DN1 Review of Clinical Data

NDA (Serial Number)	**217026**
Applicant:	**Acadia Pharmaceuticals**
Drug:	**Trofinetide**
Proposed Indication:	**For treatment of Rett Syndrome in adults and pediatric patients 2 years of age and older**
Date Received / Agency:	**07/12/2022**
Date Review Completed:	**03/08/2023**
Reviewer:	**Michelle Campbell, PhD**

1. Background

This marketing application is for trofinetide, a synthetic analogue of the naturally occurring N-terminal tripeptide of insulin-like-growth-factor-1 (IGF-1), glycine-proline-glutamate (GPE), and is developed as a solution for oral or gastrostomy tube infusion in a 200 mg/mL concentration. The applicant's proposed indication is for treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Rett syndrome is a serious and life-threatening pediatric condition leading to severe disability and early death in adults. Rett syndrome is marked by initially normal development, followed at 18 to 30 months by severe loss of language, fine motor, and gross motor skills. Development of face, hand, and body stereotypies, epilepsy, non-epileptic spells, anxiety, and growth impairment occur in most subjects. The majority of patients with Rett syndrome are dependent on a caregiver for most activities of daily living and they suffer from the multiple complications that occur with impaired mobility and dependency, such as scoliosis, contractures, and pneumonia amongst others. Patients with Rett syndrome have a reduced life expectancy into the forties or fifties.

Rett syndrome has substantial unmet medical need. There are no therapies indicated specifically for the treatment of Rett syndrome. All the treatments currently used are solely for management of the numerous complications of the disorder. These treatments include medications for epilepsy, constipation, and other systemic features, physical therapies to compensate for neurological impairment, and surgical therapies for dysphagia, contracture, and scoliosis.

This review will focus only on the appropriateness of the clinical outcome assessments used by the applicant in its development program. For a complete review of safety and efficacy data, see Dr. Dimyan's clinical review.

2. Summary of Submission

<u>Study Design</u>

ACP-2566-003 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, cohort designed study. The study population were females aged 5 to 20 years old with a genetically confirmed diagnosis of Rett syndrome. They were screened for inclusion, underwent a baseline visit at which time they were randomized 1:1 to trofinetide weight-based daily dosing or placebo. They underwent treatment for 12 weeks with outcome visits at week 2, 6, and 12. If the subject completed the study but did not enroll in the open-label extension (OLE), Study ACP-2566-004, then they had a 30-day post-treatment-end follow-up visit. The objectives were to measure effectiveness via two co-primary endpoints, the Rett syndrome Behavior Questionnaire (RSBQ) and the Clinical Global Impression of Improvement score (CGI-I).

Diagnostic Criteria

Females aged 5 to 20 years with a diagnosis of typical or classical Rett syndrome by 2010 diagnostic criteria were included. Documentation of a known disease-causing mutation of the MeCP2 gene was required from a College of American Pathologists or Clinical Laboratory Improvement Act/Amendment certified lab. Participants were stratified into 3 age groups (5 to 10, 11 to 15, 16 to 20) and by baseline RSBQ (<35 or ≥ 35).

Key Inclusion/Exclusion Criteria:

- Weight ≥12 kg
- Rett syndrome Clinical Severity Score (RTT-CSS) score 10 to 36
- Clinical Global Impression-Severity (CGI-S) score ≥4
- No loss or degradation within 6 months of the following:
    - ambulation (gait, coordination, independence of walking/standing)
    - hand function
    - speech
    - nonverbal communication
    - social skills (using eye gaze, body, social attentiveness to indicate communicative intent)
    - stable seizure pattern or no seizures within 8 weeks

- concomitant anticonvulsants and psychoactive medications stable for 4 weeks or discontinued at least 2 weeks or 5 half-lives (whichever is greater) prior

- concomitant non-pharmacological therapy stable for 4 weeks or discontinued at least 2 weeks prior

Key Exclusion Criteria at Baseline:

- Free of treatment with the following within 12 weeks of Baseline:

    - growth hormone

    - IGF-1

    - insulin

- Current clinically significant diseases within these systems:

    - cardiovascular

    - endocrine

    - renal

    - hepatic

    - respiratory

    - gastrointestinal

    - cerebrovascular

    - brain trauma

    - uncorrected visual or hearing

    - malignancy, current or history

- Plan for surgery during trial

- Abnormal basic laboratory tests

Study Endpoints

Co-Primary Efficacy Endpoints

The co-primary endpoints for ACP-2566-003 were the RSBQ and CGI-I. The RSBQ is a 45-item observer rated outcome (ObsRO) that asks caregivers to rate a set of symptom occurrences over the previous two weeks as "not true as far as you know," "somewhat or sometimes true," or "very true or often true." All but 1 of the 45 items are worded as a predominant pathological symptom of Rett syndrome, and hence higher scores represent more or worse symptoms of the disease. Because item 31 of the RSBQ rates the subject on ability to use "eye gaze to convey feelings, needs, and wishes", the numerical ratings of 1, 2, 3 are opposite in quality to the rest of the RSBQ. Therefore, after administration, the scoring of this item was reversed to calculate the derived RSBQ which was used as the co-primary endpoint. Of note, this reversal was not used as part of the stratification of subject randomization by baseline RSBQ. In scoring for ACP-2566-003, the 45 items were divided into 8 domains (Table 1). It should be noted that in the prior study, NEU-2566-RETT-002, which is reviewed for confirmatory evidence, items 11 and 26 were included in the body rocking and expressionless face subscale and item 31 was not included in any subscale. The RSBQ was administered by trained personnel at baseline and visits 3, 4, 5.

Table 1 RSBQ Subscales and Assigned Items in ACP-2566-003

RSBQ subscale	Number	RSBQ subscale items (Description)
General mood	2	spells of screaming for no apparent reason during the day
	14	abrupt changes in mood
	15	certain periods when performs much worse than usual
	16	times when appears miserable for no apparent reason
	22	screams hysterically for long periods of time and cannot be consoled
	29	times when irritable for no apparent reason
	30	spells of inconsolable crying for no apparent reason during the day
	36	vocalizes for no apparent reason
Breathing problems	1	times when breathing is deep and fast
	5	times when breath is held
	6	air or saliva expelled from mouth with force
	19	swallows air
	25	abdomen fills with air and sometimes feels hard
Hand behaviors	18	does not use hands for purposeful grasping
	20	hand movements uniform and monotonous
	21	has frequent naps during the day
	24	restricted repertoire of hand movement
	35	has difficulty in breaking/stopping hand stereotypies

	43	amount of time spent looking at an object is longer than time spent manipulating or holding
Repetitive face movements	4	makes repetitive movements involving fingers around tongue
	28	makes mouth grimaces
	32	makes repetitive tongue movements
	34	makes grimacing expressions with face
Body rocking/ expressionless face	12	expressionless face
	17	seems to look through people into the distance
	31	uses eye gaze to convey feelings, needs and wishes (reversed)
	33	rocks self when hands are prevented from moving
	40	tendency to bring hands together in front of chin or chest
	41	rocks body repeatedly
Night-time behaviors	13	spells of screaming for no apparent reason during the night
	37	spells of laughter for no apparent reason during the night
	42	spells of inconsolable crying for no apparent reason during the night
Fear/anxiety	7	spells of apparent anxiety/fear in unfamiliar situations
	9	seems frightened when sudden changes in body position
	10	times when parts of body held rigid
	38	spells of apparent panic
Walking/Standing	39	Walks with stiff legs
	23	Although can stand independently tends to lean on objects or people
Items not included in subscales	3	Makes repetitive hand movements with hands apart
	8	Grinds teeth
	11	Shifts gaze with a slow horizontal turn of head
	26	Spells of laughter for no apparent reason during the day
	27	Has wounds on hands a result of repetitive hand movements
	44	Appears isolated
	45	Vacant 'staring' spells
Source: Applicant Created Table as part of response to information requestion from division regarding the use of subscale scores in the two studies ACP-2566-003 and NEU-2566-RETT-002		

The CGI-I is a clinician rated outcome (CRO) measuring global clinical impression, specifically of improvement. The CGI-I is administered as a 7-point scale where the clinician rates the subject's condition in the previous week from 1 (very much improved) to 7 (very much worse). It was administered at Visits 3, 4, 5 along with the CGI-S which was a secondary measure. Training of CGI-I raters included a standard presentation, quiz, and discussion of 6 vignettes with gold-standard ratings and a quiz with 2 vignettes on which concordance with gold-standard raters was required (1 point on 1 vignette, gold standard on the other). The CGI-I was anchored to the raters' experience with the Rett syndrome population and required the rater to have a certain set of qualifications or to undergo specialized training.

Secondary Endpoints

The main secondary endpoint for this study was the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Social Composite Score (CSBS-DP-IT-SCS). The CSBS-DP-IT is a caregiver rated outcome checklist of 24 items broken into 7 subscales of behavior. The first 13 items in 3 subscales, "emotion and eye gaze", "communication", and "gestures" make up the social composite score. Those 3 subscales ask the primary caregiver to rate the frequency of particular behaviors on a 3-point Likert-like scale of "not yet/sometimes/often", with higher scores indicating more normative nonverbal communicative behavior. Many of the questions begin with "Does your child" and then asks about a specific behavior. However, the first question asks, "Do you know when your child is happy and when your child is upset?". The CSBS-DP-IT was originally developed as a screening assessment of communication in otherwise healthy preverbal infants ages 6-24 months. The original intention of this screener was to detect potential communication deficits, not to categorize communication abilities or to monitor changes during development.

In ACP-2566-003, the entire 24 CSBS-DP-IT was administered to parents at baseline (Visit 2) and 3 time-points after treatment initiation (Visits 3, 4, 5). Study staff administered the CSBS-DP-IT to caregivers after receiving training, live or video, and passing a quiz and had to otherwise have experience with neurodevelopmental disorders or PROs/ObsROs. With regards to secondary endpoints, the Agency had advised the Applicant that use of the CSBS-DP-IT-SCS as a key secondary endpoint (b) (4) would require justification of its use in the older age group, justification regarding the importance of social communication in this population, individual level responses and rater information, and would be a matter of review. The Applicant cited the March 11, 2022, Externally- Led Patient Focused Drug Development meeting and scientific articles indicating the importance of communication for caregivers of patients with Rett syndrome. The Applicant also posited that given that the RSBQ only has 1 of 45 items related to communication and eye gaze, that the CSBS-DP-IT-SCS assessed the domain of communication distinctly from what could be ascertained from the RSBQ.

Exploratory, Safety, and Other Endpoints

Other ObsROs used included the Rett syndrome Caregiver Burden Inventory (RTT-CBI) and Impact of Childhood Neurologic Disability Scale (ICND). Other CROs included the Rett syndrome Clinician Rating of Hand Function (RTT-HF), Rett syndrome Clinician Rating of Ambulation and Gross Motor Skills (RTT-AMB), Rett syndrome Clinician Rating of Ability to Communicate Choices (RTT-COMC), and Rett syndrome Clinician Rating of Verbal Communication (RTT-VCOM). All of these Clinician Rating scales are actually sub-scales of the Rett Syndrome Domain Specific Visual Analog Scale (RTT-DSC), a scale used in NEU-2566-RETT-002.

Patients also underwent physical examinations, ECG, basic laboratory evaluations, drug PK labs, and subject families were provided with a diary to record seizures and spells,

dietary intake, and medication use.

3. Reviewer's Summary Comments

The clinical outcome assessments (RSBQ and CGI-I) used to support the co-primary study endpoints are assessments that are adequate in combination and suitable for use in this drug development program. The RSBQ covers the broad symptoms of Rett Syndrome. For additional details on the efficacy results of the co-primary endpoints, see Dr. Dimyan's efficacy review.

The main secondary endpoint was the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Social Composite Score (CSBS-DP-IT-SCS). The CSBS-DP-IT is a caregiver rated outcome checklist of 24 items broken into 7 subscales of behavior. The first 13 items in 3 subscales, "emotion and eye gaze", "communication", and "gestures" make up the social composite score

The CSBS-DP-IT is a checklist intended to be a screener to see if a child has communication issues. Because of this, the CSBS-DP-IT does not go in depth on various aspects of communication. The CSBS-DP-IT is intended to be used for children age 6-24 months. Finally, the 13-items that make the social composite score, do not represent the full concept of social reciprocity and this score should not suggest that it does.

The sponsor did not provide sufficient evidence to support the use of the CSBS-DP-IT in the age range in study ACP-2566-003 or explain how to score or interpret the score for the CSBS-DP-IT in a broader age range beyond 24 months. I believe the sponsor did not provide information on how to score this scale for the trial population, as the age of the population would be over 24 months. The O'Leary (2018) article used in the Applicant's investigator training to support the use of CSBS-DP-IT study ACP-2566-003 is insufficient in the details on the methods or results of the CSBS-DP-IT used in the study described in the article.

When evaluating communication and concepts related to social communication, evaluation may be best assessed by a trained expert. Additionally, the CSBS-DP-IT response options may miss informative bi-directional abilities of the child. For example, if a child loses a skill or performs the skill less frequently, the "not at this time" response option may not be the best response option.

We recognize that communication is an important to concept to families of the Rett Syndrome (Voice of the Patient Report 2022) and supportive of finding an optimize way to measuring communication in Rett Syndrome. The CSBS-DP-IT is adequate to support the overall efficacy of trofinetide. However, insufficient evidence was submitted by the Applicant for review to support CSBS-DP-IT as a fit-for-purpose to measure the concept

of social communication or social reciprocity [redacted] (b) (4)

4. Conclusions

Patients with Rett syndrome and their families have stated that each child has different array of symptoms and that these symptoms contribute to one another and impact their activities of daily living (Voice of the Patient Report 2022). The clinical outcome assessments used in the trofinetide development program were captured the broad range of symptoms of Rett syndrome and adequate to support the efficacy results. Communication, while is an important concept to families of Rett syndrome patients and captured using the CSBS-DP-IT is adequate to support the efficacy of trofinetide [redacted] (b) (4)

5. References

O'Leary, H. M., Kaufmann, W. E., Barnes, K. V., Rakesh, K., Kapur, K., Tarquinio, D. C., Cantwell, N. G., Roche, K. J., Rose, S. A., Walco, A. C., Bruck, N. M., Bazin, G. A., Holm, I. A., Alexander, M. E., Swanson, L. C., Baczewski, L. M., Poon, C., Mayor Torres, J. M., Nelson, C. A., 3rd, & Sahin, M. (2018). Placebo-controlled crossover assessment of mecasermin for the treatment of Rett syndrome. Ann Clin Transl Neurol, 5(3), 323-332. https://doi.org/10.1002/acn3.533

Rett Syndrome Voice of the Patient Report. Rett Syndrome Externally Led Patient-Focuses Drug Development Meeting, March 11, 2022. Accessed: March 8, 2022. https://rettpfdd.org/site/assets/files/1/2022-rett-syndrome-voice-of-the-patient-report.pdf

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