neuren pharmaceuticals

CORPORATE PRESENTATION

6 April 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.

HIGHLIGHTS

- Neuren is developing **2 drugs** to treat **5 debilitating childhood disorders**, targeting the underlying impairment in signalling between brain cells
- **Trofinetide** in **Phase 3** for Rett syndrome, funded by partner ACADIA:
  - Results expected in 2021, potential marketing approval in 2022
  - FDA Fast Track, Orphan Drug designation, Rare Pediatric Disease designation (eligible for tradeable Priority Review Voucher)
- Preparing for clinical trials of **NNZ-2591 for 3 disorders**:
  - Phelan-McDermid, Angelman and Pitt Hopkins syndromes
  - FDA Orphan Drug designation, compelling results in animal models
- ASX-listed (NEU) based in Melbourne, Australia
- Current market cap approx. A$100 million

VALUE PROPOSITION

MANAGEMENT TEAM

- Team responsible for Neuren's Orphan Drug programs since 2013
- Extensive international pharmaceutical business experience – Aspen, Sigma, Wyeth, Medeva, Celltech, Hospira, Quintiles, AstraZeneca, Autism Speaks, Acrux, Faulding
- Developed drugs from pre-clinical through to FDA approval
- Expertise across CMC, non-clinical, clinical, regulatory, sales & marketing
- Executed multiple partnering transactions and capital raisings

Dr Richard Treagus
Executive Chairman
Joined 2013

Jon Pilcher
Chief Financial Officer
Joined 2013

Larry Glass
Chief Science Officer
Joined 2004

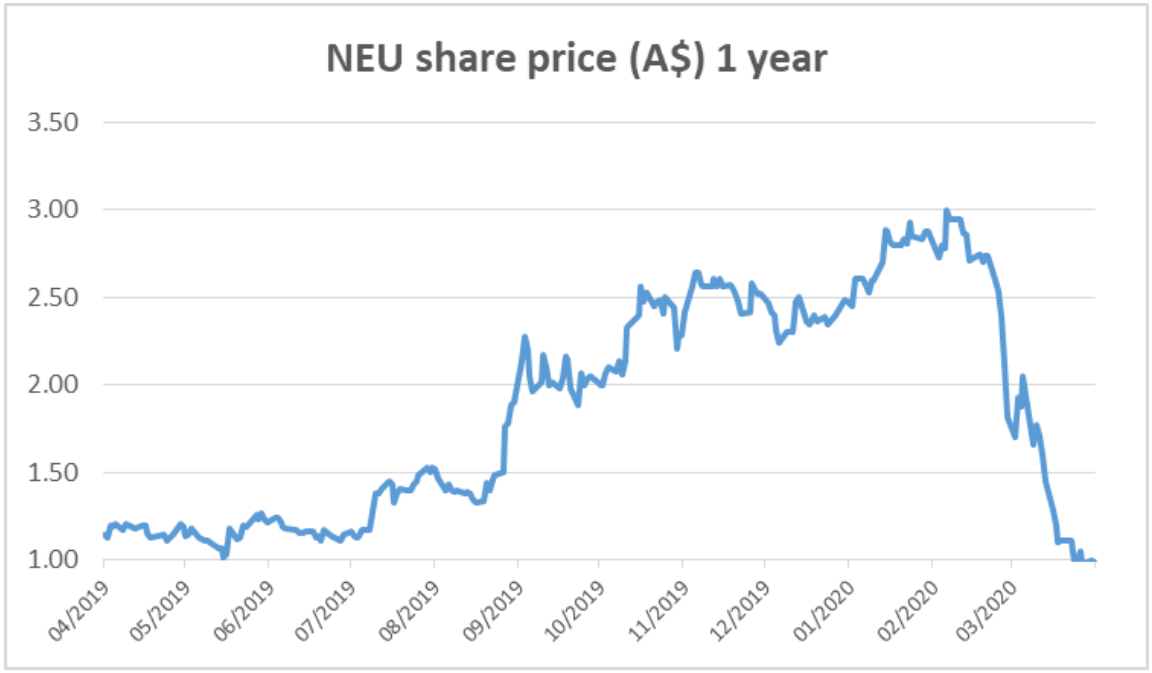
Dr Clive Blower
VP Technical Affairs
Joined 2014

Dr Nancy Jones
VP Clinical Development
Joined 2013

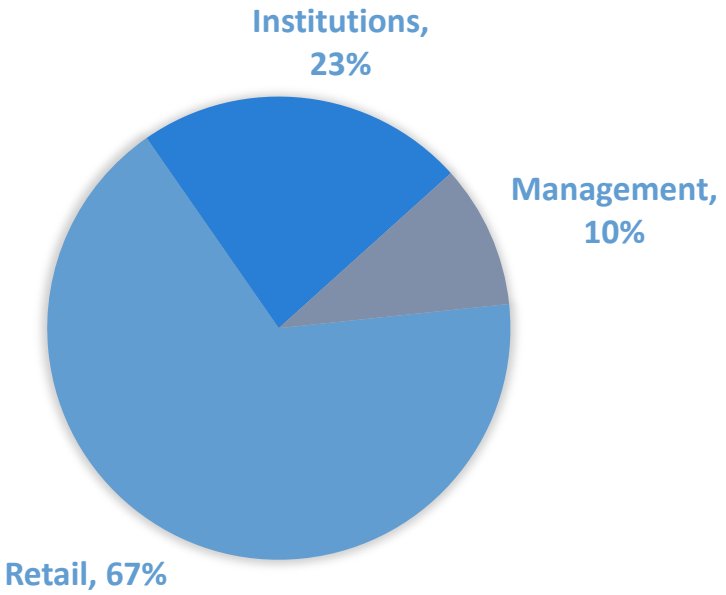
James Shaw
VP Clinical Operations
Joined 2013

STOCK INFORMATION (ASX: NEU)

52 week price range: $0.97 - $3.04



Share register composition
(100.2 million quoted shares)



Cash at 31 December 2019: $13.8 million

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

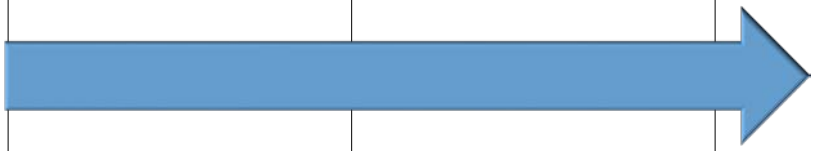
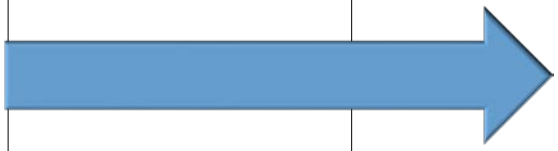
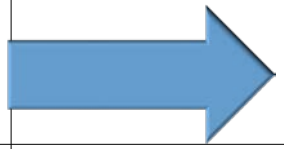
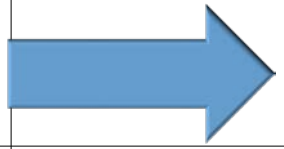
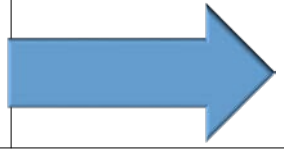
Trofinetide

- **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 clinical trials in Phelan-McDermid, Angelman and Pitt Hopkins syndromes
- Neuren retains **worldwide rights** to NNZ-2591

PRODUCT PIPELINE

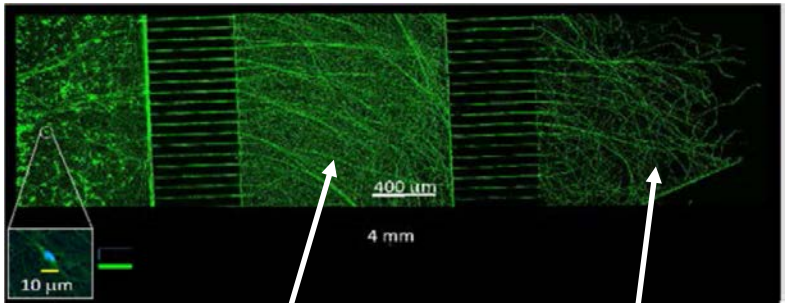
Compound	Indication	Preclinical / Phase 1	Phase 2	Phase 3	Commercial Partner
Trofinetide	Rett syndrome[1]				ACADIA Pharmaceuticals *(North America)*
	Fragile X syndrome[1]				ACADIA Pharmaceuticals *(North America)*
NNZ-2591	Phelan-McDermid syndrome[2]				
	Angelman syndrome[2]				
	Pitt Hopkins syndrome[2]				

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

[2] Orphan Drug designation in US

CORRECTING IMPAIRED SIGNALING IN NEURONS

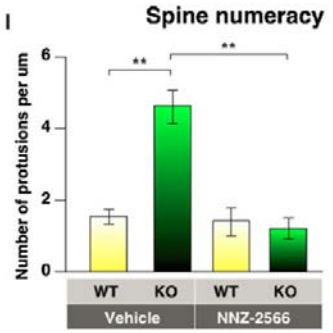
- Neurodevelopmental disorders result from different gene mutations, but all feature impaired signaling between neurons, with abnormal length and density of the dendritic spines that connect the neurons via synapses
- This impaired signaling causes behavioral, cognitive, motor and autonomic problems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

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

ESTIMATES OF PATIENT POPULATIONS AGED <60

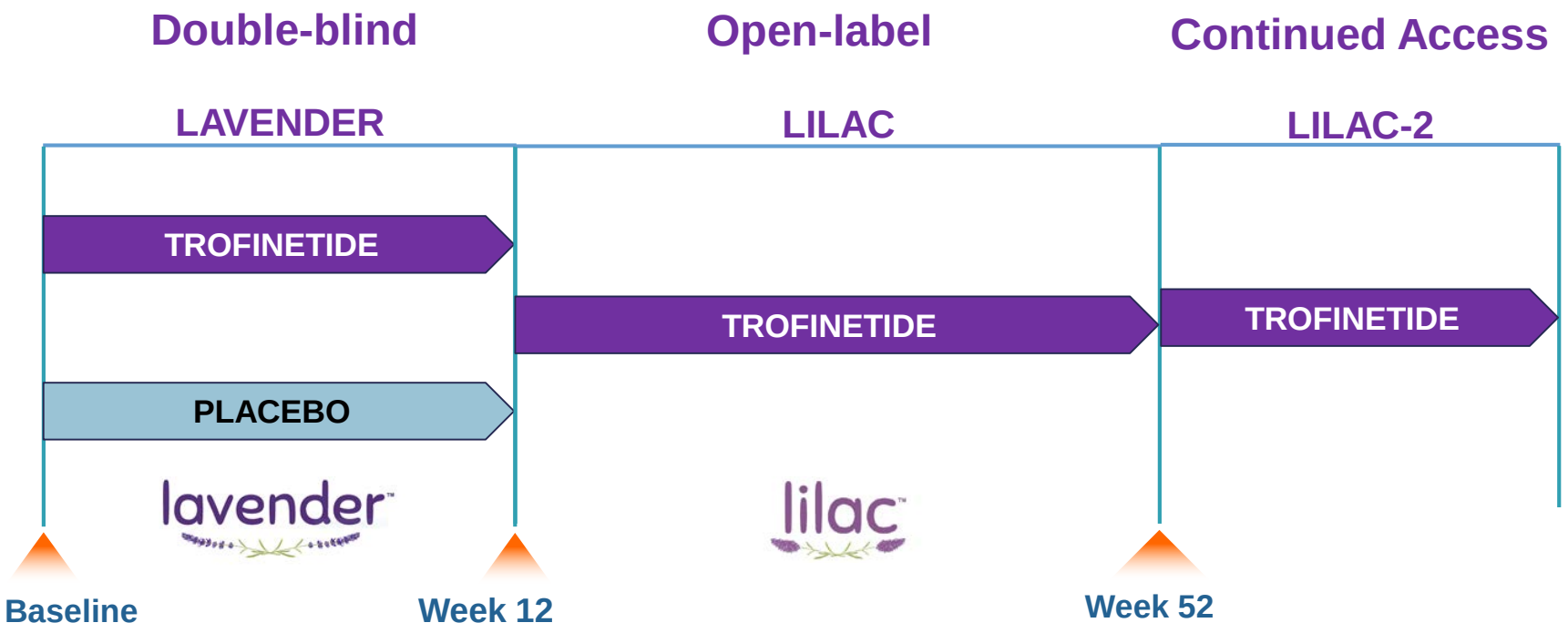
Disorder	Gene mutation	Published prevalence estimates	Potential patients US[1]	Potential patients EU/JP[1]
Rett	*MECP2*	1/10,000 to 1/15,000 females	10,000	16,000
Fragile X	*FMR1*	1/4,000 to 1/7,000 males 1/12,000 to 1/22,000 females	30,000	48,000
Phelan-McDermid	*SHANK3*	1/8,000 to 1/15,000 males and 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

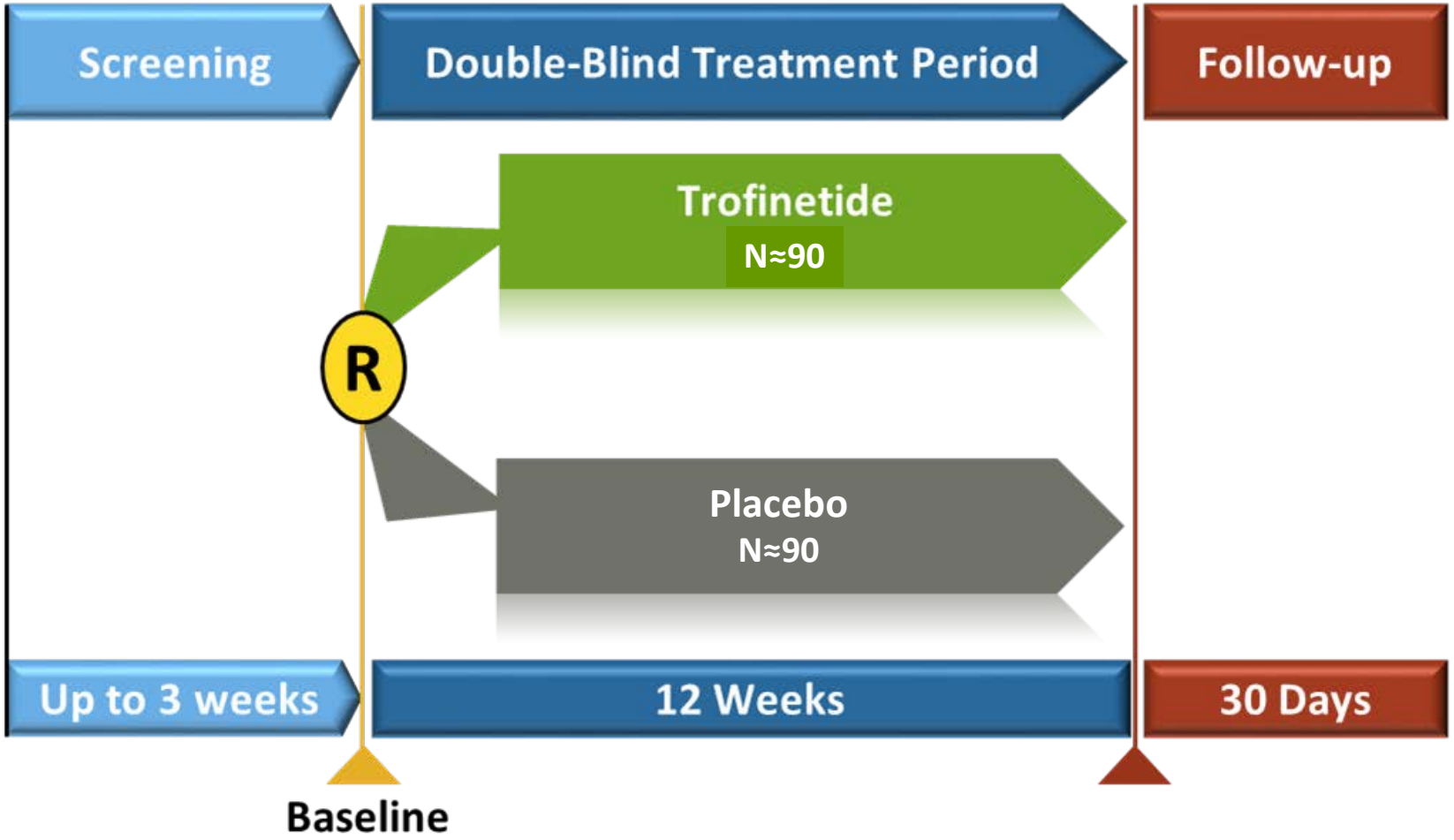
TROFINETIDE FOR RETT SYNDROME

RETT SYNDROME PHASE 3 PROGRAM



- Continuing strong support from leading Rett syndrome physicians and largest advocacy group (rettsyndrome.org)
- Initiated in October 2019, first patients have completed Lavender and commenced Lilac
- Lavender results expected in 2021, potential marketing approval in 2022
- New patient enrolment into Lavender currently paused temporarily for Covid-19

LAVENDER STUDY



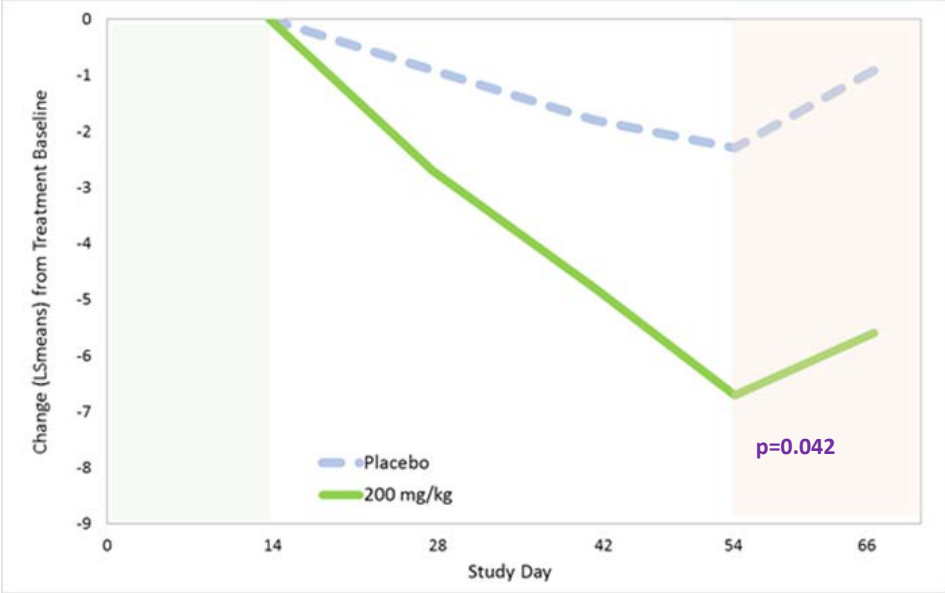
- Females with Rett syndrome aged 5 to 20 years, US sites only
- Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression of Improvement (CGI-I) at 12 weeks are co-primary efficacy endpoints

RETT SYNDROME PHASE 2 HIGHLIGHTS

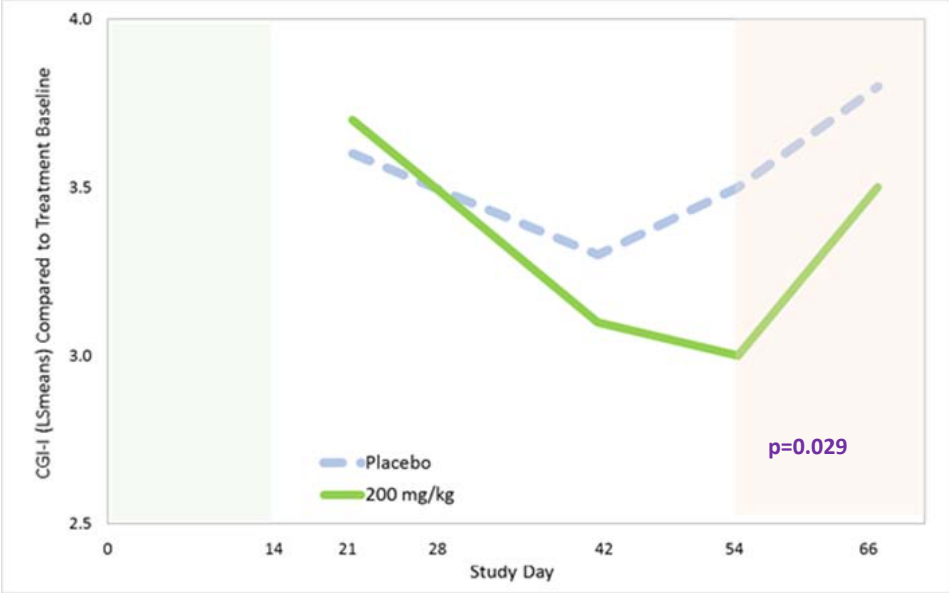
- High dose of trofinetide (n=27) achieved statistically significant and clinically meaningful efficacy compared with placebo (n=24) for each of the two Phase 3 trial primary endpoints
- Published in *Neurology®*
  - Open access: https://n.neurology.org/content/early/2019/03/27/WNL.0000000000007316
  - 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 - 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

RETT SYNDROME PHASE 3 VERSUS PHASE 2

- 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 NNZ-2591 FOR 3 INDICATIONS

- FDA granted Orphan Drug designation for Phelan-McDermid, Angelman and Pitt Hopkins
- Compelling data package assembled in preparation for clinical trials:
  - Clear and consistent efficacy in mouse models of each syndrome (*SHANK3, UBE3A, TCF4*)
  - Efficacy and optimum dose clearly demonstrated in Phelan-McDermid model
  - High oral bioavailability and blood/brain barrier penetration
  - Manufacturing process conveys significant technical and commercial advantages
- Neuren is leveraging extensive and highly relevant experience from Rett and Fragile X programs across CMC, non-clinical, clinical and regulatory
- The program of non-clinical toxicology and CMC studies required to open an IND and enable clinical trials in pediatric patients is currently in progress
- Phase 1 trial in healthy volunteers in Australia in 2020
- Planning Phase 2 trials in patients in 2021 for all three indications:
  - 12 weeks treatment of pediatric patients at US sites
  - Confirm safety and tolerability
  - Establish size of clinical response to drug, measured by CGI-I and other potential endpoints
  - Confirm optimum dose for the subsequent pivotal trials

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	√	√	√

NNZ-2591 HAS IDEAL PK CHARACTERISTICS

- 100% oral biovailability (AUC oral administration ≈ AUC intravenous administration)
- High blood-brain barrier penetration, proportional to dose:

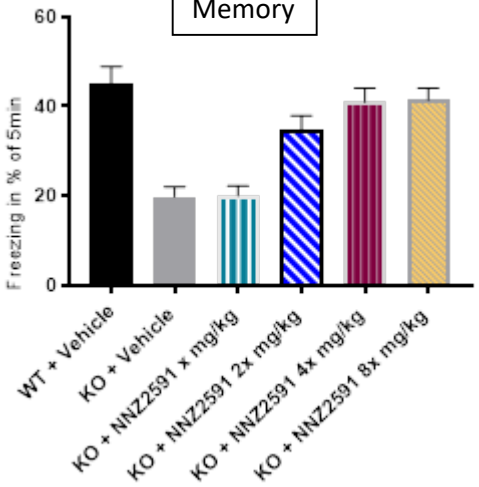
	Mean exposure to NNZ-2591		
Dose	**"A"mg/kg**	**2A mg/kg**	**Ratio of 2A mg/kg: A mg/kg**
1.5 hours post-dose:			
Cerebrospinal fluid (µg/ml)	40.4	82.2	2.03 : 1
Blood (µg/ml)	58.5	116.0	1.98 : 1
4 hours post-dose:			
Cerebrospinal fluid (µg/ml)	11.0	24.7	2.25 : 1
Blood (µg/ml)	15.6	34.2	2.19 : 1
Brain (µg/g)	22.6	37.0	1.63 : 1

Data from rodent studies

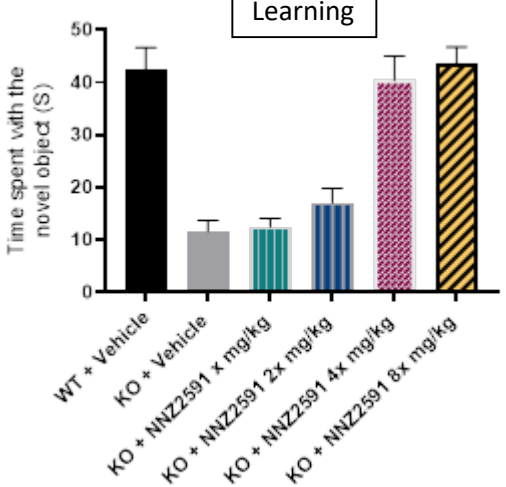
EFFICACY AND OPTIMUM DOSE IN PMS MODEL (*SHANK3*)

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.

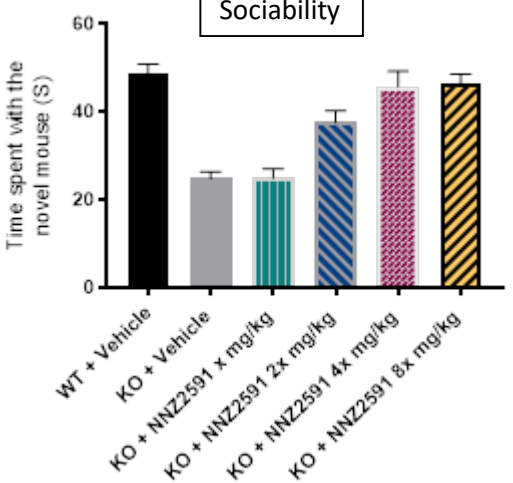
Memory



Learning



Sociability

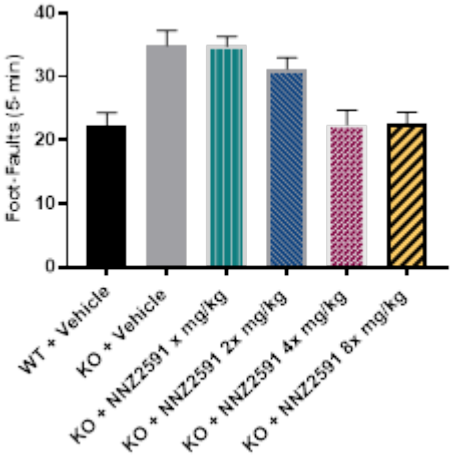


Incidence of seizures

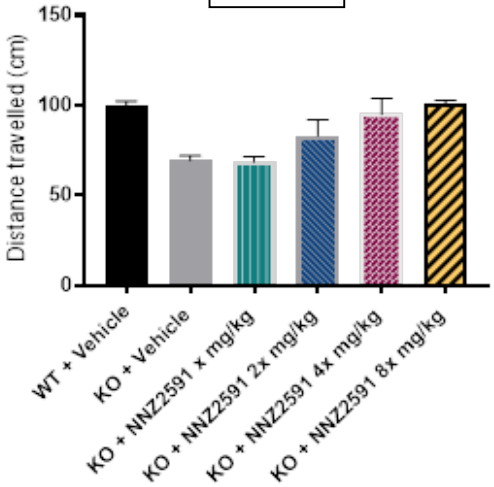
WT + vehicle	KO + vehicle	KO + x mg/kg	KO + 2x mg/kg	KO + 4x mg/kg	KO + 8x mg/kg
0%	60%	50%	30%	10%	10%

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

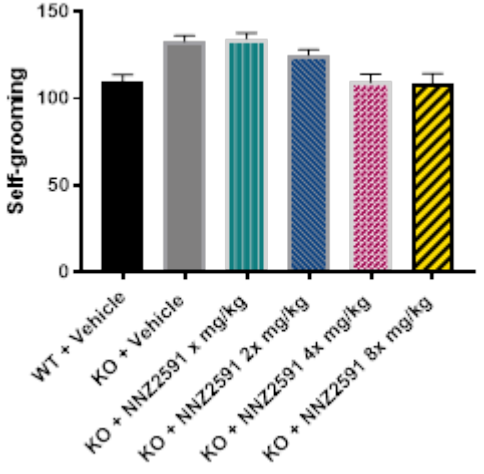
Motor function



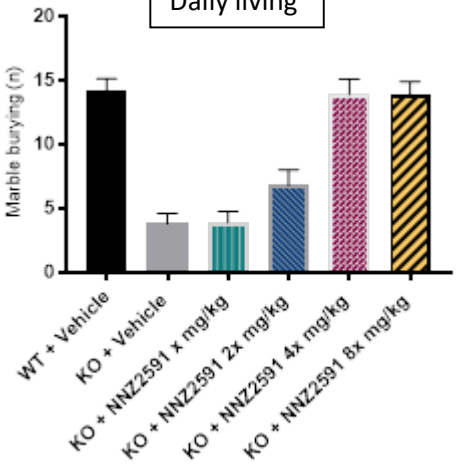
Anxiety



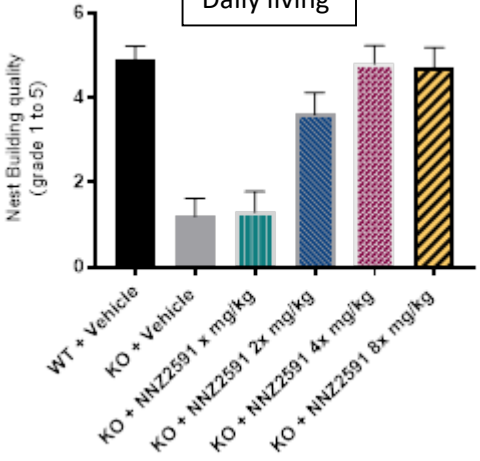
Repetitive behavior



Daily living

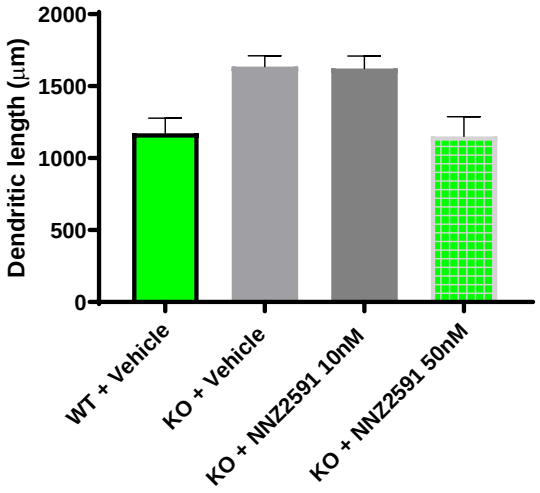


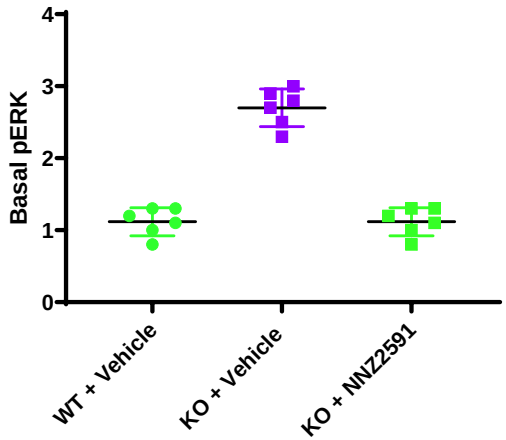
Daily living

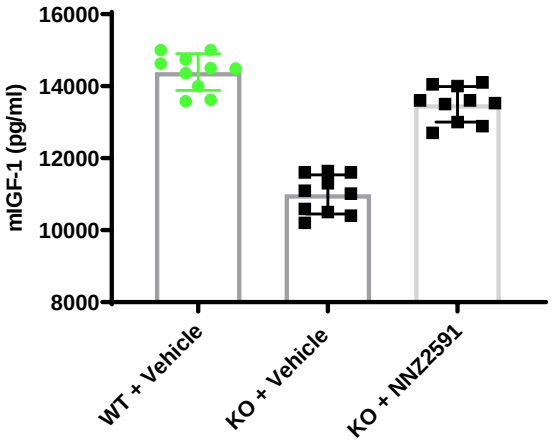


BIOCHEMICAL EFFECTS CONFIRMED IN *SHANK3* MODEL

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.

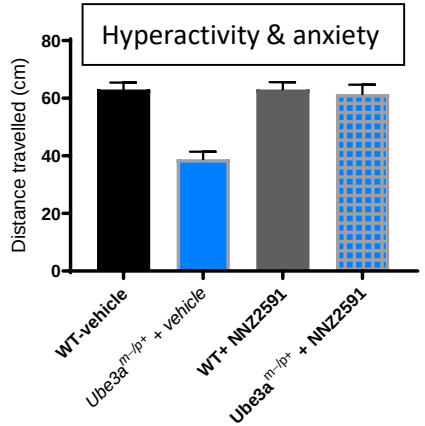


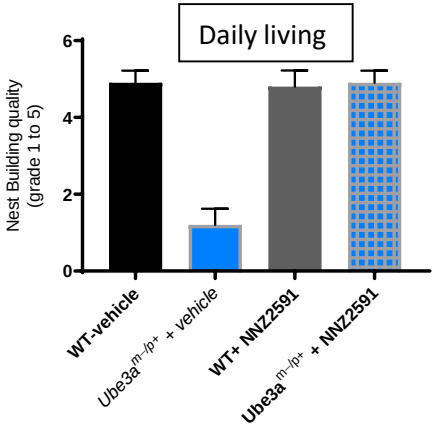


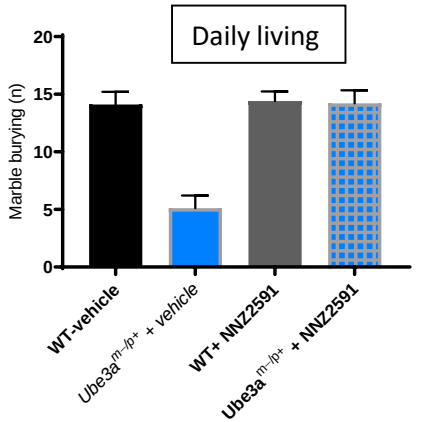


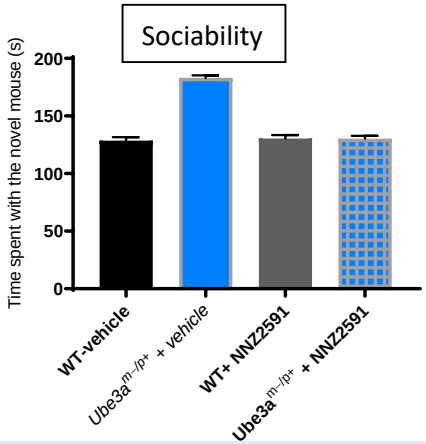
EFFICACY IN MOUSE MODEL OF AS (*UBE3A*)

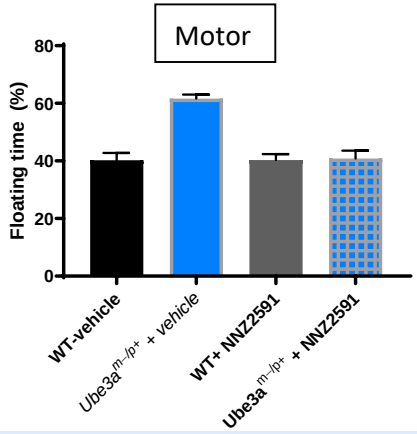
AS is caused by a deletion or mutation in the ubiquitin protein ligase E3A (*UBE3A*) gene on chromosome 15. In the *ube3a* knockout mouse model, which resembles features of AS in humans, wild type and knockout mice were each treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized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

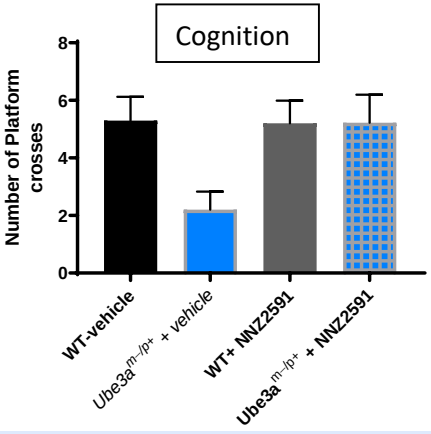






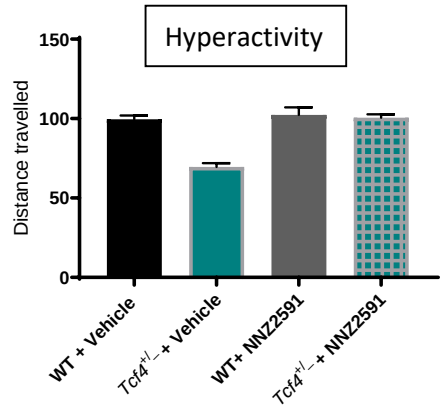


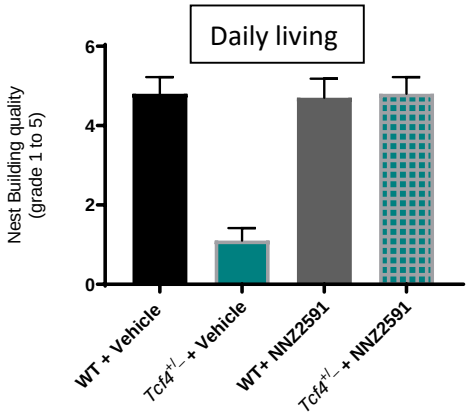


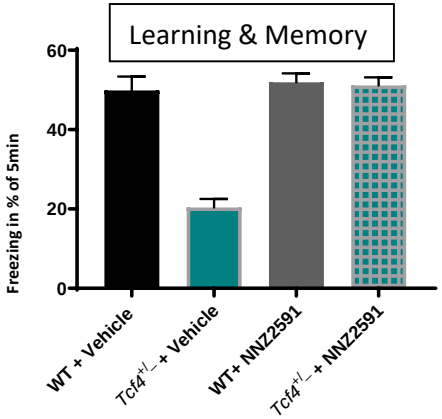


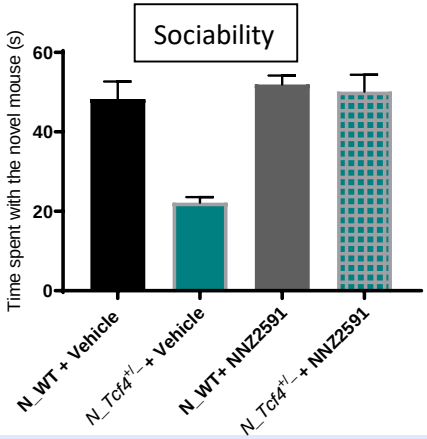
EFFICACY IN MOUSE MODEL OF PTHS (*TCF4*)

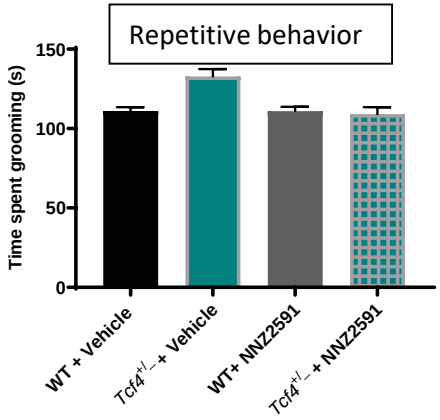
PTHS is caused by the loss of one copy or a mutation of the *TCF4* gene on chromosome 18. In the *tcf4* mutation mouse model, which exhibits features of PTHS in humans, wild type mice and knockout mice were treated with placebo or NNZ-2591 for 6 weeks. Treatment with NNZ-2591 normalized all the deficits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

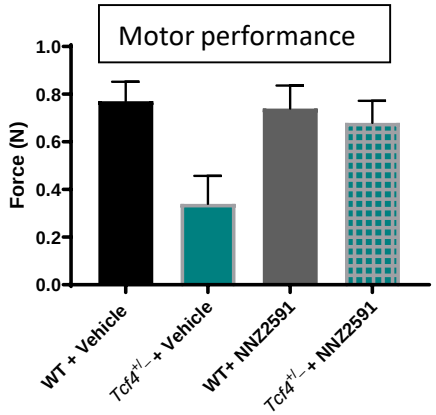












CONTACT

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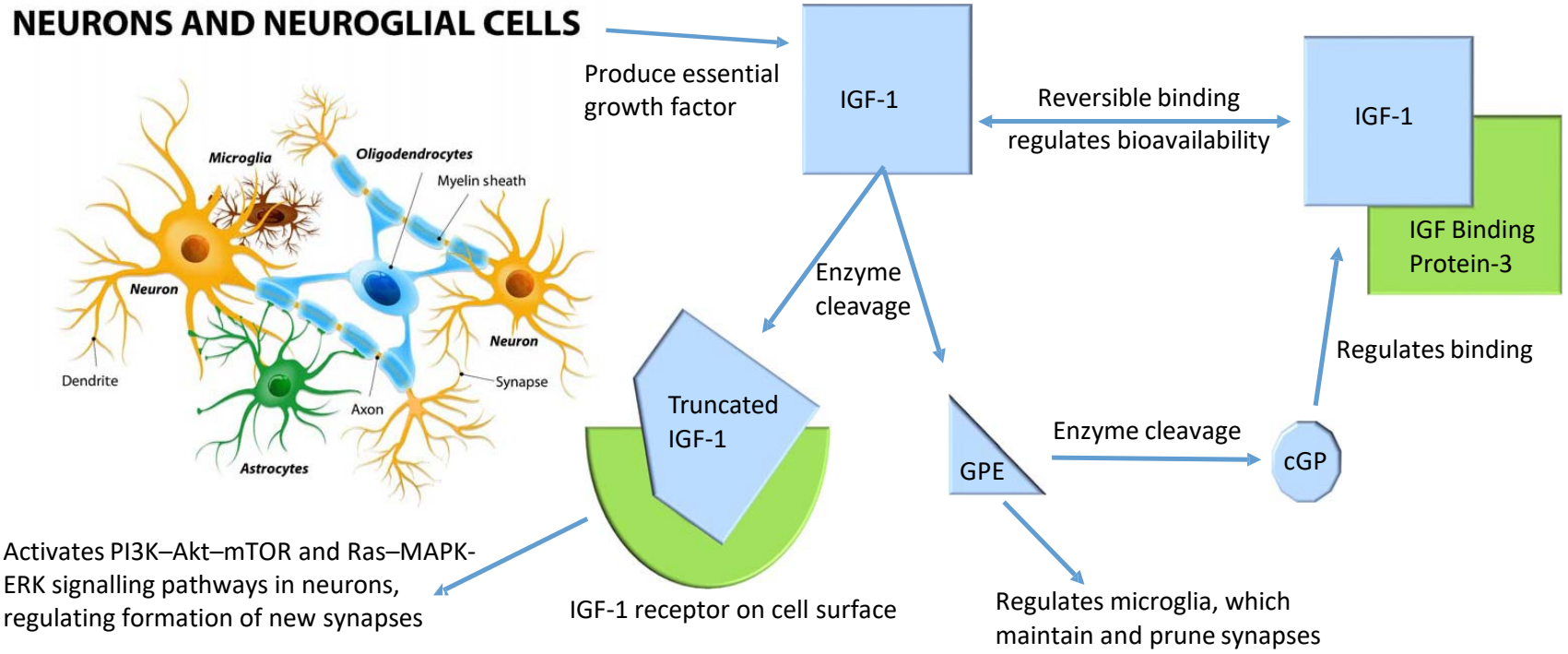
APPENDIX

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

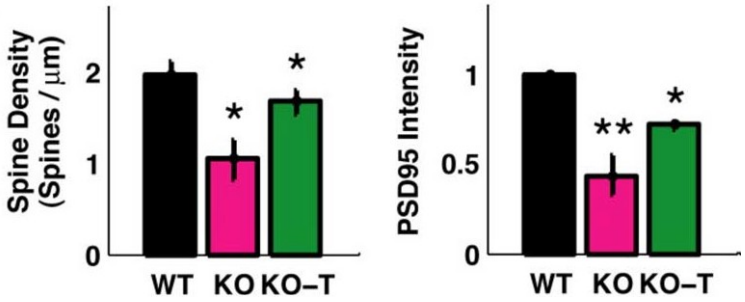


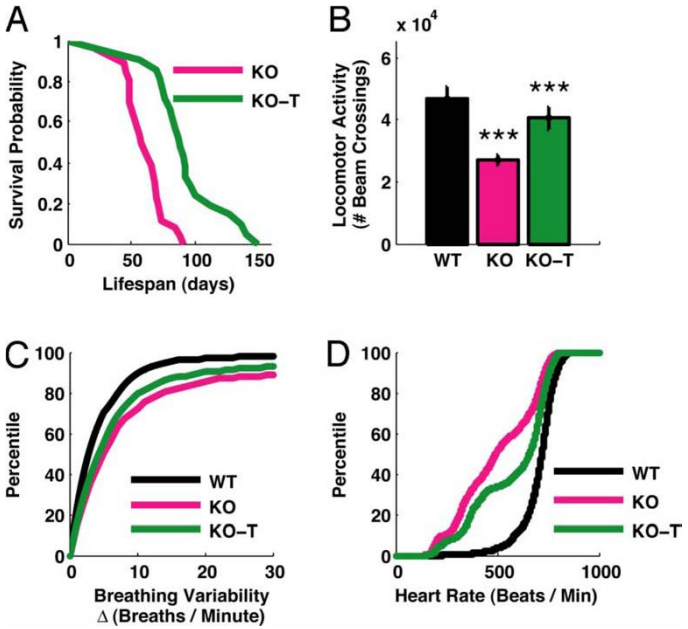
RETT SYNDROME OVERVIEW

- 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 between 6-18 months of age
- Severely disabling range of symptoms include:
  - Loss of speech and motor control
  - Neurobehavioral, cognitive and intellectual disability
  - Seizures
  - Autonomic dysfunction – breathing, cardiovascular and gastrointestinal abnormalities
- Most require life-long medical care and 24 hour supportive care – profound financial and emotional impact on families

EFFICACY IN MOUSE MODEL OF RETT SYNDROME

- In “Partial reversal of Rett syndrome like symptoms in MeCP2 mutant mice” (doi:10.1073/pnas.0812394106), Tropea et al reported that in the MeCP2 knockout mouse, introducing GPE:
  - Extended life span, improved locomotor function, ameliorated breathing patterns and reduced irregularity in heart rate
  - Increased the density of the dendritic spines that form synapses
  - Increased levels of PSD-95, a key protein for synapse maturation
  - Increased synaptic transmission signals

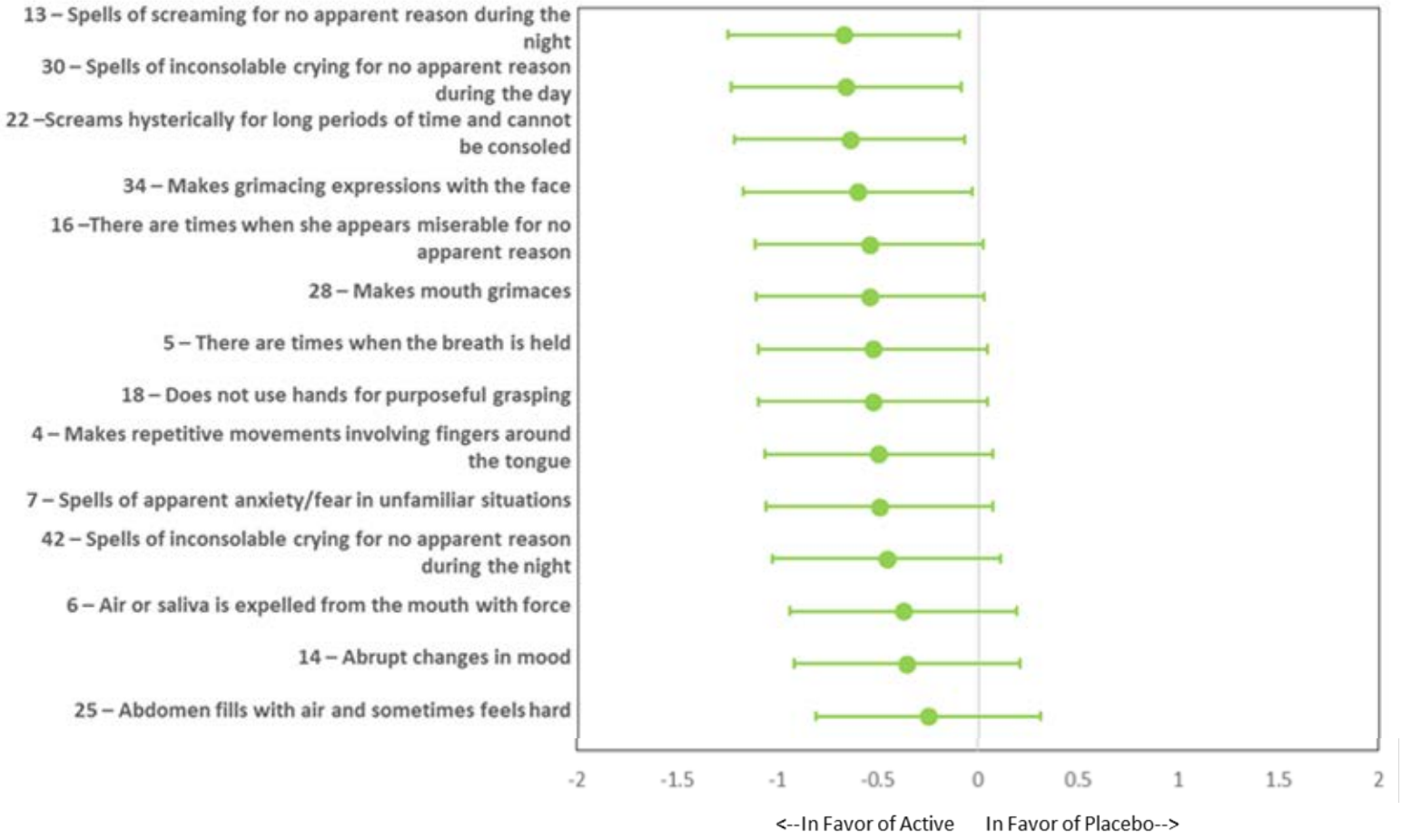




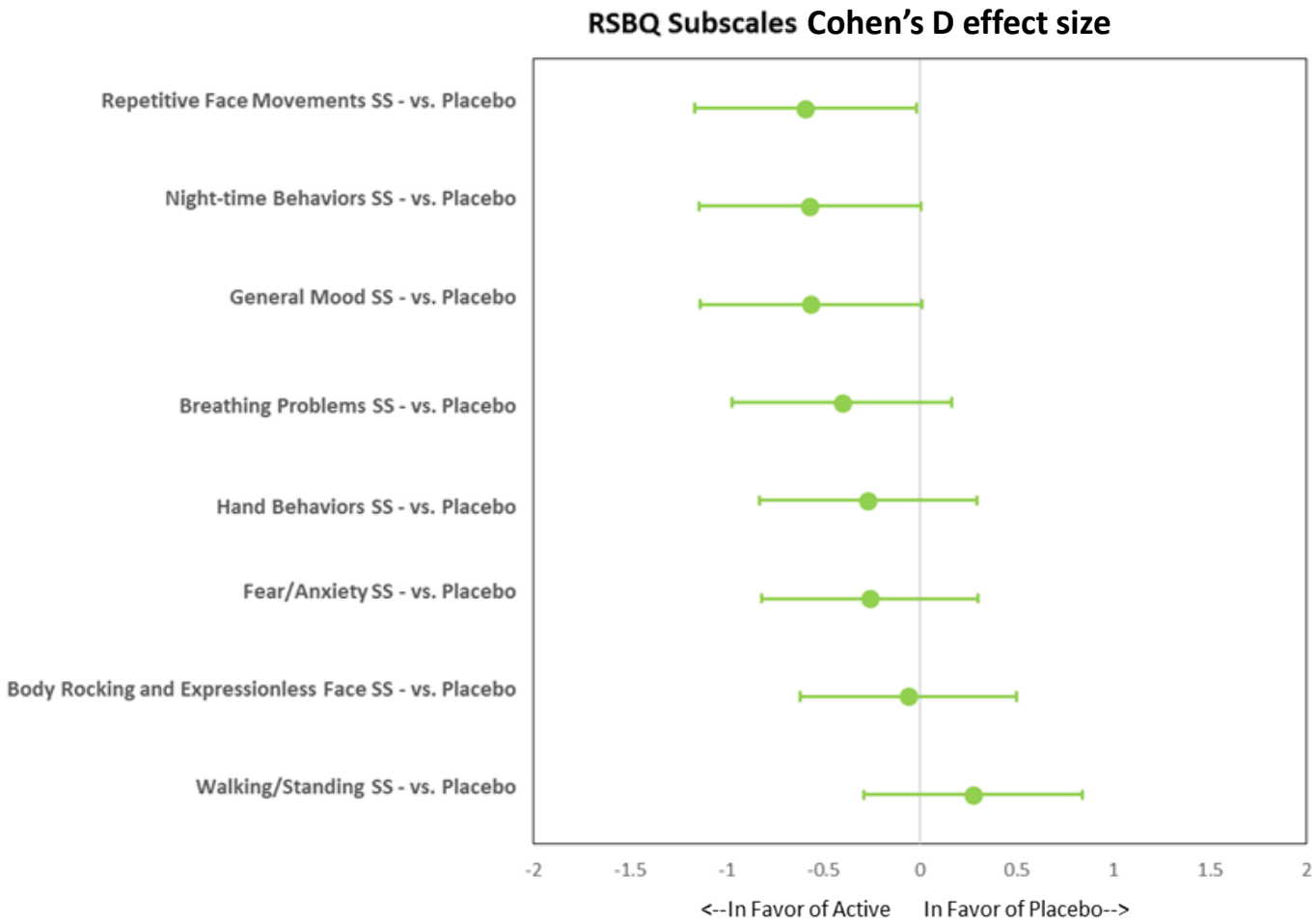
Notes: WT=wild type, KO=knockout, KO-T=knockout treated with GPE. Charts reproduced with permission.

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

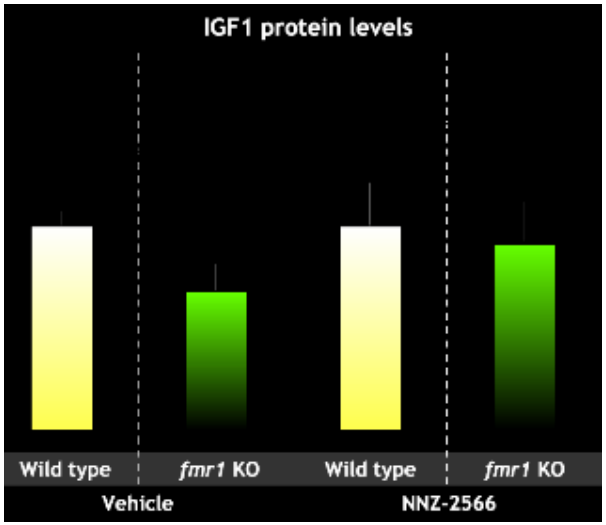


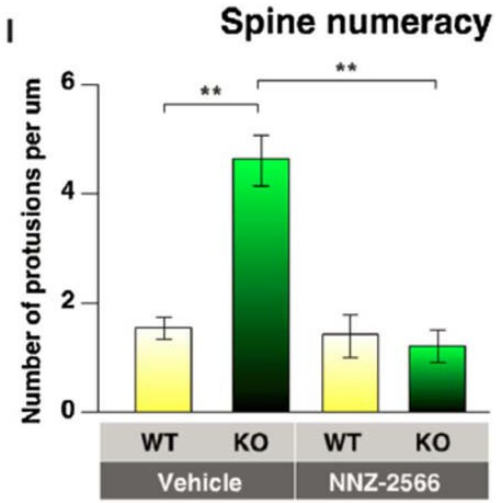
FRAGILE X SYNDROME OVERVIEW

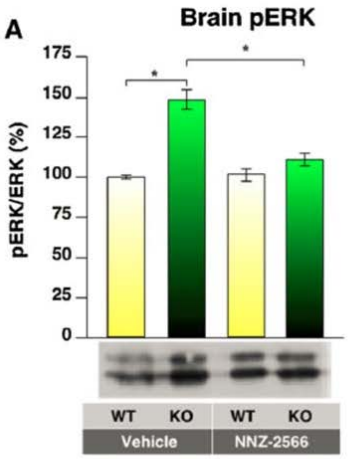
- Fragile X syndrome is an inherited X chromosome mutation with no approved treatments available
  - Estimates of people with the mutation range from 1 in 4,000 to 7,000 males and from 1 in 6,000 to 11,000 females
  - More severe in males, ~50% of the females have features of the syndrome
- The most common inherited cause of intellectual disabilities and the most common known cause of autism; symptoms include:
  - Intellectual disabilities
  - Anxiety and unstable mood
  - Seizures (~1:4)
  - ADHD and autistic behavior

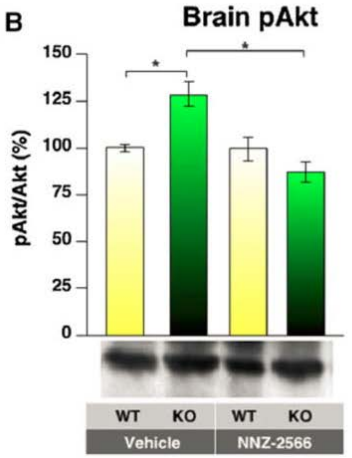
EFFICACY IN MOUSE MODEL OF FRAGILE X

- In the fmr1 knockout mouse model, trofinetide normalised mutant mice, but had no effect on wild type mice:
  - Corrected learning and memory deficits, hyperactivity and social behavior
  - Reduced dendritic spine density
  - Normalised overactive ERK and Akt signaling in the brain
  - Normalised the level of IGF-1 in the brain









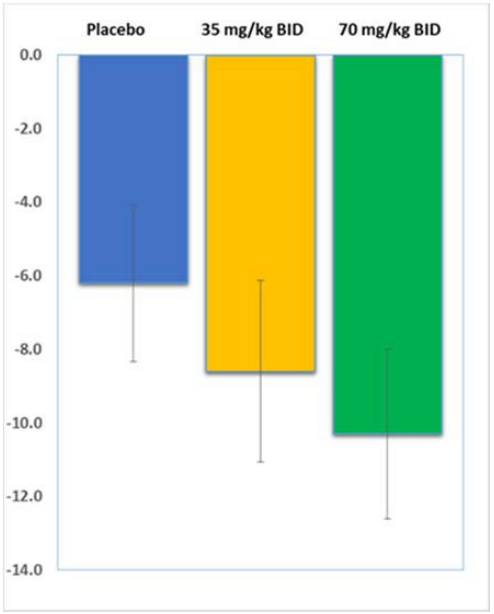
Notes: WT=wild type, KO=knockout. Trofinetide is also known as NNZ-2566.

FRAGILE X SYNDROME PHASE 2 HIGHLIGHTS

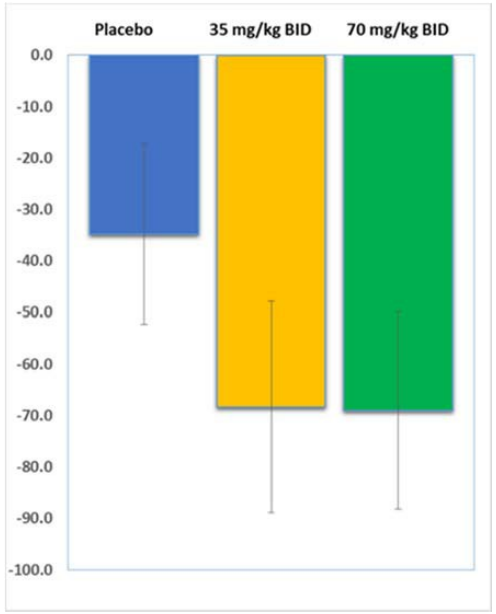
- Exploratory Phase 2 trial demonstrated encouraging efficacy trends – Neuren and ACADIA considering optimum development plan
- Double-blind, placebo-controlled Phase 2 trial of 28 days of treatment with two dose levels (35 mg/kg and 70 mg/kg of body weight twice daily)
- 70 subjects aged 12 to 45 years received treatment, with 68 subjects completing the trial
- Both dose levels were well tolerated and no safety concerns were identified
- Higher dose exceeded pre-specified targets and demonstrated consistent trends of clinical improvement, observed in both clinician and caregiver assessments
- Improvements across a range of core symptoms of Fragile X syndrome
  - Captured by new Fragile X-specific measures as well as by the Aberrant Behavior Checklist
  - Included higher sensory tolerance, reduced anxiety, better self-regulation, more social engagement
- Improvements observed with the low dose were less consistent and did not meet pre-specified targets, but there was evidence of a dose response

CORE EFFICACY MEASURES

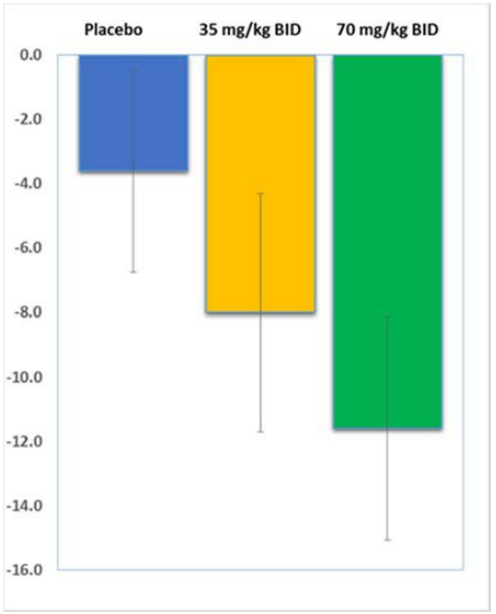
Fragile X Syndrome Rating Scale



Fragile X Syndrome Domain Specific Concerns



Aberrant Behavior Checklist (ABC) Total Score



- Analysis of mean clinical responses at end of treatment for each treatment group
- A negative value on the y-axis indicates clinical improvement