IND 114319

WRITTEN REQUEST

Acadia Pharmaceuticals, Inc.
Attention: Heather Bradley, MPH
Executive Director, Regulatory Affairs
12830 El Camino Real, Suite 400
San Diego, CA 92130

Dear Ms. Bradley:

Reference is made to your June 14, 2021, Proposed Pediatric Study Request for trofinetide.

These studies investigate the potential use of trofinetide in the treatment of Rett syndrome in pediatric patients age 2 years and older.

BACKGROUND:

These studies investigate the potential use of trofinetide in the treatment of Rett syndrome in pediatric patients age 2 years and older.

Rett syndrome (RTT) is a rare, seriously debilitating neurodevelopmental disorder which manifests in early childhood and affects primarily females. The prevalence of RTT is estimated to be between 1 in 10,000 and 1 in 15,000 females worldwide.

In approximately 96%-98% of patients diagnosed with classic RTT, the disease is caused by mutations in the X-linked *MECP2* (methyl-CpG–binding protein 2 gene [in humans]) gene. *MECP2* encodes human methyl-CpG binding protein 2 (MeCP2), which modulates gene expression by binding to methylated CpG dinucleotides, primarily by activating but also by repressing transcription. The activity of the MeCP2 protein is diminished in both neurons and astrocytes.

The main clinical features include typical early development, followed by a loss of acquired hand skills and spoken language, characteristic repetitive hand stereotypies, and either gait problems or an absence of gait. Patients with RTT cannot feed themselves and walk only with assistance. Rett syndrome patients require lifelong 24-hour care. There are no medicines currently approved for the treatment of RTT.

There are no other indications for which trofinetide may produce health benefits in pediatric patients at this time.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, requires that

neonates be considered for study as part of a BPCA requirement. Among those who are correctly diagnosed with classic RTT, the median age of diagnosis in the US is 2.7 years. Variability of RTT features may contribute to a potential 2–4 years between initial presentation of symptoms and diagnosis. Due to inability to diagnose Rett syndrome in the neonatal population and the difficulty in assessing efficacy scales in such a young cohort, trofinetide cannot feasibly be studied in neonates and/or children younger than 2 years. Therefore, studies in neonates are not included in this Written Request.

There are no approved therapies for the treatment of Rett syndrome. There are no adult studies of trofinetide in Rett syndrome; therefore, efficacy in patients 5 to < 18 years of age cannot be extrapolated from adults and will be determined by the studies outlined in the Written Request. Efficacy in patients 2 to 5 years of age will be supported by comparable exposures based on findings of efficacy in ages 5 to < 18 years of age.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

To obtain needed pediatric information on trofinetide, the Food and Drug Administration (FDA) is hereby making a formal 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, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

  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.

  Study 2: A long-term safety study of trofinetide for the treatment of females with Rett syndrome.

  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.

- *Study Objectives:*

  Study 1: To investigate the efficacy, safety, pharmacokinetics, and pharmacokinetic/pharmacodynamic relationship of treatment with oral trofinetide versus placebo in females aged 5 to <20 years with Rett syndrome

  Study 2: To evaluate the long-term safety of trofinetide in females with Rett syndrome

  Study 3: To evaluate the safety (including long-term safety), tolerability, and characterize the pharmacokinetics of trofinetide in females 2 to 5 years of age with Rett syndrome

- *Patients to be Studied:*

  - *Age groups to be studied:*

  Study 1: Females with Rett syndrome, ages 5 to <20 years

  Study 2: Females with Rett syndrome, ages 5 years and older

  Study 3: Females with Rett syndrome, ages 2 to 5 years

  - *Number of patients to be studied:*

  Study 1

  Patients should be randomized to three age groups: 5 to 10 years, 11 to 15 years, and >16 years of age. A minimum of 12 subjects in each age stratum must complete the study. There must also be a minimum of 50 patients less than 18 years of age who complete the study.

  Patients who complete Study 1 should be enrolled into the long-term safety study (Study 2).

  Study 2

  This study must include a sufficient number of pediatric patients to adequately characterize the safety of the study drug at or above the dose or doses identified as effective in an adequately designed trial. Safety data from Study 1 and Study 2 can be combined to evaluate long-term safety. There must also be a minimum of 50 patients less than 18 years of age who complete the study.

  Study 3

  The study must enroll a sufficient number of patients to adequately characterize the PK profile, as well as evaluate the safety and tolerability of escalating doses of trofinetide in these subjects. The study must include a sufficient number of subjects who are 2 to < 4 years of age at screening

to adequately characterize the PK in this population. There must be an interim PK analysis after the first dose to verify the predicted PK results and confirm the dose.

- *Study endpoints:*

☐ *Pharmacokinetic and pharmacokinetic/pharmacodynamic Endpoints:*

Study 1 and 2

Whole blood concentration of trofinetide must be assessed. Trofinetide pharmacokinetic (PK) parameters must be evaluated using a population pharmacokinetics approach.

Study 3

Whole blood concentration data for trofinetide must be assessed. Population PK analyses must be performed to characterize the PK in children 2 to 5 years of age.

☐ *Efficacy Endpoints:*

Study 1

The co-primary efficacy endpoints will be the Rett Syndrome Behaviour Questionnaire [RSBQ] and Clinical Global Impression–Improvement [CGI-I]).

The key secondary efficacy endpoint will be change from baseline to Week 12 in the Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist (CSBS-DP-IT) Social Composite Score.

☐ *Safety Endpoints (Studies 1, 2 and 3):*

- Safety outcomes included in the protocol must include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), withdrawals due to AEs, and potentially clinically important changes in routine safety assessments collected at baseline and appropriate follow-up times, e.g., vital signs (pulse rate and blood pressure), weight, height, clinical laboratory measures (chemistry, including liver function tests and bilirubin; hematology; and urinalysis), and ECGs.

  The protocol must include a plan for monitoring of all adverse events until symptom resolution or until the condition stabilizes.

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1

A detailed statistical analysis plan (SAP) and any changes or updates in the SAP must be submitted and agreed upon with the Agency before database unblinding or database lock. Sample size for each arm should be based upon 80 % power to detect a treatment difference on both of the co-primary efficacy endpoints.

Study 2

Descriptive analysis of the safety data must be provided.

Study 3

Descriptive analysis of the pharmacokinetic parameters and safety data must be provided.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - Dosage form: solution
  - Route of administration: oral or via gastrostomy tube
  - Regimen: twice daily

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

(3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that trofinetide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of

the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before 27 October 2030. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

(1) the type of response to the Written Request (i.e. complete or partial response);
(2) the status of the application (i.e. withdrawn after the supplement has been filed or pending);
(3) the action taken (i.e. approval, complete response); or
(4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[3]

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

results. Additional information on submission of such information can be found on the Clinical Trials website.[4]

If you have any questions, contact Brenda Reggettz, PharmD, Regulatory Health Project Manager, by email at Brenda.Reggettz@fda.hhs.gov or by phone at (240) 402-6220.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Neuroscience
Center for Drug Evaluation and Research

[4] www.ClinicalTrials.gov

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/

ERIC P BASTINGS
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