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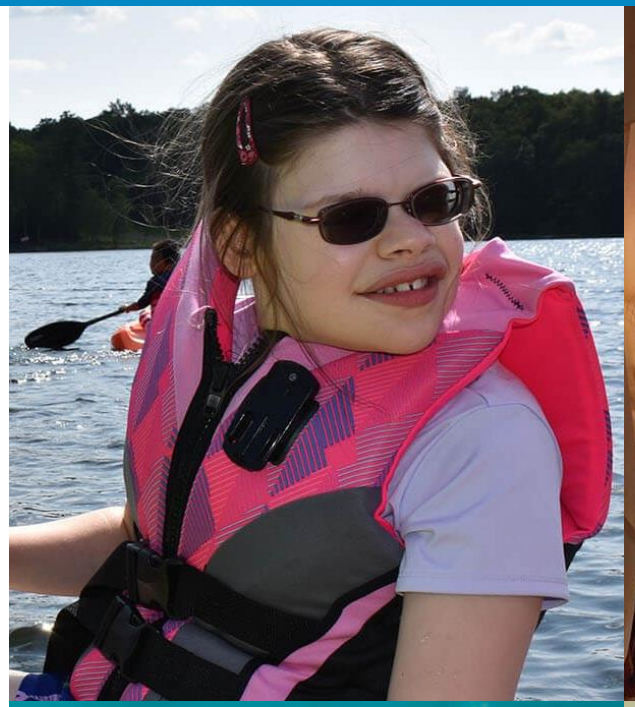
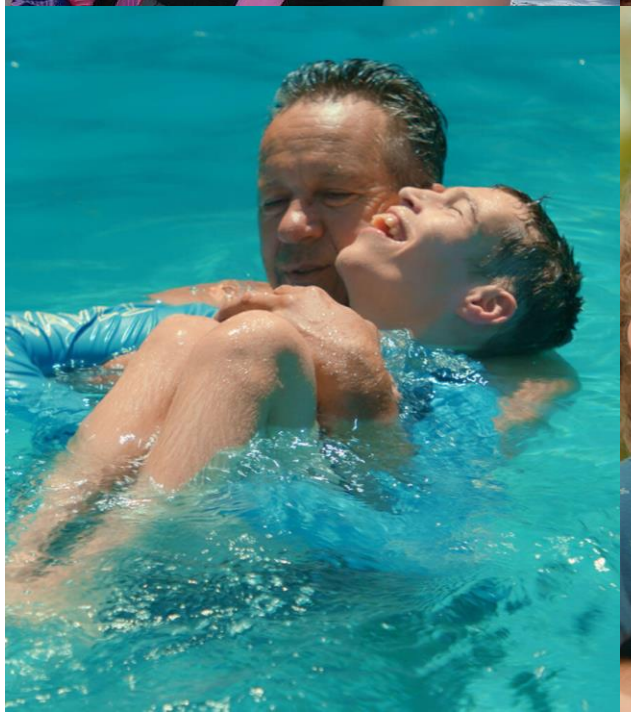
Corporate **Presentation**

29 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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Leadership in neurodevelopmental disorder therapy development

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

Daybue™ (trofinetide)

World's **1st and only** approved therapy for **Rett** Syndrome[1]

Clinical development in **5 more** neurodevelopmental disorders, all with **Orphan Drug** designation, with no existing approved therapies[2]

no royalties payable to 3rd parties

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

[1] Currently approved in US only
[2] Except growth hormone to treat some aspects of Prader-Willi syndrome

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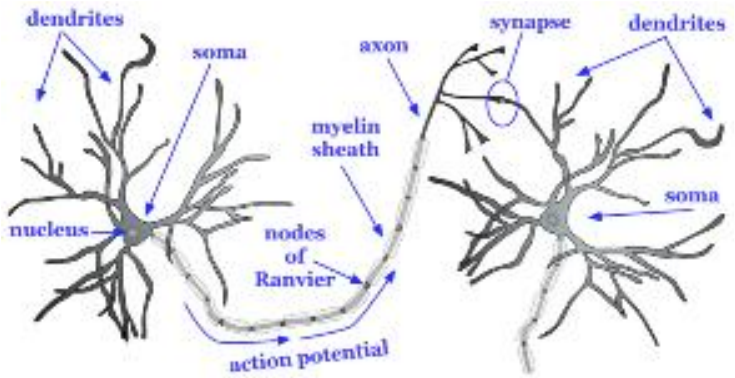
Seeking a ground-breaking impact on neurodevelopmental disorders

Rett	Fragile X	Phelan-McDermid	Angelman	Pitt Hopkins	Prader-Willi
MECP2	*FMR1*	*SHANK3*	*UBE3A*	*TCF4*	*15q11-q13*



Impaired communication between neurons, abnormal formation/pruning of dendrites & chronic inflammation

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target the critical role of IGF-1 in this upstream process, using analogs of peptides that can be taken orally as liquids

Severe impact on nearly every aspect of life		
walking and balance issues	anxiety and hyperactivity	seizures
Impaired communication	intellectual disability	Impaired social interaction
impaired hand use	sleep disturbance	gastrointestinal problems

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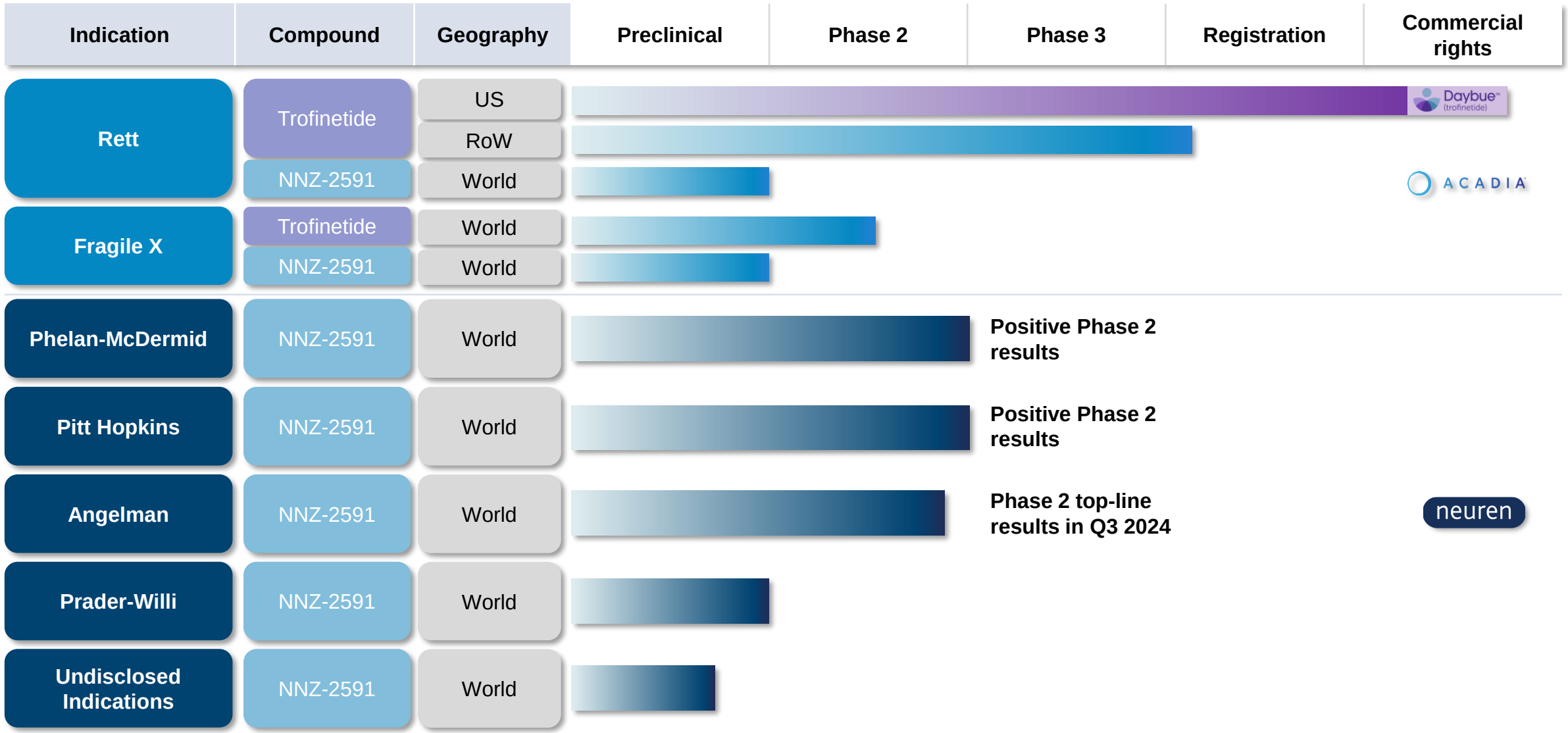
Commercial and late-stage pipeline



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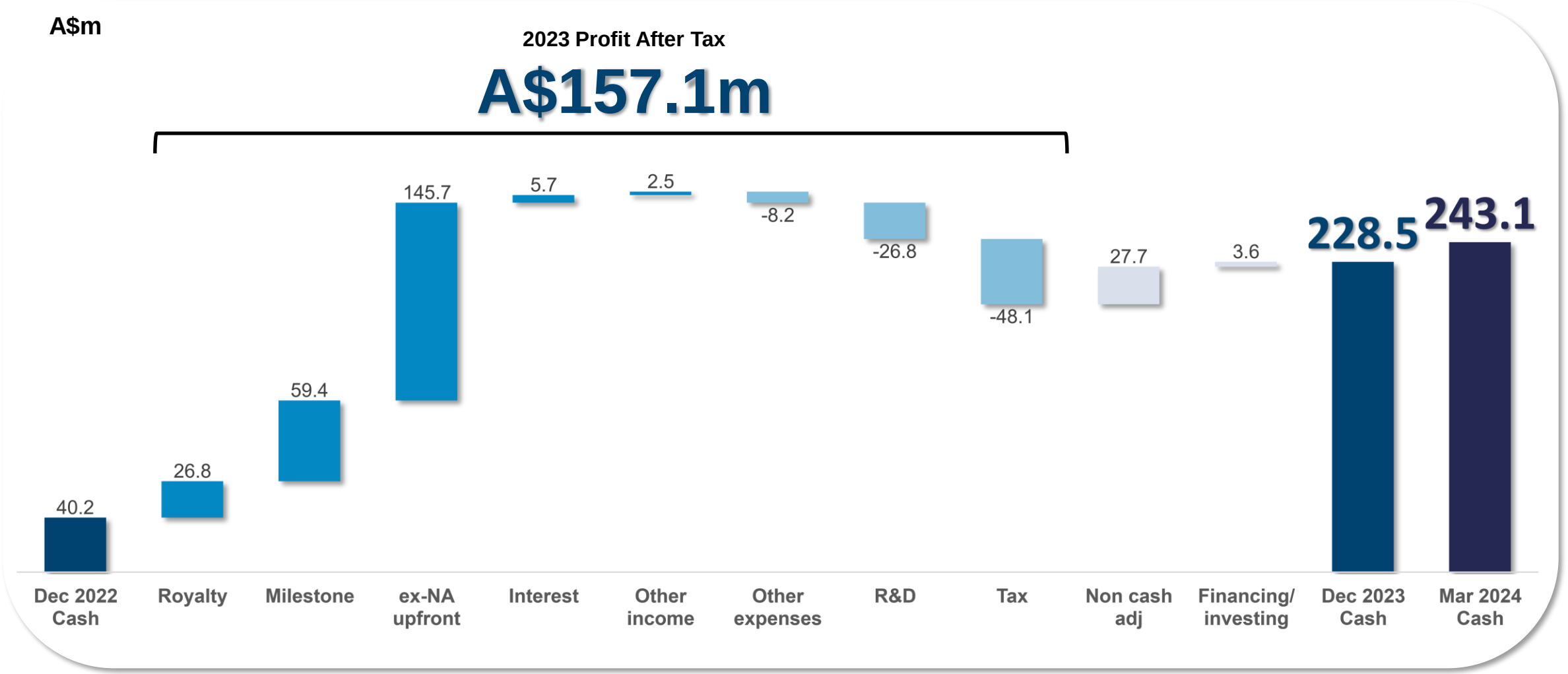
Financial strength to maximise growth opportunities



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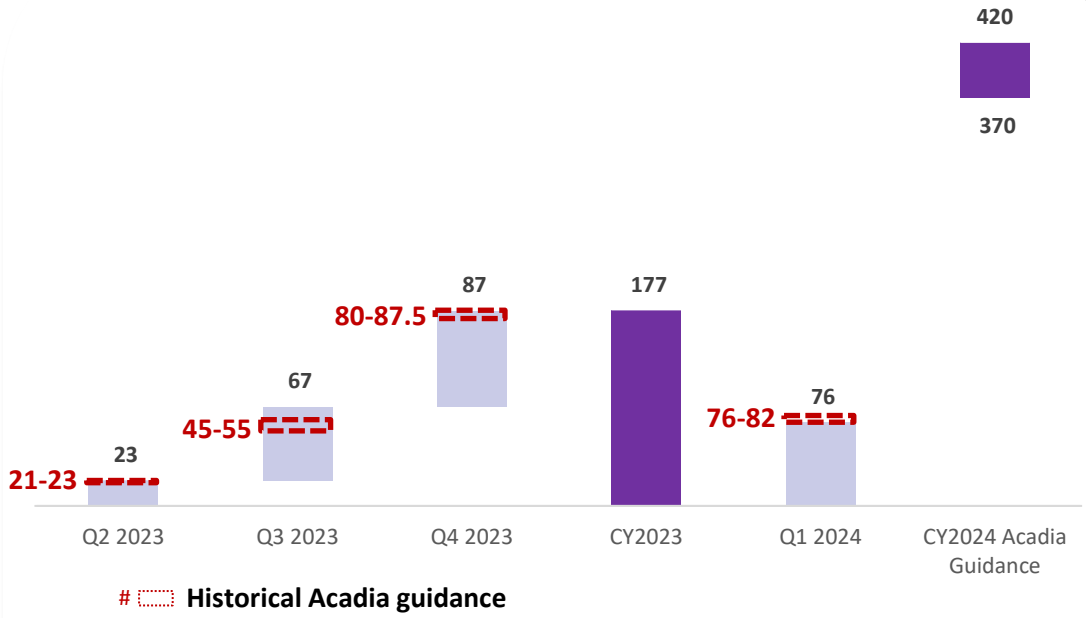
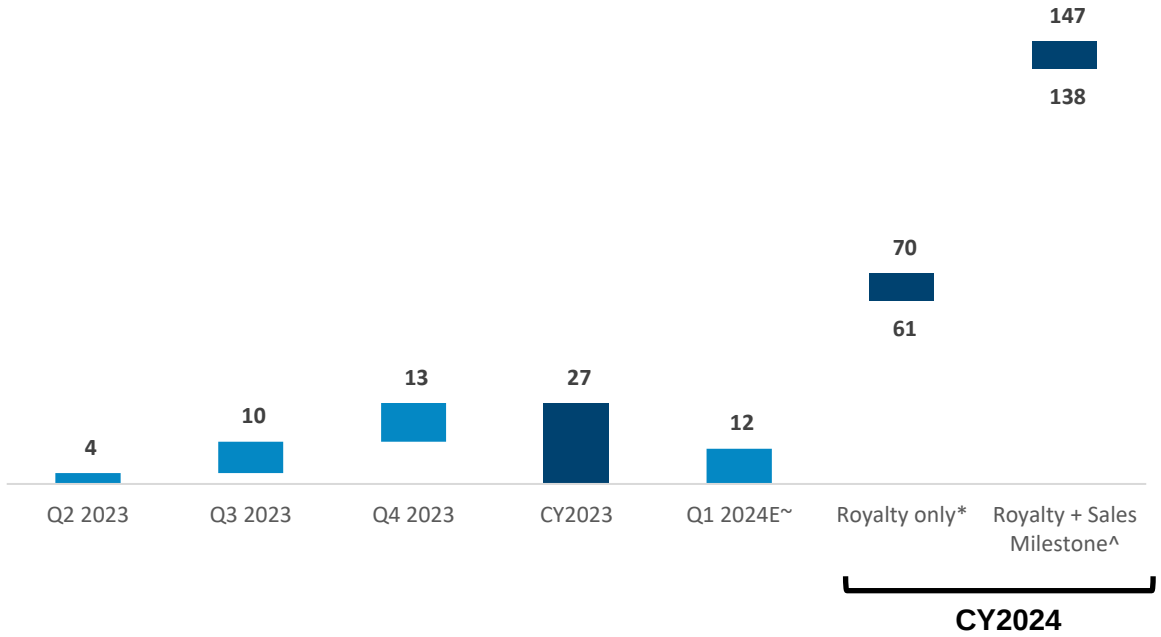
Growing sustainable income from commercialised product

DAYBUE Net Sales (US$m)



2023 net sales of US$177m
2024E net sales of US$370 – 420m

Royalty and Sales Milestone Payments to Neuren (A$m)



2023E royalty of A$27m
2024E royalty of A$61 – 70m, plus A$77m sales milestone

~ Based on 10% of DAYBUE net sales and AUDUSD of 0.652294
* Based on 10% of DAYBUE net sales up to US$250m and 12% of DAYBUE net sales between US$250m and US$500m, and AUDUSD of 0.65
^ Neuren will be entitled to US$50m sales milestones (receivable in Q1 2025) if CY2024 DAYBUE net sales reaches US$250m; assumes AUDUSD of 0.65

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Three key drivers transforming near term value

1 Realise Neuren's share of **trofinetide value in the US** through Acadia's successful commercialization of

Daybue™ (trofinetide)

2 Realise Neuren's share of **trofinetide ex-US** value through expanded global partnership with Acadia

3

Confirm efficacy of **NNZ-2591** in Phase 2 trials for multiple indications, with global rights retained by Neuren

- ✓ Positive top-line results for **Phelan-McDermid syndrome**
- ✓ Positive top-line results for **Pitt Hopkins syndrome**
- Top-line results for **Angelman syndrome** in **Q3 2024**

DAYBUE / Trofinetide

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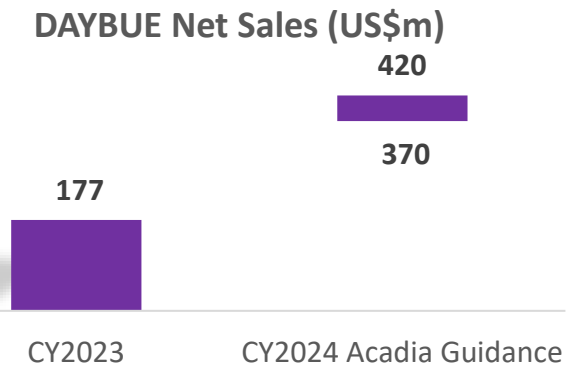
North America – DAYBUE™ US launch in April 2023

	US	Canada
Potential Rett patients	6,000 - 9,000[1]	600 - 900[1]
Currently identified Rett patients	5,000[1]	NDS accepted for priority review, potential approval around year-end 2024[3]

As of 3 May 2024: >1,300 patients initiated therapy, 862 active on therapy



Economics to Neuren:

✓	**US$10m**	**upfront in 2018**
✓	**US$10m**	**in 2022 following acceptance of NDA for review**
✓	**US$40m**	**in Q2 2023 following 1st commercial sale in the US**
	US$33m	one third share of Priority Review Voucher awarded to Acadia (assuming market value US$100m)
	US$55m	Milestone payments related to Fragile X

Tiered Royalty Rates (% of net sales)[2]

Annual Net Sales	Rates
≤US$250m	**10%**
>US$250m, ≤US$500m	**12%**
>US$500m, ≤US$750m	**14%**
>US$750m	**15%**

Sales Milestones

Net Sales in one calendar year	US$m
≥US$250m	**50**
≥US$500m	**50**
≥US$750m	**100**
≥US$1bn	**150**

[1] Acadia estimates
[2] Royalty rates payable on the portion of annual net sales that fall within the applicable range
[3] Acadia First Quarter 2024 Earnings Call presentation in May 2024

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Meaningful real world benefits reported

LILAC-2 Caregiver Exit Interviews[1]

Area/type of improvement with trofinetide reported by ≥15% of caregivers, n (%)	Caregivers N=25 (%)
Engagement with others	*11 (42.3)*
Hand use	*10 (38.5)*
Eye gaze	*8 (30.8)*
Attention/focus/concentration	*7 (26.9)*
Tobii eye trackers use	*7 (26.9)*
Ability to make sounds	*6 (23.1)*
Happier mood or disposition	*6 (23.1)*
Ability to walk	*5 (19.2)*
Alertness	*5 (19.2)*
New words	*5 (19.2)*
Seizures	*4 (15.4)*
Aware of environment	*4 (15.4)*
Repetitive hand movements	*4 (15.4)*

Real World Experience[1]

"It was her engagement level with the world outside of her – to me and to friends in school; it just blossomed, and it was like a light was turned on."

"Her verbalization definitely improved, and she started saying more things."

"Picking up things a lot more (mostly her cup), happens daily and she is now trying to drink by herself."

"Improved cognitive ability, and [the parents] are hearing new words or words they have not heard in a while."

[1] Acadia Fourth Quarter and Full Year 2023 Earnings Call presentation in Feb 2024

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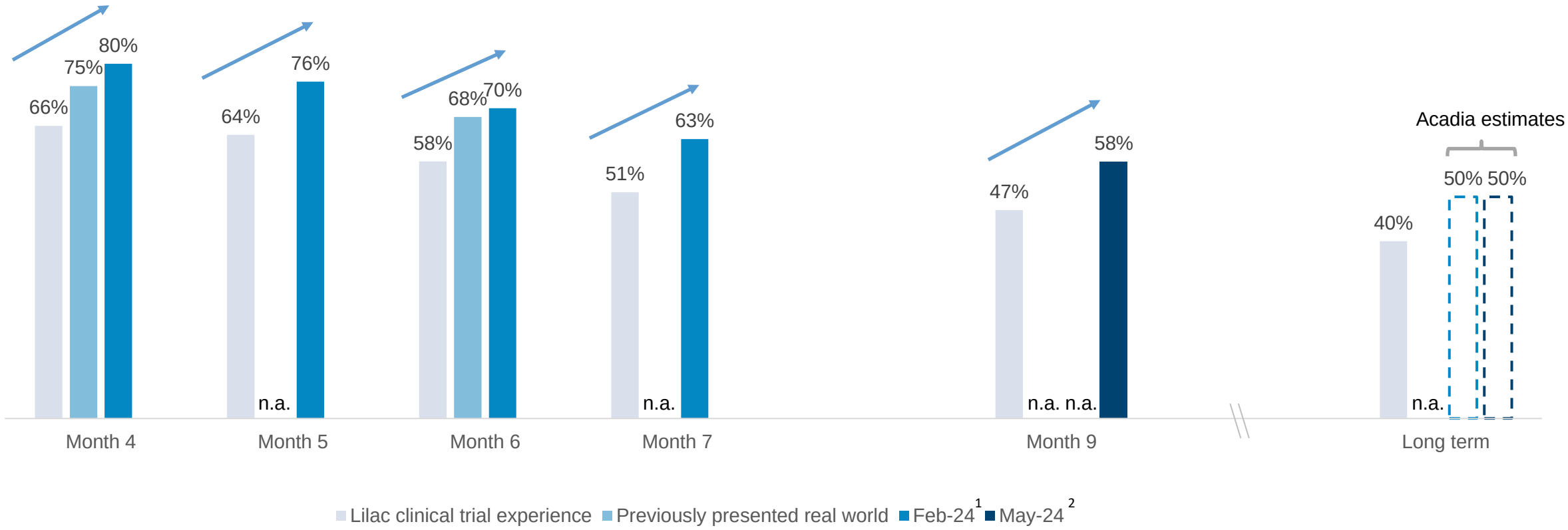
Persistency rates improving in new patient cohorts

Persistency Rates
(Based on confirmed discontinuations and patients who were 60 days past their scheduled refill)



[1] Acadia Fourth Quarter and Full Year 2023 Earnings Call presentation in Feb 2024
[2] Acadia First Quarter 2024 Earnings Call presentation in May 2024

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Outside North America

	Europe	Japan	Other
Potential Rett patients	9,000 - 14,000[1]	1,000 - 2,000[1]	~30,000[2]
Currently identified Rett patients	~4,000[2]	~800 - 1,000[2]	~2,000[2]

- **Europe:** Pediatric investigation plan (PIP) filed with and accepted by EMA, with a potential Marketing Authorisation Application filing in Q1 2025[3]
- **Japan:** Formal meeting with Japanese regulatory agency (PMDA) scheduled in 2Q24 to discuss clinical plan[3]

Economics to Neuren:

✓ **US$100m**	**upfront**
US$35m	following 1st commercial sale in Europe
US$15m	following 1st commercial sale in Japan
US$10m	following 1st commercial sale of a 2nd indication Europe
US$4m	following 1st commercial sale of a 2nd indication Japan
Sales milestones	On achievement of escalating annual net sales thresholds: Europe: up to **US$170m** Japan: up to **US$110m** RoW: up to **US$83m**
Tiered royalties	**Mid-teens to low-20s %** of net sales

[1] Acadia estimates
[2] Neuren estimates based on prevalence studies and patient organisations
[3] Acadia First Quarter 2024 Earnings Call presentation in May 2024

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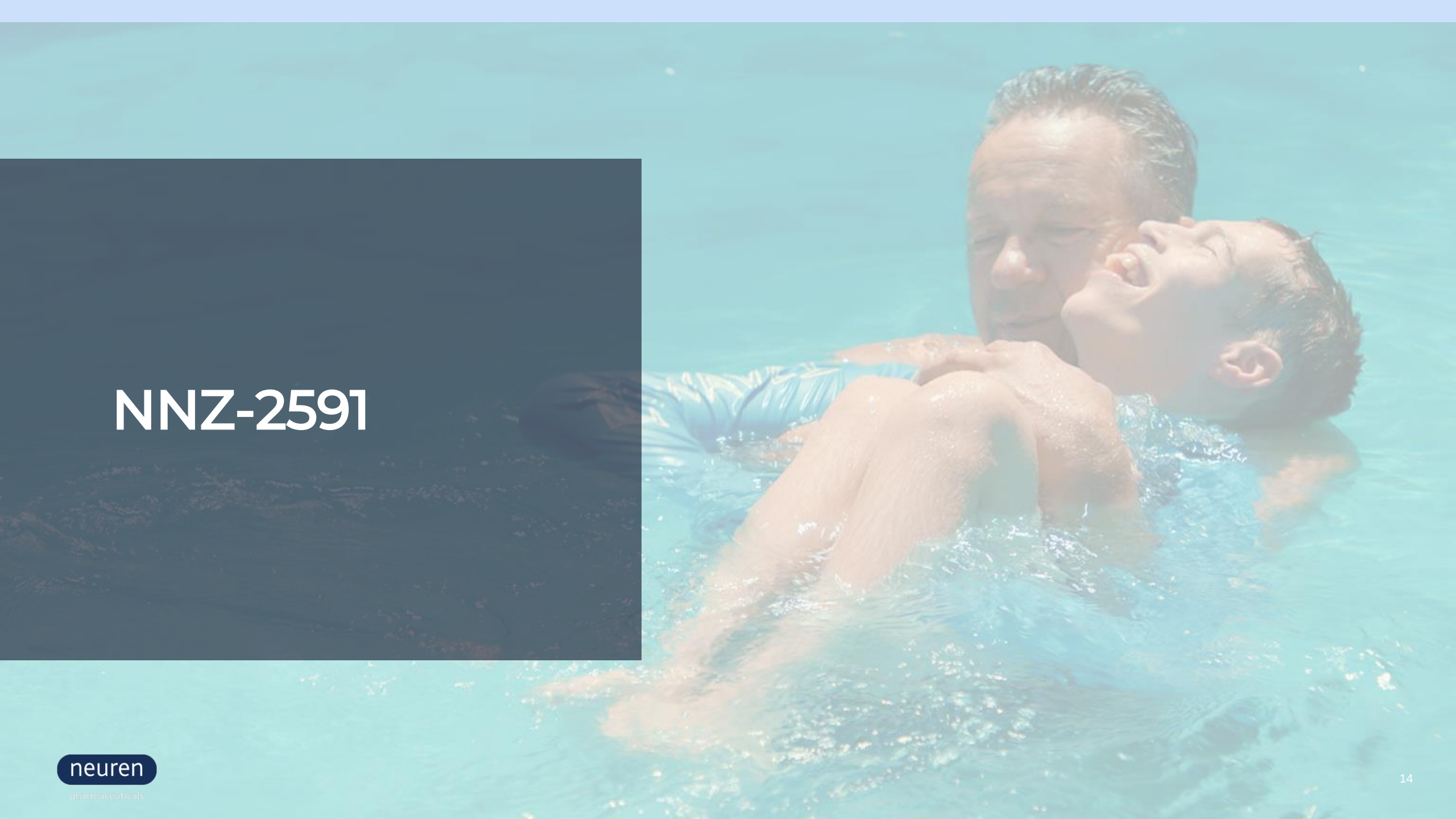
NNZ-2591



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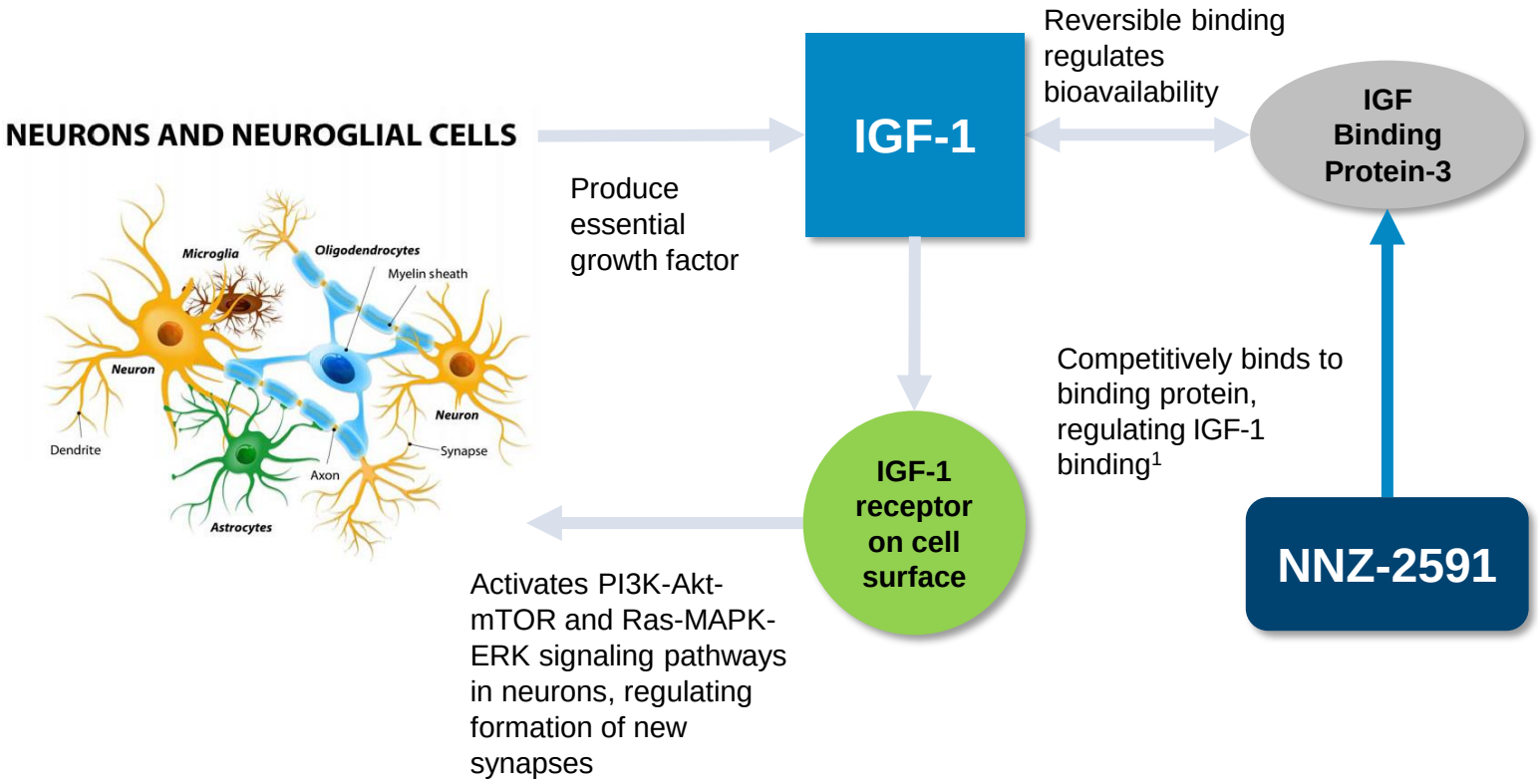
Regulating IGF-1 in the brain



- **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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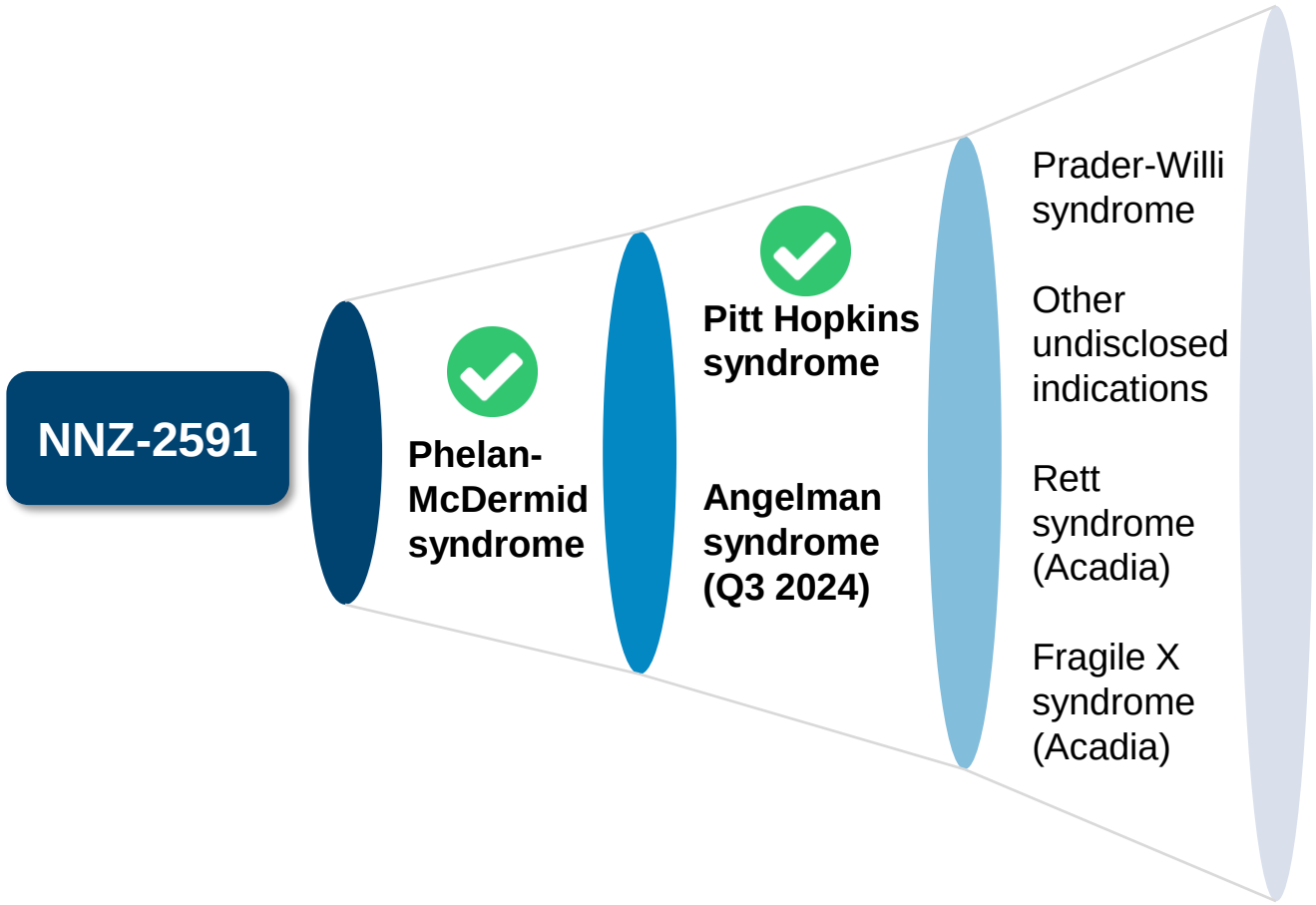
Multiple indications opportunity for NNZ-2591



- **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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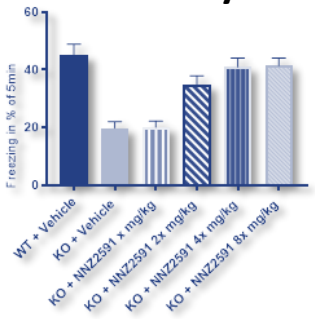
NNZ-2591 has ideal attributes leading into Phase 2

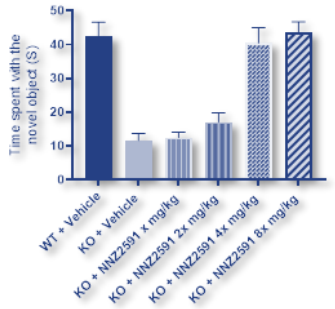
- ✓ Novel mechanism of action
- ✓ Clear and consistent efficacy in mouse models of each syndrome
- ✓ Biochemical effects in the brain confirmed
- ✓ Optimum dose identified
- ✓ Demonstrated high oral bioavailability and blood-brain barrier penetration
- ✓ IND-enabling program of non-clinical toxicology and CMC studies completed
- ✓ Proprietary drug substance manufacturing process with exceptional purity and high yield, administered as patient-friendly liquid dose
- ✓ Safe and well tolerated in Phase 1 trial
- ✓ Orphan designations from FDA and EMA
- ✓ INDs approved by FDA for Phelan-McDermid, Pitt Hopkins, Angelman and Prader-Willi syndromes

Clear efficacy and dose response in Phelan-McDermid syndrome model

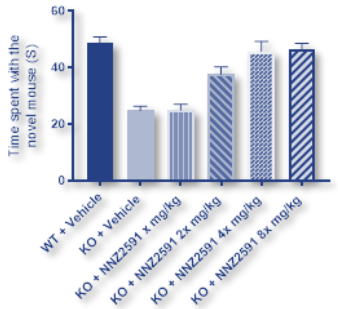
Memory



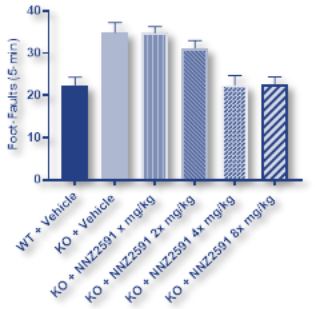
Learning



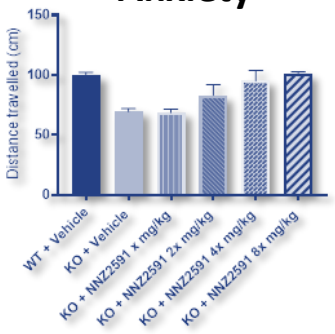
Sociability



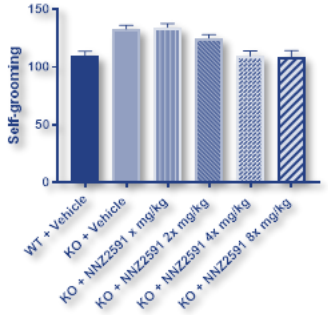
Motor function



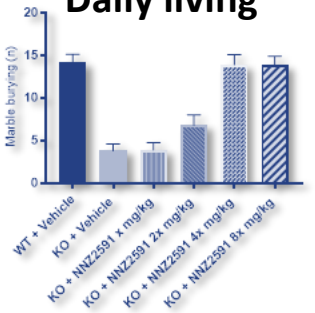
Anxiety



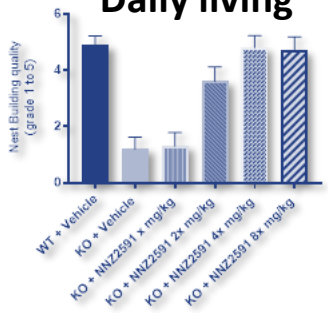
Repetitive behavior



Daily living



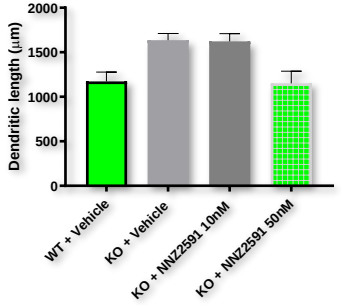
Daily living

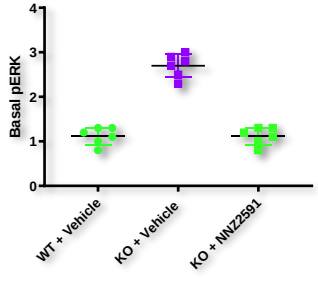


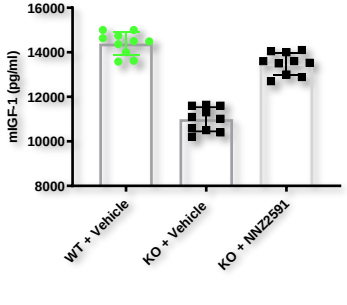
Incidence of audiogenic seizures

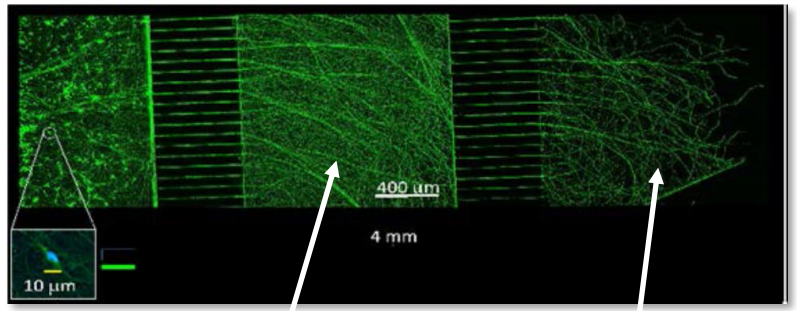
WT + vehicle	0%
KO + vehicle	60%
KO + x mg/kg	50%
KO + 2x mg/kg	30%
KO + 4x mg/kg	10%
KO + 8x mg/kg	10%

In biochemical testing, NNZ-2591 was shown to normalize the abnormal length of dendritic spines that form the synapse, the excess activated ERK protein (pERK) and the depressed level of IGF-1 in *shank3* knockout mice









Abnormal dendrites in *shank3* knockout mice cells in culture

Normalization after treatment with NNZ-2591

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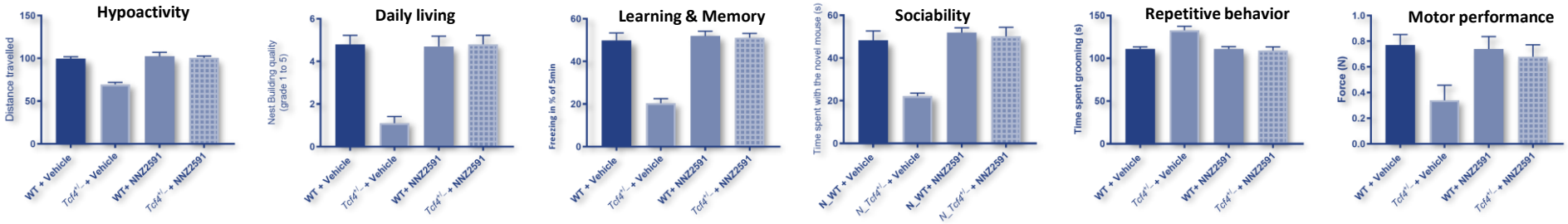
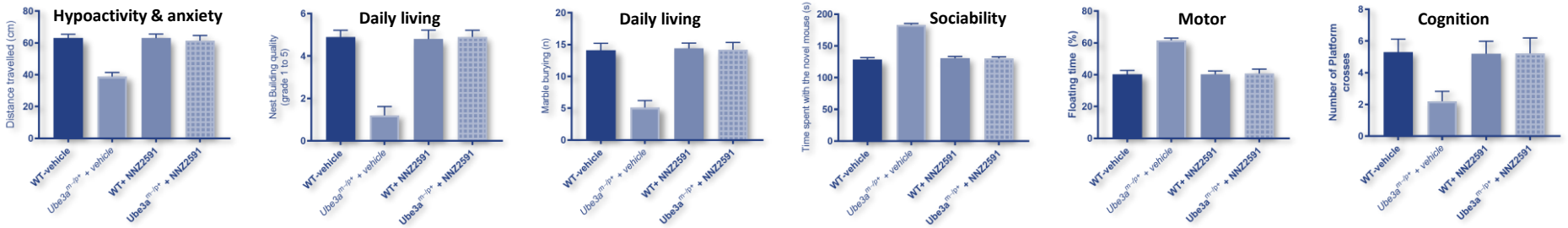
Consistent efficacy in Pitt Hopkins, Angelman and Prader-Willi models

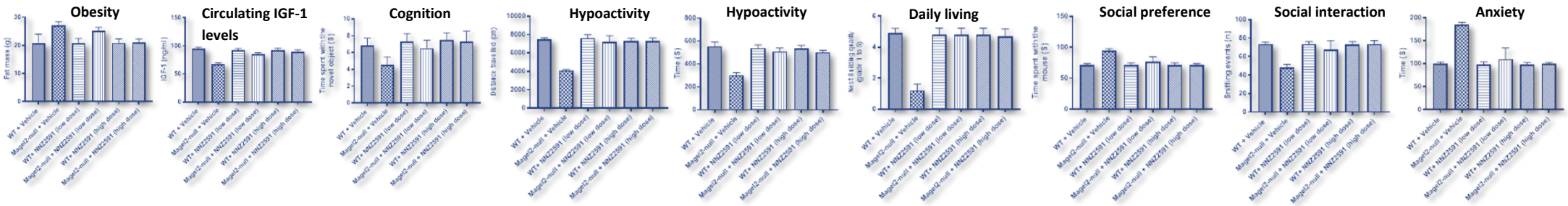
Pitt Hopkins



Angelman



Prader-Willi



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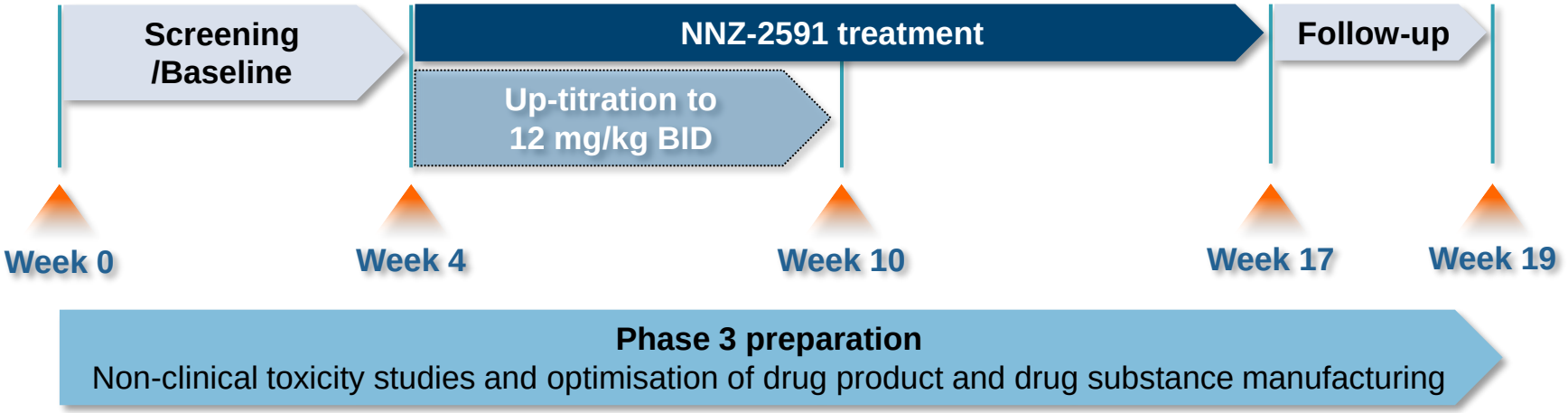
Key features of first Phase 2 trials

Overall aim – expedite data that informs the design of subsequent registration trials and prepare for Phase 3 in parallel



- Prioritising speed to data and maximising opportunity to demonstrate effects
- Confirm safety and PK in pediatric patients
- Assess treatment impact across multiple efficacy measures to select primary endpoint for registration trial
- **Positive results for Phelan-McDermid syndrome and Pitt Hopkins syndrome**
- **Top-line result for Angelman syndrome in Q3 2024**
- Manufacturing for Phase 3 commenced

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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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Phelan-McDermid syndrome (PMS)

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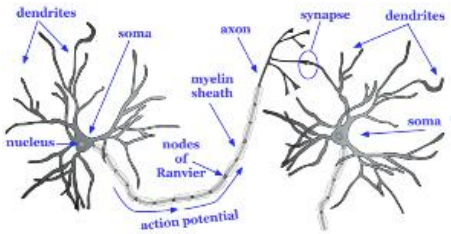
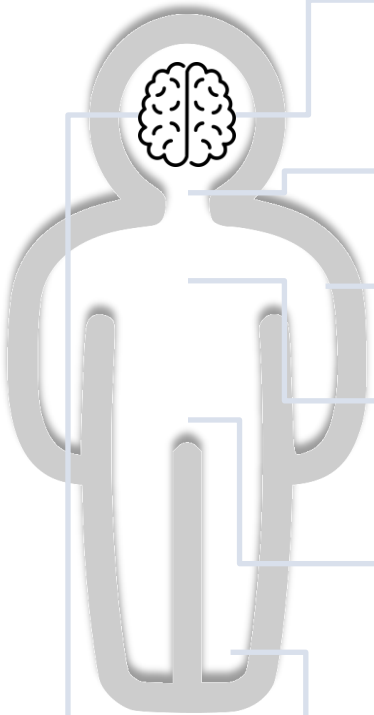
PMS has overwhelming unmet medical need

Cause of the syndrome

Deletion or variation in the *SHANK3* gene on chromosome 22

SHANK3 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 (~40% of patients)

Language deficits
Feeding difficulties

Motor delays
Low muscle tone

Sweat less, risk of overheating
High pain tolerance

Difficulties toilet training (~3/4 of patients)
GI dysfunction (most commonly constipation)

Walking abnormalities

Frequent hospitalization and heightened risk of accidents

From Voice of the Patient Report

Externally-Led Patient-Focused Drug Development Meeting 8 Nov 2022

"PMS has an overwhelming unmet medical need. *There are no FDA approved treatments for PMS despite its severely debilitating manifestations. Parents and caregivers are open to trying almost anything to try to relieve their child's suffering; most have tried an incredibly high number of treatments and approaches for symptom management, with very little success. Some received medications that caused more harm than good"*

"PMS has severe quality of life impacts on those living with the disease, as well as on parents and siblings. *Most activities of daily life, including communicating needs or wants, self-care (bathing, dressing, toileting) and socializing with peers/siblings are affected. Most individuals living with PMS rely on their parents and caregivers for all their daily needs, and many require 24-hour care."*

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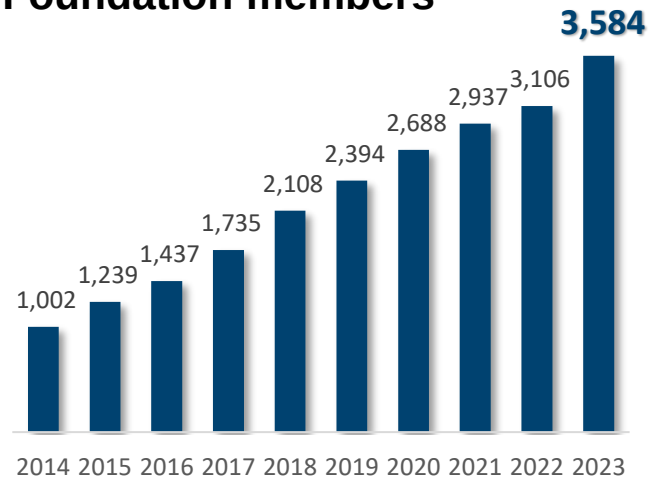
PMS is historically under-diagnosed, but this is changing

Estimated prevalence is 1% of people with autism - 1/8,000 to 1/15,000 males and females[1]

	US	Europe	Japan	China	Other[2]
Potential PMS patients	17,000 – 32,000[3]	21,000 – 41,000[3]	5,000 - 9,000[3]	51,000 – 95,000[3]	16,000 - 31,000[3]

Phelan-McDermid Syndrome Foundation members



Currently 1,739 US members

75% of PMS patients have been diagnosed with an ASD

~1% of autism patients have *SHANK3* mutations

Opportunity to accelerate diagnosis

Autism

US ADDM tracks 440k children with autism spectrum disorder

- Rising awareness
- EL-PFDD meeting with FDA in 2022
- ICD code assigned in 2023
- Enhanced genetic testing technologies
- Expanding ADDM network sites

[1] Phelan McDermid Syndrome Foundation (PMSF) (www.pmsf.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)

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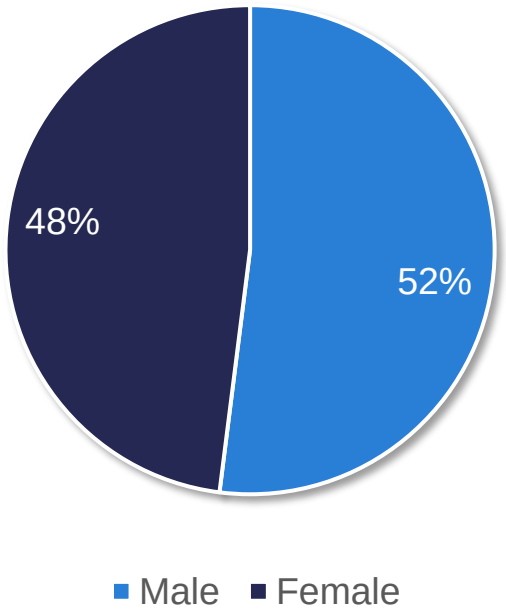
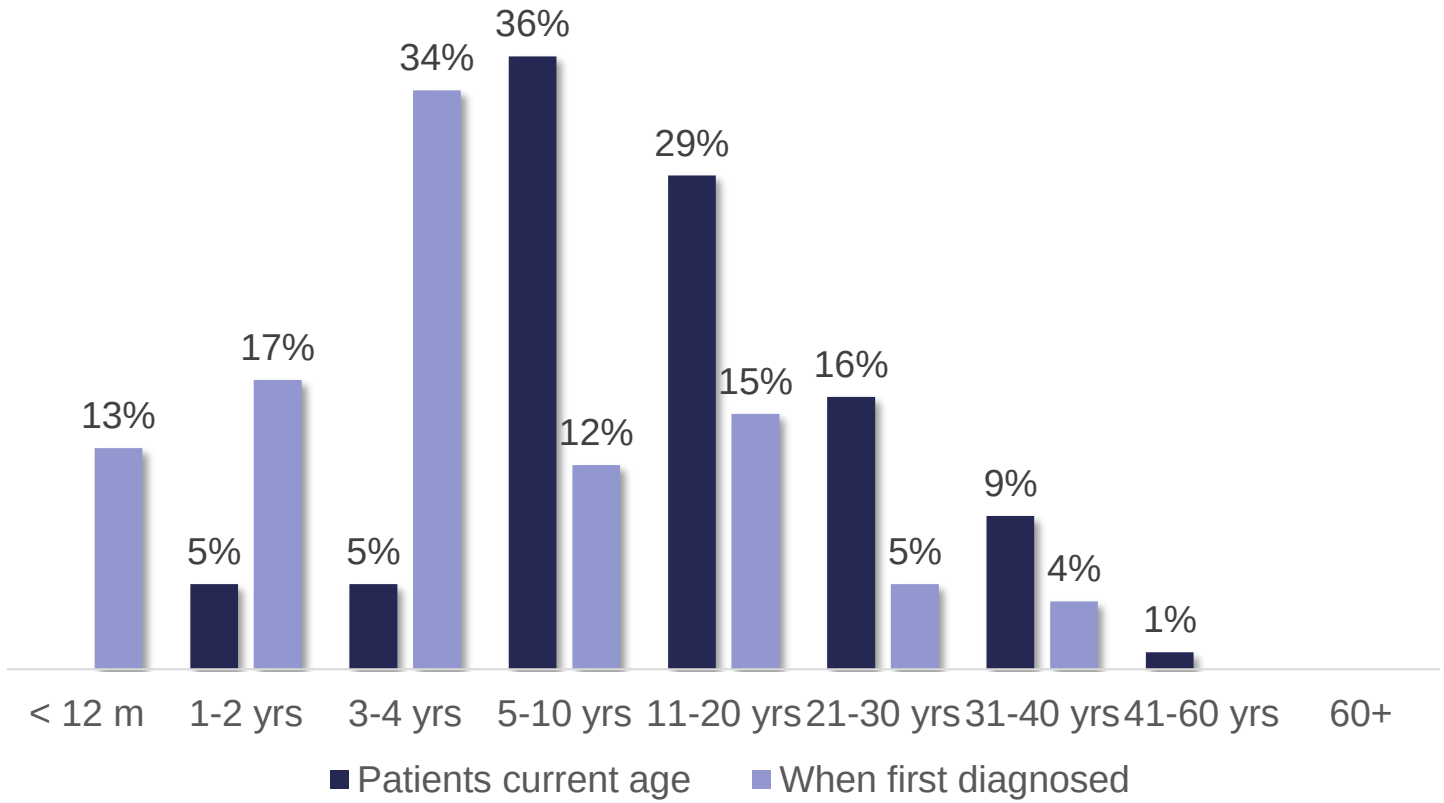
PMS affects all genders and ages

% currently diagnosed patients by gender[1]



% currently diagnosed patients by age group[1]



[1] Estimates based on survey of participants in the Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on Phelan-McDermid Syndrome 8 Nov 2022

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Neuren is leading development of a first approved treatment for PMS

Phase 2 Program Status

- Phase 2 clinical development in the US under an IND
- End of Phase 2 Meeting with FDA planned Q3 2024
- 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
neuren pharmaceuticals	**Positive Phase 2 trial**
#2	Phase 2 trial closed Jan 2021
#3	Phase 1
#4	Phase 1
#5	Pre-clinical

Neuren engaging with all stakeholders

pmsf

cureSHANK

Leading clinicians

FDA

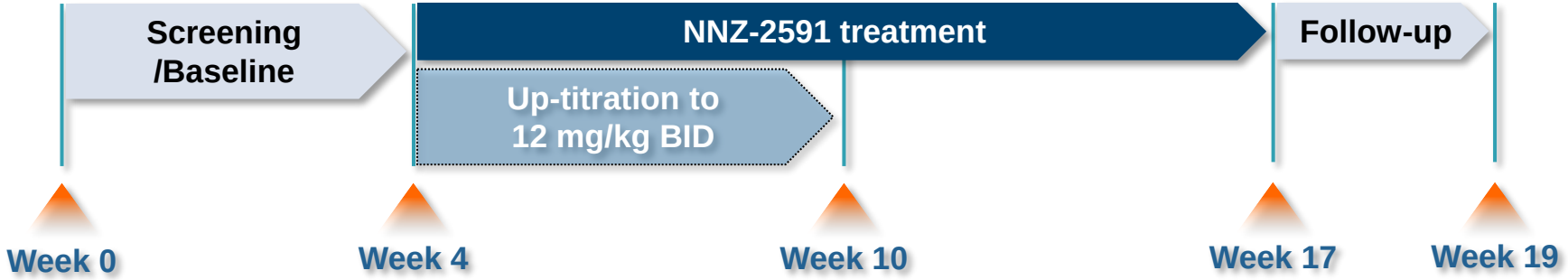
Neuren's Phase 2 trial in children with PMS

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

4 US sites: Rush University, Massachusetts General Hospital, Boston Children's Hospital and Texas Children's Hospital

n subjects: 18

Age range: 3 to 12 (mean 8.6)



Endpoints

- Primary endpoints are safety, tolerability and PK
- Secondary endpoints include 14 efficacy measurements
- A key objective is selection of the best primary efficacy endpoint or endpoints for a registration study

PMS specific efficacy measurements

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

GI Health
- GIHQ

Symptom Specific
- PMS Clinician Domain Specific Rating Scale
- Caregiver Top 3 Concerns

Communication
- MB-CDI
- ORCA

Quality of Life
- QI-Disability
- ICND

Sleep
- CSHQ

Behaviour
- Aberrant Behavior Checklist-2
- Behavior Problems Inventory
- Vineland Adaptive Behavior Scales

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Phase 2 clinical trial results highlights

- **NNZ-2591 was safe and well tolerated, with no clinically significant changes in laboratory values or other safety parameters during treatment**
- **Significant improvement was assessed by both clinicians and caregivers across multiple efficacy measures**
- **Improvements were consistently seen across clinically important aspects of Phelan-McDermid syndrome, including communication, behaviour, cognition/learning and socialisation**
- **Clinician and caregiver global efficacy measures showed a level of improvement typically considered clinically meaningful:**
  - **PMS Clinical Global Impression of Improvement (CGI-I) – mean score of 2.4 with 16 out of 18 children showing improvement assessed by clinicians**
  - **PMS Caregiver Overall Impression of Change (CIC) – mean score of 2.7 with 15 out of 18 children showing improvement assessed by caregivers**
- **For 10 out of 14 efficacy endpoints, improvement from baseline on overall/total scores was statistically significant ($p<0.05$)[1]**

[1] Wilcoxon signed rank test

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Safety and tolerability summary

NNZ-2591 was safe and well tolerated

- ✓ Well tolerated
- ✓ Most Treatment Emergent Adverse Events (TEAE) were mild to moderate
  - 1 Serious TEAE (gastroenteritis) not related to study drug, occurred during safety follow-up period after end of treatment
  - 3 discontinuations due to TEAEs not related to study drug: 2 due to testing positive for COVID-19 and 1 due to seizures
- ✓ No clinically significant changes in laboratory values, electrocardiogram (ECG) or other safety parameters were observed during treatment

TEAEs in 2 or more subjects

Event	N=18 n (%)	Event	N=18 n (%)
Constipation	2 (11.1)	Somnolence	3 (16.7)
Diarrhea	2 (11.1)	Pyrexia	3 (16.7)
Nausea	2 (11.1)	Fatigue	2 (11.1)
Vomiting	2 (11.1)	Aggression	2 (11.1)
COVID-19	3 (16.7)	Insomnia	2 (11.1)
Nasopharyngitis	2 (11.1)	Decreased Appetite	3 (16.7)
Otitis Media	2 (11.1)	Rhinorrhea	2 (11.1)
Psychomotor Hyperactivity	4 (22.2)		

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Efficacy endpoints summary

- Statistically significant improvement vs baseline in **10/14** efficacy endpoints
- Mean **CGI-I** of **2.4** and Median of 2.0 with p-value <0.0001
- Mean **CIC** of **2.7** and Median of 3.0 with p-value =0.0003

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

Global

CGI-I	**<0.0001**
CIC	**0.0003**
CGI-S	**0.0156**

GI Health

GIHQ total frequency	**0.0013**

Quality of Life

QL Inventory-Disability total	**0.0066**
Impact of Childhood Neurologic Disability	0.1094

Sleep

CSHQ total	**0.0191**

Behaviour

Aberrant Behavior Checklist-2 total	**0.0013**
Behavior Problems Inventory total frequency	**0.0326**
Vineland Adaptive Behavior Scales Composite	0.1710

Symptom Specific

PMS Clinician Domain Specific Rating Scale total	**0.0156**
Caregiver Top 3 Concerns total	**0.0005**

Communication

MB-CDI Total Vocabulary	0.0647
ORCA T-Score	0.0714

[1] Wilcoxon signed rank test

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Best practice implemented for PMS-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 complete 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 domain scores	**Caregiver** gives an overall score and domain scores Also identifies the one symptom area that has most influenced his or her rating of the child's overall function
Domain Anchors	• Expressive Communication • Receptive Communication • Gross Motor Function • Fine Motor Function • Social Interaction • Cognition and Learning • Self-Care	• Communication • Social interaction • Behavior • Motor abilities • Seizures • Cognitive abilities/ability to learn • Self-care skills • GI problems • Sensory sensitivities

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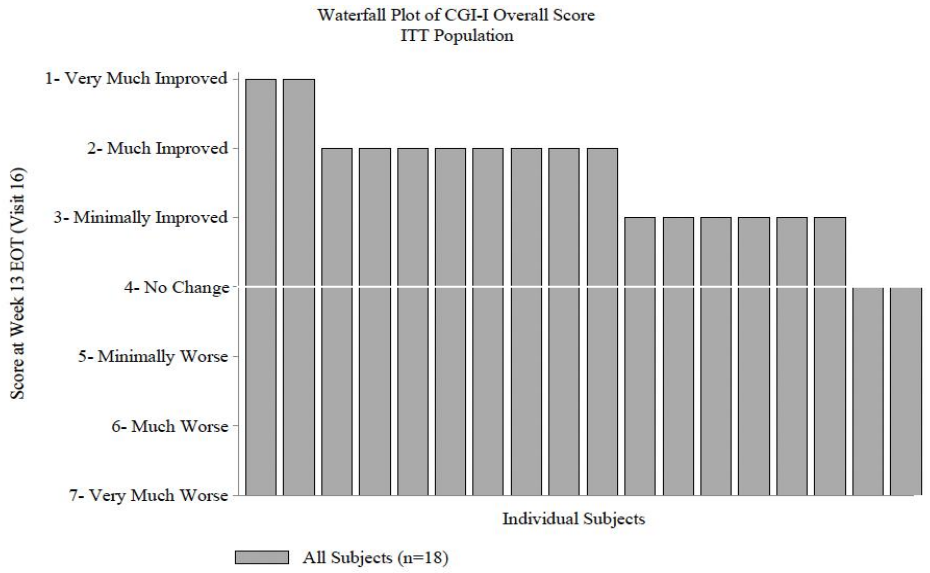
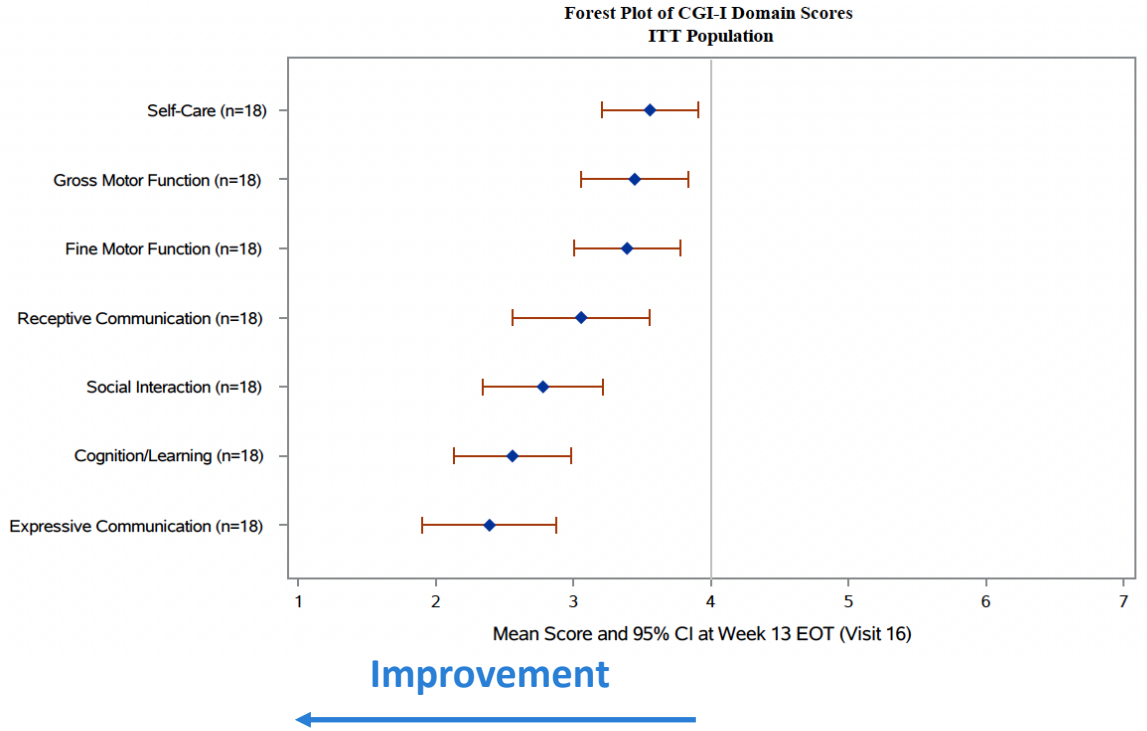
PMS CGI-I (clinician) results by subject and by domain

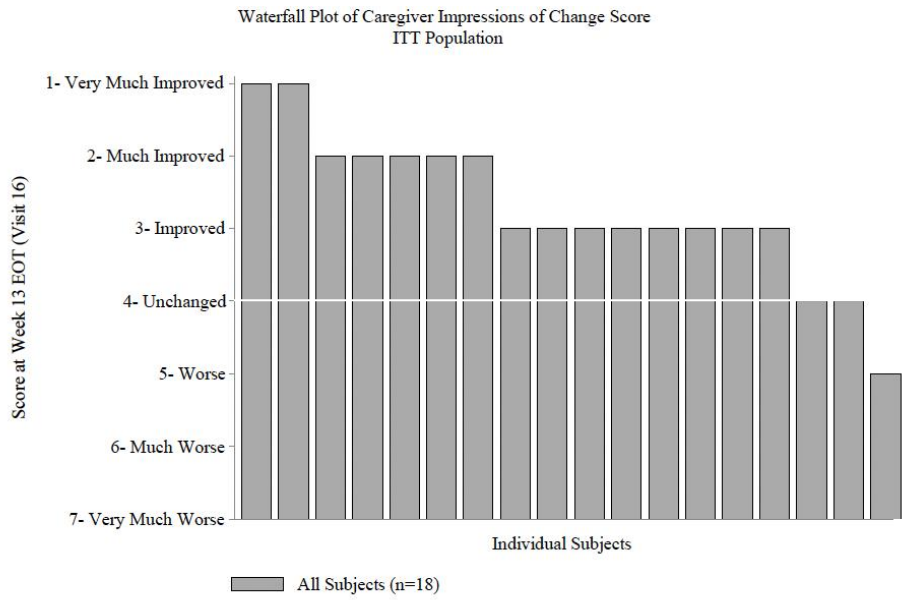
Mean CGI-I score of 2.4 with 16 out of 18 children showing improvement

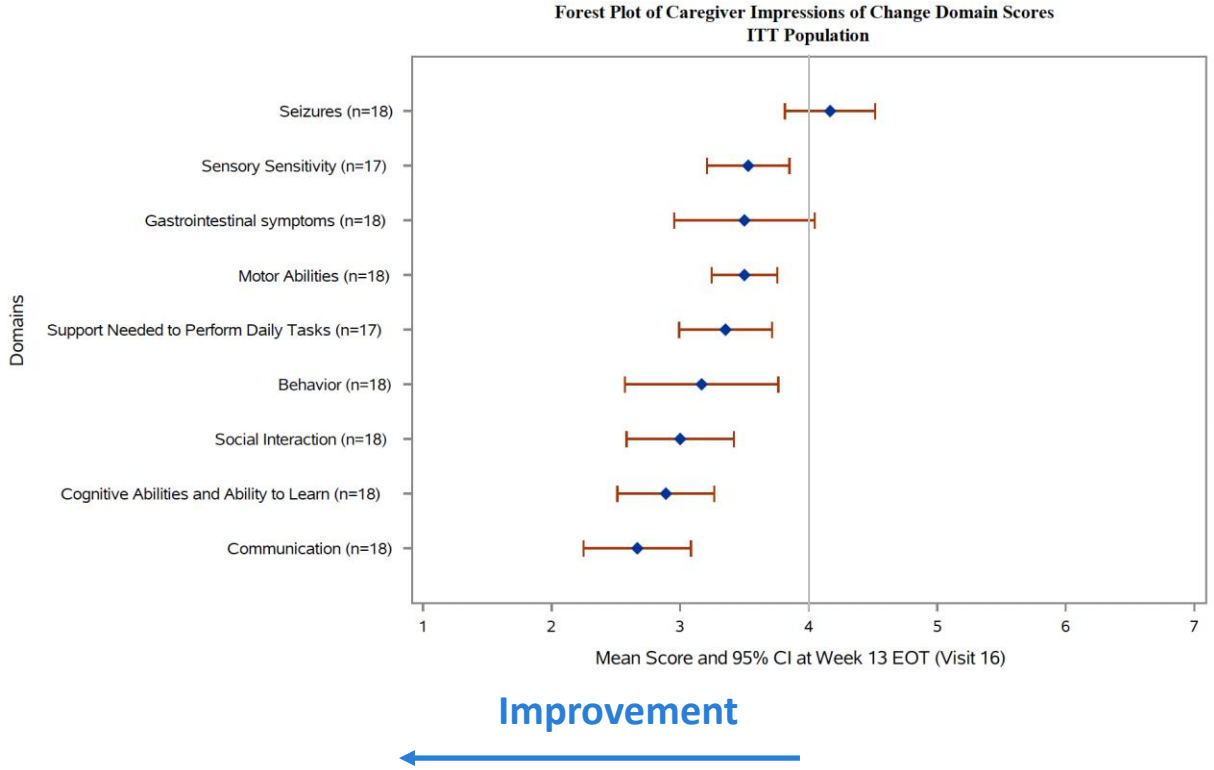




PMS CIC (caregiver) results by subject and by domain

Mean CIC score of 2.7 with 15 out of 18 children showing improvement



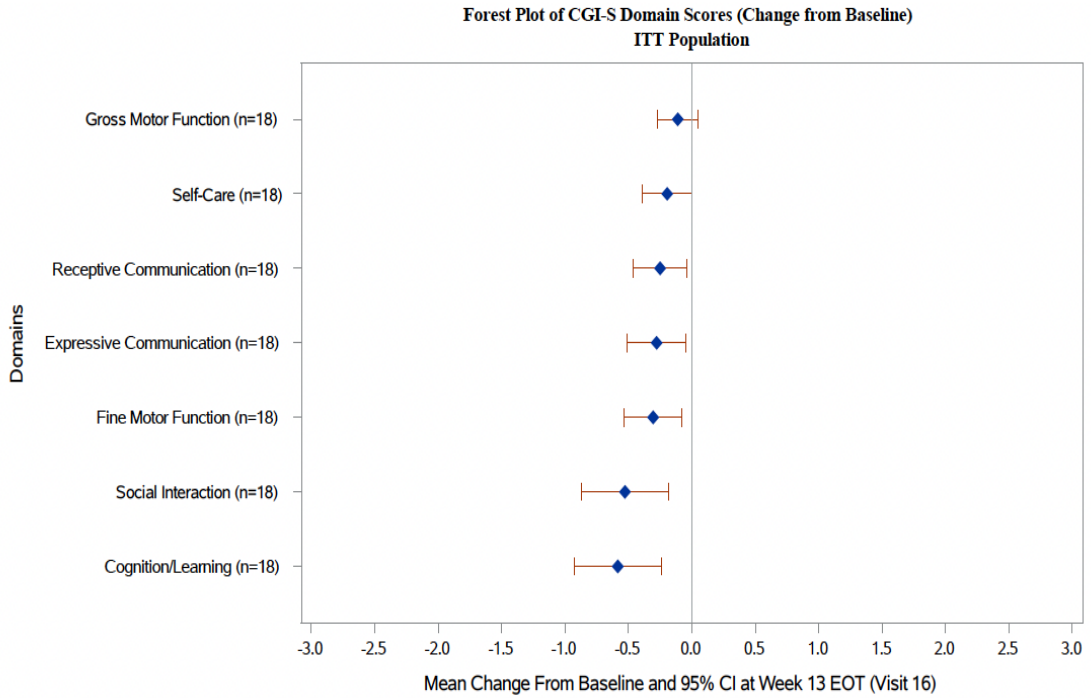


Improvement

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

7 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, behaviour, social interaction, self-care)

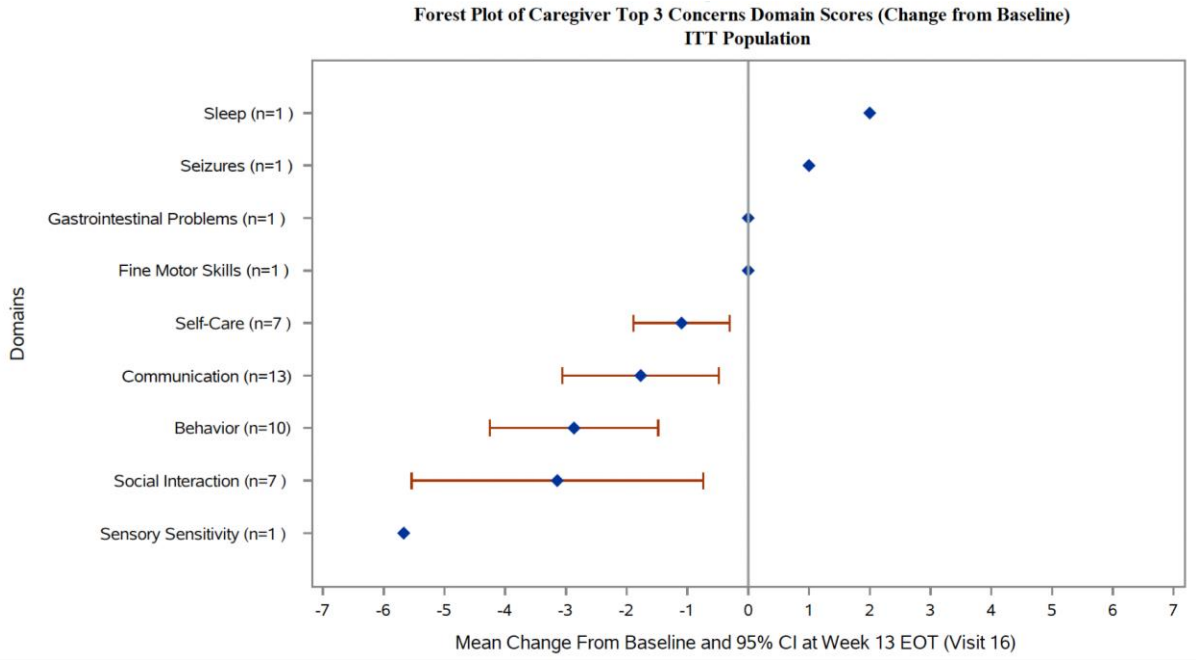
CGI-S domains



Improvement

Caregiver Top 3 Concerns

(Domains based on frequency of nomination)



Improvement

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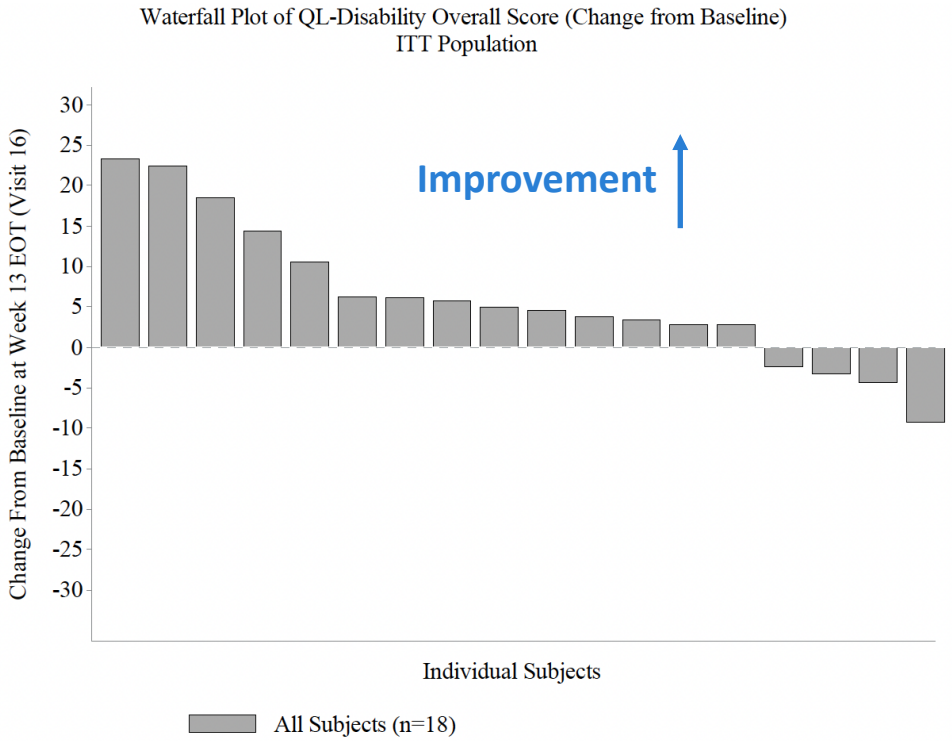
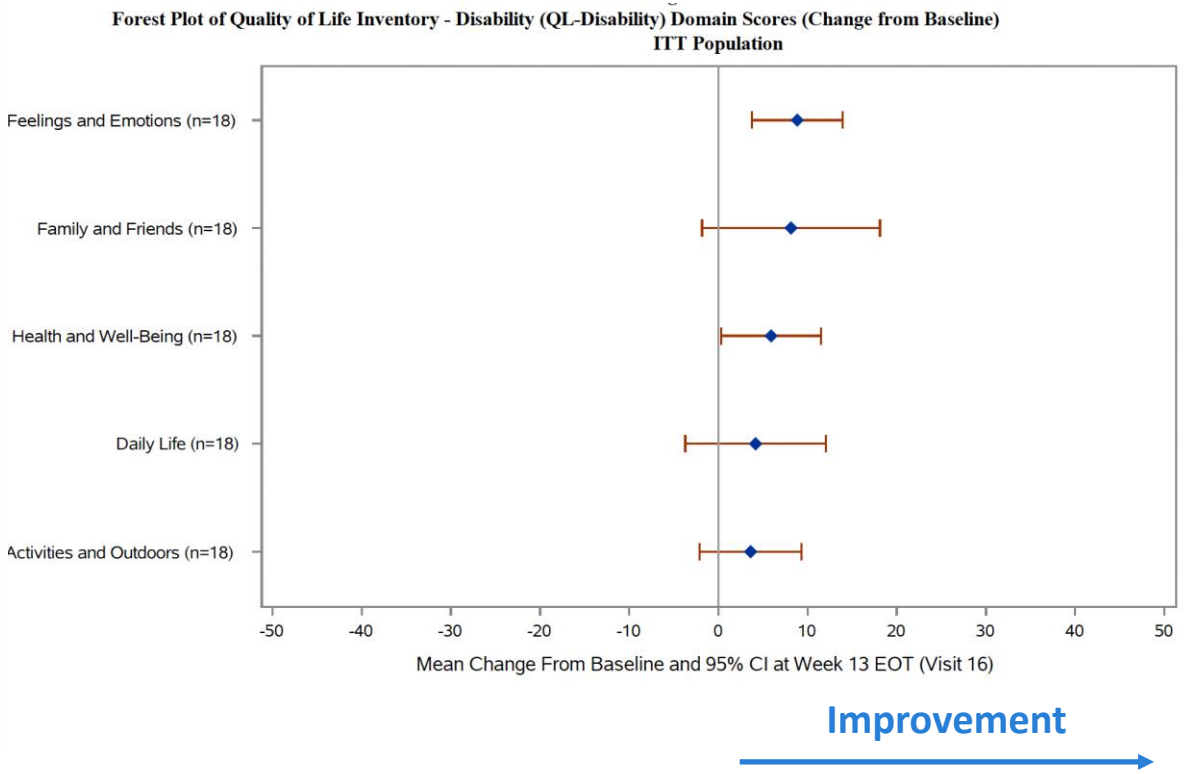
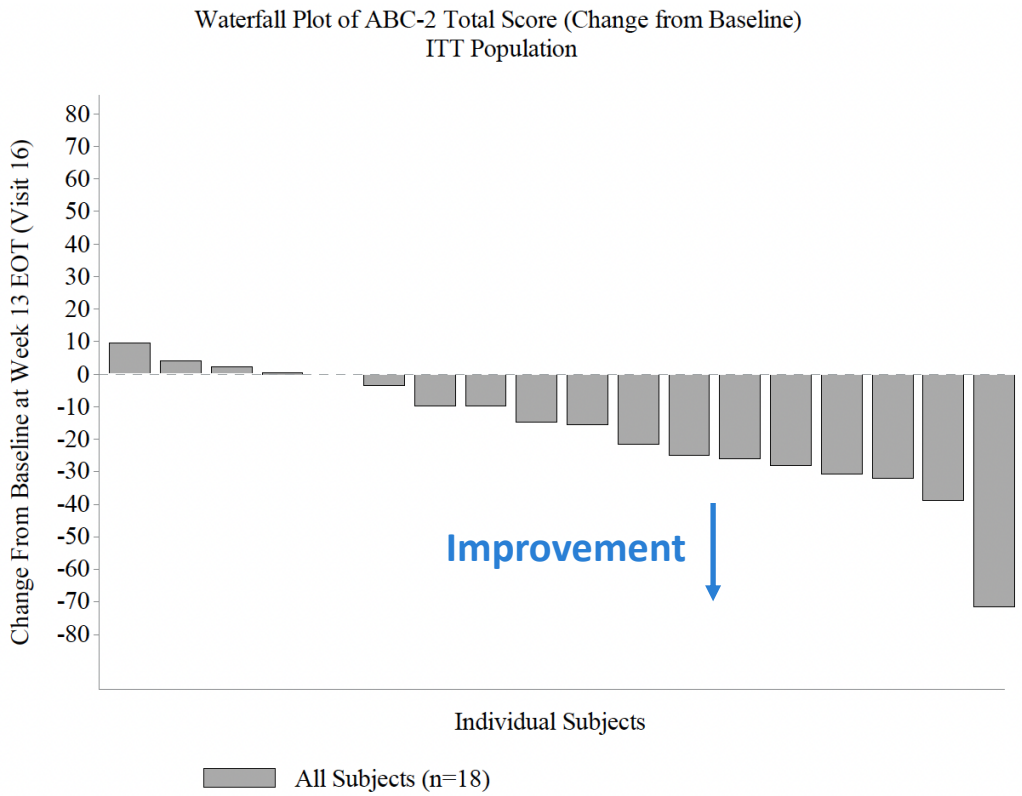
Quality of Life Inventory-Disability results by subject and by subscale

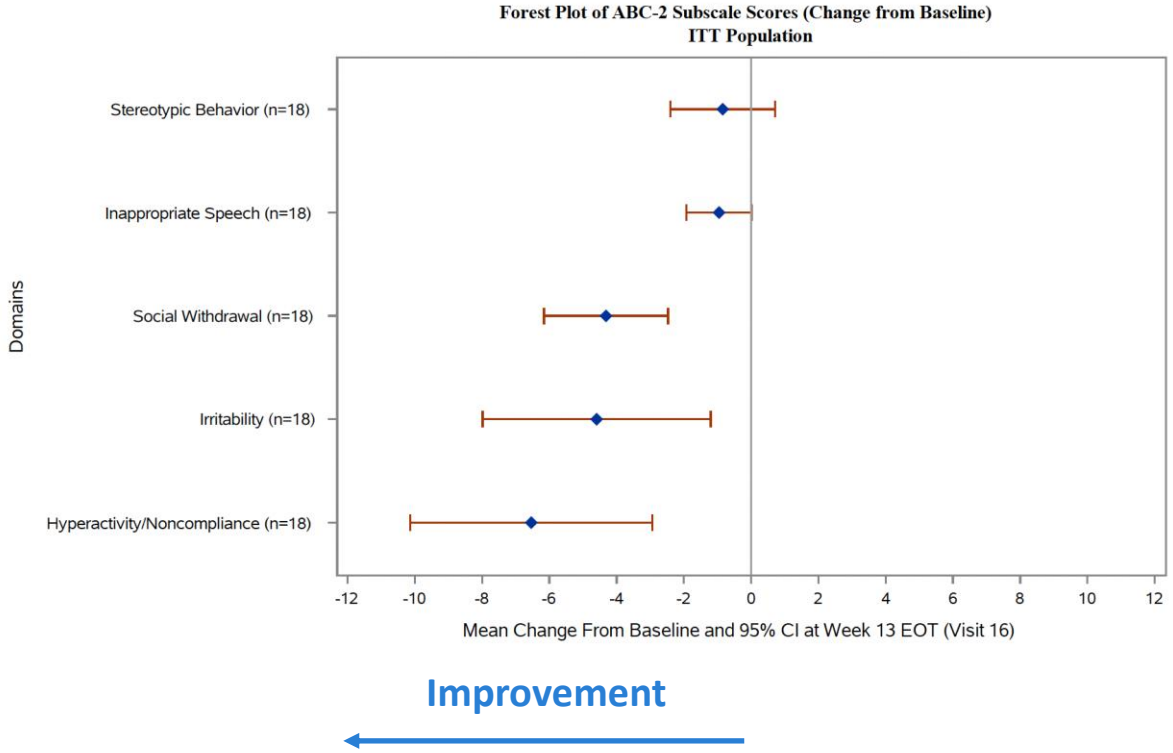




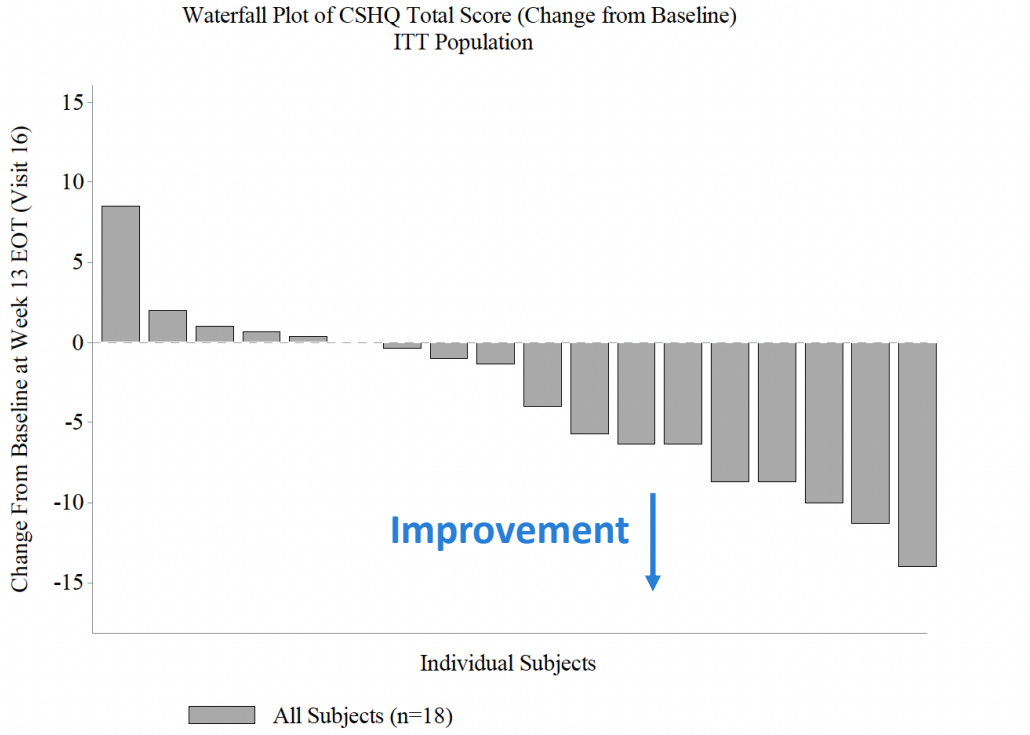
Aberrant Behavior Checklist-2 results by subject and by subscale

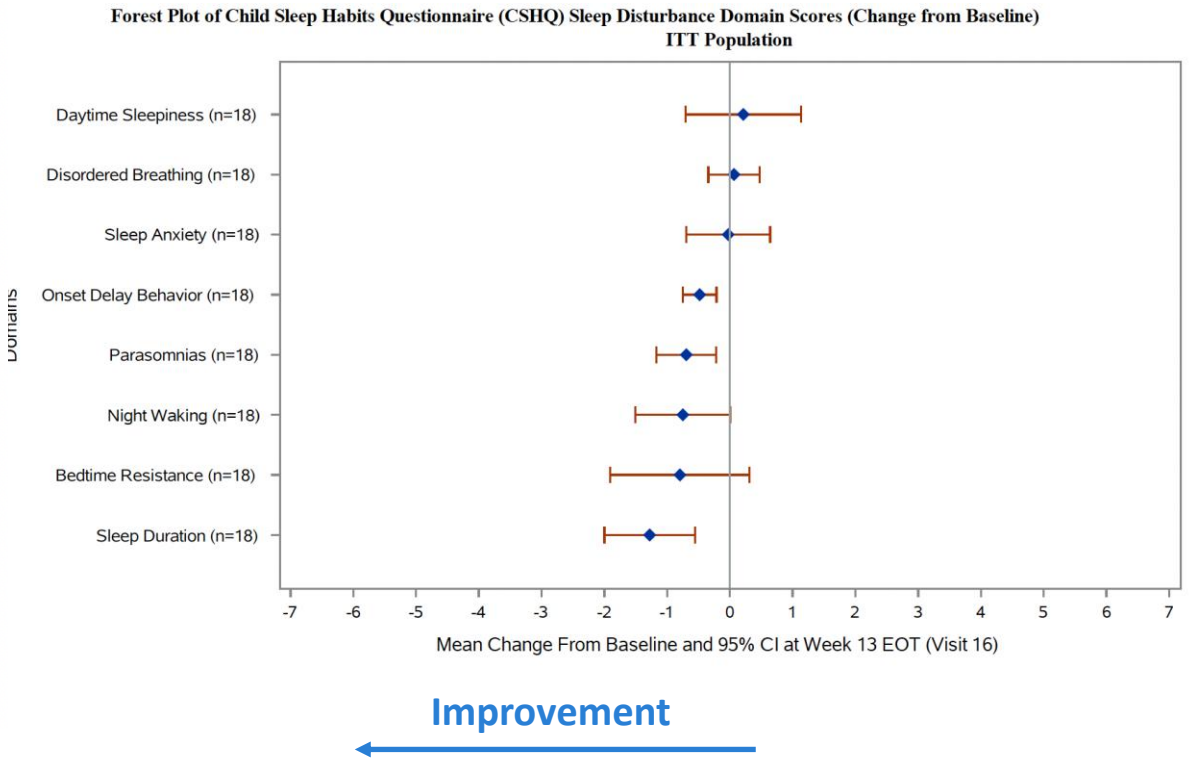


Subjects with a score of zero not shown



Child Sleep Habits Questionnaire results by subject and by subscale





Subjects with a score of zero not shown

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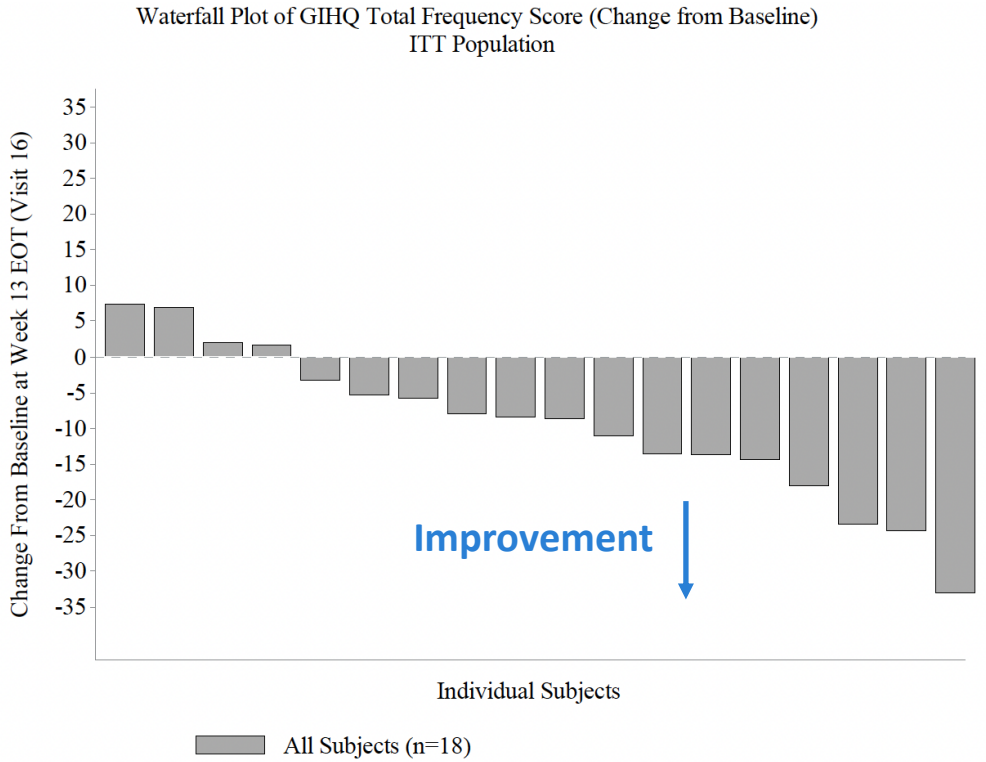
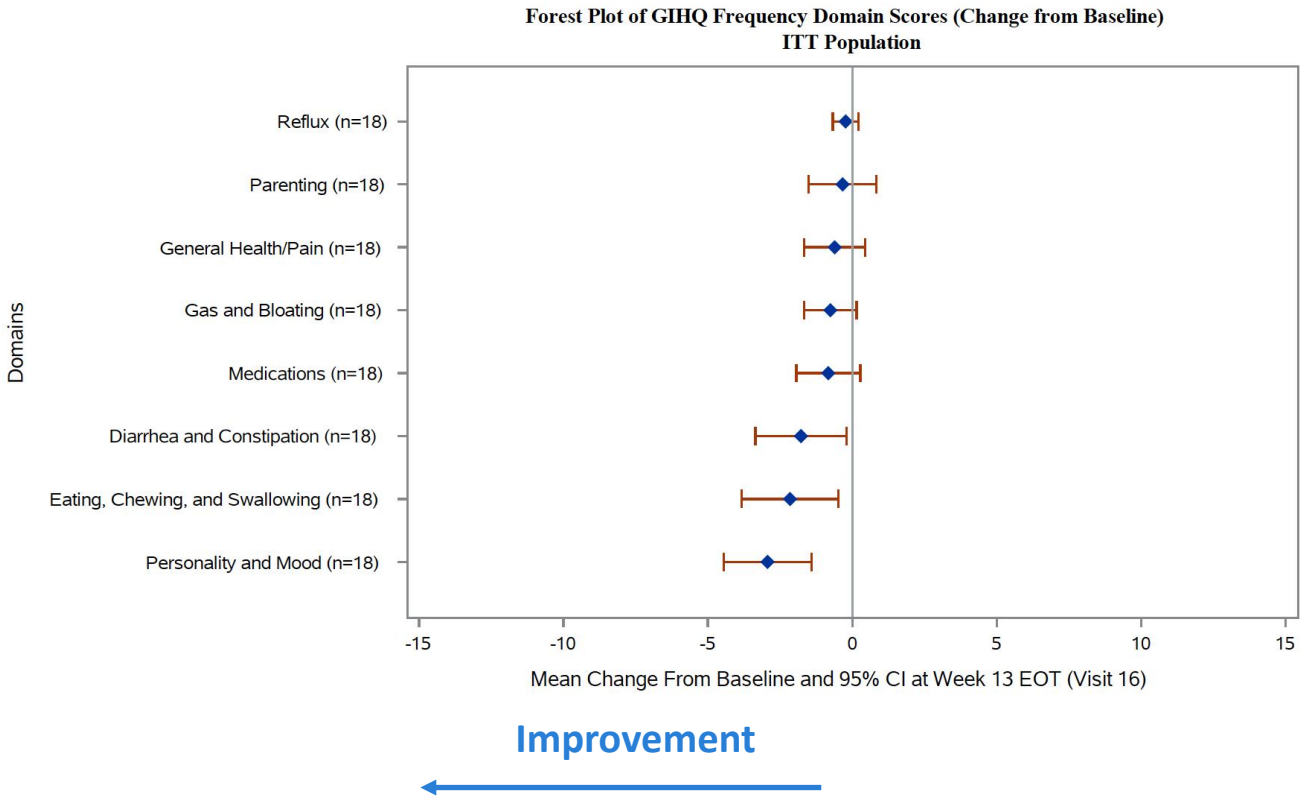
Gastrointestinal Health Questionnaire results by subject and by subscale





Acknowledgment: GIHQ developed by Kathleen J. Motil, MD, PhD, Baylor College of Medicine

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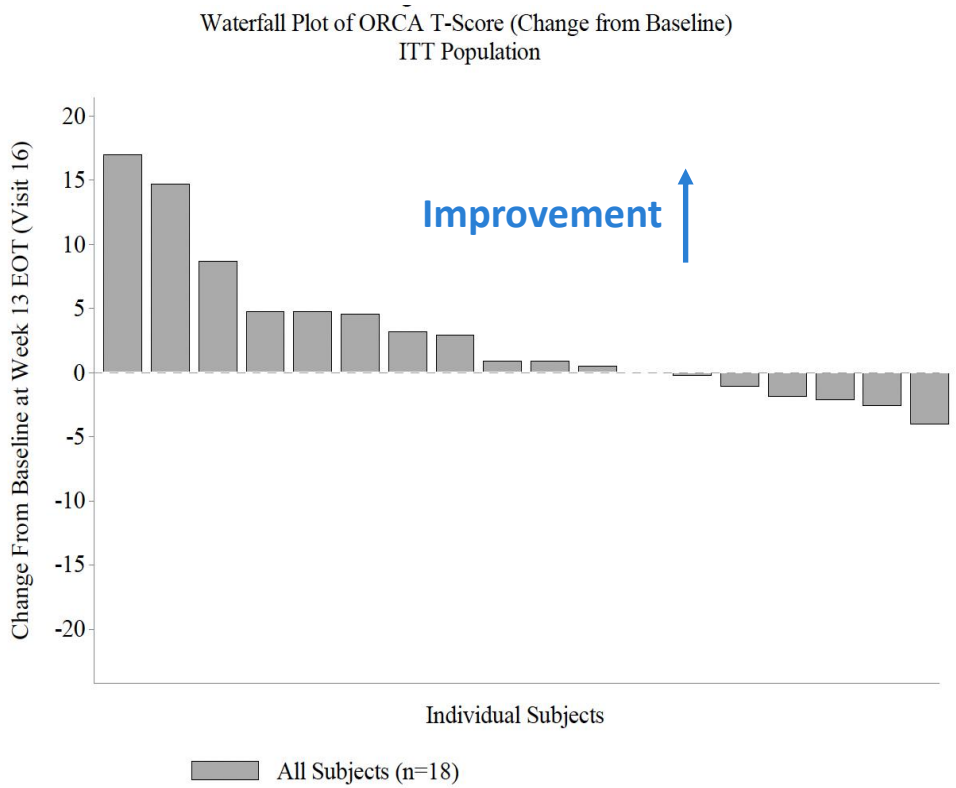
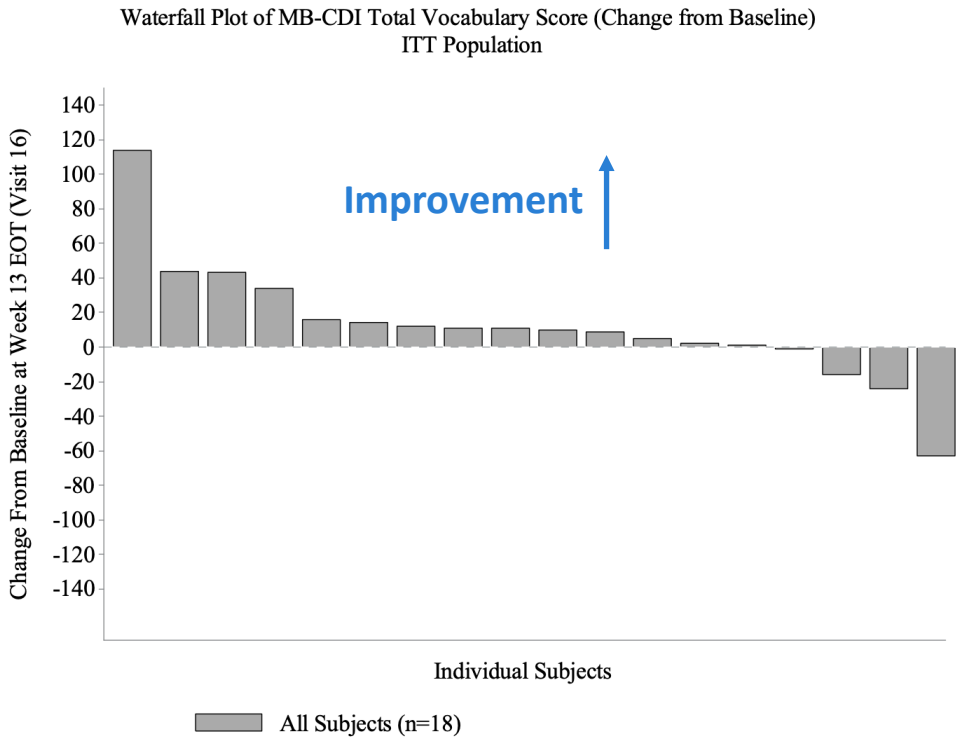
ORCA T-Score and MB-CDI Total Vocabulary results by subject

Improvements in communication observed in ORCA T-Score and MB-CDI Total Vocabulary, as well as domains/subscales in CGI-I, CGI-S, CIC and Caregiver Top 3 Concerns

ORCA T-Score



MB-CDI Total Vocabulary



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Clinician and caregiver testimonials

Clinicians

"Marked improvement in expressive language and moderate improvement in socialization."

"Teachers noted improvement in learning new skills."

"Able to focus work at school, both to the things they always enjoy and new tasks."

"Expressive communication- significant improvement in using more complex phrases, better back and forth communication. Better expressing needs. Some commentary on how mom is feeling, "I want you to be happy"."

"Expressive communication- babbling much more than baseline."

"A few 1-2 word phrases that were not at baseline "oh boy", "Hi Mama", "I love you", "oh my"."

"Gross motor- Stronger climbing ladders, comes downstairs which never did before, Walks upstairs without help (needed help at baseline)."

Caregivers

"Using more words while retaining eye contact… Improved pretend play… Initiating eye contact"

"Less scripting, less stimming… More flexible with changes… In general, they are more safe-even at bus stop"

"More focused , engaged, aware of their environment, people."

"So much happier, not throwing self to ground when can't get his way"

"More attentive and it makes for an easy learner, Now can focus better on what we are trying to teach."

"Attention span is great right now… He can focus long enough to complete tasks and try new things."

"Can now run instead of walking fast… Good balance, not needing assistance on stairs."

Pitt Hopkins syndrome (PTHS)

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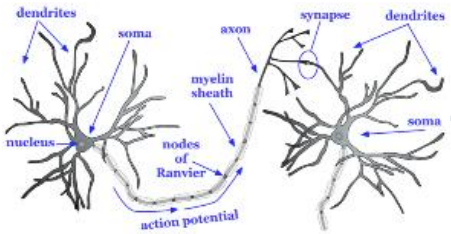
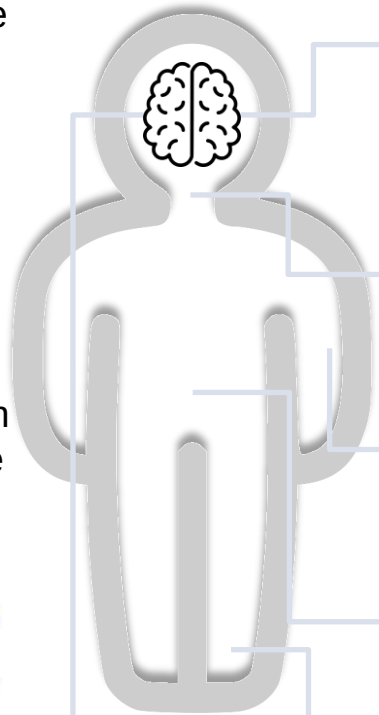
PTHS overview

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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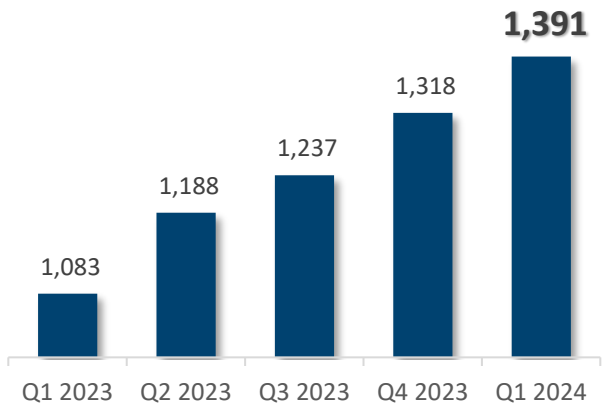
PTHS is historically under-diagnosed, but this is changing

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
neuren pharmaceuticals	**Successful Phase 2**
#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

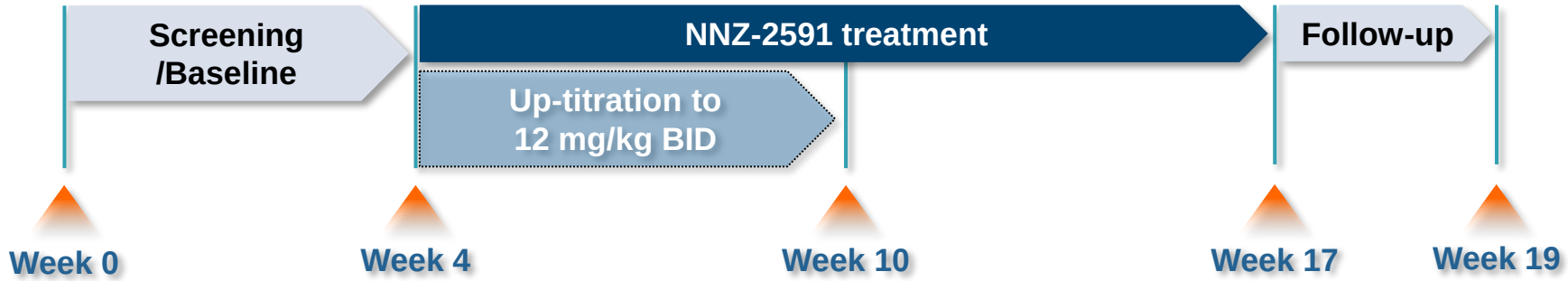
Neuren's Phase 2 trial in children with PTHS

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

n subjects: 16

Age range: 3 to 17 (mean 9.1)



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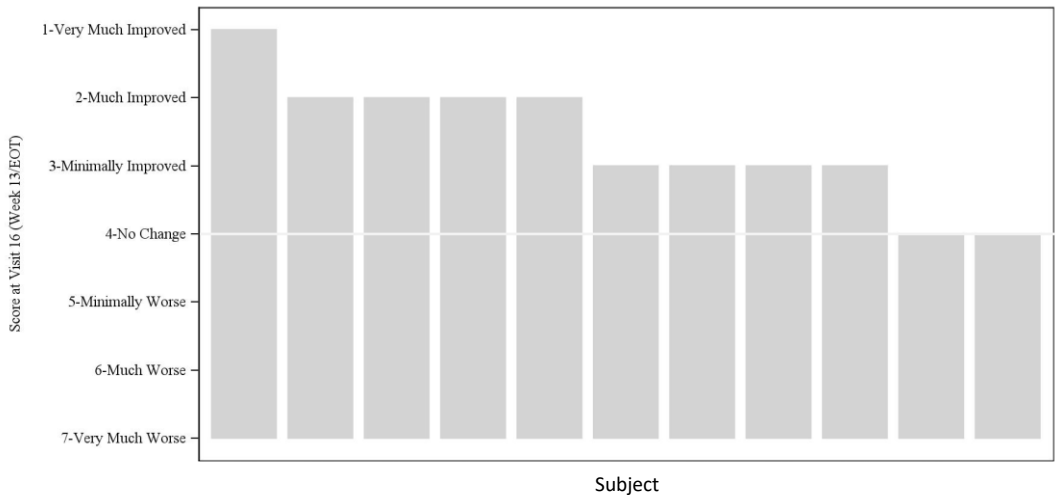
PTHS CGI-I (clinician) results by subject and by domain

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

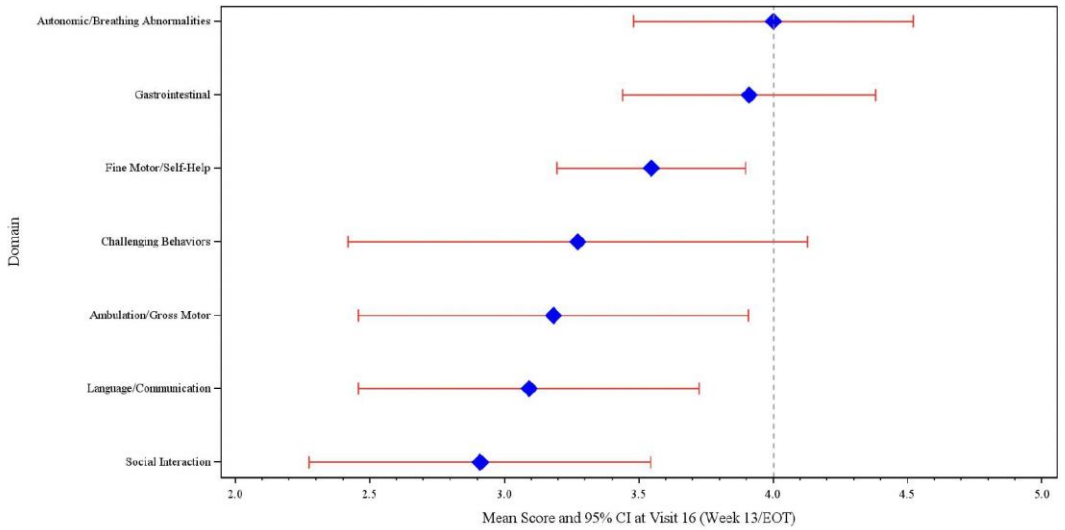
CGI-I Overall Score by subject

MITT Population



Forest Plot of mean CGI-I Domain Scores

MITT Population



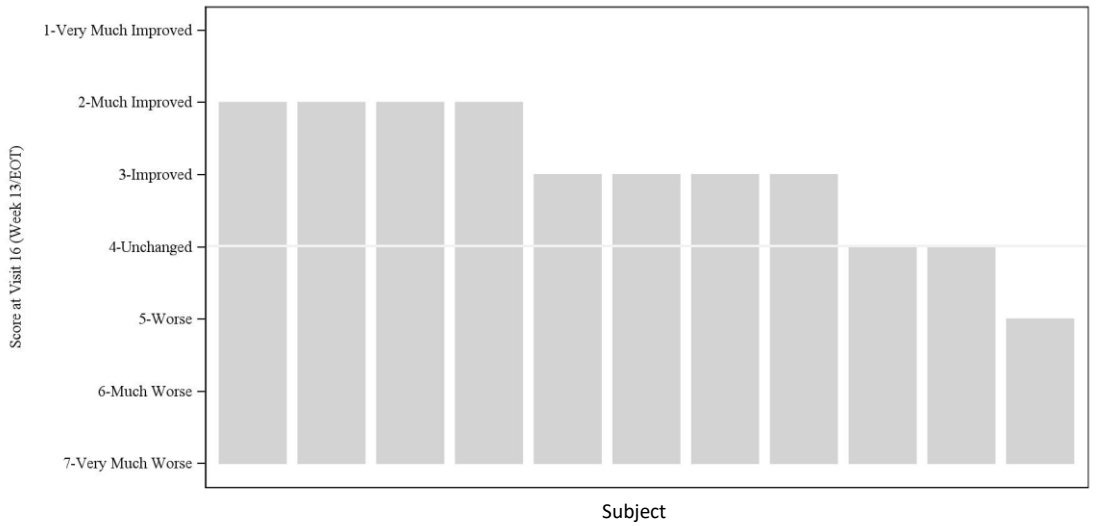
Improvement

PTHS CIC (caregiver) results by subject and by domain

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

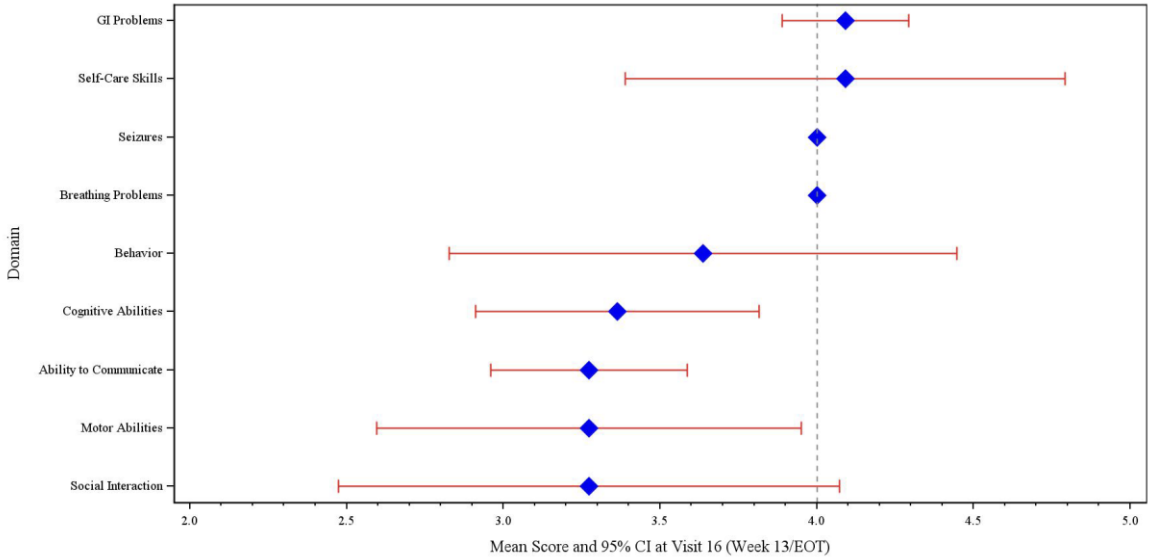
CIC Overall Score by subject

MITT Population



Forest Plot of mean CIC Domain Scores

MITT Population

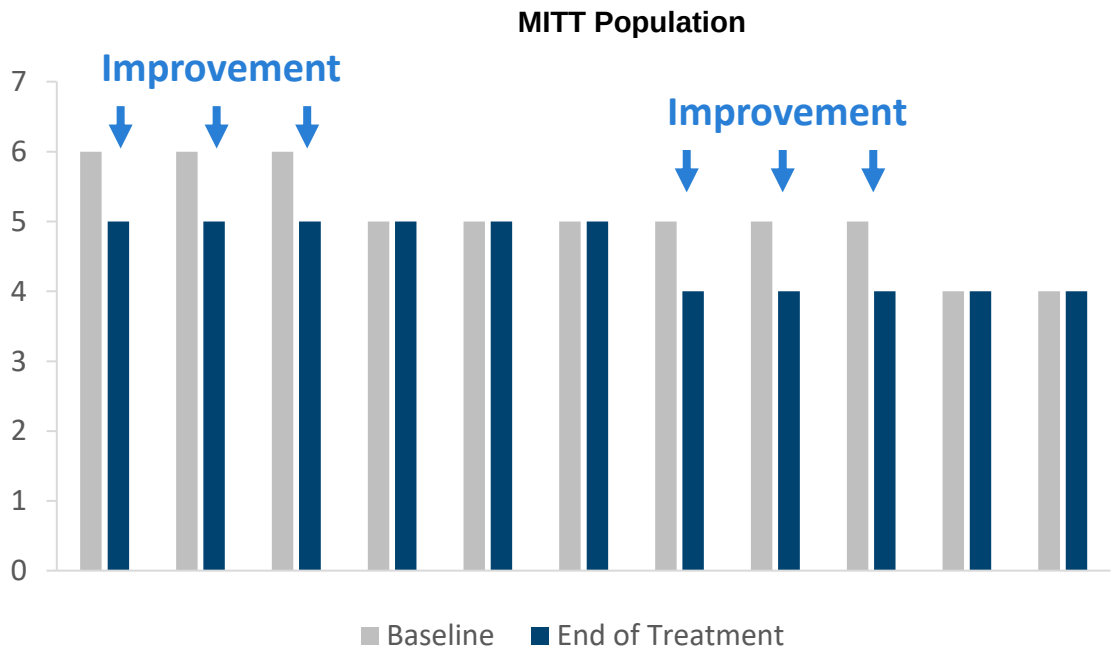


Improvement

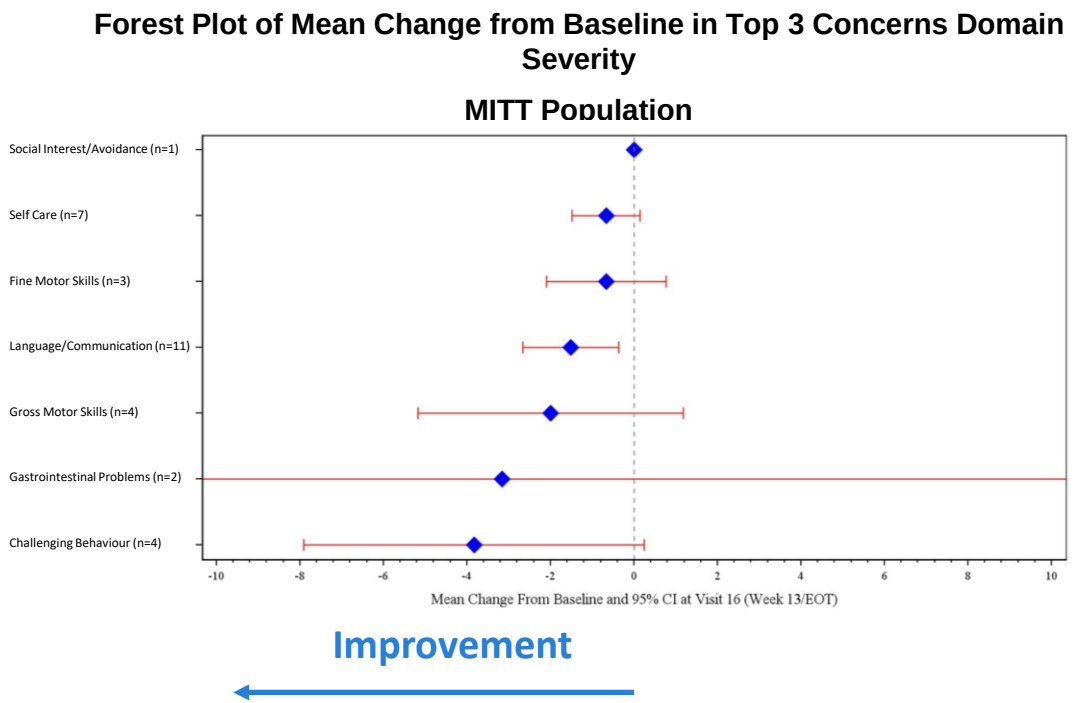
PTHS Clinical Global Impression of Severity (CGI-S) and Caregiver Top 3 Concerns results by domain

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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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."

Highlights

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Highlights

1

DAYBUE™ (trofinetide) approved by US FDA as the first and only treatment for Rett syndrome, launched by partner Acadia in Apr 2023

2

Total economics to Neuren from global trofinetide partnership with Acadia up to US$1bn[1] plus 10 to low 20s % royalties

3

Successful DAYBUE US launch, with 2023 net sales of US$177m and 2024E net sales of US$370-420m[2]

4

Accelerating Phase 2 development of NNZ-2591 in multiple indications. Positive results for Phelan-McDermid syndrome and Pitt Hopkins syndrome

5

NNZ-2591 novel mechanism of action has many more potential applications, with Rett and Fragile X licensed to Acadia

6

A$243m cash at 31 Mar 2024 – well positioned to maximize the benefits of all value creating opportunities

[1] Including payments already received and future payments
[2] Acadia guidance reiterated in First Quarter 2024 Financial Results announcement in May 2024

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