neuren
pharmaceuticals

IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

14 September 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.

Global leader in neurodevelopmental disorder therapy development

Developing new therapies for debilitating neurodevelopmental disorders that emerge in early childhood and characterised by impaired connections and signalling between brain cells

2 novel drugs, treating **6** neurodevelopmental disorders, all with **Orphan Drug** designation, with no existing approved therapies[1]

Neuren **owns all intellectual property**, with no royalties payable to 3rd parties

Incorporated in New Zealand, based in Melbourne, Australia, listed on ASX (Code: NEU)

[1] Except growth hormone to treat some aspects of Prader-Willi

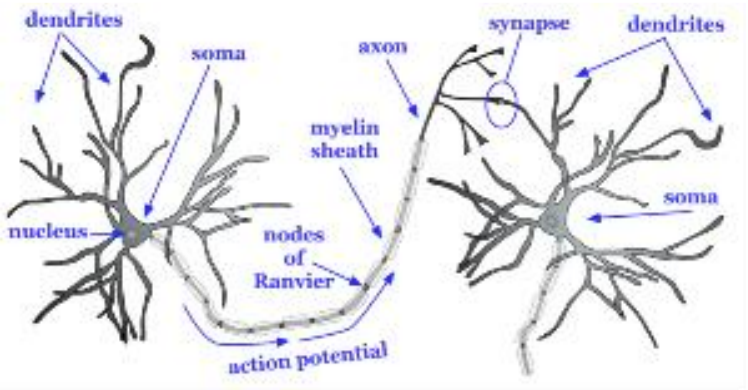
Highlights

1. NDA for trofinetide to treat Rett syndrome accepted by FDA for Priority Review with PDUFA date set for 12 March 2023
2. Potential revenue from Acadia over 2022 and 2023 for Rett syndrome in the US alone of US$83m (A$118 million)[1] plus double-digit % royalties
3. Strong partnering interest received for trofinetide outside North America
4. Accelerating Phase 2 development of NNZ-2591 in 4 indications, with potential markets 5x Rett syndrome
5. NNZ-2591 novel mechanism of action has many more potential applications
6. A$31 million cash at 30 June 2022 – well funded to execute NNZ-2591 Phase 2 trials and preparation for Phase 3

[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 0.70

Seeking a ground-breaking impact on 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

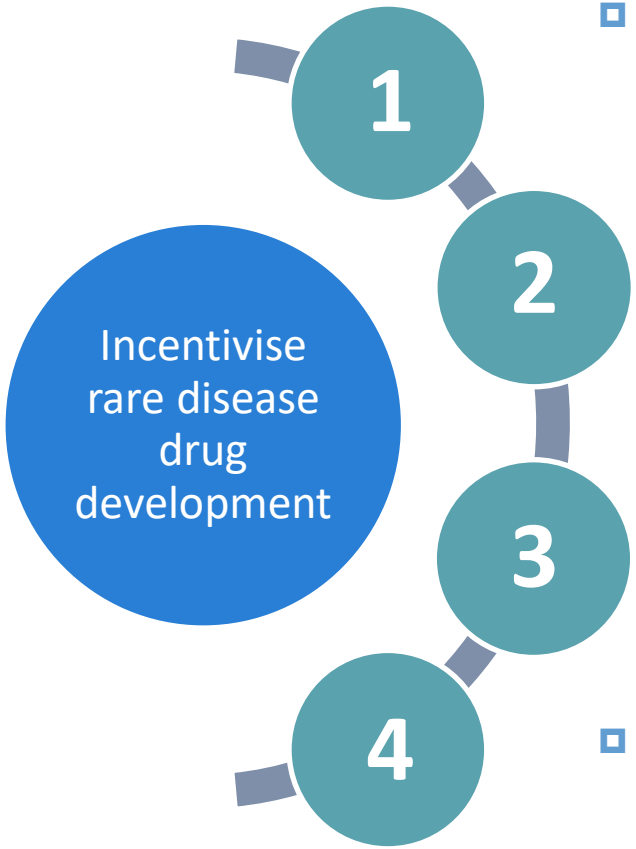
All development programs at Phase 2 or later

Compound	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Registration	Commercial rights
Trofinetide	Rett[2]					***US PDUFA date 12 Mar 2023[1]***	NA: ACADIA
	Fragile X[2]						RoW: neuren
NNZ-2591	Phelan-McDermid[3]						neuren
	Angelman[3]			***Results H1 2023***			
	Pitt Hopkins[3]						
	Prader-Willi[4]			***Results H2 2023***			

[1] Priority Review granted
[2] Orphan Drug designation in US and EU, Fast Track designation in US
[3] Orphan Drug designation in US and EU
[4] Orphan Drug designation in US

Attractiveness of Orphan Drug model

Neuren is targeting multiple “rare diseases”, but they are not “ultra-rare”

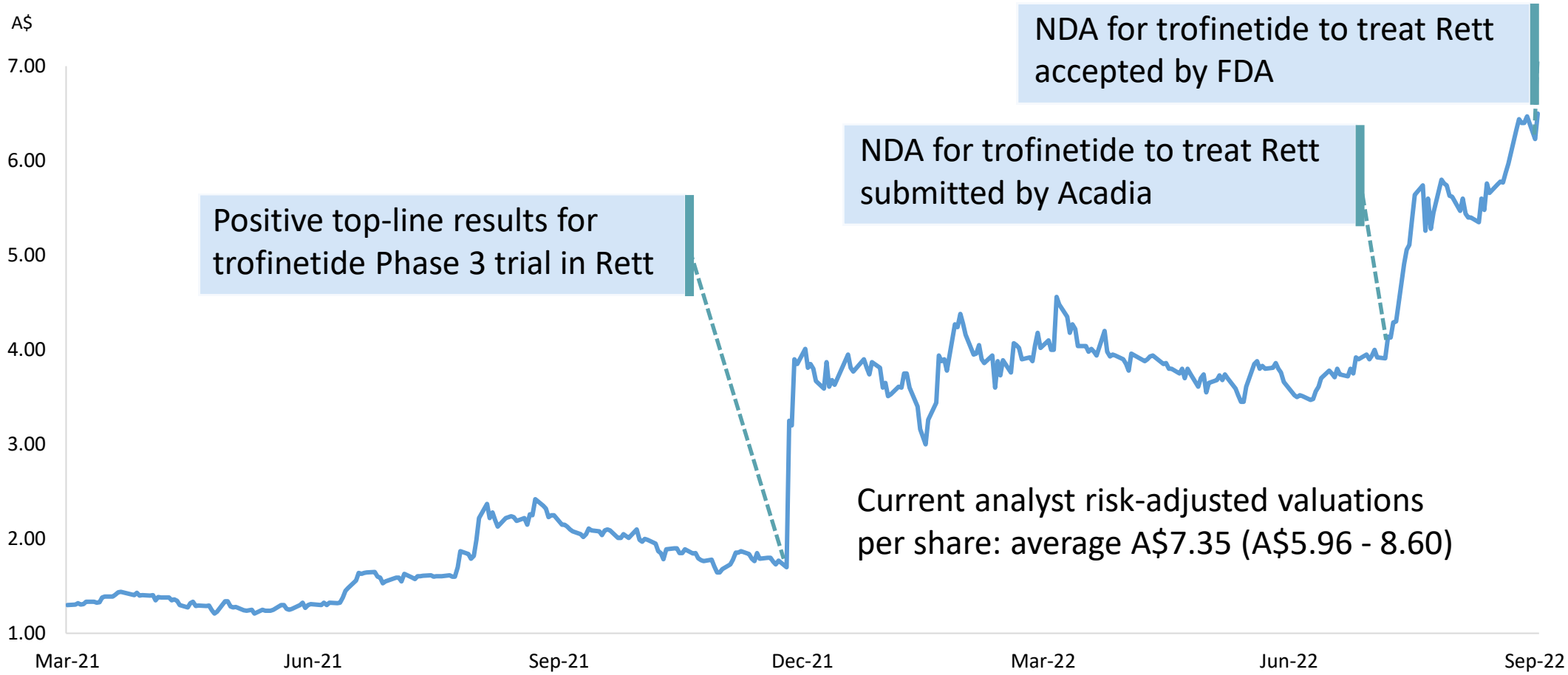


- Marketing exclusivity periods protect against generics independent of patents (7.5 years in US, 12 years in EU, 10 years in Japan, South Korea and Taiwan, China has proposed to introduce 7 years)
- Priority review by regulators (e.g. 6 months in US instead of 10 months) and higher probability of approval
- Urgent unmet need results in strong engagement from patient community and leading physicians, and immediate access to known patients
- Attractive pricing environment (average US Orphan Drug price of US$186,758 per patient p.a. in 2017[1])

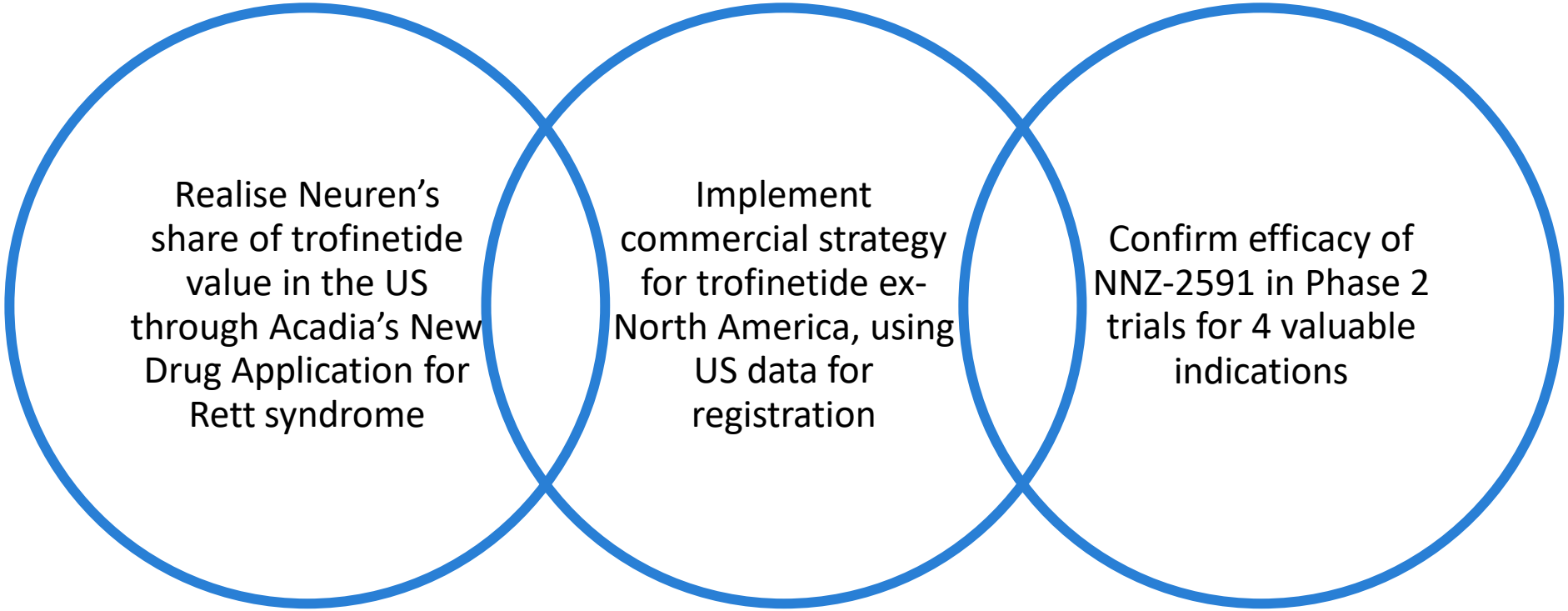
[1] AHIP

Transformation has begun

Last 18 Months Share Price Performance



Three key drivers transforming near term value

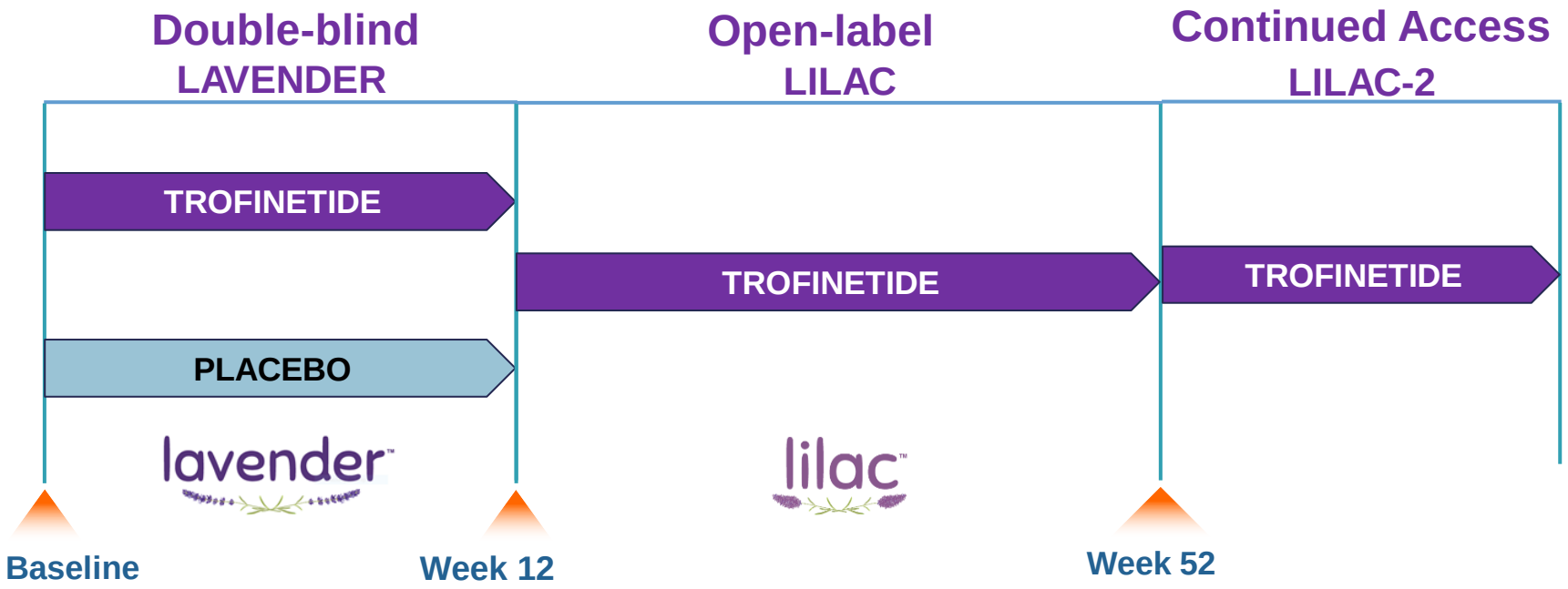


Rett syndrome Phase 3 and NDA

- Acadia submitted NDA in July 2022 for treatment of Rett syndrome in patients two years of age and older
- 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
- FDA accepted NDA for Priority Review - PDUFA action date set for 12 March 2023
- FDA advised that at this time it is not planning to hold an Advisory Committee meeting

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



Robustly positive Lavender™ top-line efficacy results

		Placebo	Trofinetide
Co-Primary Endpoints	**Rett Syndrome Behaviour Questionnaire (RSBQ)** (change from baseline to week 12)	-1.7	-5.1
	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	3.5
	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	-0.1
	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 commercial opportunity largely de-risked

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

North America

- Neuren potential revenue from Acadia:

✓ **US$10m**	**in 2022 following acceptance of NDA for review**
US$40m	in 2023 following first commercial sale in the US
US$33m	in 2023 one third share of Priority Review Voucher estimated value[2]
Up to **US$350m**	on achievement of thresholds of annual net sales
double digit %	tiered, escalating royalties on net sales

- Peak annual sales potential in US at least US$500m[3]
- Orphan exclusivity plus patents to 2040

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] Potential patient estimates derived by applying the mid-point of the published prevalence estimate range to the populations under 60 years
[2] Assuming Rare Pediatric Disease Priority Review Voucher is awarded upon approval of a NDA and has a market value of US$100m
[3] Acadia 2Q18 Earnings Call presentation and Jefferies Healthcare Conference 2 June 2021

5x 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 potential patients globally

NNZ-2591 has ideal attributes leading into Phase 2

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- ✓ Novel mechanism of action
- ✓ Clear and consistent efficacy in mouse models of each syndrome
- ✓ Biochemical effects in the brain confirmed
- ✓ Optimum dose identified
- ✓ 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

Clear and consistent efficacy in animal models

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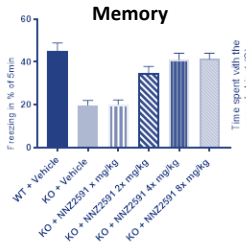
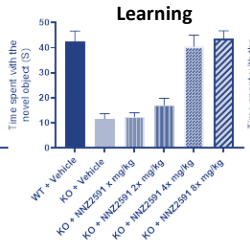
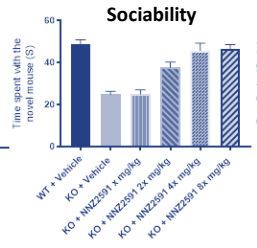
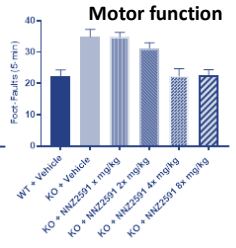
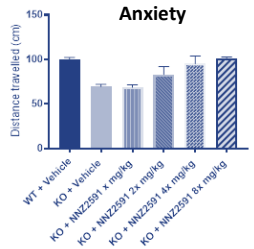
Phelan-McDermid

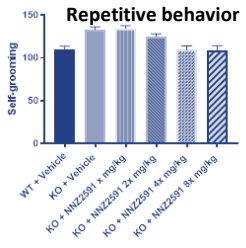


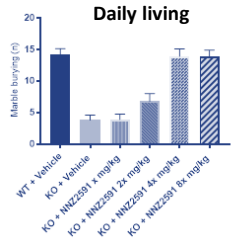


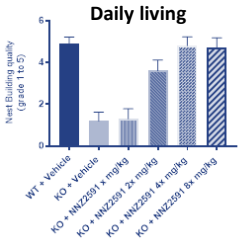








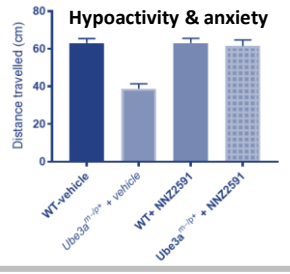


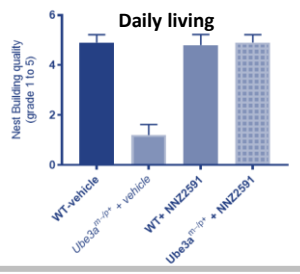


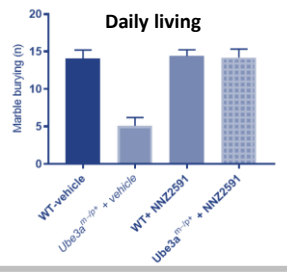
Incidence of seizures

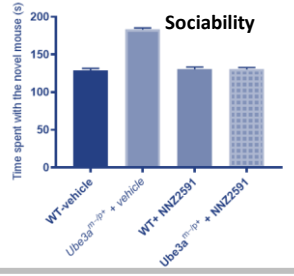
WT + vehicle	0%
KO + vehicle	60%
KO + x mg/kg	50%
KO + 2x mg/kg	30%
KO + 4x mg/kg	10%
KO + 8x mg/kg	10%

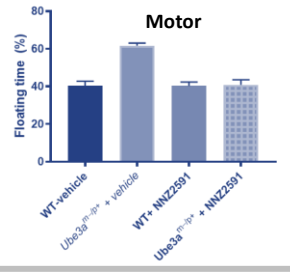
Angelman

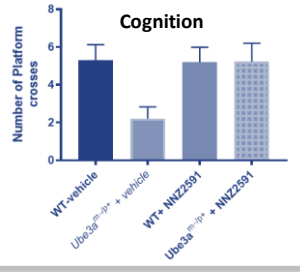




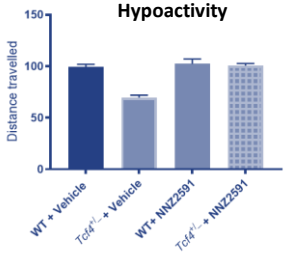


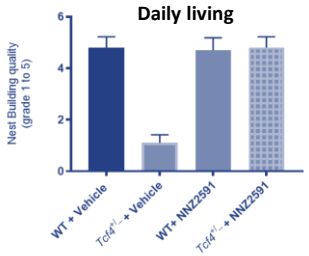


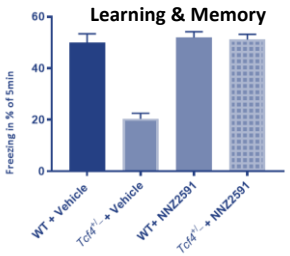


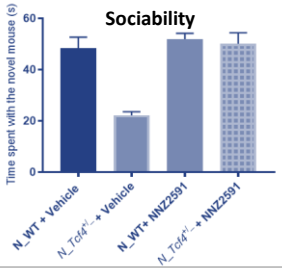


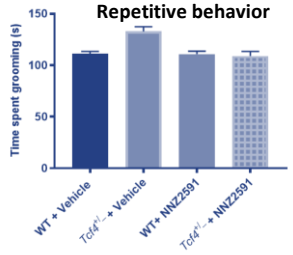
Pitt Hopkins

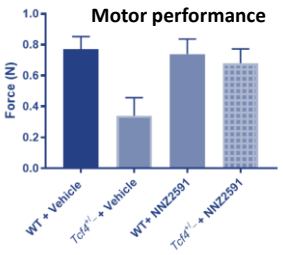




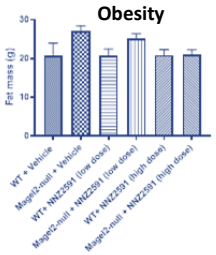


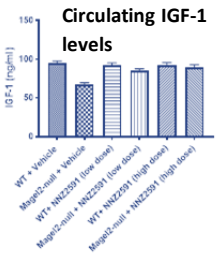


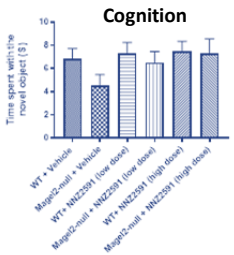


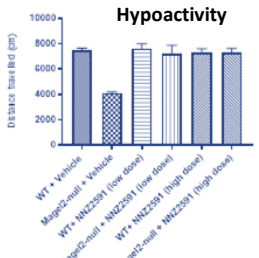


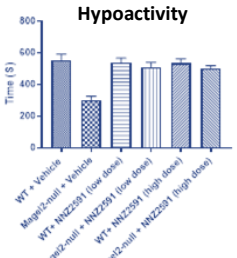
Prader-Willi

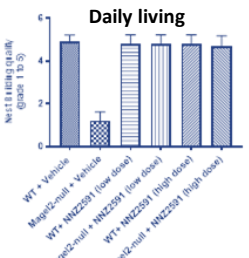


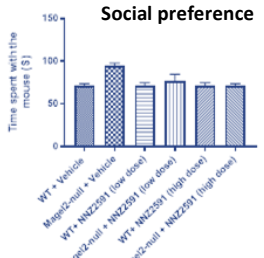


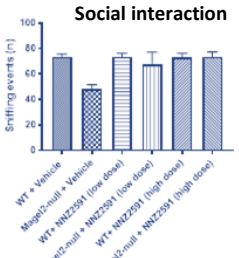


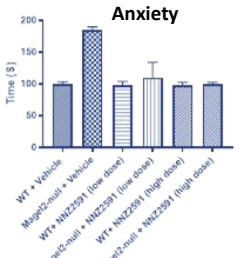






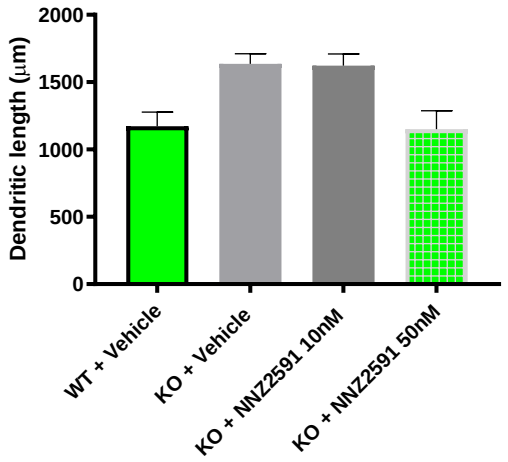


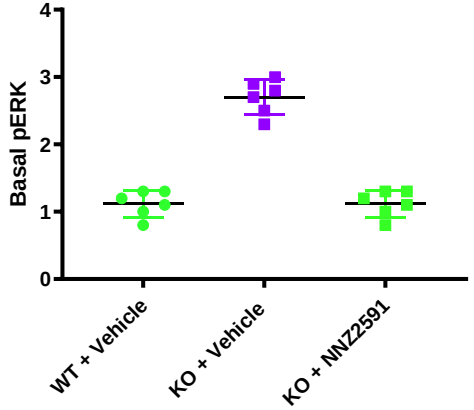


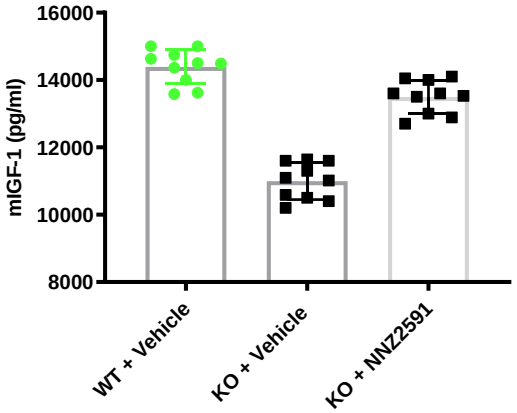


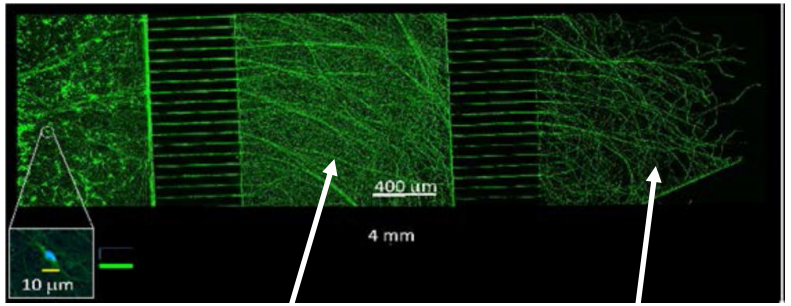
Biochemical effects confirmed

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

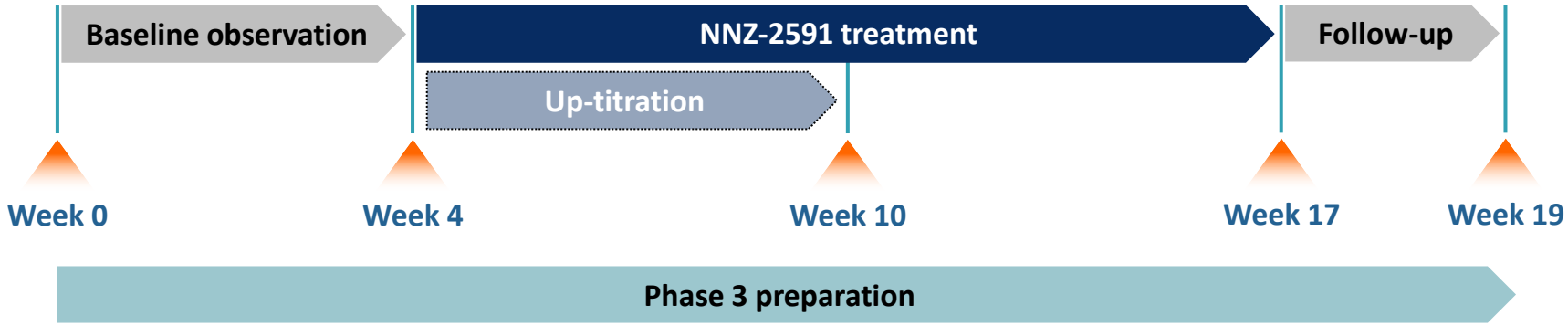
Normalisation after treatment with NNZ-2591

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
- Maximising opportunity to demonstrate effects
- Confirm safety and PK in pediatric patients
- Assess treatment impact across multiple efficacy measures to select primary endpoint for registration trial

	Angelman	Phelan-McDermid	Pitt Hopkins
n subjects	Up to 20	Up to 20	Up to 20
Age group	3 to 17	3 to 12	3 to 17
Location	Australia	US	US



On track to deliver significant value upside over next 18 months

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Prader-Willi syndrome Phase 2 trial results (H2 2023)

Phase 2 trial results in Angelman, Phelan-McDermid and Pitt Hopkins syndromes (H1 2023)

Approval of NDA for Rett syndrome (Q1 2023)

Commercial partnerships ex-North America for Rett syndrome

Commence Prader-Willi syndrome Phase 2 trial (file IND Q4 2022)

✓ FDA acceptance of NDA filing for Rett syndrome

✓ Commence Phelan-McDermid and Pitt Hopkins syndromes Phase 2 trials

✓ Acadia submits New Drug Application (NDA) for Rett syndrome

✓ Commence Phase 2 trial in Angelman syndrome

CONTACT

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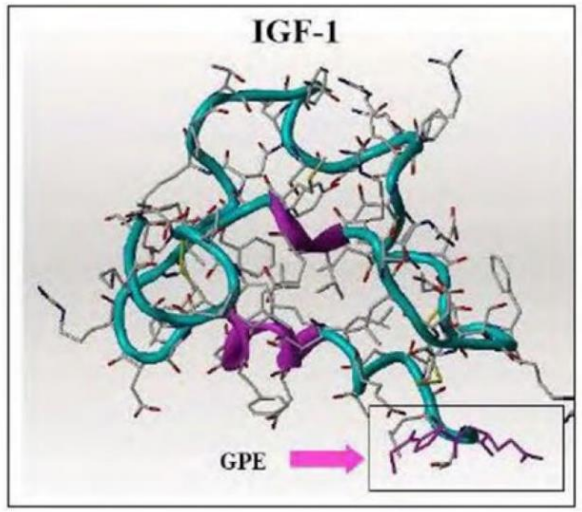
Appendix

Novel mechanisms of action - trofinetide

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:

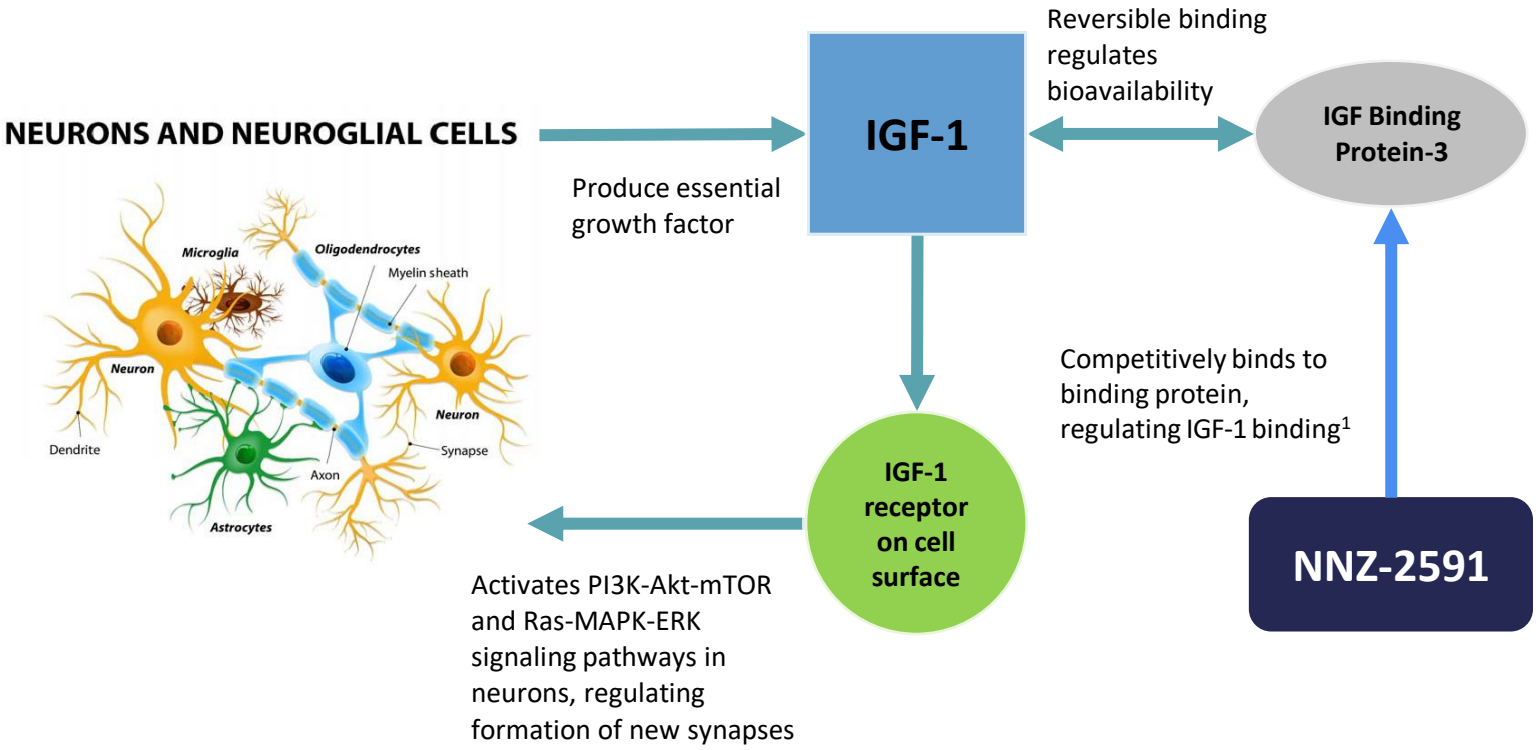
- Insufficient formation of new synapses by neurons
- Excessive pruning of existing synapses by overactive microglia

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

Novel mechanisms of action – NNZ-2591



- **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

[1] doi: 10.1038/srep04388: Guan et al, 2017: Cyclic glycine-proline (cGP) regulates IGF-1 homeostasis by altering the binding of IGFBP-3 to IGF-1