neuren pharmaceuticals

CORPORATE PRESENTATION

18 August 2020

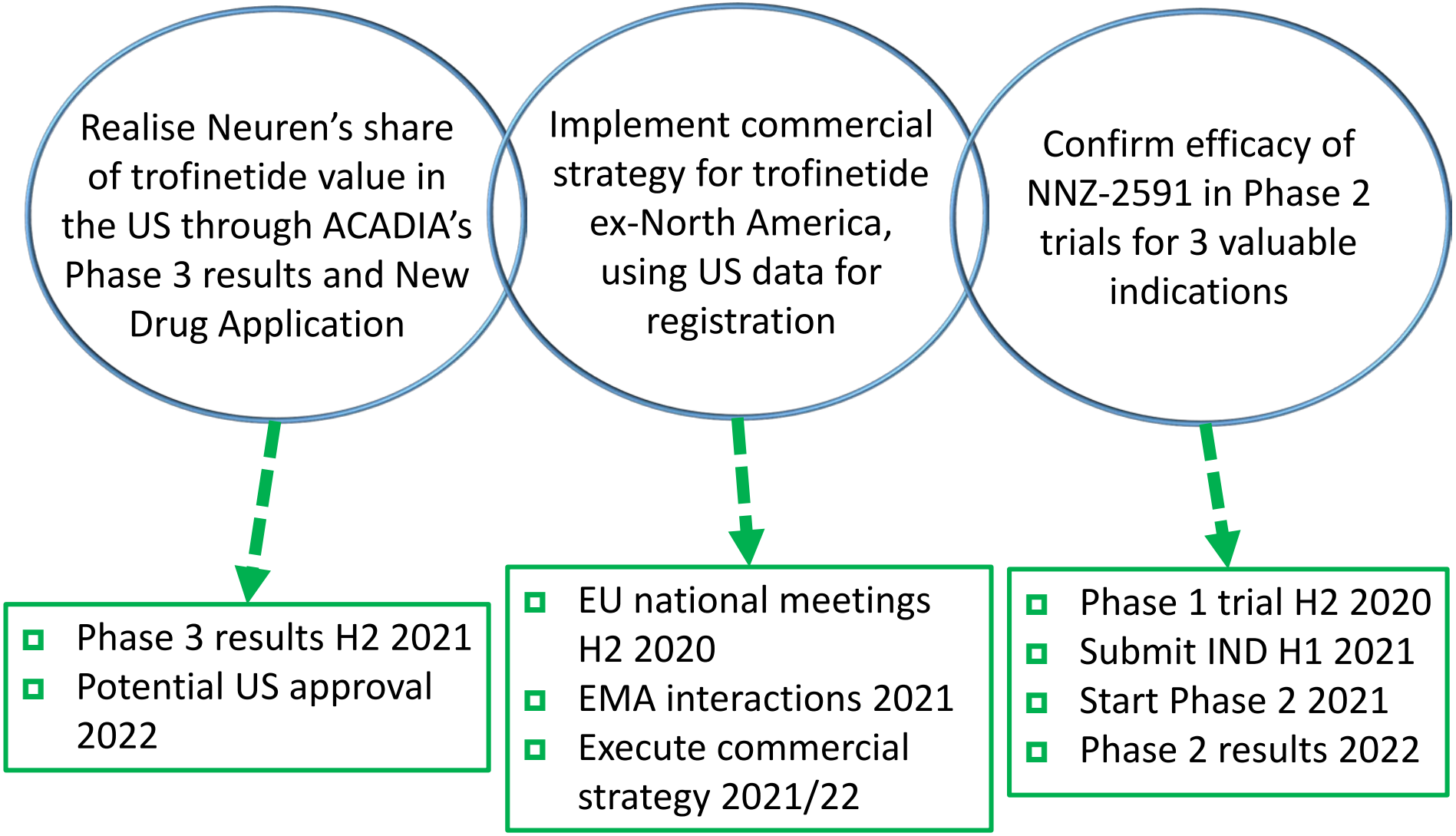
FORWARD LOOKING STATEMENTS

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.

NEUREN'S CURRENT STRONG POSITION

- Developing **2 drugs** to treat **5 debilitating childhood disorders**, which have no approved therapies – lead program in Phase 3
- **Orphan Drug** provides regulatory incentives and commercial protection
- **Trofinetide** partnered with **ACADIA** (NASDAQ:ACAD) for North America
  - Up to US$455m milestone payments plus double digit % royalties
  - Free and full access to US data for ex-North America registration
- **Trofinetide** in **Phase 3 trial for Rett syndrome**, funded by ACADIA:
  - Results expected in H2 2021, potential marketing approval in 2022
  - FDA Fast Track, Priority Review, Rare Pediatric Disease designation
- Funds secured for **Phase 2 trials of NNZ-2591 in 3 disorders**
- Drugs based on naturally occurring molecules target the underlying **impairment in signalling between brain cells**; no royalties payable

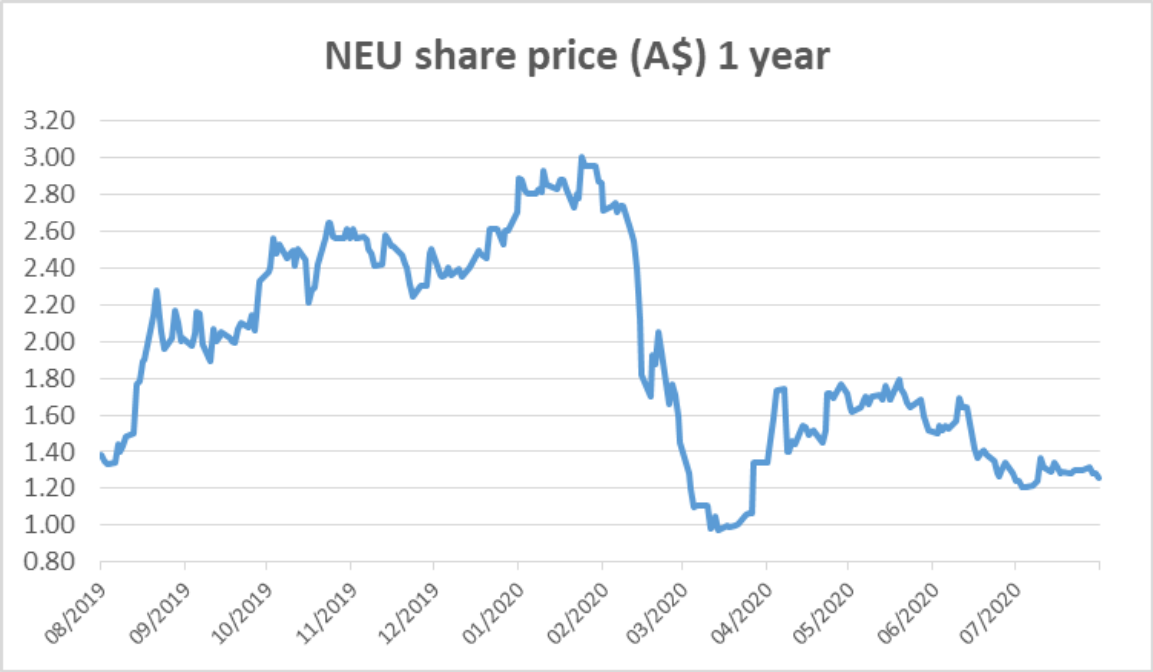
THE FUTURE - THREE KEY VALUE DRIVERS



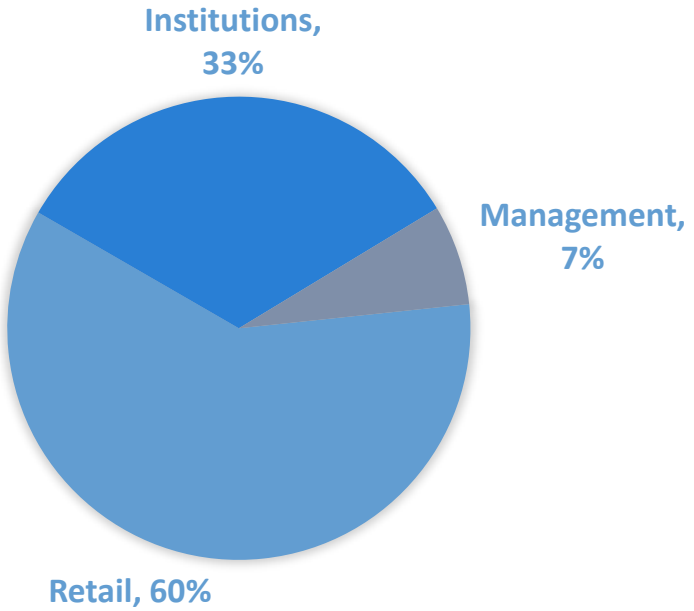
STOCK INFORMATION (ASX: NEU)

Current risk-adjusted valuations:
Bell Potter - $3.05, MST Access - $3.32

52 week price range: A$0.97 - A$3.04



Share register composition
(114 million quoted shares – top 20 hold 51%)

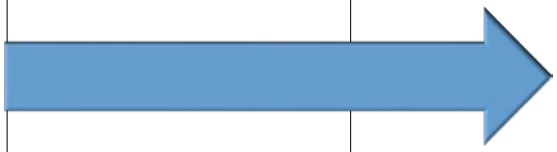
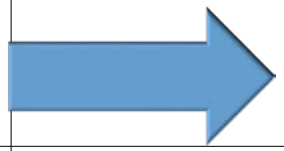
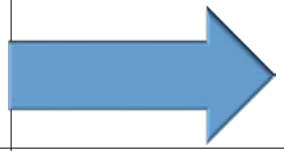
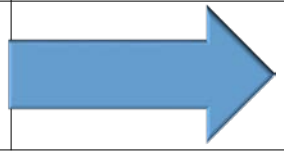


A$28 million cash at 30 June 2020 including placement proceeds
A$20m Placement at $1.40 supported by institutions in Australia, NZ, UK and Hong Kong

KEY MESSAGES

- ACADIA's Q2 earnings call on 5 August re-confirmed trofinetide Phase 3 trial continuing and results expected in H2 2021
- $28 million cash following successful capital raise supported by international institutions
- Funding now in place to generate Phase 2 data for NNZ-2591 in 3 indications
- NNZ-2591 potentially more valuable than trofinetide if Phase 2 confirms consistent efficacy seen in animal models
- NNZ-2591 Phase 1 trial in healthy volunteers continuing in Western Australia – Phase 2 to start in 2021
- Advisory discussions underway with regulatory authorities in Europe for trofinetide in Rett syndrome

PRODUCT PIPELINE

Compound	Indication	Preclinical / Phase 1	Phase 2	Phase 3	Commercial Partner
Trofinetide	Rett syndrome[1]				ACADIA Pharmaceuticals *(North America)*
	Fragile X syndrome[1]				ACADIA Pharmaceuticals *(North America)*
NNZ-2591	Phelan-McDermid syndrome[2]				
	Angelman syndrome[2]				
	Pitt Hopkins syndrome[2]				

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

[2] Orphan Drug designation in US

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

ESTIMATES OF PATIENT POPULATIONS AGED <60

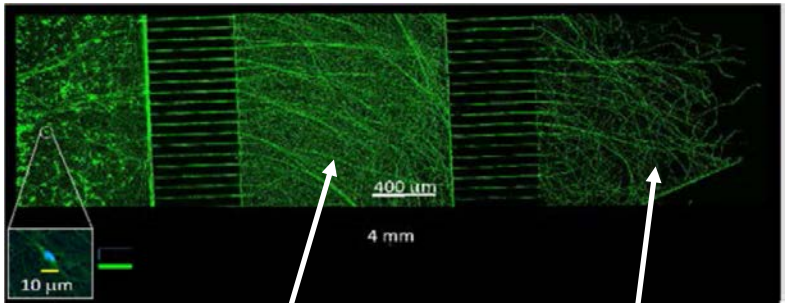
Disorder	Gene mutation	Published prevalence estimates	Potential patients US[1]	Potential patients EU/JP[1]
Rett	*MECP2*	1/10,000 to 1/15,000 females	10,000	16,000
Fragile X	*FMR1*	1/4,000 to 1/7,000 males 1/12,000 to 1/22,000 females	30,000	48,000
Phelan-McDermid	*SHANK3*	1/8,000 to 1/15,000 males and females	22,000	35,000
Angelman	*UBE3A*	1/12,000 to 1/24,000 males and females	14,000	22,000
Pitt Hopkins	*TCF4*	1/11,000 to 1/41,000 males and females[2]	10,000	16,000

[1] The estimates of potential patients are derived by applying the mid-point of the prevalence estimate range to the populations under 60 years

[2] The prevalence of chromosome 18q21 deletions was estimated as 1/34,000 to 1/41,000. If deletions are found in one third of individuals with Pitt Hopkins syndrome, the frequency of the syndrome could be as high as 1:11,000

CORRECTING IMPAIRED SIGNALING IN NEURONS

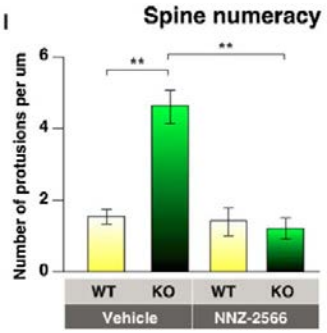
- Neurodevelopmental disorders result from different gene mutations, but all feature impaired signaling between neurons, with abnormal length and density of the dendritic spines that connect the neurons via synapses
- This impaired signaling causes behavioral, cognitive, motor and autonomic problems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

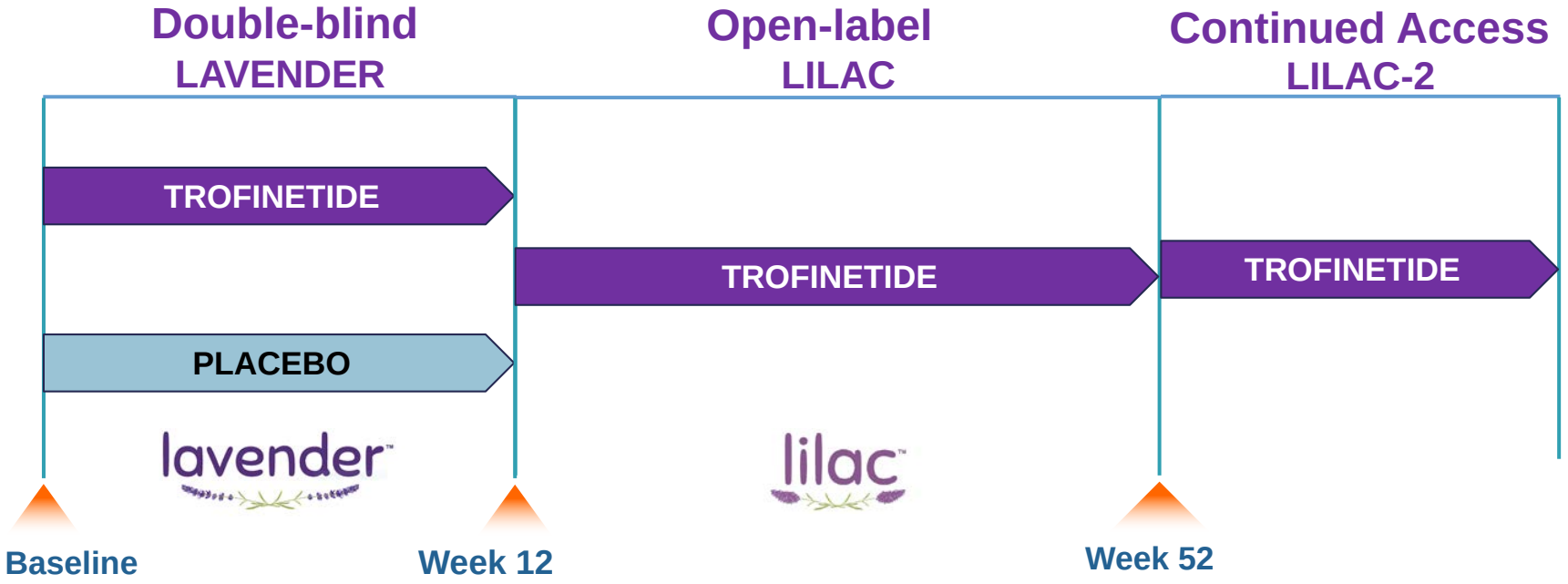
TROFINETIDE FOR RETT SYNDROME

RETT SYNDROME OVERVIEW

- Rett syndrome is a debilitating and life-threatening neurological disorder with no approved medicines
- It is caused by a non-inherited mutation on the X chromosome. Estimated incidence of 1 in 10,000 – 15,000 live female births
- After normal development for the first 6 months of life, girls experience a period of rapid regression commencing between 6-18 months of age and stabilizing by 4-5 years of age

- Severely disabling range of symptoms include:
  - Loss of speech and motor control
  - Neurobehavioral, cognitive and intellectual disability
  - Autonomic dysfunction – breathing, cardiovascular and gastrointestinal abnormalities
  - Seizures
- Most require life-long medical care and 24 hour supportive care – profound financial and emotional impact on families

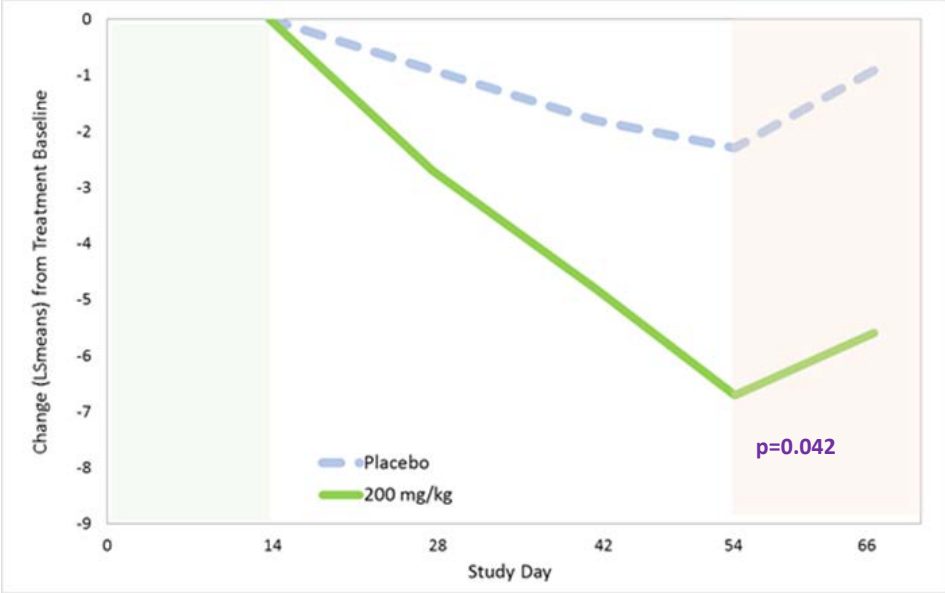
RETT SYNDROME PHASE 3 PROGRAM



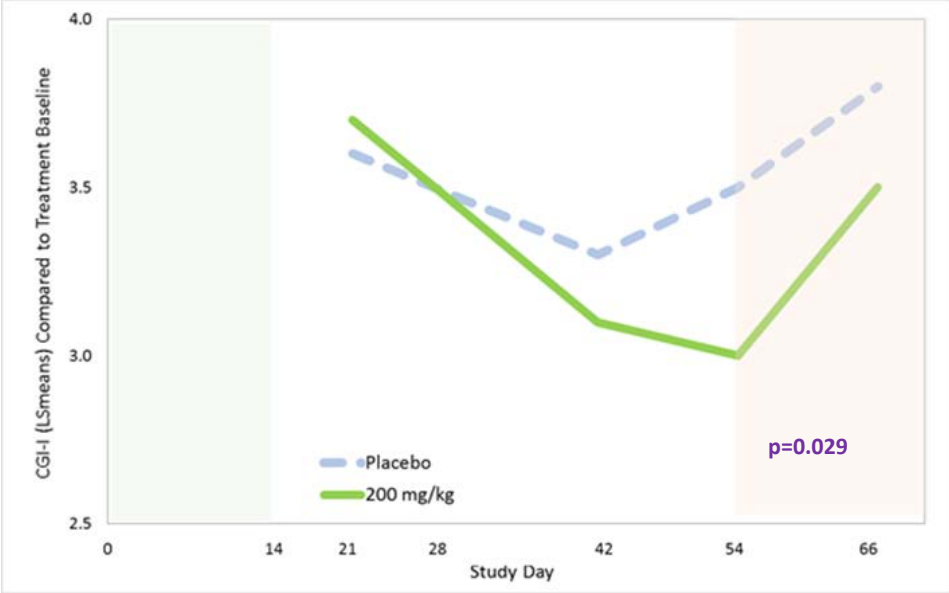
- 180 females aged 5 to 20 years
- RSBQ (caregiver) and CGI-I (physician) at 12 weeks are co-primary efficacy endpoints - both were positive in the Phase 2 trial
- Continuing strong support from leading physicians and Rettsyndrome.org
- First patients have completed Lavender and commenced Lilac; new patient enrolment into Lavender recommenced in June 2020 after pause of 3 months for Covid-19
- Lavender results expected in H2 2021, potential marketing approval in 2022

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

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 PHELAN-MCDERMID, ANGELMAN AND PITT HOPKINS SYNDROMES

ADVANCING TO PHASE 2 IN 3 INDICATIONS

- Clear and consistent efficacy in mouse models of Phelan-McDermid, Angelman and Pitt Hopkins syndromes
- Biochemical effects in the brain and dose response confirmed in Phelan-McDermid model
- Following review of data, FDA granted Orphan Drug designation for all 3 syndromes
- Phase 1 trial to characterize safety and PK in adult healthy volunteers currently in progress
- The program of non-clinical toxicology and CMC studies required to open an IND in H1 2021 for clinical trials in pediatric patients is nearing completion
- Recent placement secured funding to start Phase 2 trials in patients in 2021 for all three indications
- Neuren is leveraging extensive and highly relevant experience from Rett and Fragile X programs across CMC, non-clinical, clinical and regulatory

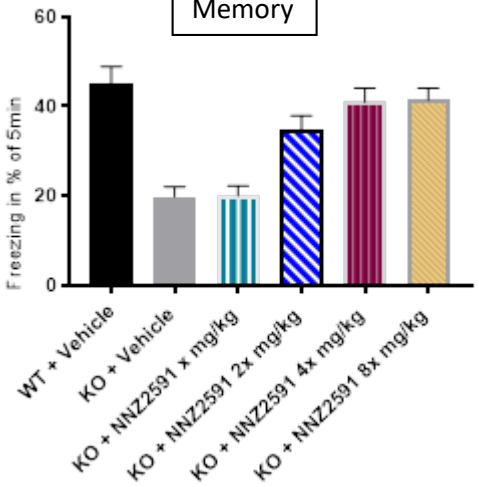
CLINICAL PROFILE OF PMS, AS and PTHS

Characteristic	Phelan-McDermid (PMS)	Angelman (AS)	Pitt Hopkins (PTHS)
Intellectual disability	√	√	√
Anxiety and hyperactivity	√	√	
Speech impairment	√	√	√
Motor and balance problems	√	√	
Sleep disturbance	√	√	√
Seizures	√	√	√
Breathing irregularities	√		√
Gastrointestinal issues	√	√	√
Autistic features	√	√	√

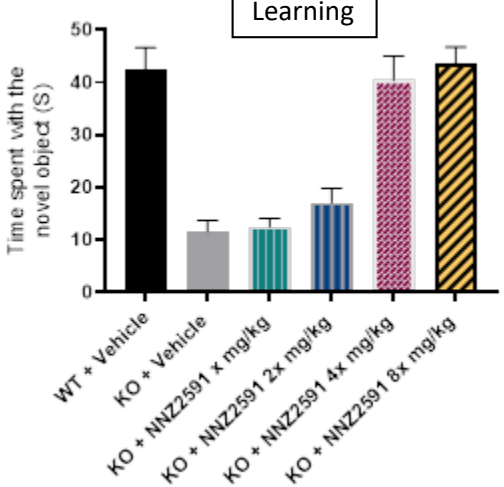
EFFICACY AND OPTIMUM DOSE IN PMS MODEL (*SHANK3*)

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.

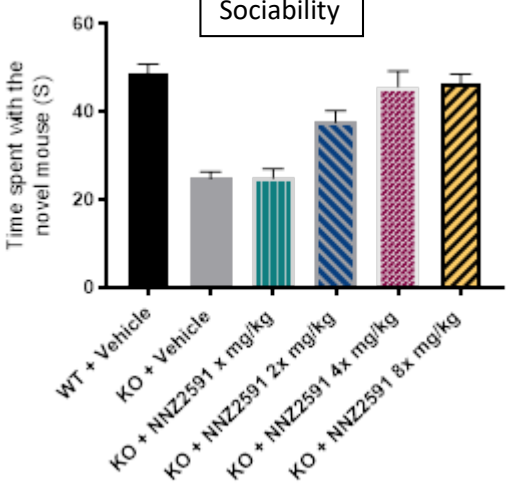
Memory



Learning



Sociability

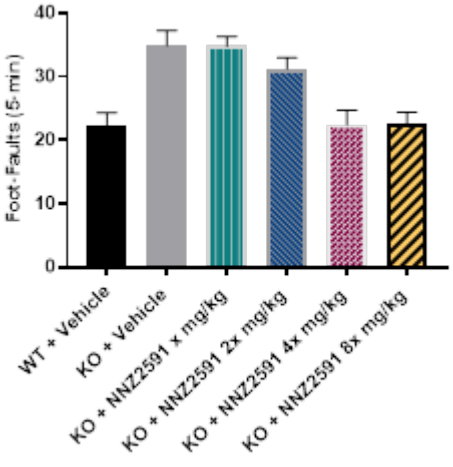


Incidence of seizures

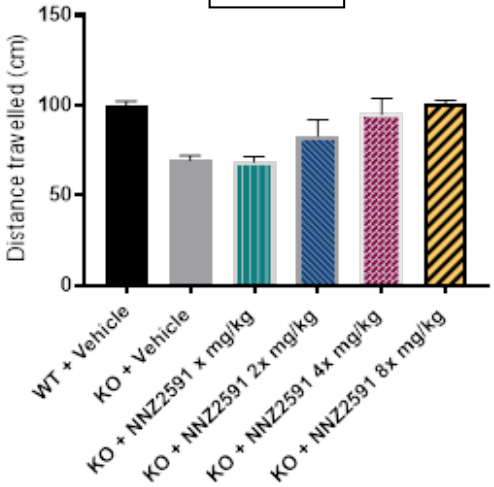
WT + vehicle	KO + vehicle	KO + x mg/kg	KO + 2x mg/kg	KO + 4x mg/kg	KO + 8x mg/kg
0%	60%	50%	30%	10%	10%

EFFICACY AND OPTIMUM DOSE IN PMS MODEL (*SHANK3*)

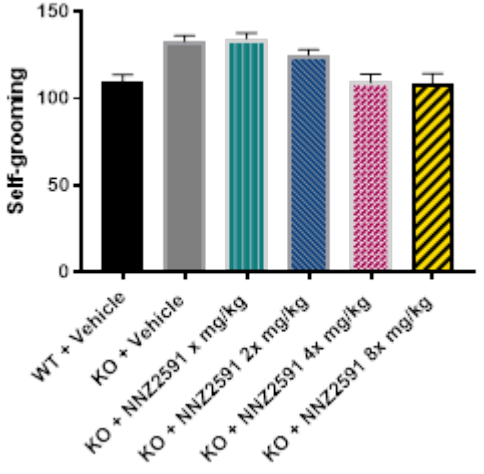
Motor function



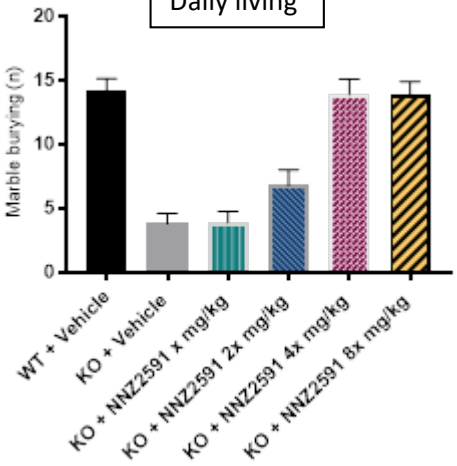
Anxiety



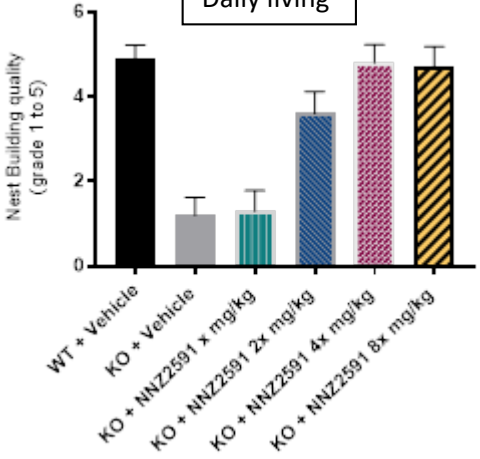
Repetitive behavior



Daily living

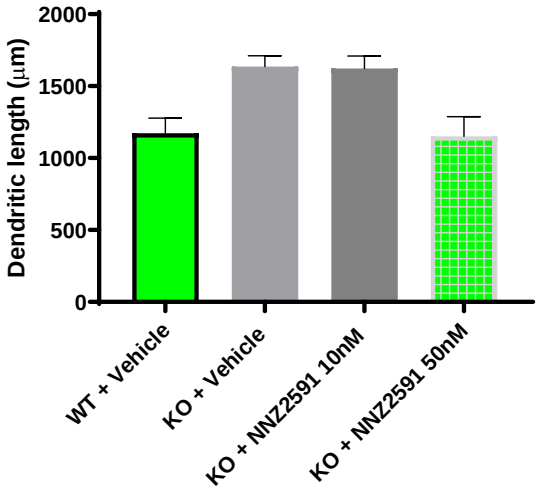


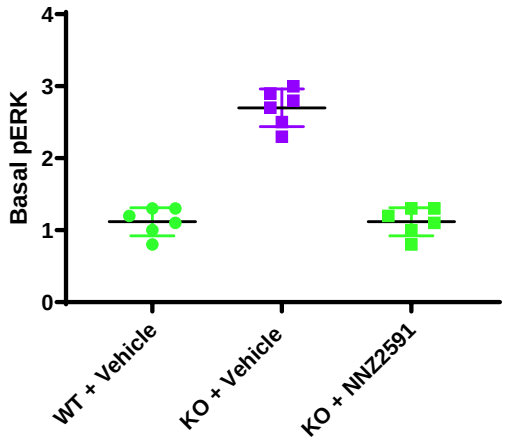
Daily living

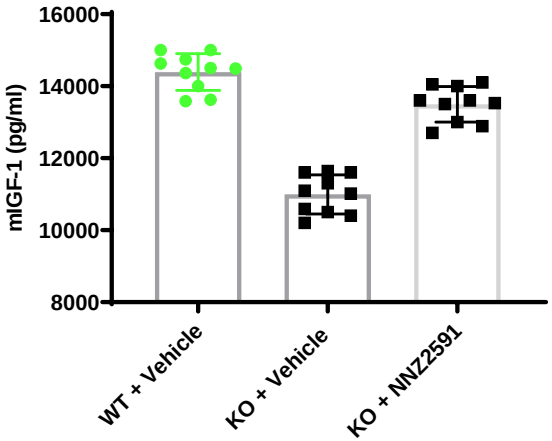


BIOCHEMICAL EFFECTS CONFIRMED IN *SHANK3* MODEL

In additional 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.

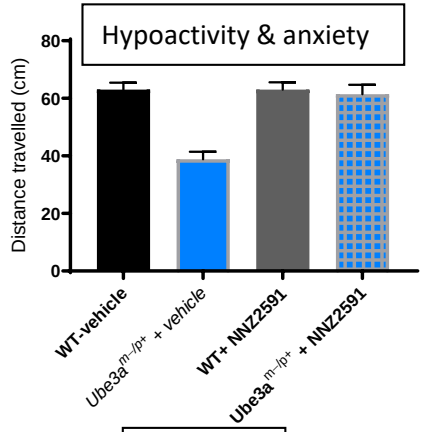


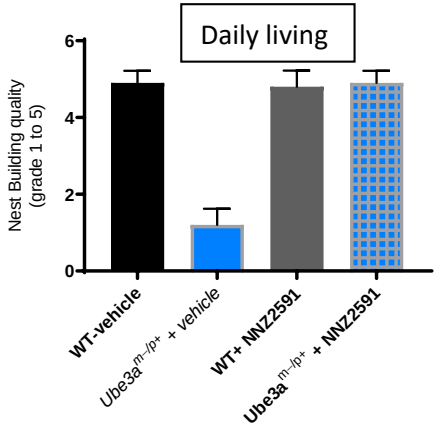


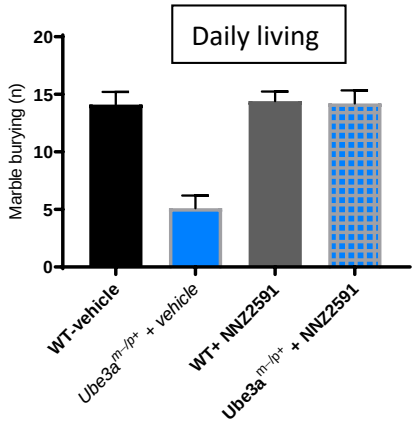


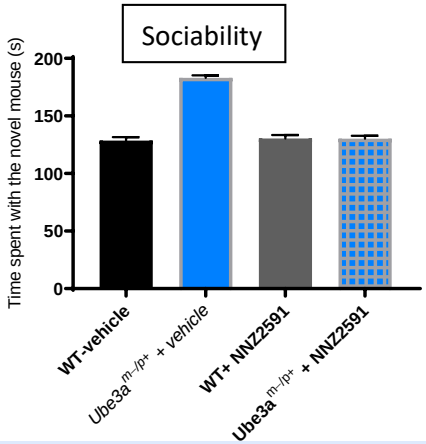
NNZ-2591 EFFICACY IN AS MOUSE MODEL (*UBE3A*)

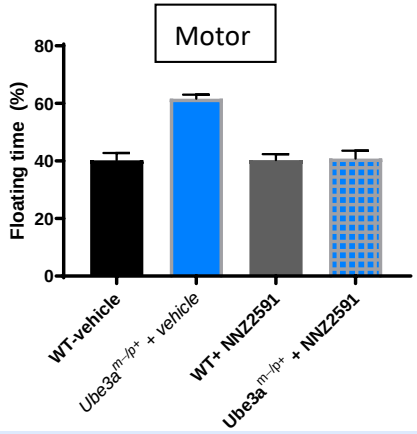
AS is caused by a deletion or mutation in the ubiquitin protein ligase E3A (*UBE3A*) gene on chromosome 15. In the *ube3a* knockout mouse model, which resembles features of AS in humans, wild type and knockout mice were each treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized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

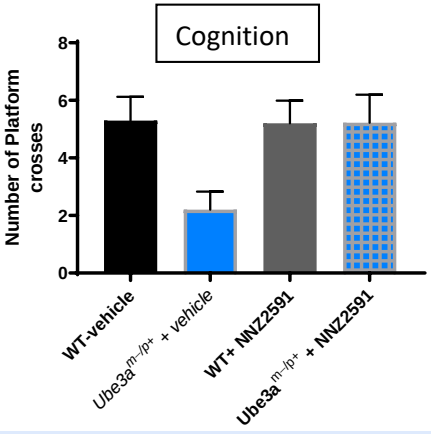






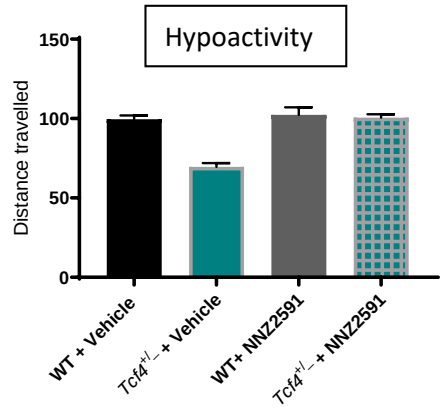


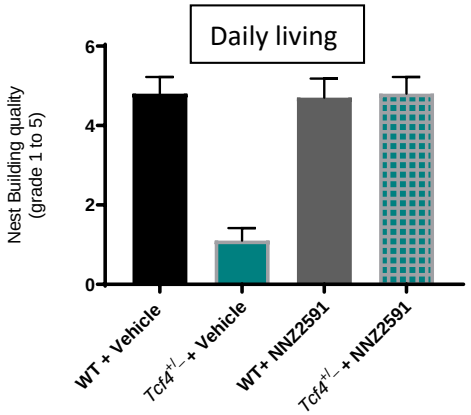


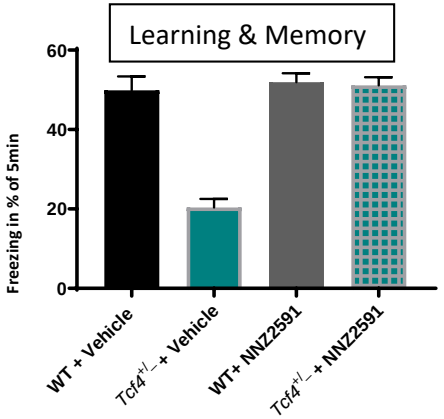


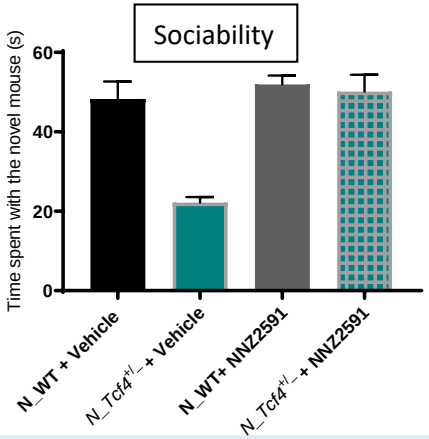
NNZ-2591 EFFICACY IN PTHS MOUSE MODEL (*TCF4*)

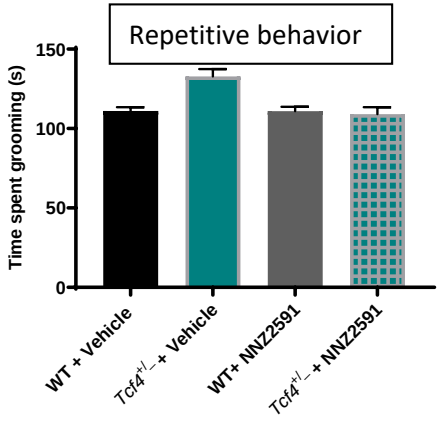
PTHS is caused by the loss of one copy or a mutation of the *TCF4* gene on chromosome 18. In the *tcf4* mutation mouse model, which exhibits features of PTHS in humans, wild type mice and knockout mice were treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized all the deficits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

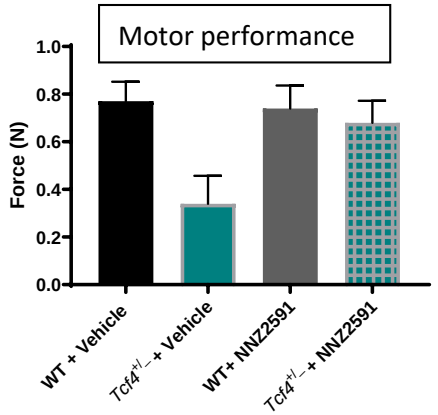












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APPENDIX

NEUREN'S BUSINESS SUMMARY

- Significant commercial opportunities with no approved drug therapies
- Strong support from leading physicians and patient advocacy groups
- Using regulatory incentives – Orphan Drug, Fast Track, Priority Review
- Protected by Orphan Drug exclusivity periods as well as issued patents

- Synthetic analogs replicate the activity of natural molecules related to IGF-1 (a critical growth factor for brain cells)
- More stable, orally bioavailable and readily cross the blood-brain barrier

Trofinetide

- **Phase 3 for Rett syndrome**, Phase 2 for Fragile X syndrome
- North American partner ACADIA **funds development** and commercialises in the US, Neuren receives up to **US$455m plus double-digit royalties plus one third of PRV value**
- Neuren retains **100% of value outside North America** with full access to use US regulatory package

NNZ-2591

- Preparing for Phase 2 trials in Phelan-McDermid, Angelman and Pitt Hopkins syndromes
- Neuren retains **worldwide rights** to NNZ-2591

MANAGEMENT TEAM

- Team responsible for devising and executing 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 and capital raisings

Jon Pilcher
Chief Executive Officer
Joined 2013

Larry Glass
Chief Science Officer
Joined 2004

Dr Clive Blower
VP Technical Affairs
Joined 2014

Dr Nancy Jones
VP Clinical Development
Joined 2013

James Shaw
VP Clinical Operations
Joined 2013

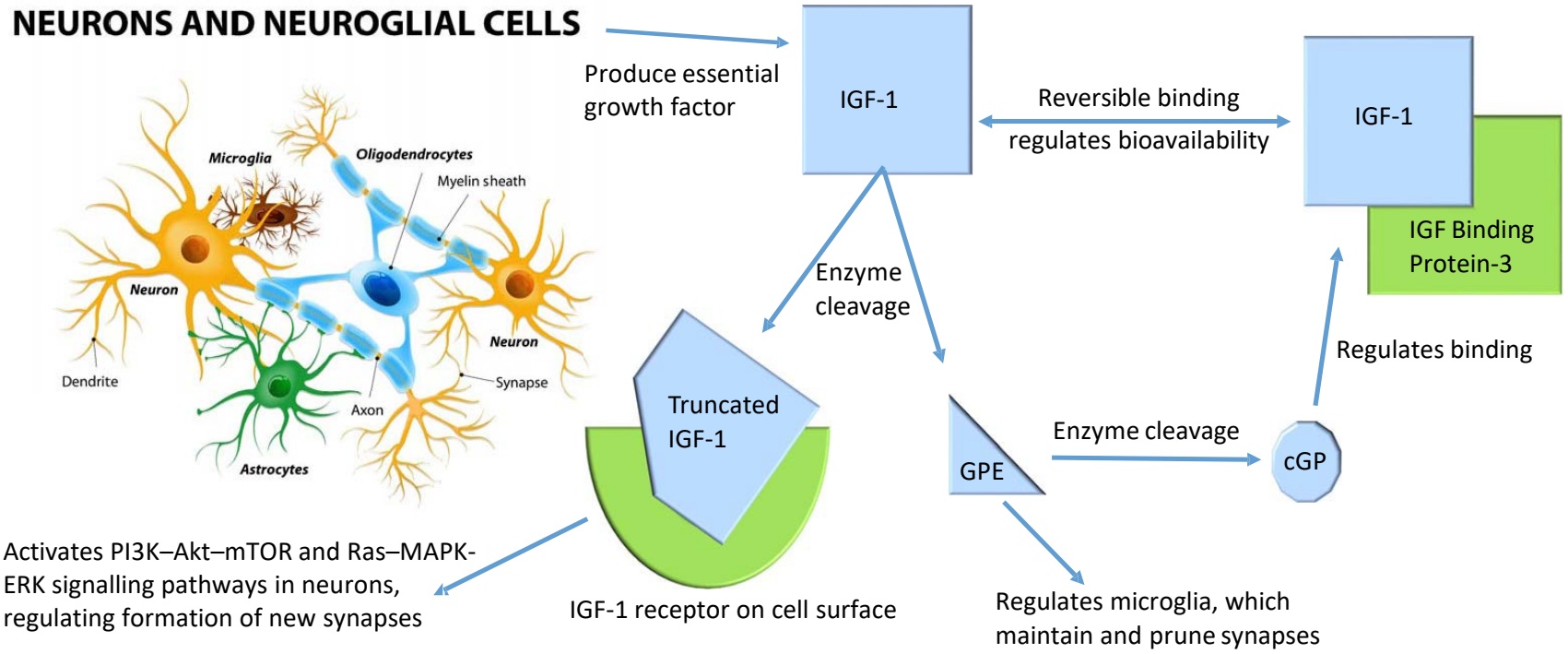
MARKET EXCLUSIVITY AND PATENTS

- Regulators provide exclusivity periods for products with orphan drug designation:
  - US – 7 years from marketing authorization, plus 6 months if approved for pediatric use
  - European Union – 10 years from marketing authorization, plus 2 years if approved for pediatric use
  - Japan – 10 years from marketing authorization
- All patents are owned by Neuren with no royalties payable; 5 years extension for one patent for each of trofinetide and NNZ-2591 should be available after first marketing approval:
  - Trofinetide composition of matter issued in US, Europe – expiry 2022
  - Trofinetide for Rett syndrome and Fragile X syndrome issued in US – expiry 2032
  - Trofinetide for autism spectrum disorders issued in Europe, Japan, Australia and Israel, pending in Canada and Brazil – expiry 2032
  - NNZ-2591 composition of matter issued in US, Europe, Japan – expiry 2024
  - NNZ-2591 for neurodevelopmental disorders issued in US, Europe and Japan – expiry 2034

NORMAL BIOLOGY OF IGF-1 IN THE BRAIN

Neuren's **trofinetide** and **NNZ-2591** are synthetic analogues of GPE and cGP which occur naturally in the brain:

- Replicate the activity of the natural molecules
- More stable and orally bioavailable
- Readily cross the blood-brain barrier

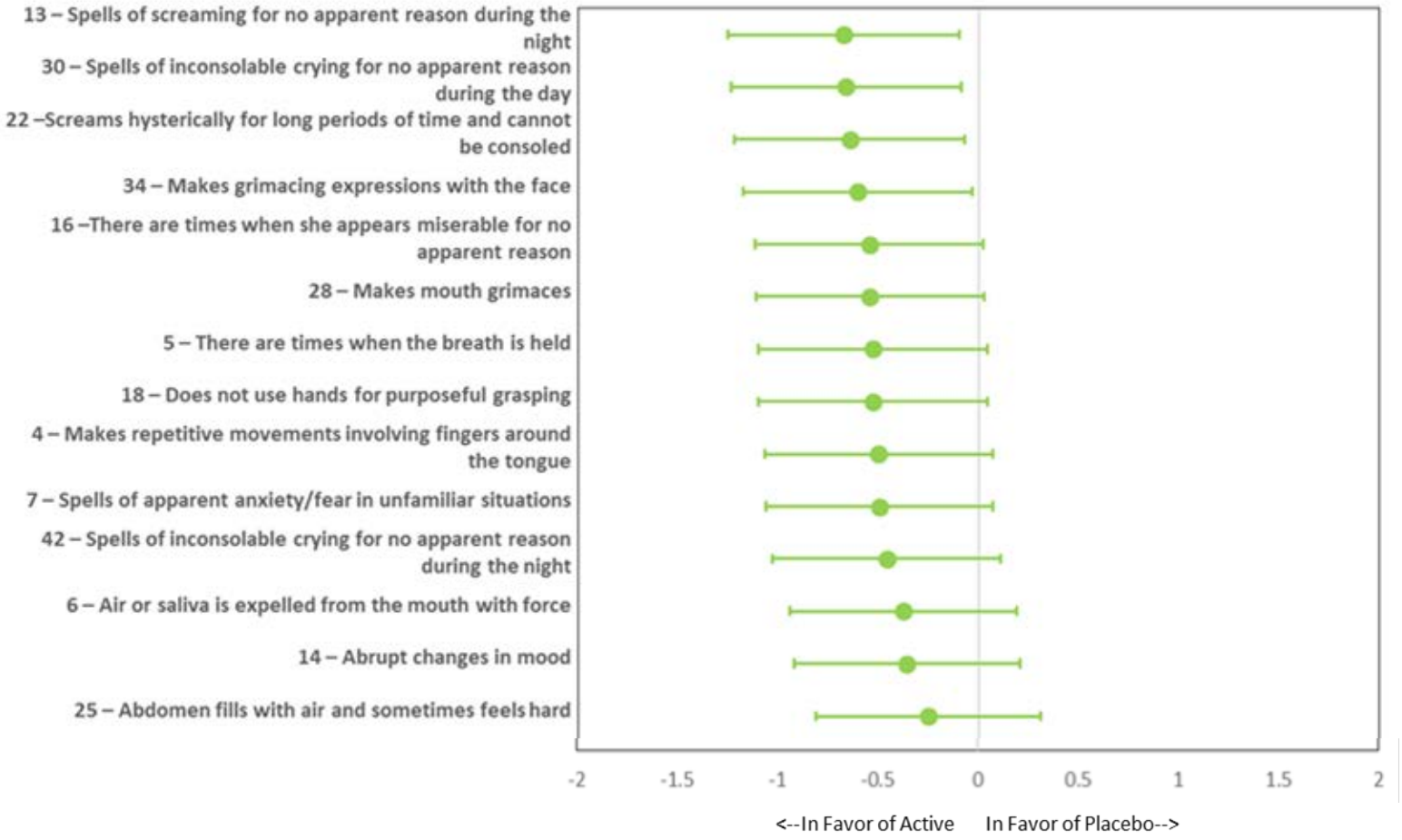


RETT SYNDROME PHASE 2 HIGHLIGHTS

- High dose of trofinetide (n=27) achieved statistically significant and clinically meaningful efficacy compared with placebo (n=24) for each of the two Phase 3 trial primary endpoints
- Published in *Neurology®*
  - Open access: https://n.neurology.org/content/early/2019/03/27/WNL.0000000000007316
  - Editorial "Turning the tide on targeted treatments for neurodevelopmental disorders"
- Girls aged 5 to 15 years with Rett syndrome were treated for 6 weeks only
- Conducted at 12 US hospitals, led by world-leading Rett syndrome clinicians and supported by Rettsyndrome.org
- Clinical improvement continued increasing through to end of treatment, suggesting further improvement with longer dosing
- Trofinetide was well tolerated with no safety concerns identified

RETT SYNDROME PHASE 2 TRIAL - RSBQ ITEMS

RSBQ items with largest Cohen's D effect size in favour of active



RETT SYNDROME PHASE 2 TRIAL - RSBQ SUBSCALES