ACADIA

Lavender™ Study Positive Top-line Results for the Treatment of Rett Syndrome

December 6, 2021

Agenda

Introduction	**Mark Johnson** | Vice President, Investor Relations
Opening Remarks	**Steve Davis** | Chief Executive Officer **Serge Stankovic, M.D., M.S.P.H** | President
International Rett Syndrome Foundation	**Dominique Pichard, M.D.** | Chief Scientific Officer at IRSF
Lavender Study Results	**Kathie M. Bishop, Ph.D.** | Chief Scientific Officer and Head of Rare Disease
Closing Remarks	**Steve Davis** | Chief Executive Officer
Q&A	Also available for Q&A: **Brendan Teehan** | Chief Operating Officer, Head of Commercial **Mark Schneyer** | Interim Chief Financial Officer and Chief Business Officer

Forward-Looking Statements

This presentation contains forward-looking statements. These statements relate to future events and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed in or implied by such forward-looking statements. Each of these statements is based only on current information, assumptions and expectations that are inherently subject to change and involve a number of risks and uncertainties. Forward-looking statements include, but are not limited to, statements related to: the potential benefits of trofinetide as a treatment for Rett syndrome or other disorders and the potential markets for trofinetide; and currently anticipated impacts of COVID-19 on Acadia's business, including its commercial sales operations, current and planned clinical trials, and supply chain.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions (including the negative thereof) intended to identify forward-looking statements. Given the risks and uncertainties, you should not place undue reliance on these forward-looking statements. For a discussion of the risks and other factors that may cause our actual results, performance or achievements to differ, please refer to our annual report on Form 10-K for the year ended December 31, 2020 as well as our subsequent filings with the SEC. The forward-looking statements contained herein are made as of the date hereof, and we undertake no obligation to update them for future events.

Opening Remarks

Steve Davis, CEO

Serge Stankovic, President

Rett Syndrome: Significant Unmet Need

Epidemiology[1,2]	• Rare; occurring worldwide in approximately 1 in 10,000 to 15,000 female births (~6,000 to 9,000 patients in the U.S.)
Impact[1]	• Debilitating neurologic disease occurring primarily in females • Causes problems in brain function with rapid decline commencing around 6 to 18 months of age • Can have the following symptoms: – Cognitive, sensory, emotional, motor impairment – Loss of spoken communication – Loss of independence – Loss of purposeful hand use

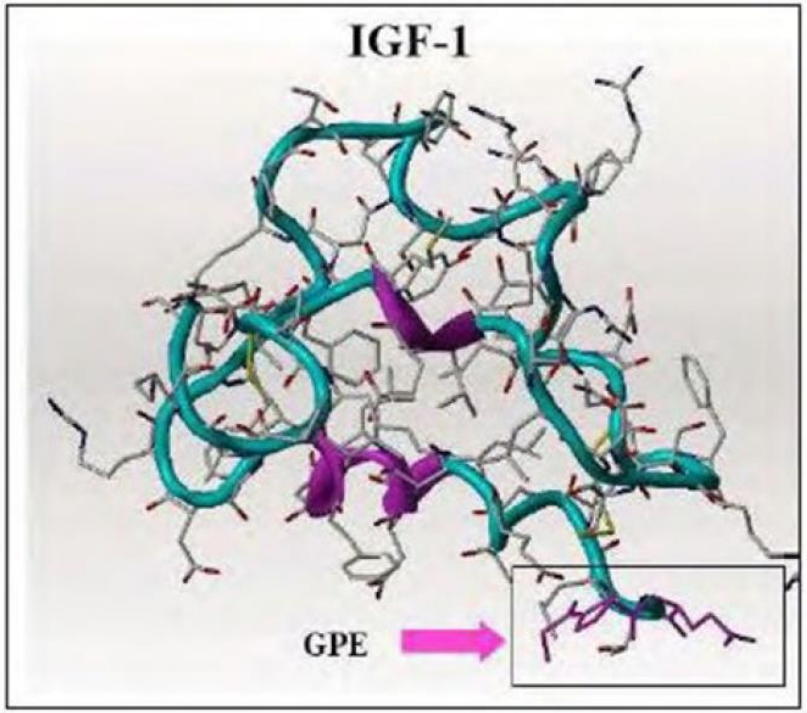
No FDA-approved treatment for Rett syndrome

[1]National Institute of Mental Health. Rett Syndrome Fact Sheet. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Rett-Syndrome-Fact-Sheet. Accessed July 20, 2020.
[2]US prevalence estimate based on incidence rates from the National Institutes of Health – National Institute of Neurological Disorders and Stroke.
Provided December, 6, 2021 as part of an oral presentation and is qualified by such; contains forward-looking statements; actual results may vary materially; Acadia disclaims any duty to update.

Trofinetide for the Treatment of Rett Syndrome

Trofinetide

Trofinetide is an investigational drug and a novel synthetic analog of GPE, the amino-terminal tripeptide of IGF-1



Proposed Mechanism of Action[1]

In Rett syndrome:

- Insufficient formation of new synapses by neurons
- Excessive pruning of existing synapses by overactive microglia

Trofinetide is thought to:

- Improve synaptic function and restore synaptic structure
- Inhibit overactivation of inflammatory microglia and astrocytes
- Increase the amount of IGF-1 in the brain

Patent protection:

- Method of treating Rett syndrome patent with expected patent term extension to end of 2035

GPE=glycine-proline-glutamate; **IGF-1**= Insulin-like growth factor 1

[1]Chahrour, Science, 2008; Itoh, J Neuropath Exp Neurol, 2007; Bourguignon, Brain Res, 1999; Tropea, PNAS, 2009.

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Lavender Study: Top-line Efficacy Results

Co-Primary Endpoints: Statistically significant separation from placebo

- *Rett Syndrome Behaviour Questionnaire (RSBQ)*
- *Clinical Global Impression of Improvement (CGI-I)*

Key Secondary Endpoint: Statistically significant separation from placebo

- *CSBS-DP-IT Social Composite Score*

Consistent efficacy observed across age ranges and severity of disease

Pre-NDA meeting with FDA planned for 1Q22

CSBS-DP-IT Social = Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score

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International Rett Syndrome Foundation

Dominique Pichard, MD

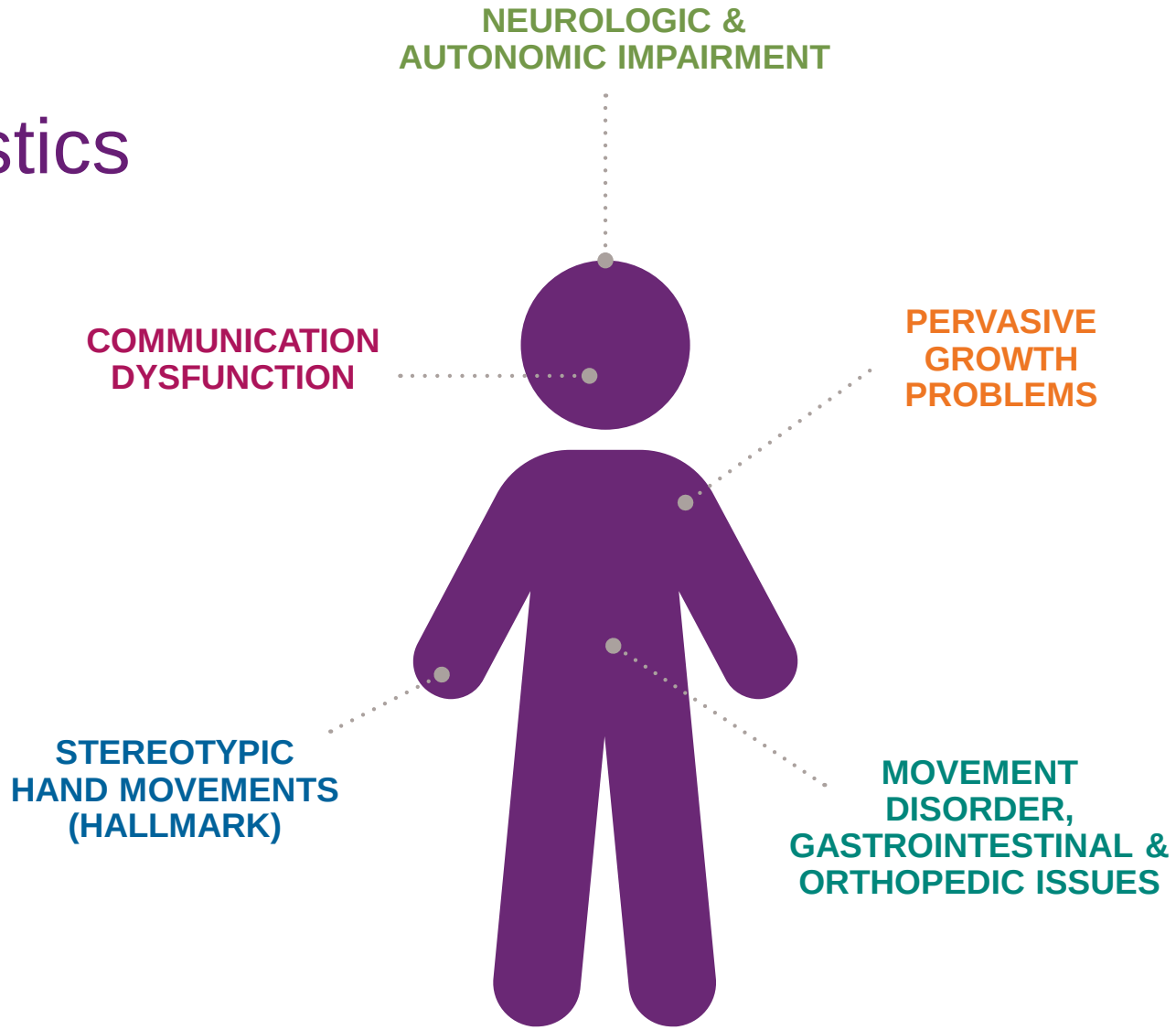
Chief Scientific Officer of IRSF

What is Rett syndrome?

Rett syndrome is a rare neurodevelopmental disorder.

- Progressive, not degenerative
- One in 10,000 female babies affected
- Typical child with Rett syndrome cannot speak, use her hands, walk, eat, or breathe easily
- Longevity well into adulthood
- No FDA approved treatments

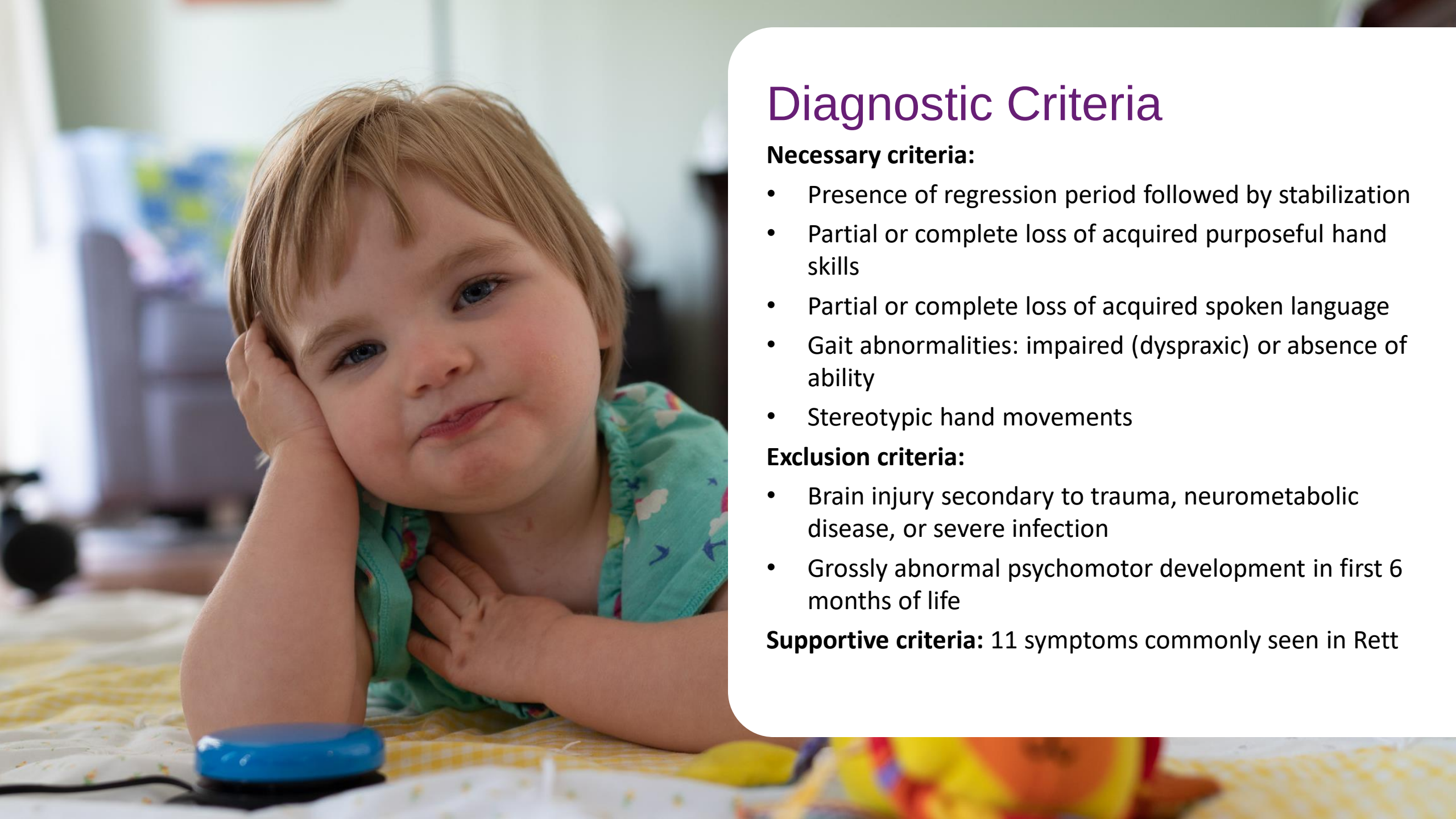
Characteristics



Rett Syndrome Looks Like

- Cerebral Palsy
- Autism
- Epilepsy
- Parkinson's
- Anxiety
- Reflux
- Chronic constipation
- Scoliosis
- Sleep disorder
- …all in one child

  who also can't speak



Diagnostic Criteria

Necessary criteria:

- Presence of regression period followed by stabilization
- Partial or complete loss of acquired purposeful hand skills
- Partial or complete loss of acquired spoken language
- Gait abnormalities: impaired (dyspraxic) or absence of ability
- Stereotypic hand movements

Exclusion criteria:

- Brain injury secondary to trauma, neurometabolic disease, or severe infection
- Grossly abnormal psychomotor development in first 6 months of life

Supportive criteria: 11 symptoms commonly seen in Rett

Repetitive Hand Movements

What's the impact if someone with Rett can't control their hand movements?

- Can't pick up objects and learn how to use them
- Can't take a shower or dress or feed themselves
- Can't play with toys
- Can't open doors, turn on music or movies, get a drink of water

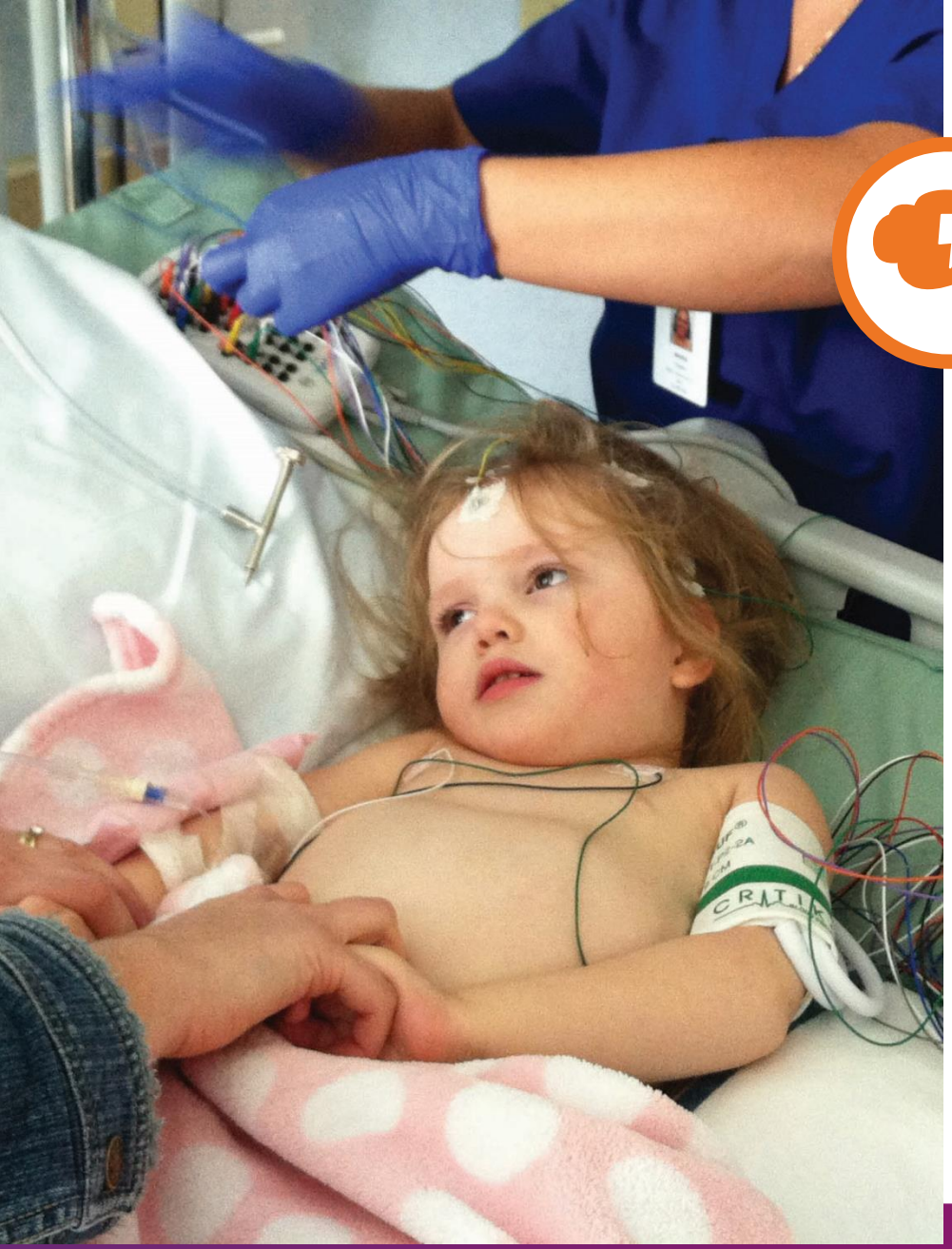
The caregiver must always be the hands for their child

Sleep Disturbances

What's the impact if someone with Rett can't sleep through the night?

- The sleep of the entire family is disrupted
- No sleepovers – think about siblings too
- Visits to family and friends are difficult, or impossible
- There is extreme fatigue with frequent daily naps
- Learning is disrupted

For caregivers, it's like having an infant in the house, forever



Seizures

What's the impact if someone with Rett suffers from epilepsy?

- The child can never enjoy a moment of privacy, she can never be left alone
- Many doctor visits, medication changes, side effects
- Missed school, social activities, disrupts life's continuity
- There is extreme post-ictal fatigue and sensory sensitivity, can't eat or drink
- Skills and cognition may suffer
- Fall risks if ambulatory
- Fear SUDEP

For caregivers, it's relentless and you're powerless, when will the earthquake hit?

Breathing

What's the impact if someone with Rett can't breathe steadily?

- She can't eat easily
- Can't focus
- Might feel dizzy, affects ambulation
- Breath-holding, hyperventilating, swallowing air, apneas, shallow breathing all feel differently one thing for sure: not behavioral, can't will it to stop

For caregivers, it's relentless and you're powerless, always

Anxiety

What's the impact if someone with Rett can't regulate their emotions?

- She has loud unpredictable outbursts
- If ambulatory, possible flight risk
- Might self-harm (head banging, hair pulling)
- Might unintentionally harm others – parents, siblings, caregivers, other students
- Behavior modification and medications partially effective
- Possible placement outside of the home

For caregivers, it's relentless, you become isolated, more difficult to find respite providers

GI

What's the impact if someone with Rett is working all day to take in nutrition or have a bowel movement?

- Chewing/swallowing can regress over time
- Increase in behaviors
- Can't focus
- Failure to thrive: gastrostomy tube
- Aspiration risk, repeat pneumonias: fundoplication
- Constipation medications mildly effective

For caregivers, it consumes the day, worrisome school oversight, public changing areas difficult to find for teens/adults leading to less community access

Orthopedic

What's the impact if someone with Rett has scoliosis/kyphosis, hip dysplasia, contractures?

- Pain
- Balance and fall hazard
- Durable Medical Equipment (DME) – braces, positioning devices, wheelchairs, bathing chair, adapted transportation
- Potential loss of ambulation
- Pneumonia risk increase
- Corrective surgeries
- Difficulty accessing communication devices

For caregivers, moves and transfers become more difficult, time added to the day for using equipment; equipment failure breakdowns and modifications ongoing

Communication

What's the impact if someone with Rett is nonverbal?

- Repetitive hand movements prevent sign language, writing, typing
- Trapped in a body that can hear, smell, feel, taste but not speak
- Cannot communicate needs, wants, pain, and more
- Mental health affected: frustration, anxiety, loneliness, depression
- Potential for abuse or neglect to go undetected
- Education and learning suffers: receptive far higher than expressive

For caregivers, relentless anticipation of every need all day, every day

Rett Syndrome Behaviour Questionnaire (RSBQ)

- Validated 45 item rating scale, completed by the caregiver
- 8 general neurobehavioral areas specific to Rett
- Score: 0 (not true), 1 (sometimes true), 2 (often true)
- Has been correlated with functioning & quality of life in Rett
- Example: “Spells of inconsolable crying for no apparent reason during the night”

Lavender Results

Kathie M. Bishop

Chief Scientific Officer and
Head of Rare Disease

Lavender: Pivotal Phase 3 Study

Pivotal, Randomized, Double-blind, Placebo-controlled, Multi-center Study

Co-primary efficacy endpoints

1. RSBQ
2. CGI-I

Key secondary efficacy endpoint

1. CSBS-DP-IT

Open-label extension studies: Lilac and Lilac-2

Baseline Characteristics
Full Analysis Set

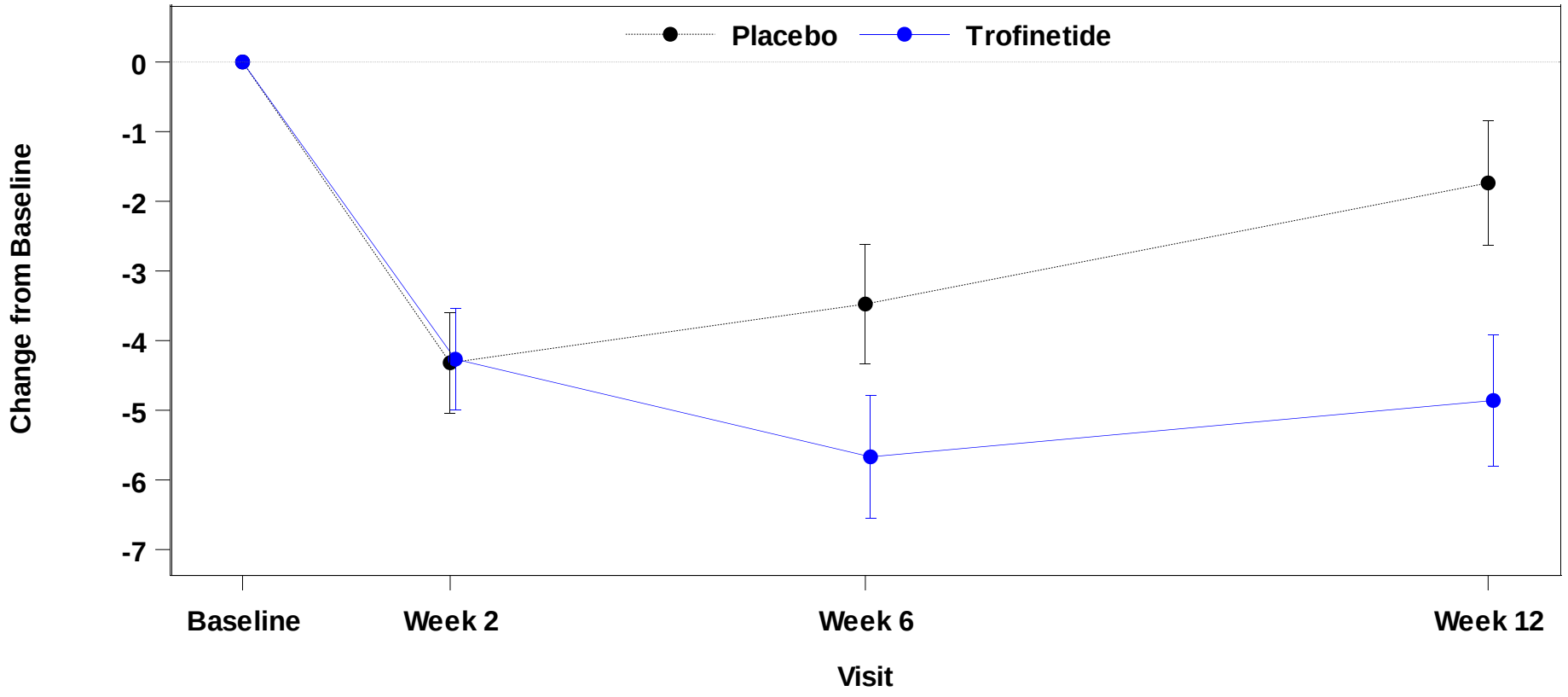
	Placebo (N=93) n (%)	Trofinetide (N=91) n (%)	Total (N=184) n (%)
Average Age in Years	10.8	11.0	10.9
Age Categories, n (%)			
5 to 10 Years	52 (55.9)	48 (52.7)	100 (54.3)
11 to 15 Years	23 (24.7)	24 (26.4)	47 (25.5)
16 to 20 Years	18 (19.4)	19 (20.9)	37 (20.1)
Baseline CGI-S score	4.9	4.9	4.9
Baseline CGI-S Category, n (%)			
4=Moderately ill	32 (34.4)	31 (34.1)	63 (34.2)
5=Markedly ill	42 (45.2)	37 (40.7)	79 (42.9)
6=Severely ill	18 (19.4)	23 (25.3)	41 (22.3)
7=Among the most extremely ill patients	1 (1.1)	- -	1 (0.5)

CGI-S = Clinical Global Impression – Severity

Top-line Efficacy Results
Full Analysis Set

	Placebo	Trofinetide
Primary Endpoints:		
RSBQ (Change from baseline to week 12) Mean (SE)	-1.7 (0.98)	-5.1 (0.99)
Two-sided p-value		***0.0175***
Effect Size; Cohen's d		**0.37**
CGI-I (Score at week 12) Mean (SE)	3.8 (0.06)	3.5 (0.08)
Two-sided p-value		***0.0030***
Effect Size; Cohen's d		**0.47**
Key Secondary Endpoint:		
CSBS-DP-IT Social Composite Score (Change from baseline to week 12) Mean (SE)	-1.1 (0.28)	-0.1 (0.28)
Two-sided p-value		***0.0064***
Effect Size; Cohen's d		**0.43**

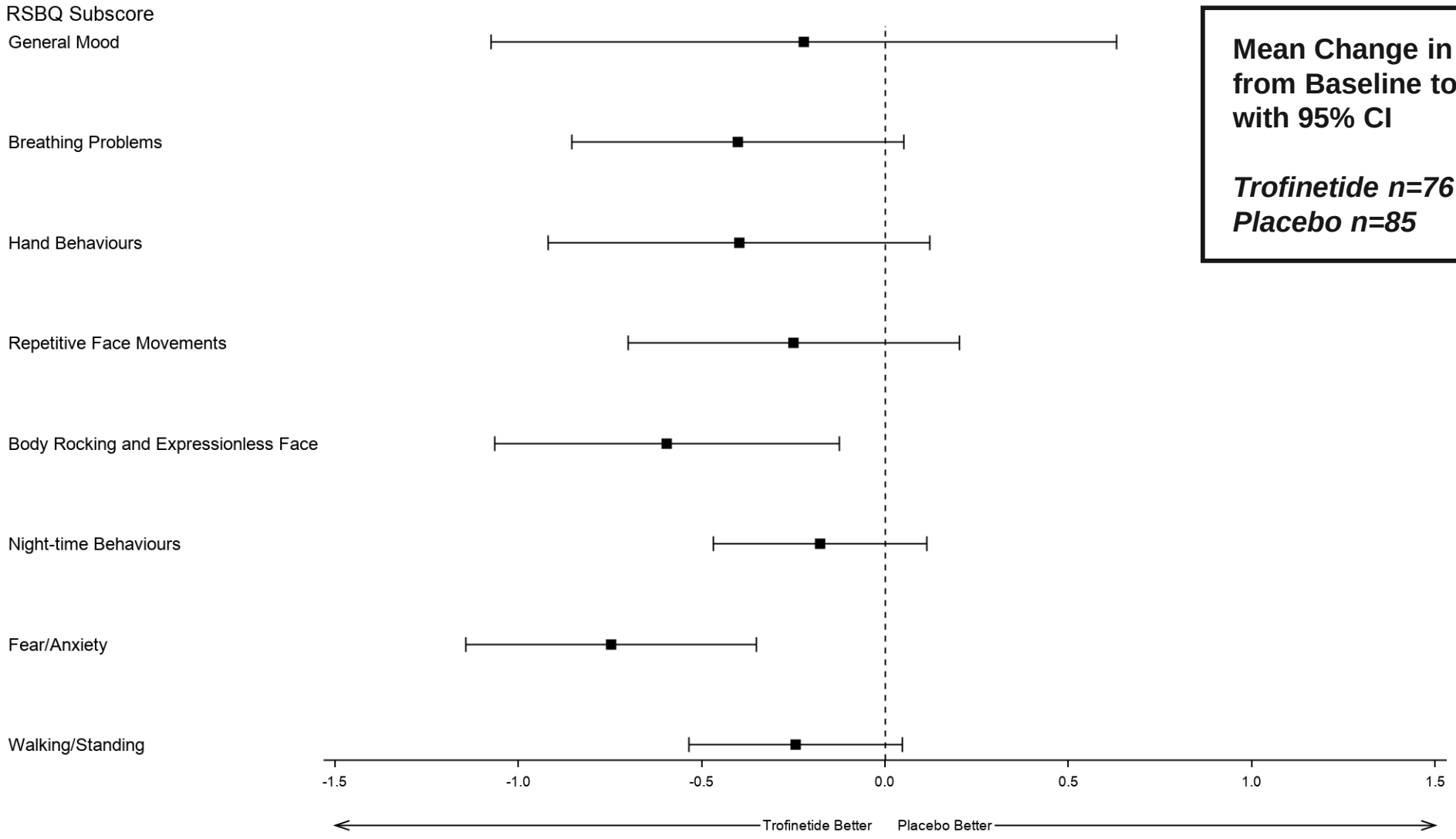
RSBQ Change from Baseline by Visit
Full Analysis Set



RSBQ:
p-value = 0.0175
Effect Size = 0.37

Number of Subjects				
Placebo	93	90	92	85
Trofinetide	91	90	83	76

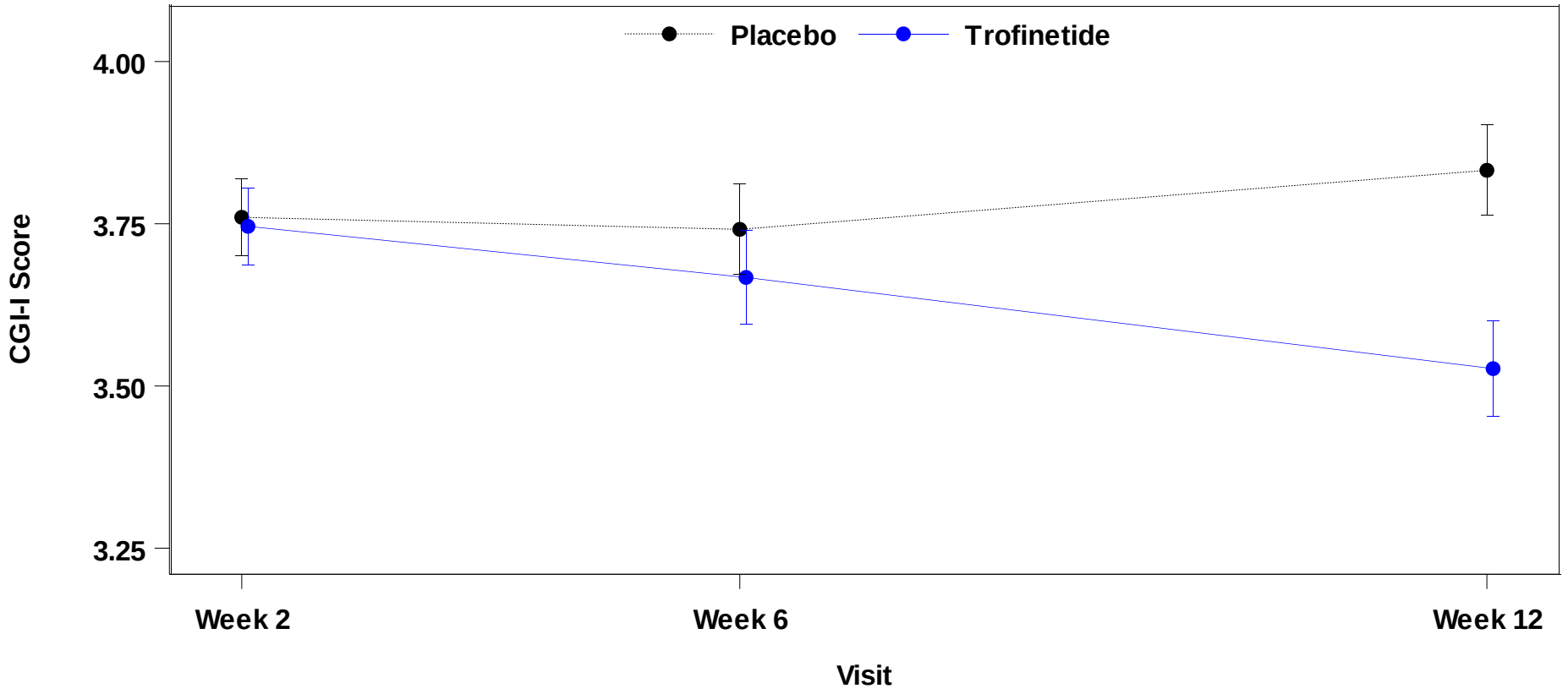
RSBQ Subscores Treatment Difference
Full Analysis Set



Mean Change in Subscore from Baseline to Week 12 with 95% CI

Trofinetide n=76
Placebo n=85

CGI-I Score by Visit
Full Analysis Set



CGI-I at Week 12:
p-value = 0.0030
Effect Size = 0.47

Number of Subjects			
Placebo	90	92	86
Trofinetide	90	83	77

Summary of Treatment-Emergent Adverse Events
Safety Analysis Set

	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Any Treatment-Emergent Adverse Event (TEAE)	51 (54.3)	86 (92.5)
Any Serious TEAE	3 (3.2)	3 (3.2)
Any TEAE Leading to Drug Withdrawn	2 (2.1)	16 (17.2)
Any Fatal TEAE	- -	- -

TEAEs ≥5% in Either Treatment Group
Safety Analysis Set

Preferred Term	Placebo (N=94) n (%)			Trofinetide (N=93) n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhea	15 (16.0)	3 (3.2)	--	39 (41.9)	34 (36.6)	2 (2.2)
Vomiting	8 (8.5)	1 (1.1)	--	18 (19.4)	6 (6.5)	1 (1.1)
Seizure	3 (3.2)	2 (2.1)	--	3 (3.2)	5 (5.4)	--
Pyrexia	2 (2.1)	2 (2.1)	--	7 (7.5)	1 (1.1)	--
Decreased appetite	1 (1.1)	1 (1.1)	--	2 (2.2)	3 (3.2)	--
Irritability	--	--	--	3 (3.2)	2 (2.2)	1 (1.1)

Closing Remarks

Steve Davis

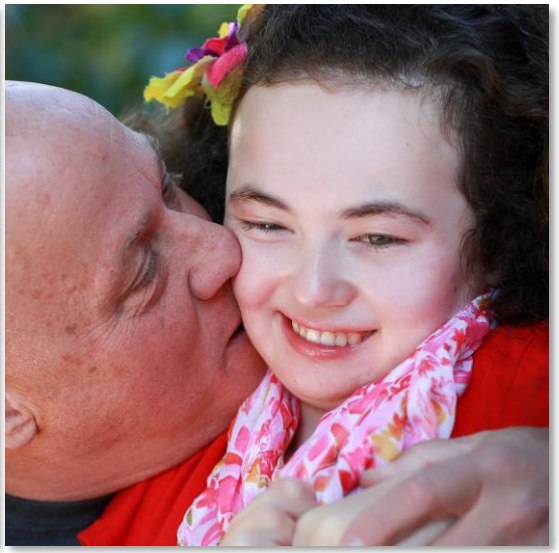
CEO

Next Steps for Trofinetide in Rett Syndrome

Trofinetide has been granted:

- Rare Pediatric Disease designation
- Fast-Track Status
- Orphan Drug designation

Pre-NDA meeting with FDA planned for 1Q22



NDA will be based on:

Pivotal Efficacy	Supportive Efficacy	Safety Database
Positive Phase 3 Lavender Study	Positive Phase 2 Study for Trofinetide in Rett syndrome[1]	Safety and Tolerability Data from Completed & Ongoing Studies

[1]Glaze DG, et al. Neurology. 2019;92(16):e1912-e1925.

Program Development Pipeline

Program	Indication	Phase 1	Phase 2	Phase 3	Marketed
NUPLAZID® (pimavanserin)[1]	Parkinson's Disease Psychosis				
Pimavanserin[2]	Dementia-Related Psychosis				
Pimavanserin	Negative Symptoms of Schizophrenia				
Trofinetide[3]	Rett Syndrome				
ACP-044	Postoperative Pain				
ACP-044	Osteoarthritis Pain				
ACP-319[4]	Schizophrenia and Cognition in Alzheimer's				

[1]NUPLAZID (pimavanserin) is only approved in the U.S. by the FDA for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.
[2]Acadia received a CRL for its sNDA for pimavanserin for the treatment of DRP. Acadia is in an ongoing discussion with FDA to align on next steps.
[3]Acadia has an exclusive license to develop and commercialize trofinetide in North America from Neuren Pharmaceuticals.
[4]Acadia has an exclusive worldwide license to develop and commercialize ACP-319 and other M1 PAM program compounds from Vanderbilt University.
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Q&A Session