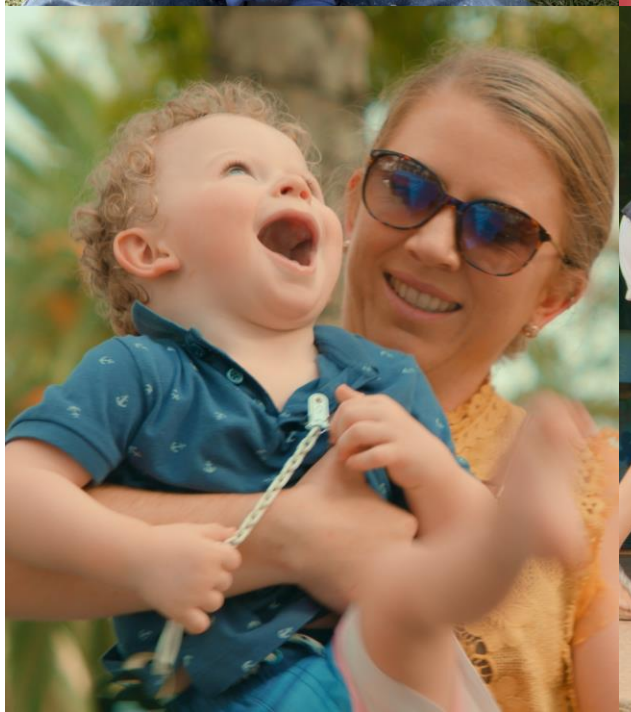
neuren pharmaceuticals

NNZ-2591 Angelman syndrome Phase 2 trial top-line results

9 August 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.

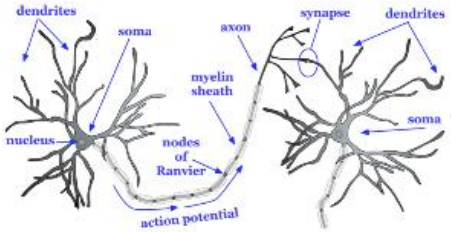
neuren
pharmaceuticals

Angelman syndrome (AS) overview

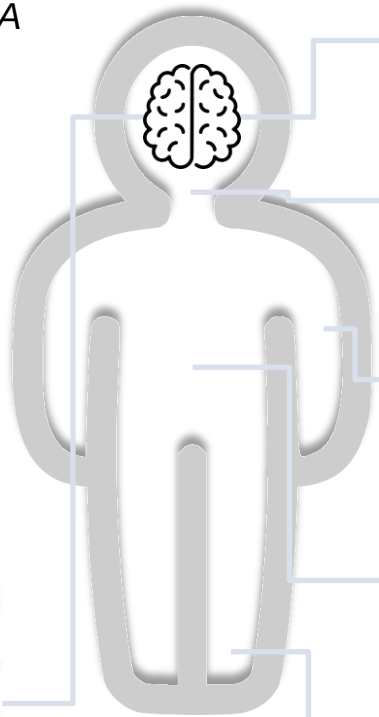
Cause of the syndrome

Deletion or variation in the maternal allele of the *UBE3A* gene on chromosome 15

UBE3A protein plays a role in the formation, maintenance and function of dendrites and synapses



Broad and severe impact on life



Intellectual impairment
Behavioural issues
Sleep disorders
Seizures

Language deficits
Sucking or feeding difficulties

Motor delays
Hand-flapping
Ataxia

Curvature of the spinal cord
Hypopigmentation
GI dysfunction (constipation)

Movement and balance disorder

Patients stories

"It has impacted our lives in almost every aspect. Day-to-day challenges are always present. Rowan brings us incredible joy, and we are so happy to be his parents. We are no longer saving for college but saving for Rowan's long-term care, legal navigating, and learning about special needs trusts. We need to find ways to protect and care for Rowan for the rest of his life, even after we are gone…Rowan not being able to tell us how his day was, or if he doesn't feel right. Wanting to make sure he has friends and is included in social settings. We don't want him to be left behind because of his diagnosis."[1]

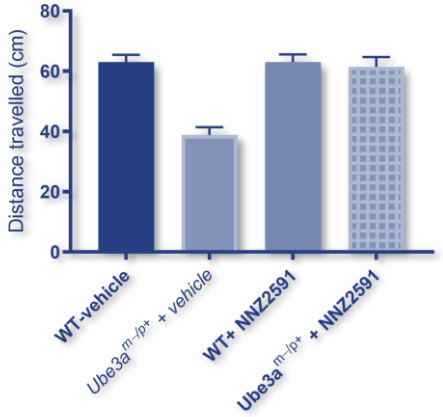
"When I got the call about his diagnosis while I was at work, I immediately started looking up information online to learn about Angelman syndrome, as we had never heard of it before. I looked at the possibilities and what to expect, and I was devastated and torn-up inside… we can and will do whatever we can to make sure Drew reaches his maximum potential, whatever that might be."[2]

[1] https://unitedbrainassociation.org/2021/03/23/rowan-smiths-brain-story
[2] https://globalgenes.org/story/journey-towards-a-diagnosis-diagnosing-a-rare-form-of-angelman-syndrome/

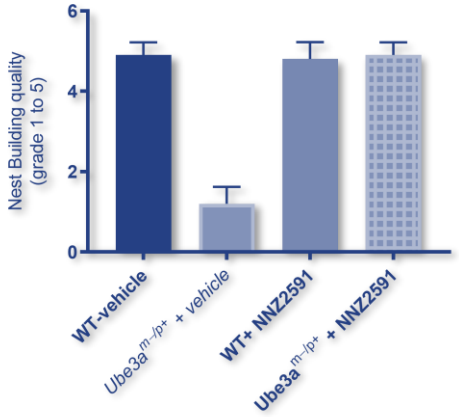
neuren pharmaceuticals

Consistent efficacy observed for NNZ-2591 in *Ube3a*$^{m-/p+}$ mouse model of AS

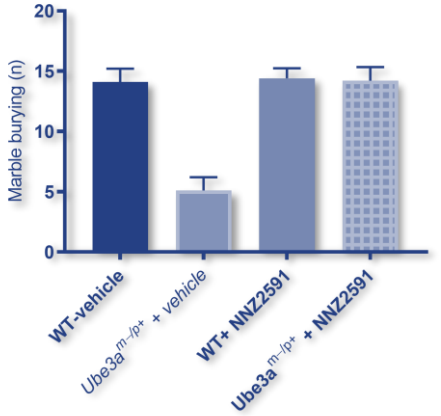
Hypoactivity & anxiety



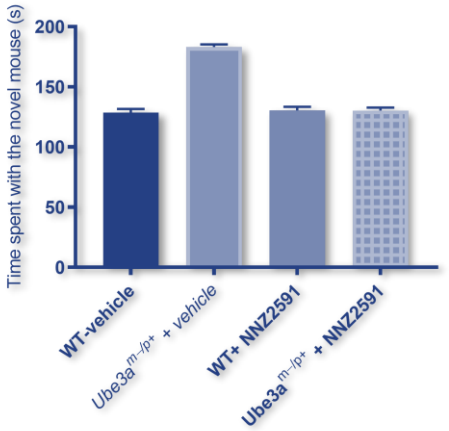
Daily living



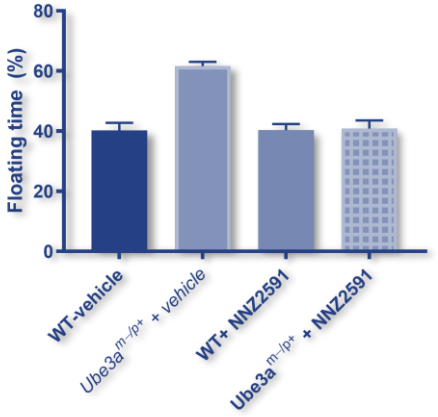
Daily living



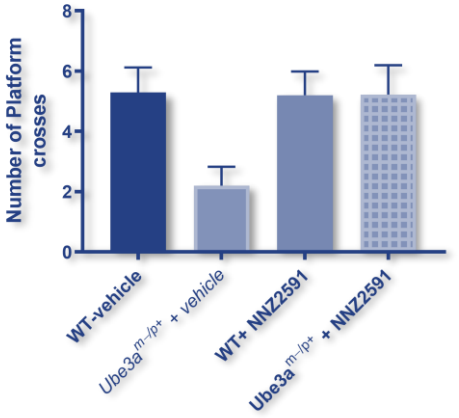
Sociability



Motor



Cognition



neuren pharmaceuticals

Phase 2 clinical trial results highlights

- **NNZ-2591 was safe and well tolerated, with no serious adverse events and no meaningful trends in laboratory values or other safety parameters during treatment**
- **Clinician and caregiver global efficacy measures specifically designed for AS showed a level of improvement from baseline that was statistically significant[1] and considered clinically meaningful:**
  - **AS Clinical Global Impression of Improvement (CGI-I) - mean score of 3.0, with 11 out of 13 children showing improvement assessed by clinicians (p=0.0010)**
  - **AS Caregiver Overall Impression of Change (CIC) – mean score of 3.2, with 8 out of 12 children showing improvement assessed by caregivers (p=0.0273)**
- **Every child in the younger age segment of 3-12 years showed improvement measured by both the CGI-I (mean score 2.8 p=0.0078) and the CIC (mean score 2.6 p=0.0078)**
- **Improvements were seen in clinically important aspects of Angelman syndrome, including communication, behavior, cognition and motor abilities**
- **Results further strengthen confidence in potential of NNZ-2591 for multiple neurodevelopmental disorders, independent of origin of underlying genetics**

[1] Wilcoxon signed rank test $p<0.05$

neuren pharmaceuticals

Phase 2 Clinical Trial Design

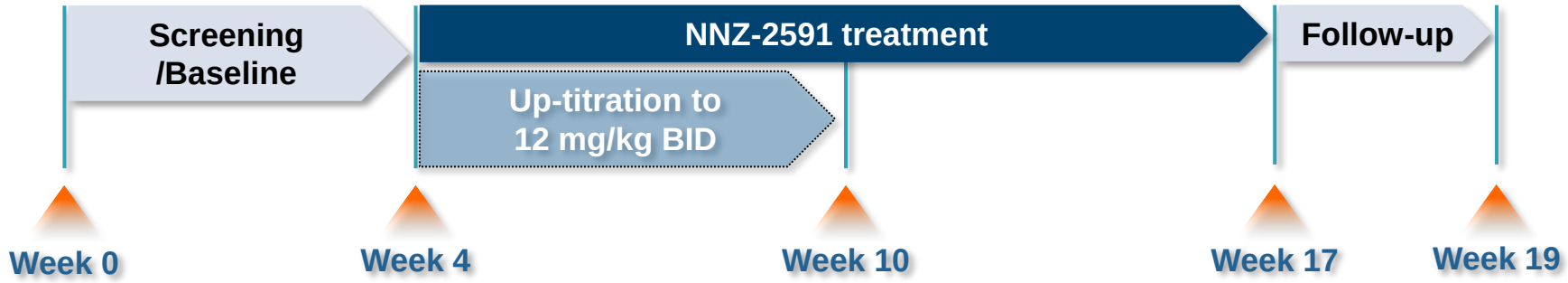
neuren pharmaceuticals

Neuren's Phase 2 trial in children with Angelman syndrome

First study in pediatric patients, to inform future development

3 AU sites: Austin Health, Sydney Children's Hospital, Children's Health Queensland Hospital

16 subjects, age 4-17



Primary endpoints

Safety, tolerability and PK

Secondary endpoints

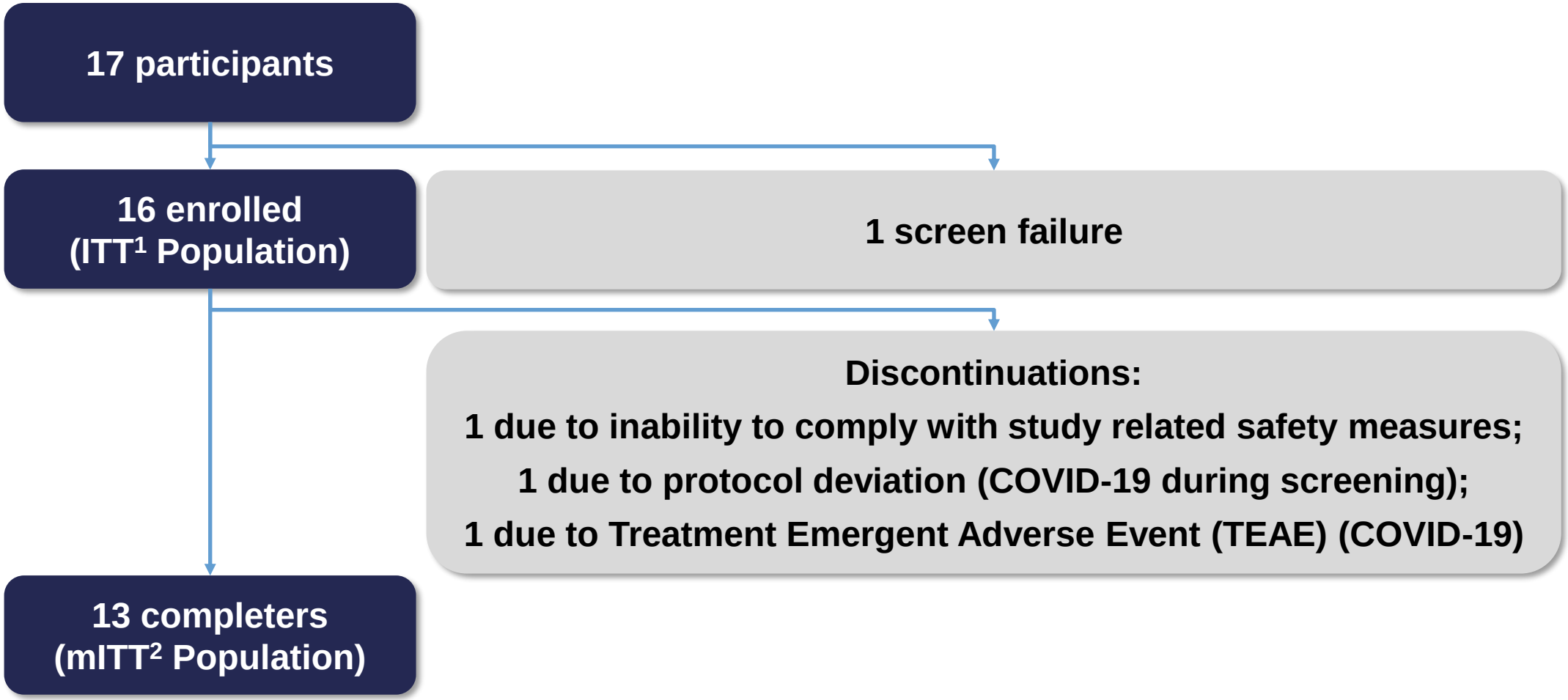
A range of efficacy measurements, including measures specifically designed for AS and measures used in other developmental conditions

Key global measures specifically designed for AS: **CGI-I, CIC and CGI-S**

Bayley Scales of Infant and Toddler Development (Bayley-4) included as exploratory efficacy measures, although designed to measure outcomes over a longer time period than the duration of this trial.

neuren pharmaceuticals

Participant Disposition



[1] Intention-to-Treat
[2] Modified Intention-to-Treat

neuren pharmaceuticals

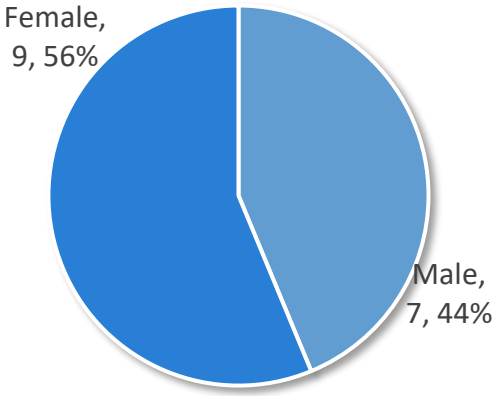
Enrolled demographics

Low Developmental Quotient (DQ) score reflecting severity of the syndrome

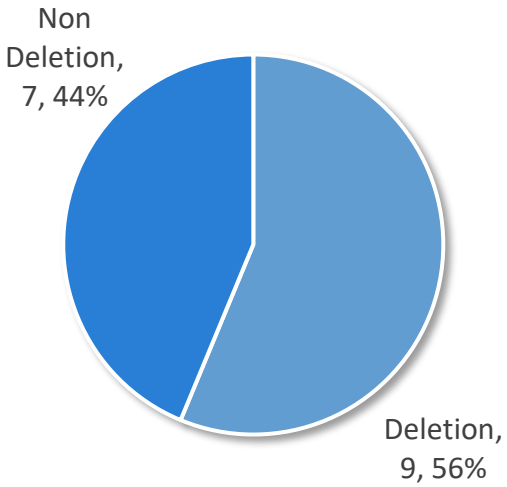
Age

Mean	10.1yrs
Median	9.5yrs
3-12yrs:	N = 6
13-17yrs:	N = 10

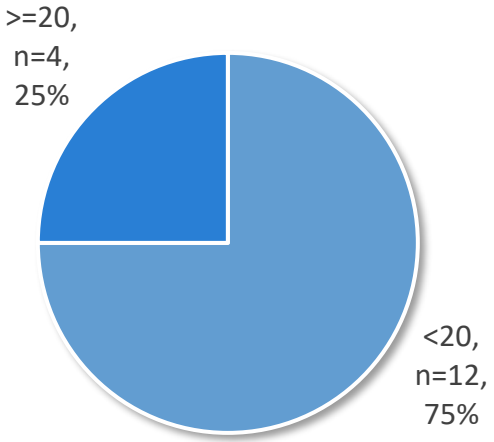
Sex



Genotype



Cognitive level (non-verbal DQ)



Completers average DQ: 12

CGI-S (at Baseline)

Mean (SD): 4.8 (0.75)

Safety and Tolerability

neuren pharmaceuticals

Safety and tolerability summary

NNZ-2591 was safe and well tolerated

- ✓ Well tolerated
- ✓ Most TEAEs were mild to moderate, and not drug related
  - 0 Serious TEAE
  - 1 discontinuation due to TEAE (COVID-19)
- ✓ 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 (%)
Viral Infection	5 (31)	Drooling	2 (13)
Nasopharyngitis	4 (25)	Epistaxis	2 (13)
Seizure	4 (25)	Insomnia	2 (13)
Upper Respiratory Tract Infection	3 (19)	Pyrexia	2 (13)
Somnolence	3 (19)	Skin Abrasion	2 (13)
Constipation	3 (19)	Urinary Tract Infection	2 (13)
Diarrhea	2 (13)	Vomiting	2 (13)

neuren pharmaceuticals

Efficacy

neuren pharmaceuticals

Best practice implemented for AS-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	• Sleep • Behavior • Communication • Gross Motor Function • Fine Motor/Oral Motor Function	• Behavior • Communication • Motor abilities • Seizures • Cognitive abilities/ability to learn • Self-care skills • GI Problems

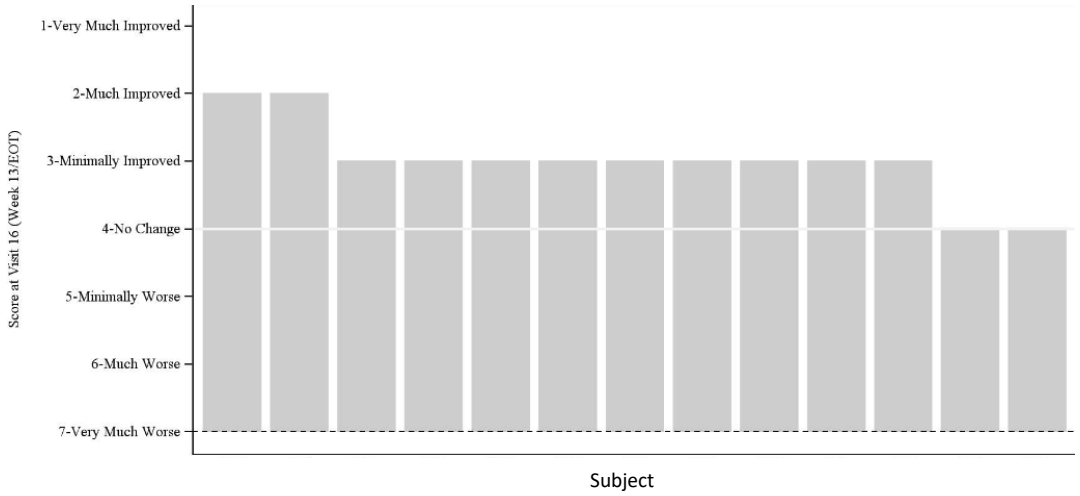
neuren pharmaceuticals

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

Mean CGI-I score of 3.0 (p=0.0010) with 11 out of 13 children showing improvement

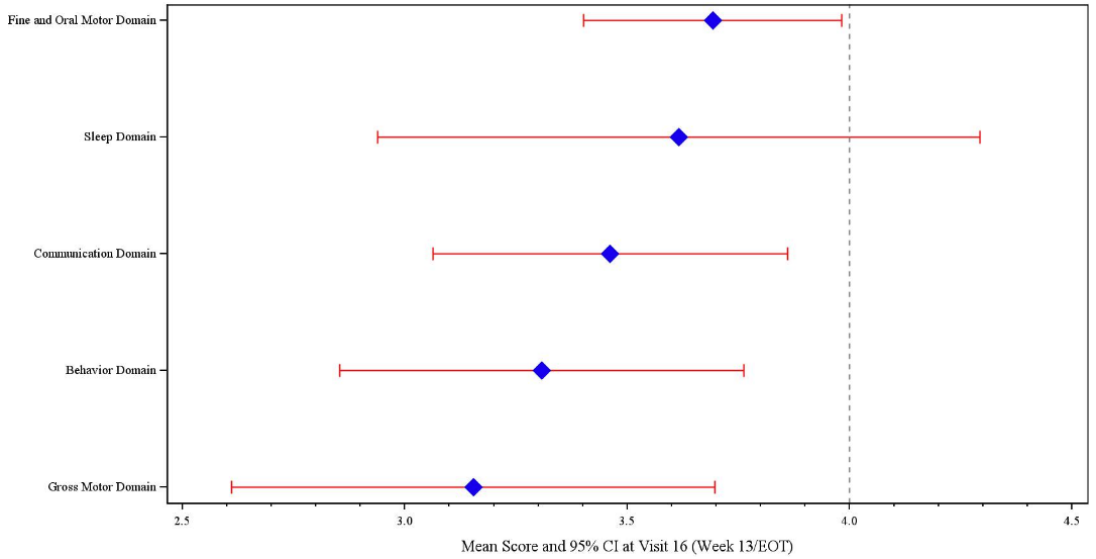
CGI-I Overall Score by subject

mITT Population



Forest Plot of mean CGI-I Domain Scores

mITT Population



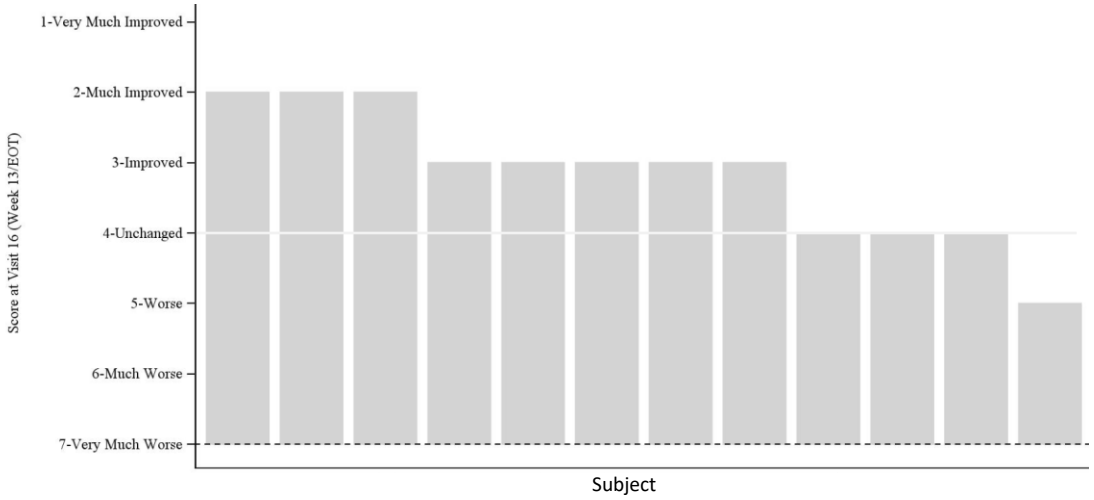
Improvement

AS CIC (caregiver) results by subject and by domain

Mean CIC score of 3.2 (p=0.0273) with 8 out of 12[1] children showing improvement

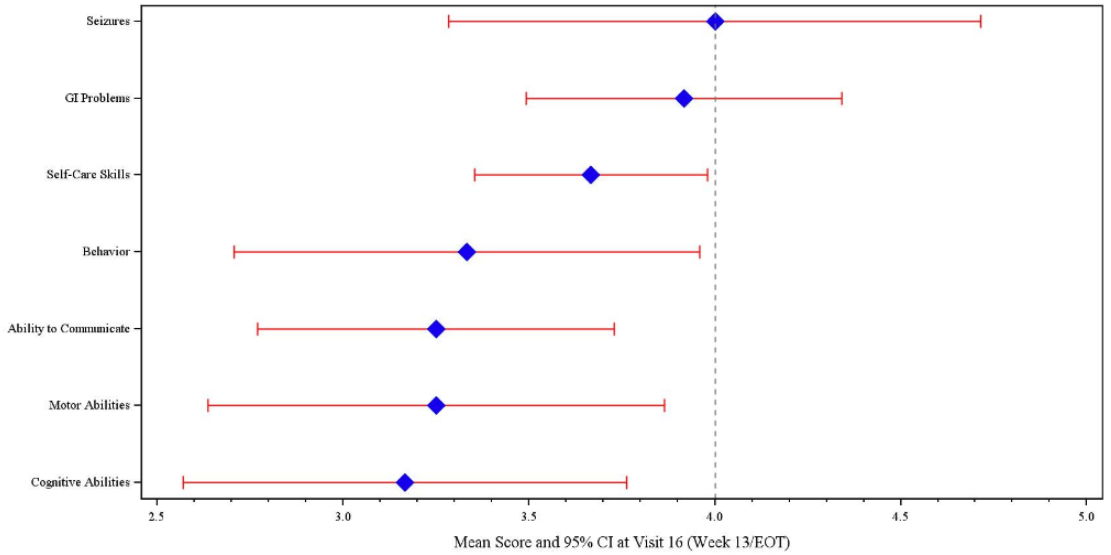
CIC Overall Score by subject

mITT Population



Forest Plot of mean CIC Domain Scores

mITT Population



Improvement

[1] Score for one subject inadvertently not completed by caregiver at site visit

neuren pharmaceuticals

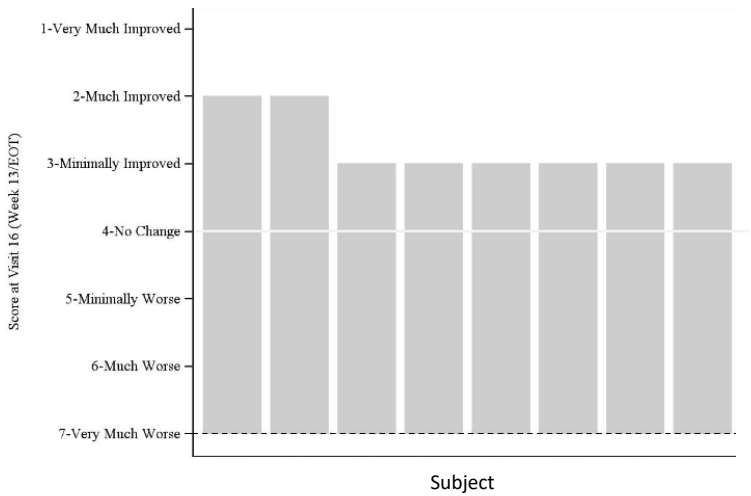
All children in 3 to 12 years age group improved

Mean CGI-I of 2.8 (p=0.0078) and mean CIC of 2.6 (p=0.0078) with all children showing improvements

CGI-I Overall Score by subject

3-12 year old age group

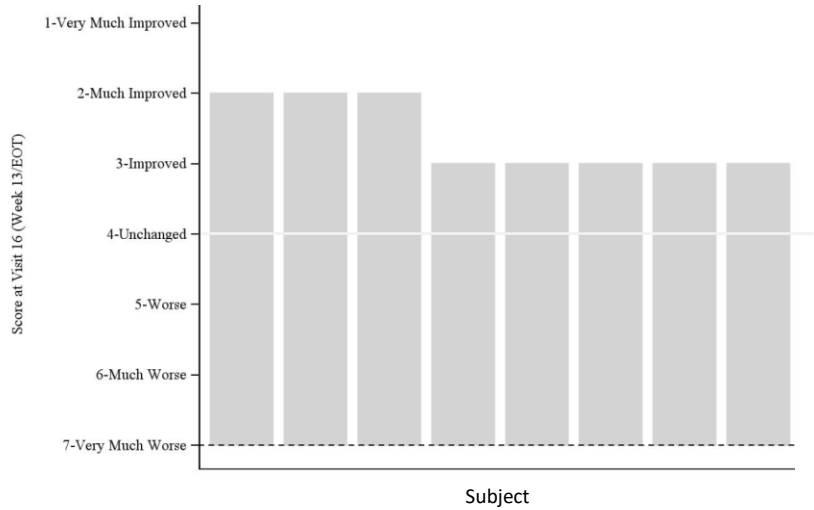
mITT Population



CIC Overall Score by subject

3-12 year old age group

mITT Population



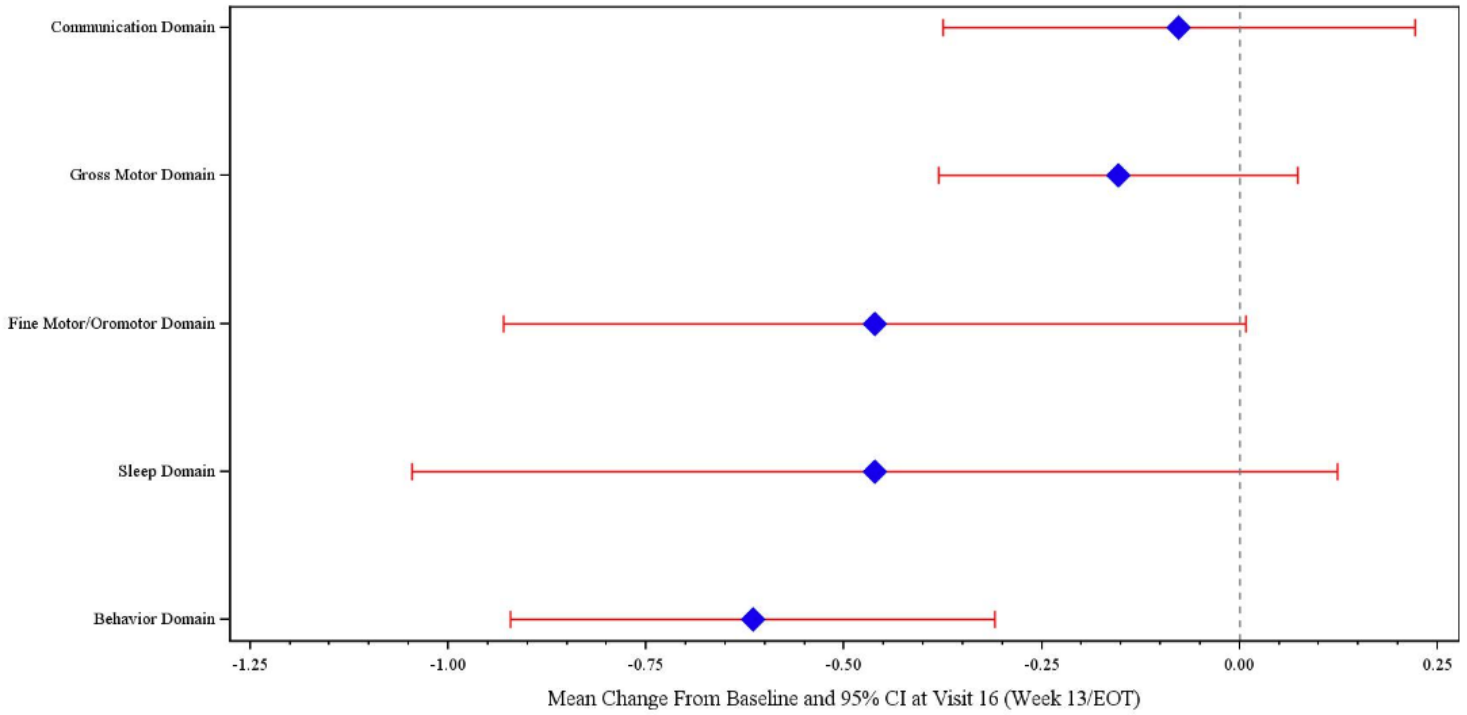
neuren pharmaceuticals

AS Clinical Global Impression of Severity (CGI-S)

4 subjects improved by one point on the overall CGI-S score after 13 weeks of treatment

Forest Plot of Change from Baseline in CGI-S Domain Scores

mITT Population



Improvement

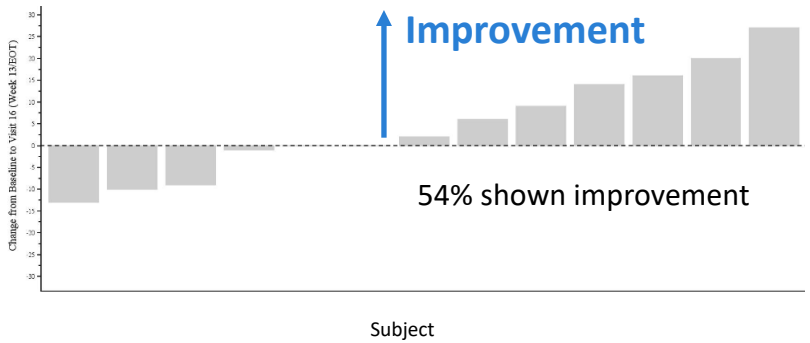
neuren pharmaceuticals

Bayley-4 scales (raw scores)

Improvements observed despite treatment period of only 13 weeks

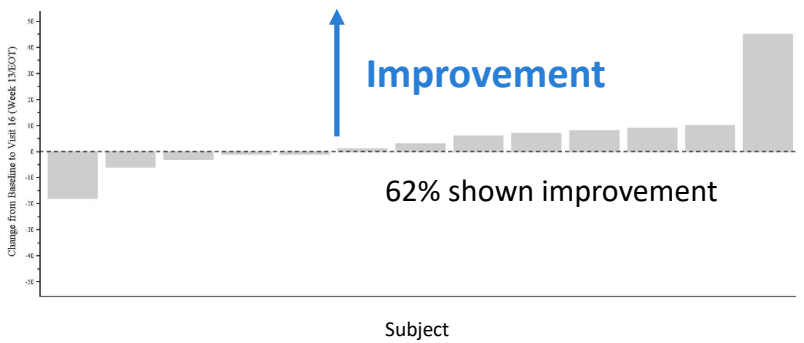
Cognitive Score by subject

mITT Population



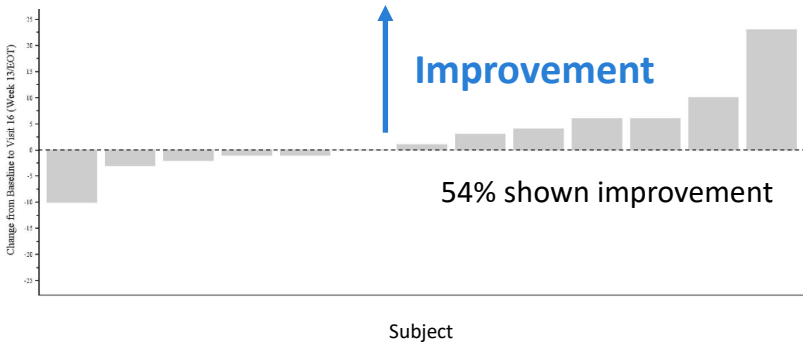
Fine Motor Score by subject

mITT Population



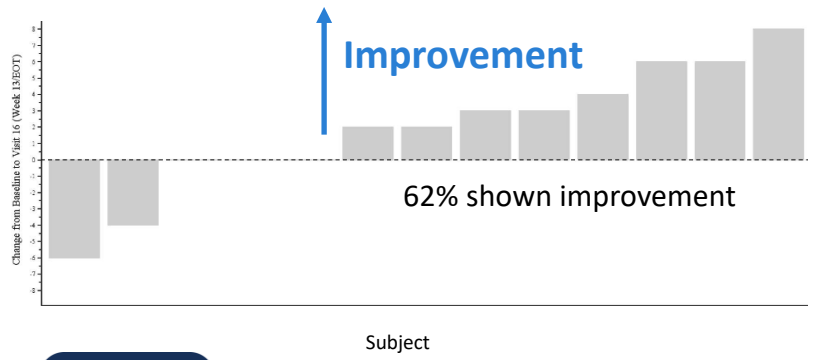
Gross Motor Score by subject

mITT Population



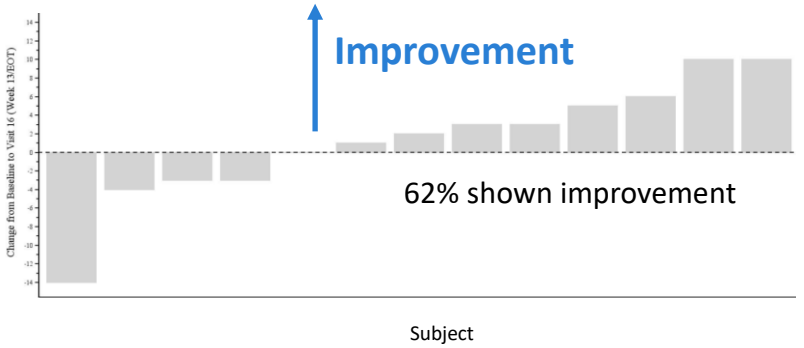
Expressive Communication Score by subject

mITT Population



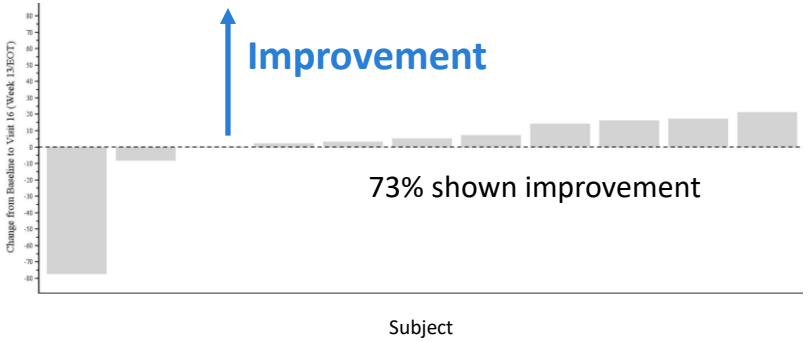
Receptive Communication Score by subject

mITT Population



Social-Emotional Score by subject

mITT Population



neuren pharmaceuticals

Clinician and caregiver testimonials

Clinicians

"Sleeps longer hours greater than 8 per night. Night awakenings only to be covered but back to sleep on their own. Wakes up much less."

"Much Calmer. Focuses better. Hand flapping stopped."

"Understands more. Everything they are asked to do."

"Steadier on feet. More balanced. Less cautious. Stair/curb climbing managed on their own this week."

"Family feel understanding more and more aware and feel this is coming out as being more upset at times (ie expressing feelings/needs)."

"Following verbal instructions well without visual cues (asking to get up or go to Grandmother)."

Caregivers

"…is more settled and focus on what they are doing …also much more calmer than before."

"More focused, balance, concentrate longer."

"Shows more gestures by pointing and showing."

"Can pick up small objects and try to do a puzzle"

"Can sit at a table with the family without too much behaviors spitting and hitting."

"Improved sleep, balance, no hand flapping, calmer."

AS opportunity

neuren pharmaceuticals

AS has a well established global clinical environment

Estimated prevalence is 1/10,000 to 1/20,000 males and females[1]

	US	Europe	Japan	China	Other[2]
Potential AS patients	12,000 – 25,000[3]	16,000 – 32,000[3]	3,000 - 7,000[3]	38,000 – 76,000[3]	12,000 - 25,000[3]

Natural history study since 2006 enrolled 550+ patients to date

NIH funded
2006 – 2014

~300 patients across 6 sites in the US

FDA funded
2018 – 2022

~150 patients across 10 sites in North America

ABOM funded
2022 – present

Global Angelman Syndrome Registry established in Sep 2016

GLOBAL ANGELMAN SYNDROME REGISTRY

Currently **2,510** registered patients across 95 countries (966 in US and Canada)[4]

[1] Angelman Syndrome Foundation (ASF) (www.angelman.org), Facts About Angelman Syndrome
[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] https://www.angelmanregistry.info/ as at August 2024

neuren pharmaceuticals

Neuren has one of the leading programs for AS

Neuren Program Status

- Orphan Drug designation in US and EU
- Phase 2 clinical development under US FDA IND
- Eligible for Rare Pediatric Disease Designation Priority Review Voucher program

Leading products in development

Company	Modalities	Delivery Mechanism	Product Development Stage
#1	RNA	Spinal injections	Phase 3 to commence by end of 2024
#2	RNA	Spinal injections	Phase 3 to commence H1 2025
neuren pharmaceuticals	Small Molecule	Oral	**Successful Phase 2**
#4	Small Molecule	Oral	Phase 2a (top line results 2025E[1])

Neuren engaging with all stakeholders

angelman SYNDROME FOUNDATION

fast cureangelman.org

Leading clinicians

FDA

[1] Broker estimates

neuren pharmaceuticals

NNZ-2591 as a multi-indication platform

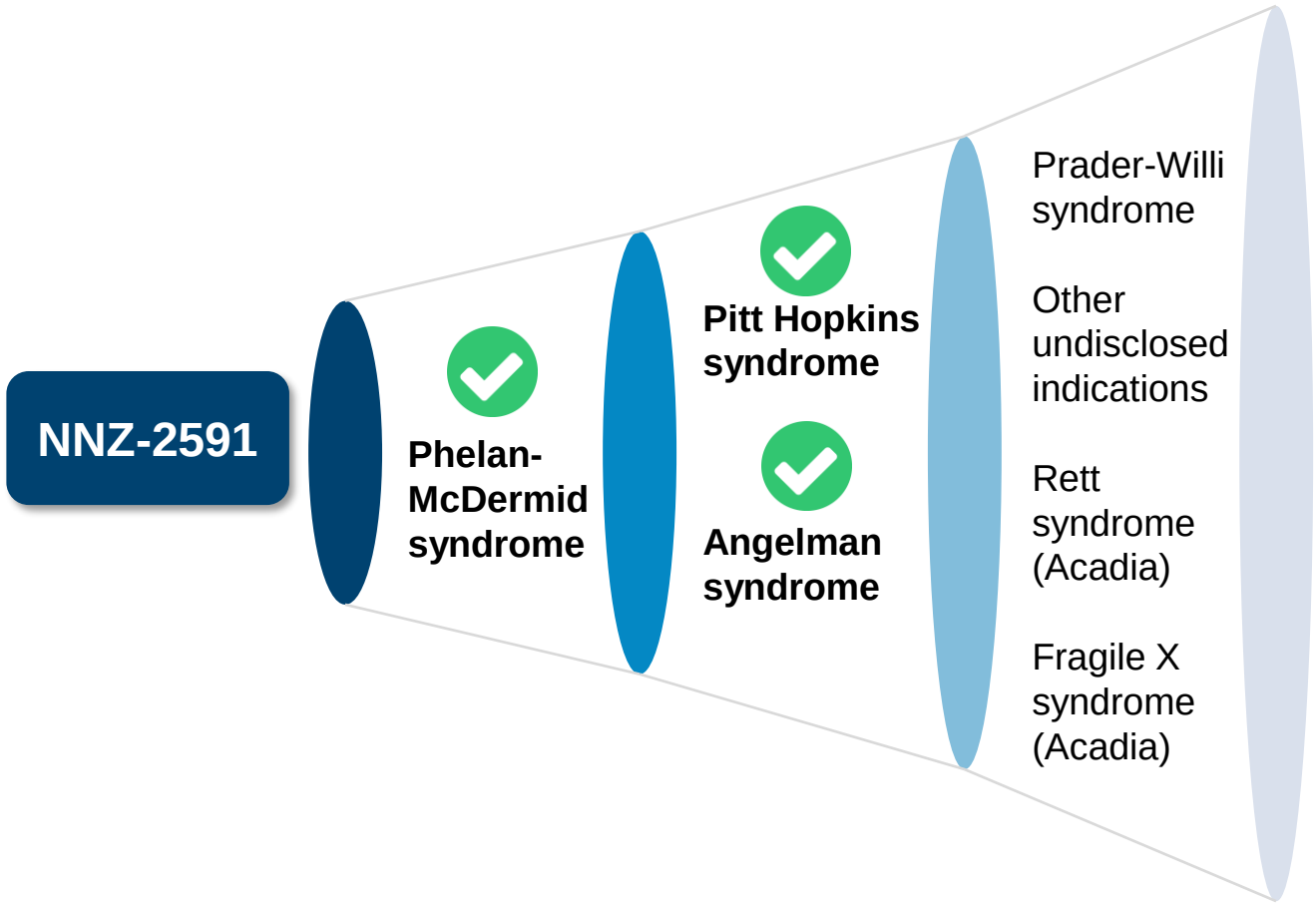
neuren pharmaceuticals

Phase 2 trial results validating multi-indication platform

	Phelan-McDermid syndrome N=18, 13 weeks	Pitt Hopkins syndrome N=11, 13 weeks	Angelman syndrome N=13, 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	Safe and well tolerated, with no meaningful trends in laboratory values or other safety parameters during treatment	
Serious TEAEs	1 unrelated to drug	0	0	
Mean CGI-I (% shown improvement)	2.4 (89%)	2.6 (82%)	*All* 3.0 (85%)	*3-12 yr old* 2.8 (100%)
Mean CIC (% shown improvement)	2.7 (83%)	3.0 (73%)	*All* 3.2 (67%)	*3-12 yr old* 2.6 (100%)
# patients had CGI-S improvement of 1 (% of patients)	7 (39%)	6 (55%)	4 (31%)	
Consistent improvement in clinically important aspects	Communication, behavior, cognition, social	Communication, social, cognition, motor	Communication, behavior, cognition, motor	

neuren pharmaceuticals

Multiple indications opportunity for NNZ-2591



- **Positive results from Phelan McDermid syndrome, Pitt Hopkins syndrome and Angelman syndrome Phase 2 trials**
- **End of Phase 2 meeting with FDA for Phelan McDermid syndrome scheduled for September 2024**
- US IND open for Prader-Willi syndrome
- Advancing non-clinical studies in multiple undisclosed indications
- Rett and Fragile X syndromes are licensed to Acadia, with same economics to Neuren as trofinetide; Neuren retains worldwide rights to all other indications

neuren pharmaceuticals

CONTACT

investorrelations@neurenpharma.com

neuren pharmaceuticals