neuren pharmaceuticals

FIGHTING NEURODEVELOPMENTAL DISORDERS

23 March 2021

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.

PIVOTAL YEAR FOR NEUREN IN 2021

- 5 Orphan Drug indications in clinical development:
  - **Rett syndrome in Phase 3 funded by US partner, results in Q4 2021**
  - **Phase 2 trials in 3 disorders commencing in 2021**
  - Serious neurological disorders in children, no approved therapies
  - Orphan drugs have higher probability of approval and commercial advantages
- **Trofinetide** partnered with **ACADIA** (NASDAQ:ACAD) for North America
  - Up to US$455m milestone payments
  - Double digit % royalties
  - One third of RPD Priority Review Voucher value
  - ACADIA funds all development
  - **Neuren has free access to US data for ex-North America registration**
- **NNZ-2591** advancing for 4 indications – global rights retained

PRODUCT PIPELINE

Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Commercial Partner
Trofinetide	Rett syndrome[1]				***Results Q4 2021***	ACADIA *(North America)*
	Fragile X syndrome[1]					ACADIA *(North America)*
NNZ-2591	Phelan-McDermid syndrome[2]			***Commence 2021***		
	Angelman syndrome[2]			***Commence 2021***		
	Pitt Hopkins syndrome[2]			***Commence 2021***		
	Prader-Willi syndrome			***TBA***		

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

[2] Orphan Drug designation in US and EU

COMMERCIAL ADVANTAGES OF ORPHAN DRUGS

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

- Ability to target a leadership position with little competition
- Higher pricing
- Serious and urgent unmet need results in more supportive regulatory environment
- Strong support from patient community and leading physicians
- Immediate access to known patients means large sales organisation less important
- Smaller and fewer Phase 3 trials
- Statistics show higher probability of regulatory approval
- Regulatory exclusivity periods eliminate patent risk

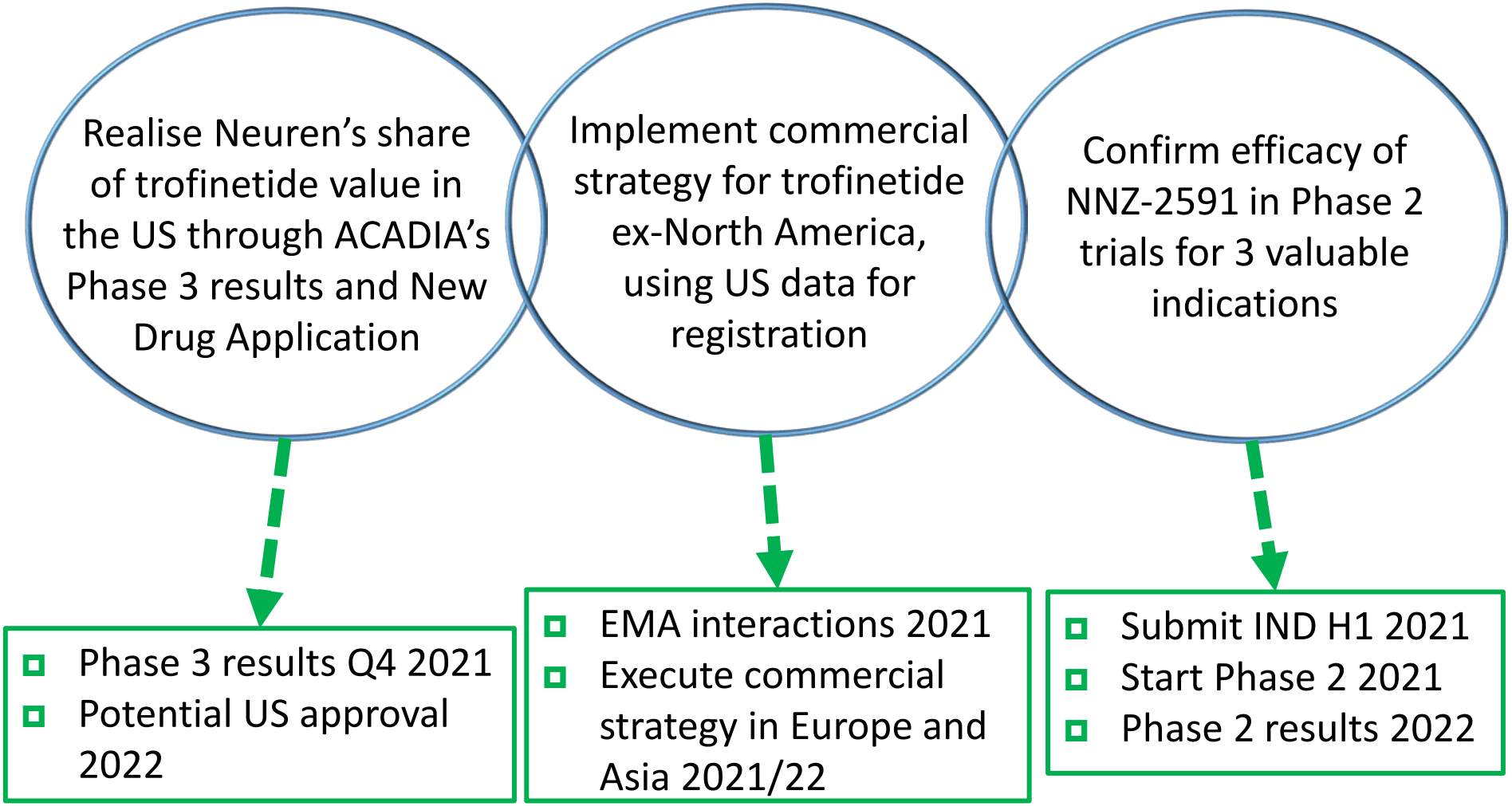
ESTIMATES OF TARGET PATIENT POPULATIONS

Disorder	Gene mutation	Published prevalence estimates	Potential patients		
			US[1]	Europe[1]	Asia[1, 2]
Trofinetide:					
Rett	*MECP2*	1/10,000 to 1/15,000 females	10,000	13,000	37,000
Fragile X	*FMR1*	1/4,000 to 1/7,000 males 1/12,000 to 1/22,000 females	30,000	38,000	112,000
NNZ-2591:					
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

[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

THREE KEY DRIVERS OF FUTURE VALUE



2021 MILESTONES

- ✓ 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

Submit NNZ-2591 INDs to FDA

Complete enrolment in trofinetide Rett syndrome Phase 3

Commence NNZ-2591 Phase 2 trials

Orphan designation in US and EU for Prader-Willi syndrome

Trofinetide Rett syndrome Phase 3 results

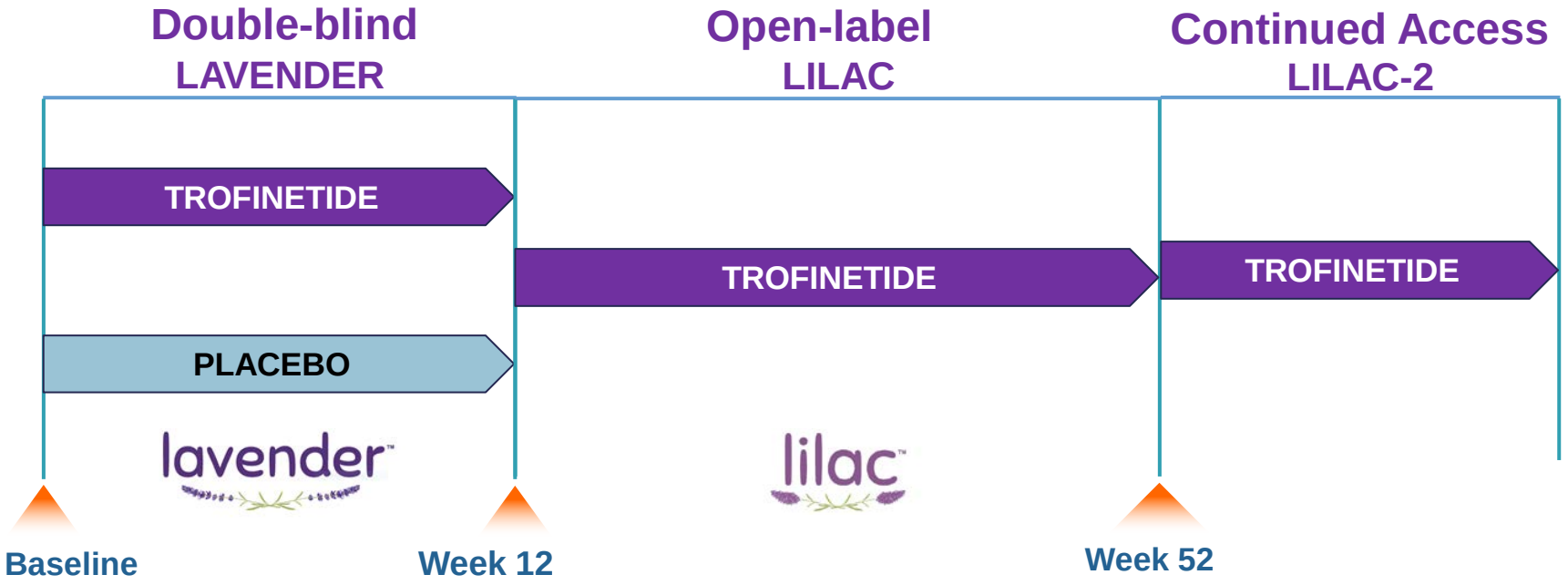
TROFINETIDE FOR RETT SYNDROME

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 free and full 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 (2019 sale average US$100m)
Non-compete	Neuren may not develop a competing product in indications for which ACADIA develops and commercialises trofinetide

RETT SYNDROME PHASE 3 PROGRAM



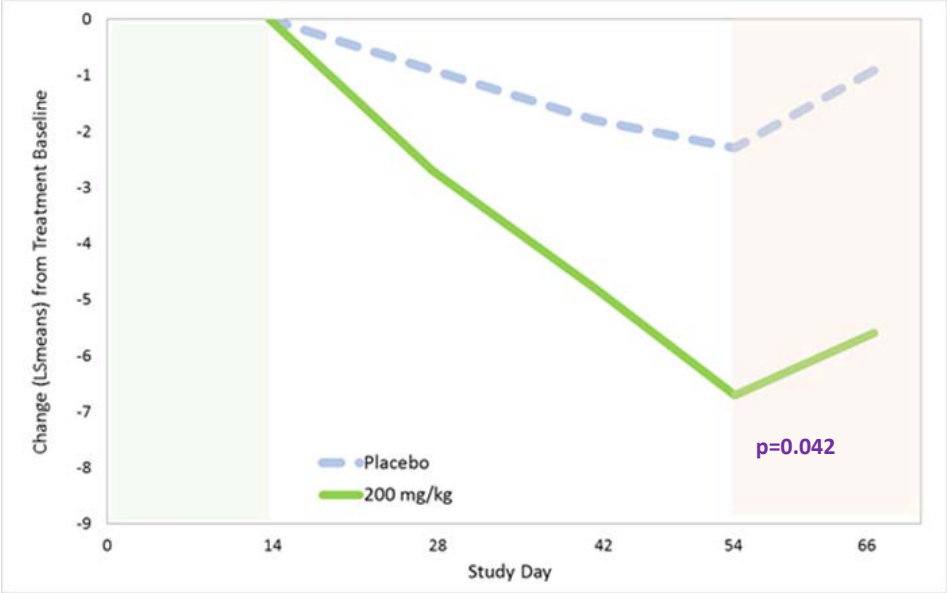
- 180 females aged 5 to 20 years
- RSBQ (caregiver) and CGI-I (physician) at 12 weeks are co-primary efficacy endpoints - both were positive in the Phase 2 trial
- Continuing strong support from leading physicians and Rettsyndrome.org
- Lavender results expected in Q4 2021, potential marketing approval in 2022

MAXIMISING PROBABILITY OF SUCCESS

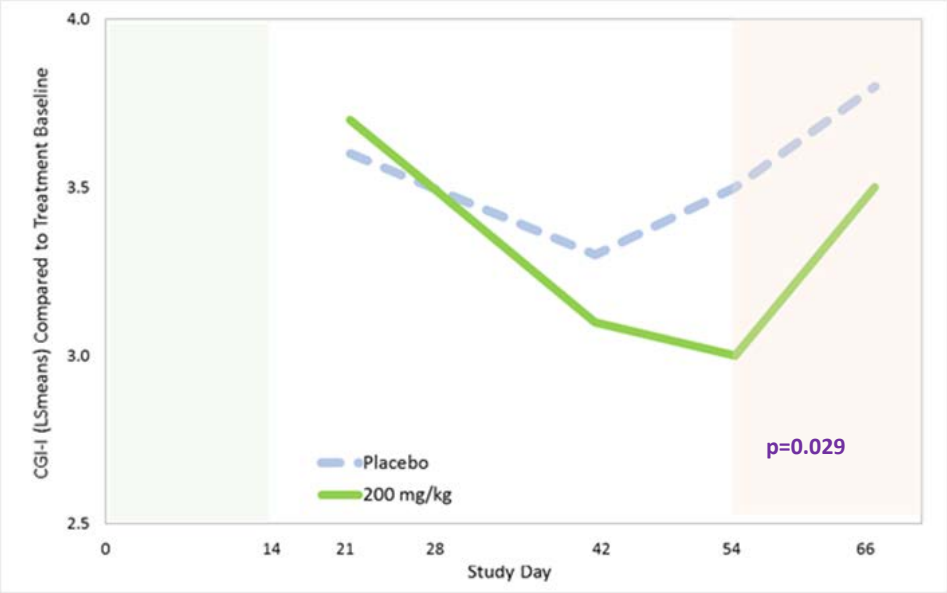
- The Phase 3 co-primary endpoints were both positive in the Phase 2 trial
- In the Phase 2 trial clinical improvement continued increasing through to end of treatment - the Phase 3 trial at 12 weeks is twice the duration of the Phase 2 trial
- The Phase 3 sample size at approx. 90 per group is more 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

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

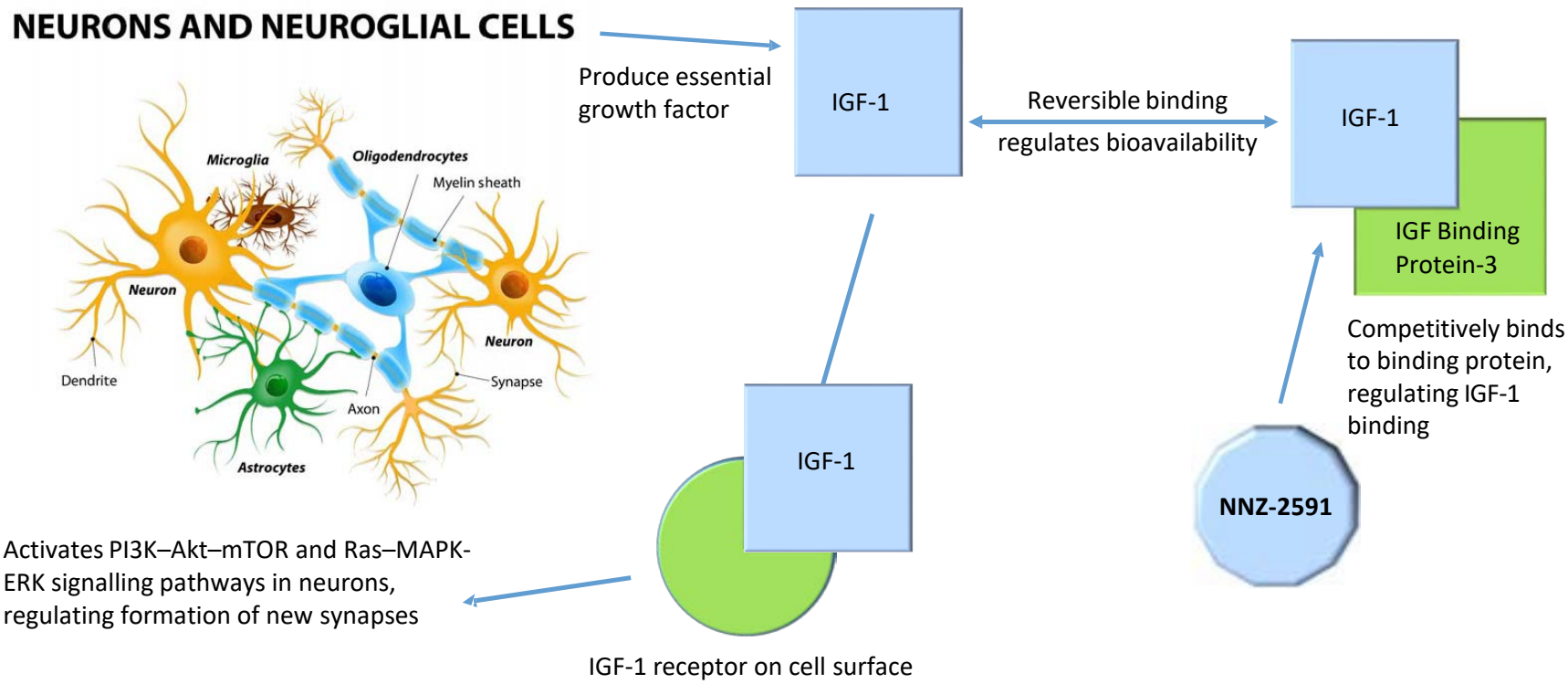
NNZ-2591 FOR MULTIPLE NEURODEVELOPMENTAL DISORDERS

NNZ-2591 MECHANISM OF ACTION

NNZ-2591 is a synthetic analog of 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



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

NNZ-2591 FOUNDATIONS IN PLACE TO REALISE VALUE

2022

Phase 2 data in multiple indications

2021

INDs approval by FDA

Phase 2 trials in multiple indications

2020

- **Identify optimum dose**
- **Develop and scale-up manufacturing**
- **Initiate 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**

COMMENCING PHASE 2 IN MULTIPLE INDICATIONS

Neuren is leveraging experience from Rett and Fragile X programs across CMC, non-clinical, clinical and regulatory to execute rapid development

- ✓ Clear and consistent efficacy in mouse models of Phelan-McDermid, Angelman, Pitt Hopkins and Prader-Willi syndromes
- ✓ Biochemical effects in the brain and dose response confirmed in Phelan-McDermid model
- ✓ Demonstrated high oral bioavailability and blood-brain barrier penetration
- ✓ Orphan Drug designation from FDA and EMA for Phelan-McDermid, Angelman and Pitt Hopkins (Prader-Willi to be submitted)
- ✓ IND-enabling program of non-clinical toxicology and CMC studies completed
- ✓ Proprietary drug substance manufacturing process with exceptional purity and high yield, patient-friendly liquid formulation
- ✓ 7 days dosing safe and well tolerated in Phase 1 trial

FDA meeting and submit INDs in H1 2021 before starting Phase 2 trials in patients – 12 weeks treatment in children

PHASE 1 CLINICAL TRIAL HIGHLIGHTS

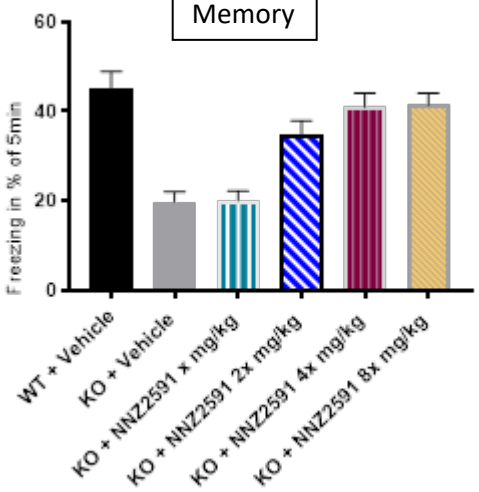
- Twice daily dosing for 7 days was safe and well tolerated at all dose levels tested in healthy volunteers
- No SAEs, no clinically significant findings in lab or cardiac tests
- All AEs mild or moderate and resolved during the trial
- At highest dose all AEs were mild apart from one moderate
- Most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

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

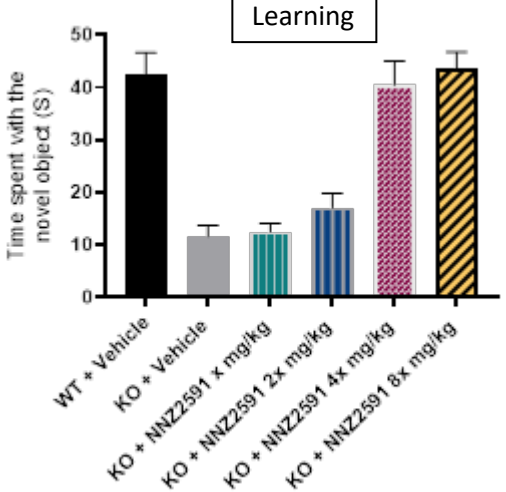
CONSISTENT EFFICACY AND DOSE RESPONSE IN PHELAN-MCDERMID MODEL

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.

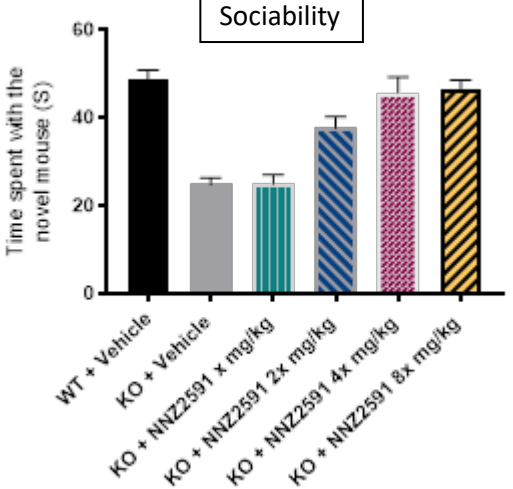
Memory



Learning



Sociability

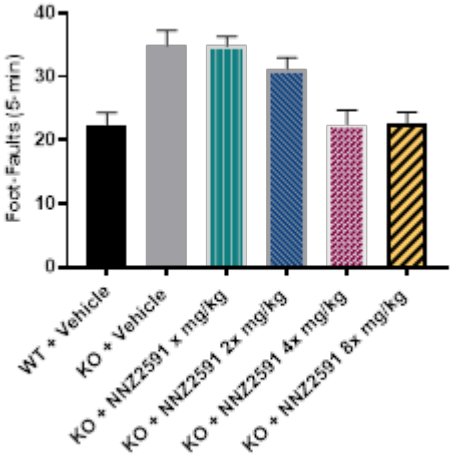


Incidence of seizures

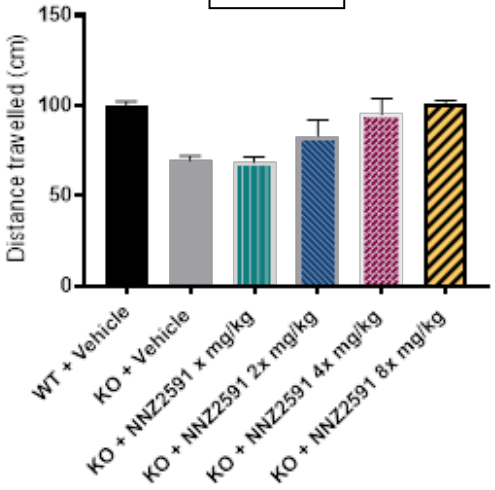
WT + vehicle	KO + vehicle	KO + x mg/kg	KO + 2x mg/kg	KO + 4x mg/kg	KO + 8x mg/kg
0%	60%	50%	30%	10%	10%

CONSISTENT EFFICACY AND DOSE RESPONSE IN PHELAN-MCDERMID MODEL

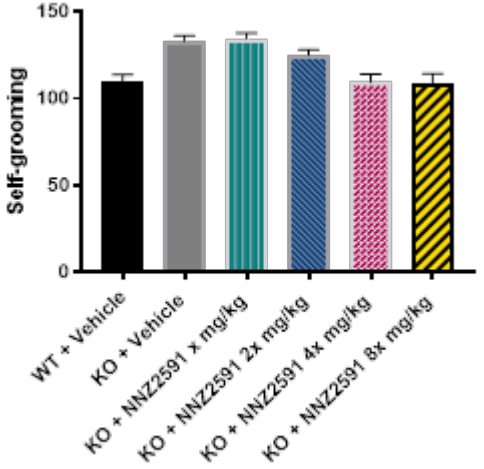
Motor function



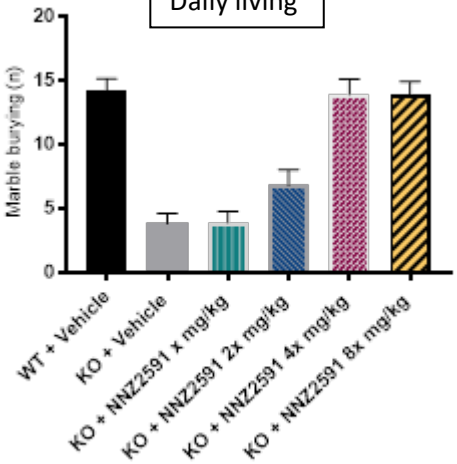
Anxiety



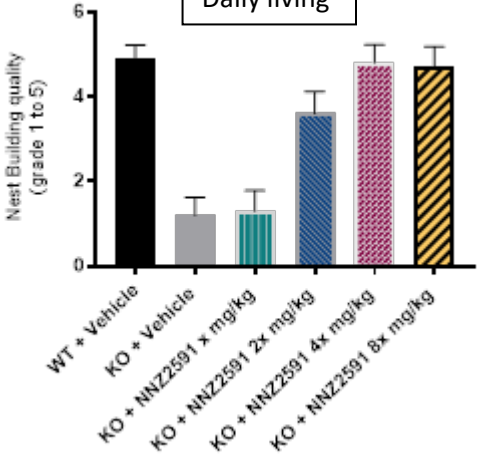
Repetitive behavior



Daily living

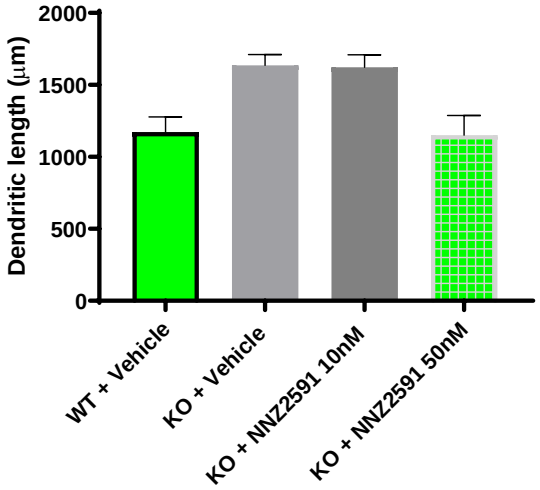


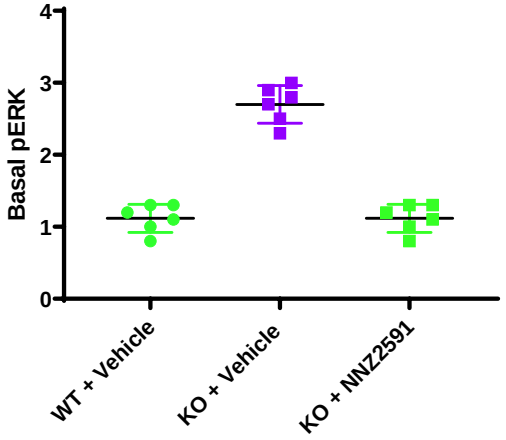
Daily living

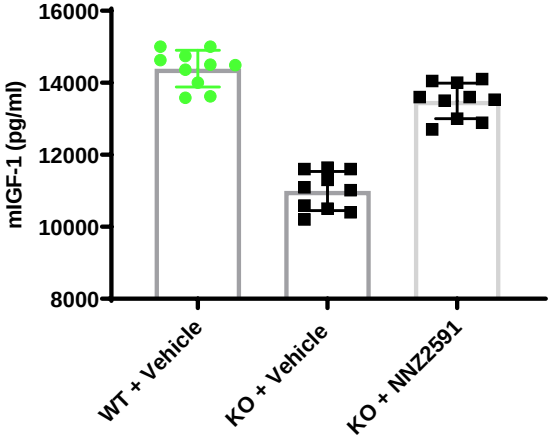


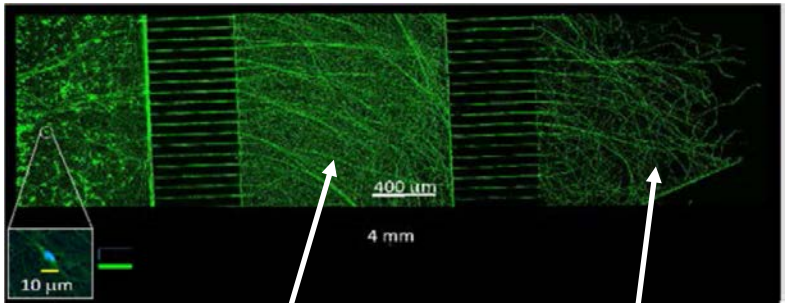
BIOCHEMICAL EFFECTS CONFIRMED IN *SHANK3* MODEL

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.







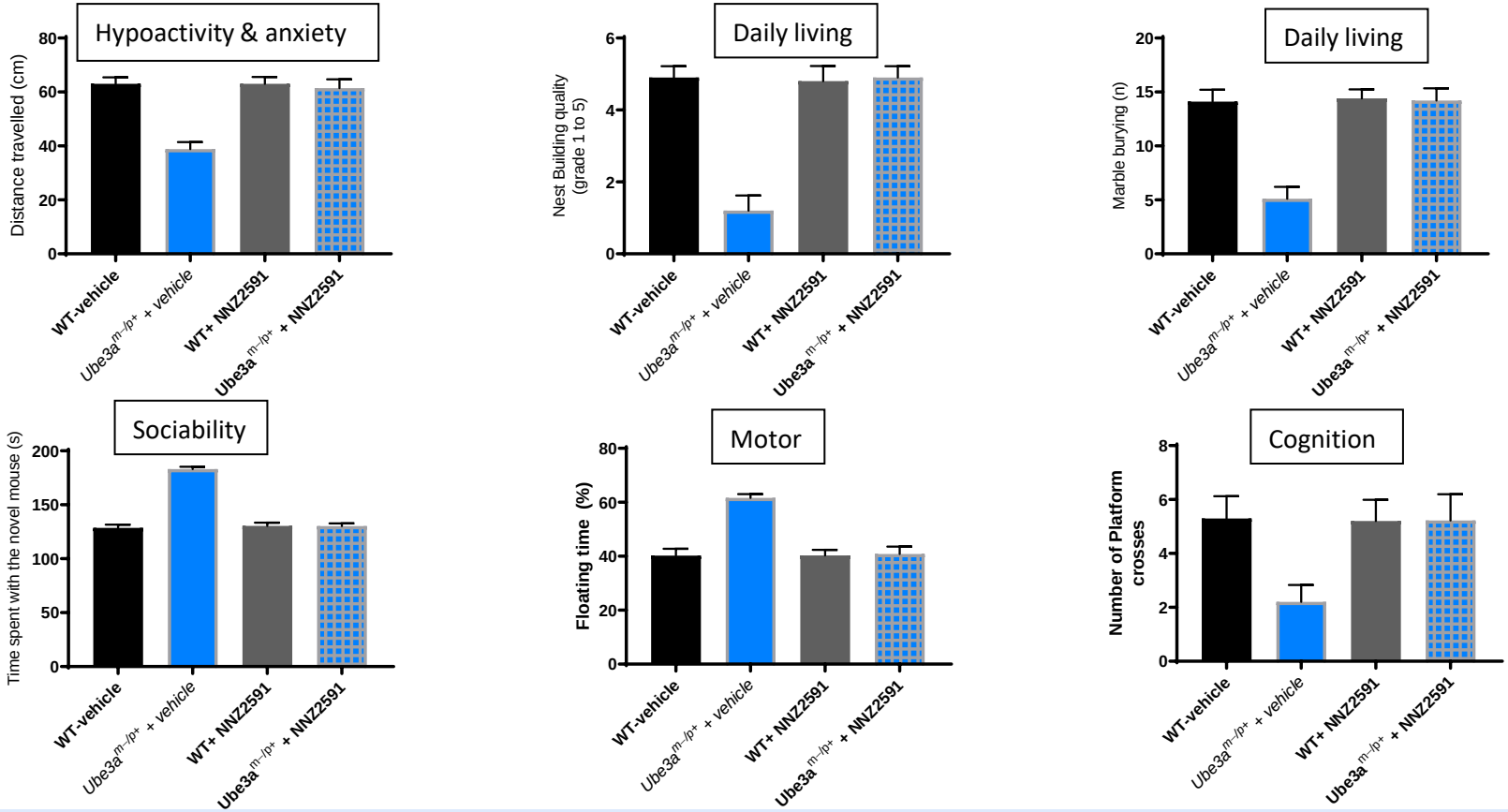


Abnormal dendrites in shank3 knockout mice

Normalisation after treatment with NNZ-2591

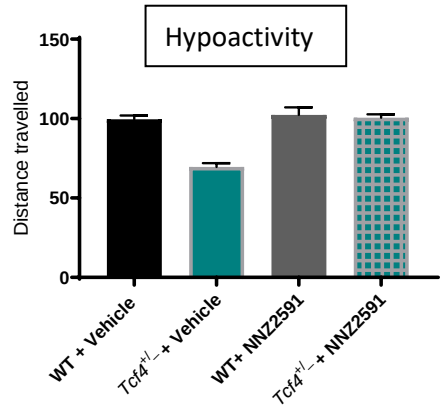
CONSISTENT EFFICACY IN ANGELMAN MODEL

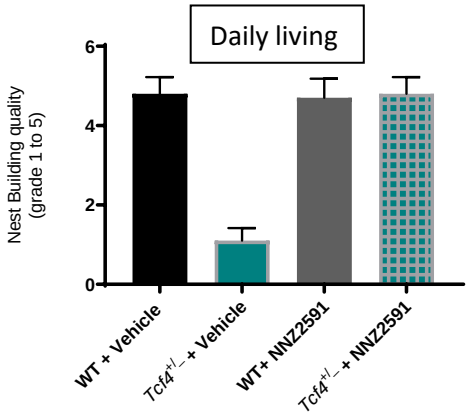
AS is caused by a deletion or mutation in the ubiquitin protein ligase E3A (*UBE3A*) gene on chromosome 15. In the *ube3a* knockout mouse model, which resembles features of AS in humans, wild type and knockout mice were each treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized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

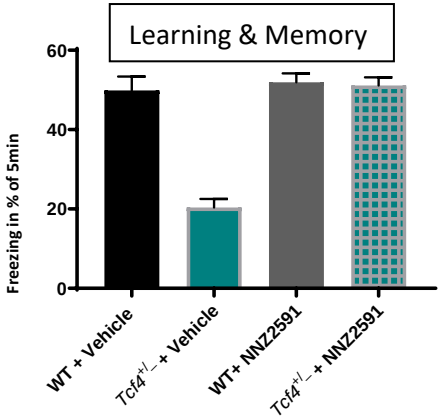


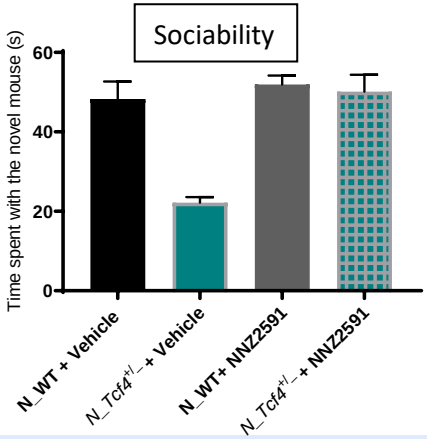
CONSISTENT EFFICACY IN PITT HOPKINS MODEL

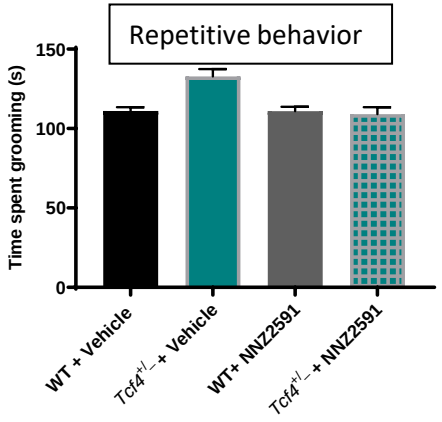
PTHS is caused by the loss of one copy or a mutation of the *TCF4* gene on chromosome 18. In the *tcf4* mutation mouse model, which exhibits features of PTHS in humans, wild type mice and knockout mice were treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized all the deficits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

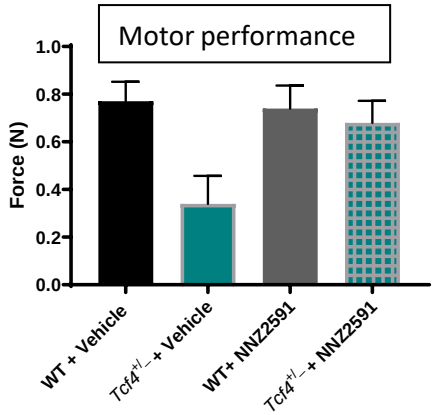






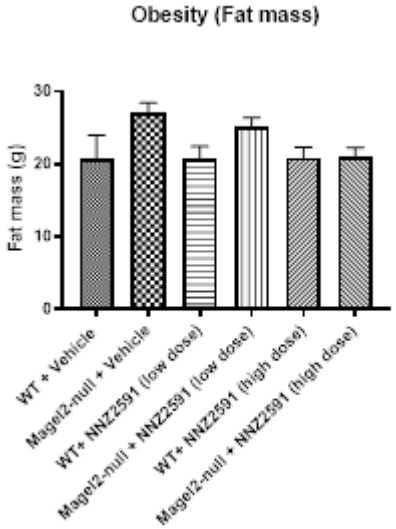


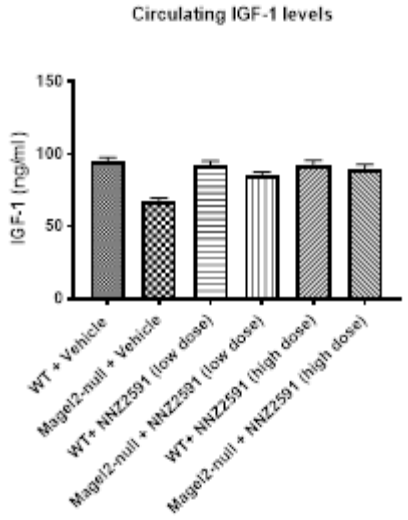


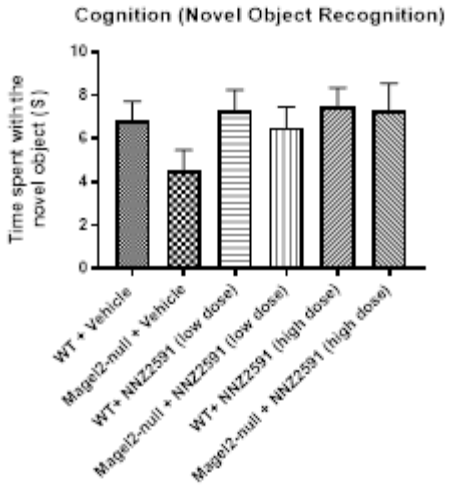


CONSISTENT EFFICACY IN PRADER-WILLI MODEL

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.



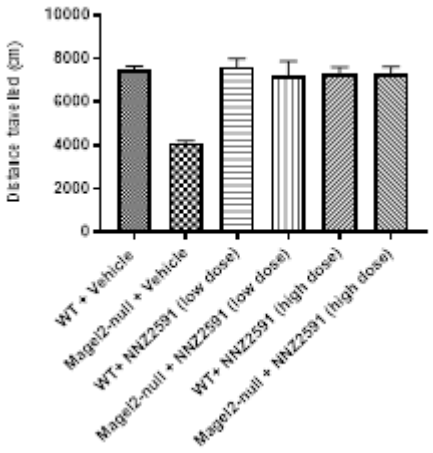




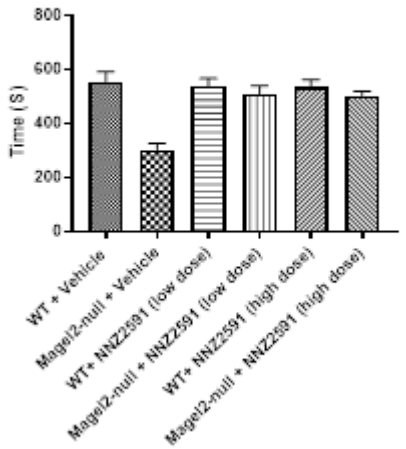
Insulin levels (pM)					
WT plus vehicle	*Magel2* -null plus vehicle	WT plus NNZ-2591 low dose	*Magel2* -null plus NNZ-2591 low dose	WT plus NNZ-2591 high dose	*Magel2* -null plus NNZ-2591 high dose
110	173	112	143	115	119

CONSISTENT EFFICACY IN PRADER-WILLI MODEL

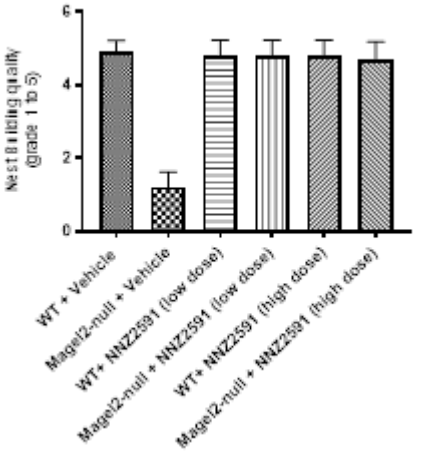
Hypoactivity (Open Field distance travelled)



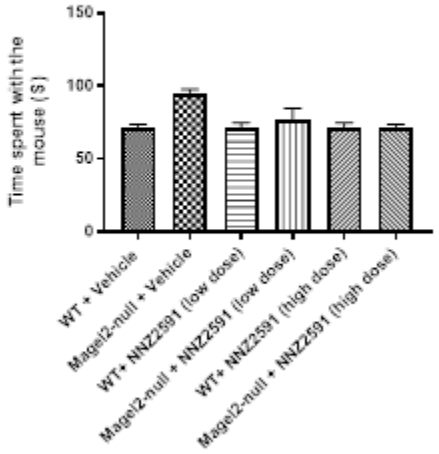
Hypoactivity (Open Field time spent active)



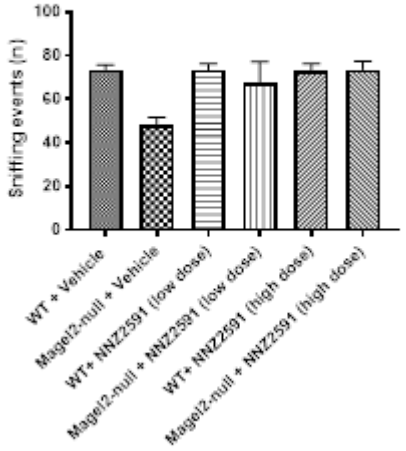
Daily living (Nest building)



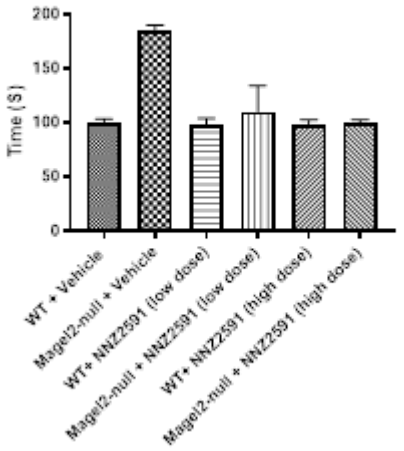
Social preference (novel mouse)



Social Interaction (Sniffing events)



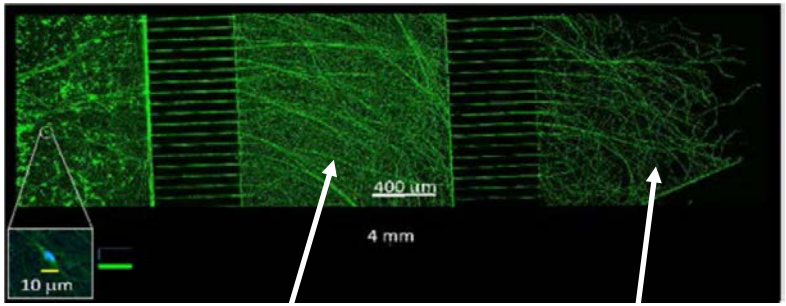
Anxiety (Elevated Plus maze, time spent in open arm)



APPENDIX

CORRECTING IMPAIRED SIGNALING IN NEURONS

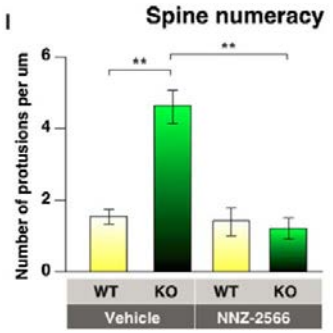
- Neurodevelopmental disorders result from different gene mutations, but all feature impaired signaling between neurons, with abnormal length and density of the dendritic spines that connect the neurons via synapses
- This impaired signaling causes behavioral, cognitive, motor and autonomic problems
- Trofinetide and NNZ-2591 can correct 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*)

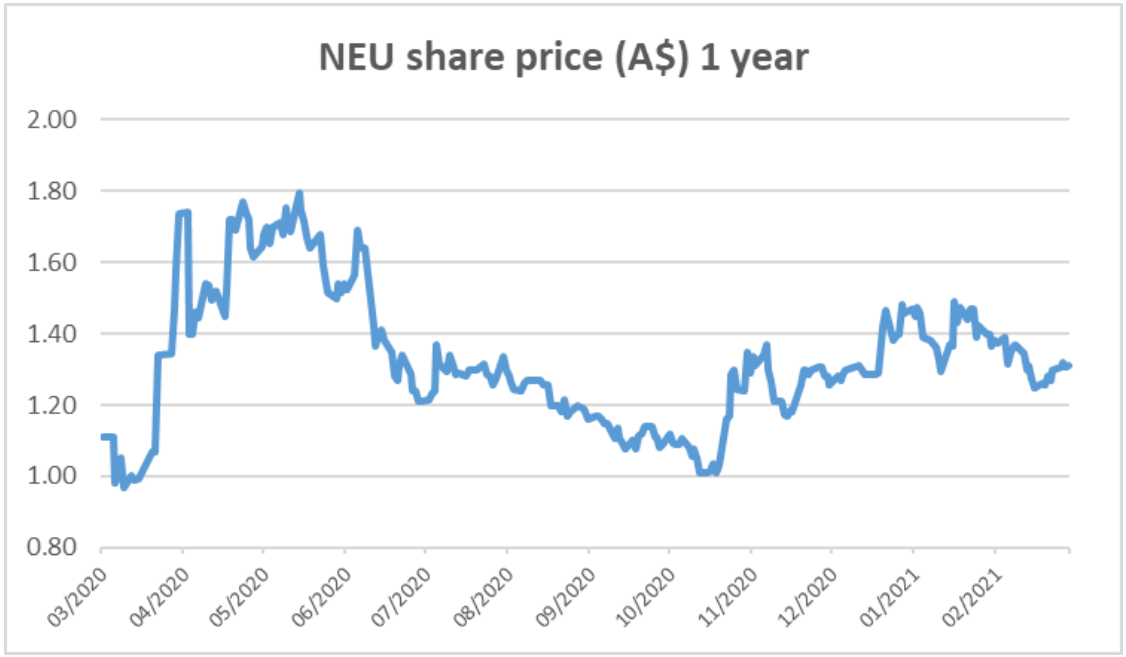


Correction in fmr1 knockout mice after treatment with trofinetide (NNZ-2566)

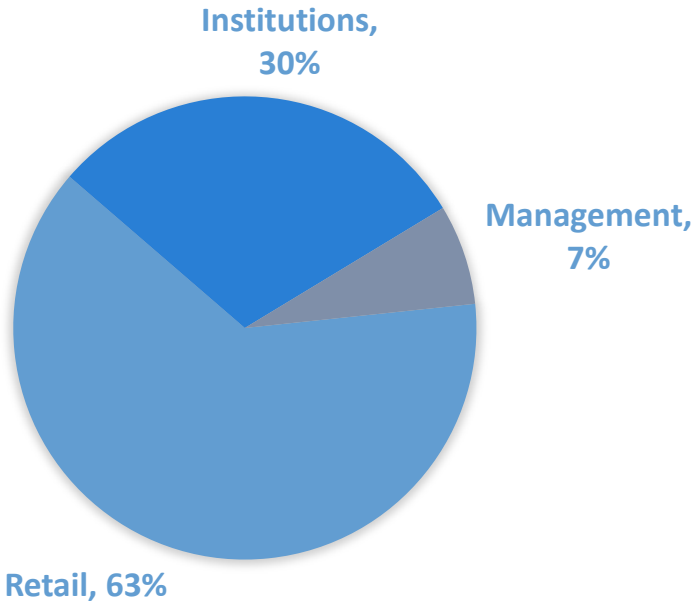
STOCK INFORMATION (ASX: NEU)

Current risk-adjusted valuations:
MST Access - $3.93, Bell Potter - $3.10

52 week price range: A$0.97 - A$1.84



Share register composition (114 million quoted shares – top 20 hold 50%)



A$24 million cash at 31 December 2020
A$20m placement at $1.40 in June 2020 supported by institutions in Aus, NZ, UK, Hong Kong

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 Technical Affairs

Dr Nancy Jones
VP Clinical Development

James Shaw
VP Clinical 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

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