Summary Memo

Date	March 24, 2026
From	Michael Dimyan, MD Natalie Getzoff, MD Emily Freilich, MD
NDA/BLA #	217026
eCTD Sequence	0080 and 0086
Supplement #	8
Material Reviewed	Submissions in eCTD sequences 0080 and 0086
Date Received	September 30, 2025
PDUFA Goal Date	March 30, 2026
Sponsor	Acadia Pharmaceuticals, Inc
Proprietary Name (non-proprietary name)	Daybue (trofinetide)
Indication	For the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older
Action Recommended	Approval

1. Executive Summary

On March 10, 2023, Daybue (trofinetide) was approved for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older (NDA 217026). Trofinetide (NNZ-2566) is a synthetic analog of the tripeptide glycine-proline-glutamate (GPE) that was initially developed under IND 114319 for the treatment of Rett syndrome. The initial IND was submitted on November 20, 2012, and was allowed to proceed on December 20, 2012.

On October 8, 2021, FDA issued a Pediatric Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA), for three studies, a double-blind, placebo-controlled study of trofinetide to assess efficacy and safety in children 5 years old and older, a chronic open-label study to assess long term safety, and an open-label pharmacokinetic study to assess extrapolation of efficacy to children between the ages of 2 and 5 years.

The original 2023 approval for the treatment of Rett syndrome was based on the final clinical study report (CSR) for the first study (ACP-2566-004), and the interim CSRs for the second two studies. On January 24, 2025, the Applicant submitted the final complete CSRs for both Study 2 and Study 3 (under IND 114319 sequences 0221 and 0222), which were reviewed by the Division..

In the current submission, received September 30, 2025, the Applicant has submitted a labeling supplement proposing updating labeling to include the final sample sizes based on all studies being complete, along with the final CSR for a second chronic open-label study (ACP-2566-004). Based on the clinical review, the final CSRs reveal no significant changes in efficacy or safety and confirm the final sample sizes of the studies to be reported in the USPI, and the team recommends approval . We agree with the recommendation of the team that this labeling supplement should be approved.

In addition, this submission included a request for pediatric exclusivity based on completion of the Pediatric Written Request. The request was reviewed by the Division and by the Pediatric Exclusivity Board and was granted on February 18, 2026.

2. Introduction and Background

Trofinetide (NNZ-2566) is a synthetic analog of the tripeptide glycine-proline-glutamate (GPE) that was developed under IND 114319 for the treatment of Rett syndrome. The initial IND was submitted on November 20, 2012, and was allowed to proceed on December 20, 2012. On October 8, 2021, FDA issued a Written Request to submit information from the three studies described below:

1. Study 1: A randomized, double-blind, placebo-controlled, parallel-group study of trofinetide for the treatment of female patients aged 5 to <20 years with Rett syndrome.
2. Study 2: A long-term safety study of trofinetide for the treatment of females with Rett syndrome.
3. Study 3: An open-label, safety, and pharmacokinetics study of trofinetide for the treatment of females two to five years of age with Rett syndrome.

On March 10, 2023, Daybue (trofinetide) was approved for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. Data from a single, adequate, and well-controlled, clinical trial (Study ACP-2566-003, PWR Study 1) was the primary basis of support of the effectiveness of trofinetide for the treatment of Rett syndrome, with an interim study report from study ACP-2566-004 (PWR Study 2) providing long-term safety data, along with its subsequent continuing longer-term extension study ACP-2566-005, and an interim study report from study ACP-2566-009 (PWR Study 3) providing the data required for extrapolation for patients aged two to five years.

As part of the original NDA application, the Sponsor submitted a Request for Pediatric Exclusivity Determination on July 12, 2022. On December 22, 2022, the Agency advised, and the Sponsor agreed, to withdraw their Request for Pediatric Exclusivity Determination until all 3 studies and completed, and all subjects in Study 3 had accumulated safety data with at least one year of treatment with trofinetide.

On January 24, 2025, the Applicant submitted the final complete clinical study reports (CSRs) for both Study 2 and Study 3 (under IND 114319 sequences 0221 and 0222) which were reviewed by the Division.[1] In its review, the Division found no significant changes in the overall safety profile of the drug, given that the long-term study ACP-2566-004 was near completion at the time of submission and was stopped after marketing approval. In addition, 13 of the 15 subjects completed ACP-2566-009 with >12 months of treatment and also did not change the overall benefit/risk analysis.

In the current submission, received September 30, 2025, the Applicant has submitted a labeling supplement incorporating updated clinical trial experience with final sample sizes based on study completion and draft annotated labeling. Based on an information request from the Agency, on March 13, 2026, the Sponsor submitted the final CSR for study ACP-2566-005, the second long term extension for Study 1.

[1] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af807add29

ACP-2566-005 was designed as a second long-term extension for treatment of subjects for up to 139 weeks. This extension was after the 12-week double-blind, placebo-controlled treatment of ACP-2566-003 and 40-week open-label treatment in ACP-2566-004. Of the 77 subjects who entered the study, 61 remained in the study at the time of study closure when trofinetide was approved for marketing. The CSR indicates that the mean duration of exposure to trofinetide was 61 weeks. Combined with its preceding studies, ACP-2566-005 demonstrated that some subjects maintained an improvement in the RSBQ for up to 104 weeks. The Sponsor noted a mean improvement in the RSBQ of 9.8 points in the subjects at the end of ACP-2566-005 greater than the 4.9 point improvement noted for treated patients after 12 weeks of treatment in the double-blind treatment period; however, it is notable that 16 subjects dropped out of the study, so the mean improvement score may be high due to selection bias. The CGI-I remained at 3.2, similar to the CGI-I of 3.1 in study ACP-2566-003.

Finally, no new safety signals were identified. There were four deaths during ACP-2566-005, which were due to cardiac arrest, sudden unexpected death in epilepsy, bleeding from gastric ulcer after spinal surgery, and a case of vomiting and aspiration after gastrostomy tube placement. The last case had been reported and reviewed as part of the original NDA review. Otherwise, the most common adverse events in ACP-2566-005 were consistent with those previously identified for the drug that appeared greater than placebo in study ACP-2566-003, including diarrhea, nausea/vomiting, fever, and seizure.

No new product quality, nonclinical, or clinical pharmacology data were included in the submission.

3. Proposed Revisions to the Labeling

The Applicant proposed minor edits to the numbers of treated subjects in *Sections 6.1 Clinical Trials Experience* and *8.4 Pediatric Use* of the USPI, which are outlined below with each associated reviewer assessment.

Proposed Revision:

In controlled and uncontrolled trials in patients with Rett syndrome, 260 patients ages 2 to 40 years were treated with DAYBUE, including 112 (b) (4) patients treated for more than 6 months, 92 (b) (4) patients treated for more than 1 year, and 44 (b) (4) patients treated for more than 2 years.

Clinical Reviewer Assessment

My analysis of a joined and concatenated ADSL dataset file for ACP-2566-003, ACP-2566-004, ACP-2566-005, and ACP-2566-009 confirmed the Sponsor's exposure sizes of 112 subjects who received treatment for >6 months, 92 subjects who received treatment for >12 months, and 44 subjects who received treatment for >24 months.

Proposed Revision:

Pediatric Patients with Rett Syndrome 2 to 4 Years of Age

In an open-label study in pediatric patients 2 to 4 years of age with Rett syndrome (N=15), a total of 13 patients received DAYBUE for at least 12 weeks and 10 (b) (4) patients received DAYBUE for at least 12 (b) (4) months. Adverse reactions in pediatric patients 2 to 4 years of age treated with DAYBUE were similar to those reported in adult and pediatric patients 5 years of age and older with Rett syndrome in Study 1.

Clinical Reviewer Assessment

I confirmed these counts using the complete datasets for ACP-2566-003, ACP-2566-004, ACP-2566-005, and ACP-2566-009.

Proposed revision:

and Clinical Studies (14)]. Use of DAYBUE or DAYBUE STIX in patients 2 to 4 years of age is supported by evidence from Study 1 and pharmacokinetic and safety data in 15 (b) (4) pediatric patients 2 to 4 years of age treated with DAYBUE- (b) (4) *[see Dosage and Administration (2.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Clinical Reviewer Assessment

From the ADSL dataset file for ACP-2566-009 I confirmed that 15 subjects received trofinetide in ACP-2566-009. Two subjects received treatment for only 2 months, one for 5 months, and the remaining 12 received treatment for greater than 12 months.

4. Advisory Committee Meeting

None required, as this drug is not a new molecular entity.

5. Pediatrics

Trofinetide is approved for treatment of Rett syndrome in adults and pediatric patients 2 years and older.

6. Conclusions

This labeling supplement was submitted as part of the Applicant's submission for pediatric exclusivity as it includes the final report requested by the Agency regarding the treatment of the subjects in the 2- to 5-year age group for at least 12 months. No new safety signals were identified when the final CSRs for the long-term extension and younger age group studies (PWR studies 2 and 3) were submitted and reviewed.

The Applicant proposes updating the clinical trial exposure sizes and durations based on the finalized CSRs.

7. Recommendation

The Applicant has provided data to support updated clinical trial population numbers and durations of exposure in the labeling. Pediatric exclusivity was granted based on review of the Pediatric Written Request and communicated to the Applicant on February 18, 2026.

No new safety signals were identified. There are no outstanding unresolved issues.

The revised labeling should be approved.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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