ACADIA®

acadia
medical affairs

Acadia Pharmaceuticals Inc. is providing this letter in response to your unsolicited request for medical information. It is for scientific exchange and individual educational purposes only, and should not be copied or distributed. Information included in this letter may not be consistent with the US FDA-approved Prescribing Information for DAYBUE® (trofinetide) or may be related to unapproved uses of DAYBUE. This letter is not intended to advocate any unapproved or approved use, indication, dosage, or other treatment-related decision. Acadia strives to provide current, accurate, and fair-balanced information in compliance with current industry information dissemination guidelines.

For further information regarding Indication and Important Safety Information for DAYBUE, please click here: Prescribing Information.

12830 El Camino Real • Suite 400. • San Diego, California 92130 • USA • Tel. 858.558.2871 • Fax 858.558.2872 • www.acadia-pharm.com

DAYBUE™ (trofinetide): Efficacy and Safety in Female Patients Older than 20 with Rett Syndrome

This letter is provided in response to your specific request for information regarding the efficacy and safety of trofinetide in female patients over the age of 20 with Rett syndrome (RTT).

Relevant Labeling Information[1]

- DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Summary

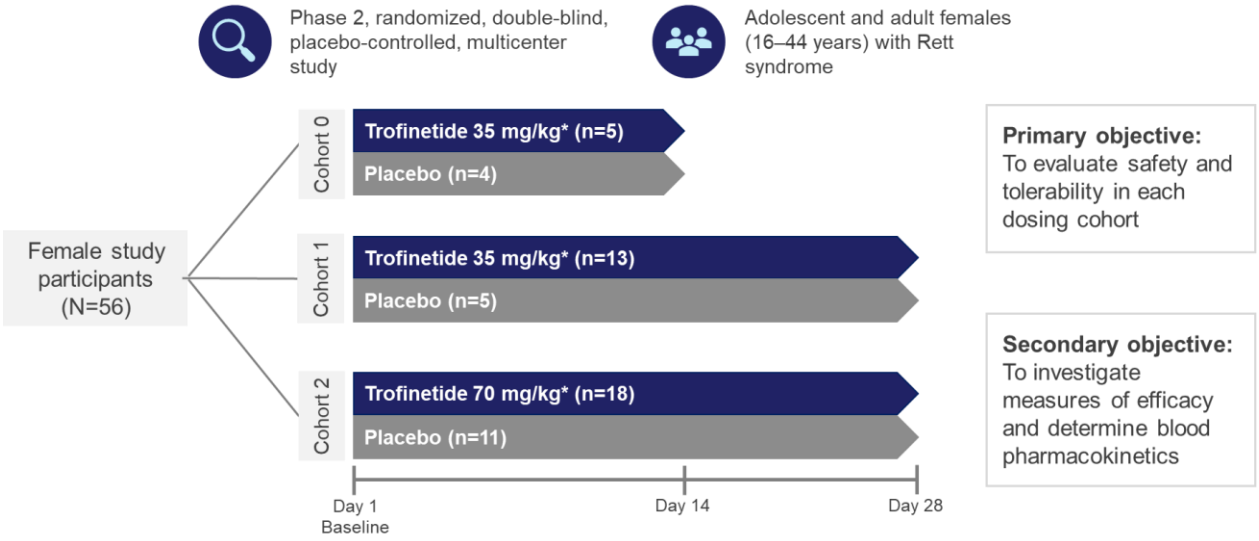
- The **ACP-2566-001 (Study 001)** was an exploratory, Phase 2, double-blind, placebo-controlled, dose-escalation study in 56 adolescent and adult female participants with RTT to assess the safety and tolerability of trofinetide.[2]
- Trofinetide was administered orally at doses of 35 mg/kg twice daily and 70 mg/kg twice daily for up to 28 days.[2]
- The **mean age** for all participants (modified intent to treat [mITT], N=55) was 25.3 years (range: 15.9 to 44.2 years). The maximum age in the trofinetide group was 40.8 years.[2]
- **Trofinetide was tolerable over 28 days;** the most common reported treatment-emergent adverse event (TEAE) with a higher incidence vs placebo was diarrhea (39% [7/18] in the trofinetide 35 mg/kg twice daily group vs 15% [3/20] in the placebo group).[2]

Study 001

Study 001 was an exploratory randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase 2 study in adolescent and adult female participants with RTT (**Figure 1**).[2,3] The secondary measures of efficacy used in the study provided insight into potential efficacy measures for future studies.[2]

Initially, participants were randomly assigned in a 2:1 ratio to trofinetide or placebo for 14 days in the first of 2 sequential dose cohorts (35 mg/kg twice daily for cohort 1 and 70 mg/kg twice daily for cohort 2).[2] After 9 participants were enrolled in cohort 1 and following review by an independent Data and Safety Monitoring Committee, the protocol was amended to extend the treatment period to 28 days for cohort 1. The 9 participants receiving only 14 days of treatment are referred to as cohort 0. Selected inclusion and exclusion criteria for Study 001 are shown in **Table 1**.[3]

Figure 1. Study Design for Study 001[2,3]



**Treatments were given orally twice daily. Participants were up-titrated to their assigned dose based on a predefined dosing schedule.*

Table 1. Selected Inclusion and Exclusion Criteria for Study 001[3]

Selected inclusion criteria
• Classic RTT with a proven mutation in the *MECP2* gene • Aged between 16 years and 45 years • Severity rating on the Rett Syndrome Natural History/Clinical Severity Scale between 10 and 36 • CGI-S score of ≥4 • Stable on current concomitant medications for ≥4 weeks • Able to swallow the study drug provided as a liquid solution or via gastrostomy tube
Selected exclusion criteria
• No detectable abnormality of the EEG during screening assessment • Actively undergoing regression • Screening QT/QTcF interval >450 milliseconds • History of risk factors for torsade de pointes • Prior QT/QTcF prolongation that was controlled with medication, in which normal QT/QTcF intervals could only be achieved with medication • Previous clinically significant QT/QTcF prolongation that was deemed to presently put the participant at increased risk of clinically significant QT/QTcF prolongation • Current treatment with insulin

Abbreviations: CGI-S=Clinical Global Impression-Severity; EEG=electroencephalogram; MECP2=Methyl-CpG Binding Protein 2; QTcF=corrected QT interval using Fridericia's correction method; RTT=Rett syndrome.

Baseline Characteristics

The mean age of all participants in the mITT population was 25.3 years (range: 15.9 to 44.2 years); the maximum age in the trofinetide group was 40.8 years.[2] Most participants were White (89%, 49/55 participants); and the mean body mass index of all participants was 21.84 kg/m^2. Baseline severity on the Clinical Severity Scale (CSS) and Motor Behavior Assessment (MBA) total and change index scores was overall balanced between treatment groups within cohorts and across cohorts (**Table 2**).

Table 2. Baseline Demographics and Disease Characteristics in Study 001 (mITT population*)[2]

	Cohort 0		Cohort 1		Cohort 2	
	Placebo n=4	35 mg/kg n=5	Placebo n=5	35 mg/kg n=13	Placebo n=11	70 mg/kg n=17
Age, years						
Mean (SD)	22.43 (4.610)	26.65 (8.775)	32.09 (9.324)	22.62 (5.582)	27.09 (8.357)	24.52 (5.853)
Median	22.20	25.38	33.93	20.62	25.21	23.90
Min, Max	17.4, 27.9	17.6, 40.8	18.5, 44.2	15.9, 31.0	16.3, 43.9	17.1, 35.9
Ethnicity, n (%)						
Hispanic or Latino	2 (50)	0	1 (20)	0	0	2 (12)
Not Hispanic or Latino	2 (50)	5 (100)	4 (80)	13 (100)	11 (100)	15 (88)
Race, n (%)						
White	3 (75)	5 (100)	5 (100)	10 (77)	11 (100)	15 (88)
Black or African American	1 (25)	0	0	3 (23)	0	1 (6)
Asian	0	0	0	0	0	1 (6)
Severity scores, mean (SD)						
CSS total score	23.3 (6.29)	25.0 (3.46)	20.2 (8.11)	22.9 (7.98)	25.4 (6.22)	24.5 (6.64)
MBA total score	49.5 (9.33)	56.6 (8.53)	44.6 (13.41)	47.9 (15.29)	48.4 (8.50)	49.8 (12.37)
CSS change index score	8.3 (0.96)	7.8 (1.92)	8.2 (2.39)	8.4 (2.47)	9.1 (2.55)	8.4 (1.84)
MBA change index score	24.0 (4.83)	24.6 (3.65)	21.2 (5.81)	20.8 (5.81)	22.4 (3.80)	23.1 (5.97)

**One (1) participant discontinued the study before receiving any study medication.*
Abbreviations: CSS=Clinical Severity Scale; MBA=Motor Behavior Assessment Scale; mITT=modified intent to treat; SD=standard deviation.

Safety Results

The most commonly reported TEAEs (i.e. >2 participants in either active treatment group) with a higher incidence compared with the placebo group were diarrhea (39% in the 35 mg/kg group vs 15% in the placebo group), irritability (22% in the 35 mg/kg group vs 15% in the placebo group), and somnolence (17% in the 70 mg/kg group vs 5% in the placebo group; **Table 3**).[2]

Table 3. Incidence of TEAEs by Combined Cohorts During the Treatment Period in Study 001 (ITT Population)*[2]

System Organ Class Preferred Term, n (%)	Placebo (n=20)	35 mg/kg (n=18)	70 mg/kg (n=18)	Total (N=56)
Reported ≥1 TEAE	15 (75)	17 (94)	10 (56)	42 (75)
Gastrointestinal disorders				
Diarrhea	3 (15)	7 (39)	2 (11)	12 (21)
Vomiting	0	0	2 (11)	2 (4)
General disorders and administration site conditions				
Pyrexia	4 (20)	2 (11)	0	6 (11)
Infections and infestations				
Upper respiratory tract infection	1 (5)	1 (6)	2 (11)	4 (7)
Injury, poisoning, and procedural complications				
Fall	3 (15)	1 (6)	0	4 (7)

System Organ Class Preferred Term, n (%)	Placebo (n=20)	35 mg/kg (n=18)	70 mg/kg (n=18)	Total (N=56)
Nervous system disorders				
Somnolence	1 (5)	0	3 (17)	4 (7)
Drooling	0	1 (6)	2 (11)	3 (5)
Tremor	2 (10)	1 (6)	0	3 (5)
Complex partial seizures	0	0	2 (11)	2 (4)
Convulsion	2 (10)	0	0	2 (4)
Psychiatric disorders				
Irritability	3 (15)	4 (22)	0	7 (13)
Agitation	1 (5)	2 (11)	1 (6)	4 (7)
Insomnia	0	2 (11)	2 (11)	4 (7)
Hypervigilance	2 (10)	1 (6)	0	3 (5)
Mood swings	0	2 (11)	0	2 (4)
Sleep disorder	0	1 (6)	1 (6)	2 (4)
Respiratory, thoracic, and mediastinal disorders				
Cough	1 (5)	1 (6)	0	2 (4)
Skin and subcutaneous tissue disorders				
Rash	2 (10)	0	0	2 (4)

**TEAEs reported in at least 2 participants in either active treatment group.*
Abbreviations: ITT=intent to treat; TEAE=treatment-emergent adverse event.

Three (3) participants experienced serious TEAEs, none of which were deemed related to treatment with trofinetide.[2] One (1) participant discontinued due to serious TEAEs. Most TEAEs were mild or moderate in intensity and were not considered related to study drug. No deaths were reported during the study. Clinical laboratory tests, electrocardiograms, vital signs, and physical examinations (including fundoscopy and tonsil hypertrophy) indicated no time-dependent or dose-dependent trends.

Efficacy Results

Results from the group-level analysis by individual cohort showed that trofinetide at 70 mg/kg twice daily exceeded the minimum requirement for efficacy based on prespecified criteria.

References

1. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. **[Link]**
2. Glaze DG, Neul JL, Percy A, et al. A Double-Blind, Randomized, Placebo-Controlled Clinical Study of Trofinetide in the Treatment of Rett Syndrome. *Pediatr Neurol.* 2017;76:37-46. **[PubMed]**
3. Acadia Pharmaceuticals Inc. Data on File. In. San Diego, CA.