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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): Results from the Phase 3 LAVENDER™ Study

This letter is provided in response to your specific request for information regarding the results from the Phase 3 clinical trial of trofinetide in Rett syndrome (RTT).

Summary

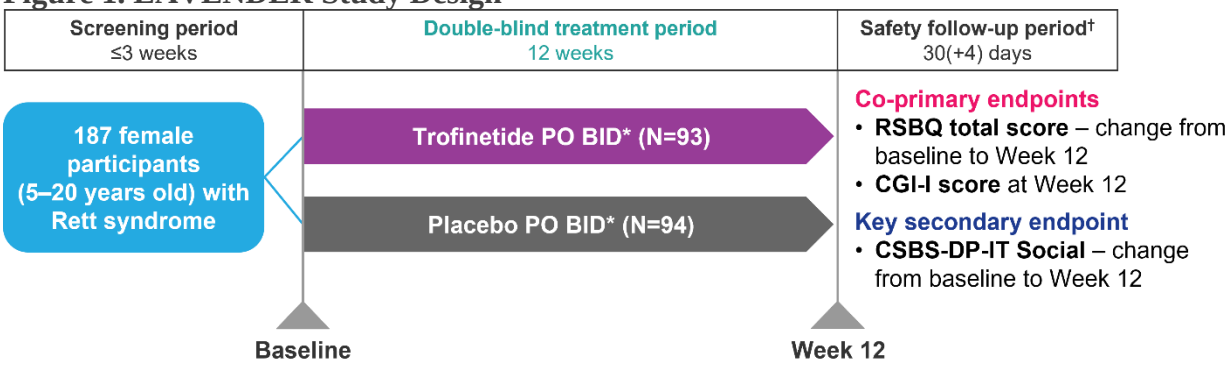
- The 12-week **Phase 3 LAVENDER study** evaluated the efficacy and safety of trofinetide in 187 female participants (5–20 years old) with RTT.[1]
- A statistically significant improvement over placebo was demonstrated for both **co-primary endpoints**.[1] On the Rett Syndrome Behaviour Questionnaire (RSBQ) total score, the least squares mean (LSM) change from baseline to Week 12 was -4.9 for trofinetide (N=91) vs. -1.7 for placebo (N=93) (LSM treatment difference -3.2 [95% CI -5.7, -0.6]; p=0.018; effect size=0.37). The LSM Clinical Global Impression-Improvement (CGI-I) score at Week 12 was 3.5 for trofinetide vs. 3.8 for placebo (LSM treatment difference -0.3 [95% CI -0.5, -0.1]; p=0.003; effect size=0.47).[1,2]
- **Treatment emergent adverse events (TEAEs)** were reported in 92.5% of participants in the trofinetide arm (N=93) and 54.3% in the placebo arm (N=94), with TEAEs leading to discontinuation in 17.2% and 2.1%, respectively, and serious TEAEs in 3.2% of each group.[1]
- The most **common TEAEs** were diarrhea (80.6% with trofinetide vs. 19.1% with placebo) and vomiting (26.9% with trofinetide vs. 9.6% with placebo). Most TEAEs of diarrhea and vomiting in the trofinetide group (97.3% and 96.0%, respectively) were characterized as mild-to-moderate.[1]

Phase 3 LAVENDER Study (ACP-2566-003)

This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study in 187 female participants (5–20 years old) with a diagnosis of typical RTT according to the Rett Syndrome Diagnostic Criteria and a documented disease-causing mutation in the *MECP2* gene (**Figure 1**).[1,2]

Participants received trofinetide 30–60 mL BID or placebo, based on the participant's weight at baseline (**Table 1**). The primary objective of this study was to investigate the efficacy of treatment with oral trofinetide versus placebo in girls and women with RTT. Co-primary efficacy endpoints measured symptoms using the caregiver-assessed RSBQ total score (change from baseline to Week 12) and the clinician-assessed CGI-I (score at Week 12). The key secondary endpoint was change from baseline to Week 12 in the CSBS-DP-IT Social.[1,3]

Figure 1. LAVENDER Study Design[1,3]



**Dose based on participant's body weight at baseline.*
†The LAVENDER follow-up visit does not take place if the participant rolls over into the open-label extension study.
Abbreviations: BID=twice a day; CGI-I=Clinical Global Impression-Improvement; CSBS-DP-IT Social=Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score; PO=oral; RSBQ=Rett Syndrome Behaviour Questionnaire.

Table 1. Dosing Schedule Based on Weight at Baseline[1]

Weight	Dose	Total Daily Dose
12-20 kg	30 mL BID	60 mL
>20-35 kg	40 mL BID	80 mL
>35-50 kg	50 mL BID	100 mL
>50 kg	60 mL BID	120 mL

Abbreviation: BID=twice daily.

Selected inclusion and exclusion criteria are shown in **Table 2**.

Table 2. Selected Inclusion and Exclusion Criteria[4,5]

Selected inclusion criteria
• Female subjects 5 to 20 years of age, inclusive, at screening • Body weight ≥12 kg at screening • Can swallow the study medication provided as a liquid solution or can take it by gastrostomy tube • Classic/typical RTT • Documented disease-causing mutation in the *MECP2* gene • At least 6 months post regression at screening • Severity rating of 10–36, inclusive, on the RTT Clinical Severity Scale at screening • CGI-S score of ≥4 • Stable pattern of seizures, or had no seizures, within 8 weeks of screening
Selected exclusion criteria
• Had been treated with insulin within 12 weeks of baseline • Current clinically significant cardiovascular, endocrine (such as hypo- or hyperthyroidism, Type 1 diabetes mellitus, or uncontrolled Type 2 diabetes mellitus), renal, hepatic, respiratory or gastrointestinal disease (such as celiac disease or inflammatory bowel disease) or major surgery planned during the study • A history of, or current, cerebrovascular disease or brain trauma • Significant, uncorrected visual or uncorrected hearing impairment • A history of, or current, malignancy • A known history or symptoms of long QT syndrome

Abbreviations: CGI-S=Clinical Global Impression-Severity; MECP2=Methyl-CpG Binding Protein 2; RTT=Rett syndrome.

Baseline Characteristics

Demographic and baseline disease characteristics were well balanced between the treatment groups.[1] In the Randomized Analysis Set (all randomized participants),[3] the mean (standard deviation [SD]) age of participants was 10.9 (4.62) years overall, with a mean (SD) baseline CGI-S score of 4.9 (0.76) (**Table 3**). In the respective trofinetide and placebo groups, 40.9% and 41.5% of participants were administered study medication via gastrostomy tube.[1]

Table 3. Baseline Demographics and Disease Characteristics – Randomized Analysis Set*[1]

	Placebo (N=94)	Trofinetide (N=93)	Total (N=187)
Age, years (mean ± SD)	10.9 ± 4.57	11.0 ± 4.69	10.9 ± 4.62
Age categories, n (%)			
5 to 10 Years	52 (55.3)	49 (52.7)	101 (54.0)
11 to 15 Years	24 (25.5)	25 (26.9)	49 (26.2)
16 to 20 Years	18 (19.1)	19 (20.4)	37 (19.8)
Primary race, n (%)			
White	90 (95.7)	82 (88.2)	172 (92.0)
Black or African American	1 (1.1)	1 (1.1)	2 (1.1)
Asian	1 (1.1)	5 (5.4)	6 (3.2)
Native Hawaiian or other Pacific Islander	0	1 (1.1)	1 (0.5)
Other	2 (2.1)	4 (4.3)	6 (3.2)
RTT-CSS score at screening (mean ± SD)	24.2 ± 6.68	24.1 ± 6.40	24.1 ± 6.53
RSBQ total score (mean ± SD)	44.4 ± 12.13	43.8 ± 11.42	44.1 ± 11.76
RSBQ severity, n (%)			
<35	25 (26.6)	23 (24.7)	48 (25.7)
≥35	69 (73.4)	70 (75.3)	139 (74.3)
Baseline CGI-S score (mean ± SD)	4.9 ± 0.76	4.9 ± 0.77	4.9 ± 0.76
Baseline CGI-S category, n (%)			
1 (Normal) to 3 (Mildly ill)	0	0	0
4 (Moderately ill)	33 (35.1)	32 (34.4)	65 (34.8)
5 (Markedly ill)	42 (44.7)	38 (40.9)	80 (42.8)
6 (Severely ill)	18 (19.1)	23 (24.7)	41 (21.9)
7 (Among the most extremely ill patients)	1 (1.1)	0	1 (0.5)
CSBS-DP-IT Social (mean ± SD)	8.9 ± 3.23	8.7 ± 3.32	8.8 ± 3.27

**No significant differences (p≤0.05) were detected between the study groups.*
Abbreviations: CGI-S=Clinical Global Impression-Severity; CSBS-DP-IT Social = Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score; CSS=clinical severity scale; RSBQ = Rett Syndrome Behaviour Questionnaire; RTT=Rett syndrome; SD=standard deviation.

MECP2 mutations were categorized as mild, moderate, or severe based on categories used to report findings from the Rett Syndrome Natural History Study (**Table 4**).[1,6] In the Safety Analysis Set (all randomized participants who received ≥1 dose of study medication), 75.3% of participants in the trofinetide group (N=93) had a history of constipation, compared with 78.7% in the placebo group (N=94) (**Table 4**).[1]

Table 4. *MECP2* Gene Mutation Severity and Selected Medical History – Safety Analysis Set*[1]

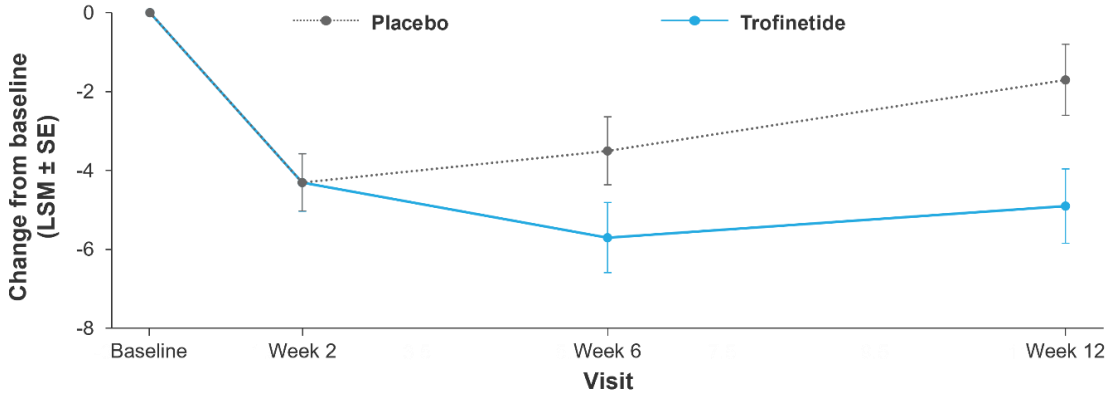
	Placebo (N=94)	Trofinetide (N=93)
***MECP2* gene mutation severity, n (%)**		
Mild	37 (39.4)	30 (32.3)
Moderate	8 (8.5)	13 (14.0)
Severe	46 (48.9)	46 (49.5)
Unknown	3 (3.2)	4 (4.3)
Selected medical history, n (%)		
Constipation	74 (78.7)	70 (75.3)
Seizure	47 (50.0)	40 (43.0)
Epilepsy	16 (17.0)	20 (21.5)
Focal dyscognitive seizures	1 (1.1)	2 (2.2)
Partial seizures	1 (1.1)	2 (2.2)
Status epilepticus	2 (2.1)	1 (1.1)
Gastrostomy	34 (36.2)	37 (39.8)

**No significant differences (p≤0.05) were detected between the study groups.*
Abbreviations: MECP2=Methyl-CpG Binding Protein 2; RTT=Rett syndrome.

Efficacy Results

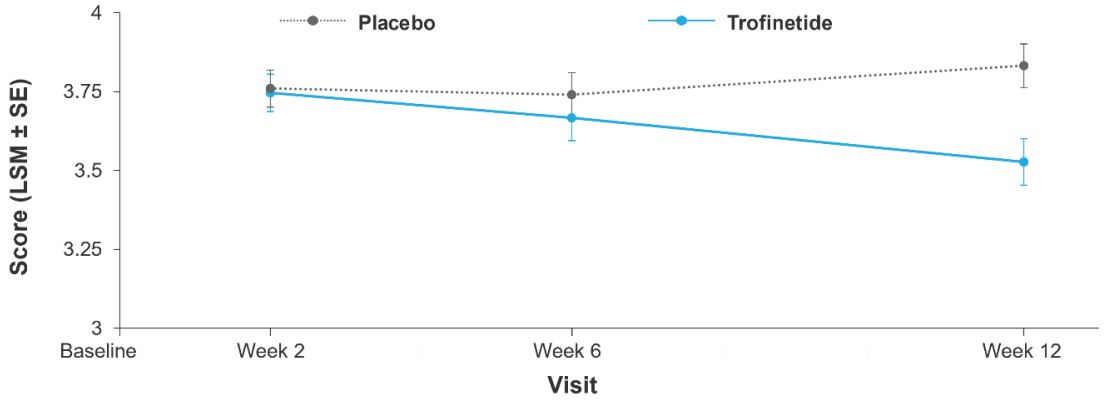
In the Full Analysis Set (all randomized participants who received ≥1 dose of study medication and who have both a baseline value and ≥1 post-baseline value for the RSBQ total score or who have ≥1 post-baseline value for the CGI-I score), a statistically significant improvement over placebo was demonstrated for both co-primary endpoints.[1,3] The mean (SE) change from baseline to Week 12 in the RSBQ total score was -5.1 (0.99) and -1.7 (0.98) in the trofinetide and placebo groups, respectively. Based on the MMRM analysis, the LSM change from baseline to Week 12 on the RSBQ was -4.9 vs. -1.7 for trofinetide and placebo, respectively (LSM treatment difference -3.2 [95% CI -5.7, -0.6]; p=0.018; effect size=0.37; **Figure 2**). The LSM CGI-I score at Week 12 was 3.5 vs. 3.8 for trofinetide and placebo, respectively (LSM treatment difference -0.3 [95% CI -0.5, -0.1]; p=0.003; effect size=0.47; **Figure 3** and **Figure 4**).[1,2]

Figure 2. RSBQ Change from Baseline by Visit (LSM ± SE) (OC; MMRM) – Full Analysis Set[1]



Abbreviations: LSM=least squares mean; MMRM=mixed model repeated measures; OC=observed cases; RSBQ=Rett Syndrome Behaviour Questionnaire; SE=standard error.

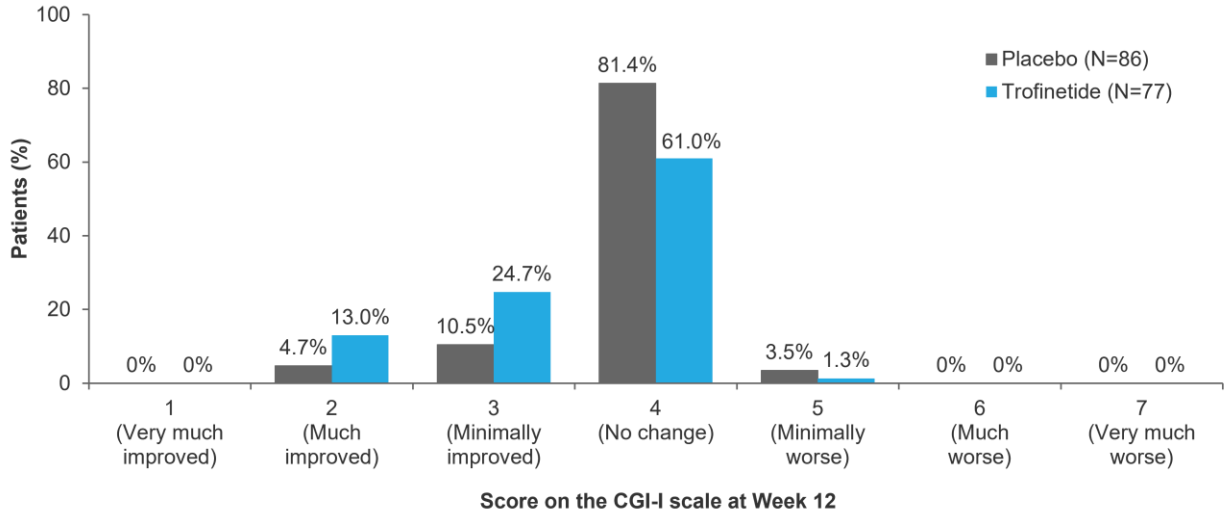
Figure 3. CGI-I Score by Visit (LSM ± SE) (OC; MMRM) – Full Analysis Set[1]



Placebo, n=	90	92	86
Trofinetide, n=	90	83	77

Abbreviations: CGI-I=Clinical Global Impression-Improvement; LSM=least squares mean; MMRM=mixed model repeated measures; OC=observed cases; SE=standard error.

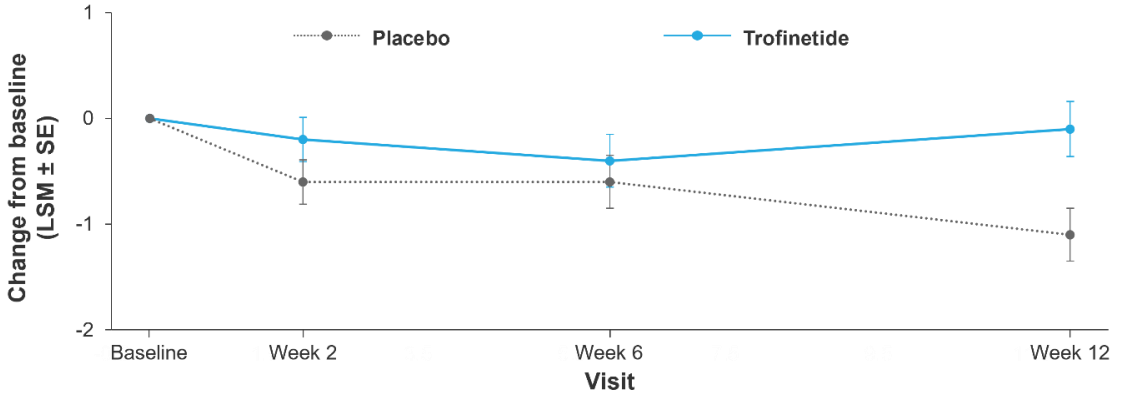
Figure 4. Distribution of CGI-I Scores for Patients Completing LAVENDER – Full Analysis Set[2]



Abbreviation: CGI-I=Clinical Global Impression-Improvement.

Trofinetide additionally demonstrated a statistically significant separation over placebo on the key secondary endpoint, the LSM change from baseline to Week 12 in CSBS-DP-IT Social. The score was -0.1 vs. -1.1 for trofinetide and placebo, respectively (LSM difference of 1.0 [95% CI 0.3 to 1.7]; p=0.006; effect size=0.43; **Figure 5**).[1] This secondary endpoint analysis should be interpreted with caution for the following reasons: the CSBS-DP-IT Social is intended to be a screening tool to identify potential communication issues in otherwise healthy infants/toddlers; this tool has not been validated for use in patients with Rett syndrome; and the 13-items that make the social composite score do not represent the full concept of social reciprocity.

Figure 5. CSBS-DP-IT Social Composite Score Change from Baseline by Visit (LSM ± SE) (OC; MMRM) – Full Analysis Set[7,8]



Abbreviations: CSBS-DP-IT Social=Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score; LSM=least squares mean; MMRM=mixed model repeated measures; OC=observed cases; SE=standard error.

Safety Results

In the Safety Analysis Set, in the respective trofinetide and placebo groups, at least one TEAE was reported in 86 (92.5%) and 51 (54.3%) participants (**Table 5**). No deaths were reported.[1]

Table 5. Summary of TEAEs – Safety Analysis Set[8]

	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Any TEAE	51 (54.3)	86 (92.5)
Any serious TEAE	3 (3.2)	3 (3.2)
Any related TEAE	20 (21.3)	78 (83.9)
Any related serious TEAE	1 (1.1)	2 (2.2)
Any TEAE leading to drug withdrawn	2 (2.1)	16 (17.2)*
Any severe TEAE	3 (3.2)	6 (6.5)
Any fatal TEAE	0	0

**During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs based on subject narratives, to be 18 (19%). This was reviewed and agreed upon by Acadia.*
Abbreviations: NDA=New Drug Application; TEAE=treatment-emergent adverse event.

TEAEs ≥5% in either treatment group are shown in **Table 6**. The most common TEAEs were diarrhea (80.6% with trofinetide vs. 19.1% with placebo), of which 97.3% in the trofinetide arm were characterized as mild-to-moderate, and vomiting (26.9% with trofinetide vs. 9.6% with placebo), of which 96% in the trofinetide arm were characterized as mild-to-moderate (**Table 6** and **Table 7**),[1] with the following definitions:[3]

- Mild: easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities.
- Moderate: sufficiently discomforting to interfere with normal everyday activities.
- Severe: incapacitating and/or preventing normal everyday activities.

Table 6. TEAEs in ≥5% in Either Treatment Group – Safety Analysis Set[1]

Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Diarrhea	18 (19.1)	75 (80.6)
Vomiting	9 (9.6)	25 (26.9)
Seizure	5 (5.3)	8 (8.6)
Pyrexia	4 (4.3)	8 (8.6)
Decreased appetite	2 (2.1)	5 (5.4)
Irritability	0	6 (6.5)

Abbreviation: TEAE=treatment-emergent adverse event.

Table 7. TEAEs in ≥5% in Either Treatment Group by Severity – Safety Analysis Set[1]

Preferred Term	Placebo (N=94) n (%)			Trofinetide (N=93) n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhea	15 (16.0)	3 (3.2)	0	39 (41.9)	34 (36.6)	2 (2.2)
Vomiting	8 (8.5)	1 (1.1)	0	18 (19.4)	6 (6.5)	1 (1.1)
Seizure	3 (3.2)	2 (2.1)	0	3 (3.2)	5 (5.4)	0
Pyrexia	2 (2.1)	2 (2.1)	0	7 (7.5)	1 (1.1)	0
Decreased appetite	1 (1.1)	1 (1.1)	0	2 (2.2)	3 (3.2)	0
Irritability	0	0	0	3 (3.2)	2 (2.2)	1 (1.1)

Abbreviation: TEAE=treatment-emergent adverse event.

Serious TEAEs were observed in 3.2% of study participants in both the trofinetide and placebo groups.[1] Serious TEAEs were bacteremia/urinary tract infection/bronchiolitis (n=1), COVID-19 pneumonia (n=1), and seizure (n=1) in the participants treated with trofinetide, and respiratory distress (n=1), constipation (n=1), and pneumatosis intestinalis (n=1) in the participants treated with placebo.[1]

Study treatment discontinuation rates related to TEAEs were 17.2% in the trofinetide group as compared to 2.1% in the placebo group (**Table 8**). In the trofinetide group, TEAEs leading to discontinuation of study drug were most commonly reported for diarrhea (12.9%), decreased appetite (3.2%), and lethargy and seizure (2.2% each).[1] All of the TEAEs leading to discontinuation of study drug were considered related to study drug, except for 1 case of arthralgia in the placebo group.[8]

Changes in laboratory tests, electrocardiograms and vital signs were generally small and similar in the treatment groups; none were considered clinically meaningful.[1] Small, transient changes in alanine aminotransferase values were reported in seven of 92 (7.6%) and three of 93 (3.2%) participants in the trofinetide and placebo groups, respectively. These changes were not associated with notable changes in other liver function tests, and no instances met Hy's law criteria.[1,9]

Table 8. TEAEs Leading to Discontinuation of Study Drug – Safety Analysis Set[1,8]

Preferred Term	Placebo (N=94)		Trofinetide (N=93)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n
Any TEAE Leading to discontinuation of study drug	**2 (2.1)**	**2**	**16 (17.2)***	**23**
Diarrhea	0	0	12 (12.9)†	12
Decreased appetite	0	0	3 (3.2)	3
Lethargy	0	0	2 (2.2)	2
Seizure	0	0	2 (2.2)	2
Frequent bowel movements	0	0	1 (1.1)	1
Gastroesophageal reflux disease	0	0	1 (1.1)	1
Vomiting	0	0	1 (1.1)	1
Weight decreased	0	0	1 (1.1)	1
Arthralgia	1 (1.1)	1	0	0
Pneumatosis intestinalis	1 (1.1)	1	0	0

**During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs based on subject narratives, to be 18 (19%). This was reviewed and agreed upon by Acadia.*

†During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs of diarrhea based on subject narratives, to be 14 (15%). This was reviewed and agreed upon by Acadia.

Abbreviations: NDA=New Drug Application; TEAE=treatment-emergent adverse event.

References

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