial Partner
Trofinetide	Rett syndrome[1]					ACADIA (North America)
	Fragile X syndrome[1]					ACADIA (North America)
NNZ-2591	Phelan-McDermid syndrome[2]			***Commence H1 2022 Results H1 2023***		
	Angelman syndrome[2]					
	Pitt Hopkins syndrome[2]					
	Prader-Willi syndrome[3]			***Commencement expected mid-2022***		

[1] Orphan Drug designation in US and EU, Fast Track designation in US

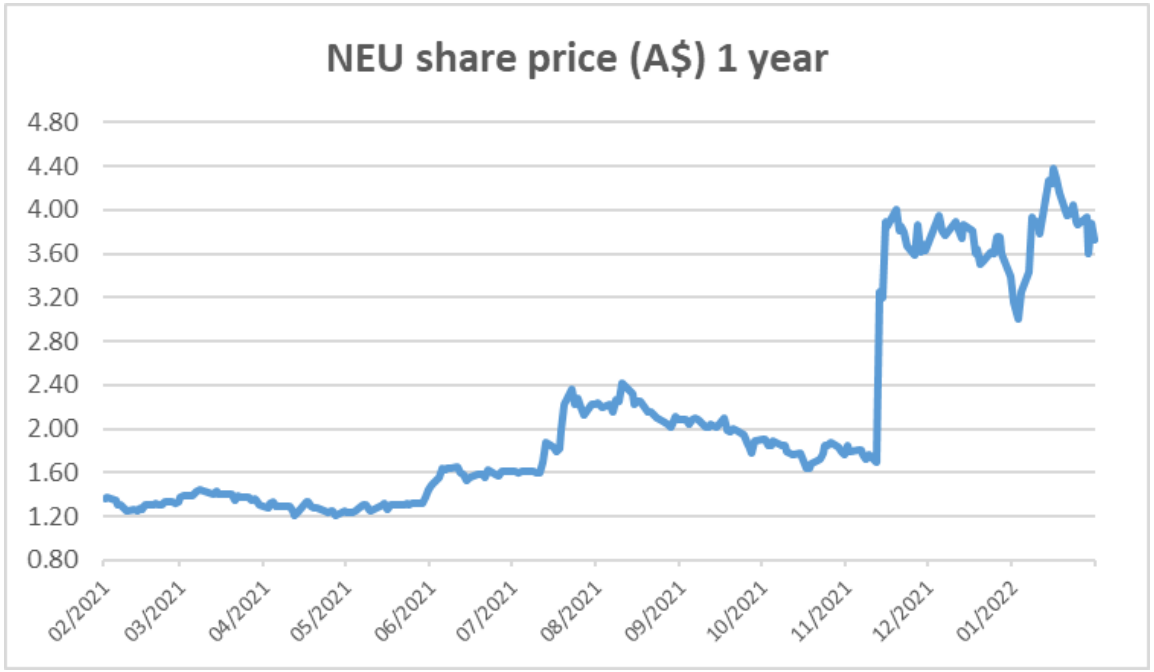
[2] Orphan Drug designation in US and EU [3] Orphan Drug designation in US

THREE KEY DRIVERS TRANSFORMING NEAR TERM VALUE

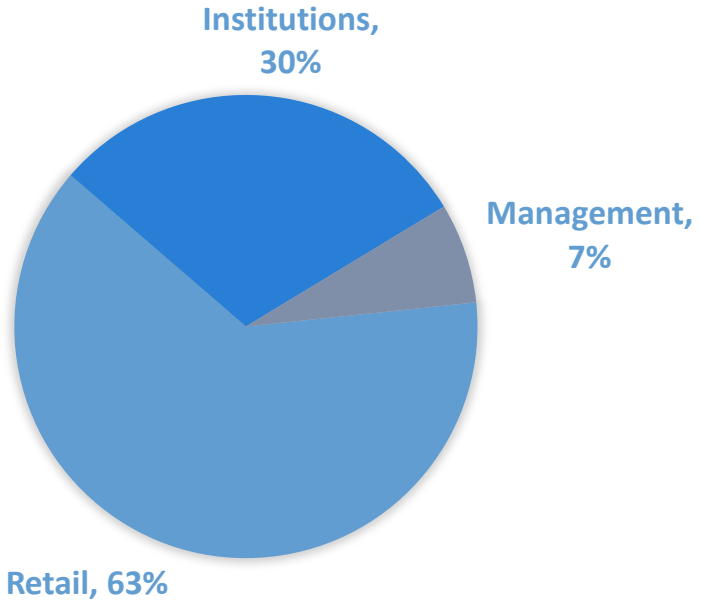
STOCK INFORMATION (ASX: NEU)

Current analyst risk-adjusted valuations per share: A$5.10 – A$7.70

52 week price range: A$1.20 - A$4.49



Current share register composition (126 million quoted shares – top 20 hold 50%)



A$37 million cash at 31 December 2021 – well funded to execute NNZ-2591 Phase 2 trials and preparation for Phase 3

KEY MILESTONES IN NEXT 18 MONTHS

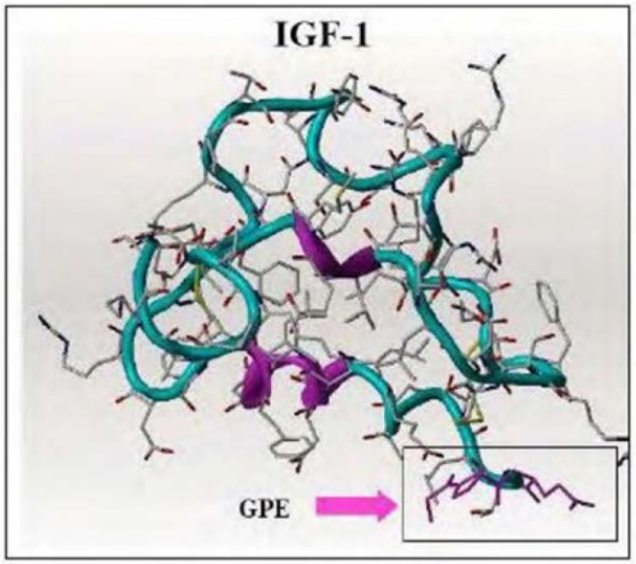
- Acadia pre-NDA meeting with FDA for Rett syndrome (Q1 2022)
- Commence Phase 2 trials in Angelman, Phelan-McDermid and Pitt Hopkins syndromes
- Acadia New Drug Application (NDA) for Rett syndrome (mid-2022)
- Commence Prader-Willi syndrome Phase 2 trial
- Commercial partnerships ex-North America for Rett syndrome
- Approval of NDA for Rett syndrome (Q1 2023)
- Phase 2 trial results in 4 indications (H1 2023)

TROFINETIDE FOR RETT SYNDROME

TROFINETIDE FOR RETT SYNDROME

Trofinetide

- Trofinetide is an investigational drug and a novel synthetic analog of GPE, the amino-terminal tripeptide of IGF-1



GPE=glycine-proline-glutamate; IGF-1= Insulin-like growth factor 1

Proposed Mechanism of Action[1]

Rett syndrome features:

- Insufficient formation of new synapses by neurons
- Excessive pruning of existing synapses by overactive microglia

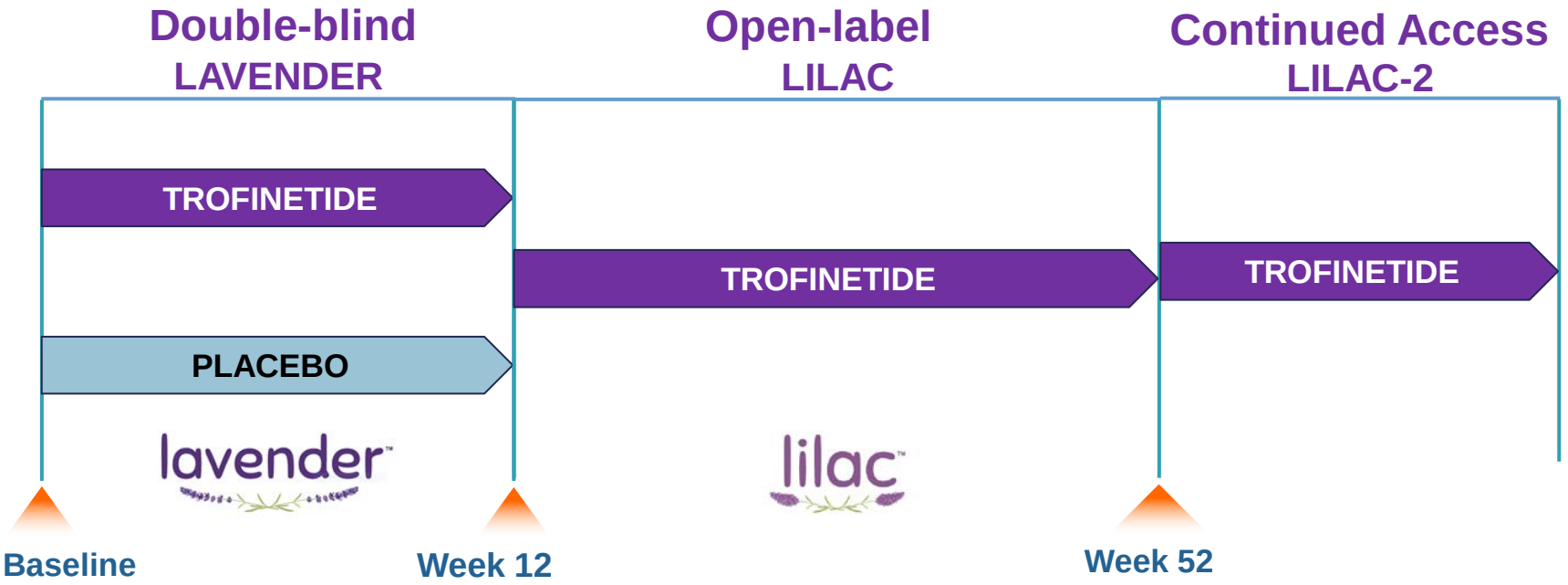
Trofinetide is thought to:

- Improve synaptic function and restore synaptic structure
- Inhibit overactivation of inflammatory microglia and astrocytes
- Increase the amount of IGF-1 in the brain

[1] Chahrour, Science, 2008; Itoh, J Neuropath Exp Neurol, 2007; Bourguignon, Brain Res, 1999; Tropea, PNAS, 2009
Source: Acadia Lavender Study Results Presentation https://ir.acadia-pharm.com/static-files/84457c64-60ab-4b2f-a166-edc1d465f4a8

RETT SYNDROME PHASE 3 AND NDA

- Acadia plans to submit NDA mid-2022; Orphan Drug qualifies for 6 months Priority Review, which means potential for approval in Q1 2023
- NDA based on pivotal efficacy from positive Phase 3 trial, supportive efficacy from Neuren's positive Phase 2 trial, safety data from completed and ongoing studies



- LAVENDER randomised, double-blind, placebo-controlled trial:
  - 187 females aged 5 to 20 years
  - RSBQ (caregiver) and CGI-I (physician) at 12 weeks co-primary efficacy endpoints

LAVENDER TOP-LINE EFFICACY RESULTS

	Placebo	Trofinetide
Primary Endpoints:		
Rett Syndrome Behaviour Questionnaire (RSBQ) (Change from baseline to week 12)	-1.7 (0.98)	-5.1 (1.38)
p-value		***p=0.0175***
Effect Size; Cohen's d		**0.37**
Clinical Global Impression of Improvement (CGI-I) (Score at week 12)	3.8 (0.06)	3.5 (0.08)
p-value		***p=0.0030***
Effect Size; Cohen's d		**0.47**
Key Secondary Endpoint:		
CSBS-DP-IT Social Composite Score (Change from baseline to week 12)	-1.1 (0.28)	-0.1 (0.28)
p-value		***p=0.0064***
Effect Size; Cohen's d		**0.43**

Source: Acadia Lavender Study Top-Line Results Presentation https://ir.acadia-pharm.com/static-files/84457c64-60ab-4b2f-a166-edc1d465f4a8

RETT SYNDROME OPPORTUNITY

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

[1] Potential patient estimates derived by applying the mid-point of the published prevalence estimate range to the populations under 60 years

North America

- Neuren potential revenue from Acadia:
  - US$10 million in 2022 following acceptance of NDA for review
  - US$40 million in 2023 following first commercial sale in the US
  - US$33 million in 2023 one third share of Priority Review Voucher estimated value[1]
  - Up to US$350 million on achievement of thresholds of annual net sales
  - Tiered, escalating double digit percentage royalties on net sales
- Peak annual sales potential in US at least US$500m[2]
- Orphan exclusivity plus patent to 2035

Ex-North America

- Partnering interest from multiple companies for individual countries and broader regions
- Neuren has full access to US data for registration ex-North America
- Strong interest from families, advocacy groups and physicians
- Lower diagnosis rates expected to increase with awareness and accelerate with availability of a treatment

[1] Assuming Rare Pediatric Disease Priority Review Voucher is awarded upon approval of a NDA and has a market value of US$100m

[2] Acadia 2Q18 Earnings Call presentation and Jefferies Healthcare Conference 2 June 2021

NNZ-2591 FOR MULTIPLE NEURODEVELOPMENTAL DISORDERS

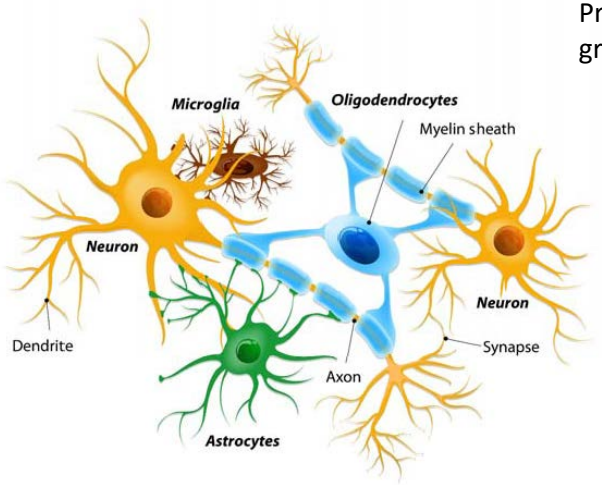
NNZ-2591 MECHANISM OF ACTION

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[1]

NNZ-2591

IGF-1

IGF-1 receptor on cell surface

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

[1] *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*

FIVE TIMES LARGER OPPORTUNITY FOR NNZ-2591

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

- **Current opportunity for NNZ-2591 is more than 5 times the Rett Syndrome opportunity[3]**
- **There are many other neurodevelopmental disorders potentially relevant for NNZ-2591 mechanism of action**
- **Neuren retains global rights**

[1] Estimates derived by applying the mid-point of the prevalence estimate range to the populations under 60 years
[2] Asia comprises Japan, Korea, Taiwan, Israel and urban populations of China and Russia
[3] Based on number of addressable patients globally

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
- ✓ Orphan designations from FDA and EMA

KEY FEATURES OF FIRST PHASE 2 TRIALS

Overall aim – expedite data that enables subsequent trials to be designed as registration trials and prepare for Phase 3 in parallel

- Prioritising speed to data:
  - AS trial in Australia, PMS and PTHS trials in US
  - Up to 20 patients in each trial, all patients receive drug
- Maximising opportunity to demonstrate effects:
  - Pediatric patients
  - 13 weeks' treatment following well-characterised baseline period
- Confirm safety and PK in pediatric patients
- Assess treatment impact across multiple efficacy measures to select primary endpoint for registration trial
- Commencing H1 2022, results expected in H1 2023
- Executing foundational preparations for Phase 3 across all indications

CONTACT

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APPENDIX 1 – NNZ-2591 DATA

PHASE 1 CLINICAL TRIAL HIGHLIGHTS

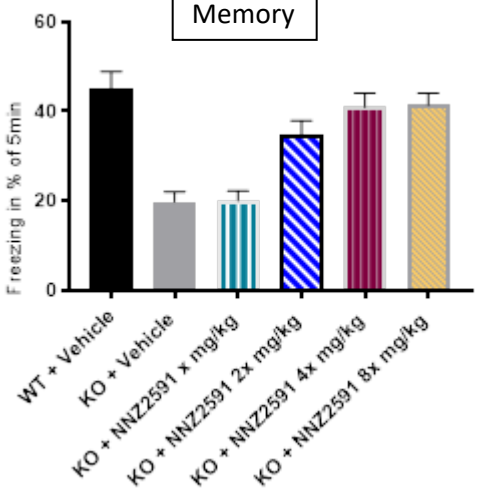
- Twice daily dosing for 7 days in healthy volunteers was safe and well tolerated at the dose level to be tested in Phase 2 trials
  - No SAEs, no clinically significant findings in lab or cardiac tests
  - All AEs mild or moderate and resolved during the trial
  - At highest dose all AEs were mild apart from one moderate
  - Most common AE was drowsiness

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

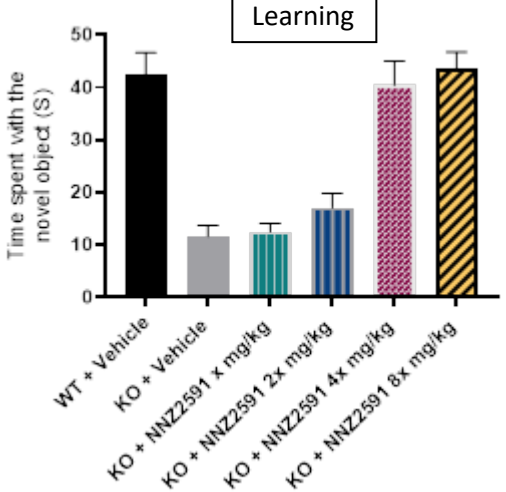
CONSISTENT EFFICACY AND DOSE RESPONSE IN PHELAN-MCDERMID MODEL

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 2nd highest dose as optimum dose, informing dose selection for clinical trials in patients.

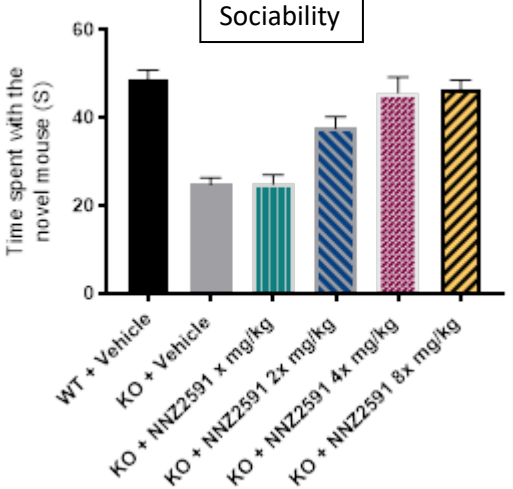
Memory



Learning



Sociability

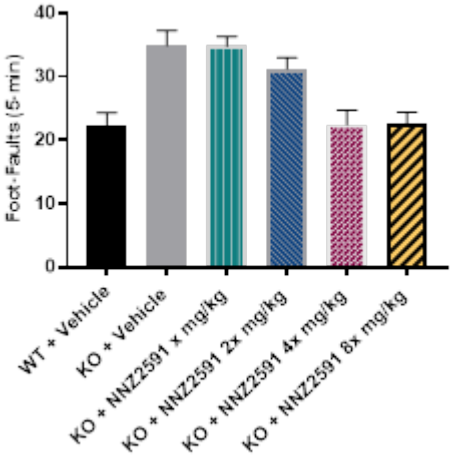


Incidence of seizures

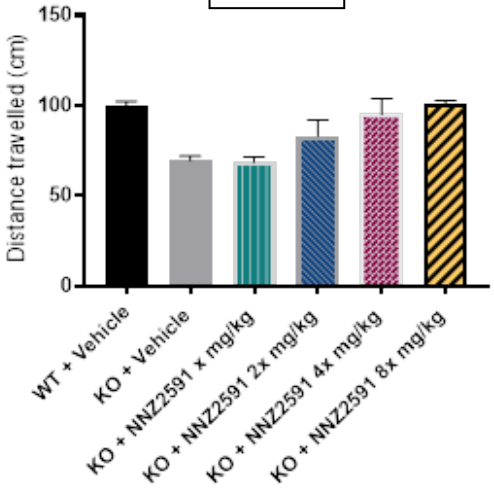
WT + vehicle	KO + vehicle	KO + x mg/kg	KO + 2x mg/kg	KO + 4x mg/kg	KO + 8x mg/kg
0%	60%	50%	30%	10%	10%

CONSISTENT EFFICACY AND DOSE RESPONSE IN PHELAN-MCDERMID MODEL

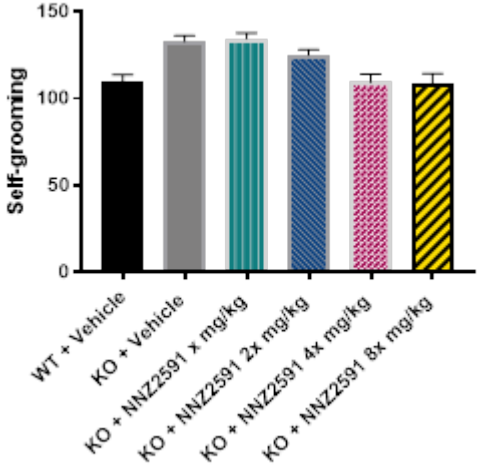
Motor function



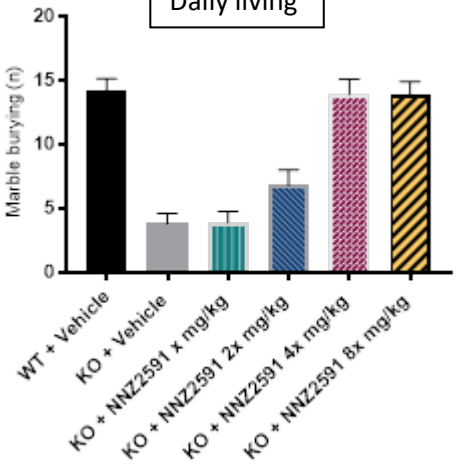
Anxiety



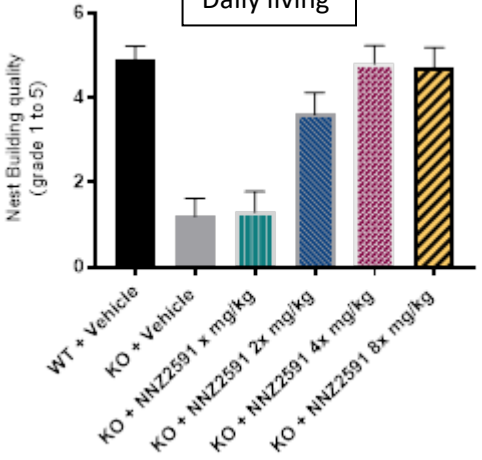
Repetitive behavior



Daily living

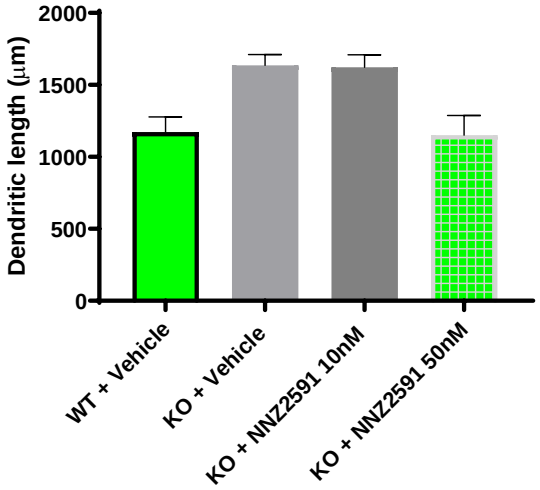


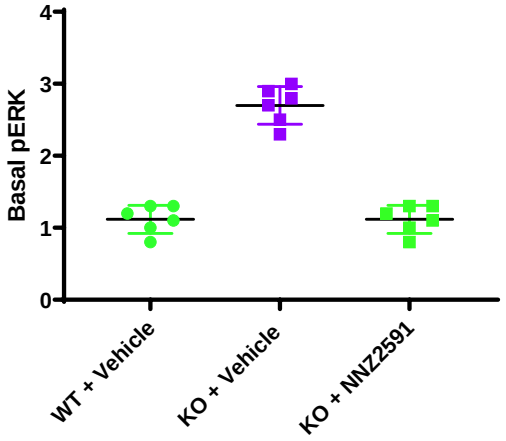
Daily living

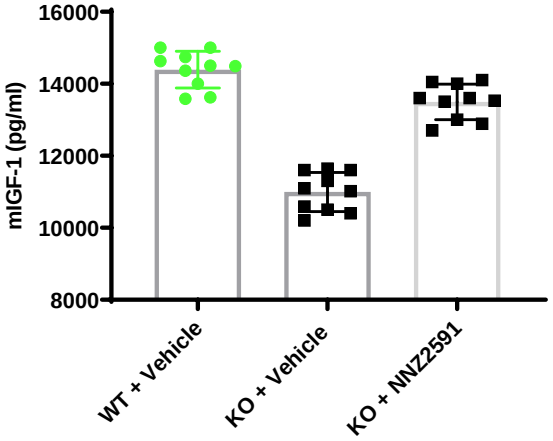


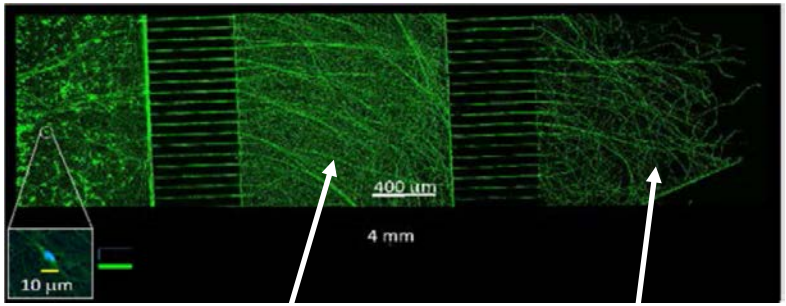
BIOCHEMICAL EFFECTS CONFIRMED IN *SHANK3* MODEL

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.







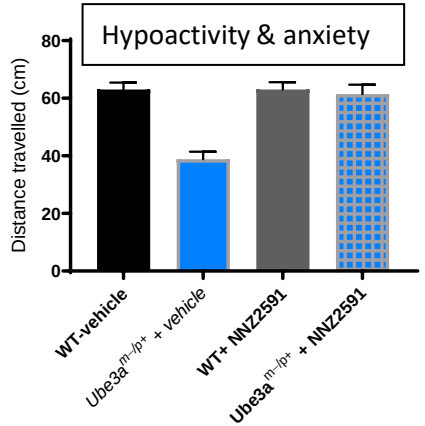


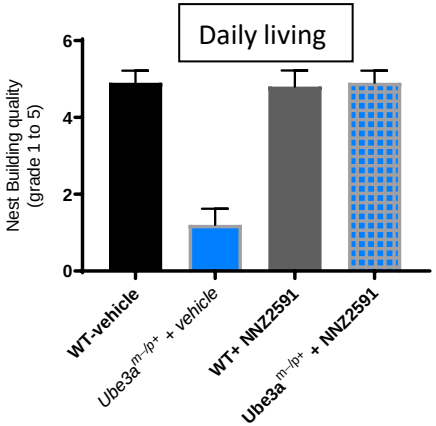
Abnormal dendrites in shank3 knockout mice

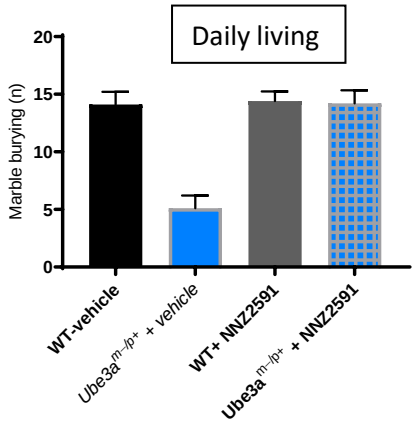
Normalisation after treatment with NNZ-2591

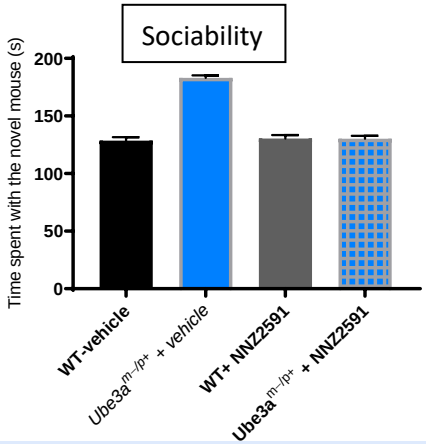
CONSISTENT EFFICACY IN ANGELMAN MODEL

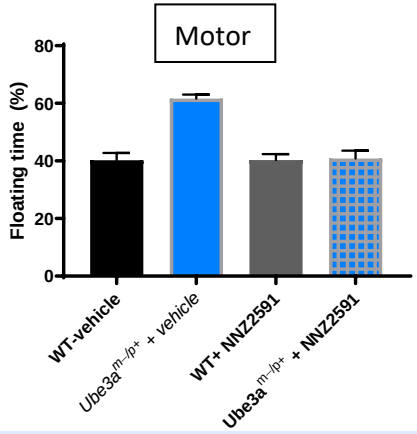
AS is caused by a deletion or mutation in the ubiquitin protein ligase E3A (*UBE3A*) gene on chromosome 15. In the *ube3a* knockout mouse model, which resembles features of AS in humans, wild type and knockout mice were each treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized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

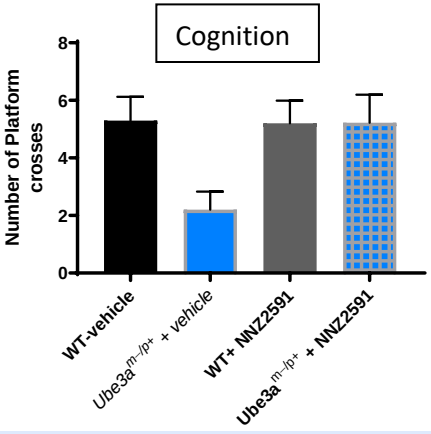






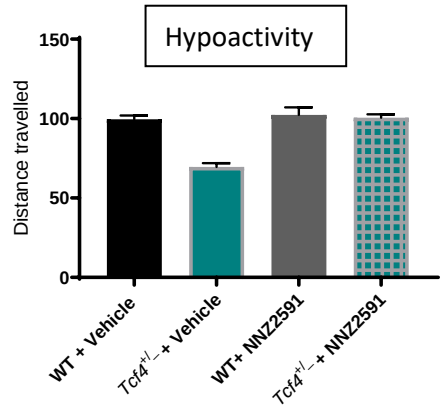


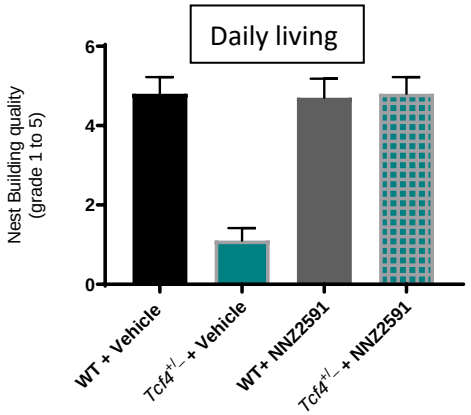


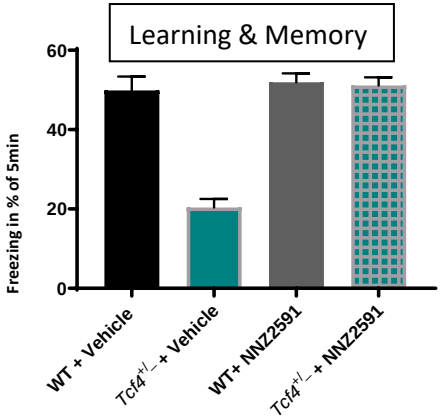


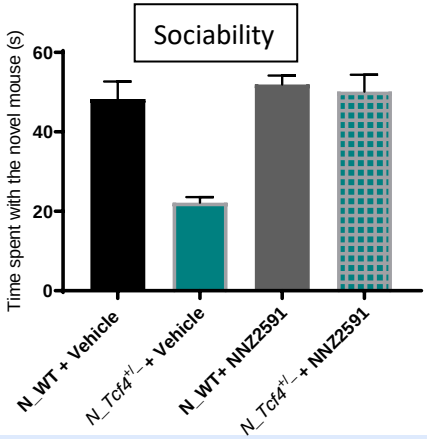
CONSISTENT EFFICACY IN PITT HOPKINS MODEL

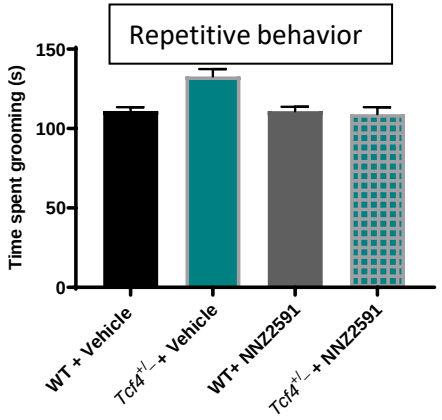
PTHS is caused by the loss of one copy or a mutation of the *TCF4* gene on chromosome 18. In the *tcf4* mutation mouse model, which exhibits features of PTHS in humans, wild type mice and knockout mice were treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized all the deficits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

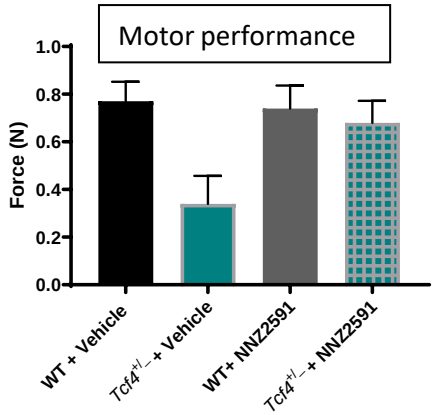






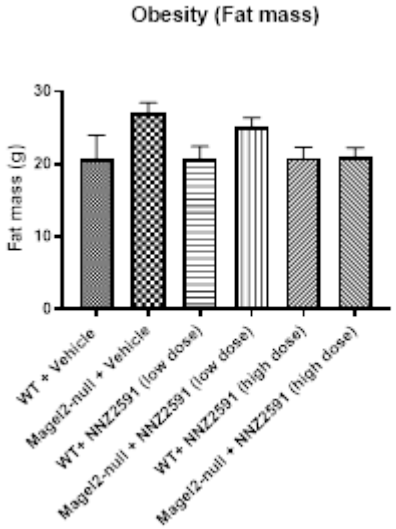


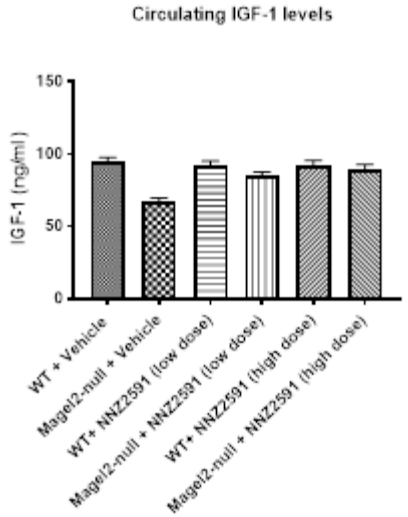


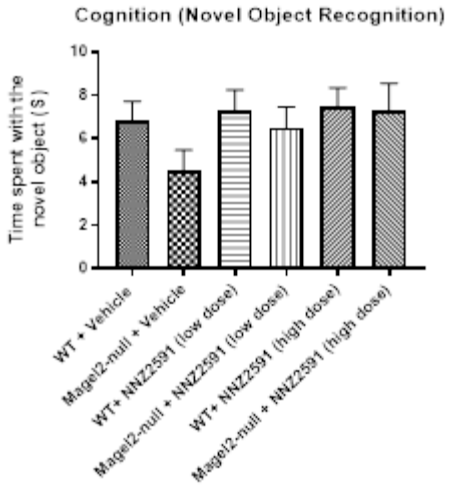


CONSISTENT EFFICACY IN PRADER-WILLI MODEL

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.



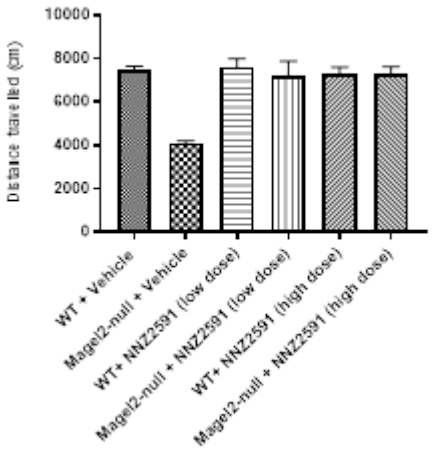




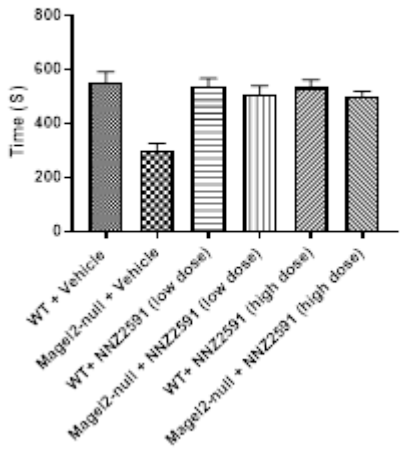
Insulin levels (pM)					
WT plus vehicle	*Magel2* -null plus vehicle	WT plus NNZ-2591 low dose	*Magel2* -null plus NNZ-2591 low dose	WT plus NNZ-2591 high dose	*Magel2* -null plus NNZ-2591 high dose
110	173	112	143	115	119

CONSISTENT EFFICACY IN PRADER-WILLI MODEL

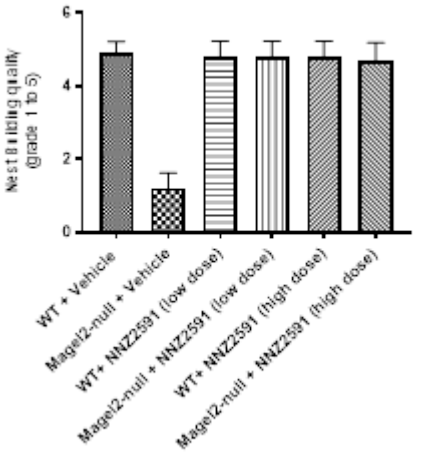
Hypoactivity (Open Field distance travelled)



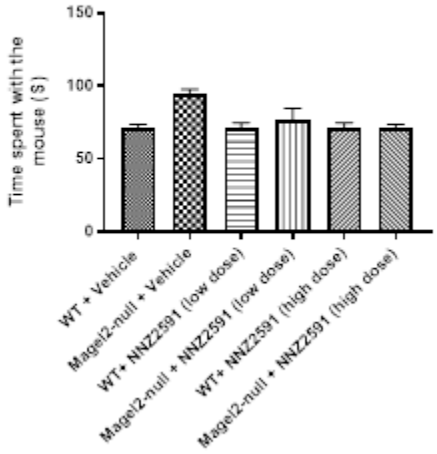
Hypoactivity (Open Field time spent active)



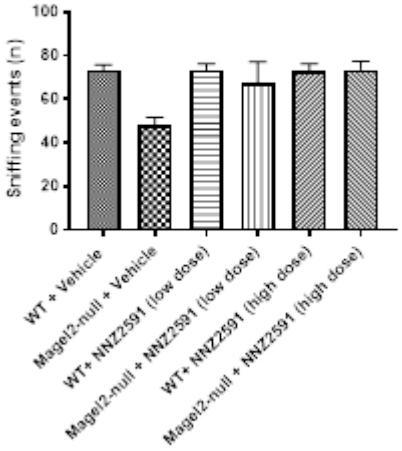
Daily living (Nest building)



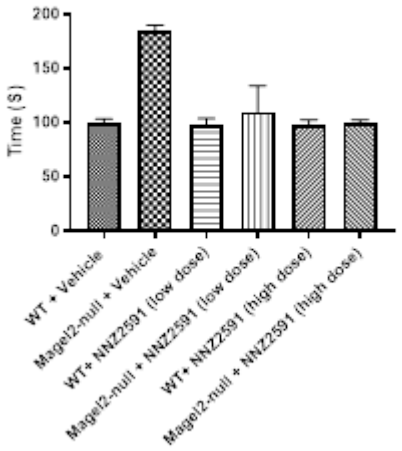
Social preference (novel mouse)



Social Interaction (Sniffing events)



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



APPENDIX 2 – TROFINETIDE LICENCE

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