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NNZ-2591 Pitt Hopkins syndrome Phase 2 trial top-line results

27 May 2024

IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

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.

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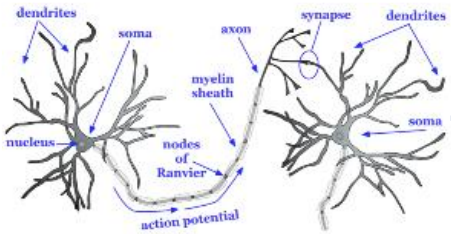
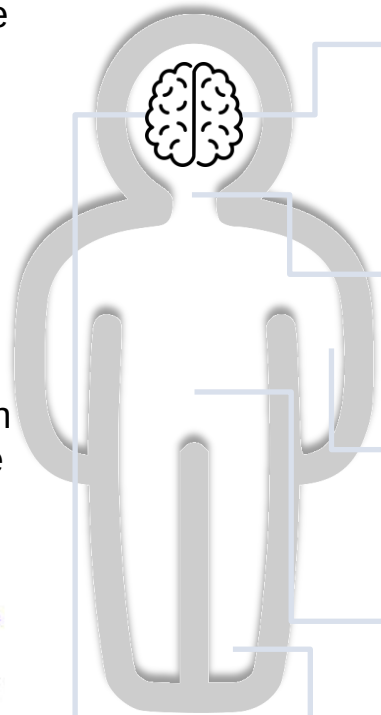
Pitt Hopkins syndrome has overwhelming unmet medical need

Cause of the syndrome

Deletion or variation in the *TCF4* gene on chromosome 18

TCF4 protein plays a role in the formation, maintenance and function of dendrites and synapses





Broad and severe impact on life

Intellectual impairment
Behavioural issues
Sensory processing disorder
Sleep disorders
Seizures
Vision impairment (severe myopia)

Language deficits

Breathing problems (hyperventilation, apnea, breath-holding)
Feeding difficulties

Motor impairments including hypotonia (low muscle tone) and gross and fine motor delays

GI dysfunction (gastroesophageal reflux and constipation)

Walking abnormalities

Patients stories

Pitt Hopkins Research Foundation

"She was tested earlier for Angelman and Rett Syndrome, but they were of course negative. I had a strange feeling that something was wrong with her already when she was a newborn…I started to see different doctors with her, but they just told me nothing was wrong, until we met a Neurologist who told us that she had Cerebral Palsy and that she would not able to walk, ever…She doesn't talk but when she was about one year old she was saying a few words that never ever came back..."

"Caleb is currently 10 months old and he does not sit or roll yet and is not really interested in toys. He is currently in an early intervention program and is going through physical therapy, and sees a vision teacher and special education teacher…It has not been an easy journey thus far. I still do not how and where I get all my strength from. I know things will only get harder as he gets older but I am ready to accept the challenge and take each day as it comes."

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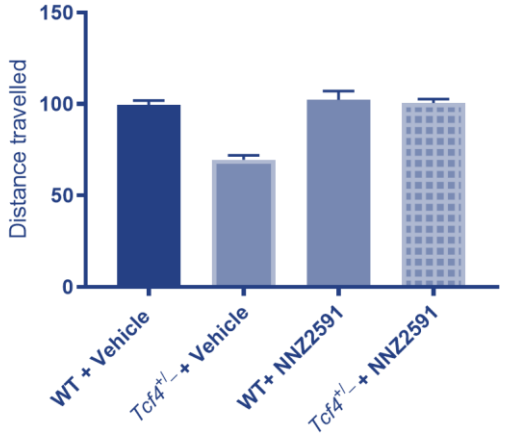
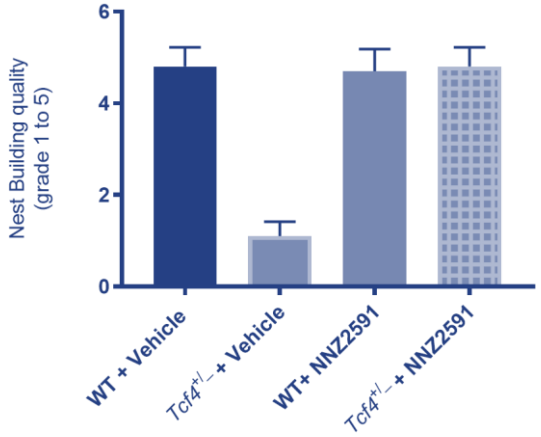
Consistent efficacy observed for NNZ-2591 in *TCF4* mouse model

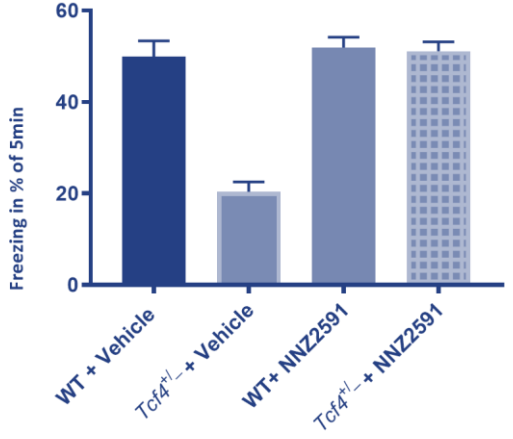
Hypoactivity



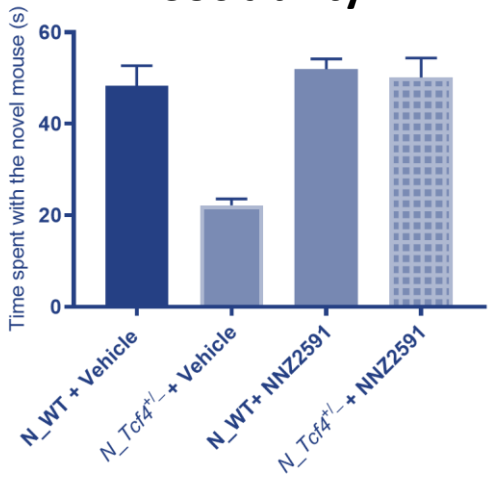
Daily living



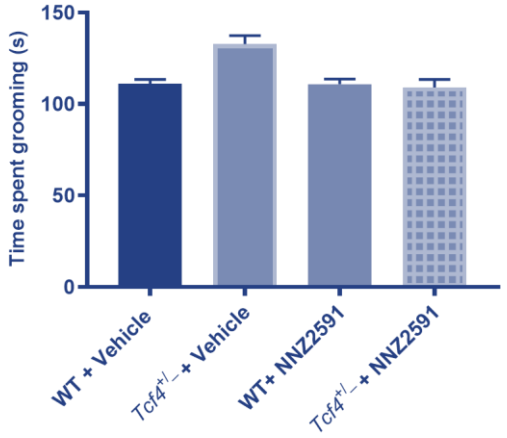
Learning & Memory



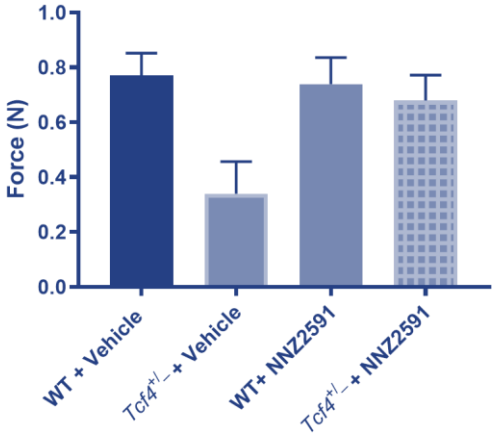
Sociability



Repetitive behavior



Motor performance



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Phase 2 clinical trial results highlights

- **NNZ-2591 was safe and well tolerated, with no meaningful trends in laboratory values or other safety parameters during treatment**
- **Statistically significant improvement from baseline assessed by both clinicians and caregivers in all 4 efficacy measures specifically designed for Pitt Hopkins syndrome ($p<0.05$)[1]**
- **Clinician and caregiver global efficacy measures showed a level of improvement considered clinically meaningful:**
  - **PTHS Clinical Global Impression of Improvement (CGI-I) – mean score of 2.6 with 9 out of 11 children showing improvement assessed by clinicians**
  - **PTHS Caregiver Overall Impression of Change (CIC) – mean score of 3.0 with 8 out of 11 children showing improvement assessed by caregivers**
- **Improvements were seen in clinically important aspects of Pitt Hopkins syndrome, including communication, social interaction, cognition and motor abilities**

[1] Wilcoxon signed rank test

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Phase 2 Clinical Trial Design

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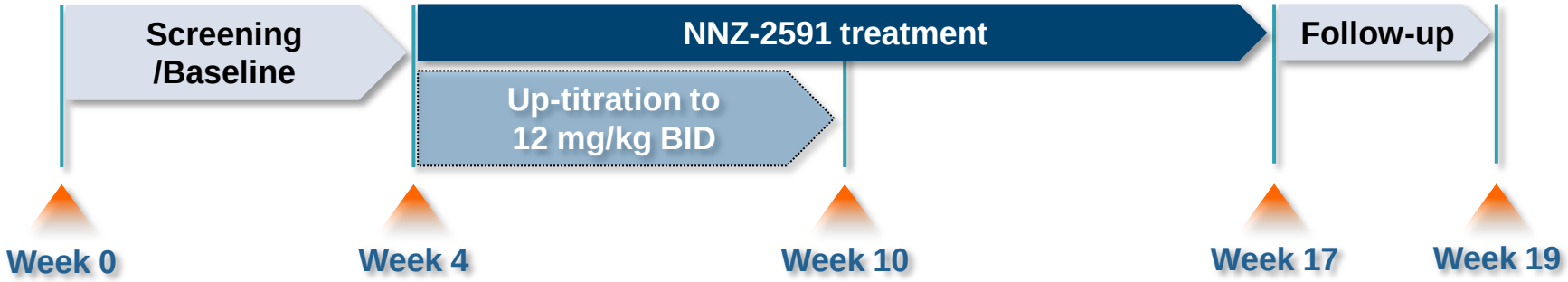
Neuren's Phase 2 trial in children with Pitt Hopkins syndrome

First study in pediatric patients, collecting the data needed to design a registration study

5 US sites: Rush University, UTSW, UCSF, UAB, Colorado Children's Hospital

16 subjects, age 3-17



Endpoints

- Primary endpoints were safety, tolerability and PK
- Secondary endpoints included 14 efficacy measurements, including 4 specifically designed for PTHS
- A key objective is selection of the best primary efficacy endpoint or endpoints for a registration study

PTHS specific efficacy measurements

Global

- CGI-I
- Caregiver Impression of Change (CIC)
- CGI-S

Symptom Specific

- Caregiver Top 3 Concerns

\+ 10 other non PTHS specific measures that had been used in other conditions

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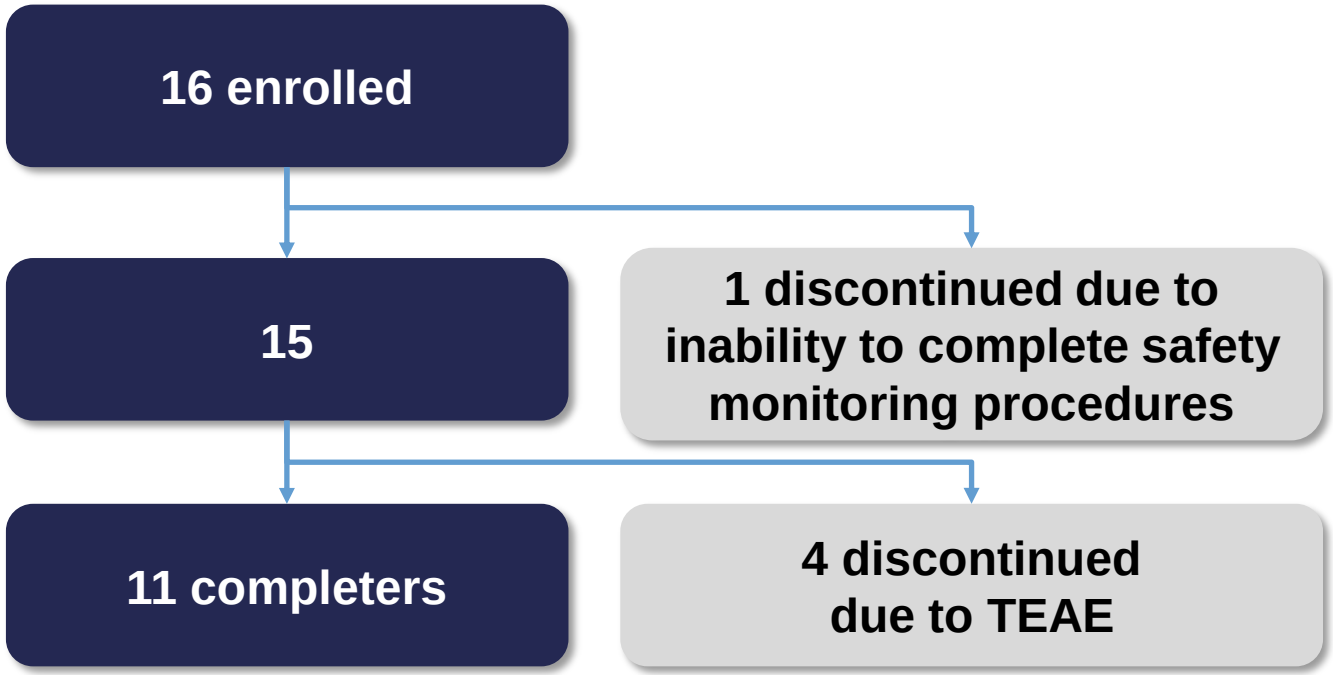
Participant Disposition



- Discontinuations due to TEAEs, all mild/moderate, all resolved:
  - 2 due to TEAEs unrelated to drug (COVID-19 and mild vomiting, diarrhea, lethargy)
  - 1 due to moderate constipation, self injury, abdominal distention, fatigue
  - 1 due to mild sleep disorder, constipation

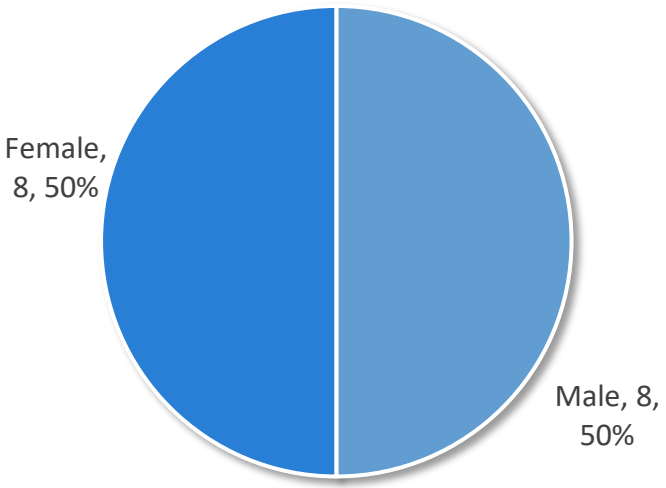
Participant demographics

Low IQ/DQ reflecting severity of the syndrome

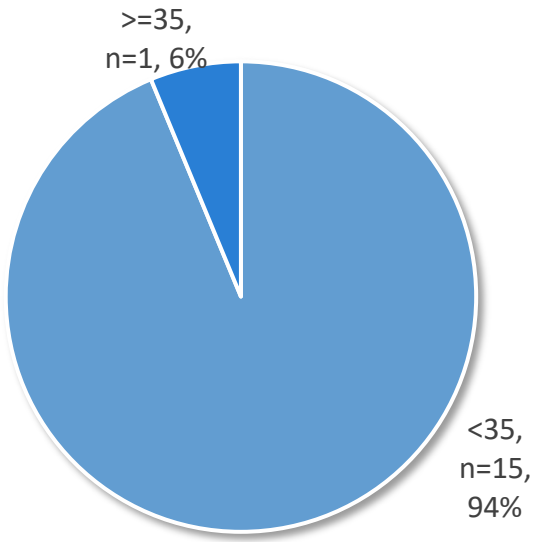
Age

Mean	9.1yrs
Median	9.5yrs
3-12yrs:	N = 11
13-17yrs:	N = 5

Sex



Cognitive level (non-verbal IQ/DQ)



Completers average DQ: 12

CGI-S (at Baseline)

Mean (SD)
5.0 (0.69)

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Safety and Tolerability

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Safety and tolerability summary

NNZ-2591 was safe and well tolerated

- ✓ Well tolerated
- ✓ All Treatment Emergent Adverse Events (TEAE) were mild to moderate, mostly not drug related
  - 0 Serious TEAE
  - 4 discontinuations due to TEAEs, all mild/moderate, all resolved
- ✓ No meaningful trends in laboratory values, electrocardiogram (ECG) or other safety parameters were observed during treatment

TEAEs in 2 or more subjects

Event	N=16 n (%)		Event	N=16 n (%)	
Constipation	3 (19)	2 mild, 1 mod	Contusion	2 (13)	all mild
Diarrhea	4 (25)	all mild	Gastroenteritis-viral	2 (13)	1 mild, 1 mod
Vomiting	2 (13)	all mild	Nasopharyngitis	3 (19)	all mild
Fatigue	4 (25)	3 mild, 1 mod	Cough	2 (13)	all mild
Somnolence	2 (13)	all mild	Rhinorrhea	2 (13)	all mild
Irritability	2 (13)	all mild	Decreased appetite	2 (13)	all mild

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Efficacy

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Efficacy endpoints summary

- Mean **CGI-I** of **2.6** and Median of 3.0 with p-value = 0.0039
- Mean **CIC** of **3.0** and Median of 3.0 with p-value =0.0234
- Statistically significant improvement vs baseline in **4/4 PTHS specific** endpoints

Efficacy measures and p-values[1] (Total/Overall scores)

PTHS Specific Endpoints

	Completers (MITT) N=11	Including discontinued N=15
CGI-I	0.0039	0.0205
CIC	0.0234	0.0137
CGI-S	0.0313	0.0078
Caregiver Top 3 Concerns	0.0077	0.0024

- Changes from baseline for the measures that were not designed for PTHS were not statistically significant

[1] Wilcoxon signed rank test

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Best practice implemented for PTHS-specific CGI-I and CIC measures

- Both CGI-I and CIC scores reflect overall improvement from baseline
  - **1 – Very Much Improved**
  - **2 – Much Improved**
  - **3 – Minimally Improved**
  - **4 – No Change**
  - **5 – Minimally Worse**
  - **6 – Much Worse**
  - **7 – Very Much Worse**
- All clinician raters completed training to calibrate scoring and interpretation of the scoring anchors amongst raters
- Training was done at study start up and a follow-up calibration training was done during the study

	Clinical Global Impression of Improvement (CGI-I)	Caregiver Impression of Change (CIC)
Scoring	**Clinician** gives an overall score and scores each domain	**Caregiver** gives an overall score and scores each domain Also identifies the one symptom area that has most influenced his or her rating of the child's overall function
Domain Anchors	• Language/Communication • Social Interaction • Ambulation/Gross Motor • Fine Motor/Self-Help • GI Issues • Autonomic/Breathing Abnormalities • Challenging Behaviors	• Communication • Social interaction • Motor abilities • Self-care skills • GI Problems • Breathing Problems • Behavior • Seizures • Cognitive abilities/ability to learn

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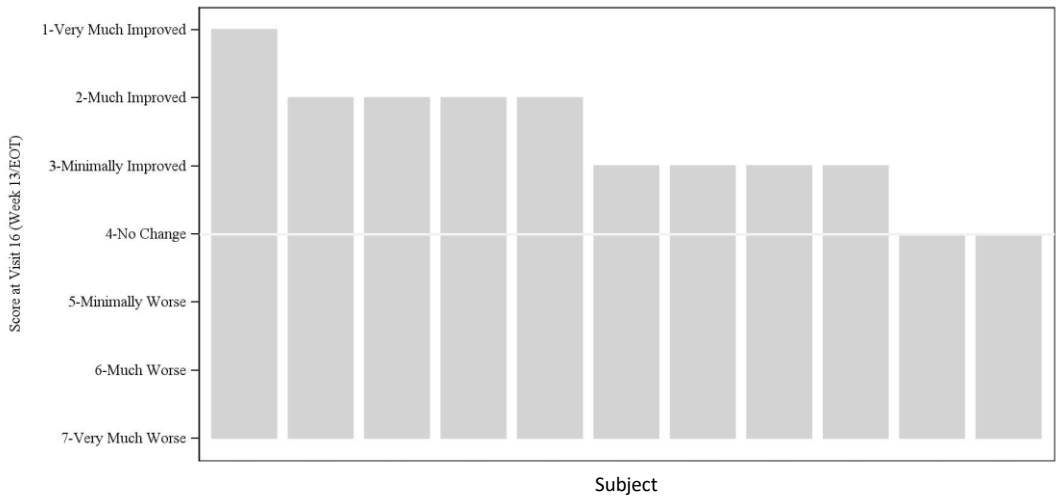
PTHS CGI-I (clinician) results by subject and by domain

Mean CGI-I score of 2.6 with 9 out of 11 children showing improvement

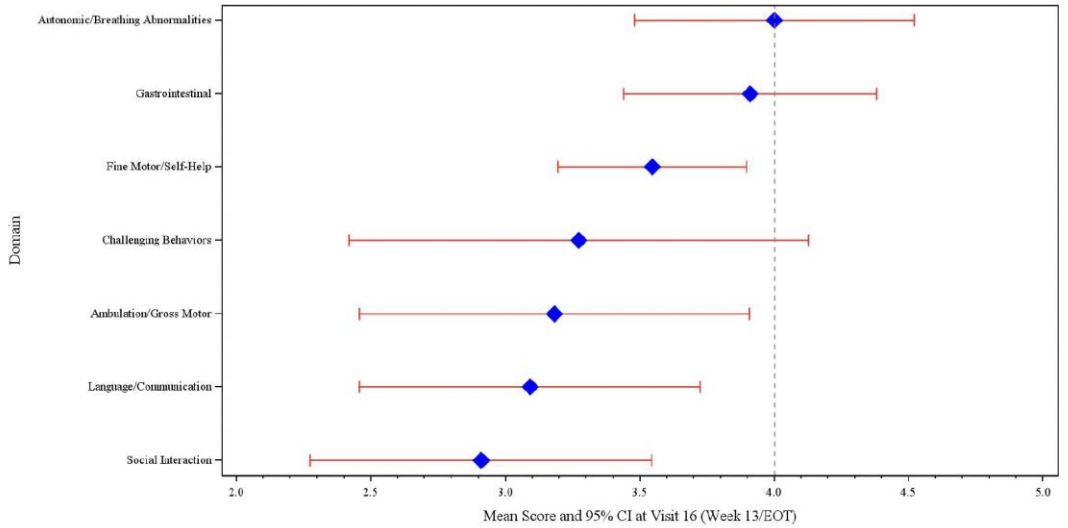
CGI-I Overall Score by subject

MITT Population



Forest Plot of mean CGI-I Domain Scores

MITT Population



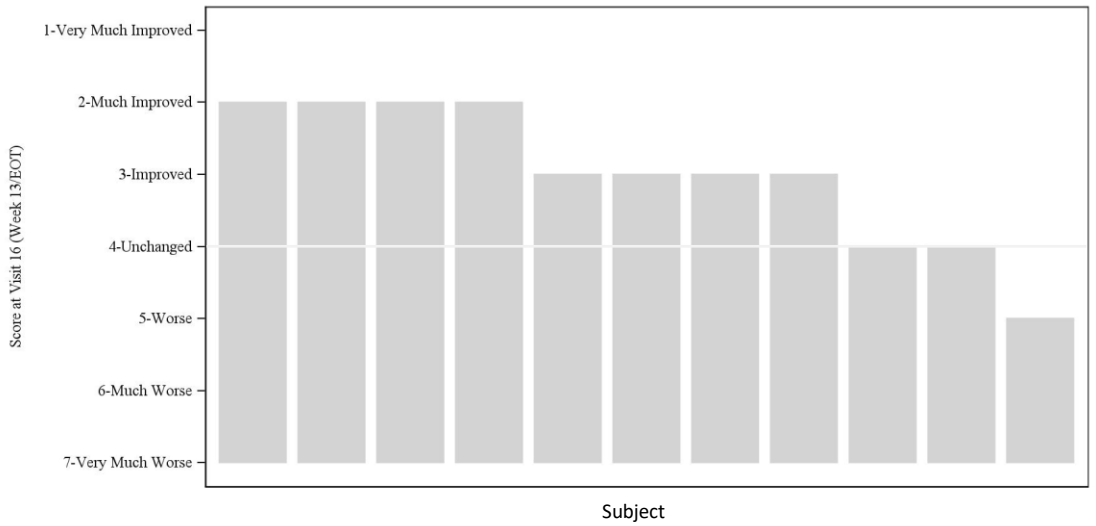
Improvement

PTHS CIC (caregiver) results by subject and by domain

Mean CIC score of 3.0 with 8 out of 11 children showing improvement

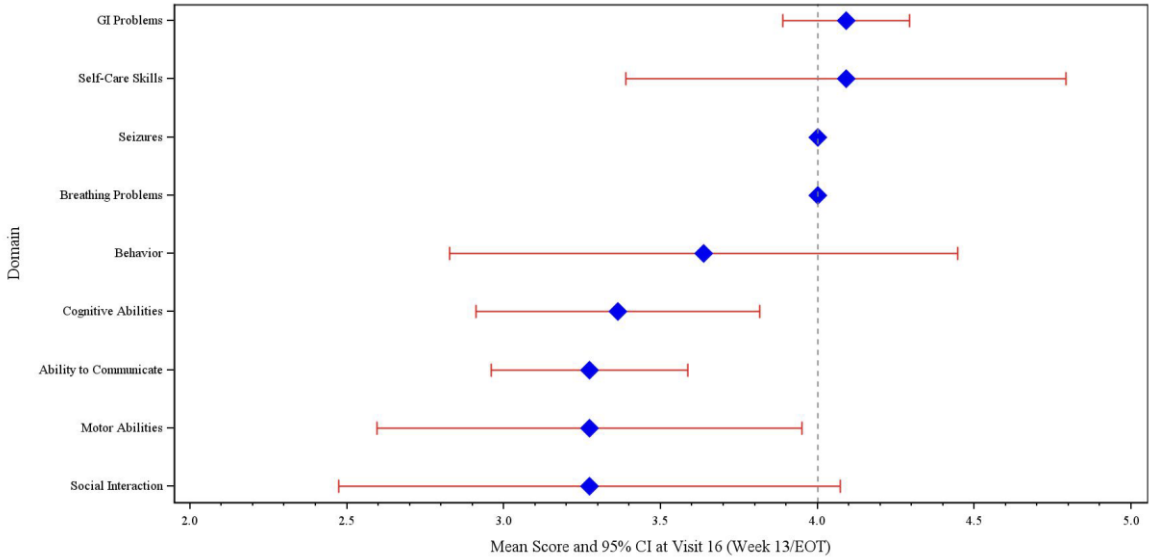
CIC Overall Score by subject

MITT Population



Forest Plot of mean CIC Domain Scores

MITT Population

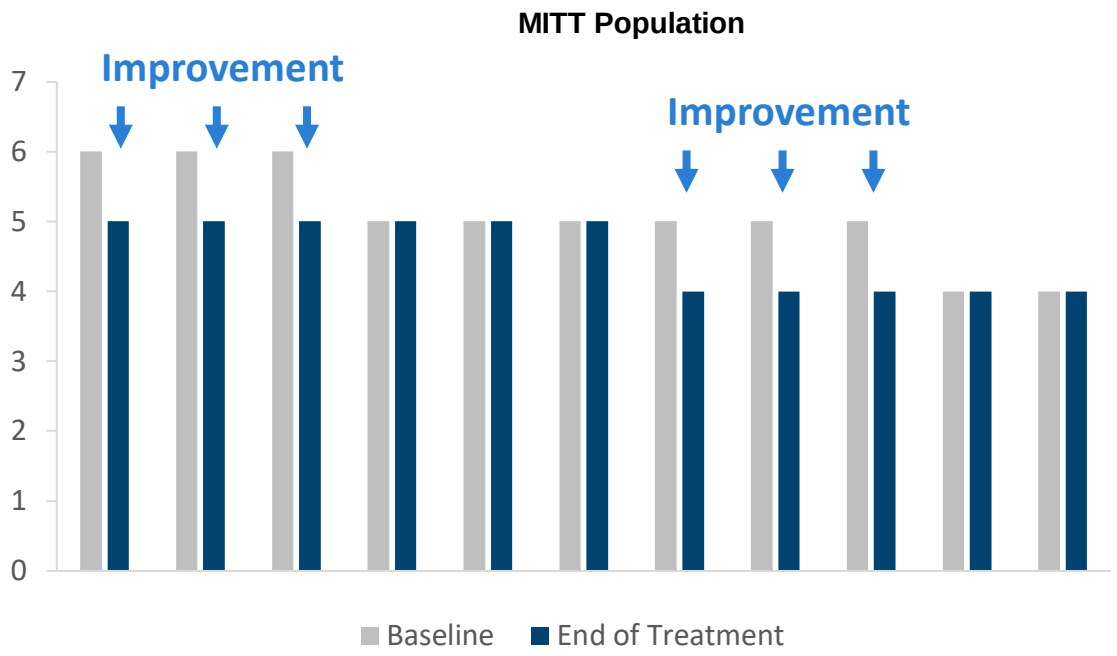


Improvement

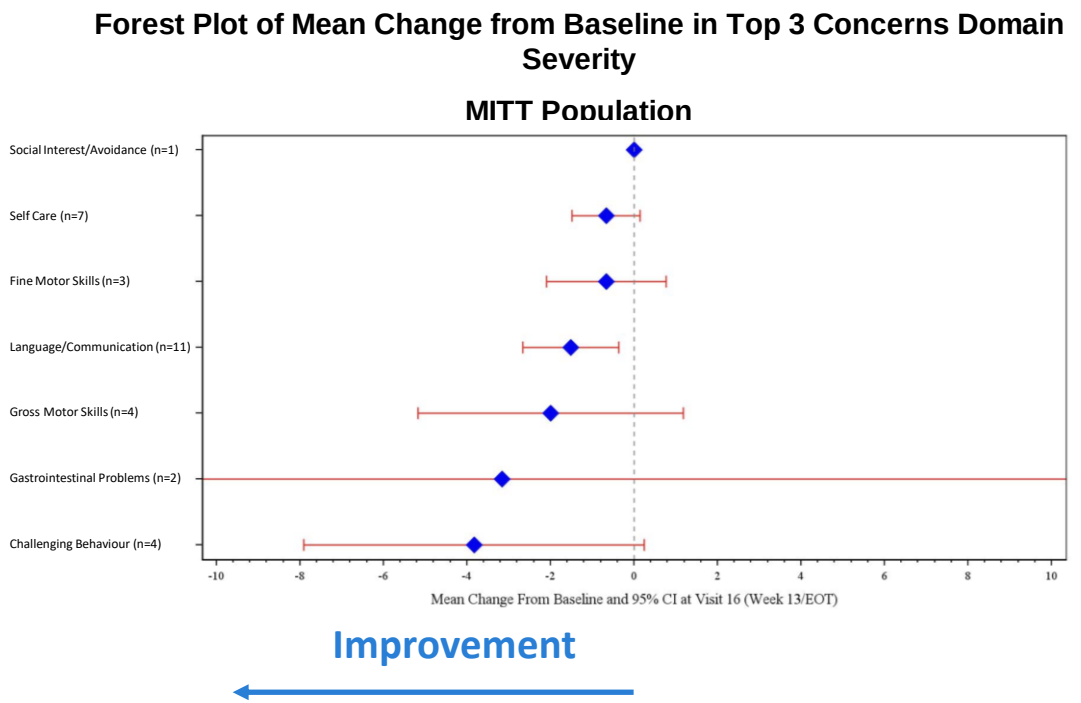
PTHS Clinical Global Impression of Severity (CGI-S) and Caregiver Top 3 Concerns results by domain

6 subjects improved by one point on the overall CGI-S score after 13 weeks of treatment and improvement was observed in the most common concerns of caregivers (communication, self care, behaviour, motor skills)

CGI-S Scores



Caregiver Top 3 Concerns
(Domains and frequency of nomination)



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Testimonials

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Clinician and caregiver testimonials

Clinicians

"Increased babbling and jargoning….More inflections with eye contact and consonant sounds rather than just noises."

"Decreased frequency and intensity of smacking and hairpulling."

"Supported stepping increased over last few months…Now taking steps without trainer with parent support."

"Improved expressive communication: 2 additional words, uses AAC device to ask for food. Increase vocalization."

"Less breath holding. More opinionated. More social interest."

"Able to match items/pictures…moved from 4 pictures to 6 pictures."

"Improved motor skills. Better motor coordination getting in car."

Caregivers

"Is now able to explore environment… can move towards people to initiate contact and… can seek out whatever … wants to play with."

"Can seem to hold on to things for longer periods without letting go."

"Stability when walking improved."

"Listen to conversation + follow some discussions, able to understand when we're talking about…"

"Far less hyper and easily able to concentrate better… is able to concentrate and master tasks that … has been working on for years (getting in and out of car independently, catching a ball)."

"More intentional movements… been more gentle with almost all interactions."

"Almost constant babbling and even has said "hi" and "more.""

"More calm and attentive, especially looking at faces and eyes."

PTHS opportunity

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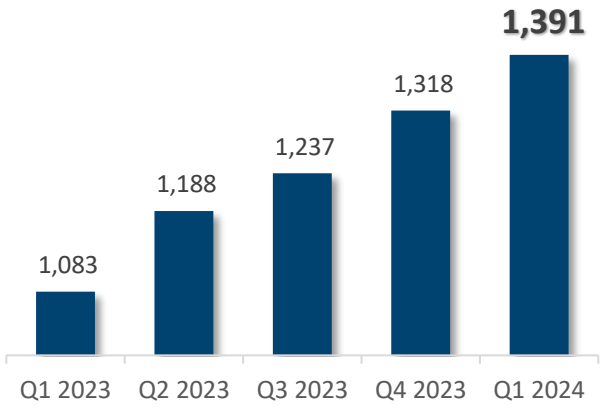
PTHS is historically under-diagnosed, but this is changing

Estimated prevalence is 1/34,000 to 1/41,000 males and females[1]

	US	Europe	Japan	China	Other[2]
Potential PTHS patients	6,000 – 7,000[3]	8,000 – 9,000[3]	1,000 - 2,000[3]	18,000 – 22,000[3]	6,000 - 7,000[3]

Pitt Hopkins Syndrome Census – initiated Q1 2023[1]



Currently 497 in US & Canada, 329 in EMA & UK, 248 in China, 60 in ANZ

Clinical similarities between PTHS, Rett and Angelman syndromes calling for TCF4 screening in suspected Rett or Angelman patients[4]

Opportunity to accelerate diagnosis

Autism

US ADDM tracks 440k children with autism spectrum disorder

- Rising awareness
- ICD code assigned in 2020
- Enhanced genetic testing technologies
- Expanding ADDM network sites

[1] Pitt Hopkins Research Foundation (PHRF) (pitthopkins.org)
[2] Brazil, Israel, South Korea, Australia and New Zealand
[3] Estimates based on United Nations population data 2022, derived by applying the estimated prevalence range to the populations under 60 years (urban population only for China)
[4] Takano et al, "Two percent of patients suspected of having Angelman syndrome have TCF4 mutations" Clin Genet. 2010 Sep;78(3):282-8; Armani et al, "Transcription factor 4 and myocyte enhancer factor 2C mutations are not common causes of Rett syndrome" Am J Med Genet A. 2012;158A(4):713–9

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Neuren is leading development of a first approved treatment for PTHS

Neuren Program Status

- Positive Phase 2 trial
- Clinical development in the US under an IND
- Orphan Drug designation in US and EU
- Eligible for Rare Pediatric Disease Designation Priority Review Voucher program

Limited products in development

Company	Product Development Stage
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#2	Phase 2 *(research institute sponsored, focusing on GI symptoms)*
#3	Phase 1/2a trial *(not yet recruiting)*
#4	*Preclinical*

Neuren engaging with all stakeholders

PITT HOPKINS RESEARCH FOUNDATION

Leading clinicians

FDA

NNZ-2591 as multi-indication platform

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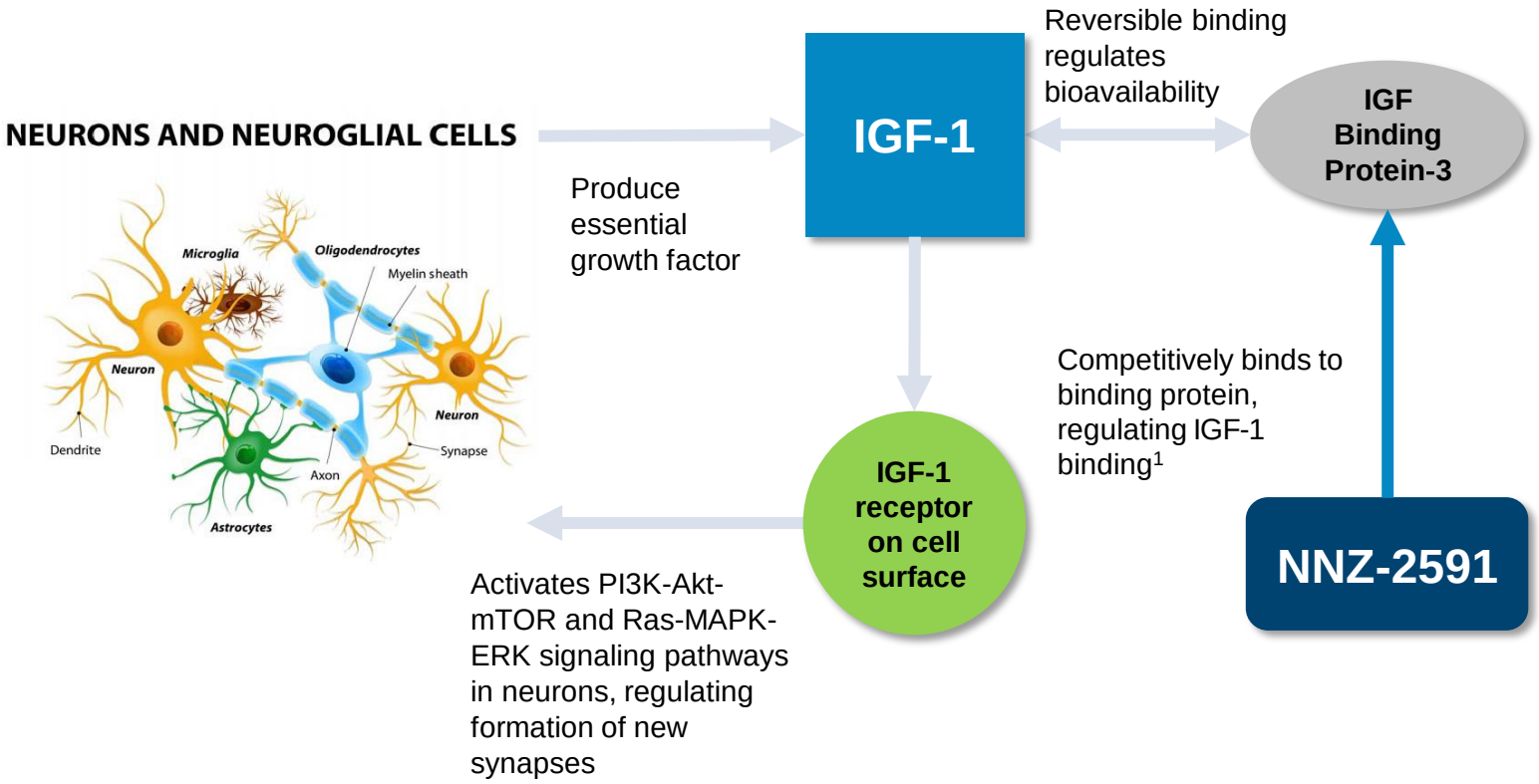
Regulating IGF-1 in the brain



- **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

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Phase 2 trial results validating multi-indication platform

	Phelan-McDermid syndrome N=18, 13 weeks	Pitt Hopkins syndrome N=11, 13 weeks
General safety & tolerability	Safe and well tolerated, with no meaningful trends in laboratory values or other safety parameters during treatment	Safe and well tolerated, with no meaningful trends in laboratory values or other safety parameters during treatment
Serious TEAEs	1 unrelated to drug	0
Mean CGI-I	2.4 (89% shown improvement)	2.6 (82% shown improvement)
Mean CIC	2.7 (83% shown improvement)	3.0 (73% shown improvement)
# patients had CGI-S improvement of 1	7 (39%)	6 (55%)
# syndrome-specific efficacy measures statistically significant[1]	5/5	4/4

[1] Wilcoxon signed rank test

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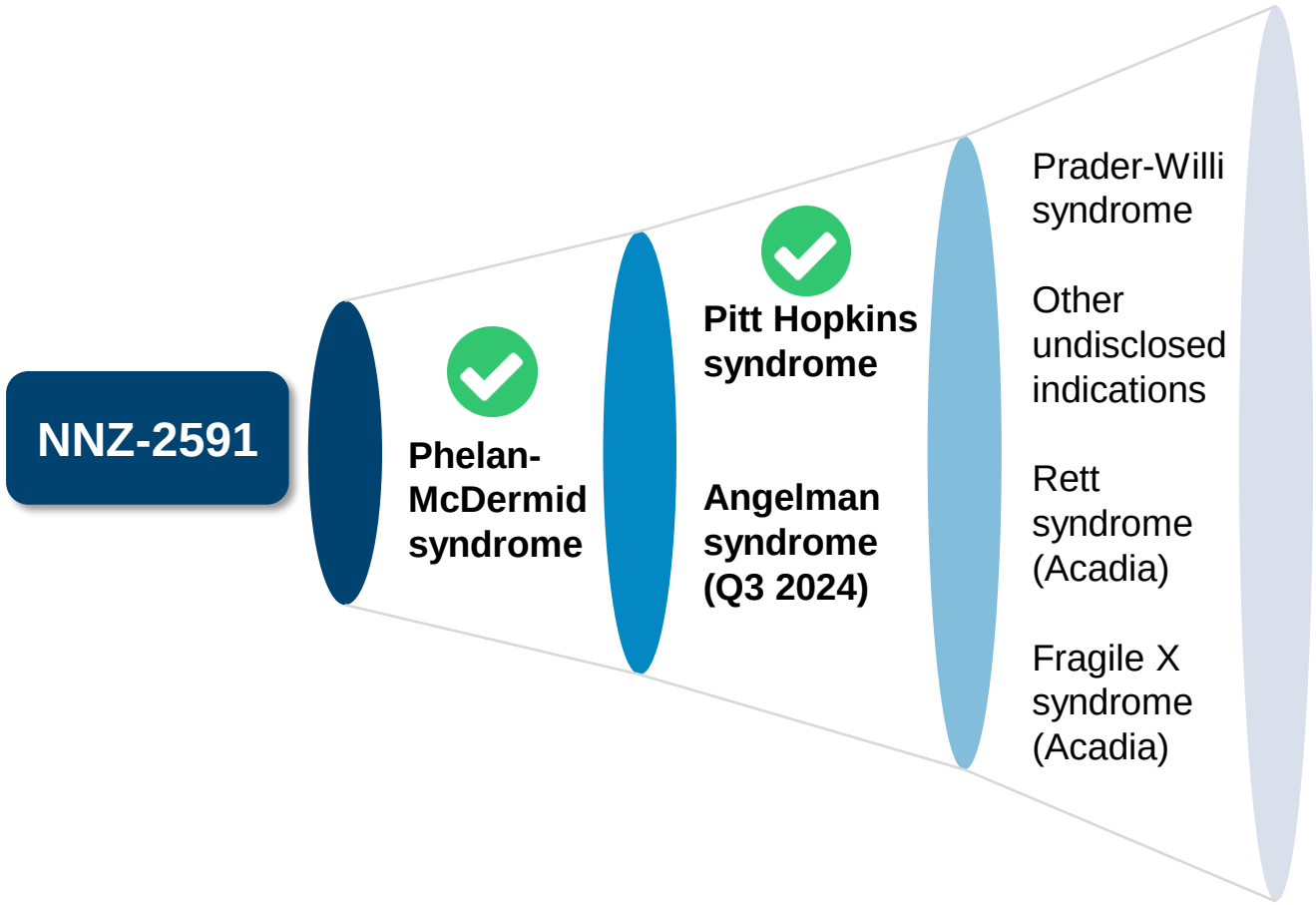
Good safety profile supports review of trial protocol for future indications

- Positive data from Phelan McDermid syndrome and Pitt Hopkins syndrome Phase 2 trials support review and potential optimisation of existing Phase 2 trial protocol for Prader-Willi syndrome and future indications, subject to FDA agreement
  - To reduce excessive burden on patients and their families
  - To enhance competitiveness vs ongoing Prader-Willi syndrome trials in the US
  - To expedite future development in other indications
- Prader-Willi syndrome Phase 2 trial has been paused, pending review of the trial protocol post planned End of Phase 2 Meeting with the FDA in Q3 2024 for Phelan-McDermid syndrome
- Pre-clinical studies are ongoing for other indications that could potentially move into Phase 2 with an optimised protocol

Multiple indications opportunity for NNZ-2591



- **Positive results from Phelan McDermid syndrome and Pitt Hopkins syndrome Phase 2 trials**
- **Top-line results from Angelman syndrome Phase 2 trial expected in Q3 2024**
- **End of Phase 2 meeting with FDA for Phelan McDermid syndrome planned Q3 2024**
- The mechanism of action of NNZ-2591 is relevant for many other neurodevelopmental synaptopathies
- Rett and Fragile X syndromes are licensed to Acadia, with same economics to Neuren as trofinetide; Neuren retains worldwide rights to all other indications

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CONTACT

Jon Pilcher, CEO
jpilcher@neurenpharma.com
+61 438 422 271

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