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NNZ-2591
Phelan-McDermid syndrome
Phase 2 trial top-line results

18 December 2023

IMPROVING THE LIVES OF PEOPLE WITH NEURODEVELOPMENTAL DISABILITIES

Forward looking statements

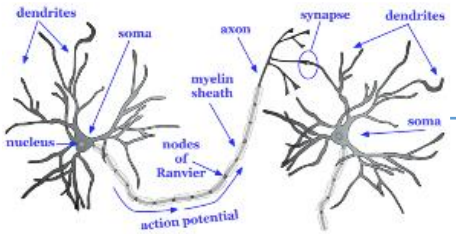
This presentation contains forward looking statements that involve risks and uncertainties. Although we believe that the expectations reflected in the forward looking statements are reasonable at this time, Neuren can give no assurance that these expectations will prove to be correct. Actual results 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.

Phelan-McDermid syndrome has overwhelming unmet medical need

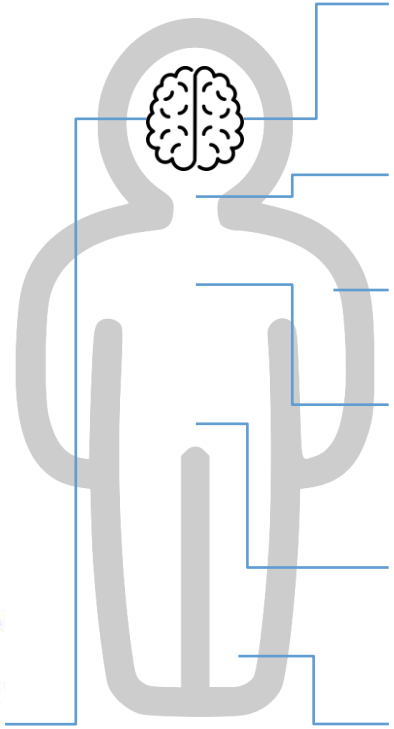
Cause of the syndrome

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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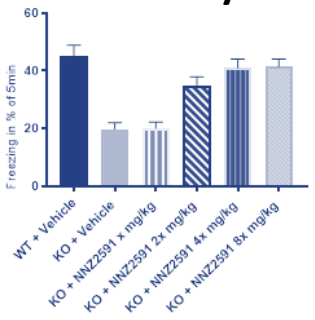
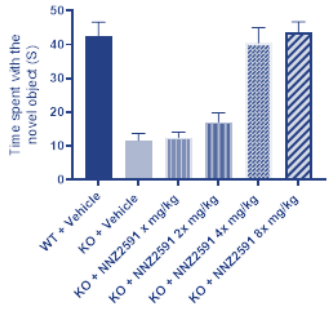
Consistent efficacy and clear dose response for NNZ-2591 in shank3 model

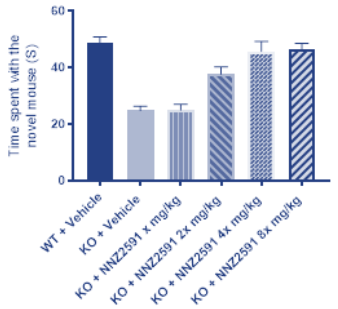
Memory



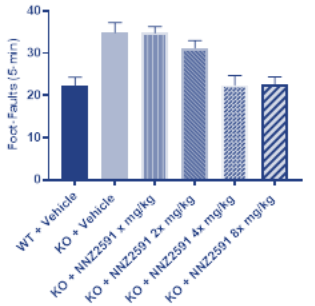
Learning



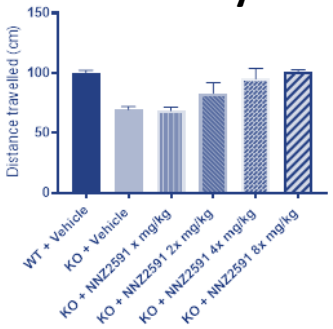
Sociability



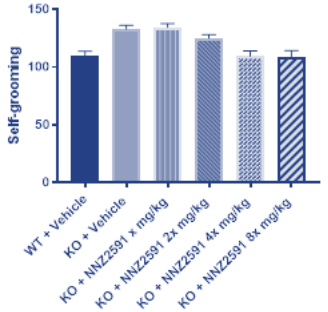
Motor function



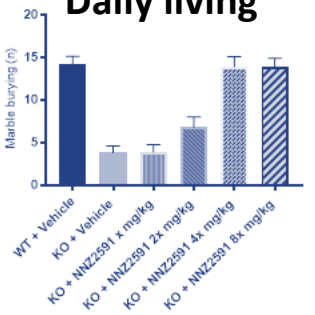
Anxiety



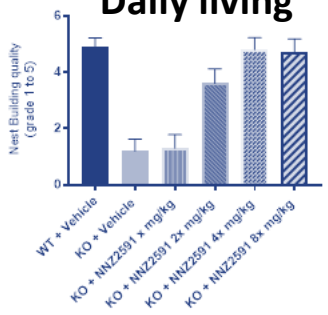
Repetitive behavior



Daily living



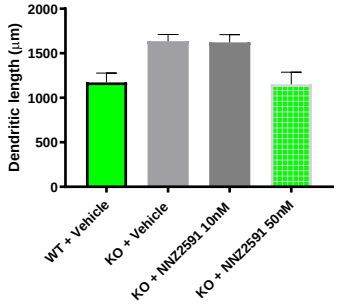
Daily living

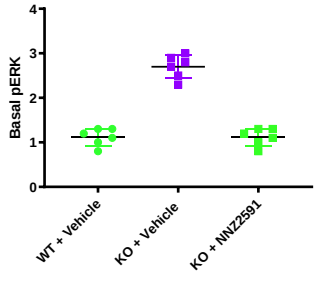


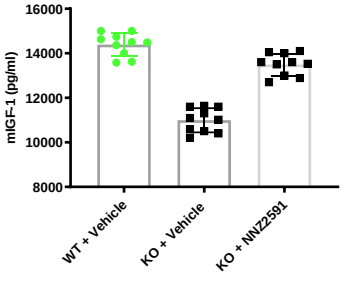
Incidence of audiogenic seizures

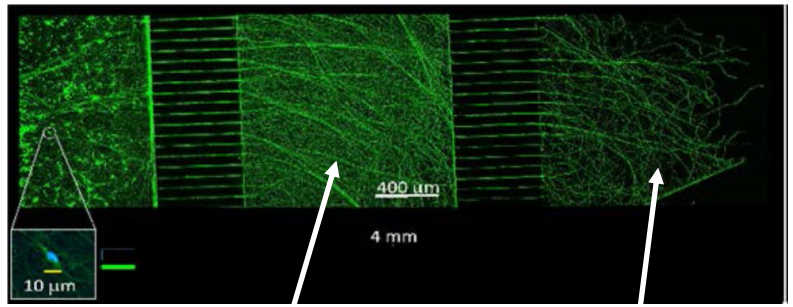
WT + vehicle	0%
KO + vehicle	60%
KO + x mg/kg	50%
KO + 2x mg/kg	30%
KO + 4x mg/kg	10%
KO + 8x mg/kg	10%

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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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:**
  - **Clinical Global Impression of Improvement (CGI-I) – mean score of 2.4 with 16 out of 18 children showing improvement assessed by clinicians**
  - **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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Phase 2 Clinical Trial Design

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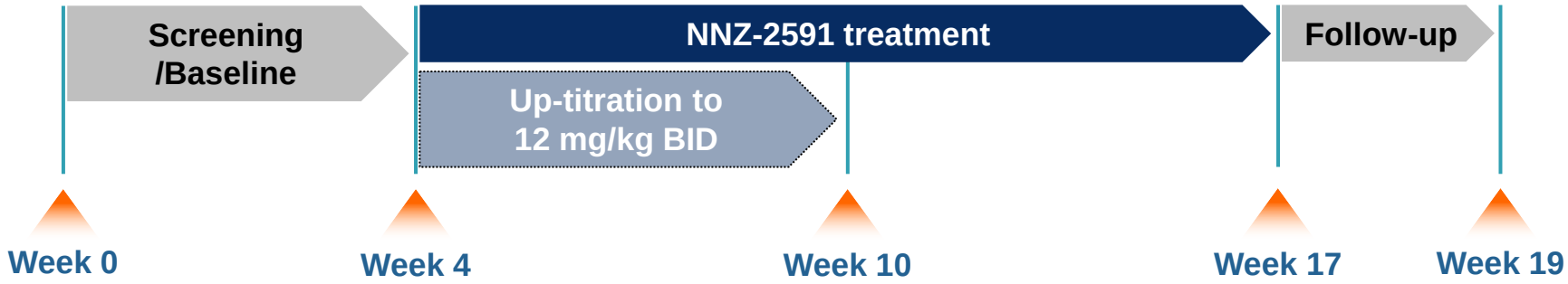
Neuren's Phase 2 trial in children with Phelan-McDermid syndrome

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: Up to 20

Age range: 3 to 12



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

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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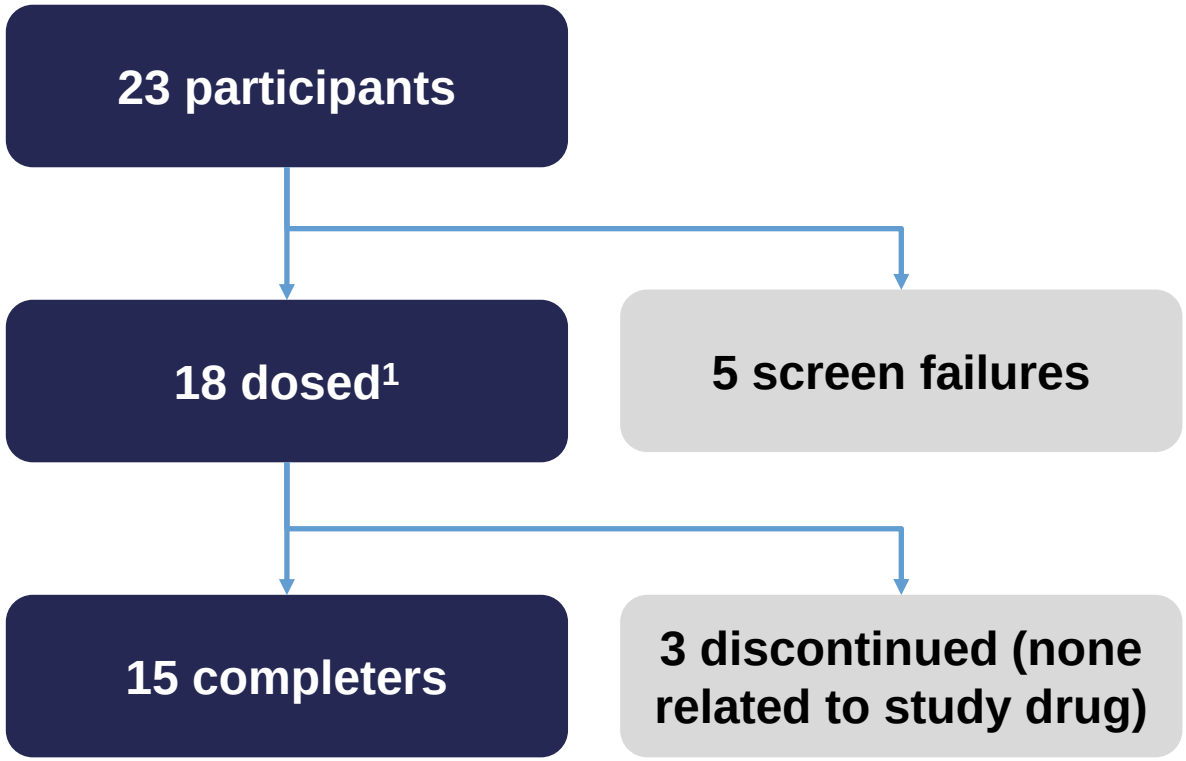
Participant disposition



[1] All 18 subjects contributed to safety and efficacy data

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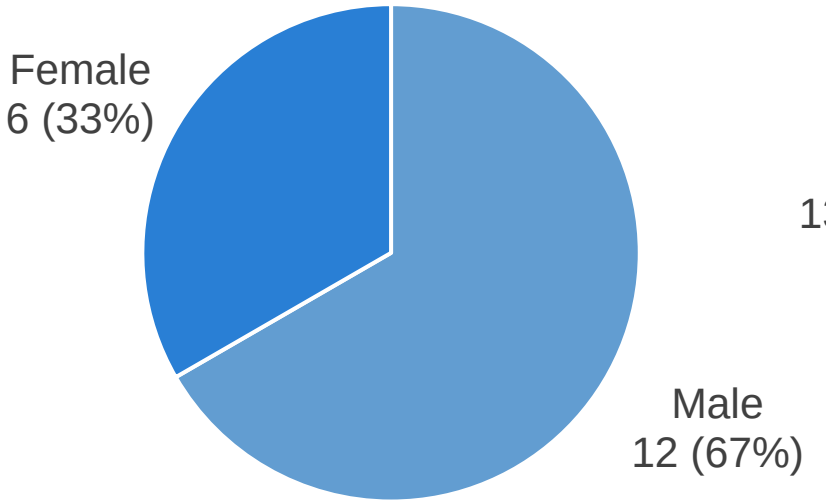
Dosed participant demographics

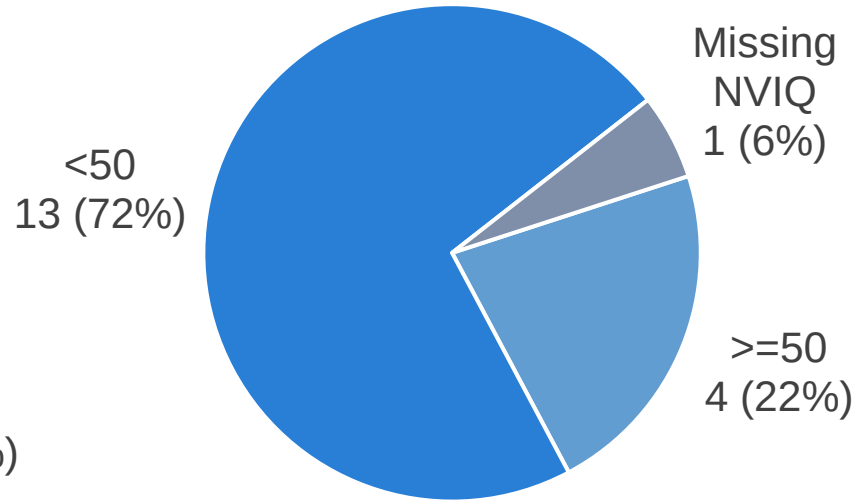
Age

Mean	8.6 yrs
Median	8.3 yrs
Min - Max	4.4 – 13.0 yrs

Sex



Cognitive level (non-verbal IQ/DQ)



Safety and Tolerability

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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	NNZ-2591 (N=18) n (%)	Event	NNZ-2591 (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)		

Efficacy

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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 CGI-I and CIC measures in PMS

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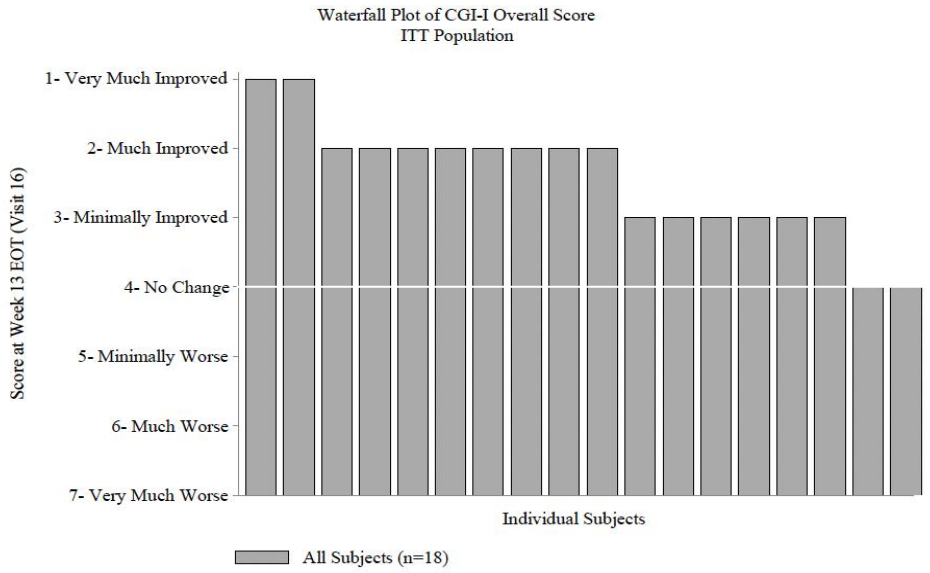
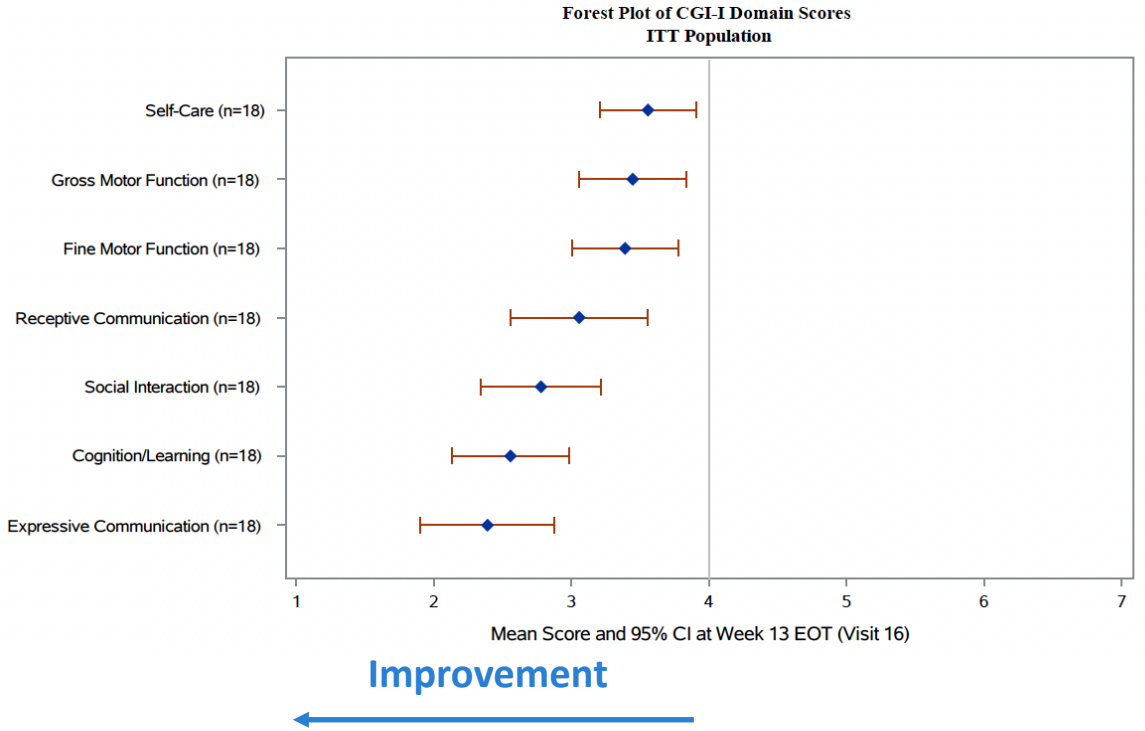
CGI-I (clinician) results by subject and by domain

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





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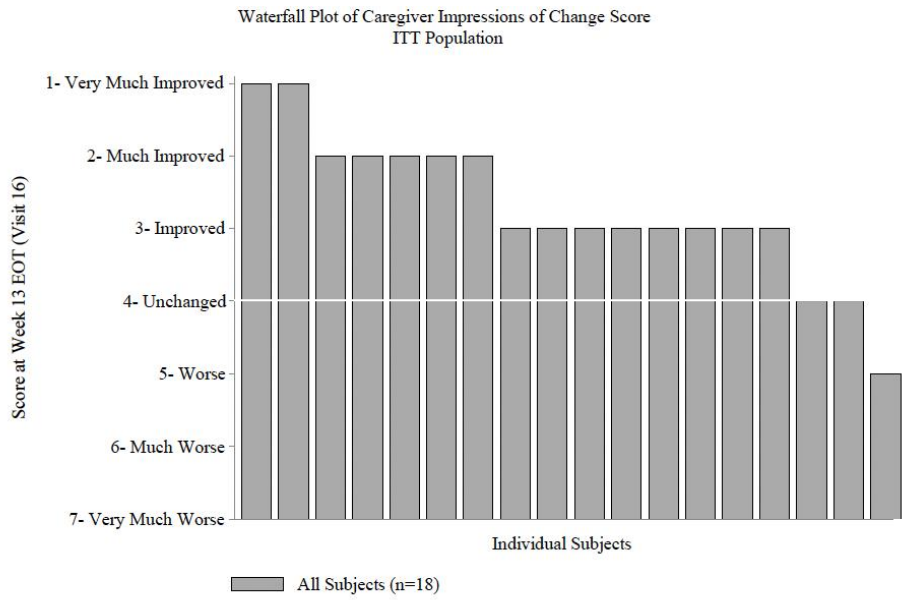
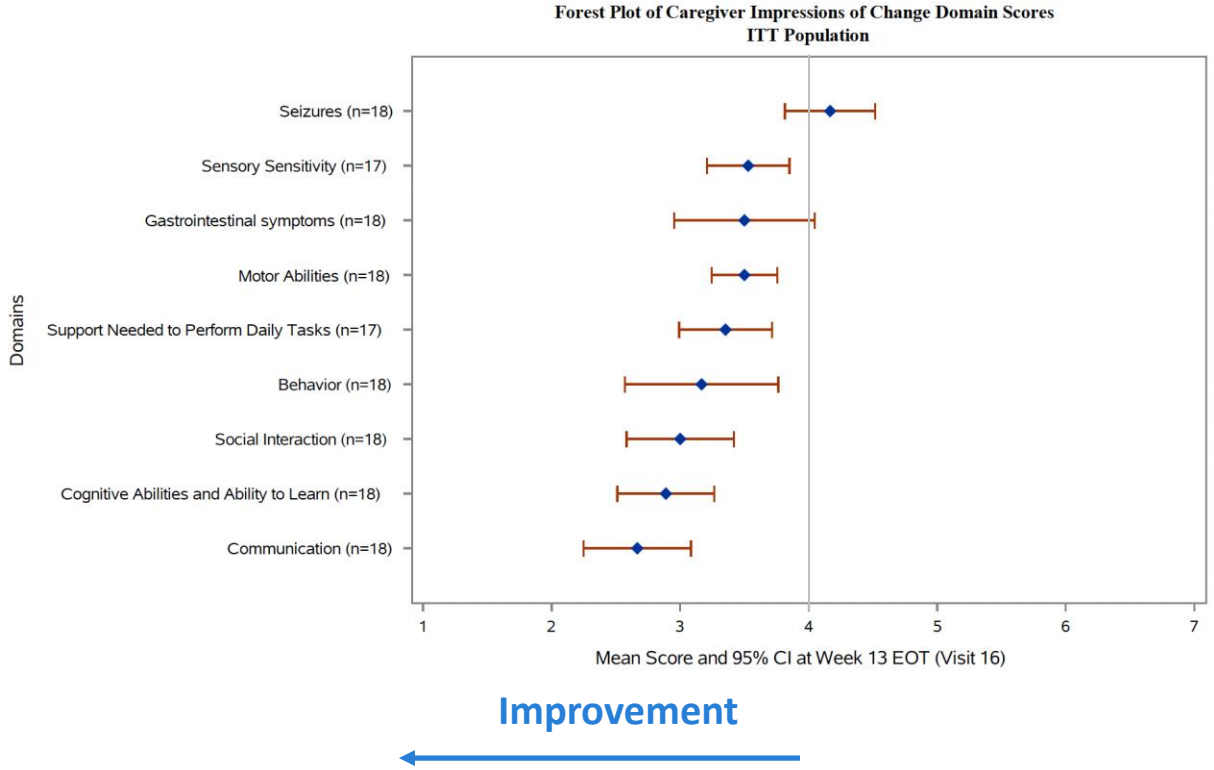
CIC (caregiver) results by subject and by domain

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



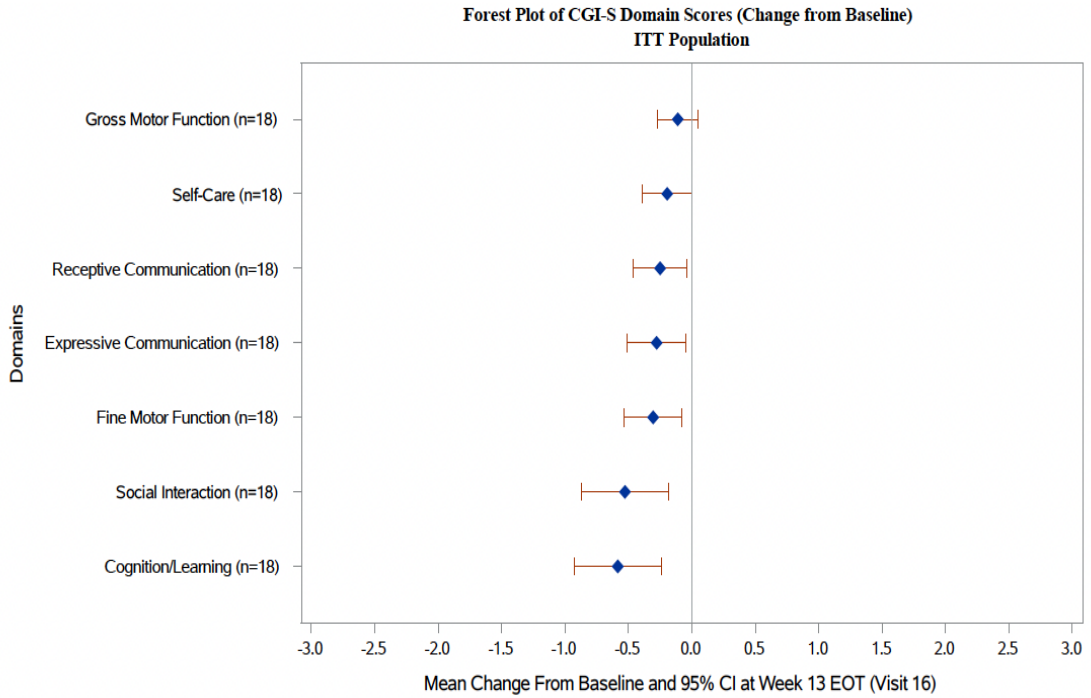


Improvement

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)

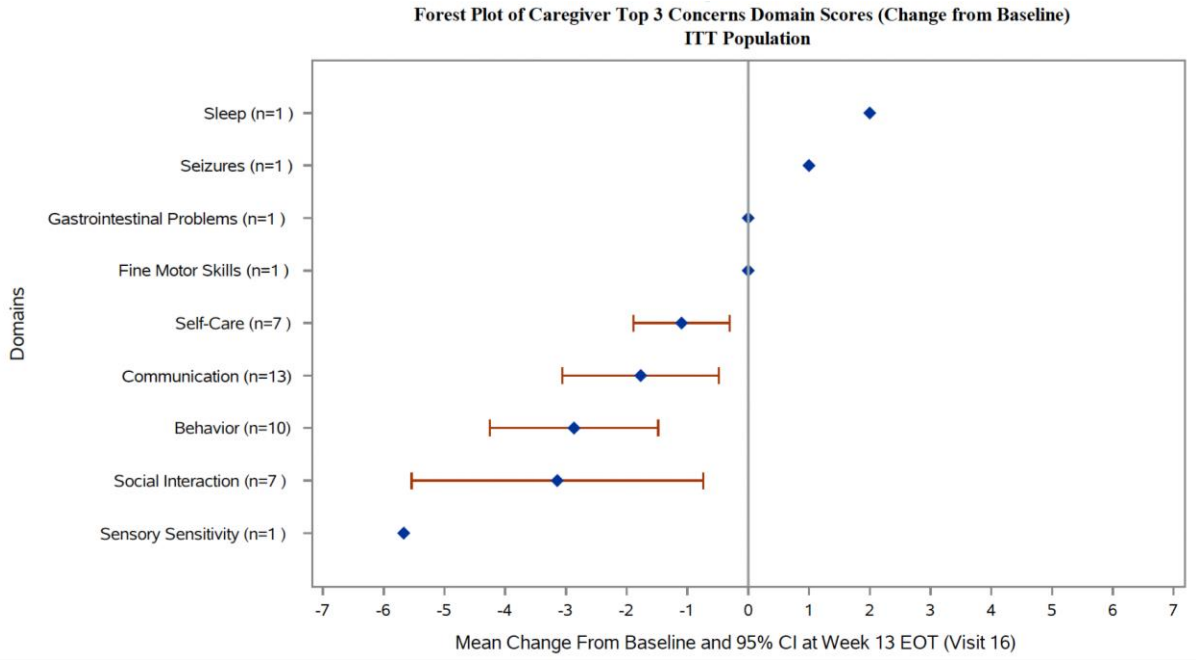
CGI-S domains



Improvement

Caregiver Top 3 Concerns

(Domains based on frequency of nomination)



Improvement

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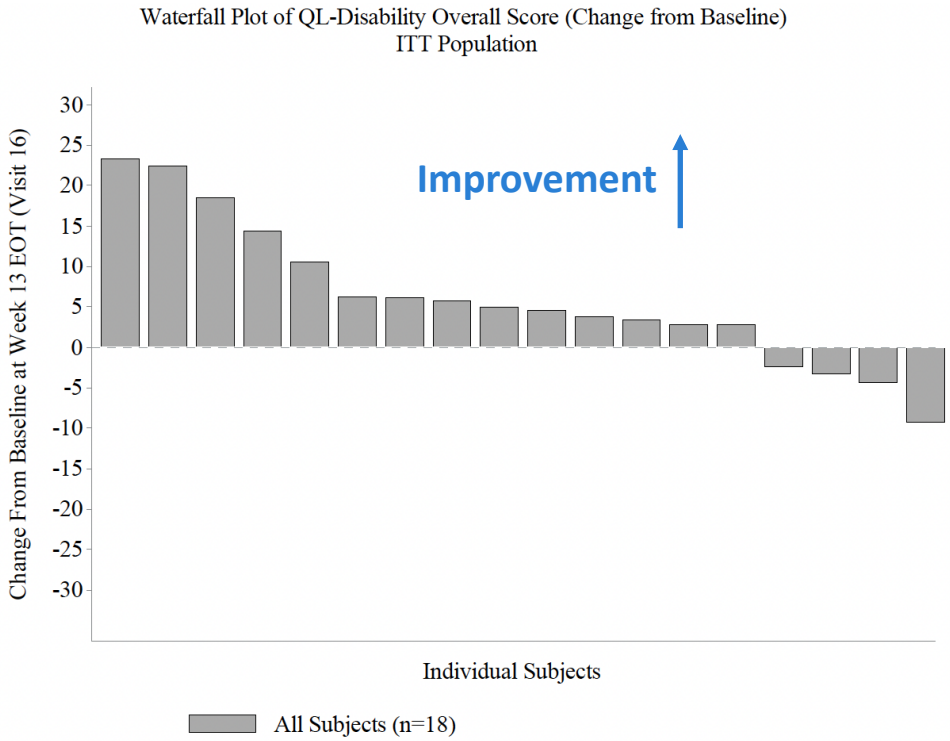
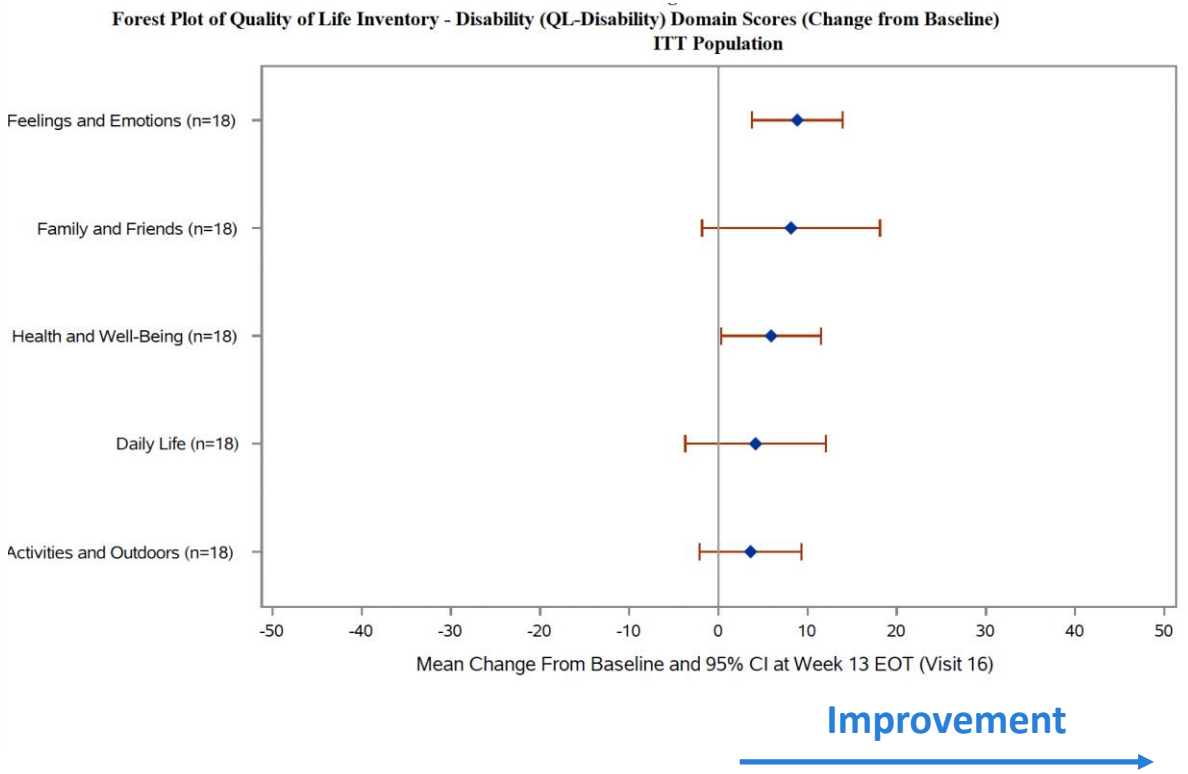
Quality of Life Inventory-Disability results by subject and by subscale





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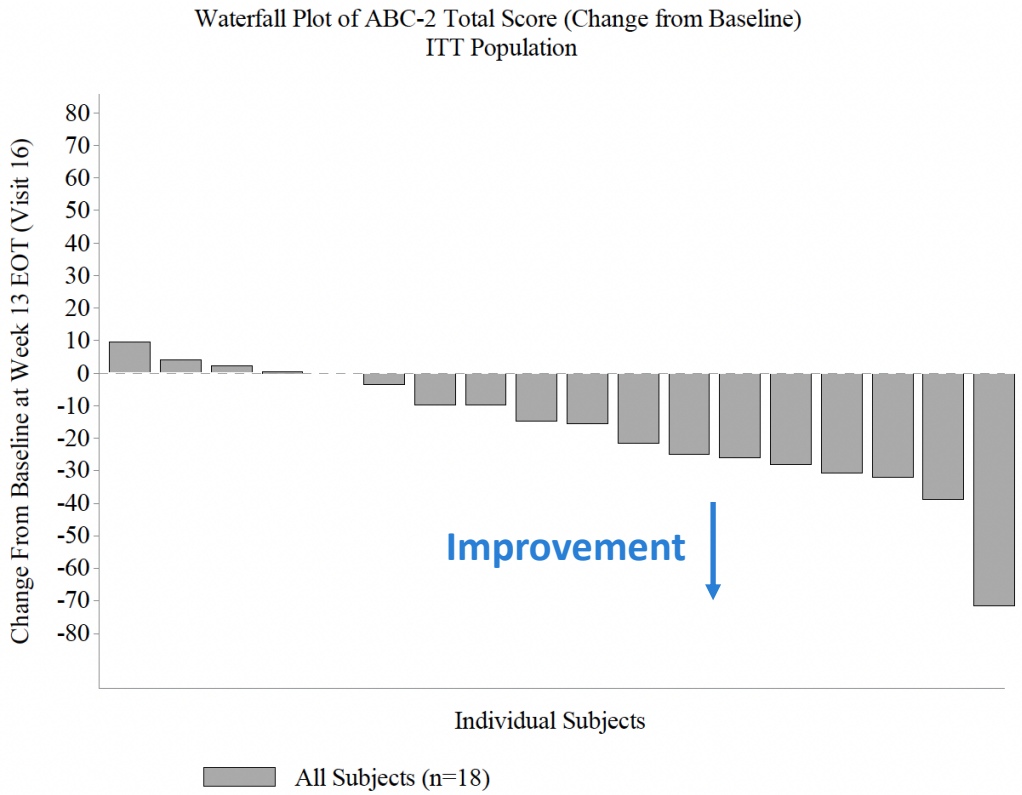
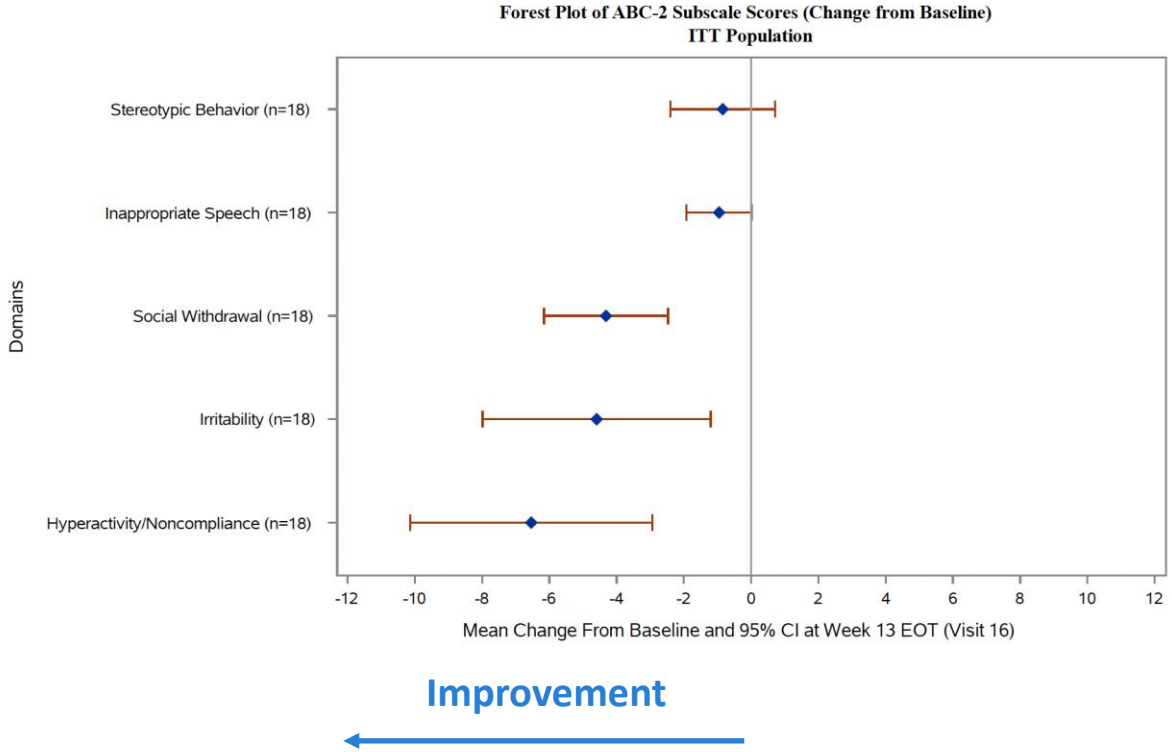
Aberrant Behavior Checklist-2 results by subject and by subscale



Subjects with a score of zero not shown



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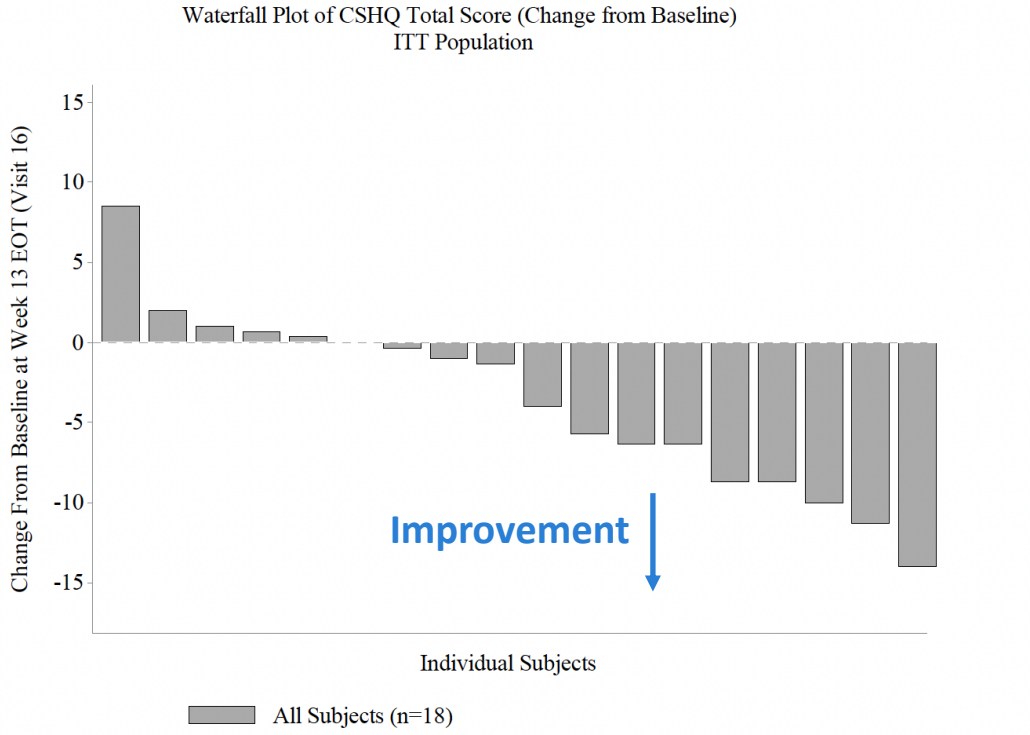
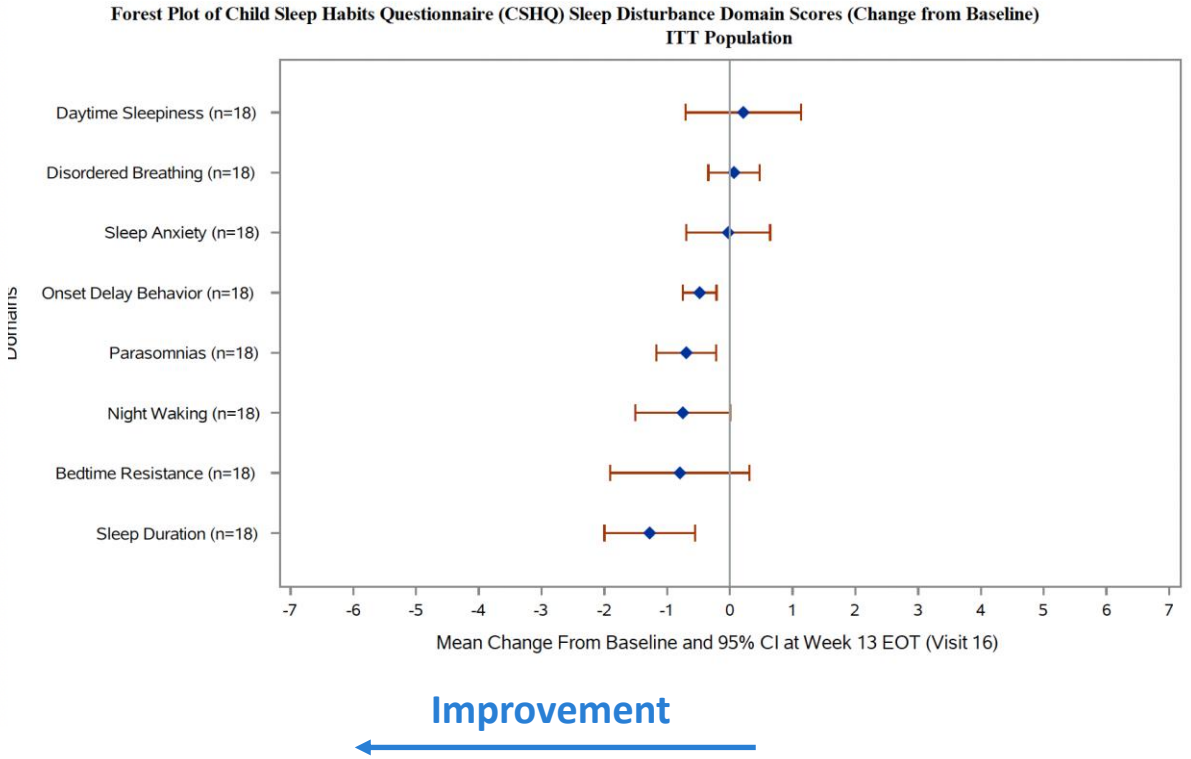
Child Sleep Habits Questionnaire results by subject and by subscale





Subjects with a score of zero not shown

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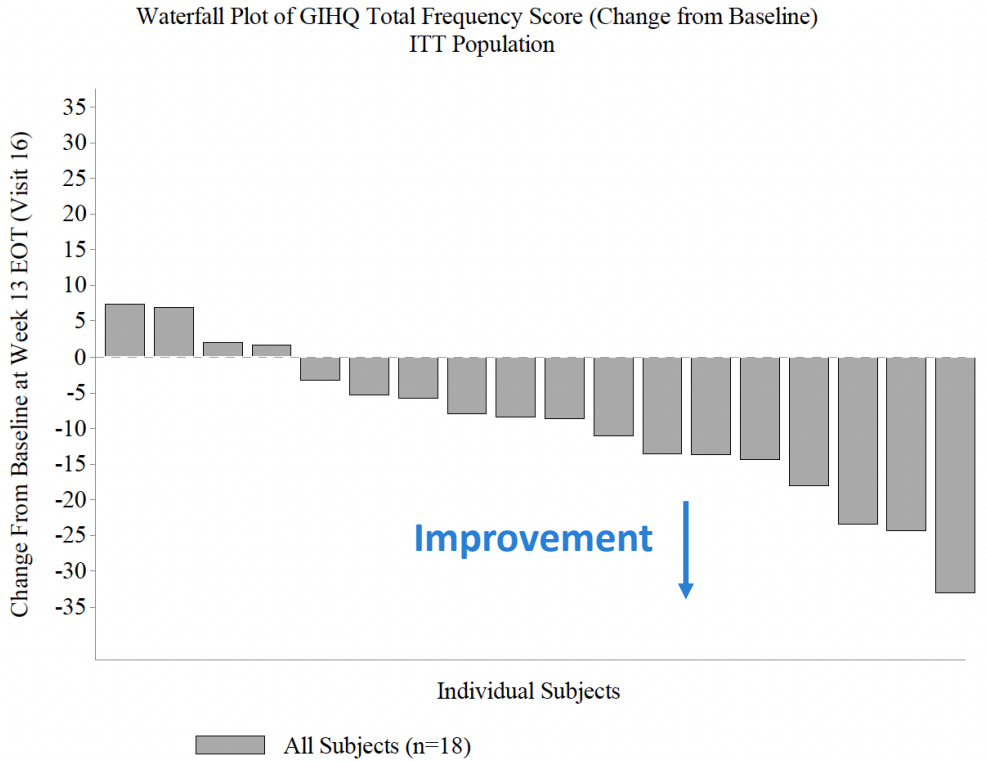
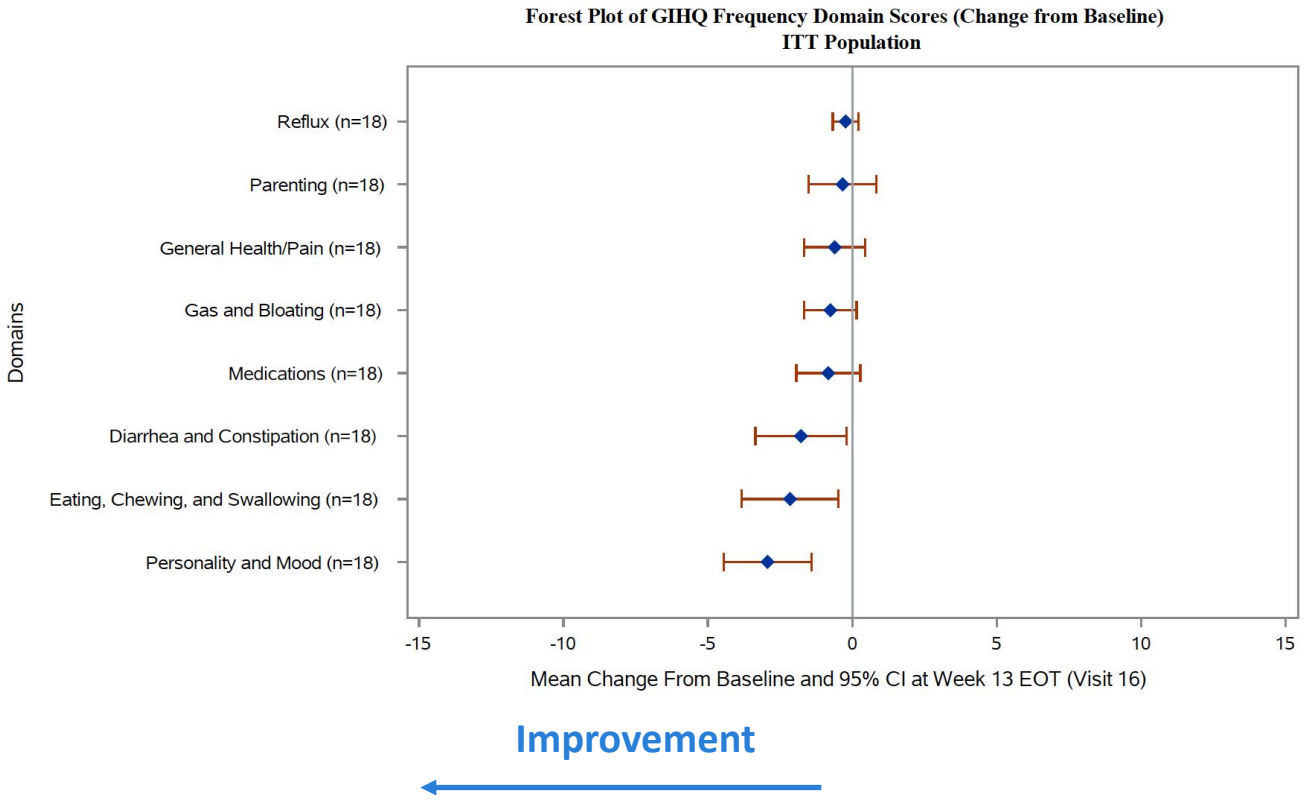
Gastrointestinal Health Questionnaire results by subject and by subscale





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

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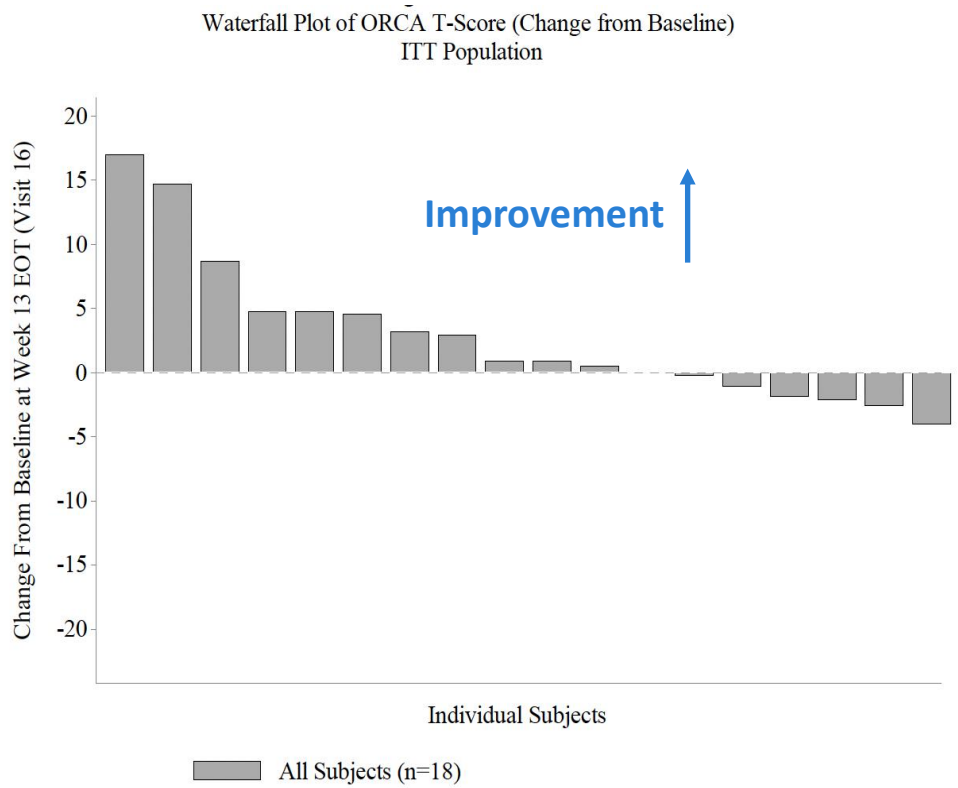
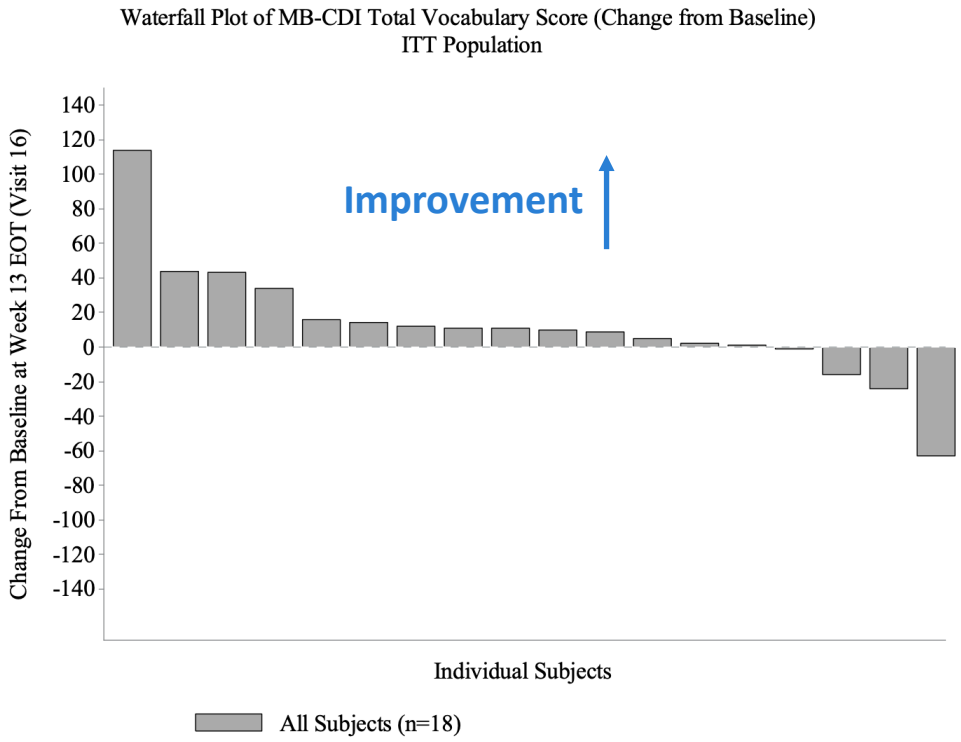
ORCA T-Score and MB-CDI Total Vocabulary results by subject

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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Testimonials

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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."

PMS opportunity

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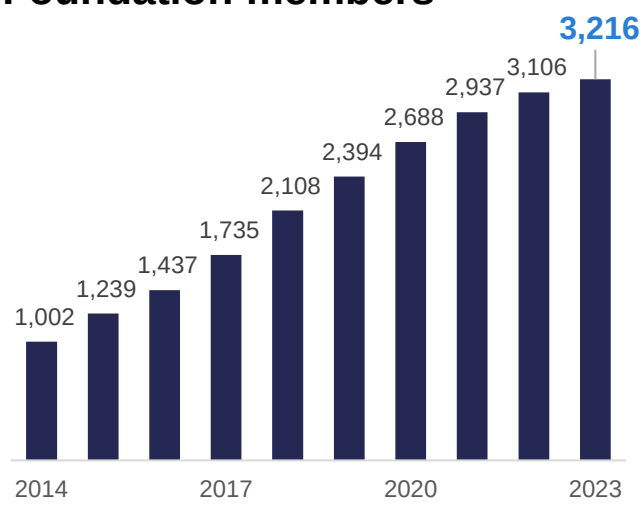
PMS is historically under-diagnosed, but this is changing

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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Neuren is leading development of a first approved treatment for PMS

Phase 2 Program Status

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

Limited products in development

Company	Product Development Stage
neuren pharmaceuticals	**Phase 2** ***(successful)***
#2	Phase 2 trial *(closed Jan 2021)*
#3	Phase 1
#4	Pre-clinical
#5	Pre-clinical

Neuren engaging with all stakeholders

pmsf

cureSHANK

Leading clinicians

FDA

NNZ-2591 in development for multiple neurodevelopmental disorders

Disorder	Gene mutation	Published prevalence estimates	Potential patients		
			US[1]	Europe[1]	RoW[1, 2]
Phelan-McDermid	*SHANK3*	1/8,000 to 1/15,000 males and females	24,000	31,000	103,500
Pitt Hopkins	*TCF4*	1/34,000 to 1/41,000 males and females	6,000	8,000	28,000
Angelman	*UBE3A*	1/12,000 to 1/24,000 males and females	16,000	20,000	66,000
Prader-Willi	*15q11-q13*	1/10,000 to 1/30,000 males and females	17,000	21,000	72,000
			63,000	**80,000**	**270,000**

- The mechanism of action of NNZ-2591 is relevant for many other neurodevelopmental synaptopathies
- Top-line results from Pitt Hopkins syndrome Phase 2 trial expected in Q2 2024

[1] Estimates derived by applying the mid-point of the prevalence estimate range to the populations under 60 years
[2] RoW comprises Japan, China (urban population), Brazil, Israel, South Korea, Australia and New Zealand

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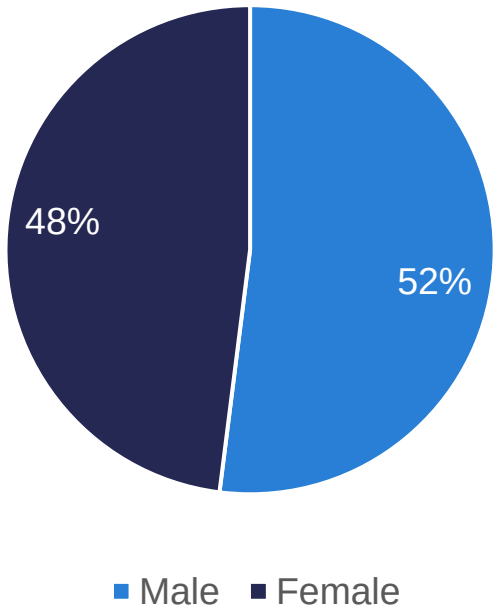
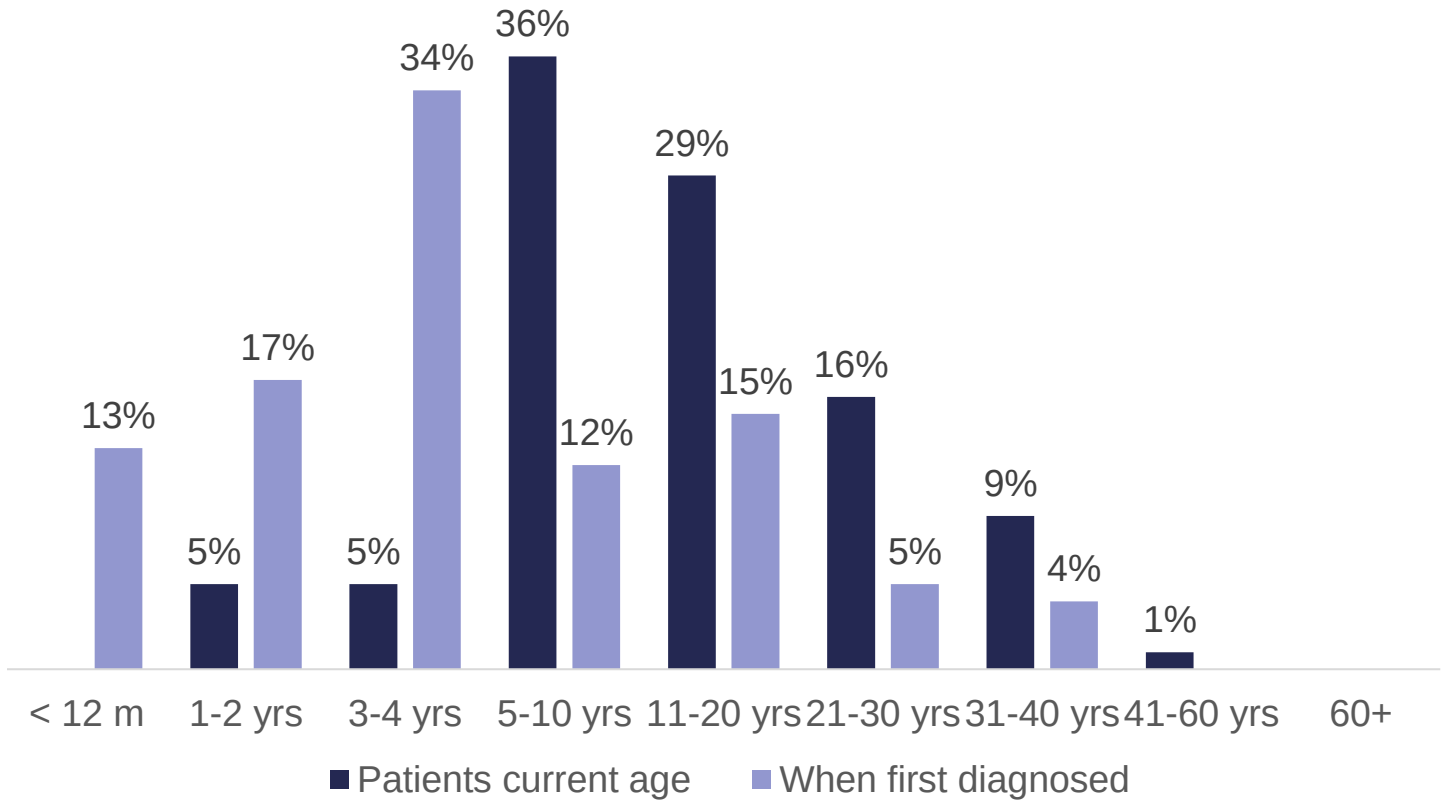
Phelan McDermid syndrome affects all genders and ages

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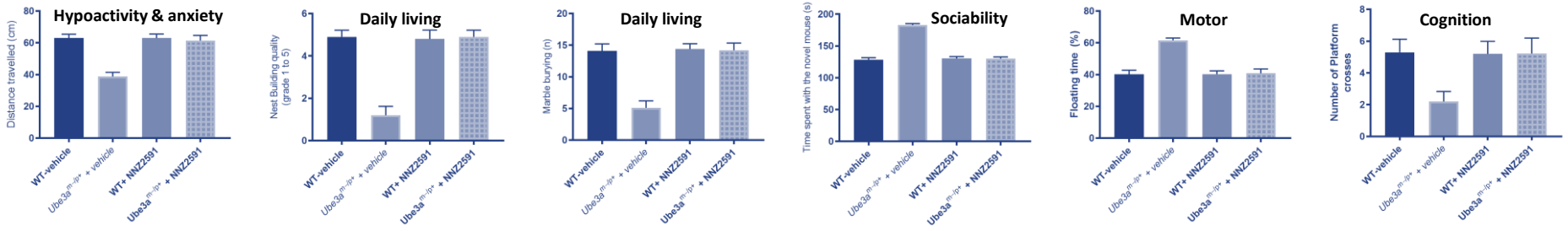
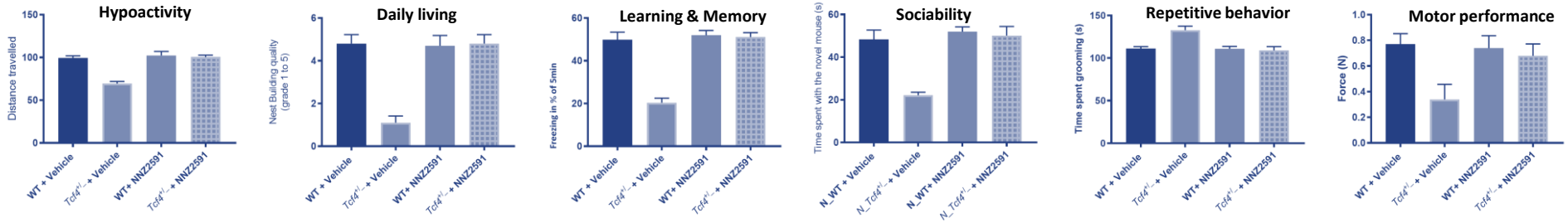
Consistent efficacy in Pitt Hopkins, Angelman and Prader-Willi models

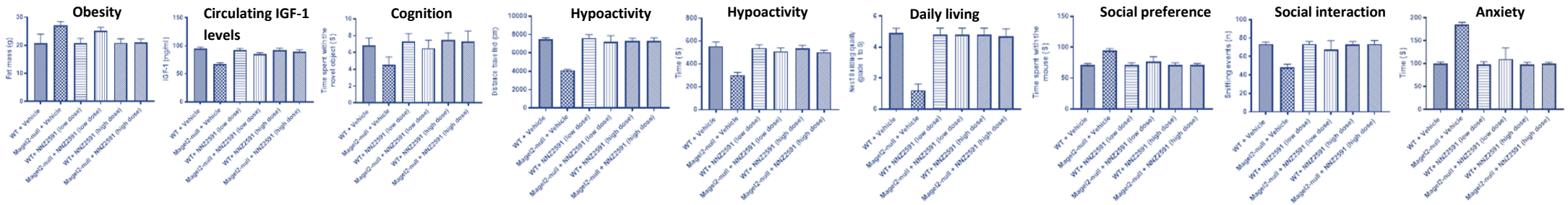
Angelman



Pitt Hopkins



Prader-Willi



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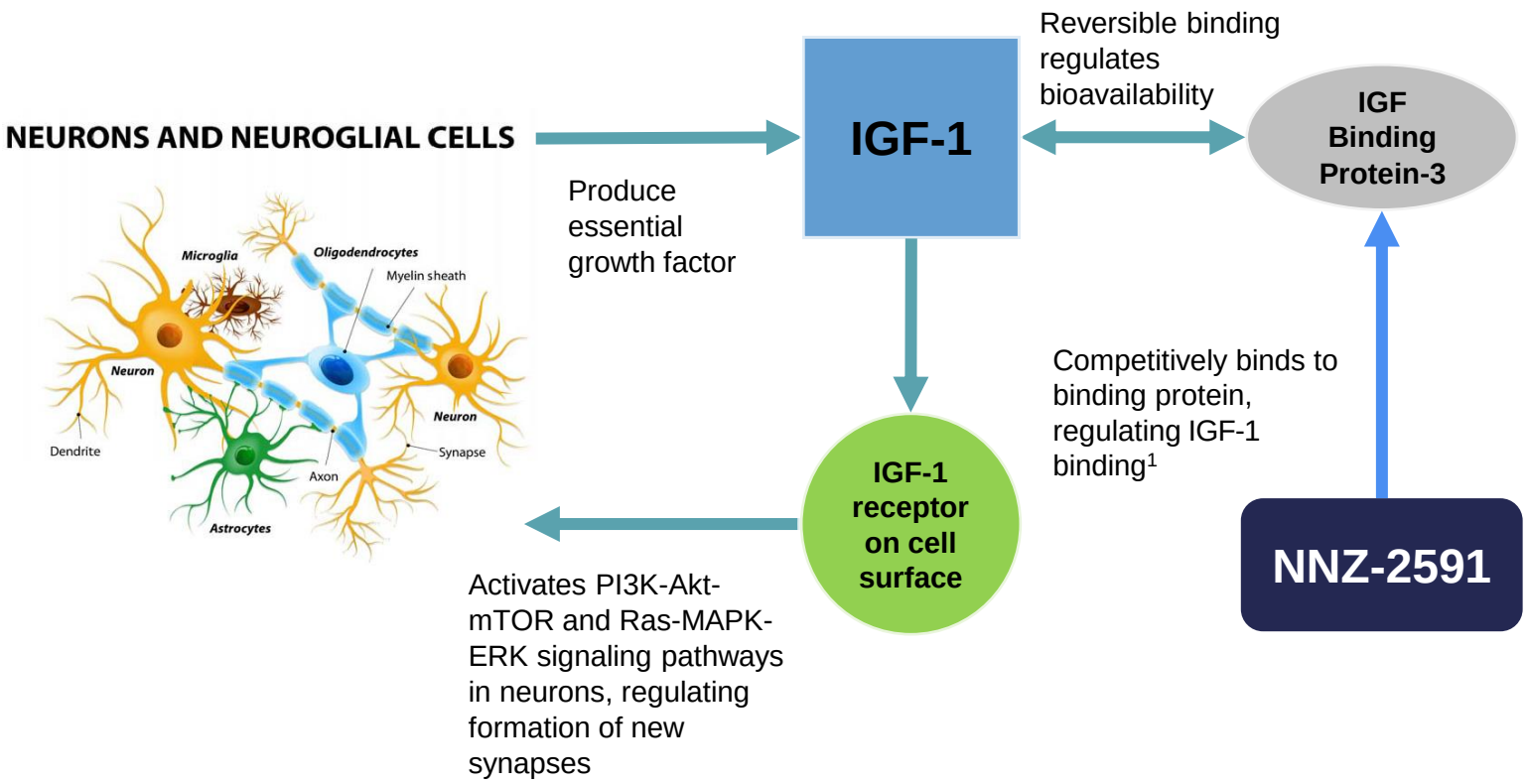
Novel mechanisms of action – NNZ-2591



- **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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